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Prenatal exposure to tailpipe and non-tailpipe tracers of particulate matter pollution and autism spectrum disorders

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Declaration of Competing Interest

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.

Ethical approval

Both KPSC and University of Southern California Institutional Review Boards approved this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.107736.

Abstract

Background: Traffic-related air pollution exposure is associated with increased risk of autism spectrum disorder (ASD). It is unknown whether carbonaceous material from vehicular tailpipe emissions or redox-active non-tailpipe metals, eg. from tire and brake wear, are responsible. We assessed ASD associations with fine particulate matter ($PM_{2.5}$) tracers of tailpipe (elemental carbon [EC] and organic carbon [OC]) and non-tailpipe (copper [Cu]; iron [Fe] and manganese [Mn]) sources during pregnancy in a large cohort.

Methods: This retrospective cohort study included 318,750 children born in Kaiser Permanente Southern California (KPSC) hospitals during 2001–2014, followed until age 5. ASD cases were identified by ICD codes. Monthly estimates of $PM_{2.5}$ and $PM_{2.5}$ constituents EC, OC, Cu, Fe, and Mn with 4 km spatial resolution were obtained from a source-oriented chemical transport model. These exposures and NO_2 were assigned to each maternal address during pregnancy, and associations with ASD were assessed using Cox regression models adjusted for covariates. PM constituent effect estimates were adjusted for $PM_{2.5}$ and NO_2 to assess independent effects. To distinguish ASD risk associated with non-tailpipe from tailpipe sources, the associations with Cu, Fe, and Mn were adjusted for EC and OC, and vice versa.

Results: There were 4559 children diagnosed with ASD. In single-pollutant models, increased ASD risk was associated with gestational exposures to tracers of both tailpipe and non-tailpipe emissions. The ASD hazard ratios (HRs) per inter-quartile increment of exposure) for EC, OC, Cu, Fe, and Mn were 1.11 (95% CI: 1.06–1.16), 1.09 (95% CI: 1.04–1.15), 1.09 (95% CI: 1.04–1.13), 1.14 (95% CI: 1.09–1.20), and 1.17 (95% CI: 1.12–1.22), respectively. Estimated effects of Cu, Fe, and Mn (reflecting non-tailpipe sources) were largely unchanged in two-pollutant models adjusting for $PM_{2.5}$, NO_2, EC or OC. In contrast, ASD associations with EC and OC were markedly attenuated by adjustment for non-tailpipe sources.

Conclusion: Results suggest that non-tailpipe emissions may contribute to ASD. Implications are that reducing tailpipe emissions, especially from vehicles with internal combustion engines, may not eliminate ASD associations with traffic-related air pollution.

Keywords

Autism; $PM_{2.5}$ constituents; Traffic air pollution; Tailpipe; Non-tailpipe

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by varying degrees of repetitive and stereotyped behaviors, restricted interests, social and communication impairments and sensory disturbances (Elsabbagh, 2020; Pagalan et al., 2019; Xu et al., 2019; Zhang et al., 2010). ASD is a multifactorial condition with high heritability. Early studies focused mainly on understanding the role of genetic risk factors because of high heritability of ASD. However, the rapid increase in autism prevalence led to study of other factors (CDC, 2021). There is growing evidence that environmental factors may increase risk for ASD (Karimi et al., 2017).

$PM_{2.5}$ (ambient particles with aerodynamic diameter ≤ 2.5 μm) may increase ASD risk, based on epidemiological and toxicological studies (Chun et al., 2020; Costa et al., 2017). *In utero* exposure to near-roadway air pollution, particularly from non-freeway sources, also has been associated with risk of ASD (Carter et al., 2022; Volk et al., 2013, 2011).

Historically, vehicular emissions have been one of the most significant contributors to particulate matter (PM) pollution in urban areas (Karagulian et al., 2015). Vehicles emit primary particles directly to the atmosphere; they also emit a complex mixture of volatile and semi-volatile gases that can react to form condensable products that contribute to secondary particulate matter. Primary particle emissions can be classified as tailpipe or non-tailpipe depending on the emissions source (Zhang et al., 2020). Non-tailpipe PM is produced from brake, tire, and road wear (i.e., particles generated from road surface due to the abrasion by vehicles tires) and the resuspension of road dust (Piscitello et al., 2021). Emission standards for tailpipe particles from motor vehicles are increasingly stringent, but non-tailpipe PM emissions are largely unregulated. As a result, the proportion of vehicular PM emissions from non-tailpipe mechanisms has substantially increased in recent years as exhaust emissions decrease, and this trend likely will accelerate with increasing use of electric vehicles (Fussell et al., 2022; Timmers and Achten, 2016). Therefore, distinguishing effects of tailpipe from non-tailpipe emissions may have important public health and regulatory implications for ASD and other diseases associated with $PM_{2.5}$.

Emerging modeling tools in atmospheric chemistry are applicable to epidemiological studies, as they allow predictions of spatial–temporal distributions of non-tailpipe particles from brake and tire wear, and from re-suspended dust rich in trace metals, including copper (Cu), iron (Fe), zinc (Zn), manganese (Mn), calcium (Ca), barium (Ba), titanium (Ti), zirconium (Zr), antimony (Sb), and tin (Sn) (Charron et al., 2019; Zhang et al., 2020); combustion of diesel and gasoline fuels emit tailpipe carbonaceous materials e.g., elemental carbon (EC), and organic carbon (OC) (Habre et al., 2021; Platt et al., 2017). Toxicological studies suggest that non-tailpipe emissions have the potential to induce inflammation and oxidative stress (Fussell et al., 2022; Gerlofs-Nijland et al., 2019; Jeong et al., 2020), pathways with a central role in the known adverse health effects of exposure to air pollution (Leni et al., 2020). Tracers of tailpipe and of non-tailpipe emissions in ambient $PM_{2.5}$ may be correlated, which makes it difficult to identify an independent effect of non-tailpipe particles.

We previously found that exposure to EC and OC, and to near-roadway air pollution, were associated with increased ASD risk in a large retrospective pregnancy cohort (Carter et al., 2022; Rahman et al., 2022a). We have now assessed whether ASD was associated with tracers for non-tailpipe exposure and whether these associations were independent of associations with $PM_{2.5}$, near-roadway air pollution, and tailpipe emissions. Determining whether tailpipe and non-tailpipe particles have independent associations with adverse health outcomes may lead to more targeted regulation to better protect public health.

2. Materials and methods

2.1. Study population

The retrospective pregnancy cohort included mother–child pairs with singleton deliveries between January 1, 2001, and December 31, 2014 at Kaiser Permanente Southern California (KPSC) hospitals. KPSC is a large integrated healthcare system with over 4.5 million members. KPSC membership is diverse and similar in socioeconomic characteristics to the region's census demographics (Koebnick et al., 2012). Maternal social and demographic characteristics, pregnancy health information, and maternal residential address history were extracted from KPSC's well-established, integrated electronic medical records (EMR) system. Maternal addresses during pregnancy were geocoded using ArcGIS, and geocodes were assessed for exposure assignment suitability (ArcGIS, 2020). Addresses based only on street name, 5-digit postal code, locality, or administrative unit were considered too uncertain to be used for exposure assignments. Derivation of study sample size is shown in Figure S1 in the supplement.

Singleton births with KPSC membership at age 1 (n = 370,723) were included in the analytical data set. Children were routinely screened for potential ASD risk starting at age 18 months during regular well-child visits at KPSC. The median age of ASD diagnosis in this cohort was 3.0 years (Table 1). Therefore, children were followed from birth through EMR until clinical diagnosis of ASD, death, loss to follow-up or age 5, whichever came first. Most ASD was diagnosed before age 5 [71.6 %]. A total of 51,973 births was excluded due to missing sex, maternal race/ethnicity and age at delivery, implausible age of delivery or birth weight (n = 666), maternal age at delivery (n = 159), and incomplete maternal residential address history in pregnancy, or due to geocodes not suitable for exposure assignment (n = 51,148). The final data analysis included 318,750 mother–child pairs with complete data on residential estimates of $PM_{2.5}$ composition exposures.

Both KPSC and University of Southern California Institutional Review Boards approved this study with waiver of individual subject consent.

2.2. ASD ascertainment

Outcome measures were the presence or absence of an ASD diagnosis during the follow-up period, identified by ICD- 9 codes 299.0, 299.1, 299.8, 299.9 for EMR records before October 1, 2015 (date of KPSC implementation of ICD-10 codes) and subsequently ICD-10 codes F84.0, F84.3, F84.5, F84.8, F84.9. Codes from at least two separate visits were required for a verified ASD diagnosis, as described in previous studies (Coleman et al., 2015; Jo et al., 2019; Xiang et al., 2018, 2015).

2.3. Tailpipe and non-tailpipe air pollution exposure assessment

We have previously identified prenatal exposure to $PM_{2.5}$ as a risk factor for ASD in this cohort (Jo et al., 2019; Rahman et al., 2022b). For the current analysis we used exposure fields for $PM_{2.5}$ mass and chemical species generated by the UCD/CIT (University of California Davis/California Institute of Technology) Source Oriented Chemical Transport model (CTM). $PM_{2.5}$ mass and five constituents of $PM_{2.5}$ reflecting tailpipe and non-tailpipe

source were selected a priori based on the available data: EC and OC represent tailpipe traffic emissions and Cu, Fe, and Mn represent non-tailpipe traffic emissions.

The UCD/CIT CTM uses meteorological fields generated by the Weather Research and Forecast (WRF) model and geographically resolved emissions estimates from the California Air Resources Board (CARB), the Global Fire Emissions Database (GFED), and the Model of Emissions of Gases and Aerosols from Nature (MEGAN) to predict airborne PM concentrations. The model calculations track the mass and number concentrations of the PM constituents in particle diameters ranging from 0.01 to 10 μm through calculations that describe emissions, transport, diffusion, deposition, coagulation, gas- and particle phase chemistry, and gas-to-particle conversion (Hu et al., 2014a, 2014b). The UCD/CIT model was applied to estimate ground-level concentrations of 50 PM constituents over the major population regions in California using a 4-km grid resolution for the period from 2000 through 2016 (Hu et al., 2014a, 2014b; Yu et al., 2019). Model predictions were saved at hourly time resolution and averaged to longer times as needed. Predicted concentrations were evaluated against ambient measurements at all available locations and times. Bias corrections were applied using a regression model based on PM source contributions and chemical composition. Good correlations between final predictions and measurements ($r >$ 0.8) were demonstrated for many of the $PM_{2.5}$ species at most of the monitoring stations, particularly for the monthly, seasonal, and annual averages. For example, modeled monthly $PM_{2.5}$ EC was correlated with measurements with $r = 0.94$ (8 sites).

We previously examined the association of ASD diagnosis with prenatal NO_2 exposure in this cohort. NO_2 was also included in this study as a marker of tailpipe emission, especially to assess whether the association of ASD diagnosis with non-tailpipe emissions tracers were independent of NO_2. The NO_2 exposure model is described elsewhere in detail (Di et al., 2020). Briefly, multiple predictor variables, including meteorological variables, land-use variables, Moderate Resolution Imaging Spectroradiometer (MODIS) derived aerosol optical depth (AOD) measurements, chemical transport model predictions, emission inventories, and other variables were used to estimate daily 1-hr maximum NO_2 at a resolution of 1 km × 1 km across the contiguous United States. The model had good performance with 10-fold cross- validated R^2 0.79.

Average exposures to EC, OC, Cu, Fe, and Mn, $PM_{2.5}$ mass, and NO_2 were assigned to maternal address during the entire pregnancy. Exposures were time-weighted to account for changes of subject addresses during pregnancy.

2.4. Covariates

We selected covariates a priori based on expert knowledge and past literature on air pollution exposures and ASD (Jo et al., 2019; Pagalan et al., 2019; Ritz et al., 2018). We included child sex, maternal race/ethnicity, maternal age at delivery, parity, education, maternal history of comorbidity [$>=$1 diagnosis of heart, lung, kidney, or liver disease; cancer], median family household income in census tract of residence, birth year, and an indicator variable for season (dry from April-October; wet from November-March)]. Models were adjusted for birth year as a potential confounder because of the known time trends in ASD incidence and PM concentration levels. Birth year was included as a non-linear term with

a penalized spline of 4 degrees of freedom based on Akaike Information Criterion (AIC). In sensitivity analyses birth year was modeled as a fixed effect. Further adjustments were made for maternal pre-pregnancy diabetes mellitus and obesity (BMI ≥ 30 kg/m^2), as both were shown to be risk factors for ASD in this cohort (Xiang et al., 2015). We did not adjust or birth weight or gestational age were, because these variables are on the casual pathway between air pollution and ASD (Becerra et al., 2013; Bekkar et al., 2020; Gardener et al., 2011; Raz et al., 2018).

2.5. Statistical analyses

We fitted Cox proportional hazards models to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) for associations of ASD with exposure to tailpipe tracers and non-tailpipe tracers during pregnancy. For each of the five constituents, in addition to running separate single-pollutant models adjusted for the above-mentioned covariates, we fitted two-pollutant models to assess whether the association with each component remained after controlling for $PM_{2.5}$ mass, which we have shown previously to be associated with ASD in this cohort (Rahman et al., 2022b). To distinguish the adverse effects of non-tailpipe exposures from tailpipe emissions, for the effects estimate of non-tailpipe $PM_{2.5}$ components (i.e., Cu, Fe, and Mn), we constructed an additional set of two-pollutant model, adjusting for NO_2, which is commonly used as a marker of tailpipe emissions (Chen et al., 2021). In addition, we ran separate two-pollutant models examining the associations with non-tailpipe tracers Cu, Fe, and Mn, adjusting for EC and OC, and vice- versa. We did not model combinations of $PM_{2.5}$ components reflecting the same source in two-pollutant models because many were highly correlated (Supplementary Table 1). The proportional hazards assumption of the Cox proportional hazard model was assessed using the Schoenfeld residual plot. No clear non–random patterns against follow-up time were observed.

The UCD/CIT Source-oriented CTM model used a base-year inventory from the year 2000 adjusted with year-specific statewide scaling factors when predicting $PM_{2.5}$ constituents for the year 2001–2009. Area sources were scaled based on the California Almanac of Emissions, while Mobile sources were scaled using the EMissions FACtor (EMFAC) model. All scaling factors reflect growth due to increased activity and control due to the adoption of more efficient and less polluting devices. A 2010 base emissions inventory with year-specific adjustment factors was used for predicting $PM_{2.5}$ constituents for the years 2010–2014. The methods employed to represent the changes to emissions patterns over time produce step changes across the boundary years when the base inventory was updated for some sources. Increased concentrations of some non-tailpipe tracers were predicted in the later 2010–2014 period, probably due to the use of different emission inventories for the later time period. We examined associations with exposure during the entire 2000–2014 period and separately for 2000–2009 and for 2010–2014. HRs and 95 % CIs were scaled to the pregnancy interquartile range (IQR) in concentration for each constituent. Statistical significance was set at p-value < 0.05. All analyses were performed using R Statistical Software (v3.5.2; R Core Team 2021).

3. Results

After censoring children at age 5, 4559 were diagnosed with ASD over a median of 4.0 years follow up during 2001–2014 (2129 during 2001–2009 and 2433 during 2010–2014). Participant demographics are shown in Table 1. Children with ASD were over 4 times more likely to be boys (n = 3703) than girls (n = 856). Children diagnosed with ASD were more likely to have older, nulliparous mothers with maternal comorbidities, pre-pregnancy diabetes, and pre-pregnancy obesity than children who were not diagnosed with ASD.

Pregnancy average concentrations of EC, OC, Cu, Fe, and Mn at maternal residential addresses across all years were 669, 2536, 11.8, 305, and 5.36 ng/m^3, respectively (Supplementary Table 1). Moderate to high correlation was observed among tailpipe and among non-tailpipe tracers due to their common sources. For example, Cu had a correlation of 0.95 and 0.88 with Fe and Mn, respectively. Similarly, EC had a correlation of 0.83 with OC. Correlations among the constituents were even stronger when stratified by years 2001–2009 and 2010–2014. The yearly trend and distribution of concentrations of these constituents is shown in Supplementary Figure 2. EC and OC concentrations decreased over time from 2001 to 2009 and were relatively stable from 2010 to 2014, likely reflecting trends in the adoption of newer diesel engines. Cu, Fe, and Mn concentration also decreased from 2001 to 2009, but increased in a step-change in years after 2010, probably due to changes in the underlying emissions inventory.

In single-pollutant models, all components were associated with increased ASD risks in the entire cohort from 2001 to 2014 (Table 2). For each IQR increase in concentration during pregnancy, HRs (and 95 % CI) for the ASD associations with EC, OC, Cu, Fe, and Mn were 1.11 (95 % CI: 1.06–1.16), 1.09 (95 % CI: 1.04–1.15), 1.08 (95 % CI: 1.00–1.15), 1.14 (95 % CI: 1.09–1.20), and 1.17 (95 % CI: 1.12–1.22), respectively. In the two-pollutant models, the association of each constituent was robust to adjustment for $PM_{2.5}$. The associations of Cu, Fe, and Mn were also robust to adjustment for NO_2, EC, and OC. In contrast, HRs for the associations of EC and OC were markedly attenuated in two-pollutant models adjusting for Cu, Fe, or Mn; except for EC adjusted for Cu, the ASD associations with tracers for tailpipe emissions were not statistically significant in these two-pollutant models.

In analyses restricted to years 2001–2009, HRs for associations of each constituent with ASD diagnosis were substantially larger compared to the analysis for all years (Table 2). The associations of Cu, Fe, and Mn were robust to adjustment for NO_2, EC, and OC. HRs for associations of EC and OC were markedly attenuated and became non-significant after adjusting for Cu, Fe, and Mn, as in the entire cohort. EC and OC were negatively associated with ASD after co-adjustment for non-tailpipe tracers, estimates that were statistically significant for OC. However, all constituents were highly correlated (Supplementary Table 1). In 2010 to 2014, only Mn was associated with ASD in single-pollutant models, and the observed association was not attenuated in two- pollutant models adjusting for total $PM_{2.5}$, NO_2, EC or OC. Although no ASD associations with Cu and Fe were found in single pollutant models, associations were markedly stronger in two-pollutant models adjusting for $PM_{2.5}$, NO_2, EC or OC and were statistically significant.

4. Discussion

Many previous studies have found associations between prenatal exposure to $PM_{2.5}$ and increased ASD risk (Chun et al., 2020; Lin et al., 2022), including studies of this cohort (Jo et al., 2019; Rahman et al., 2022b). We also reported that pregnancy exposure to near-roadway air pollution from non-freeway sources was significantly associated with ASD risk in this cohort (Carter et al., 2022). In a more recent study, we used $PM_{2.5}$ constituent estimates from two independent exposure models; i) the same SO-CTM used in this analysis and ii) a hybrid model (Van Donkelaar et al., 2019) to examine ASD associations with four major $PM_{2.5}$ constituents (EC, OC, nitrate [NO_3], and sulfate [SO_4]), which are available from both exposure models. Among these four constituents, EC and OC from both models were associated with ASD risk (Rahman et al., 2022a). In the current study, specific constituents were used to distinguish ASD risk associated with tailpipe exhaust emissions from non-tailpipe emissions. In this large population-based pregnancy cohort, ASD diagnosis in the entire cohort was associated with tracers of both tailpipe (EC and OC) and non-tailpipe (Cu, Fe and Mn) $PM_{2.5}$ in single pollutant models. Associations with $PM_{2.5}$ trace metals reflecting non-tailpipe source were robust to adjustment for total $PM_{2.5}$ and for NO_2, EC, and OC, markers of combustion-related air pollution from vehicular sources. These results suggest that estimates of non-tailpipe traffic related air pollution effects on ASD diagnosis were independent of effects of tailpipe emissions. In contrast, the ASD associations with $PM_{2.5}$ constituents reflecting tailpipe source were not independent of associations with non-tailpipe sources. In addition, the strength of ASD associations with non-tailpipe emissions were substantially stronger and more consistent in the sub-cohort born in 2001–2009 than in 2010–2014.

Brake and tire wear emissions and re-suspended dust are among the primary contributors to Cu, Fe, and Mn in ambient air. Prior studies identified Cu, in particular, and Fe as ambient tracers for brake wear (Demir et al., 2022; Hagino et al., 2016; Jeong et al., 2019; Oroumiyeh, 2021; Oroumiyeh et al., 2022; Pakbin et al., 2011; Thorpe and Harrison, 2008; Viana et al., 2008). Mn is considered a tracer for brake wear (Charron et al., 2019; Demir et al., 2022; Jeong et al., 2019; Zhang et al., 2020). EC and OC have been considered tracers of traffic emissions for the last two decades (Demir et al., 2022; Hasheminassab et al., 2014; Rahman and Thurston, 2022; Soleimanian et al., 2019; Thorpe and Harrison, 2008; Thurston et al., 2011; Viana et al., 2008), including in studies specific to the Los Angeles air basin (Hasheminassab et al., Soleimanian et al., Oroumiyeh et al., and Pakbin et al.). These have also been used as tracers for tailpipe emissions in large European consortium investigations such as ESCAPE (European Cohort Study for Air Pollution Effects) (de Hoogh et al., 2013) and in MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution) (Kai et al., 2014). In addition, the UCD/CIT CTM model enabled us to calculate the contribution of sources to the constituents. Our data suggest that brake and tire wear contributed 87.7 % of the Cu, 63.5 % of the Fe, and 39.9 % of the Mn. Thus, all reflect non-tailpipe emissions to a greater or lesser extent, and consistent health effects across all three suggests a non-tailpipe source. Similarly, the SO-CTM provided us the contribution of primary EC and OC to the on-road gasoline and diesel $PM_{2.5}$ in this dataset. Our data suggest that primary EC and OC

constitute about 98 % of the primary on-road gasoline $PM_{2.5}$ mass and 63 % of the primary on-road diesel $PM_{2.5}$ mass.

Traffic emissions are not the only source of EC and OC in ambient air. They may be emitted from industrial sources as well. Biomass burning and secondary organic aerosol (SOA) contribute to OC, but there is little biomass burning in southern California, with the exception of occasional wildfires that have become substantially more frequent only since the time of the predictions used in this study. A source apportionment study conducted in the Los Angeles air basin reported that biomass burning contribution to total OC ranges between only 3–12 % depending on the location (Soleimanian et al., 2019). In addition, EC and OC considered in this study are primary so SOA will contribute essentially nothing to the primary OC estimate reflective of tailpipe emissions. Similarly, Cu, Fe, and Mn may not be exclusively from non-tailpipe emission sources. Emission released from metallurgical industries can contribute to these trace metals in the atmosphere. Fe and Mn can also have crustal sources (Cesari et al., 2016; Viana et al., 2008).

Our novel observations of increased ASD risks associated with Cu, Fe and Mn add to the growing evidence from a few previous epidemiological studies supporting the adverse neurodevelopmental effects of $PM_{2.5}$ metal exposures. Among 2897 children in the BREATHE project, fine particulate matter Cu exposure was associated with poorer motor performance and detectable brain damage in developing children (Pujol et al., 2016). In 7246 children from 4 European birth cohorts, higher airborne Fe exposure at birth was adversely associated with fine motor function in childhood (Lubczyńska et al., 2017). An autopsy study found associations of higher exposure to particulate matter Mn with neuroinflammation and with up-regulation of frontal lobe interleukin-1β and COX2 (Calderón-Garcidueñas et al., 2013). The possible mechanism by which $PM_{2.5}$ and its constituents affect fetal brain development may include maternal systemic oxidative stress and proinflammatory cytokine production (Leni et al., 2020; Xu et al., 2012), resulting in placental and endothelial dysfunction and increased fetal oxidative stress that may disrupt differentiation and organization of the fetal brain (Block et al., 2012; Block and Calderón-Garcidueñas, 2009˜). Cu, Fe, and Mn are transition metals that produce oxidative stress by generating reactive oxygen species (Schaumann et al., 2004; Verma et al., 2015, 2014; Zhang et al., 2021b, 2021a). PM can cross the placental barrier, directly reaching the developing fetus (Bové et al., 2019; Muoth et al., 2016; Wick et al., 2010). Cu, Fe, and Mn are water-soluble; therefore, it is plausible that the water-soluble form of these metals cross the placental barrier and harm the developing brain.

The markedly weaker associations of non-tailpipe $PM_{2.5}$ components with ASD diagnosis observed in the 2010–2014 sub-cohort could be due to reduced statistical power in the smaller cohort, although strong associations were seen in the earlier cohort of comparable size. It is also possible that differences in the exposure model in the later years may have influenced the associations. Emission inventories are the most important input for any chemical transport model. The tire and brake wear emissions used for the years 2000–2009 and the years 2010–2014 have similar spatial patterns, but there is a step change in the emissions intensity in the later time period. Changes to tire and brake wear emissions would have occurred more gradually in the real world. The number of vehicle miles traveled

(VMT) in the greater Los Angeles region increased between 2000 and 2007, decreased slightly during the economic recession, and then resumed increasing in the year 2011. It is likely that non-tailpipe emissions in the real world followed a similar time trend, but the time patterns in the emissions used in our study do not appear to reflect this variability (Figure 2 in supplement). We conducted a sensitivity analysis adjusting (with a fixed effect) for birth year to determine whether the main conclusions are influenced by uncertainty in the time trends of tire and brake wear emissions. (Adjusting for birth year as a fixed effect removes the effect of any yearly temporal confounding). Results were largely unchanged from the primary analysis in which we treated birth year as non-linear. These results suggest that the observed associations were largely driven by the spatial contrast of $PM_{2.5}$ constituents. This conclusion is consistent with several prior studies that reported that spatial contrast of traffic related air pollution remained stable for up to 10 years (Cesaroni et al., 2012; Chen et al., 2021; Eeftens et al., 2011). This may be especially true for non-tailpipe Cu, Fe, and Mn because these were not regulated during the period of study. Nevertheless, differences in modeling exposure predictions in the later years may underlie both the unexpected marked increase in exposure to Cu, in particular, in the later cohorts and the smaller effect estimates. This data set and other newly available predictions of particle components have not been used extensively in health studies. We have identified distributions of exposure to particle components that warrant investigation to be sure the data are appropriate for epidemiological studies.

The ASD associations with tailpipe exhaust constituents EC and OC were positive in single pollutant models in the entire cohort and in the 2001–2009 sample (Table 2). In the 2010–2014 sample there was no association, broadly consistent with single pollutant models of non- tailpipe emissions. However, associations with EC and OC adjusted for non-tailpipe emissions were protective in all 3 sets of analyses, results which were unexpected based on epidemiological and toxicological studies. These anomalous results with changing direction of association may be spurious, reflecting the high correlations of constituents considered in this study. EC has been most widely investigated in previous studies; it has been associated with several health outcomes, including decreased cognitive function and attention (Achilleos et al., 2017; Chiu et al., 2013; Suglia et al., 2008). However, there has been little previous evaluation of health effects of tailpipe emissions adjusted for non-tailpipe sources. In Southern California, diesel and gasoline engine exhaust are the main sources of EC. The evidence on the neurotoxicity of EC (e.g., diesel exhaust particles) from rodent studies is inconclusive. Some rodent studies reported that diesel exhaust particles may cause developmental neurotoxicity and adversely impact behavior and motor activity (Suzuki et al., 2010; Yokota et al., 2009), whereas some other studies reported limited evidence of neurotoxicity of diesel exhaust particles (Morris-Schaffer et al., 2019b, 2019a). Unlike Cu, Fe, and Mn, EC is an insoluble species of PM. Several studies reported oxidative potential of EC particles (Antiñolo et al., 2015; Li et al., 2013; McWhinney et al., 2013), but the underlying mechanism is unclear. There is a growing consensus that reactive oxygen species are not produced by EC alone, but by other co-emissions, such as semi-volatile organic compounds and PAHs that are adsorbed onto the EC core (Basagaña et al., 2016; Fang et al., 2017; Grahame et al., 2014; Hopkins et al., 2018; Li et al., 2022). OC is also a major component of motor vehicle exhaust and has been associated with

health outcomes including mortality, but to our knowledge OC neurodevelopmental effects have not been examined in epidemiological studies. Organic carbon compounds, including quinones and PAHs, have been shown to be associated with oxidative stress and lipid peroxidation (Gurbani et al., 2013; Jeng et al., 2011; Wang et al., 2017).

$PM_{2.5}$ is currently regulated by mass concentration. Identification of the constituents responsible for ASD-$PM_{2.5}$ associations could lead to targeted regulation of $PM_{2.5}$ mass from a specific source, which could help to achieve optimal public health benefits from $PM_{2.5}$ mitigation actions. In this study HRs of ASD risk were scaled for comparison to IQR increase in concentrations of each constituent. The HRs for non-tailpipe constituents were largely comparable to ASD HR associated with IQR increase in $PM_{2.5}$ during entire pregnancy (1.10 (95 % CI: 1.02, 1.19) per 5.56 $\mu g/m^3$). Because each traffic-related constituent mass is only a small proportion of $PM_{2.5}$, these traffic-related constituents, especially from non-tailpipe sources, are particularly hazardous (if the associations we have observed are causal), that is, the traffic-related $PM_{2.5}$ is more potent on a per mass basis than total $PM_{2.5}$ and may be driving the ASD-$PM_{2.5}$ association.

Among many strengths, this study is the first to examine the ASD association with traffic-related $PM_{2.5}$ constituents in a large representative cohort and to disentangle the ASD risk associated with traffic non-exhaust emissions from that of exhaust emissions. A large body of evidence on the detrimental effects of traffic-related air pollution on asthma incidence, lung function, cardiovascular disease and mortality has led to regulation of vehicular exhaust emissions (HEI, 2022, 2010). There is limited evidence from epidemiological studies on health effects of non-tailpipe emission sources, and thus, these emission sources have not been targeted for regulation in the past. More epidemiological studies are needed to determine possible health effects of non-exhaust emissions in order to reduce public health risk. We also acknowledge some limitations. The study did not report the association between trimester-specific average $PM_{2.5}$ constituents and ASD diagnosis, because the trimester-average constituent exposure estimates were highly correlated with the pregnancy-average estimates. These correlation coefficient ranged from 0.85 to 0.95, depending on the $PM_{2.5}$ species, so distinguishing effects of different trimesters was not possible. Therefore, the use of average exposures across the nine months of pregnancy are appropriate. $PM_{2.5}$ constituents data used in this analysis were available at 4 km spatial resolution, which limited our ability to assess fine scale variability of the traffic related $PM_{2.5}$ constituents. The consequence of this exposure misclassification for epidemiological investigations due to coarser spatial resolution is likely to be to underestimate effects, because the misclassification will likely be non- differential to the outcome. We also did not account for other relevant time-activity patterns such as exposure during time the mother spent at work or in outdoor exercise that would increase ventilation rate and dose. These seem unlikely to explain the difference between tailpipe and non-tailpipe emission associations we observed.

In summary, results of this study, using emerging new exposure assessment tools for epidemiological applications, suggest that prenatal exposure to non-tailpipe emissions may contribute to ASD risk. Implications are that future conventional combustion engine vehicles with markedly reduced tailpipe emissions may not eliminate ASD associations with traffic-related air pollution. In contrast, widespread adoption of electric vehicles with zero tailpipe

emissions and lower non-tailpipe emissions due to regenerative braking may reduce, but not eliminate, future ASD associations with traffic-related air pollution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The authors declare they have no actual or potential competing interests. Joel Schwartz declares that he has testified on behalf of the U.S. Department of Justice in a case involving a Clean Air Act violation. Frederick Lurmann is employed by Sonoma Technology, Inc., Petaluma, CA.

Data availability

Data will be made available on request.

References

Achilleos S, Kioumourtzoglou M-A, Wu C-D, Schwartz JD, Koutrakis P, Papatheodorou SI, 2017. Acute effects of fine particulate matter constituents on mortality: A systematic review and meta-regression analysis. Environ. Int. 109, 89–100. 10.1016/j.envint.2017.09.010. [PubMed: 28988023]

Antiñolo M, Willis MD, Zhou S, Abbatt JPD, 2015. Connecting the oxidation of soot to its redox cycling abilities. Nat. Commun. 6, 6812. 10.1038/ncomms7812. [PubMed: 25873384]

ArcGIS, 2020. The geocoding process. 2020 [WWW Document]. URL https://desktop.arcgis.com/en/arcmap/latest/manage-data/geocoding/the-geocoding-process.htm (accessed 11.13.21).

Basagaña X, Esnaola M, Rivas I, Amato F, Alvarez-Pedrerol M, Forns J, López-Vicente M, Pujol J, Nieuwenhuijsen M, Querol X, Sunyer J, 2016. Neurodevelopmental Deceleration by Urban Fine Particles from Different Emission Sources: A Longitudinal Observational Study. Environ. Health Perspect. 124, 1630–1636. 10.1289/EHP209. [PubMed: 27128166]

Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B, 2013. Ambient air pollution and autism in Los Angeles County, California. Environ. Health Perspect. 121, 380–386. 10.1289/ehp.1205827. [PubMed: 23249813]

Bekkar B, Pacheco S, Basu R, DeNicola N, 2020. Association of Air Pollution and Heat Exposure With Preterm Birth, Low Birth Weight, and Stillbirth in the US: A Systematic Review. JAMA Netw. open 3, e208243.

Block ML, Calderón-Garcidueñas L, 2009. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 32, 506–516. 10.1016/j.tins.2009.05.009. [PubMed: 19716187]

Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, Cory-Slechta DA, Costa D, Diaz-Sanchez D, Dorman DC, Gold DR, Gray K, Jeng HA, Kaufman JD, Kleinman MT, Kirshner A, Lawler C, Miller DS, Nadadur SS, Ritz B, Semmens EO, Tonelli LH, Veronesi B, Wright RO, Wright RJ, 2012. The outdoor air pollution and brain health workshop. Neurotoxicology 33, 972–984. 10.1016/j.neuro.2012.08.014. [PubMed: 22981845]

Bové H, Bongaerts E, Slenders E, Bijnens EM, Saenen ND, Gyselaers W, Van Eyken P, Plusquin M, Roeffaers MBJ, Ameloot M, Nawrot TS, 2019. Ambient black carbon particles reach the fetal side of human placenta. Nat. Commun. 10, 3866. 10.1038/s41467-019-11654-3. [PubMed: 31530803]

Calderón-Garcidueñas L, Serrano-Sierra A, Torres-Jardón R, Zhu H, Yuan Y, Smith D, Delgado-Chávez R, Cross JV, Medina-Cortina H, Kavanaugh M, Guilarte TR, 2013. The impact of environmental metals in young urbanites' brains. Exp. Toxicol. Pathol. 65, 503–511. 10.1016/j.etp.2012.02.006. [PubMed: 22436577]

Carter SA, Rahman MM, Lin JC, Shu YH, Chow T, Yu X, Martinez MP, Eckel SP, Chen JC, Chen Z, Schwartz J, Pavlovic N, Lurmann FW, McConnell R, Xiang AH, 2022. In utero exposure to near-roadway air pollution and autism spectrum disorder in children. Environ. Int. 158, 106898 10.1016/j.envint.2021.106898.

CDC, 2021. Data & Statistics on Autism Spectrum Disorder [WWW Document]. URL https://www.cdc.gov/ncbddd/autism/data.html.

Cesari D, Amato F, Pandolfi M, Alastuey A, Querol X, Contini D, 2016. An inter-comparison of PM10 source apportionment using PCA and PMF receptor models in three European sites. Environ. Sci. Pollut. Res. 23, 15133–15148. 10.1007/s11356-016-6599-z.

Cesaroni G, Porta D, Badaloni C, Stafoggia M, Eeftens M, Meliefste K, Forastiere F, 2012. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. Environ. Heal. 11, 48. 10.1186/1476-069X-11-48.

Charron A, Polo-Rehn L, Besombes J-L, Golly B, Buisson C, Chanut H, Marchand N, Guillaud G, Jaffrezo J-L, 2019. Identification and quantification of particulate tracers of exhaust and non-exhaust vehicle emissions. Atmos. Chem. Phys. 19, 5187–5207. 10.5194/acp-19-5187-2019.

Chen J, Rodopoulou S, de Hoogh K, Strak M, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, Brandt J, Cesaroni G, Concin H, Fecht D, Forastiere F, Gulliver J, Hertel O, Hoffmann B, Hvidtfeldt UA, Janssen NAH, Jockel KH, Jørgensen J, Katsouyanni K, Ketzel M, Klompmaker JO, Lager A, Leander K, Liu S, Ljungman P, Macdonald CJ, Magnusson PKE, Mehta A, Nagel G, Oftedal B, Pershagen G, Peters A, Raaschou-Nielsen O, Renzi M, Rizzuto D, Samoli E, van der Schouw YT, Schramm S, Schwarze P, Sigsgaard T, Sørensen M, Stafoggia M, Tjønneland A, Vienneau D, Weinmayr G, Wolf K, Brunekreef B, Hoek G, 2021. Long-term exposure to fine particle elemental components and natural and cause-specific mortality—a pooled analysis of eight european cohorts within the ELAPSE project. Environ. Health Perspect. 129, 1–12. 10.1289/EHP8368.

Chiu Y-H-M, Bellinger DC, Coull BA, Anderson S, Barber R, Wright RO, Wright RJ, 2013. Associations between traffic-related black carbon exposure and attention in a prospective birth cohort of urban children. Environ. Health Perspect. 121, 859–864. 10.1289/ehp.1205940. [PubMed: 23665743]

Chun HK, Leung C, Wen SW, McDonald J, Shin HH, 2020. Maternal exposure to air pollution and risk of autism in children: A systematic review and meta-analysis. Environ. Pollut. 256, 113307 10.1016/j.envpol.2019.113307.

Coleman KJ, Lutsky MA, Yau V, Qian Y, Pomichowski ME, Crawford PM, Lynch FL, Madden JM, Owen-Smith A, Pearson JA, Pearson KA, Rusinak D, Quinn VP, Croen LA, 2015. Validation of Autism Spectrum Disorder Diagnoses in Large Healthcare Systems with Electronic Medical Records. J. Autism Dev. Disord. 45, 1989–1996. 10.1007/s10803-015-2358-0. [PubMed: 25641003]

Costa LG, Cole TB, Coburn J, Chang Y-C, Dao K, Roqué PJ, 2017. Neurotoxicity of traffic-related air pollution. Neurotoxicology 59, 133–139. 10.1016/j.neuro.2015.11.008. [PubMed: 26610921]

de Hoogh K, Wang M, Adam M, Badaloni C, Beelen R, Birk M, Cesaroni G, Cirach M, Declercq C, Dedel˙ e A, Dons E, de Nazelle A, Eeftens M, Eriksen K, Eriksson C, Fischer P, Gražulevičiene R, Gryparis A, Hoffmann B, Jerrett M, Katsouyanni K, Iakovides M, Lanki T, Lindley S, Madsen C, Mölter A, Mosler G, Nádor G, Nieuwenhuijsen M, Pershagen G, Peters A, Phuleria H, Probst-Hensch N, Raaschou-Nielsen O, Quass U, Ranzi A, Stephanou E, Sugiri D, Schwarze P, Tsai M-Y, Yli-Tuomi T, Varró MJ, Vienneau D, Weinmayr G, Brunekreef B, Hoek G, 2013. Development of Land Use Regression Models for Particle Composition in Twenty Study Areas in Europe. Environ. Sci. Technol. 47, 5778–5786. 10.1021/es400156t. [PubMed: 23651082]

Demir T, Karakas D, Yenisoy-Karakas S, 2022. Source identification of exhaust and non-exhaust traffic emissions through the elemental carbon fractions and Positive Matrix Factorization method. Environ. Res. 204, 112399 10.1016/j.envres.2021.112399.

Di Q, Amini H, Shi L, Kloog I, Silvern R, Kelly J, Sabath MB, Choirat C, Koutrakis P, Lyapustin A, Wang Y, Mickley LJ, Schwartz J, 2020. Assessing no2 concentration and model uncertainty with high spatiotemporal resolution across the contiguous united states using ensemble model averaging. Environ. Sci. Technol. 54, 1372–1384. 10.1021/acs.est.9b03358. [PubMed: 31851499]

Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G, 2011. Stability of measured and modelled spatial contrasts in NO(2) over time. Occup. Environ. Med. 68, 765–770. 10.1136/oem.2010.061135. [PubMed: 21285243]

Elsabbagh M, 2020. Linking risk factors and outcomes in autism spectrum disorder: Is there evidence for resilience? BMJ 368. 10.1136/bmj.l6880.

Fang T, Zeng L, Gao D, Verma V, Stefaniak AB, Weber RJ, 2017. Ambient Size Distributions and Lung Deposition of Aerosol Dithiothreitol-Measured Oxidative Potential: Contrast between Soluble and Insoluble Particles. Environ. Sci. Technol. 51, 6802–6811. 10.1021/acs.est.7b01536. [PubMed: 28548846]

Fussell JC, Franklin M, Green DC, Gustafsson M, Harrison RM, Hicks W, Kelly FJ, Kishta F, Miller MR, Mudway IS, Oroumiyeh F, Selley L, Wang M, Zhu Y, 2022. A Review of Road Traffic-Derived Non-Exhaust Particles: Emissions, Physicochemical Characteristics, Health Risks, and Mitigation Measures. Environ. Sci. Technol. 10.1021/acs.est.2c01072.

Gardener H, Spiegelman D, Buka SL, 2011. Perinatal and neonatal risk factors for autism: A comprehensive meta-analysis. Pediatrics 128, 344–355. 10.1542/peds.2010-1036. [PubMed: 21746727]

Gerlofs-Nijland ME, Bokkers BGH, Sachse H, Reijnders JJE, Gustafsson M, Boere AJF, Fokkens PFH, Leseman DLAC, Augsburg K, Cassee FR, 2019. Inhalation toxicity profiles of particulate matter: a comparison between brake wear with other sources of emission. Inhal. Toxicol. 31, 89–98. 10.1080/08958378.2019.1606365. [PubMed: 31066325]

Grahame TJ, Klemm R, Schlesinger RB, 2014. Public health and components of particulate matter: the changing assessment of black carbon. J. Air Waste Manag. Assoc. 64, 620–660. 10.1080/10962247.2014.912692. [PubMed: 25039199]

Gurbani D, Bharti SK, Kumar A, Pandey AK, Ana GREE, Verma A, Khan AH, Patel DK, Mudiam MKR, Jain SK, Roy R, Dhawan A, 2013. Polycyclic aromatic hydrocarbons and their quinones modulate the metabolic profile and induce DNA damage in human alveolar and bronchiolar cells. Int. J. Hyg. Environ. Health 216, 553–565. 10.1016/j.ijheh.2013.04.001. [PubMed: 23735462]

Habre R, Girguis M, Urman R, Fruin S, Lurmann F, Shafer M, Gorski P, Franklin M, McConnell R, Avol E, Gilliland F, 2021. Contribution of tailpipe and non-tailpipe traffic sources to quasi-ultrafine, fine and coarse particulate matter in southern California. J. Air Waste Manag. Assoc. 71, 209–230. 10.1080/10962247.2020.1826366. [PubMed: 32990509]

Hagino H, Oyama M, Sasaki S, 2016. Laboratory testing of airborne brake wear particle emissions using a dynamometer system under urban city driving cycles. Atmos. Environ. 131, 269–278. 10.1016/j.atmosenv.2016.02.014.

Hasheminassab S, Daher N, Ostro BD, Sioutas C, 2014. Long-term source apportionment of ambient fine particulate matter (PM2.5) in the Los Angeles Basin: A focus on emissions reduction from vehicular sources. Environ. Pollut. 193, 54–64. 10.1016/j.envpol.2014.06.012. [PubMed: 25005887]

HEI, 2010. Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects.

HEI, 2022. Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution.

Hopkins LE, Laing EA, Peake JL, Uyeminami D, Mack SM, Li X, Smiley- Jewell S, Pinkerton KE, 2018. Repeated Iron-Soot Exposure and Nose-to-brain Transport of Inhaled Ultrafine Particles. Toxicol. Pathol. 46, 75–84. 10.1177/0192623317729222. [PubMed: 28914166]

Hu J, Zhang H, Chen S-H, Wiedinmyer C, Vandenberghe F, Ying Q, Kleeman MJ, 2014a. Predicting Primary PM2.5 and PM0.1 Trace Composition for Epidemiological Studies in California. Environ. Sci. Technol. 48, 4971–4979. 10.1021/es404809j. [PubMed: 24694302]

Hu J, Zhang H, Chen S, Ying Q, Wiedinmyer C, Vandenberghe F, Kleeman MJ, 2014b. Identifying PM2.5 and PM0.1 Sources for Epidemiological Studies in California. Environ. Sci. Technol. 48, 4980–4990. 10.1021/es404810z. [PubMed: 24552458]

Jeng HA, Pan C-H, Diawara N, Chang-Chien G-P, Lin W-Y, Huang C-T, Ho C-K, Wu M-T, 2011. Polycyclic aromatic hydrocarbon-induced oxidative stress and lipid peroxidation in relation to immunological alteration. Occup. Environ. Med. 68, 653–658. 10.1136/oem.2010.055020. [PubMed: 21126960]

Jeong CH, Wang JM, Hilker N, Debosz J, Sofowote U, Su Y, Noble M, Healy RM, Munoz T, Dabek-Zlotorzynska E, Celo V, White L, Audette C, Herod D, Evans GJ, 2019. Temporal and spatial variability of traffic-related PM2.5 sources: Comparison of exhaust and non-exhaust emissions. Atmos. Environ. 198, 55–69. 10.1016/j.atmosenv.2018.10.038.

Jeong CH, Traub A, Huang A, Hilker N, Wang JM, Herod D, Dabek-Zlotorzynska E, Celo V, Evans GJ, 2020. Long-term analysis of PM2.5 from 2004 to 2017 in Toronto: Composition, sources, and oxidative potential. Environ. Pollut. 263, 114652 10.1016/j.envpol.2020.114652.

Jo H, Eckel SP, Wang X, Chen JC, Cockburn M, Martinez MP, Chow T, Molshatzki N, Lurmann FW, Funk WE, Xiang AH, McConnell R, 2019. Sex-specific associations of autism spectrum disorder with residential air pollution exposure in a large Southern California pregnancy cohort. Environ. Pollut. 254, 113010 10.1016/j.envpol.2019.113010.

Kai Z, V. LT, Amanda G, A. SA, Martha D,L, B.G. D, K.J. D, A.S., 2014. Characterizing Spatial Patterns of Airborne Coarse Particulate (PM10–2.5) Mass and Chemical Components in Three Cities: The Multi-Ethnic Study of Atherosclerosis. Environ. Health Perspect. 122, 823–830. 10.1289/ehp.1307287. [PubMed: 24642481]

Karagulian F, Belis CA, Dora CFC, Prüss-Ustün AM, Bonjour S, Adair-Rohani H, Amann M, 2015. Contributions to cities' ambient particulate matter (PM): A systematic review of local source contributions at global level. Atmos. Environ. 120, 475–483. 10.1016/j.atmosenv.2015.08.087.

Karimi P, Kamali E, Mousavi SM, Karahmadi M, 2017. Environmental factors influencing the risk of autism. J. Res. Med. Sci. Off. J. Isfahan Univ Med. Sci. 22, 27. 10.4103/1735-1995.200272.

Koebnick C, Langer-Gould AM, Gould MK, Chao CR, Iyer RL, Smith N, Chen W, Jacobsen SJ, 2012. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. Perm. J. 16, 37–41. 10.7812/tpp/12-031.

Leni Z, Künzi L, Geiser M, 2020. Air pollution causing oxidative stress. Curr. Opin. Toxicol. 20–21, 1–8. 10.1016/j.cotox.2020.02.006.

Li Q, Shang J, Zhu T, 2013. Physicochemical characteristics and toxic effects of ozone-oxidized black carbon particles. Atmos. Environ. 81, 68–75. 10.1016/j.atmosenv.2013.08.043.

Li J, Wang Y, Steenland K, Liu P, van Donkelaar A, Martin RV, Chang HH, Caudle WM, Schwartz J, Koutrakis P, Shi L, 2022. Long-term effects of PM2.5 components on incident dementia in the northeastern United States. Innov. 3, 100208 10.1016/j.xinn.2022.100208.

Lin L-Z, Zhan X-L, Jin C-Y, Liang J-H, Jing J, Dong G-H, 2022. The epidemiological evidence linking exposure to ambient particulate matter with neurodevelopmental disorders: A systematic review and meta-analysis. Environ. Res. 209, 112876 10.1016/j.envres.2022.112876.

Lubczyńska MJ, Sunyer J, Tiemeier H, Porta D, Kasper-Sonnenberg M, Jaddoe V´WV, Basagaña X, Dalmau-Bueno A, Forastiere F, Wittsiepe J, Hoffmann B, Nieuwenhuijsen M, Hoek G, de Hoogh K, Brunekreef B, Guxens M, 2017. Exposure to elemental composition of outdoor PM(2.5) at birth and cognitive and psychomotor function in childhood in four European birth cohorts. Environ. Int. 109, 170–180. 10.1016/j.envint.2017.09.015. [PubMed: 28988795]

McWhinney RD, Badali K, Liggio J, Li S-M, Abbatt JPD, 2013. Filterable Redox Cycling Activity: A Comparison between Diesel Exhaust Particles and Secondary Organic Aerosol Constituents. Environ. Sci. Technol. 47, 3362–3369. 10.1021/es304676x. [PubMed: 23470039]

Morris-Schaffer K, Merrill A, Jew K, Wong C, Conrad K, Harvey K, Marvin E, Sobolewski M, Oberdörster G, Elder A, Cory-Slechta DA, 2019a. Effects of neonatal inhalation exposure to

ultrafine carbon particles on pathology and behavioral outcomes in C57BL/6J mice. Part. Fibre Toxicol. 16, 10. 10.1186/s12989-019-0293-5. [PubMed: 30777081]

Morris-Schaffer K, Merrill AK, Wong C, Jew K, Sobolewski M, Cory-Slechta DA, 2019b. Limited developmental neurotoxicity from neonatal inhalation exposure to diesel exhaust particles in C57BL/6 mice. Part. Fibre Toxicol. 16, 1. 10.1186/s12989-018-0287-8. [PubMed: 30612575]

Muoth C, Aengenheister L, Kucki M, Wick P, Buerki-Thurnherr T, 2016. Nanoparticle transport across the placental barrier: pushing the field forward! Nanomedicine 11, 941–957. 10.2217/nnm-2015-0012. [PubMed: 26979802]

Oroumiyeh F, Jerrett M, Del Rosario I, Lipsitt J, Liu J, Paulson SE, Ritz B, Schauer JJ, Shafer MM, Shen J, Weichenthal S, Banerjee S, Zhu Y, 2022. Elemental composition of fine and coarse particles across the greater Los Angeles area: Spatial variation and contributing sources. Environ. Pollut. 292, 118356 10.1016/j.envpol.2021.118356.

Oroumiyeh F, 2021. Characterization of particulate matter from non-exhaust traffic emissions.

Pagalan L, Bickford C, Weikum W, Lanphear B, Brauer M, Lanphear N, Hanley GE, Oberlander TF, Winters M, 2019. Association of Prenatal Exposure to Air Pollution with Autism Spectrum Disorder. JAMA Pediatr. 173, 86–92. 10.1001/jamapediatrics.2018.3101. [PubMed: 30452514]

Pakbin P, Ning Z, Sioutas C, Shafer MM, Schauer JJ, 2011. Seasonal and spatial coarse particle elemental concentrations in the los angeles area. Aerosol Sci. Technol. 45, 949–963. 10.1080/02786826.2011.571309.

Piscitello A, Bianco C, Casasso A, Sethi R, 2021. Non-exhaust traffic emissions: Sources, characterization, and mitigation measures. Sci. Total Environ. 766, 144440 10.1016/j.scitotenv.2020.144440.

Platt SM, El Haddad I, Pieber SM, Zardini AA, Suarez-Bertoa R, Clairotte M, Daellenbach KR, Huang R-J, Slowik JG, Hellebust S, Temime-Roussel B, Marchand N, de Gouw J, Jimenez JL, Hayes PL, Robinson AL, Baltensperger U, Astorga C, Prévôt ASH, 2017. Gasoline cars produce more carbonaceous particulate matter than modern filter-equipped diesel cars. Sci. Rep. 7, 4926. 10.1038/s41598-017-03714-9. [PubMed: 28706240]

Pujol J, Fenoll R, Macià D, Martínez-Vilavella G, Alvarez-Pedrerol M, Rivas I, Forns J, Deus J, Blanco-Hinojo L, Querol X, Sunyer J, 2016. Airborne copper exposure in school environments associated with poorer motor performance and altered basal ganglia. Brain Behav. 6, e00467–e. 10.1002/brb3.467.

Rahman MM, Thurston G, 2022. A hybrid satellite and land use regression model of source-specific PM2.5 and PM2.5 constituents. Environ. Int. 163, 107233 10.1016/j.envint.2022.107233.

Rahman MM, Carter SA, Lin JC, Chow T, Yu X, Martinez MP, Chen Z, Chen J-C, Rud D, Lewinger JP, van Donkelaar A, Martin RV, Eckel SP, Schwartz J, Lurmann F, Kleeman MJ, McConnell R, Xiang AH, 2022a. Associations of Autism Spectrum Disorder with PM2.5 Components: A Comparative Study Using Two Different Exposure Models. Environ. Sci. Technol. 10.1021/acs.est.2c05197.

Rahman MM, Shu YH, Chow T, Lurmann FW, Yu X, Martinez MP, Carter SA, Eckel SP, Chen JC, Chen Z, Levitt P, Schwartz J, McConnell R, Xiang AH, 2022b. Prenatal Exposure to Air Pollution and Autism Spectrum Disorder: Sensitive Windows of Exposure and Sex Differences. Environ. Health Perspect. 130, 17008. 10.1289/EHP9509. [PubMed: 35040691]

Raz R, Levine H, Pinto O, Broday DM, Yuval, Weisskopf MG, 2018. Traffic-Related Air Pollution and Autism Spectrum Disorder: A Population-Based Nested Case-Control Study in Israel. Am. J. Epidemiol. 187, 717–725. 10.1093/aje/kwx294. [PubMed: 29020136]

Ritz B, Liew Z, Yan Q, Cuia X, Virk J, Ketzel M, Raaschou-Nielsen O, 2018. Air pollution and autism in Denmark. Environ. Epidemiol. 2, e028. [PubMed: 31008439]

Schaumann F, Borm PJA, Herbrich A, Knoch J, Pitz M, Schins RPF, Luettig B, Hohlfeld JM, Heinrich J, Krug N, 2004. Metal-rich ambient particles (particulate matter 2.5) cause airway inflammation in healthy subjects. Am. J. Respir. Crit. Care Med. 170, 898–903. 10.1164/rccm.200403-423OC. [PubMed: 15229099]

Soleimanian E, Mousavi A, Taghvaee S, Sowlat MH, Hasheminassab S, Polidori A, Sioutas C, 2019. Spatial trends and sources of PM2.5 organic carbon volatility fractions (OCx) across the Los Angeles Basin. Atmos. Environ. 209, 201–211. 10.1016/j.atmosenv.2019.04.027.

Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ, 2008. Association of black carbon with cognition among children in a prospective birth cohort study. Am. J. Epidemiol. 167, 280–286. 10.1093/aje/kwm308. [PubMed: 18006900]

Suzuki T, Oshio S, Iwata M, Saburi H, Odagiri T, Udagawa T, Sugawara I, Umezawa M, Takeda K, 2010. In utero exposure to a low concentration of diesel exhaust affects spontaneous locomotor activity and monoaminergic system in male mice. Part. Fibre Toxicol. 7, 7. 10.1186/1743-8977-7-7. [PubMed: 20331848]

Thorpe A, Harrison RM, 2008. Sources and properties of non-exhaust particulate matter from road traffic: A review. Sci. Total Environ. 400, 270–282. 10.1016/j.scitotenv.2008.06.007. [PubMed: 18635248]

Thurston GD, Ito K, Lall R, 2011. A source apportionment of U.S. fine particulate matter air pollution. Atmos. Environ. 45, 3924–3936. 10.1016/j.atmosenv.2011.04.070.

Timmers VRJH, Achten PAJ, 2016. Non-exhaust PM emissions from electric vehicles. Atmos. Environ. 134, 10–17. 10.1016/j.atmosenv.2016.03.017.

Van Donkelaar A, Martin RV, Li C, Burnett RT, 2019. Regional Estimates of Chemical Composition of Fine Particulate Matter Using a Combined Geoscience-Statistical Method with Information from Satellites, Models, and Monitors. Environ. Sci. Technol. 53, 2595–2611. 10.1021/acs.est.8b06392. [PubMed: 30698001]

Verma V, Fang T, Guo H, King L, Bates JT, Peltier RE, Edgerton E, Russell AG, Weber RJ, 2014. Reactive oxygen species associated with water-soluble PM2.5 in the southeastern United States: spatiotemporal trends and source apportionment. Atmos. Chem. Phys. 14, 12915–12930. 10.5194/acp-14-12915-2014.

Verma V, Fang T, Xu L, Peltier RE, Russell AG, Ng NL, Weber RJ, 2015. Organic Aerosols Associated with the Generation of Reactive Oxygen Species (ROS) by Water-Soluble PM2.5. Environ. Sci. Technol. 49, 4646–4656. 10.1021/es505577w. [PubMed: 25748105]

Viana M, Kuhlbusch TAJ, Querol X, Alastuey A, Harrison RM, Hopke PK, Winiwarter W, Vallius M, Szidat S, Prévôt ASH, Hueglin C, Bloemen H, Wåhlin P, Vecchi R, Miranda AI, Kasper-giebl A, Maenhaut W, Hitzenberger R, 2008. Source apportionment of particulate matter in Europe: A review of methods and results 39, 827–849. 10.1016/j.jaerosci.2008.05.007.

Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R, 2011. Residential proximity to freeways and autism in the CHARGE study. Environ. Health Perspect. 119, 873–877. 10.1289/ehp.1002835. [PubMed: 21156395]

Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R, 2013. Traffic-related air pollution, particulate matter, and autism. JAMA psychiatry 70, 71–77. 10.1001/jamapsychiatry.2013.266. [PubMed: 23404082]

Wang I-J, Karmaus WJJ, Yang C-C, 2017. Polycyclic aromatic hydrocarbons exposure, oxidative stress, and asthma in children. Int. Arch. Occup. Environ. Health 90, 297–303. 10.1007/s00420-017-1198-y. [PubMed: 28175985]

Wick P, Malek A, Manser P, Meili D, Maeder-Althaus X, Diener L, Diener P-A, Zisch A, Krug HF, von Mandach U, 2010. Barrier capacity of human placenta for nanosized materials. Environ. Health Perspect. 118, 432–436. 10.1289/ehp.0901200. [PubMed: 20064770]

Xiang AH, Wang X, Martinez MP, Walthall JC, Curry ES, Page K, Buchanan TA, Coleman KJ, Getahun D, 2015. Association of maternal diabetes with autism in offspring. JAMA - J. Am. Med. Assoc. 313, 1425–1434. 10.1001/jama.2015.2707.

Xiang AH, Wang X, Martinez MP, Page K, Buchanan TA, Feldman RK, 2018. Maternal Type 1 Diabetes and Risk of Autism in Offspring. JAMA 320, 89–91. 10.1001/jama.2018.7614. [PubMed: 29936530]

Xu X, Deng F, Guo X, Lv P, Zhong M, Liu C, Wang A, Tzan K, Jiang SY, Lippmann M, Rajagopalan S, Qu Q, Chen LC, Sun Q, 2012. Association of systemic inflammation with marked changes in particulate air pollution in Beijing in 2008. Toxicol. Lett. 212, 147–156. 10.1016/j.toxlet.2012.05.014. [PubMed: 22617750]

Xu G, Strathearn L, Liu B, O'Brien M, Kopelman TG, Zhu J, Snetselaar LG, Bao W, 2019. Prevalence and Treatment Patterns of Autism Spectrum Disorder in the United States, 2016. JAMA Pediatr. 173, 153–159. 10.1001/jamapediatrics.2018.4208. [PubMed: 30508021]

Yokota S, Mizuo K, Moriya N, Oshio S, Sugawara I, Takeda K, 2009. Effect of prenatal exposure to diesel exhaust on dopaminergic system in mice. Neurosci. Lett. 449, 38–41. 10.1016/j.neulet.2008.09.085. [PubMed: 18938223]

Yu X, Venecek M, Kumar A, Hu J, Tanrikulu S, Soon ST, Tran C, Fairley D, Kleeman MJ, 2019. Regional sources of airborne ultrafine particle number and mass concentrations in California. Atmos. Chem. Phys. 19, 14677–14702. 10.5194/acp-19-14677-2019.

Zhang X, Lv CC, Tian J, Miao RJ, Xi W, Hertz-Picciotto I, Qi L, 2010. Prenatal and perinatal risk factors for autism in China. J. Autism Dev. Disord. 40, 1311–1321. 10.1007/s10803-010-0992-0. [PubMed: 20358271]

Zhang J, Peng J, Song C, Ma C, Men Z, Wu J, Wu L, Wang T, Zhang X, Tao S, Gao S, Hopke PK, Mao H, 2020. Vehicular non-exhaust particulate emissions in Chinese megacities: Source profiles, real-world emission factors, and inventories. Environ. Pollut. 266, 115268 10.1016/j.envpol.2020.115268.

Zhang Z, Weichenthal S, Kwong JC, Burnett RT, Hatzopoulou M, Jerrett M, van Donkelaar A, Bai L, Martin RV, Copes R, Lu H, Lakey P, Shiraiwa M, Chen H, 2021a. Long-term exposure to iron and copper in fine particulate air pollution and their combined impact on reactive oxygen species concentration in lung fluid: a population-based cohort study of cardiovascular disease incidence and mortality in Toronto. Canada. Int. J. Epidemiol. 50, 589–601. 10.1093/ije/dyaa230. [PubMed: 33367589]

Zhang Z, Weichenthal S, Kwong JC, Burnett RT, Hatzopoulou M, Jerrett M, van Donkelaar A, Bai L, Martin RV, Copes R, Lu H, Lakey P, Shiraiwa M, Chen H, 2021b. A Population-Based Cohort Study of Respiratory Disease and Long-Term Exposure to Iron and Copper in Fine Particulate Air Pollution and Their Combined Impact on Reactive Oxygen Species Generation in Human Lungs. Environ. Sci. Technol. 55, 3807–3818. 10.1021/acs.est.0c05931. [PubMed: 33666410]

Table 1

Characteristics of children, with and without autism spectrum disorder (ASD).

	Children, No. (%) or median (interquartile range)		
Characteristics	**Overall (n = 318750)**	**With ASD (n = 4559)**	**Without ASD (n = 314191)**
Sex			
Male (%)	163 181 (51.2)	3703 (81.2)	159 428 (50.7)
Female (%)	155 569 (49.8)	856 (18.8)	154 763 (49.3)
Follow-up year after birth, median [IQR *], years	4.0 [4.0, 4.0.]	3.0 [2.3, 3.7]	4.0 [4.0, 4.0]
Maternal age at delivery, median [IQR *], years	30.4 [26.3, 34.3]	31.3 [27.5, 35.2]	30.4 [26.2, 34.3]
Parity; N (%) 0	111 981 (35.1)	1844 (40.4)	110 137 (35.1)
1	104 561 (32.8)	1495 (32.8)	103 066 (32.8)
>2	84 176 (26.4)	903 (19.8)	83 273 (26.5)
Unknown	18 032 (5.7)	317 (7.0)	17 715 (5.6)
Maternal Education; N (%)			
High school or lower	112 096 (35.2)	1335 (29.3)	110 761 (35.3)
Some college	94 524 (29.7)	1477 (32.4)	93 047 (29.6)
College graduate or higher	109 087 (34.2)	1713 (37.6)	107 374 (34.2)
Unknown	3043 (1.0)	43 (0.7)	3009 (1.0)
Household annual income[a]; N (%)			
<$30,000	24 027 (7.5)	325 (7.1)	23 710 (7.5)
$30,000-$49,999	100 575 (31.6)	1436 (31.5)	99 139 (31.6)
$50,000-$69,999	98 015 (30.7)	1415 (31.0)	96 593 (30.7)
$70,000-$89,999	55 611 (17.4)	801 (17.5)	54 816 (17.4)
> $90,000	40 512 (12.7)	582 (12.8)	39 933 (12.7)
Race/ethnicity; N (%)			
Non-Hispanic white	81 050 (25.4)	956 (21.0)	80 094 (25.5)
Non-Hispanic black	29 773 (9.3)	477 (9.8)	29 326 (9.3)
Hispanic	161 414 (50.6)	2300 (50.4)	159 114 (50.6)
Asian/Pacific Islander	39 974 (12.5)	744 (16.3)	39 230 (12.5)
Other	6539 (2.1)	112 (2.5)	6427 (2.0)
Any history of maternal comorbidity[b]; N (%)	46 717 (14.6)	839 (18.4)	45 878 (14.6)
Pre-pregnancy diabetes[c]; N (%)	10 248 (3.2)	242 (5.3)	10 006 (3.2)
Pre-pregnancy obesity[d]; N (%)	53 354 (16.7)	1049 (23.0)	52 305 (16.6)
Year of birth, N (%)			
2001–2007	152 750 (47.9)	1802 (39.5)	164 198 (52.2)
2008–2014	166 000 (52.1)	2757 (60.5)	149 993 (47.2)

*Abbreviations: IQR, interquartile range.

[a]Census tract level median household income.

[b]>=1 diagnosis of heart, lung, kidney, or liver disease; cancer.

[c] Type I and Type II diabetes diagnosed before pregnancy.

[d] Pre-pregnancy BMI>=30.

Table 2

Hazard ratios (HRs) of ASD scaled to interquartile increase in EC, OC, Cu, Fe, and Mn during pregnancy, estimated from single-pollutant and two-pollutant models for 2001–2014, 2001–2009, and 2010–2014.*.

		Year, 2001–2014	Year, 2001–2009	Year, 2010–2014
Pollutant of interest	**Co-adjusted pollutant**	**HR (95 % CI)**	**HR (95 % CI)**	**HR (95 % CI)**
Tailpipe tracers				
EC	None (single-pollutant model)	1.11 (1.06, 1.16)	1.25 (1.18, 1.33)	0.97 (0.91, 1.04)
	$PM_{2.5}$	1.16 (1.09, 1.23)	1.29 (1.18, 1.42)	1.03 (0.94, 1.12)
	Cu	1.08 (1.02, 1.14)	0.91 (0.80, 1.05)	0.93 (0.84, 1.03)
	Fe	1.01 (0.95, 1.09)	0.95 (0.84, 1.08)	0.89 (0.80, 1.00)
	Mn	0.99 (0.92, 1.06)	0.94 (0.83, 1.08)	0.88 (0.80, 0.97)
OC	None (single-pollutant model)	1.09 (1.04, 1.15)	1.18 (1.11, 1.26)	0.99 (0.93, 1.06)
	$PM_{2.5}$	1.14 (1.05, 1.23)	1.13 (1.00, 1.27)	1.09 (0.99, 1.20)
	Cu	1.03 (0.96, 1.11)	0.85 (0.76, 0.95)	0.94 (0.81, 1.10)
	Fe	0.94 (0.87, 1.02)	0.86 (0.78, 0.96)	0.87 (0.75, 1.01)
	Mn	0.93 (0.87, 1.00)	0.86 (0.77, 0.97)	0.87 (0.78, 0.96)
Non-tailpipe tracers				
Cu	None (single-pollutant model)	1.08 (1.00, 1.15)	1.46 (1.36, 1.58)	1.00 (0.94, 1.07)
	$PM_{2.5}$	1.08 (1.03, 1.13)	1.62 (1.45, 1.80)	1.08 (0.99, 1.18)
	NO_2	1.09 (1.04, 1.15)	1.51 (1.38, 1.64)	1.06 (0.98, 1.14)
	EC	1.07 (1.01, 1.13)	1.58 (1.37, 1.82)	1.06 (0.96, 1.17)
	OC	1.06 (1.00, 1.13)	1.67 (1.49, 1.88)	1.05 (0.92, 1.21)
Fe	None (single-pollutant model)	1.14 (1.09, 1.20)	1.43 (1.33, 1.54)	1.02 (0.96, 1.08)
	$PM_{2.5}$	1.19 (1.12, 1.26)	1.58 (1.42, 1.76)	1.15 (1.05, 1.25)
	NO_2	1.17 (1.11, 1.23)	1.45 (1.34, 1.57)	1.07 (1.00, 1.15)
	EC	1.13 (1.06, 1.21)	1.49 (1.32, 1.69)	1.11 (1.00, 1.23)
	OC	1.19 (1.11, 1.29)	1.61 (1.44, 1.80)	1.13 (1.00, 1.29)
Mn	None (single-pollutant model)	1.17 (1.12, 1.22)	1.43 (1.32, 1.54)	1.06 (1.00, 1.12)
	$PM_{2.5}$	1.22 (1.15, 1.29)	1.59 (1.42, 1.78)	1.20 (1.12, 1.29)
	NO_2	1.19 (1.13, 1.25)	1.46 (1.34, 1.59)	1.11 (1.05, 1.18)
	EC	1.18 (1.11, 1.25)	1.50 (1.31, 1.71)	1.14 (1.06, 1.23)
	OC	1.22 (1.15, 1.30)	1.61 (1.43, 1.81)	1.15 (1.07, 1.25)

*All the models were adjusted for child sex, maternal race/ethnicity, maternal age at delivery, parity, education, maternal comorbidities, household income, birth year (non-linear), season (wet/dry), and pre-pregnancy diabetes. In 2001–2014, the IQRs (ng/m^3) for EC, OC, Cu, Fe, and Mn during pregnancy were 383.42, 1360.09, 8.12, 162.31, and 2.78, respectively. In 2001–2009, the IQRs (ng/m^3) for EC, OC, Cu, Fe, and Mn during pregnancy were 411.18, 1353.11, 5.97, 139.45, and 2.58, respectively. In 2010–2014, the IQRs (ng/m^3) for EC, OC, Cu, Fe, and Mn during pregnancy were 329.10, 1249.74, 11.06, 169.56, and 2.75, respectively.