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The Associations of Autism Spectrum Disorder with $PM_{2.5}$ Components: A Comparative Study Using Two Different Exposure Models

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AUTHORS CONTRIBUTIONS

The contributions of the authors were as follows. Study conceptualization and design: M.R., A.H.X., and R.M; Drafting of the manuscript: M.R. with the help of R.M., A.H.X. and S.C.; statistical analysis: M.R., J.C.L., and S.P.E.; critical revision of the manuscript for important intellectual content: all authors; obtained funding: A.H.X. and R.M.; Administrative, technical, or material support: M.P.M., T.C., A.H.X., F.W.L., M.J.K. M.J.K., A.V, R.V.M. generated spatially and temporally resolved exposure estimates of the $PM_{2.5}$ constituents for 15 years. All authors approved the final draft of the manuscript.

CONFLICT OF INTERESTS

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

Supporting Information

The supporting information is available online.

Correlation between $PM_{2.5}$, EC/BC, OM, NO_3^-, and SO_4^{2-} in each trimester, based on a SO-CTM and a hybrid model (Tables S1-S3); Associations of ASD with EC/BC, OM, NO_3^-, and SO_4^{2-} from a SO-CTM and a hybrid model (Tables S4-S5); Associations of ASD with $PM_{2.5}$ from a SO-CTM and a hybrid model during entire pregnancy and each trimester (Table S7); Derivation of sample (Figure S1); The relative contribution of each component to the total $PM_{2.5}$ mass during entire pregnancy (Figure S2); The distribution of $PM_{2.5}$, EC/BC, OM, NO_3^-, and SO_4^{2-} in each trimester, based on a SO-CTM and a hybrid model (Figure S3).

ETHICAL APPROVAL

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

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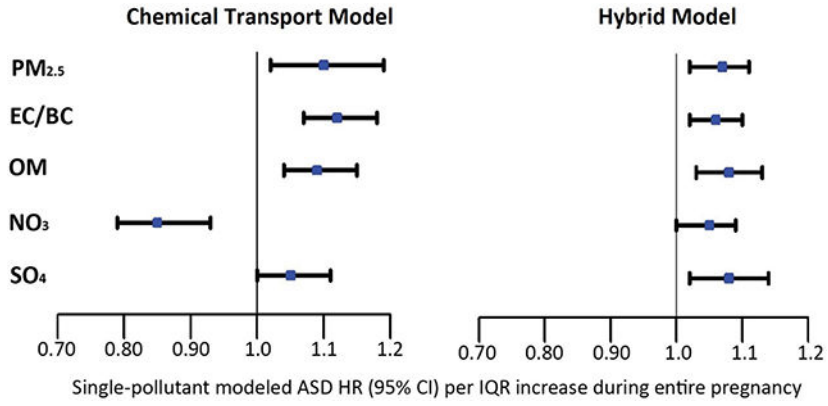
Abstract

This retrospective cohort study examined associations of autism spectrum disorder (ASD) with prenatal exposure to major fine particulate matter ($PM_{2.5}$) components estimated using two independent exposure models. The cohort included 318,750 mother-child pairs with singleton deliveries in Kaiser Permanente Southern California hospitals from 2001-2014 and followed until age five. ASD cases during follow-up (N=4559) were identified by ICD codes. Prenatal exposures to $PM_{2.5}$, elemental (EC) and black carbon (BC), organic matter (OM), nitrate (NO_3^-), and sulfate (SO_4^{2-}) were constructed using (i) a source-oriented chemical transport model and (ii) a hybrid model. Exposures were assigned to each maternal address during the entire pregnancy, first, second, and third trimester. In single-pollutant models, ASD was associated with pregnancy-average $PM_{2.5}$, EC/BC, OM, and SO_4^{2-} exposures from both exposure models, after adjustment for covariates. The direction of effect estimates was consistent for EC/BC and OM, and least consistent for NO_3^-. EC/BC, OM and SO_4^{2-} were generally robust to adjustment for other components and for $PM_{2.5}$. EC/BC and OM effect estimates were generally larger and more consistent in the first and second trimester and SO_4^{2-} in the third trimester. Future $PM_{2.5}$ composition health effects studies might consider using multiple exposure models and a weight of evidence approach when interpreting effect estimates.

Graphical Abstract



Keywords

$PM_{2.5}$; $PM_{2.5}$ chemical components; autism spectrum disorders; prenatal exposures; exposure models

INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by social communication impairments, sensory disturbances and repetitive behaviors with restricted interests; approximately one-third have intellectual disability [1-4]. ASD imposes substantial lifetime social and economic costs on affected families and communities [5]. In the

United States, lifetime cost of supporting an individual with ASD with intellectual disability is an estimated $2.4 million [6]. Early etiologic studies on ASD focused on the role of genetic risk factors because there is high heritability. However, only 20% of diagnoses are due to spontaneous single gene or chromosomal mutations [7,8]; the remaining causes are likely multifactorial.

A growing number of epidemiological studies have reported associations between prenatal exposure to particulate matter (PM) with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) and increased risk for ASD [9-11]. In all prior studies on this relationship, $PM_{2.5}$ has been considered as a homogenous pollutant, but in reality $PM_{2.5}$ is comprised of a heterogeneous mixture of solid and liquid particles with varying chemical composition that reflects sources of particles and may determine toxicity [12-16]. Elemental carbon/black carbon (EC/BC), organic matter (OM), nitrate (NO_3^-), and sulfate (SO_4^{2-}) are the major components [17]. Understanding the effects of different chemical components of $PM_{2.5}$ on ASD risk could lead 1) to better understanding of mechanisms underlying PM effects on the brain and 2) to better prevention strategies, improved health impact assessments, and potentially to source-specific ambient air quality standards.

In recent years, exposure assessment methods have been developed to characterize the $PM_{2.5}$ composition at fine spatial and temporal resolution. Several models for estimating $PM_{2.5}$ composition have been developed and applied to studying mortality but results have not been consistent [14,18-22]. This inconsistency might be explained in part by methodological differences in exposure assessment methods [23-27]. In the current study, we used exposure component estimates from two independent exposure models: (i) a source-oriented chemical transport model (CTM) and (ii) a hybrid model that uses a chemical transport model, satellite observations, and ground-based measurements. The aim of this study was to assess the association of ASD with prenatal exposure to $PM_{2.5}$ and its major components, including EC/BC, OM, NO_3^-, and SO_4^{2-}, at residences in a large population-based pregnancy cohort. In addition, we assessed the consistency of associations with components estimated with each of the two modeling approaches.

MATERIALS AND METHODS

Study Population

This population-based retrospective pregnancy 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 with over 4.5 million members across Southern California. KPSC membership is diverse and broadly representative of the region's sociodemographic characteristics [28]. 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 [29]. Addresses based only on street name, 5-digit postal code, locality, or administrative unit were considered too uncertain to be geolocated into the correct grid used for exposure assignments.

Singleton births with KPSC membership at age 1 (n=370,723) were eligible to be included in this study. Children were routinely screened for potential ASD risk starting at age 18 months during regular well-child visits at KPSC. A total of 51,973 births was excluded due to 1) missing gender, maternal race/ethnicity and age at delivery, implausible age of delivery or birth weight (n=666); 20) maternal age at delivery (n=159); 3) incomplete maternal residential address history in pregnancy or 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. Derivation of study sample size is shown in Figure S1 in the supplement.

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

Outcome ASD

The outcome was ASD diagnosis before age 5. Children were followed from birth through the EMR until clinical diagnosis of ASD, loss to follow-up, or age 5, whichever came first. ASD diagnosis was identified by International Classification of Diseases (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) or ICD-10 codes F84.0, F84.3, F84.5, F84.8, F84.9 for EMR records after October 1, 2015. Codes from at least two separate visits were required to establish an ASD diagnosis, as described previously [30-33].

Exposures to $PM_{2.5}$ and Components

Air pollution exposure estimation was conducted using two methods: i) Source-Oriented Chemical Transport Model (SO-CTM) developed by University of California Davis/ California Institute of Technology (UCD/CIT); and ii) hybrid model that integrates CTM outputs, satellite observations, and ground-based measurements developed by Atmospheric Composition Analysis Group now at Washington University in St. Louis (WUACAG). We estimated ASD associations with $PM_{2.5}$ and four major $PM_{2.5}$ chemical components (EC and conceptually equivalent BC; OM, the mass of oxygen, hydrogen, and nitrogen together with organic carbon [34]; NO_3^-; and SO_4^{2-} that are available from both exposure models.

Monthly estimates of $PM_{2.5}$, BC, OM, NO_3^-, and SO_4^{2-} with a 1 km spatial resolution were obtained from the WUACAG hybrid model (version V4.NA.02) [35]. This modelling framework integrates satellite observations of aerosol optical depth from multiple satellite products (MISR, MODIS Dark Target, MODIS and SeaWiFS, Deep Blue, and MODIS MAIAC) and $PM_{2.5}$ simulated by GEOS-Chem (http://geos-chem.org) chemical transport model with 12.5 km resolution to estimate ground-level mass concentrations of $PM_{2.5}$. Ground level observations of $PM_{2.5}$ were then incorporated via geographically weighted regression to produce final $PM_{2.5}$ surfaces for North America between 2000 and 2016 at 1 km × 1 km resolution. Later, GEOS-Chem chemical transport model simulation was used to partition this $PM_{2.5}$ into seven $PM_{2.5}$ chemical components (i.e., BC, NO_3^-, OM, ammonium [NH_4^+], SO_4^{2-}, dust, and sea-salt). These $PM_{2.5}$ components were then statistically fused into corresponding ground-level measurements, to produce a spatially complete representation over North America for the study period. The model performances

of monthly estimates over the United States assessed by 10-fold cross validations were highest for SO_4^{2-} (R^2 = 0.90, bias= 0.03 μg/m^3, root mean standard deviation =0.3 μg/m^3), followed by NO_3^- (R^2 = 0.78, bias= 0.01 μg/m^3, RMSD= 0.3 μg/m^3), BC (R^2 = 0.68, bias= 0.01 μg/m^3, RMSD= 0.1 μg/m^3), OM (R^2 = 0.55, bias= −0.01 μg/m^3, RMSD= 0.6 μg/m^3).

BC was available as EC from the SO-CTM model. Monthly estimates of $PM_{2.5}$, EC, OM, NO_3^-, and SO_4^{2-} with a 4 km spatial resolution were obtained from SO-CTM model for the time between 2000 and 2014. This model was developed for the California region only. Calculated meteorological fields and emissions estimates for different sources were used to predict airborne PM concentrations. Using the extensive emissions inventory in California, the model calculations track the mass and number concentrations of PM components 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 [36,37]. Good correlations between 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. Monthly SO-CTM predicted $PM_{2.5}$ EC, OM, NO_3^-, and SO_4^{2-} was correlated with measurements with r = 0.96 (bias= −0.05 μg/m^3, root mean squared error, RMSE= 0.17 μg/m^3), 0.97 (bias= 0.11 μg/m^3, RMSE= 0.46 μg/m^3), 0.75 (bias= −1.24 μg/m^3, RMSE= 2.16 μg/m^3), and 0.67 (bias= −0.81 μg/m^3, RMSE= 1.75 μg/m^3), respectively, in the Los Angeles Basin.

Exposures to $PM_{2.5}$ and these selected components were assigned to maternal address during the entire pregnancy, first trimester, second trimester, and third trimester. Monthly exposure estimates that did not correspond exactly to a trimester were assigned proportionally based on overlap of the trimesters. Exposures were also time-weighted to account for changes of maternal addresses during pregnancy.

Covariates

Covariates were selected a priori based on past literature on air pollution exposures and ASD [3,30,38], including child sex, maternal parity, maternal self-reported education and race/ethnicity, maternal history of comorbidity [>=1 diagnosis of heart, lung, kidney, or liver disease; cancer], maternal age at delivery, median family household income in census tract of residence, birth year, and an indicator variable for season (Dry= April-October; Wet= November-March)]. Birth year was included as a non-linear term with 4 degrees of freedom to adjust for the non-linear relationship between birth year and ASD. Maternal pre-pregnancy obesity (BMI ≥ 30 kg/m^2) and diabetes during pregnancy were also included as covariates, as both were shown to be risk factors for ASD in our study cohort [31].

Statistical Analyses

The associations of ASD with $PM_{2.5}$ and its major components were evaluated using Cox-proportional hazard models (HR) and 95% confidence intervals (CI). We first fitted single pollutant models. The HRs of the associations were scaled to the interquartile range (IQR) increase in concentration of $PM_{2.5}$ and of each component of $PM_{2.5}$ during the entire pregnancy, so that the population HRs for each pollutant were for conceptually similar pollutant increments. Children from families with more than one ASD child were included

in the study sample. Standard errors were estimated using robust sandwich estimators to control for potential correlation for families. Timing of the exposure and associated windows of vulnerability are important issues for air pollution neuro-epidemiology, because they have potential to guide preventive interventions. We previously reported that increased prenatal $PM_{2.5}$ exposure during the first two trimesters (up to 27 gestational weeks) of pregnancy was associated with subsequent risk of ASD in childhood [39]. Susceptible windows of exposure to $PM_{2.5}$ components may be different from those for $PM_{2.5}$. Therefore, we fitted models with trimester specific average exposures of each component. To evaluate the independence of $PM_{2.5}$ and component associations, we adjusted the single component models for the total $PM_{2.5}$. So that estimates were comparable across trimesters and entire pregnancy, the trimester-specific estimates were also scaled to the entire pregnancy interquartile range (IQR) increase in concentration for $PM_{2.5}$ and each component of $PM_{2.5}$. We also subtracted each component's mass separately from $PM_{2.5}$ mass (denoted as 'remainder $PM_{2.5}$') and included the 'remainder $PM_{2.5}$' in the model. Because the results of adjustment for total $PM_{2.5}$ and for remainder $PM_{2.5}$ were very similar, for parsimony we have shown only the adjustment for remainder $PM_{2.5}$, because unlike $PM_{2.5}$, the remainder $PM_{2.5}$ does not include the component. We assessed the consistency of the direction and magnitude of associations between ASD and specific $PM_{2.5}$ components across both exposure modeling strategies. We also examined correlations of components in each exposure model; in exploratory analyses we ran multi-component models. All models were adjusted for the covariates described above. 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.

All statistical analyses were performed in R Statistical Software (v3.5.2; R Core Team 2021).

RESULTS

Participant demographics are shown in Table 1. Among the cohort, 4559 (1.4%) were diagnosed with ASD before age 5. Boys were over 4 times more likely to have ASD (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.

The relative contribution of components to the total $PM_{2.5}$ mass during pregnancy is shown in Figure 2 in the supplement. These contributions varied between the two models. For the SO-CTM model, the four major components (excluding "other") accounted for 60% of $PM_{2.5}$ mass. For the hybrid model, these components accounted for 83.5%. OM accounted for 41.3% of the hybrid model predicted $PM_{2.5}$ but only for 17.8% of the SO-CTM $PM_{2.5}$. BC accounted for 12.2% of hybrid predicted $PM_{2.5}$; EC for 4.6% of SO-CTM $PM_{2.5.}$ In contrast, the contributions of NO_3^- and SO_4^{2-} to the hybrid $PM_{2.5}$ were a little smaller than the proportion contributed to the SO-CTM $PM_{2.5}$.

The estimated mean (14.2) and IQR (5.6) $\mu g/m^3$ of the predicted SO-CTM $PM_{2.5}$ differed from the hybrid model (15.2; 3.7 $\mu g/m^3$). (See Figure 1). The greatest discrepancy between

the models was for carbon, for which the EC mean (0.7 μg/m^3) and IQR (0.4 μg/m^3) were about half as large as for BC (mean 1.9 (0.8) μg/m^3). EC and BC represent similar components; there is no universally agreed conversion, but the two-fold difference probably represents both differences between mass of EC and BC, and differences between modeling approaches. SO-CTM OM mean 2.5 (IQR 1.4) μg/m^3 also differed markedly from hybrid OM, 6.3 (2.0) μg/m^3; SO-CTM NO_3^- mean 3.6 (IQR 2.1) μg/m^3 differed a little from hybrid NO_3^-, 3.1 (1.2) μg/m^3; and SO-CTM SO_4^{2-} mean 1.7 (IQR 0.5) μg/m^3 differed minimally from hybrid SO_4^{2-} (1.5 (0.5) μg/m^3. The exposure distribution during each trimester window for $PM_{2.5}$ and its major components was similar to the pregnancy average distribution (Supplementary Figures 3A-3C).

In each exposure modeling approach, pregnancy-average $PM_{2.5}$ was highly correlated with each of its components, highest with NO_3^- (R=0.87) and lowest with SO_4^{2-} (0.69; Table 2). Between the components, correlations were low to moderate within each exposure model, with the exception of SO-CTM EC and OM (R=0.85). Between exposure models, the correlation for $PM_{2.5}$ was 0.80. Components from the two models were moderately correlated (EC with BC 0.61, OM 0.63, SO_4^{2-} 0.46), with the exception of NO_3^- (0.78). The patterns of correlations for $PM_{2.5}$ and its major components in each trimester were similar to those observed during the entire pregnancy (Supplementary Tables 1-3).

The pregnancy-average ASD HR point estimates scaled per IQR increase corresponding to each component are shown in Table 3. Adverse associations with OM and SO_4^{2-} were observed using either exposure model and effect estimates across models were generally similar after adjustment for the remainder $PM_{2.5}$. The EC HR 1.12 (95% CI 1.07, 1.18) using the SO-CTM model was larger than the equivalent BC (1.06; 95% CI 1.02, 1.10), using the hybrid exposure model, but CI overlapped. EC effect estimates were robust to co-adjustment, BC was attenuated by adjustment for remainder $PM_{2.5}$. NO_3^- was inversely associated with ASD in models adjusted for remainder $PM_{2.5}$ and this was statistically significant for the SO-CTM model.

In exploratory models, associations of ASD with each PM component adjusted for all other components simultaneously generally were similar to associations adjusted for remainder $PM_{2.5}$, with some exceptions (Table 3). To understand the marked attenuation of the OM SO-CTM multicomponent-adjusted exposure estimate, compared with the model adjusted for remainder $PM_{2.5}$, we examined which of the three co-pollutant components was responsible for the attenuation of the OM effect, by running 2-component models with OM. Adjustment for NO_3^- or SO_4^{2-} did not change the OM effect estimate; adjustment for EC reduced the OM HR to 0.99 (95% CI 0.92. 1.07), suggesting that it may be an artifact of the high correlation of EC with OM (0.85 from Table 2).

Associations of ASD with EC/BC and OM across exposure modeling approaches in single pollutant models were similar to the pregnancy-average associations in the first and second trimester and were generally robust to adjustment for remainder $PM_{2.5}$ and other components (Supplement Tables 4-6). As during the entire pregnancy, OM was highly correlated with EC and adjustment of the OM effect estimate for EC and other components resulted in marked attenuation of the HR in the first (to HR 1.02; 95% CI 0.96, 1.08) and

second trimester (to HR 1.00; 95% CI 0.94, 1.07). Associations with SO_4^{2-} were stronger in the third trimester, moreso for the hybrid model (HR 1.10; 95% CI 1.04, 1.16 in single pollutant model robust to co-pollutant adjustment) than for the SO-CTM exposure effect estimate.

In single-pollutant models, increased exposures to $PM_{2.5}$ during the entire pregnancy were associated with increased ASD risk (Supplementary Table 7). In two-pollutant models the $PM_{2.5}$ effect estimates were markedly attenuated by adjustment for OM using either exposure model; there was an inverse association of $PM_{2.5}$ with ASD in models adjusted for EC (HR 0.92; 95% CI 0.83, 1.02) but not for BC (HR 1.05; 95% CI 0.98, 1.12). Effect estimates were similar or larger than in single pollutant models after adjusting for other components. ASD associations with single-pollutant $PM_{2.5}$ were also consistently positive using both exposure modeling approaches in each trimester, and associations were statistically significant except for the third trimester SO-CTM model. As for the pregnancy average exposures, $PM_{2.5}$ effect estimates were attenuated by adjustment for components, especially by EC or OM and in the SO-CTM models.

DISCUSSION

Average exposure to $PM_{2.5}$ component EC/BC, OM and SO_4^{2-} during pregnancy in a large population-based cohort was associated with small increases in ASD risk using both the SO-CTM and hybrid exposure models, although estimates from some health models were attenuated by adjustment for remainder $PM_{2.5}$. Associations of prenatal $PM_{2.5}$ itself with ASD were consistently positive using both exposure modeling approaches in single pollutant models, but were markedly attenuated in models adjusted for EC and OM. Associations using different modeling approaches were generally similar, at least in direction. A notable exception was NO_3^-, which had very different ASD associations depending on the modeling approach. Trimester-specific analysis revealed that EC/BC and OM exposure in the first and second trimester had significant associations with ASD; SO_4^{2-} showed stronger associations with ASD in the third trimester.

Our results suggest that associations of $PM_{2.5}$ with ASD previously observed in this cohort may be explained by components rather than by total $PM_{2.5}$ mass [30,39]. $PM_{2.5}$ was highly correlated across exposure modeling approaches and showed the most consistent positive associations in single pollutant models. However, $PM_{2.5}$ associations were markedly attenuated by adjustment for components, in particular by EC and OM in the SO-CTM model and by BC or OM in the pregnancy average and first and second trimester models. These components were only moderately correlated with $PM_{2.5}$ (from Table 2) and the large data set provides more confidence that $PM_{2.5}$ effects were confounded by these components and that attenuation of $PM_{2.5}$ effect estimates was not due to high correlation.

There were differences between the SO-CTM and hybrid modeling approaches that could have affected the health associations in both magnitude and direction. For example, the SO-CTM model was developed for California only, whereas the hybrid model was developed for all North America. The state-specific model might be considered superior for this application, because the information available in California may better capture the

intra-regional variability of the $PM_{2.5}$ components. However, the SO-CTM model provide estimates at 4km spatial resolution. Primary EC and BC, in particular, have steep spatial gradients from major roadway sources, so exposure misclassification might be less in the hybrid model with 1km resolution. In contrast, SO_4^{2-}, which occurs as a result of secondary formation from precursor sulfur dioxide, has comparatively smoother spatial variation than other $PM_{2.5}$ components, so the spatial resolution should have little impact on the accuracy of the exposure assignment from each model. OM includes both primary and secondary particles, including emissions from vehicular and industrial fuel combustion and natural sources, and secondary organic carbon produced by photochemical reactions of gaseous precursors in the atmosphere. A limitation of the current study is that only primary OM from the SO-CTM was used in the exposure analysis because predictions of secondary OM were judged to be uncertain. This likely explains part of the markedly larger estimated exposure from the hybrid model than from the SO-CTM model. Thus, each exposure model has qualitative strengths and weaknesses, which are difficult to assess quantitatively.

In spite of the differences between exposure models, we found generally consistent results using both models, at least in the direction of the association of components with ASD. An exception was NO_3^- (which was positively associated in the hybrid model and inversely associated in the SO-CTM model). NO_3^- prediction is particularly challenging because it is largely secondary aerosol, originating from the atmospheric oxidation of NO_x (nitrogen dioxide, NO_2 and nitrous oxide), and in addition is semi-volatile; it is possible that the two measurement sites in southern California are insufficient to support accurate NO_3^- predictions in the hybrid modeling system, and/or some systematic error in the SO-CTM predicted NO_3^- may have led to bias. Mechanisms for NO_3^- associations with autism (either protective or increased risk) have not been published in peer-reviewed literature. Further investigation is needed to assess the reasons for this divergence in exposure estimates between the two models.

The general consistency of associations with other components estimated using different exposure methods increases the level of confidence in the observed ASD associations. Using different modeling approaches also helps prevent over- or under-interpretation of the importance of associations based on a single exposure models. For example, the pregnancy average HR for EC (1.12; CI 1.07, 1.18) from Table 3, which was not attenuated by adjustment for other components and remainder $PM_{2.5}$, might be interpreted as robust evidence for a causal effect; however, if only the BC hybrid model were used, the conclusion might be that effects were confounded by the remainder $PM_{2.5}$ (with a reduction of HR from 1.06 (1.02, 1.10) in the single pollutant BC model HR to 1.03 (0.98, 1.09) after adjusting for remainder $PM_{2.5}$. A few previous studies of other outcomes reported some heterogeneity in component effect estimates in terms of statistical significance, magnitude, and direction of association, depending on the exposure assessment method used [23-27]. Modeling components at local spatial scale for epidemiological studies is relatively new compared to well validated models of $PM_{2.5}$. Future $PM_{2.5}$ composition health effects studies might consider using multiple exposure models and a weight of evidence approach when interpreting effect estimates of associations.

There have been few studies on the developmental neurotoxicity of $PM_{2.5}$ components [40,41], compared with a large emerging body of work examining $PM_{2.5}$ mass [9-11], and none to our knowledge has examined the association with ASD risk in children. There has been limited prior epidemiological study of neurotoxicity of EC/BC exposure, and results were not consistent [42-46]. Exposure to prenatal EC/BC or $PM_{2.5}$ absorbance (a proxy for EC) was associated with increased hyperactivity/inattention among adolescents [44] and worse memory in urban children [42], no association with childhood cognitive and psychomotor development [43], and with verbal IQ in minimally adjusted, but not in fully adjusted models [45]. Rodent studies of EC neurotoxicity (largely from diesel exhaust particles) have also been inconclusive [47,48,49,50]. Mechanisms for effects are not clear, although several studies reported high oxidative potential of EC particles [51-53]. EC/BC effects may also be a proxy for other co-emissions, such as semi-volatile organic compounds and polycyclic aromatic hydrocarbon, that are adsorbed onto the EC core [54-58]. To the best of our knowledge, neurodevelopmental effects of prenatal OM exposure has not been examined either in epidemiological or animal studies. The pregnancy average and third trimester association with SO_4^{2-} is also novel. There is little SO_4^{2-} in Southern California; emissions from ships in the Long Beach/Los Angeles port complex are a major source.

Our study has several strengths. First, it leveraged a large, diverse pregnancy cohort with standard diagnostic criteria for ASD. The KPSC cohort is representative of the Southern California population [59], and thus results are relevant to similar populations across the United States; the regulated air pollutants in the region (with the exception of SO_4^{2-}) encompass most of the entire range and mixture across the U.S. Exposure was assigned from validated prediction models, accounting for change of address during pregnancy. ASD associations with PM components were adjusted for key confounders such as maternal pre-pregnancy health status, season of conception, and year of birth, obtained from the high quality KPSC EMR. Finally, the multi-pollutant modelling strategies accounted for effects of the remainder $PM_{2.5}$. We acknowledge some limitations. Mother's time-activity patterns were not available for this analysis. Knowledge of the accuracy and uncertainty of the exposure model estimates of PM chemical components is limited by the much smaller observational database than is available for $PM_{2.5}$ mass.

In summary, prenatal exposure to some $PM_{2.5}$ component EC/BC, OM, and to a lesser extent SO_4^{2-}, were associated with increased ASD risk. However, the strength and statistical significance of some effect estimates differed between exposure models. The results of this study are consistent with the emerging literature indicating that different exposure assessment models may be responsible for some of the heterogeneity in effect estimates across studies using different PM composition exposure models. Unlike $PM_{2.5}$, which has been studied in epidemiological studies for decades, models for most $PM_{2.5}$ components for use in epidemiological studies are only recently available. Better understanding of the role of $PM_{2.5}$ components and their sources could lead to targeted regulatory interventions to reduce the health effects of particulate air pollution. Eventually, component-specific air pollution control policies merit consideration in regulatory strategies for reducing adverse effects of $PM_{2.5}$ [60].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SYNOPSIS

This study provided novel evidence of ASD risk resulting from prenatal exposure to fine particle components.

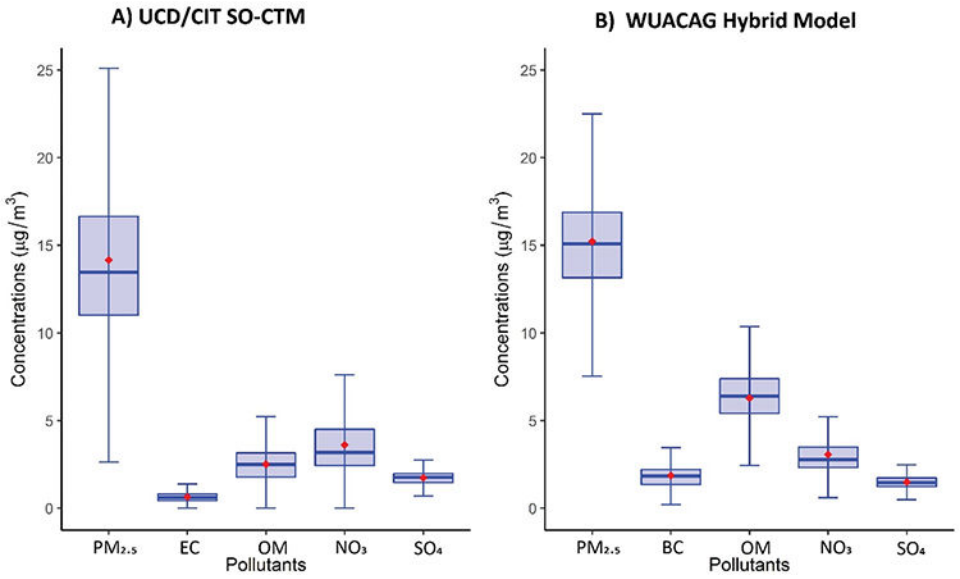

Figure 1.

The distribution of $PM_{2.5}$ and its major components during entire-pregnancy based on A) source-oriented chemical transport model and B) hybrid model, during the study period from 2001 – 2014.

Table 1.

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

Characteristics	Children, No. (%) or median (interquartile range)		
	Overall (n =318 750)	With ASD (n= 4559)	Without ASD (n= 314 191)
Sex; N (%)			
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.

Pearson correlation matrix of entire-pregnancy estimates of $PM_{2.5}$, EC/BC, OM, NO_3^-, and SO_4^{2-} from a source-oriented chemical transport model and a hybrid model.

		UCD/CIT SO-CTM Model					WUACAG Hybrid Model				
		$PM_{2.5}$	**EC**	**OM**	**NO_3^-**	**SO_4^{2-}**	**$PM_{2.5}$**	**BC**	**OM**	**NO_3^-**	**SO_4^{2-}**
UCD/CIT SO-CTM Model	$PM_{2.5}$	1.00									
	EC	0.75	1.00								
	OM	0.74	0.85	1.00							
	NO_3^-	0.87	0.55	0.44	1.00						
	SO_4^{2-}	0.69	0.40	0.31	0.47	1.00					
WUACAG Hybrid Model	$PM_{2.5}$	0.80	0.68	0.67	0.67	0.46	1.00				
	BC	0.56	0.61	0.56	0.43	0.26	0.78	1.00			
	OM	0.57	0.59	0.63	0.35	0.32	0.81	0.48	1.00		
	NO_3^-	0.82	0.65	0.59	0.78	0.46	0.91	0.61	0.62	1.00	
	SO_4^{2-}	0.52	0.34	0.27	0.43	0.46	0.59	0.17	0.47	0.59	1.00

Table 3.

Associations of ASD with entire-pregnancy average exposures to EC/BC, OM, NO_3^-, and SO_4^{2-} from a source-oriented chemical transport model and a hybrid model.

UCD/CIT SO-CTM Model			WUACAG Hybrid Model		
Primary Exposure of Interest	**Adjusted Pollutant (s)**	**HR (95% CI)**	**Primary Exposure of Interest**	**Adjusted Pollutant (s)**	**HR (95% CI)**
EC	Single pollutant	1.12 (1.07, 1.18)	**BC**	Single pollutant	1.06 (1.02, 1.10)
	Remainder $PM_{2.5}$	1.15 (1.09, 1.23)		Remainder $PM_{2.5}$	1.03 (0.98, 1.09)
	$OM+NO_3^-+SO_4^{2-}$	1.13 (1.06, 1.21)		$OM+NO_3^-+SO_4^{2-}$	1.04 (0.98, 1.09)
OM	Single pollutant	1.09 (1.04, 1.15)	**OM**	Single pollutant	1.08 (1.03, 1.13)
	Remainder $PM_{2.5}$	1.09 (1.03, 1.16)		Remainder $PM_{2.5}$	1.08 (1.02, 1.15)
	$EC+NO_3^-+SO_4^{2-}$	1.02 (0.95, 1.10)		$BC+NO_3^-+SO_4^{2-}$	1.05 (0.99, 1.13)
NO_3^-	Single pollutant	0.85 (0.79, 0.93)	**NO_3^-**	Single pollutant	1.05 (1.00, 1.09)
	Remainder $PM_{2.5}$	0.76 (0.70, 0.84)		Remainder $PM_{2.5}$	0.98 (0.92, 1.05)
	$EC+OM+SO_4^{2-}$	0.79 (0.72, 0.86)		$BC+OM+SO_4^{2-}$	0.97 (0.91, 1.03)
SO_4^{2-}	Single pollutant	1.05 (1.00, 1.11)	**SO_4^{2-}**	Single pollutant	1.08 (1.02, 1.14)
	Remainder $PM_{2.5}$	1.04 (0.99, 1.10)		Remainder $PM_{2.5}$	1.05 (0.99, 1.12)
	$EC+OM+NO_3^-$	1.05 (0.99, 1.10)		$EC+OC+NO_3^-$	1.06 (0.99, 1.13)

*All the models were adjusted for child sex, maternal race/ethnicity, maternal age at delivery, parity, education, maternal comorbidities, household income (census tract level), birth year (non-linear), season (wet/dry), and pre-pregnancy diabetes. The hazard ratios were scaled to the inter-quartile (IQR) increase in concentration of each air pollutant during pregnancy. Based on UCD/CIT SO-CTM, the IQRs ($\mu g/m^3$) for $PM_{2.5}$, EC, OM, NO_3^-, and SO_4^{2-} during pregnancy were 5.56, 0.38, 1.38, 2.07, and 0.52, respectively. Based on WUACAG Hybrid Model, the IQRs ($\mu g/m^3$) for $PM_{2.5}$, BC, OM, NO_3^-, and SO_4^{2-} during pregnancy were 3.73, 0.84, 1.98, 1.15, and 0.50, respectively.