Title

Maternal exposure to aircraft emitted ultrafine particles during pregnancy and likelihood of ASD in children.

Authors

Carter, Sarah
Rahman, Md
Lin, Jane
et al.

Publication Date

2023-08-01

DOI

10.1016/j.envint.2023.108061

Peer reviewed

HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2023 September 01.

Published in final edited form as:

Environ Int. 2023 August ; 178: 108061. doi:10.1016/j.envint.2023.108061.

Maternal exposure to aircraft emitted ultrafine particles during pregnancy and likelihood of ASD in children

Sarah A. Carter[a,1], **Md Mostafijur Rahman**[b,1], **Jane C. Lin**[a], **Ting Chow**[a], **Xin Yu**[c], **Mayra P. Martinez**[a], **Pat Levitt**[h], **Zhanghua Chen**[b], **Jiu-Chiuan Chen**[b], **Sandrah P. Eckel**[b], **Joel Schwartz**[d,e], **Frederick W. Lurmann**[f], **Michael J. Kleeman**[g], **Rob McConnell**[b,2], **Anny H. Xiang**[b,*,2]

[a]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA

[b]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

[c]Spatial Science Institute, University of Southern California, Los Angeles, CA, USA

[d]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[e]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[f]Sonoma Technology, Inc., Petaluma, CA, USA

[g]Department of Civil and Environmental Engineering, University of California, Davis, Davis, CA, USA

[h]Department of Pediatrics and Program in Developmental Neuroscience and Neurogenetics, Keck School of Medicine, The Saban Research Institute, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA, USA

Abstract

*Corresponding author at: Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S Los Robles Ave, Pasadena, CA 91101, USA. anny.h.xiang@kp.org (A.H. Xiang).

[1]Sarah A. Carter and Md Mostafijur Rahman contributed equally and serve as joint first authors.

[2]Rob McConnell and Anny H. Xiang contributed equally and serve as joint senior authors.

CRediT authorship contribution statement

Sarah A. Carter: Conceptualization, Writing – original draft, Writing – review & editing. **Md Mostafijur Rahman:** Conceptualization, Writing – original draft. **Jane C. Lin:** Software, Formal analysis, Validation, Data curation. **Ting Chow:** Software, Formal analysis, Validation, Data curation. **Xin Yu:** Conceptualization. **Mayra P. Martinez:** Resources, Project administration, Data curation. **Zhanghua Chen:** Conceptualization, Writing – original draft. **Jiu-Chiuan Chen:** Methodology. **Sandrah P. Eckel:** Methodology. **Joel Schwartz:** Conceptualization, Writing – original draft. **Frederick W. Lurmann:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Rob McConnell:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. **Anny H. Xiang:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108061.

Background: There is increasing evidence for adverse health effects associated with aircraft-emitted particulate matter (PM) exposures, which are largely in the ultrafine ($PM_{0.1}$) size fraction, but no previous study has examined neurodevelopmental outcomes.

Objective: To assess associations between maternal exposure to aircraft ultrafine particles (UFP) during pregnancy and offspring autism spectrum disorder (ASD) diagnosis.

Methods: This large, representative cohort study included 370,723 singletons born in a single healthcare system. Demographic data, maternal health information, and child's ASD diagnosis by age 5 were extracted from electronic medical records. Aircraft exposure estimates for $PM_{0.1}$ were generated by the University of California Davis/California Institute of Technology Source Oriented Chemical Transport model. Cox proportional hazard models were used to assess associations between maternal exposure to aircraft $PM_{0.1}$ in pregnancy and ASD diagnosis, controlling for covariates.

Results: Over the course of follow-up, 4,554 children (1.4 %) were diagnosed with ASD. Increased risk of ASD was associated with maternal exposure to aircraft $PM_{0.1}$ [hazard ratio, HR: 1.02, (95 % confidence interval (CI): 1.01–1.03) per IQR = 0.02 $\mu g/m^3$ increase during pregnancy. Associations were robust to adjustment for total $PM_{0.1}$ and fine particulate matter ($PM_{2.5}$), near-roadway air pollution, and other covariates. Noise adjustment modestly attenuated estimates of UFP effects, which remained statistically significant.

Discussion: The results strengthen the emerging evidence that maternal particulate matter exposure during pregnancy is associated with offspring ASD diagnosis and identify aircraft-derived $PM_{0.1}$ as novel targets for further study and potential regulation.

Keywords

Air pollution; Aircraft emissions; Childhood neurodevelopment; Autism spectrum disorders

1. Introduction

Emerging epidemiological evidence has shown that exposure to ultrafine particles (UFP) is associated with adverse health effects (Bendtsen et al., 2021), including respiratory illness (Habre et al., 2018; Kunzli et al., 2009), cardiovascular disease (Pope et al., 2015), and brain cancer (Wu et al., 2021). UFP are less than 100 nm in diameter and are of particular concern because their size allows them to penetrate tissues and translocate from the lungs to the blood and up the olfactory nerve to the brain (Kumar et al., 2013). Along with traffic, aircraft are a major source of UFP in urban areas (Hudda and Fruin, 2016), as high temperatures in jet engines nucleate particulate matter (PM), generating very small particles (Stacey and Pope, 2020).

Few studies have examined associations between aircraft PM and child health. In a study of mothers living within 15 km of Los Angeles International Airport, exposure to UFP from aircraft during pregnancy was associated with increased risk of preterm birth, associations that remained after adjustment for noise pollution and traffic-related emissions (Wing et al., 2020). Recent epidemiological research reported that UFP exposure during pregnancy was associated with changes in neurodevelopment in young children (Guxens

et al., 2018; Klocke et al., 2018). The associations reported with preterm birth (Wing et al., 2020) are also relevant to studies of aircraft PM exposure during pregnancy and child neurodevelopment, as preterm birth has been established as a risk factor for autism spectrum disorder (ASD) (Crump et al., 2021). ASD is a neurodevelopmental condition characterized by communication difficulties, repetitive behaviors, and deficits in social behavior (Maenner et al., 2016). ASD etiology is multifactorial and includes genetic, environmental, and perinatal factors (Hallmayer et al., 2011; Geschwind, 2011; Wang et al., 2017), including PM exposure (Jo et al., 2019; Rahman et al., 2022; Lin et al., 2022; Yu, 2019).

Despite existing literature concerning health risks associated with aircraft emissions in children and adults, to our knowledge, no previous study has assessed the relationship between maternal exposure to aircraft PM during pregnancy and likelihood of offspring ASD. Additionally, there may be differences in health outcomes related to exposure to commercial or military aircraft emissions. These forms of aviation may differ by flight paths, number of flights or fuel type. Southern California has several military bases, many of which fly military aircraft. Epidemiological evidence of the health effects of traffic related air pollution has resulted in regulation to reduce vehicular emissions (EPA, 2023). Aircraft emissions are weakly regulated under the United Nations' International Civil Aviation Organization (ICAO) in 2017 and 2020. Understanding associations between aircraft emissions and health is an important public health question. Examining associations between exposure to aircraft emissions during pregnancy and child ASD risk will help provide evidence to inform public health policy aiming to reduce the exposure and risk.

2. Materials and methods

2.1. Study population

This is a population-based retrospective pregnancy cohort study that included mother–child pairs of singleton deliveries between January 1, 2001 and December 31, 2014 at Kaiser Permanente Southern California (KPSC) hospitals. Follow-up was through December 31, 2019. KPSC is a large integrated healthcare system with over 4.5 million members in Kern, Los Angeles, Orange, Riverside, San Diego, San Bernardino, and Ventura counties. 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. Addresses based only on street name, 5-digit postal code, locality, or administrative unit were considered too uncertain to be used for air pollution exposure assignments and were excluded.

Singleton births with KPSC membership at age 1 (n = 370,723) were included in the analytical data set. A total of 52,645 births was excluded due to missing sex, maternal race/ethnicity and age at delivery, implausible age of delivery or birth weight (n = 666); or maternal age under 15 years or over 55 years (n = 159); and/or incomplete maternal residential address history in pregnancy; or addresses deemed too uncertain for accurate exposure assignment (n = 51,820). Participants' addresses were geocoded using ArcGIS, which was used to assess the suitability of the air pollution exposure assignments (Desktop,

2020). Geocodes with SCORE of 90–100 and ADDRESS TYPE of point address or street address were considered suitable, based on analyses designed to include only mothers who could be geocoded to 1 km^2 spatial resolution (a more rigorous spatial resolution than the 4 km^2 spatial resolution of the aircraft source exposure, described below) as previously described (Rahman et al., 2022). Addresses based only on street name, postal zip code, administrative unit (city or town) usually had SCORES < 90; ArcGIS generally geocodes these to the zip code or administrative unit centroid; these were excluded from the analytic dataset. However, these less certain addresses were assigned exposures for use in sensitivity analyses. The final data analysis included 318,078 mother–child pairs with complete data on residential estimates of aircraft-related particulate air pollution exposures. Derivation of study sample size is shown in eFigure 1 in the supplement.

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

2.2. ASD ascertainment

The outcome was ASD diagnosis before age 5. Children were followed from birth through EMR until clinical diagnosis of ASD, loss to follow-up, or age 5, whichever came first. Children were routinely screened for potential likelihood of ASD starting at age 18 months during regular well-child visits at KPSC. The presence or absence of an ASD diagnosis during the follow-up period was 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 previously described (Jo et al., 2019; Coleman et al., 2015; Xiang et al., 2015; Xiang et al., 2018).

2.3. Aircraft PM, near-roadway air pollution, and noise exposure assessment

This analysis used aircraft exposure estimates for $PM_{0.1}$ (ultrafine) and $PM_{2.5}$ generated by the UCD/CIT (University of California Davis/California Institute of Technology) Source Oriented Chemical Transport model (CTM). In addition to aircraft PM, the UCD/CIT SO-CTM model developed exposure estimates for $PM_{0.1}$ and $PM_{2.5}$ from other emission sources, such as on-road traffic and off-road traffic, which were utilized in this study to control for confounding. The UCD/CIT SO-CTM uses meteorological estimates 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. All airports in California are included in CARB's aircraft emission inventory. This study utilizes CARB data from all airports present in Southern California counties covered by KPSC. CARB's aircraft emissions inventory accounts for typical flight path information including both take-off and landing, and for changes in the number of flights over time, all of which affect predicted exposure fields for aircraft particles. The regional signal of aircraft contributions to ambient UFP concentrations reported by CARB's inventory is consistent with past measurements downwind of major airports like Los Angeles International (Yu, 2019). 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., 2014; Hu et al., 2014; Hu et al., 2015). This modelling takes into consideration the dominant regional gradients of isolated airports separated by large distances (Yu, 2019). The aircraft PM exposure fields tracked by the model represent the primary PM emissions from aircraft and do not include the secondary PM formed from gaseous NOx and VOC aircraft emissions.

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., 2014; Hu et al., 2014; Hu et al., 2015; 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. The bias in CTM predictions at each monitoring location was combined with the CTM predicted concentrations of primary particles emitted from nine different source categories and the concentrations of secondary nitrate and sulfate particulate matter to form a time-series that was analyzed using multi-linear regression (MLR). 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 (Yu et al., 2019). For example, monthly $PM_{2.5}$ elemental carbon was correlated with measurements with $r = 0.94$ (8 sites). Model estimated source-specific PM has been applied in several prior epidemiological studies of health effects (Laurent et al., 2014; Laurent et al., 2016; Laurent et al., 2016; Ostro et al., 2010; Ostro et al., 2015).

Average exposures to aircraft $PM_{0.1}$ and $PM_{2.5}$ mass were assigned to maternal addresses during the entire pregnancy. Exposures were time-weighted to account for changes of subject addresses during pregnancy. However, $PM_{0.1}$ and $PM_{2.5}$ were highly correlated (r = 1.0). Because the primary particle mass derived from aircraft emissions was in the UFP fraction or just slightly larger size, only results for UFP are presented (see Discussion Section for further details).

Exposures to average near-roadway air pollution from freeway and nonfreeway sources during pregnancy were estimated at maternal residential addresses using the California Line Source Dispersion Model (CALINE4) (Pe, 1992), which was associated with ASD in this cohort (Carter et al., 2022).

Noise exposure data were obtained from a geospatial model (Mennitt, 2016). This model provided predictions of time-integrated sound levels during 2000–2014 from anthropogenic sources, including aircraft, at 270-m spatial resolution across the contiguous United States. The estimates of sound levels are available separately from daytime (7am—7pm) and nighttime (7pm—7am). We used median A-weighting sound pressure (L50) for daytime and nighttime as metrics of noise exposure, assigned to maternal addresses during pregnancy.

2.4. Covariates

We selected covariates a priori based on existing knowledge and past literature on air pollution exposures and ASD (Jo et al., 2019; Carter et al., 2022; Pagalan et al., 2019; Ritz et al., 2018). Covariates included were child sex, maternal race/ethnicity, maternal age at delivery (ages 15 through 55), parity, maternal 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 known time trends in ASD incidence and aircraft air pollution 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). 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). Gestational age at delivery, preterm birth and birth weight were not considered as covariates, because they may be on the casual pathway between prenatal air pollution and ASD (Bekkar et al., 2020; Gardener and Buka, 2011).

2.5. Statistical analyses

We fitted Cox proportional hazards models to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) for ASD risk associated with exposure to aircraft $PM_{0.1}$ during pregnancy. Linearity of association of ASD risk with aircraft $PM_{0.1}$ was examined using general additive Cox models with a smoothing spline (with 3 degrees of freedom). No significant deviations from linearity were found. We also fitted several two-pollutant models to assess whether the ASD association with aircraft $PM_{0.1}$ remained after controlling for total $PM_{0.1}$ (Rahman et al., 2022) and $PM_{2.5}$ mass, non-freeway and freeway dispersion-modeled near-roadway air pollution exposures, which we have shown previously to be associated with ASD in this cohort (Carter et al., 2022), and UCD/CIT SO-CTM developed on-road traffic $PM_{0.1}$ estimates. We also adjusted for both daytime and nighttime noise. Additional analyses tested for interactions of aircraft $PM_{0.1}$ exposure with child's sex. Sensitivity analyses investigated the influence of $PM_{0.1}$ from military aircraft on associations with ASD by excluding mothers living within 20 km of a military base. In further sensitivity analyses, we added mothers excluded from the analytical sample due largely to addresses not meeting the quality standard to geocode to the household, and we repeated selected key analyses to see if the estimates of effect were changed.

HRs and 95 % CIs were scaled to the interquartile range (IQR) increase in concentration of aircraft $PM_{0.1}$ during pregnancy. All analyses were performed using R Statistical Software (v3.5.2; R Core Team 2021).

2.6. Role of the funding source

The funding agencies had no role in the design of the study, the analysis or interpretation of data, or the preparation or approval of the manuscript.

3. Results

Participant demographics and residential information are displayed in Table 1. Over the course of follow-up, 4,554 children (1.4 %) were diagnosed with ASD. Among children with ASD diagnoses, 3,700 (81 %) were males. Compared to children without ASD, children with ASD had greater proportions of older, nulliparous mothers with maternal comorbidities, pre-pregnancy diabetes, and pre-pregnancy obesity. Children with ASD were more likely to have mothers reporting Asian/Pacific Islander and non-Hispanic Black ethnicity and some college or higher educational qualifications.

Levels of aircraft $PM_{0.1}$ had no discernable time trend across the study period; levels were slightly lower between 2005 and 2009 before increasing again by 2014 (eFigure 2); Median estimated average aircraft $PM_{0.1}$ exposure during pregnancy (based on maternal residence) was 0.04 ug/m^3 (1st, 3rd quartiles: 0.03, 0.05 ug/m^3).

Aircraft $PM_{0.1}$ exposure was associated with ASD diagnosis in children (HR: 1.016; 95 % CI: 1.007–1.026). Correlations between aircraft $PM_{0.1}$ and on-road traffic $PM_{0.1}$, and nonfreeway and freeway CALINE dispersion-modeled near-roadway air pollution were ($r = -0.01$), ($r = -0.04$), and ($r = 0.08$), respectively. Adjustments for total $PM_{0.1}$ or $PM_{2.5}$ mass, $PM_{0.1}$ from on-road traffic, and for nonfreeway and freeway near-roadway air pollution in two-pollutant models did not change the magnitude or direction of the association between aircraft $PM_{0.1}$ and offspring ASD diagnosis (Table 2).

Aircraft $PM_{0.1}$ was positively correlated with daytime ($r = 0.17$) and nighttime ($r = 0.05$) noise. The adjustment for nighttime noise did not change the associations of aircraft $PM_{0.1}$ with ASD, but the adjustment for daytime noise attenuated associations (Table 2); however, the associations remained significant (HR: 1.011; 95 % CI: 1.001–1.022). When mothers living within 20 km of a military base were excluded, the magnitude of association between aircraft emissions and likelihood of ASD in children was increased (HR: 1.037; 95 % CI: 1.014–1.061). There was no significant interaction between sex of the child and aircraft $PM_{0.1}$ exposure ($p = 0.99$).

To assess the potential for selection bias due to exclusion of mothers, largely due to addresses not meeting quality standards for parcel level geocoding, sensitivity analyses were conducted. The estimated pregnancy average aircraft $PM_{0.1}$-associated ASD risk in the analytic dataset and in a dataset including in addition the mothers excluded from the main analysis were almost identical; this was the case in models with and without adjustment for total $PM_{0.1}$ and for total $PM_{2.5}$ (eTable 1). The mothers excluded and included in the analysis had almost identical median exposure across all years of the study to aircraft $PM_{0.1}$ (0.037 μg/m^3 [interquartile range 0.025, 0.051]). These analyses suggest that the exclusion based on geocoding quality did not introduce appreciable selection bias.

4. Discussion

Using a large representative pregnancy cohort of 318,078 mother–child pairs and novel aircraft PM exposure data at 4 km resolution, this study found small but statistically significant associations between maternal exposure to aircraft $PM_{0.1}$ during pregnancy and

likelihood of ASD diagnoses in children. These associations were robust to adjustment for total $PM_{0.1}$/$PM_{2.5}$ mass and for on-road traffic emissions, indicating that the influence of maternal exposure to aircraft emissions on likelihood of offspring ASD was independent of the effect of regional total particulate matter and road traffic air pollutants. These associations were also independent of residential noise levels.

Primary particulate matter emissions from aircraft engines are dominated by high concentrations of UFP (Mazaheri et al., 2009). Primary particles emitted from jet engines have a bimodal size distribution, with the first mass mode located at approximately 0.02 μm and the second mass mode peaking between 0.60 and 0.10 μm (see eFigure 3). The $PM_{0.1}$ size fraction is a subset of the $PM_{2.5}$ size fraction, and so the exposure patterns for aircraft primary $PM_{0.1}$ and $PM_{2.5}$ are highly correlated. The predicted concentrations of metal and other components, primary organics, elemental carbon, primary nitrate and sulfate are similar in each particle size bin. The PM sulfate is produced by the oxidation of sulfur contained in the jet fuel. This hygroscopic component will cause the aircraft particles to grow due to water condensation as they age in the atmosphere. The concentration of primary aircraft particles reported here does not include secondary particulate matter produced by atmospheric chemistry. These secondary concentrations are tracked in the exposure calculations, but they are included as part of other exposure variables such as total $PM_{0.1}$ mass, or $PM_{2.5}$ nitrate, etc.

While there have been limited epidemiological investigations on the health effects of aircraft emissions during pregnancy, previous literature has reported associations between maternal exposure to aircraft emissions during pregnancy and preterm births (Wing et al., 2020; Wing et al., 2022). Aircraft particles are enriched in redox-active poly aromatic hydrocarbons and metals (Bendtsen et al., 2021). These nanosized particles are inhaled into the lower respiratory tract, cross the alveolar barrier, and translocate into the systemic circulation (Bendtsen et al., 2021). A short-term health effects study conducted in the Los Angeles area reported that airport-related UFPs were associated with higher systemic inflammation in adults with asthma (Habre et al., 2018). Animal models have shown that exposure to airport pollutants increases inflammation and genotoxicity (Bendtsen et al., 2019). Particulate matter can cross the placental barrier (Chen et al., 2021). Since aircraft PM is dominated by ultrafine particles, it is possible that they cross the placental barrier and induce oxidative stress and inflammation in fetal tissues (Bongaerts et al., 2020; Morales-Rubio et al., 2019; Calderon-Garciduenas et al., 2022; Cory-Slechta et al., 2019). Oxidative stress in pregnancy may also impair placental function, compromising the transfer of oxygen and nutrients to the fetus (Schoots et al., 2018); this pathway has been linked to fetal growth restriction, low birthweight, and the fetal programming of chronic diseases (Rodriguez-Rodriguez et al., 2018; Wu et al., 2015; Arogbokun et al., 2021). Additionally, several studies have reported associations between $PM_{2.5}$ exposure during pregnancy and systemic inflammation, which may impact fetal neurodevelopment (Wei et al., 2016; Saghazadeh et al., 2019; Campbell et al., 2009; Kleinman et al., 2008).

We tested the independence of the aircraft PM association with ASD by adjusting for several metrics of traffic related air pollution. The strength of associations did not change after adjustment for roadway traffic air pollutants in two-pollutant models. Unlike near-roadway

air pollution which has steep gradients near roadways, aircraft emissions result in broad exposures over residences on flight paths and have relatively high concentrations of UFP present in areas near landing aircraft (Hudda and Fruin, 2016; Austin et al., 2021; Hudda et al., 2014).

Noise level is relatively high near airports so the observed effects of aircraft PM could be confounded by noise; we adjusted our models for estimated daytime and nighttime noise levels to assess the independence of the aircraft PM association. Daytime (but not nighttime) noise attenuated HRs of the significant association slightly, suggesting that part of the association with aircraft PMs may have been due to residential noise exposure during pregnancy.

Previous research has identified exposure to military aircraft fuel and emissions, which is distinct from those of commercial aircraft, as potential threats to long term health (Smith et al., 2010; Buja et al., 2005). Southern California has several military bases, many of which fly military aircraft. CTM calculations predict significantly higher concentrations of aircraft particles around military airbases compared to civilian airports due to higher concentrations of sulfur in military aircraft fuel. Ambient measurements to confirm these enhanced concentrations are not available. In this study, the exclusion of pregnant women living near military bases strengthened the associations between aircraft emissions and offspring ASD. It may be that the fewer number of departures and landings at military bases meant that people living close to these locations were exposed to less aircraft emissions in general than those living in closer proximity to commercial airports (Waitz and Lee, 2005). No previous study has considered whether associations between PM exposure and ASD differ by household proximity to military aircraft bases. Further research into differences between commercial and military aircraft emission exposures and their effects is warranted.

This study utilized a large, diverse longitudinal cohort, which provided health and residential EMR data for mother–child pairs across Southern California, as well as information concerning relevant confounders. The KPSC cohort is representative of the study population, allowing results to be broadly generalized at least to Southern California. This study was also strengthened by the consideration of PM mass in ultrafine size fraction, on-road traffic emissions, and noise, several other neurotoxic exposures common to urban environments. While detailed information about aircraft on military bases, such as number of flights or type of fuel used, was not available, maternal residential data allowed for sensitivity analyses concerning the influence of proximity to military bases during pregnancy on ASD diagnoses in children. This study has some limitations. Paternal information was unavailable; therefore, we were unable to control for paternal contributions to ASD risk. Information on mothers' time-activity during pregnancy (time spent by mothers at work, in transit, or leisure) were not included in these models but could have affected aircraft PM exposures estimated only at home. Although we adjusted for noise exposure, noise specific to aircraft was not available to us and could be more relevant to this analysis.

5. Conclusion

Maternal exposure to aircraft $PM_{0.1}$ during pregnancy was associated with increased risk of ASD diagnoses in children. Associations remained after adjusting for total PM and on-road traffic emissions; they were attenuated yet remained significant after adjusting for daytime noise. The results of this study suggest that the risk of offspring ASD after maternal exposure to aircraft emissions during pregnancy is independent of the effect of total PM mass, road traffic air pollutants, and noise. Aircraft emissions are an important source of PM and a potential target of regulation to better protect public health.

Funding:

National Institutes of Environmental Health Sciences and Kaiser Permanente Southern California Direct Community Benefit Funds. Joel Schwartz was supported by EPA grant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank KPSC patients for helping us improve care using information collected via our electronic health record systems.

Funding

This study was supported by National Institutes of Environmental Health Sciences (R01 ES029963 (Xiang, McConnell); R56ES028121 (Xiang); P30ES007048 (McConnell), and partly supported by Kaiser Permanente Southern California Direct Community Benefit Funds. Joel Schwartz was supported by EPA grant RD-835872. The funding agencies had no role in the design of the study, the analysis or interpretation of data, or the preparation or approval of the manuscript.

Data availability

The data that has been used is confidential.

References

Arogbokun O, Rosen E, Keil AP, Milne GL, Barrett E, Nguyen R, et al. , 2021. Maternal Oxidative Stress Biomarkers in Pregnancy and Child Growth from Birth to Age 6. J. Clin. Endocrinol. Metab 106 (5), 1427–1436. [PubMed: 33524128]

Austin E, Xiang J, Gould TR, Shirai JH, Yun S, Yost MG, et al. , 2021. Distinct Ultrafine Particle Profiles Associated with Aircraft and Roadway Traffic. Environ. Sci. Tech 55 (5), 2847–2858.

Bekkar BPS, 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). [PubMed: 32556259]

Bendtsen KM, Brostrom A, Koivisto AJ, Koponen I, Berthing T, Bertram N, et al. , 2019. Airport emission particles: exposure characterization and toxicity following intratracheal instillation in mice. Part. Fibre Toxicol 16 (1), 23. [PubMed: 31182125]

Bendtsen KM, Bengtsen E, Saber AT, Vogel U, 2021. A review of health effects associated with exposure to jet engine emissions in and around airports. Environ. Health 20 (1), 10. [PubMed: 33549096]

Bongaerts E, Nawrot TS, Van Pee T, Ameloot M, Bove H, 2020. Translocation of (ultra)fine particles and nanoparticles across the placenta; a systematic review on the evidence of in vitro, ex vivo, and in vivo studies. Part. Fibre Toxicol 17 (1), 56. [PubMed: 33138843]

Buja A, Lange JH, Perissinotto E, Rausa G, Grigoletto F, Canova C, et al. , 2005. Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. Toxicol. Ind. Health 21 (10), 273–282. [PubMed: 16463960]

Calderon-Garciduenas L, Perez-Calatayud AA, Gonzalez-Maciel A, Reynoso-Robles R, Silva-Pereyra HG, Ramos-Morales A, et al. , 2022. Environmental Nanoparticles Reach Human Fetal Brains. Biomedicines. 10 (2).

Campbell A, Araujo JA, Li H, Sioutas C, Kleinman M, 2009. Particulate matter induced enhancement of inflammatory markers in the brains of apolipoprotein E knockout mice. J. Nanosci. Nanotechnol 9 (8), 5099–5104. [PubMed: 19928188]

Carter SA, Rahman MM, Lin JC, Shu YH, Chow T, Yu X, et al. , 2022. In utero exposure to near-roadway air pollution and autism spectrum disorder in children. Environ. Int 158, 106898. [PubMed: 34627014]

Chen H, Oliver BG, Pant A, Olivera A, Poronnik P, Pollock CA, et al. , 2021. Particulate Matter, an Intrauterine Toxin Affecting Foetal Development and Beyond. Antioxidants (Basel) 10 (5).

Coleman KJ, Lutsky MA, Yau V, Qian Y, Pomichowski ME, Crawford PM, et al. , 2015. Validation of Autism Spectrum Disorder Diagnoses in Large Healthcare Systems with Electronic Medical Records. J. Autism Dev. Disord 45 (7), 1989–1996. [PubMed: 25641003]

Cory-Slechta DA, Sobolewski M, Marvin E, Conrad K, Merrill A, Anderson T, et al. , 2019. The Impact of Inhaled Ambient Ultrafine Particulate Matter on Developing Brain: Potential Importance of Elemental Contaminants. Toxicol. Pathol 47 (8), 976–992. [PubMed: 31610749]

Crump C, Sundquist J, Sundquist K, 2021. Preterm or Early Term Birth and Risk of Autism. Pediatrics 148 (3).

Desktop A. The geocoding process 2020 [Available from: https://desktop.arcgis.com/en/arcmap/latest/manage-data/geocoding/the-geocoding-process.htm.

(EPA) EPA. Control of Air Pollution From New Motor Vehicles: Heavy-Duty Engine and Vehicle Standards. 2023.

Gardener HSD, Buka SL, 2011. Perinatal and neonatal risk factors for autism: A comprehensive meta-analysis. Pediatrics 128, 344–355. [PubMed: 21746727]

Geschwind DH, 2011. Genetics of autism spectrum disorders. Trends Cogn. Sci 15 (9), 409–416. [PubMed: 21855394]

Guxens M, Lubczynska MJ, Muetzel RL, Dalmau-Bueno A, Jaddoe VWV, Hoek G, et al. , 2018. Air Pollution Exposure During Fetal Life, Brain Morphology, and Cognitive Function in School-Age Children. Biol. Psychiatry 84 (4), 295–303. [PubMed: 29530279]

Habre R, Zhou H, Eckel SP, Enebish T, Fruin S, Bastain T, et al. , 2018. Short-term effects of airport-associated ultrafine particle exposure on lung function and inflammation in adults with asthma. Environ. Int 118, 48–59. [PubMed: 29800768]

Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. , 2011. Genetic heritability and shared environmental factors among twin pairs with autism. Arch. Gen. Psychiatry 68 (11), 1095–1102. [PubMed: 21727249]

Hu JZH, Ying Q, Chen S-H, Vandenberghe F, Kleeman MJ, 2015. Long-term particulate matter modeling for health effect studies in California – Part 1: Model performance on temporal and spatial variations. Atmos. Chem. Phys 15, 3445–3461.

Hu J, Zhang H, Chen S, Ying Q, Wiedinmyer C, Vandenberghe F, et al. , 2014. Identifying PM2.5 and PM0.1 sources for epidemiological studies in California. Environ. Sci. Tech 48 (9), 4980–4990.

Hu J, Zhang H, Chen SH, Wiedinmyer C, Vandenberghe F, Ying Q, et al. , 2014. Predicting primary PM2.5 and PM0.1 trace composition for epidemiological studies in California. Environ. Sci. Tech 48 (9), 4971–4979.

Hudda N, Fruin SA, 2016. International Airport Impacts to Air Quality: Size and Related Properties of Large Increases in Ultrafine Particle Number Concentrations. Environ. Sci. Tech 50 (7), 3362–3370.

Hudda N, Gould T, Hartin K, Larson TV, Fruin SA, 2014. Emissions from an international airport increase particle number concentrations 4-fold at 10 km downwind. Environ. Sci. Tech 48 (12), 6628–6635.

Jo H, Eckel SP, Wang X, Chen JC, Cockburn M, Martinez MP, et al. , 2019. Sex-specific associations of autism spectrum disorder with residential air pollution exposure in a large Southern California pregnancy cohort. Environ. Pollut 254 (Pt A), 113010. [PubMed: 31554142]

Kleinman MT, Araujo JA, Nel A, Sioutas C, Campbell A, Cong PQ, et al. , 2008. Inhaled ultrafine particulate matter affects CNS inflammatory processes and may act via MAP kinase signaling pathways. Toxicol. Lett 178 (2), 127–130. [PubMed: 18420360]

Klocke C, Allen JL, Sobolewski M, Blum JL, Zelikoff JT, Cory-Slechta DA, 2018. Exposure to fine and ultrafine particulate matter during gestation alters postnatal oligodendrocyte maturation, proliferation capacity, and myelination. Neurotoxicology 65, 196–206. [PubMed: 29079486]

Koebnick C, Langer-Gould AM, Gould MK, Chao CR, Iyer RL, Smith N, et al. , 2012. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. Perm. J 16 (3), 37–41.

Kumar S, Verma MK, Srivastava AK, 2013. Ultrafine particles in urban ambient air and their health perspectives. Rev. Environ. Health 28 (2–3), 117–128. [PubMed: 24192498]

Kunzli N, Bridevaux PO, Liu LJ, Garcia-Esteban R, Schindler C, Gerbase MW, et al. , 2009. Traffic-related air pollution correlates with adult-onset asthma among never-smokers. Thorax 64 (8), 664–670. [PubMed: 19359271]

Laurent O, Hu J, Li L, Cockburn M, Escobedo L, Kleeman MJ, et al. , 2014. Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001–2008. Environ. Res 134, 488–495. [PubMed: 25085846]

Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, et al. , 2016. A Statewide Nested Case-Control Study of Preterm Birth and Air Pollution by Source and Composition: California, 2001–2008. Environ. Health Perspect 124 (9), 1479–1486. [PubMed: 26895492]

Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, et al. , 2016. Low birth weight and air pollution in California: Which sources and components drive the risk? Environ. Int 92–93, 471–477.

Lin LZ, Zhan XL, Jin CY, Liang JH, Jing J, Dong GH, 2022. The epidemiological evidence linking exposure to ambient particulate matter with neurodevelopmental disorders: A systematic review and meta-analysis. Environ. Res 209, 112876. [PubMed: 35134379]

Maenner MJ, Shaw KA, Baio J, EdS, Washington A, Patrick M, et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. MMWR Surveill Summ. 2020;69(4):1–12.

Mazaheri M, Johnson GR, Morawska L, 2009. Particle and gaseous emissions from commercial aircraft at each stage of the landing and takeoff cycle. Environ. Sci. Tech 43 (2), 441–446.

Mennitt DJFK, 2016. Influence factors and spatiotemporal patterns of environmental sound levels in the contiguous United States. Noise Control Eng. J 64, 342–353.

Morales-Rubio RA, Alvarado-Cruz I, Manzano-Leon N, Andrade-Oliva MD, Uribe-Ramirez M, Quintanilla-Vega B, et al. , 2019. In utero exposure to ultrafine particles promotes placental stress-induced programming of renin-angiotensin system-related elements in the offspring results in altered blood pressure in adult mice. Part. Fibre Toxicol 16 (1), 7. [PubMed: 30691489]

Ostro B, Lipsett M, Reynolds P, Goldberg D, Hertz A, Garcia C, et al. , 2010. Long-term exposure to constituents of fine particulate air pollution and mortality: results from the California Teachers Study. Environ. Health Perspect 118 (3), 363–369. [PubMed: 20064787]

Ostro B, Hu J, Goldberg D, Reynolds P, Hertz A, Bernstein L, et al. , 2015. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort. Environ. Health Perspect 123 (6), 549–556. [PubMed: 25633926]

Pagalan L, Bickford C, Weikum W, Lanphear B, Brauer M, Lanphear N, et al. , 2019. Association of Prenatal Exposure to Air Pollution With Autism Spectrum Disorder. JAMA Pediatr. 173 (1), 86–92. [PubMed: 30452514]

Pe B, 1992. A review of the development and application of the CALINE3 and 4 models. Atmos Environ. Part B Urban Atmos 26 (3), 379–390.

Pope CA 3rd, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR, et al. , 2015. Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality. Circ. Res 116 (1), 108–115. [PubMed: 25348167]

Rahman MM, Shu YH, Chow T, Lurmann FW, Yu X, Martinez MP, et al. , 2022. Prenatal Exposure to Air Pollution and Autism Spectrum Disorder: Sensitive Windows of Exposure and Sex Differences. Environ. Health Perspect 130 (1), 17008. [PubMed: 35040691]

Ritz B, Liew Z, Yan Q, Cui X, Virk J, Ketzel M, et al. , 2018. Air pollution and Autism in Denmark. Environ. Epidemiol 2 (4).

Rodriguez-Rodriguez P, Ramiro-Cortijo D, Reyes-Hernandez CG, Lopez de Pablo AL, Gonzalez MC, Arribas SM, 2018. Implication of Oxidative Stress in Fetal Programming of Cardiovascular Disease. Front. Physiol 9, 602. [PubMed: 29875698]

Saghazadeh A, Ataeinia B, Keynejad K, Abdolalizadeh A, Hirbod-Mobarakeh A, Rezaei N, 2019. A meta-analysis of pro-inflammatory cytokines in autism spectrum disorders: Effects of age, gender, and latitude. J. Psychiatr. Res 115, 90–102. [PubMed: 31125917]

Schoots MH, Gordijn SJ, Scherjon SA, van Goor H, Hillebrands JL, 2018. Oxidative stress in placental pathology. Placenta 69, 153–161. [PubMed: 29622278]

Smith KW, Proctor SP, Ozonoff A, McClean MD, 2010. Inhalation exposure to jet fuel (JP8) among U.S. Air Force personnel. J. Occup. Environ. Hyg 7 (10), 563–572. [PubMed: 20694886]

Stacey BHR, Pope F, 2020. Evaluation of ultrafine particle concentrations and size distributions at London Heathrow Airport. Atomspheric. Environ 222.

Waitz IALS, Lee JJ, 2005. MILITARY AVIATION AND THE ENVIRONMENT: HISTORICAL TRENDS AND COMPARISON TO CIVIL AVIATION. J. Aircr 42 (2).

Wang C, Geng H, Liu W, Zhang G, 2017. Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis. Medicine (Baltimore) 96 (18), e6696. [PubMed: 28471964]

Wei Y, Zhang JJ, Li Z, Gow A, Chung KF, Hu M, et al. , 2016. Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: findings from a natural experiment in Beijing. FASEB J. 30 (6), 2115–2122. [PubMed: 26891735]

Wing SE, Larson TV, Hudda N, Boonyarattaphan S, Fruin S, Ritz B, 2020. Preterm Birth among Infants Exposed to in Utero Ultrafine Particles from Aircraft Emissions. Environ. Health Perspect 128 (4), 47002. [PubMed: 32238012]

Wing SE, Larson TV, Hudda N, Boonyarattaphan S, Del Rosario I, Fruin S, et al. , 2022. Aircraft noise and vehicle traffic-related air pollution interact to affect preterm birth risk in Los Angeles. California. Sci Total Environ 829, 154678. [PubMed: 35314238]

Wu AH, Fruin S, Larson TV, Tseng CC, Wu J, Yang J, et al. , 2021. Association between Airport-Related Ultrafine Particles and Risk of Malignant Brain Cancer: A Multiethnic Cohort Study. Cancer Res. 81 (16), 4360–4369. [PubMed: 34167950]

Wu F, Tian FJ, Lin Y, 2015. Oxidative Stress in Placenta: Health and Diseases. Biomed Res. Int 2015, 293271. [PubMed: 26693479]

Xiang AH, Wang X, Martinez MP, Walthall JC, Curry ES, Page K, et al. , 2015. Association of maternal diabetes with autism in offspring. J. Am. Med. Assoc 313 (14), 1425–1434.

Xiang AH, Wang X, Martinez MP, Page K, Buchanan TA, Feldman RK, 2018. Maternal Type 1 Diabetes and Risk of Autism in Offspring. J. Am. Med. Assoc 320 (1), 89–91.

Yu X, 2019. Regional sources of airborne ultrafine particle number and mass concentrations in California. Atmos. Chem. Phys 19, 14677–14702.

Yu XVM, Kumar A, Hu J, Tanrikulu S, Soon ST, et al. , 2019. Regional sources of airborne ultrafine particle number and mass concentrations in California. Atmos. Chem. Phys 19, 14677–14702.

Table 1

Cohort characteristics and comparison between children without and with ASD.

	No ASD, N = 313,524	ASD, N = 4,554
Maternal Age at Delivery in years, Median (IQR)	30.4 (26.2, 34.3)	31.3 (27.5, 35.3)
Parity, N (%)		
0	109,889 (35 %)	1,843 (40 %)
1	102,843 (33 %)	1,493 (33 %)
2	83,074 (26 %)	901 (20 %)
Unknown	17,718 (5.7 %)	317 (7.0 %)
Maternal Race/Ethnicity, N (%)		
White	79,879 (25 %)	953 (21 %)
Black	29,212 (9.3 %)	446 (9.8 %)
Hispanic	158,848 (51 %)	2,299 (50 %)
Other	6,416 (2.0 %)	112 (2.5 %)
Asian/Pacific Islander	39,169 (12 %)	744 (16 %)
Maternal Education, N (%)		
High School	110,512 (35 %)	1,334 (29 %)
Some College	92,826 (30 %)	1,473 (32 %)
College & Post	107,180 (34 %)	1,713 (38 %)
Unknown	3,006 (1.0 %)	34 (0.7 %)
Census tract household annual income (thousands of US dollars), Median (IQR)	56 (42, 75)	56 (42, 75)
History of Comorbidity, N (%)	45,801 (15 %)	838 (18 %)
Maternal diabetes, N (%)	20,026 (6.4 %)	449 (9.9 %)
Maternal obesity (BMI ≥ 30 kg/m^2), N (%)		
No	146,961 (47 %)	2,304 (51 %)
Yes	52,299 (17 %)	1,049 (23 %)
Unknown *	114,264 (36 %)	1,201 (26 %)
Sex		
Male	159,143 (51 %)	3,700 (81 %)
Birth address within 20 km of military base	22,243 (7.1 %)	300 (6.6 %)

* Height and weight at each clinical visit were not recorded in KPSC EMR until late 2006; maternal BMI data were missing for children born between 2001 and 2006.

Table 2

Adjusted Hazard ratios (HR) of ASD in children associated with maternal exposure to aircraft $PM_{0.1}$ during pregnancy.

	HR (95 % CI) for Aircraft $PM_{0.1}$
Adjustment for other ambient pollution	
None[a]	1.016 (1.007–1.026)
Adjusted for total $PM_{0.1}$	1.016 (1.007–1.026)
Adjusted for total $PM_{2.5}$	1.017 (1.007–1.027)
Adjusted for on-road traffic $PM_{0.1}$	1.017 (1.007–1.027)
Adjusted for non-freeway near-roadway air pollution*	1.017 (1.008–1.027)
Adjusted for freeway near-roadway air pollution*	1.019 (1.009–1.028)
Adjusted for nighttime noise	1.016 (1.006–1.025)
Adjusted for daytime noise	1.011 (1.001–1.022)
Excluding mothers living within 20 km of military base[b]	1.037 (1.014–1.061)

All models were adjusted for birth year, medical center, maternal age, maternal ethnicity, maternal education, parity, history of comorbidity, income at age one, season of conception, pre-pregnancy diabetes mellitus, pre-pregnancy obesity, and child's sex.

*CALINE dispersion-modeled near-roadway air pollution.

[a]Single-pollutant model results.

[b]This analysis included 295,535 mothers-child pairs, excluding 22,543 pairs living within 20 km of the military bases.