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Gestational Diabetes Mellitus, Prenatal Air Pollution Exposure, and Autism Spectrum Disorder

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Abstract

Background—Ambient air pollution and maternal diabetes may affect common biological pathways underlying adverse neurodevelopmental effects. However, joint effects of maternal diabetes and air pollution on autism spectrum disorder (ASD) have not been studied.

Objective—We evaluated whether prenatal and early-life air pollution exposure interacts with maternal diabetes status to affect ASD risk.

Methods—This retrospective cohort study included 246,420 singleton children born in Kaiser Permanente Southern California hospitals in 1999–2009. Children were followed from birth until age 5, during which 2,471 ASD cases were diagnosed. Ozone (O_3), particulate matter <2.5 μm ($PM_{2.5}$) and <10 μm in aerodynamic diameter, and nitrogen dioxide measured at regulatory air monitoring stations were interpolated to estimate exposures during preconception and each

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Authors' contributions

AHX and RM served as co-senior authors on this study based on equal contributions and expertise in air pollution epidemiology (RM) and in the analytical approaches in this data set (AHX). HJ, AHX and RM designed the study and drafted the manuscript. HJ analyzed the data with contributions from SPE and AHX. All authors contributed to the interpretation of data, read and approved the final manuscript.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of University of Southern California and Kaiser Permanente Southern California. Consent to participate is not applicable since the study was based on de-identified electronic medical records data.

Availability of data and materials

The data that support the findings of this study are available from Kaiser Permanente Southern California but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of Kaiser Permanente Southern California.

Competing interests

The authors declare that they have no competing interests.

pregnancy trimester, and first year of life at each child's birth address. Hazard ratios (HRs) for ASD were estimated adjusting for birth year, KPSC service areas, and relevant maternal and child characteristics. For each exposure window, interactions were tested between pollutants and a 4-category maternal diabetes variable (none, GDM≥24 and <24 weeks' gestation, and pre-existing type 2 diabetes). For an exposure window with statistically significant global interaction between pollutant and diabetes ($p<0.05$), pollutant-associated HRs were estimated separately for each category of maternal diabetes.

Results—There were associations of ASD with preconception, first and third trimesters, and first year of life $PM_{2.5}$, but not with other pollutants. There were, however, interactions of maternal diabetes with first trimester and first year of life O_3. Increased ASD risk was associated with first trimester O_3 among mothers with GDM <24 weeks' gestation [adjusted HR 1.50 per 15.7 ppb O_3 (95% CI: 1.08–2.09)]. No O_3 associations with ASD were observed in other categories of maternal diabetes.

Conclusions—GDM onset early in pregnancy may increase children's susceptibility to prenatal O_3-associated ASD risk. These novel findings merit further investigation.

Keywords

Air pollution; gestational diabetes mellitus; autism; pregnancy

Introduction

Autism spectrum disorder (ASD) prevalence increased dramatically during 2000–2012 from 0.7% to 1.7% in the United States (Baio et al. 2018). The increase can only partly be explained by better ascertainment (Baio 2014). Emerging evidence from both human and animal studies has identified ambient particles and other criteria pollutants as potentially modifiable risk factors for ASD (Church et al. 2017; Lam et al. 2016; Li et al. 2017). ASD has also been associated with a broad spectrum of conditions characterized by maternal immune activation (Estes and McAllister 2016; Malkova et al. 2012), including maternal diabetes during pregnancy (Alderete et al. 2018). With the rising prevalence of maternal diabetes during the same period as increases in ASD prevalence (Albrecht et al. 2010), a few studies have consistently found positive associations with maternal diabetes, especially gestational diabetes mellitus (GDM) (Bowers and Zhang 2011; Wan et al. 2018; Xiang et al. 2018; Xiang et al. 2015; Xu et al. 2014).

Particulate air pollution has shown relatively consistent associations with ASD (Lam et al. 2016). The influence of particulate matter < 2.5 μm in aerodynamic diameter ($PM_{2.5}$) on ASD risk may vary by exposure time windows, including some studies reporting associations with exposure during the first and third trimesters of pregnancy, and others showing associations with exposure during the first year of life (Flores-Pajot et al. 2016; Jo et al. 2019). Fewer studies have found prenatal and postnatal NO_2 associations with ASD risk (Flores-Pajot et al. 2016). Relatively less studied is ozone (O_3). Two studies found O_3 exposures during the second and third trimesters, and early postnatal period, respectively, were associated with ASD (Becerra et al. 2013; Jung et al. 2013). A recent study found O_3

to be a risk factor for autism only in the setting of increased child genetic copy number burden (Kim et al. 2017).

Causes of ASD in prenatal and early postnatal life are likely multi-factorial (Lyall et al. 2014). Yet few epidemiologic studies have evaluated effects of common exposures like air pollution and maternal diabetes to see if they have independent or synergistic effects. Exposure to O_3, for example, has neuroinflammatory effects, perhaps mediated by O_3-induced oxidative stress and systemic inflammation (Block and Calderón-Garcidueñas 2009; Campbell et al. 2009; Campbell et al. 2014; Rossignol and Frye 2014). Maternal hyperglycemia during pregnancy also causes systemic oxidative stress and chronic inflammation, resulting in the associated inflammatory intrauterine environment that may have adverse effects on fetal brain development (Bowers and Zhang 2011). Thus, the overlapping timing of inflammation and systemic oxidative stress induced by both O_3 and diabetes may potentially affect common biological pathways that could further increase the susceptibility to ASD, which is also characterized by systemic oxidative stress, in children (Bowers and Zhang 2011; Estes and McAllister 2016; Kim et al. 2017).

Based on recent evidence of neurotoxic effects of air pollution and of maternal diabetes, we hypothesized that the children born to mothers with diabetes during pregnancy would have a higher risk of ASD in early childhood associated with pollutant exposures than mothers without diabetes. However, one of the main challenges in examining the effects of combinations of risk factors is the large sample size required to achieve statistical power to assess these interactions. In a large, population-based pregnancy cohort from Kaiser Permanente Southern California (KPSC), we examined diabetes-specific associations of ASD with prenatal and first year of life regional pollutant exposures.

Methods

Study design and population

This retrospective cohort study included mother-child pairs with singleton deliveries in KPSC hospitals between January 1, 1999, and December 31, 2009 in 14 service areas located across Southern California (Additional file 1: Figure S1). The residential addresses extracted from birth certificate records were linked by a unique KPSC membership identifier. The primary analysis included 246,420 mother-child pairs with children enrolled as KPSC plan members at age one year, as previously described (Xiang et al. 2015), after excluding children with birth certificate addresses outside Southern California (n = 636) or addresses that could not be accurately geocoded (n = 4406), because of an address missing or not matchable to a U.S. postal service address. Follow-up was accrued until the first occurrence of 1) clinical diagnosis of ASD; 2) last date of continuous KPSC plan membership; 3) death from any cause; or 4) age five. Children were censored at age five to ensure the same follow-up time for the entire cohort, regardless of birth date. Thus, the youngest children, born in 2009, were followed through 2014. Both outcome and covariate data were extracted from the KPSC electronic medical records (EMR). Both the KPSC and the University of Southern California Institutional Review Boards approved this study.

Outcome data on ASD

KPSC neurodevelopment screening procedures included an abbreviated Checklist for Autism in Toddlers (CHAT) (Baron-Cohen et al. 2000) administered at 18- and 24-month well child visits. Children failing the screening were referred to a pediatric developmental specialist for further evaluation and ASD diagnosis (Xiang et al. 2018; Xiang et al. 2015). The presence or absence of ASD during follow-up was identified by International Classification of Diseases, Ninth Revision (ICD-9) codes 299.x or equivalent KPSC codes from the EMR from at least two separate visits, an approach validated previously (Coleman et al. 2015; Xiang et al. 2018).

Exposure assessment

Birth certificate residential addresses were geocoded using MapMarker USA Version 28.0.0.11. Exposure metrics at each geocoded address included regional O_3, $PM_{2.5}$, PM ≤10 μm in diameter (PM_{10}), and nitrogen dioxide (NO_2). Monthly averages for each pollutant between 1998–2009 were obtained from data compiled from the EPA regional air quality monitoring network. Exposure at each address was assigned based on the monthly inverse distance-squared weighted average from up to four closest regional monitoring stations within 50 km for each pollutant these. For geocoded address locations within 0.25 km of a monitor, data only from that monitoring station were used. Although the distance-weighted approach has limited accuracy in areas with sparse monitoring networks, performance is acceptable in Southern California due to the dense geographical network of historical measurements covering the region. In a previous Southern California study evaluating this method using leave-one-out validation for monthly monitoring station data, the coefficients of determination (r^2) were 0.76, 0.73, 0.53, and 0.46 for O_3, NO_2, $PM_{2.5}$ and PM_{10}, respectively, with lower R^2 values for PM attributed to the local (primary emission) dust component that is not regional (Eckel et al. 2016). Bias was less than 1 ppb or 1 $\mu g/m^3$. Each address was assigned the monthly average of the 24-hour concentrations of $PM_{2.5}$, PM_{10}, and NO_2. For O_3, the monthly average of daily maximum 8-hour concentrations was estimated. Based on the mother's last menstrual period, averages of the monthly concentrations were calculated during preconception, each trimester, the entire pregnancy and the first year of life. Preconception exposure was defined as 12 weeks before mother's last menstrual period date. First trimester exposure was defined as 0–12 weeks, second trimester as 13–26 weeks, and third trimester as 27 weeks to birth. The monthly average exposures during months overlapping these different time periods were weighted by the number of days in each period.

Maternal diabetes

As previously described (Xiang et al. 2015), maternal diabetes during index pregnancy was categorized based on ICD-9 codes, anti-diabetic medication use, and glucose values from 1-hour 50-g glucose challenge tests and/or oral glucose tolerance tests administered during pregnancy: no diabetes; GDM; and type 2 diabetes before pregnancy. KPSC follows the American College of Obstetricians and Gynecologists guidelines for screening for GDM (Committee on Practice Bulletins-Obstetrics 2018). Diagnosis of GDM was based on laboratory values confirming a plasma glucose level of 200mg/dL or higher on the glucose

challenge test or at least 2 plasma glucose values meeting or exceeding the following values on the 100-g or 75-g oral glucose tolerance test: fasting, 95 mg/dL; 1 hour, 180 mg/dL; 2 hours, 155 mg/dL; and 3 hours, 140 mg/dL (American Diabetes Association 2004; Xiang et al. 2015). Gestational age at GDM diagnosis was calculated using the date of the first glucose test result that met the GDM diagnosis criteria, date of delivery, and gestational age at delivery available in the electronic medical record. Based on previous study that found higher risk of ASD among mothers with GDM diagnosed earlier in pregnancy (Xiang et al. 2015) and routine screening of GDM starting at 24 weeks' gestation, GDM exposure was further categorized as diagnosis before or after 24 weeks' gestation.

Covariates

Potential confounders chosen a priori, based on previous associations with ASD in this cohort (Xiang et al. 2015), included sex of the child and maternal age at delivery, parity, education, self-reported race/ethnicity, history of comorbidity [≥1 diagnosis of heart, lung, kidney, or liver disease; cancer], and median family household income in the census tract of residence. A missing category was used for categorical covariates with missing data (parity [n = 4,125], education [n = 2,222], and household income [n = 1,850]). To account for temporal changes in ASD incidence rate and pollution levels, we adjusted for birth year, and to account for broad geographical characteristics associated with ASD, we adjusted for the 14 KPSC service areas. Additional pregnancy-related covariates included maternal pre-eclampsia/eclampsia, preterm birth (< 37 weeks vs. ≥ 37 weeks), and congenital anomalies.

Statistical analyses

Pearson partial correlations were calculated between pollutants within each exposure window and across multiple exposure windows, adjusted for birth year and KPSC service areas. Cox proportional hazards models were used to estimate the ASD hazard ratios (HRs) associated in separate models with each pollutant exposure, adjusting for potential confounders and for potential correlation due to multiple siblings born to the same mother by specifying family as a random effect. Additionally adjusting for covariates potentially on the causal pathway (maternal pre-eclampsia/eclampsia, preterm birth and congenital anomalies) did not change estimated effects by >10%, so these variables were not included in the final models. Restricted cubic splines identified no evidence of non-linear associations of ASD with pollutants, so pollutants were treated as continuous variables and modeled linearly. Both goodness-of-fit test and extended Cox models identified no violations of proportional hazards assumptions for all covariates, and HRs for pollutant associations were in the same direction across all follow-up time periods (1–2, >2–3, >3–4, >4–5 years of child's age).

All models were adjusted for calendar birth year as a continuous covariate and for the 14 KPSC medical center service areas, for maternal age, parity, maternal race/ethnicity, maternal education, census tract median household income, maternal history of comorbidities before pregnancy, and child sex. Because the analysis of pollutant effects on ASD were adjusted for year and service areas, we scaled each HR to be representative of exposure contrasts both within-service area and within-year. Pollutant estimates were scaled to the difference of the 95^{th} to the 5^{th} percentile of the deviations of each pregnancy

exposure from the average within the same service area in the same year. Deviations were calculated as each residential pollutant exposure value minus the within-service area, within-year mean exposure. For example, for each of the 14 service areas and 11 years (154 in total) the average $PM_{2.5}$ residential exposure and the deviations of individual $PM_{2.5}$ from this average were calculated. The 95th percentile (3.0 μg/m^3) minus the 5th percentile (−3.5 μg/m^3) of $PM_{2.5}$ deviation distributions resulted in the within-service area and within-year scale of 6.5 μg/m^3 for $PM_{2.5}$. The same procedure was used to calculate the within-service area, within-year scales for other pollutants: 16.1 μg/m^3 for PM_{10}, 10.4 ppb for NO_2, and 15.7 ppb for O_3.

HRs were also estimated for ASD association with a 4-level categorical variable for maternal diabetes (none [reference], GDM diagnosed <24 weeks' gestation, GDM diagnosed ≥24 weeks' gestation, and pre-existing type 2 diabetes). To evaluate the hypothesis that the effects of air pollution on ASD risk would be different among mothers with diabetes during pregnancy compared to mothers without diabetes, we tested for global interactions between this 4-level categorical variable for maternal diabetes and each pollutant separately in each exposure window (preconception, entire pregnancy, each trimester, and first year of life).

For pollutants and exposure windows for which the global interaction was statistically significant, we estimated separate HRs for the effect of each pollutant exposure on ASD risk among mothers with no diabetes, GDM diagnosed <24 weeks' gestation, GDM diagnosed ≥24 weeks' gestation, and pre-existing type 2 diabetes. We also examined the joint effects of maternal diabetes and pollutant exposures on ASD risk by fitting a model with the 12-category exposure (4-category diabetes by pollutant tertiles), using the lowest tertile of pollutant exposure in mothers without diabetes as reference. To evaluate the exposure dose response associations within each diabetes category, we tested for a linear trend of HRs from the lowest tertile to the highest tertile of pollutant exposure separately for mothers with no diabetes, GDM diagnosed <24 weeks' gestation, GDM diagnosed ≥24 weeks' gestation, and pre-existing type 2 diabetes. This was done by treating the categorical pollutant tertiles (coded as 1, 2, 3) as continuous variables and adjusting for potential confounders.

Two-sided statistical tests were conducted at an alpha level of 0.05, and precision was measured using 95% confidence intervals (CIs). Data analyses were conducted using SAS 9.4 (SAS Institute, Inc, Cary, NC) and R, version 3.0.2 (64 bit).

Results

Unadjusted annual ASD incidence rates (per 1,000 child-years) increased with birth year from 1.93 in 1999 to 4.03 in 2009 (Additional file 1: Figure S2) (Jo et al. 2019), a period during which national prevalence rates of ASD were also increasing (Baio 2014). There were 2471 children diagnosed with ASD in the cohort.

Levels of O_3, $PM_{2.5}$, PM_{10}, and NO_2 during the 9 months of pregnancy, averaged across the entire 2000–2009 period, were 41.6 parts per billion (ppb), 17.9 micrograms per meter-cubed (μg/m^3), 38.1 μg/m^3, and 25.1 ppb, respectively. O_3 levels remained relatively stable

across years (Additional file 1: Figure S3) (Jo et al. 2019). However, mean levels of both $PM_{2.5}$ and NO_2 decreased across years from 1999–2009. PM_{10} levels fluctuated across time, potentially reflecting variable precipitation across the years.

Levels of pollutants during the entire pregnancy averaged across the 1999–2009 period also varied between KPSC service areas (Additional file 1: Figure S4). Highest mean levels of O_3 were in Moreno Valley (52.5 ppb), and lowest mean levels of O_3 were in Downey (31.8 ppb). Highest levels of mean $PM_{2.5}$, PM_{10} and NO_2 were in Ontario (21.6 μg/m^3, 49.7 μg/m^3, 31.2 ppb, respectively), and lowest levels of $PM_{2.5}$, PM_{10}, and NO_2 were in San Diego (13.1 μg/m^3, 30.7 μg/m^3, 18.0 ppb).

Levels of $PM_{2.5}$, PM_{10}, NO_2, and O_3 during pregnancy averaged across the entire study were similar for mothers with no diabetes, GDM diagnosed <24 weeks' gestation, GDM diagnosed ≥24 weeks' gestation, and pre-existing type 2 diabetes (Additional file 1: Table S1).

Table 1 shows the associations of ASD risk with maternal and child characteristics, adjusting for birth year and KPSC service areas. Older maternal age, being first born, higher maternal education, history of maternal comorbidity, <$30,000 median family household income in the census tract of residence, and being a boy were associated with increased risk of ASD. In contrast, mothers who were multiparous and residing in a census tract with >$50,000 median household income were less likely to give birth to child with ASD.

Children born to mothers with pre-existing type 2 diabetes were at significantly increased risk of ASD compared to mothers without diabetes, after adjusting for birth year and KPSC service areas (HR = 1.60, 95% CI: 1.26, 2.16; Table 2). This association was modestly attenuated after further adjusting for other confounders (HR = 1.45, 95% CI: 1.11, 1.91). Children born to mothers with GDM diagnosed before 24 weeks' gestation were also at an increased risk of ASD; however, this positive association was attenuated after further adjusting for other confounders (HR = 1.24, 95% CI: 0.95, 1.62). In contrast, there was little association between GDM diagnosed after 24 weeks and risk of ASD (HR = 0.92, 95% CI: 0.77, 1.09).

The third trimester O_3 association with ASD was weakly positive (HR = 1.05, 95% CI: 0.99, 1.11; P=0.11), after adjusting for confounders (Table 3). In other exposure windows, there were weak associations of ASD with O_3, which were not statistically significant. There were associations with $PM_{2.5}$ exposure, including during preconception (HR = 1.11 per 6.5 μg/m^3, 95% CI: 1.03, 1.20), the entire pregnancy (HR = 1.17 per 6.5 μg/m^3, 95% CI: 1.04, 1.33), the first trimester (HR = 1.10, 95% CI: 1.02, 1.19) and the third trimester (HR = 1.08, 95% CI: 1.00, 1.18). Increased risk of ASD was also associated with first year of life $PM_{2.5}$ exposure (HR = 1.21, 95% CI: 1.05, 1.40). None of the associations of ASD with either PM_{10} or NO_2 were statistically significant.

During the first trimester (p = 0.047) and first year of life (p = 0.007), the global interactions between continuous O_3 exposure and the 4-level categorical variable for maternal diabetes (no diabetes, GDM diagnosed at <24 weeks and ≥24 weeks, and pre-existing diabetes) were statistically significant (Additional file 1: Table S2). No other pollutants in any exposure

window had statistically significant global interactions with the 4-level categorical variable for maternal diabetes.

For all O_3 exposure windows, we estimated separate HRs associated with the risk of ASD among mothers with no diabetes, GDM diagnosed at <24 weeks and ≥24 weeks, and pre-existing diabetes. Among mothers with GDM <24 weeks' gestation, increased ASD risk was associated with residential O_3 exposure during entire pregnancy and during the first trimester (HR = 1.96 per 15.7 ppb, 95% CI: 1.24, 3.11 and HR = 1.50 per 15.7 ppb, 95% CI: 1.08, 2.09, respectively; Table 4). A large increased risk was also associated with the child's O_3 exposure during the first year of life (HR = 2.01 per 15.7 ppb, 95% CI: 0.67, 6.07); however, this association was not statistically significant. No statistically significant ASD-O_3 associations within each exposure window were observed among mothers without diabetes, with GDM ≥24 weeks' gestation, or with pre-existing type 2 diabetes. In sensitivity analyses, we co-adjusted these first trimester and first year of life O_3 associations for NO_2 exposure, which was negatively correlated with O_3 (first trimester R = −0.42, first year of life R = −0.49; Additional file 1: Table S3). The estimates of O_3 effect were not substantially different after adjustment (results not shown). Other pollutants had weak associations with O_3 during these exposure windows.

To further evaluate the joint effects of maternal diabetes and O_3 on ASD risk, we fit a model with a 12-category variable combining the four maternal diabetes categories (no diabetes, GDM diagnosed at <24 weeks and ≥24 weeks, and pre-existing diabetes) by tertiles of O_3, using the lowest tertile of O_3 exposure in mothers without diabetes as the referent group (Table 5), with tertiles classified based on first trimester O_3 exposure averaged across all years (<37.7 ppb, 37.7-<44.3 ppb, and ≥44.3 ppb). By re-parameterizing this model to assess the effect of tertiles of O_3 among each diabetes category (using the first tertile as a reference), we identified statistically significant trends in O_3 effect estimates among mothers with GDM <24 weeks' gestation during the first trimester (p for trend across tertiles = 0.03) and during the first year of life (p for trend = 0.01; Figure 1). In the first trimester, the middle and high tertile associations with ASD were 1.26 (95% CI: 0.80, 1.72) and 1.97 (95% CI: 1.55, 2.39) compared with the lowest tertile; in the first year of life, the middle and high tertile associations were 1.90 (95% CI: 1.48, 2.32) and 1.93 (95% CI: 1.42, 2.44) compared with the lowest tertile. ASD was associated with pre-pregnancy diabetes, but there was little evidence for an O_3 exposure gradient in risk.

Discussion

In this first population-based cohort study examining the joint effects of air pollution and maternal diabetes during pregnancy on the risk of ASD, we observed associations of ASD with $PM_{2.5}$ during multiple prenatal and early postnatal exposure windows and with pre-existing maternal type 2 diabetes, results which we have reported previously in this cohort (Jo et al. 2019; Xiang et al. 2018). Although no associations of ASD with O_3 by itself were observed, there was substantial heterogeneity of effects by categories of diabetes/GDM during the first trimester and first year of life. Prenatal exposure to O_3 during the first trimester was associated with increased risk of ASD among mothers with GDM diagnosis before 24 weeks' gestation. In models examining effects of O_3 tertiles, there were

statistically significant associations among mothers diagnosed before 24 weeks both in the first trimester and first year of life. We did not find any heterogeneity in associations of ASD with other pollutants by maternal diabetes status. Because we observed no main effects of O_3 on ASD, caution is warranted in the interpretation of the significance of these diabetes category-specific effects.

Two epidemiologic studies have reported associations of O_3 with increased risk of ASD (Becerra et al. 2013; Jung et al. 2013), according to a recent review (Zhao et al. 2018). One study reported ASD associations with average O_3 exposure during entire pregnancy (odds ratio (OR) = 1.06 per 11.54 ppb, 95% CI: 1.01, 1.12) (Becerra et al. 2013), but not during the first trimester (OR = 1.00 per 11.54 ppb, 95% CI: 0.97, 1.03). Small increases in ASD risk were associated with second and third trimester exposures (OR = 1.02 per 11.54 ppb, 95% CI: 1.00, 1.05; OR = 1.04 per 11.54 ppb, 95% CI: 1.01, 1.06). A study from Taiwan also reported ASD association with postnatal O_3 exposure in the year preceding newly diagnosed ASD cases under 3 years of age (HR = 1.59, 95% CI: 1.42–1.78) (Jung et al. 2013). Neither of these studies examined interactions of O_3 with diabetes.

Our results suggest that O_3 by itself may not be causing ASD, but that first trimester and first year of life O_3 exposure-associated ASD requires a second “hit” from GDM during a critical early window of brain development during gestation for ASD to occur (Estes and McAllister 2016). However, although diabetes prior to pregnancy was strongly associated with ASD, O_3 was not associated with any further increased ASD risk in children of these mothers. If the observed interactions of O_3 with early onset GDM were causal, it is not clear why this interaction was not observed with pre-existing diabetes.

A limited number of animal studies provide potential explanations for why O_3 might cause ASD in the context of GDM. Adverse neurobehavioral effects have been observed after gestational exposure to O_3 in rodents (Bignami et al. 1994; Kavlock et al. 1980; Petruzzi et al. 1995; Sorace et al. 2001). Autism-related behavior deficits, including reduced social interaction and increased repetitive behavior, have been reported after early gestational O_3 exposure (Petruzzi et al. 1995). O_3-induced oxidative stress and associated systemic inflammation during pregnancy that have adverse affects on the developing fetal brain may contribute to the pathogenesis of ASD (Block et al. 2012). Moreover, maternal immune activation-related pregnancy complications such as hyperglycemia during pregnancy share common biological pathways with O_3 (Estes and McAllister 2016; Malkova et al. 2012), which causes chronic inflammation and systemic oxidative stress, and the associated inflammatory intrauterine environment that could adversely affect neurodevelopment (Bowers and Zhang 2011; Wan et al. 2018). Autism itself is associated with increased oxidative stress both in peripheral blood (Gorrindo et al. 2013) and in the brain (Rossignol and Frye 2014). Consequently, exposure to simultaneous “hits” of inflammation and systemic oxidative stress from early gestation GDM and O_3 may further increase children’s susceptibility for ASD in early childhood (Bowers and Zhang 2011; Estes and McAllister 2016; Rajagopalan and Brook 2012; Rossignol and Frye 2014). These synergistic biologic effects of O_3 and GDM may together explain our findings of O_3-associated increased risk of ASD among children born to mothers with GDM diagnosed before 24 weeks of pregnancy.

Other studies have identified synergistic effects of air pollution. A recent study that found no main effect of O_3 also observed an interaction of increased O_3 exposure with child copy number burden that was associated with increased ASD risk (Kim et al. 2017). The investigators also speculated that the key role of O_3 in producing systemic oxidative stress might increase risk associated with copy number variation. Thus, O_3 may increase risk of ASD through multiple pathways. Lower folic acid intake and high-risk genes have also been shown to have synergistic interactions with NO_2- and O_3-associated ASD (Goodrich et al. 2018; Kim et al. 2017; Volk et al. 2014). We previously reported that first trimester $PM_{2.5}$-associated ASD risk was stronger in boys in this cohort (HR = 1.18 per 6.5 μg/m^3; 95% CI, 1.08–1.27) compared to girls (HR = 0.90 per 6.5 μg/m^3; 95% CI, 0.76–1.07) (Jo et al. 2019). We examined the interaction of air pollution with gestational diabetes, because GDM is a known and common risk factor that has increased in prevalence over the course of the ASD epidemic (Albrecht et al. 2010), and is amenable to intervention to reduce the burden of ASD. In addition to diabetes, there are many other conditions, including infections during pregnancy, that result in maternal immune activation (Estes and McAllister 2016; Malkova et al. 2012) and are therefore, candidates for future exploration of interactions with air pollution to increase susceptibility to ASD in studies like the KPSC cohort resource with large sample sizes.

An important consideration is that our results were based on multiple comparisons that increased the chance of incorrectly rejecting a null hypothesis (i.e. Type 1 error). Our findings were not based on an *a priori* hypothesis that diabetes would specifically augment O_3 effects on ASD but not other pollutants. If we adjusted for multiple comparisons of the 20 interactions in total across 4 pollutants and 5 exposure windows (Additional file 1: Table S2; excluding entire pregnancy), then none of these interactions would have been statistically significant at $p = 0.05/20 = 0.0025$. Thus, our results should be interpreted as hypothesis-generating, although the interaction of O_3 x type of diabetes during the first year of life ($p = 0.007$) would have been close to significant.

This study has several strengths. The large study sample provided statistical power to assess an interaction between pollutants and maternal diabetes. Selection bias was unlikely to have influenced the results, because the cohort did not self-select and also had a high annual average 95% retention through age 5 after cohort enrollment (Xiang et al. 2015). Unlike many health systems that have only recently adopted an EMR, the KPSC EMR system has been refined and improved since its implementation in the early 1990's. Incident ASD ascertainment occurred in a clinical setting using standardized diagnostic algorithms developed through the EMR (Coleman et al. 2015), and possible systematic bias in ASD diagnosis between medical centers in the KPSC system was addressed by adjusting for KPSC service areas in our analyses. Chances of GDM misclassification were reduced compared to other studies self-reporting GDM and time of onset, because we had information on gestational age at diagnosis from the EMR, although some women with GDM may have had diabetes prior to pregnancy that was not identified until detected during pregnancy; they would have been incorrectly classified as GDM. In general, misclassification might be expected to have attenuated estimates of O_3 effects and of heterogeneity of effects across subgroups of diabetes.

The analysis controlled for various individual-level covariates that were available through the EMR, such as maternal education, that are difficult to obtain without standardized procedures in a single healthcare system. It is possible that the results were confounded by other local geographical factors such as crime and some other features of urban environments, but these would have had to vary jointly with diabetes subgroups to account for the interactions with O_3 that we observed. We also fully accounted for temporal trends of ASD and pollutants across study period, as well as for any temporal trends in ascertainment of ASD by adjusting for birth year in our analyses. The KPSC membership comprised approximately 16% of the census reference population, so results are generalizable to the population of working Southern California families (Koebnick et al. 2012). Because Southern California has large pollutant exposure gradients representative of ranges and extremes across the U.S., the results are broadly relevant to the U.S. and other countries with similar exposures.

There were some limitations. Perhaps most important, our findings should be considered to be hypothesis generating and may not reflect a true biologic interaction between GDM and O_3 since adjustment for multiple comparisons was not taken into account. Exposure concentrations estimated at the birth address were used as a proxy for personal exposure. Residential mobility during pregnancy and the first year of life, and time of mother or child away from home would have resulted in exposure measurement error. If the effect of this bias were non-differential with respect to the outcome, then the true effect of exposure could have been larger than we observed (Rothman et al. 2008).

Conclusions

GDM diagnosed before the end of the second trimester of pregnancy may increase children's susceptibility to prenatal and early life O_3-associated ASD risk. However, these hypothesis-generating findings need to be replicated in future studies with large study populations. Such studies may begin to explain the multifactorial etiology of diseases such as ASD. Further toxicological study is also needed to better understand the biological basis and timing of susceptibility during neurodevelopment and of differences in neurobehavioral effects of O_3 exposures by maternal diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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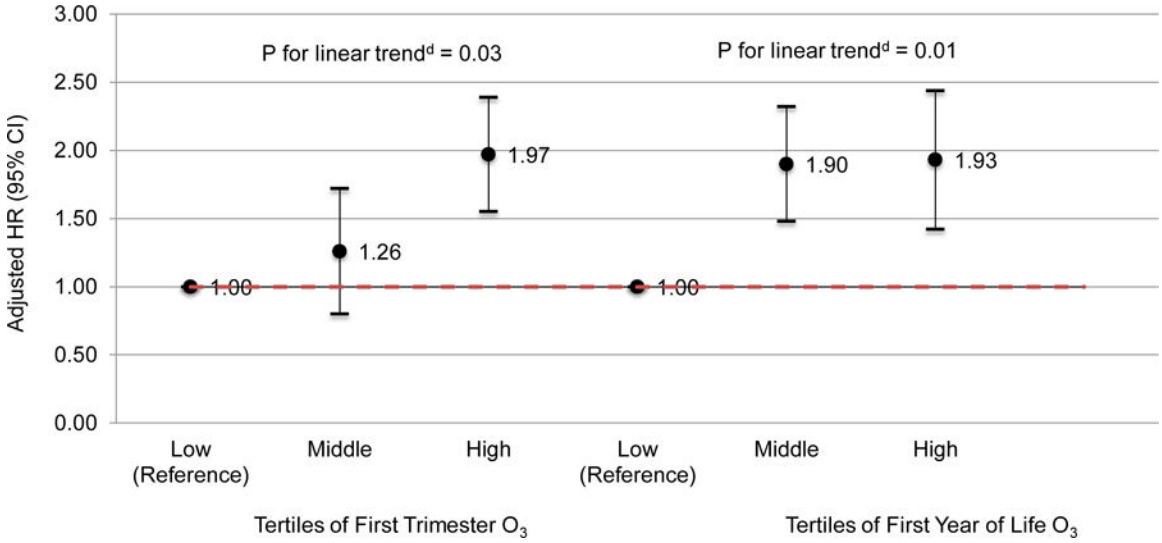

Figure 1.

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs)[a,b] for joint associations of exposures to GDM diagnosis at <24 weeks' gestation and tertiles[c] of O_3 with risk of ASD

[a]Separate models were estimated for O_3 exposures during the first trimester and first year of life, and estimates were adjusted for birth year, KPSC medical center service areas, maternal age, parity, maternal race/ethnicity, maternal education, census tract median household income, maternal history of comorbidities before pregnancy, and family specified as a random effect.

[b]Circles represent the HRs and whiskers represent the 95% CIs.

[c]Each O_3 tertile group is labeled as low, middle, high on the x-axis.

[d]P for linear trend of HRs across O_3 tertiles groups among mothers with GDM diagnosis at <24 weeks' gestation <0.05

Table 1.

Associations of maternal and child characteristics with risk of ASD

Characteristics	No. With ASD/Total	Hazard Ratio (95% CI)[a]
Maternal		
Age (per year)		1.03 (1.02–1.04)
Parity[b]		
0	1,123 / 96,964	1.00 (Reference)
1	802 / 78,494	0.87 (0.79–0.95)
≥2	511 / 66,837	0.65 (0.58–0.73)
Education[b]		
High school or lower	811 / 101,770	1.00 (Reference)
Some college	761 / 68,729	1.33 (1.19–1.48)
College graduate or higher	888 / 73,699	1.31 (1.17–1.46)
Household annual income[b,c]		
<$30,000	223 / 20,069	1.32 (1.12–1.57)
$30,000-$49,999	845 / 82,638	1.00 (Reference)
$50,000-$69,999	810 / 78,926	0.91 (0.82–1.02)
$70,000-$89,999	365 / 39,758	0.77 (0.67–0.89)
≥$90,000	228 / 25,029	0.70 (0.59–0.82)
Race/ethnicity		
Non-Hispanic white	569 / 62,774	1.00 (Reference)
Non-Hispanic black	266 / 23,855	1.09 (0.92–1.30)
Hispanic	1,216 / 126,123	0.95 (0.85–1.07)
Asian/Pacific Islander	374 / 29,774	1.13 (0.98–1.31)
Other	46 / 3,894	1.26 (0.90–1.74)
History of comorbidity[d]		
No	2,170 / 224,366	1.00 (Reference)
Yes	301 / 22,054	1.32 (1.15–1.51)
Child		
Female	441 / 120,112	1.00 (Reference)
Male	2,030 / 126,308	4.77 (4.28–5.32)

[a] Specified family as a random effect, and birth year and KPSC medical center service areas were adjusted as covariates.

[b] Hazard ratios not reported for children with missing data categories in these variables.

[c] Based on census tract median

[d] ≥1 diagnosis of heart, lung, kidney, or liver disease; cancer in mothers

Table 2.

Minimally adjusted and fully adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for associations of categories of maternal diabetes with risk of ASD

Diabetes during pregnancy	No. With ASD/Total	Minimally adjusted HR[a] (95% CI)	Fully adjusted HR[b] (95% CI)
No diabetes	2,167 / 221,330	1.00 (Reference)	1.00 (Reference)
GDM ≥24 weeks' gestation	160 / 16,112	1.01 (0.85–1.20)	0.92 (0.77–1.09)
GDM <24 weeks' gestation	73 / 4,893	1.40 (1.08–1.81)	1.24 (0.95–1.62)
Pre-existing type 2 diabetes	71 / 4,085	1.65 (1.26–2.16)	1.45 (1.11–1.91)

[a]Models for minimally adjusted hazard ratios specified family as a random effect, and birth year and KPSC medical center service areas were adjusted as covariates.

[b]Models for fully adjusted hazard ratios were adjusted for birth year, KPSC medical center service areas, maternal age, parity, maternal race/ethnicity, maternal education, census tract median household income, maternal history of comorbidities before pregnancy (≥1 diagnosis of heart, lung, kidney, liver disease or cancer), child sex, and family specified as a random effect.

Table 3.

Minimally adjusted and fully adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the association of each pollutant birth address exposure with risk of ASD

Pollutant exposure window	Minimally adjusted HR[a,b,d] (95% CI)	Fully adjusted HR[a,c,d] (95% CI)
O_3		
Preconception	0.99 (0.93–1.04)	0.98 (0.93–1.04)
Entire pregnancy	1.13 (0.99–1.28)	1.10 (0.95–1.26)
First trimester	0.97 (0.92–1.03)	0.97 (0.91–1.02)
Second trimester	1.04 (0.98–1.10)	1.03 (0.97–1.10)
Third trimester	1.05 (1.00–1.11)	1.05 (0.99–1.11)
First year of life	1.00 (0.87–1.16)	0.94 (0.80–1.11)
$PM_{2.5}$		
Preconception	1.13 (1.06–1.22)	1.11 (1.03–1.20)
Entire pregnancy	1.18 (1.06–1.32)	1.17 (1.04–1.33)
First trimester	1.11 (1.03–1.20)	1.10 (1.02–1.19)
Second trimester	1.07 (0.99–1.15)	1.06 (0.97–1.14)
Third trimester	1.09 (1.01–1.18)	1.08 (1.00–1.18)
First year of life	1.22 (1.07–1.39)	1.21 (1.05–1.40)
PM_{10}		
Preconception	1.06 (0.97–1.15)	1.05 (0.96–1.14)
Entire pregnancy	1.03 (0.91–1.16)	1.01 (0.89–1.15)
First trimester	1.02 (0.93–1.11)	1.00 (0.92–1.10)
Second trimester	1.03 (0.94–1.12)	1.02 (0.93–1.12)
Third trimester	1.01 (0.93–1.11)	1.00 (0.91–1.10)
First year of life	1.06 (0.94–1.21)	1.06 (0.92–1.22)
NO_2		
Preconception	1.09 (1.01–1.18)	1.07 (0.99–1.17)
Entire pregnancy	1.08 (0.96–1.22)	1.05 (0.91–1.20)
First trimester	1.04 (0.97–1.13)	1.03 (0.95–1.11)
Second trimester	1.02 (0.95–1.10)	1.01 (0.93–1.09)
Third trimester	1.04 (0.96–1.12)	1.02 (0.94–1.11)
First year of life	1.15 (1.00–1.31)	1.12 (0.97–1.30)

[a]Separate models were estimated for each time window.

[b]Models for minimally adjusted hazard ratios specified family as a random effect, and birth year and KPSC medical center service areas were adjusted for as covariates.

[c]Models for fully adjusted hazard ratios were adjusted for adjusted for birth year, KPSC medical center service areas, maternal age, parity, maternal race/ethnicity, maternal education, census tract median household income, maternal history of comorbidities before pregnancy (≥1 diagnosis of heart, lung, kidney, liver disease or cancer), child sex, and family specified as a random effect.

[d]Hazard ratios were scaled per 6.5 μg/m^3 $PM_{2.5}$; per 16.1 μg/m^3 PM_{10}; per 10.4 ppb NO_2; and per 15.7 ppb O_3.

Table 4.

Maternal diabetes-specific adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for O_3 per 15.7 ppb within each exposure window associated with risk of ASD

	No diabetes	Gestational diabetes mellitus		Pre-existing type 2 diabetes	*P* for interaction
		Diagnosis at ≥24 weeks' gestation	Diagnosis at <24 weeks' gestation		
No. With ASD/Total	**2,167 / 221,330**	**160 / 16,112**	**73 / 4,893**	**71 / 4,085**	
O_3 exposure window	**HR[a] (95% CI)**	**HR[a] (95% CI)**	**HR[a] (95% CI)**	**HR[a] (95% CI)**	
Preconception	0.98 (0.92–1.03)	0.95 (0.77–1.17)	1.14 (0.76–1.72)	1.09 (0.85–1.38)	0.707
Pregnancy	1.10 (0.95–1.27)	0.83 (0.53–1.29)	1.96 (1.24–3.11)	1.14 (0.53–2.46)	0.067
First trimester	0.95 (0.90–1.01)	0.90 (0.69–1.18)	1.50 (1.08–2.09)	1.07 (0.69–1.64)	0.047*
Second trimester	1.04 (0.98–1.11)	0.86 (0.72–1.03)	1.29 (0.95–1.76)	1.05 (0.66–1.65)	0.165
Third trimester	1.06 (0.99–1.12)	1.03 (0.78–1.35)	0.97 (0.73–1.30)	0.99 (0.73–1.35)	0.847
First year of life	0.93 (0.78–1.10)	0.72 (0.50–1.02)	2.01 (0.67–6.07)	1.17 (0.63–2.17)	0.007*

[a]Separate interaction models were estimated for each exposure window, which adjusted for birth year, KPSC medical center service areas, maternal age, parity, maternal race/ethnicity, maternal education, census tract median household income, maternal history of comorbidities before pregnancy (≥1 diagnosis of heart, lung, kidney, liver disease or cancer), child sex, and family specified as a random effect.

*Global P for interaction of each exposure window with 4-level categorical variable of maternal diabetes <0.05.

Table 5.

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for joint associations of exposures to maternal diabetes and tertiles of O_3 with risk of ASD

	No diabetes	Gestational diabetes mellitus		Pre-existing type 2 diabetes
		Diagnosis at ≥24 weeks' gestation	Diagnosis at <24 weeks' gestation	
	HR[a] (95% CI)	HR[a] (95% CI)	HR[a] (95% CI)	HR[a] (95% CI)
First trimester				
Low tertile (<37.7 ppb)	Reference	0.94 (0.70–1.26)	0.87 (0.53–1.44)	1.54 (0.97–2.44)
Middle tertile (37.7-<44.3 ppb)	0.97 (0.87–1.09)	1.01 (0.75–1.34)	1.10 (0.69–1.74)	1.37 (0.87–2.17)
High tertile (≥44.3 ppb)	0.94 (0.84–1.06)	0.71 (0.50–1.00)	1.71 (1.12–2.60)	1.33 (0.81–2.18)
First year of life				
Low tertile (<37.7 ppb)	Reference	1.07 (0.81–1.41)	0.87 (0.54–1.39)	1.41 (0.91–2.20)
Middle tertile (37.7-<44.3 ppb)	1.21 (1.06–1.38)	1.10 (0.82–1.48)	1.65 (1.08–2.51)	1.60 (0.98–2.60)
High tertile (≥44.3 ppb)	0.97 (0.80–1.18)	0.69 (0.46–1.05)	1.68 (1.01–2.81)	1.66 (1.01–2.75)

[a]Models were adjusted for birth year, KPSC medical center service areas, maternal age, parity, maternal race/ethnicity, maternal education, household income, maternal history of comorbidities before pregnancy, and family specified as a random effect.