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Particulate Matter Exposure, Prenatal and Postnatal Windows of Susceptibility, and Autism Spectrum Disorders

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Background: Recent studies suggest that exposure to traffic-related air pollutants, including particulate matter (PM), is associated with autism spectrum disorder (autism).

Methods: Children with autism were identified by records-based surveillance (n = 645 born in North Carolina in 1994, 1996, 1998, or 2000, and n = 334 born in the San Francisco Bay Area in California in 1996). They were compared with randomly sampled children born in the same counties and years identified from birth records (n = 12,434 in North Carolina and n = 2,232 in California). Exposure to PM less than 10 μm (PM_{10}) at the birth address was assigned to each child by a geostatistical interpolation method using daily concentrations from air pollution regulatory monitors. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for a 10 $\mu g/m^3$ increase in PM_{10} within 3-month periods from preconception through the child's first birthday, adjusting for year, state, maternal education and age, race/ethnicity, and neighborhood-level urbanization and median household income, and including a nonparametric term for week of birth to account for seasonal trends.

Results: Temporal patterns in PM_{10} were pronounced, leading to an inverse correlation between the first- and third-trimester concentrations (r = −0.7). Adjusted ORs were, for the first trimester, 0.86 (95% CI = 0.74–0.99), second trimester, 0.97 (0.83–1.15), and third trimester, 1.36 (1.13–1.63); and, after simultaneously including first- and third-trimester concentrations to account for the inverse correlation, were: first trimester, 1.01 (0.81–1.27) and third trimester, 1.38 (1.03–1.84).

Conclusions: Our study adds to previous work in California showing a relation between traffic-related air pollution and autism, and adds similar findings in an eastern US state, with results consistent with increased susceptibility in the third-trimester.

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Autism spectrum disorder (autism) is a developmental disability characterized by impaired social interaction, communication problems, and restricted and stereotyped behavior patterns. Autism manifests in functional deficits in relations and work achievement that last a lifetime, affecting an average of 1 in 68 children in the US.[1] Identifying environmental chemical exposures that contribute to autism is important, as they represent potential targets for environmental pollution reduction efforts that could prevent autism.

A potential role for air pollutants from vehicle traffic in causing autism is important to examine for several reasons. First, air pollutants are very common exposures that are amenable to policy control. Second, evidence points to a plausible biological pathway wherein components of traffic pollution cause a systemic inflammatory response,[2–4] a pathophysiological state that has deleterious impacts on the developing nervous system and has been linked to autism.[5–8] Third, several recent epidemiologic studies have found increased risk of autism associated with some traffic-related, criteria air pollutants.[9–11] One such pollutant, particulate matter, arises in part from traffic, and includes components of various sizes: particulate matter (PM_{10}), which is less than 10 μm in diameter, and fine particulate matter ($PM_{2.5}$), which is less than 2.5 μm and is included within the PM_{10} fraction. Two of the previous studies, conducted in California, found associations between both $PM_{2.5}$ and PM_{10} in pregnancy and autism.[10,11] An additional study in Taiwan examined PM exposures without finding associations with autism, but this study addressed air pollutants throughout childhood, not the prenatal and early postnatal periods that we focus on here.[12]

To further explore associations between traffic-related air pollutants and autism, we conducted a study of PM_{10} in a new

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geographic region, North Carolina, together with new data from California. We focused on air pollutant exposures occurring from preconception through the child's first birthday because these are the periods of brain development during which an environmental chemical insult may perturb neurodevelopment.[13,14] Our study design improved on previous studies by: (1) including children with the broader spectrum of autism from population-based surveillance, (2) adjusting for season of birth—a known predictor of both autism and air pollutant levels, (3) estimating air pollutant concentrations using a geospatial interpolation method with refined temporal resolution, allowing the examination of 14-day critical windows of susceptibility, and (4) adjusting for the cyclical associations of PM_{10} from one time period to another. We hypothesized that higher exposures to PM_{10} would be associated with increased prevalence of autism, and that exposures during certain prenatal and postnatal periods would be more strongly associated than others.

METHODS

Study Design and Sample

We implemented a population-based, case-cohort design in select regions of North Carolina and California, by combining data from autism surveillance systems with birth records. Our study population was defined as all singleton children without evidence of adoption or infant death, with maternal residence at birth in areas subsequently under autism surveillance. In North Carolina, this included approximately 17,500 children born in 1994, 18,000 in 1996, 20,500 in 1998, and 32,000 in 2000 from the central North Carolina counties of Alamance, Chatham, Davidson, Durham, Forsyth, Guilford, Orange, and Randolph Counties in all years, with the addition of Caswell and Rockingham counties in 1998 and 2000 and Wake County in 2000. In California, this included 77,550 children born in 1996 from 6 Bay Area counties: Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara.

For this study, birth certificate rosters were sampled for a comparison group that represented the source population, as follows: In North Carolina, we selected a 15% random sample of births in the study counties and birth years without regard to autism status, stratified by birth year. After removing infant deaths, adoptions, and multiple births, the North Carolina dataset included 2,645 children (1994), 2,729 children (1996), 3,088 children (1998), and 4,806 children (2000). In California, we selected a 3% random sample of 1996 births in the study area, and, after removing multiple births, infant deaths, known autism cases, and 16 children without a street address (which included 14 adopted children), the California control sample included 2,311 children.

Autism Ascertainment and Case Subgroups

Autism case-finding was conducted under public health surveillance in compliance with all applicable regulations for the protection of human health and educational data. The addition of birth certificate data and the assignment of air pollutant exposures for this project was approved by Institutional Review Boards at the University of North Carolina and the California Committee for the Protection of Human Subjects.

Children with autism were identified through age 8 years by active, records-based surveillance programs sponsored by the Centers for Disease Control and Prevention (CDC)—the Autism and Developmental Disabilities Monitoring Network.[15–16] Methodology of this network uses a standardized case definition of Autism Spectrum Disorder, based on the *Diagnostic and Statistical Manual, Fourth Edition–Text Revision* (DSM-IV-TR),[17] implemented by reviewing children's developmental records from participating health and educational agencies. Details on the methodology of the Autism and Developmental Disabilities Monitoring network and the service agencies participating in North Carolina and California have been previously described.[18–21]

The Autism and Developmental Disabilities Monitoring network recorded variables that further characterized the phenotype for children meeting the case definition of autism. Information on the presence of a co-occurring intellectual disability was available in both states, although the sources of this data varied slightly, as follows. In both states, intellectual disability was defined as IQ ≤ 70 on standardized intelligence tests recorded in educational or medical records. In North Carolina but not California, intellectual disability was included as a developmental disorder under active network surveillance. In California, we also included whether a designation of intellectual disability was made for children served by the California Department of Developmental Services. An additional autism subgrouping variable corresponding to autism type/severity was available only in North Carolina; Autism and Developmental Disabilities Monitoring clinicians classified a child based on a standardized algorithm corresponding to DSM-IV-TR for: (1) Autistic Disorder, or (2) Autism Spectrum Disorder-Not Otherwise Specified (ASD-NOS), which required fewer or less severe symptoms and included Asperger's Disorder and Pervasive Developmental Disorder.

In North Carolina, children were identified as cases if they resided within the surveillance regions when they were 8 years of age regardless of where they were born, whereas California children were identified as cases from statewide surveillance records only if they were born in the surveillance region. To assure correspondence between states and between the case groups and the source populations, we linked children with autism to state vital records and restricted the study sample to singleton children born within the surveillance counties, resulting in 680 children with autism in North Carolina and 346 children with autism in California.

Particulate Matter Exposure

PM_{10} exposure was assigned based on each child's birth certificate address. Both sites had access to the complete street address as recorded on birth certificates. We used

a multi-method approach to optimize the accuracy of spatial location.[22] First, we corrected and standardized all addresses using ZP4 software (version February/March 2012, Semaphore Corp., Monterey, CA). Next, we used ArcGIS (version 10.0, ESRI, Redlands, CA) to obtain latitude and longitude coordinates corresponding to each child's address by geocoding to a specific point along a street segment, assuming a consistent pattern of address numbers within a street segment. For North Carolina geocoding, the streets database was from US Census Tigerline files.[18] For California geocoding, we used the Online Geocoding Locator Service—U.S. Streets (based on 2010 Q4 street reference data, NAVTEQ, Chicago, IL). NAVTEQ is a commercial provider of address location data that has been shown to provide greater positional accuracy compared with other sources such as TeleAtlas.[22] After this initial automated run using ArcGIS, for both states we manually parsed through all unmatched addresses (resident addresses that were not located) and any potential mismatches (scores ≤ 95 out of 100 or addresses located outside the study area) using Google Maps (Map data ©2011 Google, Sanborn) satellite imagery to review, confirm, or rematch. This multi-method approach resulted in 648 cases (95%) and 12,477 controls (94%) geo-located in North Carolina and 336 cases (97%) and 2,289 controls (99%) geo-located in California.

Daily PM_{10} concentrations were assigned for each day for each child, starting 1 year before the child's birth to 1 year following birth, totaling 731 daily concentrations. Concentrations were estimated with a moving-window kriging approach using the Bayesian Maximum Entropy geostatistical method.[23–26] Primary model inputs were publicly-available PM_{10} concentrations from regulatory monitors—the Environmental Protection Agency Air Quality System.[27] We included daily concentrations or daily averages from regulatory monitors collecting hourly data, when at least 20 hourly concentrations were available.[27] These PM_{10} concentrations were used in the Bayesian Maximum Entropy framework to generate a concentration for each address/day, using nonlinear estimators to interpolate daily PM_{10} concentrations simultaneously in space and time, where concentrations from closer monitors and more recent days contributed more weight in calculations. We added the moving-window improvement to the Bayesian Maximum Entropy method that assumed that PM_{10} is not homogenous/stationary across both states, but only within a local neighborhood around each child that consisted of the 50 monitoring sites closest to the child's residence.[28] The daily PM_{10} data in that local neighborhood were pooled and used to calculate a child-specific covariance, from which a space/time separable exponential covariance model was obtained by least squares fitting.

Primary Statistical Analysis

Analyses were restricted to children who were not missing key variables, primarily maternal education, which excluded 0.7% of the records that were geo-located.

We constructed average PM_{10} concentrations within 8 *a priori* exposure periods, each approximately 3 months in length, representing the preconceptual period, each pregnancy trimester, and quarters during the first year of life (as defined in Table 1). Some exposure windows relied on an estimated date of conception, calculated as: (date of birth minus [gestational age in days minus 14]). We imputed gestational age for 0.9% of children who were missing gestational age or had biologically implausible gestational ages (defined as less than 19 weeks or more than 44 weeks). The imputation used a predictive model (R^2 of 53%) built from this dataset, which included birth weight (as continuous + quadratic term), child race (categories), child sex, state, maternal age (continuous), and cross-products between birth weight × child sex and birth weight × child race. For each exposure period, summed PM_{10} concentrations were divided by the number of days within the period. Because some children were born prior to the completion of a typical gestation, they lacked third-trimester exposures (5 cases and 41 controls) or had shorter-duration third-trimester exposures (eg, less than 60 days, 63 cases, and 739 controls).

PM_{10} concentrations calculated for rolling 14-day exposure windows during pregnancy were also examined for associations with autism. For these exposure windows, children contributed exposure time only prior to their individual date of birth, to avoid mixing prenatal and postnatal exposures. When constructing this dataset, we aligned comparable prenatal windows (eg, first 14 days following conception) using the estimated date of conception instead of the date of birth. Grouping by conception was preferred because nervous system developmental milestones progress in similar timeframes from conception, whereas aligning by the date of birth would have resulted in grouping children at different fetal developmental ages. To reduce the impact of random variability present with daily concentrations and to enhance pattern detection for the impact of short exposures, we calculated rolling 14-day averages progressing by 1-day increments.

For each PM_{10} exposure window (the eight 3-month a priori periods and each 14-day period) we estimated odds ratios (ORs) and 95% confidence intervals (CIs) of autism for a 10 $\mu g/m^3$ increase in PM_{10} concentration. A linear coding of PM_{10} was chosen because nonparametric curves (LOESS) between PM_{10} concentrations and autism exhibited monotonic trends and because this coding provided the best fit, as indicated by the lowest Akaike Information Criterion value,[29] when compared with alternate PM_{10} coding: categorical, logarithmic, and quadratic transformations.

ORs for the association of PM_{10} with autism were estimated using logistic generalized additive models (GAMs) that allowed for the inclusion of parametric and nonparametric (eg, curved) model terms, using PROC GAM in SAS 9.2 (Cary, NC). We considered season of birth as an important potential confounder because it has been shown to predict autism risk in some studies,[30,31] although not all,[32] and because PM_{10} concentrations also exhibit seasonal trends. Because we were

specifically addressing short (eg, 3-month) periods of exposure, it was important to account for temporal patterns (eg, confounding by season of birth). A nonparametric (LOESS) term for the calendar week of the child's birth (weeks 1–52) was included in the GAM to allow for temporally-precise, curvilinear adjustment for these trends. PM_{10} and all other confounders were included as parametric terms, with confounder coding selected using the Akaike Information Criterion. We adjusted for sampling and design variables (state, year, and state × year), sociodemographic factors from birth certificate data with evidence of association with autism and air pollutant levels: race/ethnicity (white non-Hispanic/black non-Hispanic, Asian non-Hispanic, other race non-Hispanic, Hispanic); maternal education (log-transformed years of education), maternal age (log-transformed); and neighborhood-level factors from census year 2000 block group data:[33,34] median household income (categories of $1,000 per year: less than 35, 35–65, 65–85, more than 85) and urbanization (100% urban or less than 100% urban).

Pronounced seasonal variation in air pollutants led to correlations (negative and positive) between exposure windows. Due to our examination of PM_{10} in 3-month time periods, these exposures were analogous to copollutant confounders, with the possibility that 1 PM_{10} concentration may have an independent association with the outcome, and, through its correlation with a PM_{10} concentration in another time period, may inflate or deflate (ie, confound) the observed OR. To adjust for this potential confounding influence, we also included terms for an additional PM_{10} window in separate models, such as adjusting the estimate of third-trimester PM_{10} for the concentration in the first trimester (and every other exposure window).

We evaluated modification by a priori factors of interest (child's sex and state), using likelihood ratio tests of cross-products between PM_{10} and the factor, and by evaluating the consistency of ORs stratified by the factor. Child's sex was examined because autism risk is 4-fold higher in boys and because child's sex has been shown to be a marker of susceptibility for other environmental exposures.[35,36] We examined modification by state because of study design differences between states (eg, surveillance source agencies) and seasonal and air pollutant speciation differences between NC and CA.

Sensitivity Analyses

Autism is a heterogeneous grouping of disorders, with case subgroups that may have different causal influences. To assess whether certain case subgroups were more or less susceptible to the influences of PM_{10} exposures, we examined the following groups separately: children with autism and co-occurring intellectual disability (n = 383, both states), autism without co-occurring intellectual disability (n = 572, both states), autistic disorder (n = 523, North Carolina only) and ASD-NOS (n = 100, North Carolina only).

To assess whether preterm birth played a role in the findings, we also repeated our primary adjusted models restricted to children born at term (at least 258 days or 37 weeks).

To assess the impact of the interpolation of gestational age on our results, we repeated our primary adjusted models, excluding children with missing, or out-of-range, gestational age.

Information on maternal tobacco use in pregnancy and marital status was available only in North Carolina. To assess the confounding influences of these factors, we compared ORs adjusted for variables included in our primary model (above) to ORs additionally adjusted for marital status (yes/no) and tobacco use in pregnancy (yes/no), within the North Carolina sample.

Because PM_{10} concentrations were estimated based on residential address, we performed a sensitivity analysis to evaluate the potential impact of residential mobility on our results. Using a subset of the North Carolina sample, we repeated our main analyses restricted to families who did not move during pregnancy. As part of a separate study including children from this sample born in 1994 and 1996 in North Carolina, we obtained address history in conjunction with LexisNexis, which provided dates when an address was reported to public sources such as utility companies, voter registration, the department of motor vehicles, etc. Within the group with pertinent address information (the traced group), we operationalized not moving during pregnancy as evidence that either the mother or father had the same address on the estimated date of conception as the address listed on the birth certificate. We then calculated adjusted ORs between PM_{10} and autism among children who could be traced, and among the nested subset of children whose families did not move during their gestation.

RESULTS

Characteristics of children differed between states (Table 2). For example, North Carolina included more black non-Hispanic children (28%, compared with 9% in California) and California included more Hispanic children (31%, compared with 9% in North Carolina). In California, mothers were older at the child's birth and the study areas were of higher income and more urban compared with North Carolina.

Compared with controls, children with autism were more likely to be boys, to be white non-Hispanic, and to have better-educated and older mothers (Table 2). Children with autism were also less likely to be born in winter months in North Carolina (OR for winter vs. summer birth = 0.84 [95% CI = 0.67 to 1.06]) and were more likely to be born in winter months in California = 1.13 ([0.82 to 1.56]).

We examined the seasonal patterns of PM_{10} exposure through the lens of average PM_{10} concentration in the third-trimester for study participants. We found that third-trimester PM_{10} concentrations exhibited different seasonal patterns in the 2 states, with higher exposures for children born in summer months in North Carolina and those born in fall and winter months in California, with minimal overlap in the

TABLE 1. PM_{10} Exposure Period Definitions

Exposure Period	Start Day	End Day	Length (days)
Preconception	80 days before EDC[a]	1 day before EDC	68–80
Trimester 1	EDC[b]	89 days after EDC[b]	89
Trimester 2	1 day after trimester 1 end	88 days after trimester 2 start[c]	34–88
Trimester 3	1 day after trimester 2 end	DOB	0–121
Pregnancy	EDC[b]	DOB	122–297
Postnatal quarter 1	1 day after DOB	91 days after DOB	91
Postnatal quarter 2	92 days after DOB	182 days after DOB	91
Postnatal quarter 3	183 days after DOB	273 days after DOB	91
Postnatal quarter 4	274 days after DOB	365 days after DOB	92

EDC indicates estimated date of conception; DOB, date of birth.
[a]Exposure data were not available for the full 80-day preconception period for children with a gestational period of greater than 300 days (n = 86).
[b]The term "EDC" was defined as follows: DOB - (# of gestational days—14)
[c]46 children did not have a full 88-day trimester 2 and did not enter the third-trimester.

PM_{10} distributions (eg, interquartile ranges) across seasons (Figure 1). Marked cyclical associations were also apparent through examining the correlation structure across developmental time windows, with inverse correlations between PM_{10} concentrations in a priori periods in opposite seasons (eg, −0.7 between the first and third trimesters) and positive correlations between periods 1 year apart (eg, 0.7 between preconception and the first postnatal quarter) (eTable 1, http://links.lww.com/EDE/A829). Long-term trends in yearly PM_{10} concentrations were not apparent, and concentrations were similar for North Carolina and California (Figure 1).

Associations between PM_{10} exposures and autism varied depending on the timing of the exposure. For example, we observed an inverse association for a 10 $\mu g/m^3$ increase in PM_{10} during the first trimester (adjusted OR = 0.86 ([0.74 to 0.99]) and a positive association for third-trimester PM_{10} (1.36 [1.13 to 1.63]) (Table 3). After adjusting for pollutant levels for additional 3-month exposure periods, results for the third trimester were not substantially changed (eg, with observed ORs of third-trimester PM_{10} adjusted for each of the 7 other 3-month time periods ranging from 1.30 to 1.38). In contrast, associations in other a priori windows were attenuated after adjusting for the third-trimester PM_{10} concentrations. For example, the first-trimester PM_{10} OR was attenuated from 0.86 to 1.01 (0.81–1.27) (Table 3). Similarly, a slight positive association observed initially with PM_{10} in the fourth postnatal quarter (1.19 ([0.98 to 1.43]) was attenuated after accounting for third-trimester PM_{10}, (0.99 [0.75 to 1.29]). When PM_{10} was averaged over the entire pregnancy, the adjusted OR was 1.08 (0.72–1.61).

Suspected time-invariant confounders such as maternal education and neighborhood income did not substantially influence associations; adjusted ORs were similar to unadjusted ORs (Table 3). In contrast, season of birth appeared to cause downward confounding in North Carolina, where the OR for PM_{10} in the third trimester and autism, prior to and following inclusion of the nonparametric term for week of birth, was 1.26 (95% CI = 0.81–1.73) compared with 1.40 (1.13–1.72) (as in Table 4). Week of birth did not appear to confound in California, with the same association estimated as 1.18 (0.81–1.73) without including week of birth, and 1.16 (0.80–1.69) when adjusting for week of birth.

Stratified by state, ORs were similar between states for most PM_{10} exposure periods except modification by state in postnatal quarters 1 and 3 (Table 4). The higher and more robust associations with the third-trimester PM_{10} concentration did not differ between the 2 states. In general, ORs from California were closer to the null compared with those from North Carolina, suggesting that overall findings may be driven by the patterns in North Carolina data.

When 14-day rolling exposure windows were examined, higher autism risk corresponded with short windows of PM_{10} exposure during late pregnancy in both states. The highest ORs were found for exposures during pregnancy weeks 31 to 36. (Figure 2)

Child sex did not modify the patterns of association between PM_{10} and autism (eTable 2, http://links.lww.com/EDE/A829).

The patterns of association observed for third-trimester PM_{10} exposure held when case subgroups were examined separately (Table 5).

We conducted several analyses to examine whether our assumptions materially affected the results. Results were unchanged when only children from term pregnancies were included, with an adjusted OR for third-trimester PM_{10} and autism of 1.42 (1.17–1.73); the OR was 1.48 (1.07–2.05) after also adjusting for first-trimester PM_{10}. Results were also unchanged when we dropped children with imputed gestational age (results not shown), and after adjusting for marital status and maternal tobacco use in pregnancy (North Carolina only, results not shown).

For our sensitivity analysis regarding the impact of residential mobility, we were able to trace the relevant address history corresponding to pregnancy for 82 children with autism and 1,721 controls (46% and 35%, respectively, of children eligible

TABLE 2. Characteristics[a] of Children with Autism Spectrum Disorders and Controls, by State

	North Carolina				California			
	Autism (n = 645)		Controls (n = 12,434)		Autism (n = 334)		Controls (n = 2,232)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Birth year								
1994	75	(12)	2,365	(19)	—	—	—	—
1996	105	(16)	2,557	(21)	334	(100)	2,232	(100)
1998	148	(23)	2,925	(24)	—	—	—	—
2000	317	(49)	4,587	(37)	—	—	—	—
Sex								
Boy	537	(83)	6,348	(51)	291	(87)	1,162	(52)
Girl	108	(17)	6,086	(49)	43	(13)	1,070	(48)
Race								
White non-Hispanic	409	(63)	7,520	(60)	142	(43)	869	(39)
Black non-Hispanic	193	(30)	3,421	(28)	27	(8)	192	(9)
Asian non-Hispanic	2	(0)	54	(0)	78	(23)	406	(18)
Other non-Hispanic	15	(2)	338	(3)	11	(3)	76	(3)
Hispanic	26	(4)	1,101	(9)	76	(23)	689	(31)
First-born								
Yes	345	(53)	5,604	(45)	155	(46)	970	(43)
No	300	(47)	6,829	(55)	179	(54)	1,262	(57)
Season of birth								
Spring (Mar, Apr, May)	158	(24)	2,984	(24)	81	(24)	572	(26)
Summer (Jun, Jul, Aug)	176	(27)	3,156	(25)	85	(25)	598	(27)
Fall (Sep, Oct, Nov)	164	(25)	3,173	(26)	84	(25)	538	(24)
Winter (Dec, Jan, Feb)	147	(23)	3,121	(25)	84	(25)	524	(23)
Maternal education								
< High school	84	(13)	2,561	(21)	44	(13)	471	(21)
High school degree or some college	306	(47)	6,061	(49)	173	(52)	1,068	(48)
College degree	255	(40)	3,812	(31)	117	(35)	693	(31)
Maternal age (years)								
≤22	106	(16)	3,209	(26)	38	(11)	396	(18)
23–34	422	(65)	7,704	(62)	217	(65)	1,421	(64)
≥35	117	(18)	1,521	(12)	79	(24)	415	(19)
Married								
Yes	481	(75)	8,559	(69)	NA	—	NA	—
No	164	(25)	3,875	(31)	—	—	—	—
Tobacco use during pregnancy								
Yes	72	(11)	1,599	(13)	NA	—	NA	—
No	573	(89)	10,827	(87)	—	—	—	—
Median household income per year[b]								
<$35,000	189	(29)	4,192	(34)	21	(6)	220	(10)
$35,000–<64,999	365	(57)	6,725	(54)	163	(49)	954	(43)
$65,000–<84,999	61	(9)	1,099	(9)	82	(25)	651	(29)
≥$85,000	30	(5)	418	(3)	68	(20)	407	(18)
100% urban[b]								
Yes	384	(60)	7,165	(58)	320	(96)	2,130	(95)
No	261	(40)	5,269	(42)	14	(4)	102	(5)
PM_{10} concentration (μg/m^3); mean (SD)								
Preconception	23.9	(4.8)	24.3	(5.0)	23.3	(5.5)	23.5	(5.5)
Trimester 1	23.6	(4.5)	24.2	(4.8)	23.6	(5.0)	23.7	(4.9)
Trimester 2	23.3	(3.8)	23.8	(4.0)	24.3	(4.7)	24.1	(4.5)
Trimester 3	24.1	(4.0)	24.0	(4.0)	23.1	(3.2)	22.9	(3.1)
Postnatal quarter 1	23.8	(4.0)	23.7	(4.0)	21.8	(2.5)	22.0	(2.4)
Postnatal quarter 2	23.2	(4.0)	23.7	(4.1)	22.6	(1.6)	22.6	(1.6)
Postnatal quarter 3	23.3	(3.8)	23.8	(4.1)	22.2	(1.8)	22.1	(1.6)
Postnatal quarter 4	23.7	(4.1)	23.7	(4.1)	22.3	(2.1)	22.3	(2.0)

Autism indicates Autism Spectrum Disorder; NA, not available; PM_{10}: Particulate Matter (10 microns in diameter or less).
[a]No. (%), unless otherwise specified.
[b]Census 2000 block group variable.

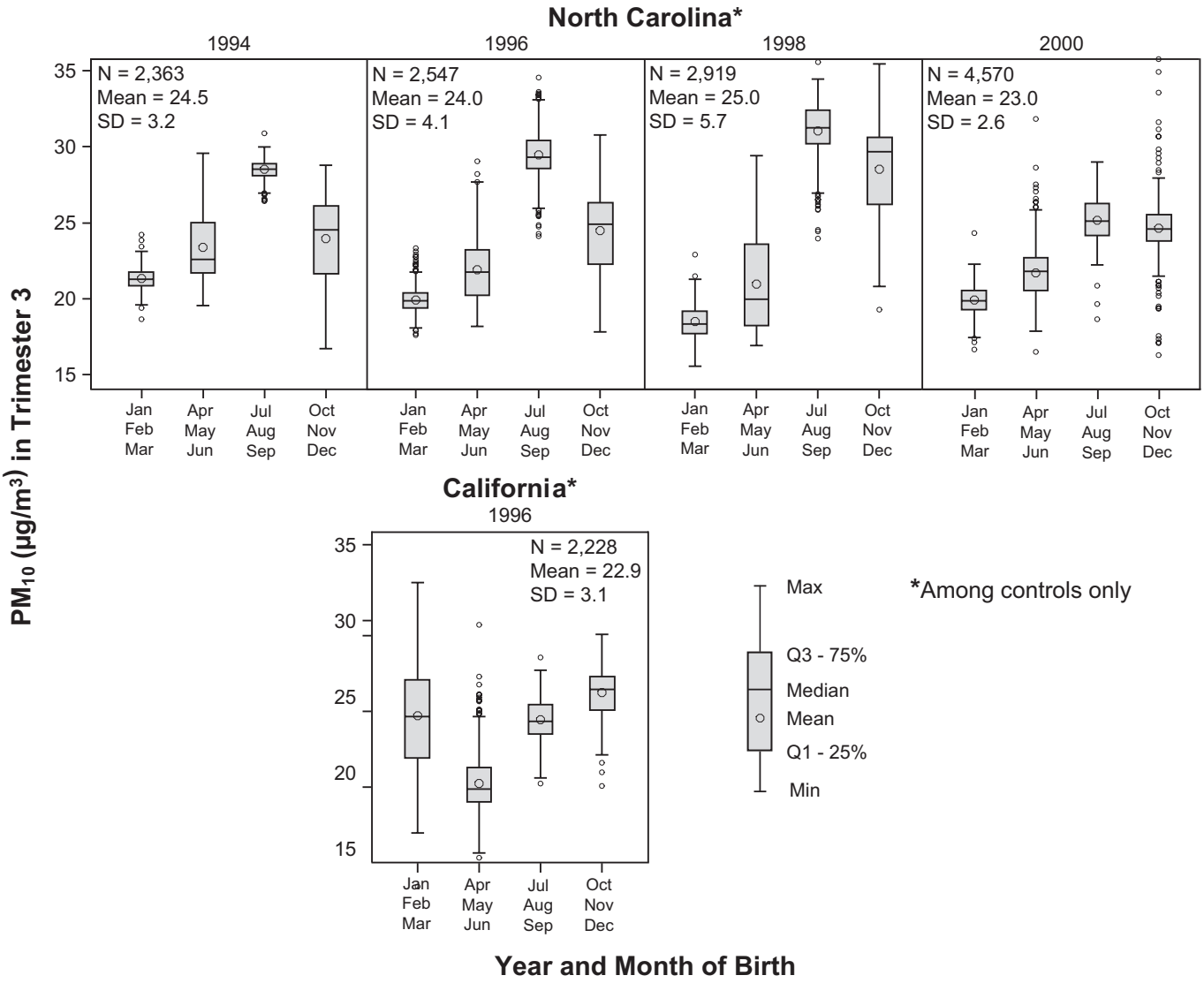

FIGURE 1. Boxplots illustrating seasonal variations in particulate matter (PM_{10}) exposures among controls during the third-trimester of pregnancy by state and birth year. In North Carolina, late-pregnancy exposure levels are higher for children born in the summer months, with lower levels for those born in winter. In California, higher late-pregnancy exposures occur for children born in the fall and winter, with lower levels for those born in the spring.

for address tracing). Traced families differed from untraced families; for example, traced families had older mothers and were from neighborhoods with higher median income (eTable 3, http://links.lww.com/EDE/A829). Results for traced children were similar to the results from all North Carolina children and also exhibited reasonable precision. For example, adjusted ORs were not elevated for first-trimester PM_{10} (0.88 [0.55 to 1.39]), whereas ORs were elevated for third-trimester PM_{10} (2.17 [1.22 to 3.86]), and remained so after also adjusting for first-trimester PM_{10}: 2.28 (0.95–5.46). Among those traced, we found that 66 children with autism (80% of traced) and 1,008 controls (59% of traced) did not change residences during pregnancy, and we expected that our assigned PM_{10} concentration would better correspond to early pregnancy for these families. Results restricted to these families were similar in pattern to all other groups, showing elevated associations for PM_{10} in the third-trimester. Adjusted ORs were, for first-trimester PM_{10}, 1.14 (0.67–1.95), for third-trimester PM_{10}, 2.60 (1.37–4.92), and for third-trimester PM_{10} also adjusted for first-trimester PM_{10}, 2.73 (1.07–6.95).

DISCUSSION

Among children born in the mid-to late-1990s in regions of North Carolina and California, we found that exposure to PM_{10} during the third-trimester of pregnancy was associated with increased risk of autism. This association was not accounted for by season of birth, mother's education, neighborhood income or urbanization, or the cyclical pattern of changing PM_{10} during early pregnancy or the first year of life.

TABLE 3. Associations of PM_{10} (10 μg/m³ increase) and Autism During Perinatal Exposure Windows for North Carolina (Born 1994–2000) and California (Born 1996) (979 Austism Cases; 14,666 Controls)

			Additionally Adjusted for a Perinatal Exposure Window[c]							
			Preconception	Trimester 1	Trimester 2	Trimester 3	Postnatal Quarter 1	Postnatal Quarter 2	Postnatal Quarter 3	Postnatal Quarter 4
	Unadjusted[a]	Adjusted[b]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Preconception	0.97 (0.85–1.11)	0.94 (0.82–1.08)	—	0.94 (0.83–1.08)	0.84 (0.67–1.06)	0.97 (0.85–1.11)	0.87 (0.71–1.05)	0.98 (0.86–1.13)	0.87 (0.73–1.03)	0.98 (0.85–1.12)
Trimester 1	0.88 (0.77–1.02)	0.86 (0.74–0.99)	0.85 (0.74–0.99)	—	0.86 (0.74–0.99)	1.01 (0.81–1.27)	0.87 (0.75–1.00)	0.92 (0.75–1.12)	0.88 (0.76–1.02)	0.89 (0.74–1.07)
Trimester 2	0.94 (0.80–1.11)	0.97 (0.83–1.15)	0.83 (0.63–1.09)	0.94 (0.80–1.11)	—	0.93 (0.79–1.09)	1.02 (0.80–1.30)	0.92 (0.78–1.09)	1.06 (0.85–1.33)	0.93 (0.79–1.10)
Trimester 3[d]	1.22 (1.01–1.46)	1.36 (1.13–1.63)	1.36 (1.13–1.63)	1.38 (1.03–1.84)	1.37 (1.14–1.64)	—	1.36 (1.13–1.63)	1.30 (1.00–1.71)	1.33 (1.10–1.59)	1.37 (1.06–1.77)
Postnatal quarter 1	1.08 (0.89–1.31)	1.09 (0.90–1.32)	1.26 (0.96–1.66)	1.08 (0.89–1.31)	1.11 (0.83–1.47)	1.09 (0.90–1.33)	—	1.06 (0.87–1.29)	0.98 (0.74–1.29)	1.09 (0.90–1.32)
Postnatal quarter 2	0.83 (0.69–1.01)	0.76 (0.63–0.93)	0.77 (0.63–0.93)	0.81 (0.62–1.07)	0.75 (0.61–0.91)	0.92 (0.68–1.23)	0.77 (0.63–0.94)	—	0.76 (0.62–0.92)	0.79 (0.61–1.03)
Postnatal quarter 3	0.85 (0.70–1.04)	0.85 (0.70–1.04)	0.76 (0.59–0.98)	0.89 (0.73–1.09)	0.82 (0.62–1.06)	0.89 (0.73–1.09)	0.84 (0.63–1.12)	0.83 (0.68–1.01)	—	0.88 (0.72–1.08)
Postnatal quarter 4	1.12 (0.92–1.35)	1.19 (0.98–1.43)	1.17 (0.97–1.43)	1.09 (0.85–1.41)	1.20 (0.99–1.46)	0.99 (0.75–1.29)	1.18 (0.98–1.43)	1.07 (0.83–1.39)	1.14 (0.94–1.39)	—

PM_{10} indicates particulate matter (10 microns in diameter or less).

[a]Odds ratios for all models were estimated using logistic generalized additive models (GAMs). Unadjusted GAM models included categorical design terms for state and birth year.

[b]Adjusted GAM models additionally included parametric terms for race/ethnicity (white non-Hispanic, black non-Hispanic, Asian non-Hispanic, other non-Hispanic, Hispanic) maternal education (no. of years of education log-transformed), maternal age (log-transformed), Census 2000 block group median household income (categories of $1,000 per year: less than 35, 35–65, 65–85, more than 85), Census 2000 block group urbanization (100% urban, less than 100% urban), and a non-parametric LOESS term for the calendar week of the child's birth (1–52).

[c]Models additionally adjusted for 1 additional perinatal exposure window at a time because of PM_{10} correlations between these exposure windows.

[d]Models have fewer observations in trimester 3 exposure window (976 cases; 14,627 controls).

TABLE 4. Association of Autism and PM_{10} (10 μg/m^3 Increase), by State (North Carolina[a]: 645 Cases, 12,434 Controls; California[b]: 334 Cases, 2,232 Controls)

	North Carolina	California	
	OR (95% CI)[c]	OR (95% CI)[c]	Test For Interaction by State[d]
Preconception	0.92 (0.77–1.09)	1.06 (0.86–1.32)	$P = 0.78$
Trimester 1	0.82 (0.68–0.98)	0.98 (0.77–1.24)	$P = 0.28$
Trimester 2	0.84 (0.68–1.04)	0.95 (0.74–1.23)	$P = 0.07$
Trimester 3	1.40 (1.13–1.72)	1.16 (0.80–1.69)	$P = 0.59$
Postnatal quarter 1	1.22 (0.99–1.51)	0.71 (0.44–1.16)	$P = 0.03$
Postnatal quarter 2	0.75 (0.61–0.92)	1.09 (0.53–2.24)	$P = 0.41$
Postnatal quarter 3	0.79 (0.64–0.97)	1.51 (0.74–3.08)	$P = 0.01$
Postnatal quarter 4	1.15 (0.94–1.41)	0.96 (0.53–1.72)	$P = 0.89$

PM_{10} indicates particulate matter (10 microns in diameter or less).
[a]North Carolina model has fewer observations in trimester 3 (no. of cases = 642; no. of controls = 12,434).
[b]California model has fewer controls in trimester 3 (no. of controls = 2,228).
[c]Odds ratios for adjusted models were estimated using logistic generalized additive models (GAMs) and included parametric terms for state, birth year, race/ethnicity (white non-Hispanic, black non-Hispanic, Asian non-Hispanic, other race non-Hispanic, Hispanic), maternal education (no. of years of education log-transformed), maternal age (log-transformed), Census 2000 block group median household income (categories of $1,000 per year: less than 35, 35–65, 65–85, more than 85), Census 2000 block group urbanization (100% urban, less than 100% urban) and a non-parametric LOESS term for the calendar week of the child's birth (1–52).
[d]*P* value corresponds to a test of the cross-product term in the model: (average PM_{10} during exposure window*state).

Our study corroborates previous work finding increased risk of autism with proximity to freeways or with higher levels of particulate matter—$PM_{2.5}$ and PM_{10}.[9–11] Our results suggest that PM_{10} exposure in the third-trimester is associated with autism, but that similar levels in earlier pregnancy do not increase the risk. This finding is consistent with all prior studies that have examined trimester-specific associations.[10,11] Our work newly suggests a potential discrete window of susceptibility during weeks 31 to 36 of pregnancy. Our design permitted this investigation of periods of susceptibility because our exposure metrics were not static (eg, distance to a roadway), but instead incorporated information on week-to-week variability in pollutant concentrations—variability that, in these 2 regions, overshadowed the state-to-state and long-term patterns. It is possible that our air pollutant estimation method was better able to resolve contrasts in exposure levels across pregnancy trimesters than were previous studies, although this hypothesis is difficult to assess. This is implied by the fact that the cyclical patterns between first-and third-trimester pollutant concentrations were much more pronounced in our northern California data (strongly inverse, PM_{10} r = −0.8) compared with a prior study in southern California (low positive, r for several criteria pollutants of 0.05 to 0.37).[10] Furthermore, we adjusted associations in 1 exposure window for concentrations in other windows, which attenuated many associations but did not change associations for PM_{10} in the third-trimester. Failing to adjust an environmental exposure in 1 pregnancy trimester for the same exposure in another trimester may lead to bias in effect estimates.[37]

Importantly, our findings pertain to an eastern region of the US (North Carolina), where weather, air pollutant composition, and the seasonal peaks in PM concentrations differ from California, the site of previous work to date.[38–42] PM_{10} arises from traffic, especially diesel traffic, as well as from wood smoke and power plants. It can be emitted directly, and also formed via chemical reactions with sulfur dioxide and nitrogen oxides in the atmosphere. Our study used inputs of PM_{10} mass, without information on chemical composition. Important constituents of PM (here pertaining to $PM_{2.5}$) include ammonium, elemental carbon, organic carbon matter, nitrate, silicon, sodium, and sulfate.[42] The relative contribution of these chemical species to PM mass varies in the US between the West coast and East coast and from season to season within the 2 coastal regions.[42] These PM compositional patterns perhaps could account for the slight differences we found in the magnitude of associations between North Carolina and California. Our data did not permit an exploration of PM composition, but further study in this area is important because different chemical species have different toxicities and point to different sources that could be the target of preventive efforts.

PM_{10} includes particulate matter that is smaller in size ($PM_{2.5}$) as well as PM between 2.5 and 10 μm. $PM_{2.5}$ is more biologically relevant to human health because it penetrates more deeply into the lungs. Although it would have been ideal to include a direct measure of $PM_{2.5}$ in our analyses, the EPA did not monitor $PM_{2.5}$ in these regions in these years, and the lack of these data is a limitation of our study. Because we did not evaluate other pollutants (eg, NO_2), as has been done in some prior studies, we were additionally unable to address copollutant confounding or the impact of mixtures.

The method we have employed to estimate PM concentrations utilized more information than in prior publications, which used distance to the nearest freeway,[9] a spatial interpolation between up to 3 or 4 closest monitoring stations,[11,12] and assignment of the value from 1 nearest regulatory

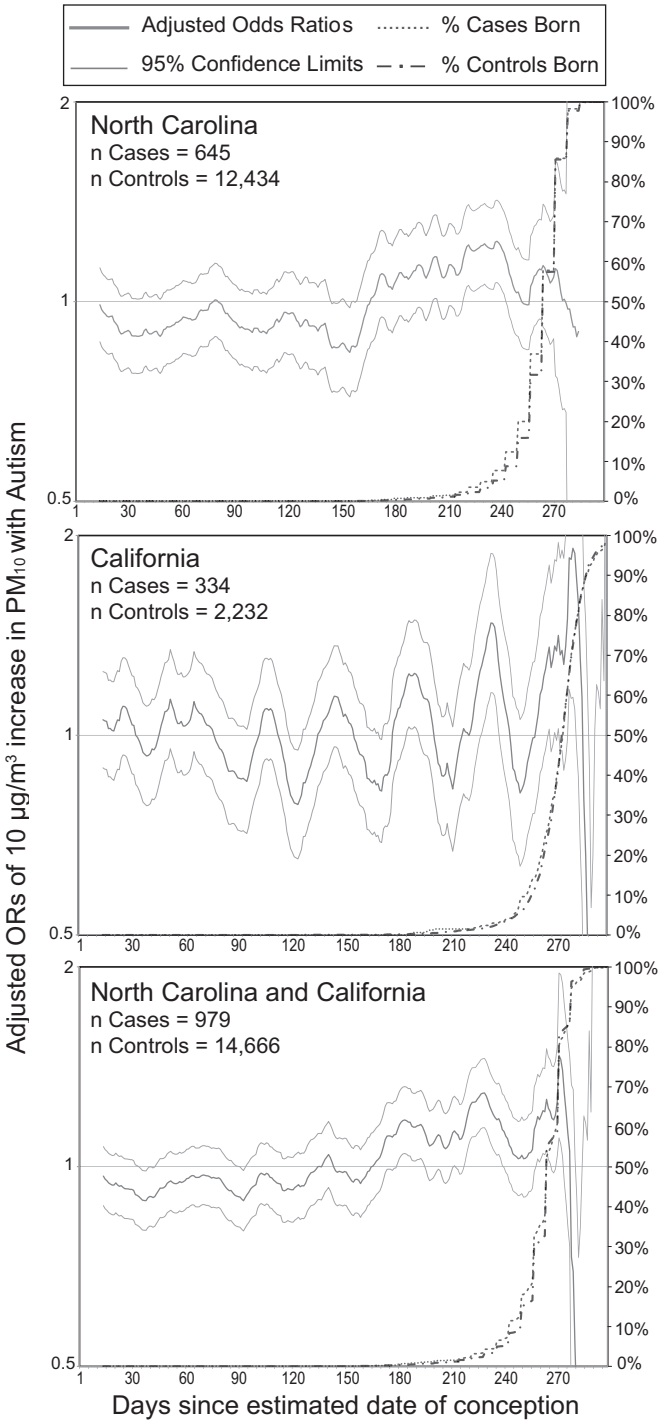

FIGURE 2. Adjusted odds ratios and 95% confidence intervals for PM_{10} concentrations (10 µg/m^3 increase) in 14-day rolling average windows throughout pregnancy and autism, by state and combined. Odds ratios for adjusted models were estimated using logistic generalized additive models (GAMs) and included parametric terms for state, birth year, race/ethnicity (white non-Hispanic, black non-Hispanic, Asian non-Hispanic, other non-Hispanic, Hispanic), maternal education (number of race years education, log-transformed), maternal age (log-transformed), Census 2000 block group median household. income (categories of $1,000 per year: less than 35, 35–65, 65–85, more than 85), Census 2000 block group urbanization (100% urban, less than 100% urban) and a nonparametric LOESS term for the calendar week of the child's birth (1–52). The percent of births for children with autism and the comparison sample is also shown.

monitor.[10] Our method, the moving-window Bayesian Maximum Entropy-kriging method, used inputs from multiple air monitors and rigorously accounted for the space/time heterogeneity and interdependencies in the data. Although this model's performance has not been directly evaluated for trimester or 14-day exposures to PM_{10}, prior evaluations for other pollutants and longer temporal periods have shown high performance of this framework. Estimates of polycyclic aromatic hydrocarbon estimation using Bayesian Maximum Entropy outperformed ordinary kriging in New York City.[43] The moving-window Bayesian Maximum Entropy enhancement, which we also employed, showed additional gains when estimating yearly $PM_{2.5}$ across the US.[28]

Yet, like all previous studies of air pollutants and autism, we assumed that an ambient model of air pollutant concentrations represented individual exposure. Although such an assumption is reasonable (eg, correlations of 0.63 between personal and fixed-station outdoor measures for children in 1 study),[44] the lack of person-based monitoring, and the resultant exposure measurement error, is the largest limitation in this study. Error will result, for example, from assuming that pregnant mothers and infants spend all their time at their residences. This error would not be expected to be related to whether a child had autism, and generally would result in bias toward the null, so that the true magnitude of an association between PM_{10} and autism may be higher than found in this study. Air pollutant measurement error due to spatial location errors may be less important in our study design, given that a large component of the variability in PM_{10} exposures in our data was due to time of year, not location in space.

A potential impact of exposure measurement error from residential mobility deserves special mention because it may affect the interpretation of periods of susceptibility, as follows. In our main analyses we relied on residential address at the time of birth to estimate PM_{10} concentrations. Exposures earlier in pregnancy (and later in postnatal life) may have potentially incurred a larger degree of exposure measurement error, because these time periods allowed more intervening time for families to move. This pattern of graduated exposure measurement error across developmental windows could account for the lack of association between PM_{10} and autism in early pregnancy and stronger associations around the time of birth. To directly assess this potential, we performed a sensitivity analysis of the impact of residential mobility on a subset from North Carolina. These results were consistent with an interpretation that PM_{10} exposures in the third-trimester, but not the first-trimester, may cause autism, because even among

TABLE 5. Association[a] of Autism and PM_{10} (10 μg/m³ increase) for Case Subgroups

	North Carolina Only		North Carolina and California	
	Autistic Disorder	ASD-NOS	Autism With Co-occurring Intellectual Disability	Autism Without Co-occurring Intellectual Disability
	Yes, n = 523[b]; No, n = 12,434[b]	Yes, n = 100[c]; No, n = 12,434[c]	Yes, n = 383[d]; No, n = 14,666[d]	Yes, n = 572[e]; No, n = 14,666[e]
Case Definition	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]
Preconception	0.90 (0.74–1.09)	0.59 (0.38–0.92)	0.82 (0.67–1.02)	0.99 (0.84–1.18)
Trimester 1	0.79 (0.64–0.97)	0.67 (0.43–1.02)	0.79 (0.63–0.99)	0.88 (0.73–1.06)
Trimester 2	0.63 (0.50–0.80)	1.31 (0.77–2.24)	1.07 (0.83–1.38)	0.91 (0.74–1.13)
Trimester 3	1.51 (1.20–1.90)	2.10 (1.25–3.54)	1.34 (1.02–1.77)	1.40 (1.10–1.77)
Postnatal quarter 1	1.67 (1.32–2.10)	0.76 (0.44–1.30)	0.88 (0.65–1.18)	1.26 (0.98–1.64)
Postnatal quarter 2	0.65 (0.52–0.82)	0.55 (0.33–0.91)	0.95 (0.71–1.29)	0.64 (0.50–0.84)
Postnatal quarter 3	0.75 (0.60–0.94)	0.96 (0.57–1.61)	0.74 (0.54–1.00)	0.96 (0.73–1.24)
Postnatal quarter 4	1.21 (0.96–1.51)	1.31 (0.80–2.13)	1.32 (0.99–1.77)	1.05 (0.82–1.36)

ASD-NOS indicates autism spectrum disorder—not otherwise specified; PM_{10}, particulate matter (10 microns in diameter or less).

[a]Odds ratios for adjusted models were estimated using logistic generalized additive models (GAMs) and included parametric terms for state, birth year, race/ethnicity (white non-Hispanic, black non-Hispanic, Asian non-Hispanic, other race non-Hispanic, Hispanic), maternal education (no. of years education log-transformed), maternal age (log-transformed), Census 2000 block group median household income (categories of $1,000 per year: less than 35, 35–65, 65–85, more than 85), Census 2000 block group urbanity (100% urban, less than 100% urbanization) and a non-parametric LOESS term for the calendar week of the child's birth (1–52).

[b]Model has fewer observations in trimester 3 (yes = 520; no = 12,399).

[c]Model has fewer observations in trimester 3 (no = 12,399).

[d]Model has fewer observations in trimester 3 (yes = 382; no = 14,627).

[e]Model has fewer observations in trimester 3 (yes = 570; no = 14,627).

families who did not change addresses, the first-trimester OR was null, whereas the third-trimester OR was elevated. This sensitivity analysis had limitations, including that the children who were traced were generally of higher socioeconomic status than the sample as a whole, and that families of children with autism moved less frequently than families from the source population.

Our design included additional strengths, including sample size (almost 1,000 children with autism), a standardized ascertainment of autism, the inclusion of less-severe subtypes, and the ability to control for some sociodemographic factors (eg, maternal education, neighborhood income). Unlike previous studies, we also adjusted for the impact of season of birth, an important potential confounder not included in prior publications. We treated season as a proxy for the currently unknown drivers of observed associations between season of conception/birth and autism, and we rigorously adjusted for season using a temporally precise and flexible statistical adjustment. This adjustment was important in reducing confounding by season of birth in North Carolina, although not California. The different confounding patterns by state were not unexpected, given that the direction of association between season of birth and PM_{10} were different for North Carolina and California. Also of note, the direction of this confounding attenuated the effect, so that when this bias was removed, the OR was stronger in North Carolina, whereas retaining similar precision, suggesting that over-adjustment for season of birth was not of concern with this approach.

The association with third-trimester PM_{10} held across different phenotypic subgroups of autism, subgroups defined by severity and by the co-occurrence of intellectual disability. The robustness of these findings to different case definitions may provide support for the importance of third-trimester PM_{10}, or could reflect a consistent bias, such as residual confounding due to unmeasured nuances of socioeconomic position that act similarly for each case subgroup. These subgroup analyses should additionally be interpreted with caution, as there is the possibility of misclassification for these variables, and they represent smaller sample sizes than the broader case group; however, if these results are valid, they suggest a lack of phenotype-specific effect.

A third-trimester window of susceptibility is consistent with theories of altered neuronal connectivity in autism. Substrates of brain connectivity (including synapse formation, myelination, and neurotransmitter receptor formation) are all in progress in late pregnancy in humans.[14] Such altered neuronal connectivity, resulting in perturbation of signaling pathways, has been implicated as the neurobiological basis of autism through some lines of molecular and pathological evidence.[45,46] Increasingly, evidence suggests that proper brain network development depends on close co-ordination with the immune system, so that disruption in the immune system could affect brain development.[5–8] Given that air pollutant exposures

such as PM_{10} cause immune impacts, (eg, a systemic cytokine response secondary to oxidative stress), an inflammatory mechanism may be responsible if late-pregnancy PM_{10} exposures truly lead to more autism.

Air pollution exposure is ubiquitous and increasingly understood to impact subtle, but important, aspects of development. Our work adds to prior research suggesting that early-life PM exposure, especially during the third-trimester of pregnancy, may be most deleterious. Additional work in this area is needed to account for other, correlated criteria pollutants and the compositional nature of PM, in order to further refine the understanding of the neurodevelopmental impacts of specific chemical pollutants during precise developmental windows.

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