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Air pollution and autism in Denmark

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Background: Previous autism spectrum disorder (ASD) and air pollution studies focused on pregnancy exposures, but another vulnerable period is immediate postnatally. Here, we examined early life exposures to air pollution from the pre- to the postnatal period and ASD/ASD subtypes in the Danish population.

Methods: With Danish registers, we conducted a nationwide case–control study of 15,387 children with ASD born 1989–2013 and 68,139 population controls matched by birth year and sex identified from the birth registry. We generated air dispersion geographic information system (AirGIS) model estimates for nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particulate matter 2.5 ($PM_{2.5}$), and particulate matter 10 (PM_{10}) at mothers' home from 9 months before to 9 months after pregnancy and calculated odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for parental age, neighborhood socioeconomic indicators, and maternal smoking using conditional logistic regression.

Results: In models that included all exposure periods, we estimated adjusted ORs for ASD per interquartile range (IQR) increase for 9 months after pregnancy with NO_2 of 1.08 (95% CI = 1.01, 1.15) and with $PM_{2.5}$ of 1.06 (95% CI = 1.01, 1.11); associations were smaller for PM_{10} (1.04; 95% CI = 1.00, 1.09) and strongest for SO_2 (1.21; 95% CI = 1.13, 1.29). Also, associations for pollutants were stronger in more recent years (2000–2013) and in larger cities compared with provincial towns/rural counties. For particles and NO_2, associations were only specific to autism and Asperger diagnoses.

Conclusions: Our data suggest that air pollutant exposure in early infancy but not during pregnancy increases the risk of being diagnosed with autism and Asperger among children born in Denmark.

Keywords: air pollution, early postnatal exposures, autism, ASD subtype, traffic

Autism spectrum disorder (ASD) includes difficulties in social interaction and communication, restricted activities and interests, and repetitive behaviors. At its extreme, it is one of the most severe neurodevelopmental disorders in children and its functional deficits have a lifelong impact. The rising prevalence of autism and ASD diagnoses has been attributed to a broadening of diagnostic criteria, increased awareness, and availability of child developmental services, as well as the inclusion of milder neurodevelopmental disorders (such as Asperger syndrome), but concerns have also been raised about changes in environmental exposures.[1–3] Although it is now acknowledged that both genes and the environment contribute to this complex disorder,[4] twin research now suggests a stronger role for environmental factors than originally proposed.[5] Air pollution is ubiquitous and has garnered increasing concerns as to whether and how it affects brain function and development. Recently, rodent studies report effects of diesel and concentrated ambient air particle exposures on brain morphology, animal behavior, inflammatory markers, and neurotransmitters.[6]

In humans, early studies of ASD and air pollution were relatively small in size (several hundred cases) and relied on crude exposure models such as county-level estimates for hazardous air pollutants including metals and volatile organic compounds or simply on proximity of residence to roadways.[7–11] More recent studies have modeled traffic-related sources of air pollution at finer scales and also used criteria pollutant air monitoring data—primarily focusing on particulate matter $PM_{2.5}$ or PM_{10}.[8,12–15] Results from epidemiologic studies of any type of ASD were recently summarized in two meta-analyses.[16,17] Both reviews supported the notion that ambient air pollution increases ASD risk but also pointed out that to date there are relatively few studies that evaluated different pollutants and that most were relatively small in size for air pollution studies. Since these reviews, two additional large studies each with thousands of cases were published, one in Sweden and another in Israel.[18,19]

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What this study adds

Even though ambient air pollution—especially particulates—exhibits neurodevelopmental toxicity in experimental studies, evidence from epidemiological studies of autism spectrum disorders (ASDs) remains equivocal. In a large study of Danish children with relatively low exposures, we estimated increased odds for traffic-related pollutants (NO_2 or particles) for autism and Asperger diagnoses but not for more broadly defined pervasive developmental disorders. We had sufficient sample size to investigate preconception, prenatal, and postnatal exposures simultaneously and found that traffic-related exposure to air pollution in early infancy but not in pregnancy increased the risk of children being diagnosed with ASD.

Unlike the only other large study conducted in Los Angeles,[12] these recent studies investigated both pre- and postnatal exposures. The Swedish study found no effects for modeled PM_{10} or NO_2 from road traffic sources for any exposure period at the very low exposure levels they reported for this population.[18] In the Israeli study, exposures were higher overall, and high NO_2 exposures during the 9 months period postnatally increased ASD risk.[19] Three previous US studies from California, North Carolina, and Pennsylvania that also assessed exposures to particles ($PM_{2.5}$ or PM_{10}) pre- as well as postnatally—both periods of biologic importance for autism—were much smaller in size.[15,20,21] These investigations also reported stronger associations with autism risk in the late gestational and postnatal period, but they did not necessarily coadjust for all period-specific exposures in the same model. In contrast, a smaller study that identified 245 ASD cases in the US nationwide Nurses Health Study (NHS) cohort supported associations with pregnancy exposures only when coadjusting for all exposures to $PM_{2.5}$ from 9 months before to 9 months after birth.[13] Given these inconsistent findings, there is a need for larger studies that allow further explorations into the types, levels, and timing of air pollution exposures when assessing ASD risk.

Here, we present results on ASD as well as specific subtypes (autism [AD], Asperger, and pervasive developmental disorders not otherwise specified [PDD-NOS]) and air pollution. Utilizing the Danish nationwide population-based registers and individual-level air pollution exposure measures, we assess the influence of early life exposure to air pollutants from traffic as well as other sources during critical periods of fetal and child development on ASD risk. Denmark has a long-standing tradition of maintaining one of the world's largest health science information data banks, and its tax-supported health care coverage for all residents has been a resource for medical research over decades. Furthermore, a validated air dispersion model based on a nationwide emissions inventory provides estimates for nitrogen dioxides (NO_2)/nitrogen oxides (NO_x), sulfur dioxide (SO_2), and particulate matter ($PM_{2.5}$ and PM_{10}) at high temporal and spatial resolution at individual addresses.

Methods

Study population

Utilizing the Danish medical registers, we compiled all ASD cases in Denmark diagnosed from 1995 to 2016 and born between 1989 and 2013 and selected population controls (without replacement) individually matched on birth year and gender at a ratio of 1:5 from the Central Population Registry (CPR), which assigns each inhabitant of Denmark a unique 10-digit identification number. For case identification, we relied on the Danish National Patient Register information on admissions and outpatient/emergency room consultations and the Danish Psychiatric Central Register (PCR) for psychiatric admissions to hospitals and outpatient clinics; we identified all ASD diagnoses using International Classification of Disease (ICD)-10 codes of F84.0, F84.1, F84.5, F84.8, or F84.9 and retrieved their date of first diagnosis. The Danish Medical Birth Registry that collects information on all births in Denmark provided us with data on maternal pregnancy history, demographics, maternal smoking in pregnancy, birth weight, gestational age, and other gestation-related factors. The same registry was the basis for control selection. Children were eligible as controls if they did not receive an autism diagnosis at any point in the specified time period. To minimize data entry errors, cases and controls were also required to have been born between 21 and 46 weeks of gestation and have a birth weight of >500 and <6800 g; mothers were required to have had addresses in Denmark throughout pregnancy and the child from birth until index date (case diagnosis date and a corresponding date for controls). Overall, we identified 20,538 cases and 101,660 population controls; but, we excluded multiple births (N = 2,944), records that were missing exposures for more than 50% of the period of interest (N = 1,150), records missing covariates (N = 25,168; of whom 79% were missing smoking data), and we additionally excluded matched sets with cases only (N = 46) or controls only (N = 9,364). This left us with 15,387 cases and 68,139 controls for complete case matched-set analyses (see Figure S1; http://links.lww.com/EE/A21). Air pollution levels did not differ more than minimally between cases and controls excluded due to missing covariates (results not shown).

Exposure assessment

The geographic information system (GIS)-based air pollution and human exposure modeling system (AirGIS) is part of the integrated Danish Air Quality Monitoring Program and the multi-scale integrated dispersion modeling system THOR developed by the Department of Environmental Science at Aarhus University (formerly Danish National Environmental Research Institute [NERI]). The system enables the calculation of ambient air pollution at high temporal (hourly) and spatial (individual address) resolution. AirGIS incorporates various sources of data including a GIS-based road network, emission factors for the Danish car fleet, and a national topographic GIS database of buildings. This allows us to estimate exposure for NO_2, $PM_{2.5}$, PM_{10}, and SO_2 covering various sources (traffic, ships, wood stoves, etc.) in Denmark based on an emissions' database from 1979 onward for a 1×1 km grid.

We retrieved maternal residential addresses from the CPR starting 9 months before until the 9 months after pregnancy starting from 1 January 1989 based on the unique personal ID numbers noting all dates of moving and addresses during this interval. Each address, identified by municipality code, street code, and house number, was linked to the Danish Address Register to obtain geographical coordinates defined in the UTM Zone 32 N, ETRS89(EPSG:3044) system with high address level precision of the geographical coordinates (within 5 meters), allowing us to successfully geocode 99.6% of all addresses. We employed AirGIS to estimate subjects' air pollution exposure during the period 1989–2013 at each address location calculated as the sum of (1) local air pollution from street traffic derived from the Operational Street Pollution Model (OSPM) which considers data on traffic (intensity, speed, and type), emission factors for the car fleet, street and building geometry, and meteorology; (2) urban background contributions in a 1×1 km^2 grid resolution calculated with the Urban Background Model (UBM), taking into account the emission density originating from all types of emissions estimated with the Spatial High Resolution Emission to Air Distribution Model (SPREAD), and average building cover and height; and (3) regional background contributions, i.e., from sources such as power plants, industry, residential heating, etc., modeled with a regional Danish Eulerian Hemispheric Model (DEHM). Based on geocodes and an exposure time interval as input, the AirGIS system automatically generates street configuration data for the street pollution model, including street orientation and width, building heights in wind sectors, traffic density, speed, and vehicle type. The AirGIS system has been validated in several studies and the model predicts both geographical and temporal variation well.[22–29] For example, the correlation (r) between modeled and measured half-year mean concentrations of NO_2 at 204 locations in greater Copenhagen was 0.90; and correlations between modeled and measured 1-month mean concentrations of NO_x and NO_2 over 12 years (1995–2006) on a busy street in Copenhagen (Jagtvej, 25,000 vehicles per day, street canyon) were 0.88 and 0.67, respectively. For $PM_{2.5}$ the correlation between calculated and predicted values varied between 0.67 and 0.86 depending on location, averaging time of the measurement, and character of the measurement series (temporal or spatial variation).[30]

Finally, we calculated time-weighted averages of air pollution exposures at all addresses over the periods "9 months before pregnancy," "pregnancy," each trimester separately, and "9 months after birth" for those who had air pollution levels for at least 50% time in each period available.

Statistical analyses

We examined the correlation of air pollution exposure measures between trimesters as well as pre- and post pregnancy to determine the potential for multi-collinearity between air pollution exposure measures. We employed the standard analytical methods for matched case–control studies,[31] conditional logistic regression, to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for all exposure intervals per interquartile range (IQR) based on the distribution of the pollutant in control. We relied on directed acyclic graphs (DAGs) to determine the causal structure for our models, identify relationships between exposures, covariates, and outcomes, and guide the selection of variables needed to control for confounding.[32] We selected the following covariates as potential confounders: maternal and paternal age (<19, 19–25, 26–30, 31–35, >35 years), location of residence (Copenhagen, its suburbs, and large cities [Aarhus, Odense, Aalborg], provincial cities and rural towns/communities), neighborhood socio-economic status (SES) employment (community-level ratio of unemployed to employed families based on the adult with the highest reported income in the birth year), neighborhood SES housing (% of council rented housing in year of birth), and maternal smoking during pregnancy (yes/no); the matching variables gender and birth year were the basis for risk sets in conditional logistic models. We generally restricted analyses to subjects who did not lack covariate data, but we also imputed missing maternal smoking, paternal age, location of residence, neighborhood SES (employment and housing) data in sensitivity analyses. When examining trimester-specific exposures, we restricted to children born at term (at least 37 weeks of gestation).

We conducted stratified analyses according to decade of birth (before and after the year 2000), child gender, and place of residence at birth (Copenhagen, suburbs, and large cities versus provincial and rural towns/communities), and also distinguished between subtypes of ASD (AD, Asperger, and PDD-NOS). Additionally, we restricted in sensitivity analyses to children diagnosed before age 5 (AD) and age 10 (Asperger), to those who received diagnoses from specialized psychiatric hospitals, and to nonmovers (in pregnancy) only to compare results to previous reports. We provide odds ratios per interquartile range increase in each pollutant. We explored multicollinearity of pollutants using the variance inflation factor (VIF), and except for NO_2 (VIF = 7–9), multicollinearity of air pollutants during different periods of pregnancy seemed weak. However, possibly due to our large sample size, even the effect estimation for NO_2 was not affected, i.e., the effect estimates did not become unstable when we included both pre- and postnatal exposures in our models.

Results

Children who received a diagnosis of ASD were—as expected—76% male and had a slightly lower mean birthweight and gestational age when comparing cases with control children. Case parents did not differ from control parents in terms of mean maternal or paternal ages, but a slightly higher proportion of parents were older than age 35 when the affected child was born (Table 1). Also, most parents of ASD children lived in larger Danish cities around the time of pregnancy and more case mothers reported smoking in pregnancy (27% vs. 22%). All modeled air pollutants declined between 1989 and 2013 (see Figure S2; http://links.lww.com/EE/A21) and prepregnancy, pregnancy, and postpregnancy exposures were moderately to highly correlated with each other (Pearson *r* of 0.60–0.91) (see Table S1; http://links.lww.com/EE/A21).

Table 1

Demographic and prenatal characteristics of ASD cases and matched population controls.

	Cases (N = 15,387)	Controls[a] (N = 68,139)
	n (%)	n (%)
Gender		
Male	11,853 (77.0)	52,561 (77.1)
Female	3,534 (23.0)	15,578 (22.9)
Birth year		
1989–1999	7,036 (45.7)	29,154 (42.8)
2000–2009	8,057 (52.4)	37,617 (55.2)
2010–2013	294 (1.9)	1368 (2.0)
Average birth weight (g) (Mean, SD)	3511.9 (631.4)	3558.5 (571.4)
Average gestational age (days) (Mean, SD)	276.0 (14.5)	276.2 (13.6)
Maternal age at delivery (years)		
≤18	95 (0.6)	453 (0.7)
19–25	3,260 (21.2)	12,758 (18.7)
26–30	5,843 (38.0)	27,158 (40.0)
31–35	4,321 (28.1)	20,412 (23.0)
>35	1,868 (12.1)	7,358 (10.8)
Paternal age at delivery (years)		
≤18	21 (0.1)	109 (0.1)
19–25	1,715 (11.2)	6,584 (9.7)
26–30	4,746 (30.8)	21,630 (31.7)
31–35	4,921 (32.0)	23,354 (34.3)
>35	3,984 (25.9)	16,462 (24.2)
Average maternal age (Mean, SD)	29.5 (5.0)	29.5 (4.7)
Average paternal age (Mean, SD)	32.2 (6.1)	32.1 (5.6)
Location at birth		
Copenhagen and large cities[b]	8,384 (54.5)	32,798 (48.1)
Provincial cities/towns[c]	5,483 (35.6)	26,718 (39.2)
Rural communities/small towns[d]	1,520 (9.9)	8,623 (12.7)
Maternal smoking during pregnancy		
Yes	4,160 (27.0)	14,982 (22.0)
No	11,227 (73.0)	53,157 (78.0)

[a]Controls are matched to cases by gender and birth year.

[b]Includes Copenhagen and its suburbs, as well as large cities (Aarhus, Odense and Aalborg).

[c]Includes larger provincial cities and towns.

[d]Includes rural areas and small towns (<10,000 inhabitants).

In covariate-adjusted models, only NO_2 and SO_2 in pregnancy and infancy (9 months after birth) and $PM_{2.5}$, but not PM_{10}, in infancy contributed to increased risk of ASD when each exposure period was modeled separately (Table 2). However, when we included all exposure periods from pre- to postpregnancy, for all four pollutants, the infancy but not pregnancy period was positively associated with ASD with ORs ranging from 1.04 to 1.21 per IQR increase in pollutant level. Furthermore, trimester-specific exposures adjusted for pre- and postnatal exposures were not associated with ASD either (Table S2; http://links.lww.com/EE/A21). Importantly, none of the parental risk factors or maternal smoking in pregnancy confounded the reported associations more than minimally in complete data analyses or in sensitivity analyses in which missing smoking data were replaced based on multiple imputation procedures (data not shown). For all pollutants, effect estimates did not change more than minimally when we excluded those who moved during the interval of interest (Table 3). In boys, effect estimates for particulate matter ($PM_{2.5}$ and PM_{10}) and SO_2 appeared stronger than in girls, whereas for NO_2 estimates appeared stronger among girls but the 95% confidence intervals of all gender-specific estimates largely overlapped. When we stratified by residential location at birth, all pollutants were positively and more strongly associated with ASD among residents of Copenhagen and its suburbs, in addition to other large cities (Aarhus, Odense, Alborg), whereas for those living in provincial towns and rural communities, only

Table 2

ORs (95% CI) from conditional logistic regression models for ASD per IQR[a] increase in air pollutants levels in different time periods (Case N = 15,387; Control N = 68,139).

		OR (95% CI)		
Exposure	**Exposure period**	**Unadjusted[b]**	**Adjusted[c]**	**Mutually adjusted[d]**
NO_2	Pregnancy	1.19 (1.16, 1.22)	1.10 (1.06, 1.13)	1.00 (0.93, 1.08)
	9 months after birth	1.20 (1.17, 1.23)	1.11 (1.07, 1.14)	1.08 (1.01, 1.15)
SO_2	Pregnancy	1.29 (1.23, 1.35)	1.12 (1.07, 1.18)	0.96 (0.90, 1.04)
	9 months after birth	1.38 (1.31, 1.45)	1.21 (1.15, 1.28)	1.21 (1.13, 1.29)
PM_{10}	Pregnancy	0.99 (0.95, 1.02)	0.97 (0.94, 1.01)	0.95 (0.91, 1.00)
	9 months after birth	1.03 (0.99, 1.06)	1.01 (0.97, 1.05)	1.04 (1.00, 1.09)
$PM_{2.5}$	Pregnancy	1.06 (1.02, 1.11)	1.00 (0.96, 1.04)	0.96 (0.91, 1.02)
	9 months after birth	1.11 (1.07, 1.15)	1.04 (1.00, 1.09)	1.06 (1.01, 1.11)

[a]IQRs in controls: NO_2: 11.41 μg/m^3; SO_2: 2.80 μg/m^3; PM_{10}: 3.80 μg/m^3; $PM_{2.5}$: 3.61 μg/m^3.

[b]These are pair matched on gender, birth year.

[c]Adjusted for maternal age, paternal age, location of birth, neighborhood SES employment, neighborhood SES housing, and maternal smoking during pregnancy.

[d]Adjusted for all other covariates listed above and all exposure periods (prepregnancy, pregnancy, and postpregnancy).

SO_2 was positively associated with ASD and confidence intervals excluded the null. Furthermore, all pollutant effect estimates were stronger for children born after 1999 and also when we excluded potentially less severe cases; i.e. AD cases diagnosed at age 5 or older and Asperger cases diagnosed after age 10. Within subtypes of ASD, positive associations were observed for all pollutants in children diagnosed with AD, and with Asperger while among children with a PDD-NOS diagnosis, only SO_2 effect estimates for infancy exposures showed increases (Table S3; http://links.lww.com/EE/A21). Finally, excluding children not diagnosed in psychiatric specialty hospitals from the analyses—assuming that these clinics achieve higher specificity in diagnosing ASDs—did not change results more than minimally.

Discussion

In this nationwide study of Danish children, we found that air pollution exposures in early infancy but not in pregnancy contributed to an increased risk of ASD, specifically to autism and Asperger diagnoses. This is the largest study addressing air pollutant influences on the risk of ASD to date, and one of the few studies that has controlled for maternal smoking in pregnancy, assessed subtypes of ASD, and co-adjusted for multiple exposure periods from preconception to infancy.

Air pollution exposure during the prenatal period has been associated with a variety of adverse birth outcomes and with brain structural and neuropsychological abnormalities in childhood.[33,34] Biologic mechanisms important for autism cover both prenatal development and postnatal maturation and include brain immune function, synaptic plasticity, brain circuitry and stem cell development, as well as selective elimination ("pruning") of excess neuronal synapses.[35] Microglia are immune cells in the brain that react to injury and inflammatory stimuli and changes in number or activation stage of microglia cells may play a role in most processes that can profoundly affect neural development including autism.[36]

Previous reports that have focused on air pollution and ASD concluded that larger additional investigations are needed to establish whether pre- or postnatal periods of fetal development are most vulnerable to these exposures.[16,17] The first study that implicated air pollutants in ASD risk was conducted in California.[10] It relied on the EPA's National Air Toxics Assessment (NATA) model for emissions of hazardous air pollutants (HAPs)—including metals, particulate, and volatile organic matter—to show that ASD diagnoses were associated with modeled census tract at birth exposures to chlorinated solvents and heavy metals. However, a study using the same NATA model in North Carolina and West Virginia found no effects for metals but positive associations (ORs between 1.4 and 1.8) with ASD for the solvent methylene chloride and for quinoline and styrene exposures.[7] Furthermore, a Pennsylvania study that focused on exposures at the census tract/zip code of birth for

Table 3

ORs (95% CI) from conditional logistic regression models for ASD per IQR[a] increase in air pollutant levels in infancy (9 months after birth) mutually adjusted for prepregnancy and pregnancy exposures; stratified models.

	OR[b] (95% CI)			
	NO_2[a]	**SO_2[a]**	**PM_{10}[a]**	**$PM_{2.5}$[a]**
All (N = 83,526)	1.08 (1.01, 1.15)	1.21 (1.13, 1.29)	1.04 (1.00, 1.09)	1.06 (1.01, 1.11)
Nonmovers (N = 74,834)	1.07 (1.00, 1.15)	1.21 (1.13, 1.29)	1.03 (0.98, 1.08)	1.04 (1.00, 1.10)
Males (N = 64,414)	1.06 (0.99, 1.14)	1.25 (1.16, 1.35)	1.05 (1.00, 1.10)	1.07 (1.01, 1.13)
Females (N = 19,112)	1.12 (0.99, 1.26)	1.11 (0.97, 1.27)	1.01 (0.93, 1.11)	1.02 (0.92, 1.12)
Born 1989–1999 (N = 36,190)	1.05 (0.96, 1.14)	1.18 (1.10, 1.27)	1.02 (0.96, 1.08)	1.04 (0.97, 1.11)
Born 2000–2013 (N = 47,336)	1.10 (1.01, 1.20)	1.34 (1.15, 1.56)	1.06 (1.00, 1.13)	1.09 (1.02, 1.16)
Copenhagen/large cities[c] (N = 25,908)	1.12 (1.04, 1.22)	1.36 (1.22, 1.50)	1.06 (1.00, 1.13)	1.09 (1.02, 1.17)
Provincial/rural[d] (N = 22,772)	1.02 (0.89, 1.15)	1.11 (1.00, 1.23)	1.00 (0.92, 1.08)	1.02 (0.94, 1.11)
Cases from psychiatric hospitals only (N = 73,174)	1.09 (1.02, 1.16)	1.23 (1.15, 1.32)	1.06 (1.01, 1.11)	1.08 (1.03, 1.14)
Younger cases only[e] (N = 36,472)	1.13 (1.02, 1.24)	1.44 (1.27, 1.62)	1.08 (1.01, 1.16)	1.14 (1.06, 1.23)

[a]IQRs in controls: NO_2: 11.41 μg/m^3; SO_2: 2.80 μg/m^3; PM_{10}: 3.80 μg/m^3; $PM_{2.5}$: 3.61 μg/m^3.

[b]Adjusted for air pollution levels during prepregnancy, pregnancy, and postpregnancy, as well as all other covariates (maternal age, paternal age, location of birth, neighborhood SES employment, neighborhood SES housing, and maternal smoking during pregnancy).

[c]Includes Copenhagen and its suburbs, and large cities, i.e., Aarhus, Odense, and Aalborg.

[d]Includes larger provincial cities/towns and rural areas and small towns (<10,000 inhabitants).

[e]Excludes AD cases with diagnosis age ≥5, Asperger/PDD-NOS cases with diagnosis age ≥10.

NATA derived neurotoxicants[9] reported an increased risk of ASD with the highest quartile of exposure to styrene, chromium, lead, arsenic, methylene chloride, and PAHs. Finally, the Nurses' Health Study which employed the NATA model nationwide to estimate exposures in maternal residential census tracts reported positive associations with ASD at the highest levels of perinatal exposures to lead, manganese, mercury, methylene chloride, and diesel, thus, corroborating various findings from previous studies conducted in multiple US states.[8] Additionally, in a study that relied on measured air toxics at women's residences close to monitoring stations in Los Angeles, increased risks of autism were estimated for children most highly exposed in pregnancy to 1,3-butadiene, meta/para-xylene, some aromatic solvents, lead, perchloroethylene, or formaldehyde.[37]

Other research that investigated the contributions of air pollutants to ASD risk used measures such as proximity to freeways, source-specific (emissions or land use regression [LUR] based) models for traffic-related pollutants, and criteria pollutants measured at ambient stations. An early study which relied on a few hundred autism cases born between 1997 and 2008 in Los Angeles reported a higher risk with residency within 309 meters of a freeway in late pregnancy and early infancy compared with those living further away.[11] For these same children, researchers also estimated high odds ratios (ORs = 1.8–3) for autism with third trimester and first year of life traffic exhaust exposure measures derived from a line-source dispersion model (CALINE4) as well as NO_2, $PM_{2.5}$, and PM_{10} from ambient monitoring stations.[15] For 7603 autism cases and ≈70,000 controls born in Los Angeles between 1995 and 2006, we previously generated traffic-related exposures (NO_2) at birth addresses from an LUR model and for $PM_{2.5}$, PM_{10}, ozone, CO, and NO_2 from routine air monitoring[12]; we estimated a 7%–12% increase in autism risk per IQR increase in LUR-derived NO_2 and monitored $PM_{2.5}$ throughout pregnancy but did not assess pre- or postpregnancy exposures. A study that combined data for almost 1000 autism cases from North Carolina and California in the mid-1990s and solely assessed PM_{10} reported that only third-trimester exposures consistently increased autism risk[20]; for the North Carolina children increased risks were also suggested with exposures during the first 4 months of life.[9] For the Nurse Health study, investigators generated particulate matter exposures from a nationwide validated spatiotemporal model and averaged monthly concentrations at maternal residential addresses from 9 months pre- to postpregnancy.[13] In this nationwide study, the fine ($PM_{2.5}$) but not coarse fraction ($PM_{2.5}$–10) of particulate matter contributed to ASD risk. Interestingly, $PM_{2.5}$ exposures in pregnancy but not during the pre- and postnatal periods increased ASD risk in fully coadjusted models, i.e., models that included all periods of exposure from pre- to postpregnancy. Furthermore, the associations were specific for the third trimester in models that examined trimesters of exposure.[13] This together with the estimated effects being somewhat stronger in boys was interpreted as in line with what is currently known about brain pathology relevant to ASD etiology[38–40]; however, we did not see consistent gender-specific effects in the Danish population. A recent study of ≈2000 ASD cases residing in Stockholm county/Sweden did not find associations with nitrogen oxides (NOx) and PM_{10} exposures from traffic sources using an air dispersion model to assess exposures at mothers' addresses registered during the pregnancy and the child's first year of life.[18] However, the modeled exposures in this study were extremely low compared with all previous US-based studies and, interestingly, in nonmovers the effect estimates for a per 10-μg/m^3 increase in NOx exposures in the first year of life were quite similar to those we estimated in our Danish study (1.09; 95% CI = 0.99, 1.21). A newly published study from Israel included children born in the mid-2000s and estimated much higher NO_2 exposures than the Swedish study relying on an optimized air dispersion model.[19] Here, only exposures in the postnatal period increased ASD risk (per IQR increase in NO_2 OR = 1.59; 95% CI = 1.18, 2.15) in models mutually adjusted for all exposure periods from 9 months pre- to postpregnancy which further corroborates our own results among Danish children. A role for early childhood exposures was previously suggested in a Taiwanese study in which air pollutant exposures (especially NO_2) modeled at the residential postal code during the 1–4 years before diagnosis increased ASD risk considerably.[41]

The biological mechanisms by which air pollution may cause autism have been explored in toxicological studies that expose rodents to air particles and show abnormalities in brain morphology, behavior, inflammatory, and neurotransmitter responses.[6] Some but not all experiments suggested sex specificity for exposures to concentrated ambient air particles during certain pre- or postnatal periods including changes in CNS neurotransmitters and glial activation across multiple brain regions.[42–44] It has also been suggested that diesel exhaust particles have endocrine-disrupting effects, affect sexual differentiation, and alter cognitive function in mice.[45,46] Traffic-related and particulate air pollutants in human studies furthermore have been shown to induce inflammation and oxidative stress, and these may be potential pathways responsible for effects of air pollution on neurologic outcomes including autism.[47–55] In particular, biomarker studies reported increases in the proinflammatory cytokines tumor necrosis factor-α and interleukins in postmortem brain tissue of autistic cases.[56] Plasma samples of children diagnosed with autism found increased plasma levels of immunoglobulin (Ig) G4 and reduced concentrations of tumor growth factor-β, related to immune response and inflammatory processes.[51,52,57] Furthermore, exposure to air pollution during pregnancy resulted in changes in IgE and in lymphocytes in cord blood samples, supporting the notion that maternal exposure to air pollution is associated with altered immune profiles in the fetus.[58,59] Additionally, maternal antibodies to fetal brain tissue were found in a subset of autism cases.[60]

AirGIS provides estimates of pollution with high address-level spatial and temporal resolution. We modeled exposures at the mothers doorstep based on addresses from the civil register allowing us to address changes in exposure due to moving. Even the best exposure model (or exposure assessment method) will imply some degree of imprecision and we did not have occupational addresses for mothers and could not address exposures she may have had in these environments from ambient or indoor sources. However, as done successfully in previous Danish studies, our ambient air exposure model relies on the same (residential) locations, and on good input data, it has been successfully validated against measurements and has proven useful in many previous epidemiological applications. Observed associations were strongest in later birth-years; the AirGIS system might predict air pollution with higher precision in more recent years, which might explain this finding. Although air pollution has decreased in Denmark over the decades we investigated, ASD diagnoses rates increased which has partially been attributed to children being diagnosed at earlier ages.[61] Whether this ASD increase reflects an increase in diagnostic sensitivity at the expense of specificity is not clear. However, reducing the specificity of a diagnosis would be expected to result in a bias toward the null and to weaken rather than strengthen the effect estimates in later years. Finally, associations with particles ($PM_{2.5}$, PM_{10}) and NO_2 air pollution were stronger among residents of larger cities than those living in provincial cities/towns and rural communities, indicating stronger associations with locally generated PM in cities, e.g., from traffic than with long-range transported PM such as secondary inorganic aerosols (sulfate—SO_4^{2-}, nitrate—NO_3^-, ammonium—NH_4^+), which distribute more similar across cities.

The Danish Psychiatric Central Register (PCR) contains data on psychiatric admissions to hospitals and wards including outpatients; it identifies autism diagnoses coded in ICD-10 code

(F84.0–F84.9) and the date of diagnosis. A recent validation study showed 94% accuracy in diagnosed autism cases from this psychiatric register, of the remaining 6%, 5% were diagnosed with an autism spectrum disorder other than autism.[62] Positive associations were consistently seen among children with AD or Asperger diagnoses, although there were no associations for NO_2 or particles with the broader category of PDD-NOS. This observation together with the stronger risks we estimated for children diagnosed before ages 5 or 10 with AD or Asperger/PDD-NOS diagnoses suggests that infancy exposures to NO_2 and particles may be most relevant for more specific diagnoses with typical onset and ages at diagnosis. A recent study of European birth cohorts assessed prenatal air pollution exposure and did not find associations with autistic traits within the borderline/clinical range.[63] Our findings for PDD-NOS suggest a possible explanation, i.e., that the null finding might be due to the nonspecific nature of the outcome definition in this previous study. An alternate explanation is that this study may have assessed the wrong exposure period because it investigated only prenatal exposures.

Conclusions

Our data suggest that exposure to air pollution in early infancy but not pregnancy increased the risk of children being diagnosed with ASD in Denmark.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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Description of the process by which someone else could obtain the data and computing code required to replicate the results reported in your submission (or explanation why data or code are not available).

This process will need to be discussed by the requester with the respective Danish data authorities who will have to grant access to these data—note: the PI of this grant does not have the right to distribute Danish health data.

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