Perinatal Exposure to Traffic-Related Air Pollution and Autism Spectrum Disorders

Tong Gong,1 Christina Dalman,2,3 Susanne Wicks,2,3 Henrik Dal,2,3 Cecilia Magnusson,2 Cecilia Lundholm,1 Catarina Almqvist,1,4 and Göran Pershagen5,6

1Department of Medical Epidemiology and Biostatistics, and 2Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden; 3Center for Epidemiology and Community Medicine, Stockholm County Council, Stockholm, Sweden; 4Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm, Sweden; 5Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; 6Center for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden

Introduction

Autism spectrum disorders (ASD) are a range of childhood neurodevelopmental disorders characterized by deficits in communication and social interaction as well as restricted repetitive behaviors (American Psychiatric Association 2013). The global prevalence appears to have increased over the past decades (Baer et al. 2006; CDC 2014; Lauritzen et al. 2004; Nassar et al. 2009), partially due to the increased awareness and changes of clinical practices. In Sweden, 1.5% of children are currently diagnosed with ASD compared with 0.8% a decade ago (Idring et al. 2015; Lundström et al. 2015). Among ASD-affected children, intellectual disability (ID) is relatively common, and those children often display significant clinical impairment (Buescher et al. 2014).

Early twin and family studies suggested ASD to be highly heritable (Bailey et al. 1995; Lichtenstein et al. 2010; Ritvo et al. 1989); however, recent studies have shown a moderate heritability for ASD (Ronald et al. 2011; Sandin et al. 2014), suggesting a substantial nongenetic component contributing to the etiology of the disorder. Moreover, twin studies have recently reported a modest genetic component but a significant environmental contribution to the correlation between ASD and IQ (Hoekstra et al. 2009, 2010). Some maternal factors such as infections during pregnancy and a history of depression or antidepressant use have been associated with ASD (Lee et al. 2015; Rai et al. 2013). There is also growing evidence that perinatal and neonatal risk factors, such as small for gestational age, preterm birth, low birth weight, and cesarean delivery, may affect the development of ASD (Buchmayer et al. 2009; Hultman et al. 2002). However, a meta-analysis did not indicate any specific pregnancy or delivery condition explaining the etiology of autism (Gardener et al. 2011).

Exposure to various air pollutants including ozone (Becerra et al. 2013; Jung et al. 2013; Volk et al. 2013), carbon monoxide (Becerra et al. 2013; Jung et al. 2013), nitrogen oxides (NOx) (Becerra et al. 2013; Jung et al. 2013; Volk et al. 2013), sulfur dioxide (Jung et al. 2013), particulate matter (PM) (Becerra et al. 2013; Jung et al. 2013; Kalkbrenner et al. 2010, 2015; Raz et al. 2015; Windham et al. 2006; Volk et al. 2013), metals (Kalkbrenner et al. 2010; Palmer et al. 2009; Windham et al. 2006), and other hazardous air pollutants (Kalkbrenner et al. 2010; Windham et al. 2006) have been linked to a modestly increased risk of ASD, which may be explained by systemic inflammation affecting the central nervous system development in utero (Allen et al. 2014). However, a recent European meta-analysis could not confirm this from those exposed to NOx and PM during perinatal life (Guxens et al. 2016). One explanation of the discrepant findings could be residual confounding from socioeconomic factors (Braveman et al. 2005; Hajat et al. 2013; Magnusson et al. 2012; Rai et al. 2012; Thomas et al. 2012). For example, a previous register-based study...
in Sweden found that lower familial socioeconomic status (SES) was associated with an increased risk of ASD through multiple dimensions of SES measures (Rai et al. 2012), which is contrary to findings from the United States (Thomas et al. 2012). Pollutant-specific effects could also contribute to the discrepant findings. In one study, the positive association was found for prenatal exposure to particulate matter with an aerodynamic diameter ≤ 2.5 μm (PM$_{2.5}$) but not to particulate matter with a diameter of ≤ 10 μm (PM$_{10}$) (Raz et al. 2015). Additionally, associations may differ for ASD with or without accompanying intellectual impairment, although this was not seen in a recent U.S. study (Kalmbrenner et al. 2015).

Our aim was to investigate the association between exposure to air pollution from road traffic and the risk of ASD in children with or without presence of ID, with careful adjustment for individual- and area-level SES as well as other potential confounders. We selected a very large study base, allowing for more informative subgroup analyses than in earlier studies.

**Methods**

**Population and Study Design**

We conducted a case–control study based on the Stockholm Youth Cohort (SYC), a prospective cohort study including all children who resided in Stockholm County for at least 4 years during 2001–2007 (Idring et al. 2012). To investigate the effect of air pollution during prenatal and postnatal periods, we selected a subpopulation from SYC including children born and living in Stockholm County all the time between 1993 and 2007 and with biological mothers living in Stockholm County 1 year before and 1 year after the child’s birth ($n = 277,478$). Each child born in Sweden or each immigrant staying in Sweden for at least 1 year is assigned a unique personal identity number, which enables accurate linkage from different health registers to various socioeconomic background information while maintaining individual anonymity (Ludvigsson et al. 2009).

The cases constituted children with ASD ($n = 5,529$) identified from the National Patient Register (NPR), the Clinical Database for Child and Adolescent Psychiatry in Stockholm (PASTILL), the Habilitation Register (HAB), and the Stockholm Regional Health Care Data warehouse (VAL) until 31 December 2011. These registers cover all public-financed health seeking pathways for ASD, with or without presence of ID, in Stockholm County during the whole study period, described in detail in a validation study (Idring et al. 2012). Diagnosis and care for ASD and ID was based on the International Classification of Diseases 9th or 10th Revision (ICD-9/10 codes: 299/F81 for ASD and 317–319/F70–79 for ID), the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV code: 299 for ASD and 317–319 for ID), or any use of habilitation services followed by an ASD diagnosis. Cases were further divided into ASD with and without ID, regardless of whichever diagnosis came first. We excluded adopted children ($n = 2$, 0.04%), multiple births ($n = 162$, 3.1%), and births that were not recorded in the Medical Birth Register ($n = 229$, 4.1%).

We selected a random sample of 20,000 children from the subpopulation of SYC as controls and further excluded 420 (2.1%) who developed ASD during follow-up. Among the remaining 19,580 controls, we excluded adopted children ($n = 15$, 0.1%), multiple births ($n = 585$, 3.1%), and births that were not recorded in the Medical Birth Register ($n = 743$, 3.8%).

**Exposure Assessment**

Detailed descriptions of the air pollution exposure assessment methodology are available in previous publications (Bellander et al. 2001; Gruzieva et al. 2012). Briefly, a Gaussian air quality dispersion model was used to estimate the temporal and spatial distribution of NO$_x$ and PM$_{10}$ in Stockholm County during the study period. This was based on emission databases for NO$_x$ in 1990, 1995, 2000, 2002–2004, and interpolations of estimated levels during the remaining years of the exposure period. PM$_{10}$ did not show any time trends during this period, and model calculations were based on the year 2004. A street canyon contribution was added for the most polluted street segments in the inner city of Stockholm with multistory houses on both sides. Comparisons between model estimated and monitoring station–measured NO$_x$ levels during the exposure period provided an $R^2$ of 0.74–0.80, indicating a moderate-to-high model performance (Johansson et al. 2008). For PM$_{10}$ the $R^2$ was 0.61 (Eneroth et al. 2006). Relevant residential addresses of the study subjects were geocoded and pollutant levels emanating from road traffic were estimated at these coordinates from the dispersion models and used to calculate annual average concentrations for NO$_x$ and PM$_{10}$. NO$_x$ is used as a marker for tail pipe emissions, such as fine particles, whereas PM$_{10}$ reflects coarse particulates, mainly originating from road dust. To account for changes in exposure levels among those moving to another residence, time-weighted NO$_x$ and PM$_{10}$ concentrations related to road traffic emissions were calculated based on all registered addresses during the pregnancy and the child’s first year of life.

**Covariates**

Information on child characteristics including birth year, sex, sibling order, gestational age, birth weight, congenital malformation and maternal characteristics including season of conception, smoking during pregnancy, and marital status at child birth were obtained from the Medical Birth Register (Swedish National Board of Health and Welfare 2003). Data regarding family characteristics at child birth including disposable income within household, maternal and paternal education, as well as employment of the mother and father were retrieved from the longitudinal integration database for health insurance and labor market studies, originally from Statistics Sweden (2016). Information on maternal and paternal age at child birth, municipality of the mother at child birth, and parental birth countries was retrieved from the Total Population Register (Statistics Sweden 2006). Furthermore, area-based SES characteristics at birth year were measured by a neighborhood deprivation index (Saritaslan et al. 2013). Neighborhood was defined by the small-area market statistics (SAMS), which is based on small socioeconomically homogeneous areas with an average of 1,000 residents. Information on welfare beneficia ries, unemployment, immigrants, divorce rate, income, education, residential mobility, and criminal conviction rate from Statistics Sweden were linked with each SAMS area to calculate a neighborhood deprivation index using principal component analysis (Saritaslan et al. 2013). The neighborhood deprivation index was further categorized into tertiles. Information on family history of psychiatric disorders including schizophrenia, bipolar disorders, ID, non-affective psychosis, and other diagnoses in the mental and behavioral disorders chapter from ICD-10 (F-diagnoses) was obtained through NPR, VAL, and PASTILL (see Table S1 for diagnostic codes).

**Statistical Analyses**

To estimate the independence of pollutants over time, we calculated correlation coefficients for NO$_x$ and PM$_{10}$ over the pregnancy period of the mother and child’s first year of life. Sociodemographic characteristics were compared among cases and controls using the $t$-test or chi-square test. To assess the association between exposure to pollutants during each specific period and ASD in children and account for differences in diagnostic practices over time and across municipalities, we used conditional logistic regression models and conditioned on calendar year and municipality of birth (see Table S2 for detailed information on classification of municipalities). First, the two air pollution components were treated as continuous variables, and fixed exposure increments per 20 μg/m$^3$ for NO$_x$ and per 10 μg/m$^3$ for PM$_{10}$.
for PM$_{10}$ were used in all models to estimate the risk of ASD overall, with and without ID. Second, pollutants were categorized into quartiles based on their distribution in each time period and the lowest quartiles served as reference group when modeling the association with ASD overall. To assess effect modification, we examined the association between continuous exposure to either pollutant and ASD overall, with and without ID by sex, sibling order, mother’s marital status, neighborhood deprivation, highest education between parents at child birth, mother’s smoking status during pregnancy, as well as residential mobility during mother’s pregnancy via inclusion of the interaction terms in the regression models. Wald tests were used to examine the statistical significance of interaction terms, using $p < 0.05$ as significance level. In sensitivity analyses, we excluded children with ASD diagnoses before 2 years of age, those born before year 2003 (when we have complete coverage on ASD diagnosis from birth from all registers), children with congenital malformation, those with either parent having any psychiatric disorders, children of foreign-born parents, children born to mothers with preeclampsia, gestational and gestational diabetes, premature rupture of the membranes, placental abruption, premature birth countries, mother’s education, father’s age, sex, birth month, sibling order, maternal age, paternal age, mother’s marital status, parents’ birth countries, mother’s education, father’s education, mother’s employment, father’s employment, disposable income within household, and neighborhood deprivation. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

The study protocol was reviewed and approved by the regional ethics review board in Stockholm, Sweden.

**Results**

Table 1 lists characteristics of the study population. Compared with controls, ASD cases were on average 2 years younger, more likely to be boys, have a parent with < 12 years of education, being unemployed, or with psychiatric disorders. Maternal characteristics were also slightly different between cases and controls. For example, mothers of cases were less often married or cohabiting, but more often smoked during pregnancy.

Figure 1 shows box plots of air pollutant levels during the pregnancy and the child’s first year of life, respectively. The arithmetic mean levels of NO$_x$ from local traffic were 11.0 μg/m$^3$ during mother’s pregnancy, and dropped somewhat to 9.8 μg/m$^3$ during the postnatal period (see Table S3). On the other hand, the yearly arithmetic mean levels of PM$_{10}$ were relatively constant (4.2–4.4 μg/m$^3$). NO$_x$ was closely correlated with PM$_{10}$ ($r^2 ≥ 0.7$) over the study period as both have local traffic as the major source.

The associations between air pollution exposure as a continuous measure and the risk of ASD overall, with and without ID, are shown in Table 2. We did not observe any differences in risk of ASD overall, with or without ID, by exposure during pregnancy to NO$_x$ or PM$_{10}$ after adjusting for potential confounders (e.g., adjusted OR was 1.02 (95% CI: 0.94, 1.10) for ASD overall per 20-μg/m$^3$ increase of NO$_x$ and 1.06 (95% CI: 0.89, 1.26) for ASD with ID, and 1.01 (95% CI: 0.93, 1.10) for ASD without ID). Corresponding ORs for an increment of 10 μg/m$^3$ of PM$_{10}$ were 1.00 (95% CI: 0.86, 1.15), 1.03 (95% CI: 0.74, 1.42), and 0.98 (95% CI: 0.84, 1.15), respectively. Results were similar for exposure during the child’s first year of life (Figure 2; see also Table S4). However, when pollutants were categorized into quartiles, children living in areas within the 3rd and 4th quartiles of air pollution exposure had a slightly lower risk of ASD overall compared with those living in areas within the least polluted quartile, especially in relation to exposure during pregnancy (Table 2). We observed no major confounding by individual or neighborhood covariates on the association between pollutant levels and ASD (Table 2; see also Table S4). However, the adjustments consistently generated somewhat lower ORs for ASD without ID, which constituted the major group among the cases.

We observed a similar pattern of associations in subgroups based on parental education (Figure 3 for ASD overall; see also Figures S2 and S3 for ASD with and without ID). There was a suggested inverse relation between air pollution exposure and ASD for those in the most deprived neighborhoods, especially for ASD without ID. A statistically significant interaction was seen for residential mobility, where a decreased risk for ASD with air pollution exposure pre- or postnatally was seen only among those changing residential address during pregnancy (all $p$-interactions $< 0.03$). Further analyses showed that moving patterns were related to SES and psychiatric illness among the parents (see Table S5). Interactions with air pollution exposure in relation to ASD were also investigated for several other characteristics, including sex, sibling order, mother’s smoking and marital status, but no statistically significant effect modification was observed (data not shown).

In sensitivity analyses including multiple births (see Table S6) or excluding children born to mothers with changing residential address during pregnancy, cases diagnosed before 2 years of age, children with congenital malformation, children born before 2003, children born to mothers with preeclampsia, pregestational and gestational diabetes, premature rupture of the membranes, placental abruption, children of foreign-born parents, children born at < 37 weeks gestation or with a birth weight < 2,500 g, we found similar patterns of results for both pollutants as in our main analysis (see Table S7). Furthermore, in analyses not conditioning on municipality of birth, we observed that exposure to NO$_x$ and PM$_{10}$ during pre- or postnatal period appeared to be associated with a decreased risk of ASD (see Table S8).

**Discussion**

Among children born between 1993 and 2007 in Stockholm County, we found that per- and postnatal exposure to either NO$_x$ or PM$_{10}$ was not associated with ASD overall, with or without ID. There was an inverse association between air pollution exposure and ASD risk for children of mothers who changed residential addresses during pregnancy, which could be partly explained by confounding by SES and psychiatric diseases in the parents. We previously reported no association between traffic-related air pollution during pre- or postnatal periods and subclinical ASD outcomes using a twin cohort from Stockholm; however, risk estimates tended to lie below one with wide confidence intervals (Gong et al. 2014). The present study showed a similar result using a much larger sample but contradicts the positive associations reported in several previous studies from the United States (Kalkbrenner et al. 2010, 2015; Raz et al. 2015; Roberts et al. 2013; Volk et al. 2011, 2013). One possible explanation for the inconsistent results could be the lower levels of air pollution in Stockholm. For example, mean levels of PM$_{10}$ in California and Taiwan were reported at about 25–36 and 58 μg/m$^3$ (Becerra et al. 2013; Jung et al. 2013; Kalkbrenner et al. 2015; Volk et al. 2013). However, the local traffic related PM$_{10}$ concentrations in the current study was 4.3 μg/m$^3$ during mother’s pregnancy and...
child’s first year of life, and the background PM10 level generated from long-distance transportation near Stockholm County has remained at a rather stable level at 10 μg/m³ across the whole study period (Burman and Norman 2013). Previous studies have generally reported on nitrogen dioxide (NO2) with mean levels in California and Taiwan of 32–43 μg/m³ (converted from 17 and 28.8 ppb with temperature at 25°C) (Becerra et al. 2013; Jung et al. 2013; Volk et al. 2013). We used NOx as a marker because it better reflects the tail-pipe emissions, but it is less often measured or reported. The average urban background levels of NO2 during the study period in Stockholm decreased from around 20 to 14 μg/m³ (Durant et al. 2014), and were thus considerably lower than the levels in the areas reported in earlier publications. Furthermore, the air pollution levels in Stockholm County, constituting the catchment area for our cohort and another cohort included in a recent European meta-analysis, are lower than in most (NOx) or
definition of 32–43 μg/m³ (converted from 17 and 28.8 ppb with temperature at 25°C) (Becerra et al. 2013; Jung et al. 2013; Volk et al. 2013). We used NOx as a marker because it better reflects the tail-pipe emissions, but it is less often measured or reported. The average urban background levels of NO2 during the study period in Stockholm decreased from around 20 to 14 μg/m³ (Durant et al. 2014), and were thus considerably lower than the levels in the areas reported in earlier publications. Furthermore, the air pollution levels in Stockholm County, constituting the catchment area for our cohort and another cohort included in a recent European meta-analysis, are lower than in most (NOx) or

table 1. Characteristics of 5,136 ASD and 18,237 randomly selected control subjects born in Stockholm, Sweden, between 1993 and 2007.

| Characteristic | Cases (n = 5,136) | Controls (n = 18,237) | p-Value |
|----------------|------------------|----------------------|---------|
| Child characteristics | | | |
| Age at end of follow-up (years) | 13.0 ± 4.1 | 11.5 ± 4.5 | < 0.0001 |
| Sex | | | |
| Male | 3,760 (73.2) | 9,408 (51.6) | < 0.0001 |
| Female | 1,376 (26.8) | 8,829 (48.4) | |
| Birth year | | | |
| 1993–1995 | 1,321 (25.7) | 3,527 (19.3) | < 0.0001 |
| 1996–1998 | 1,184 (23.1) | 3,050 (16.7) | |
| 1999–2001 | 1,088 (21.2) | 3,200 (17.5) | |
| 2002–2004 | 920 (17.9) | 4,014 (22.0) | |
| 2005–2007 | 623 (12.1) | 4,446 (24.4) | |
| Sibling order | | | |
| First child | 2,402 (46.8) | 7,785 (42.7) | < 0.0001 |
| Not first child | 2,734 (53.2) | 10,452 (57.3) | |
| Birth weight (g) | | | |
| < 2,500 | 259 (5.0) | 487 (2.6) | < 0.0001 |
| 2,500–3,000 | 576 (11.2) | 1,777 (9.7) | |
| 3,001–3,500 | 1,507 (29.3) | 5,845 (32.1) | |
| 3,501–4,000 | 1,742 (33.9) | 6,561 (36.0) | |
| > 4,000 | 1,015 (19.8) | 3,408 (19.1) | |
| Congenital malformations | | | |
| No | 4,851 (94.7) | 16,565 (90.8) | < 0.0001 |
| Yes | 274 (5.3) | 530 (2.9) | |
| Intellectual disability | | | |
| No | 4,223 (82.2) | 18,119 (99.4) | < 0.0001 |
| Yes | 913 (17.8) | 118 (0.6) | |
| Family characteristics | | | |
| Maternal age at child birth (years) | 30.5 ± 5.3 | 30.9 ± 4.9 | < 0.0001 |
| Paternal age at child birth (years) | 33.3 ± 6.6 | 33.6 ± 6.1 | < 0.0001 |
| Season of conception | | | |
| Spring (March–May) | 1,300 (25.3) | 5,008 (27.5) | 0.0042 |
| Summer (June–August) | 1,340 (26.1) | 4,784 (26.2) | |
| Autumn (September–November) | 1,288 (25.1) | 4,230 (23.2) | |
| Winter (December–February) | 1,208 (23.5) | 4,215 (23.1) | |
| Residential mobility during pregnancy | | | |
| Nonmovers | 4,025 (78.6) | 14,646 (80.5) | |
| Movers | 1,065 (21.4) | 3,551 (19.5) | |
| Parents’ birth countries | | | |
| Both from Sweden | 3,512 (68.4) | 12,796 (70.2) | 0.0013 |
| One from other countries | 889 (17.3) | 2,780 (15.2) | |
| Both from other countries | 713 (13.9) | 2,610 (14.1) | |
| Disposable income within household at birth (quintiles) | | | |
| Lowest | 586 (11.4) | 1,860 (10.2) | < 0.0001 |
| Lower middle | 1,193 (23.2) | 3,509 (19.2) | |
| Middle | 1,266 (24.7) | 4,229 (23.2) | |
| Upper middle | 1,142 (22.2) | 4,167 (23.0) | |
| Highest | 949 (18.5) | 4,452 (24.4) | |
| Neighborhood deprivation index at child birth | | | |
| 0.15 ± 0.12 | 0.02 ± 0.12 | | < 0.0001 |
| Medium (–0.55 to 0.19) | 1,643 (32.0) | 6,301 (34.6) | < 0.0001 |
| High (0.19 to 4.06) | 2,030 (39.5) | 5,607 (31.2) | |
| Mother’s education at child birth | | | |
| Low (≤ 9 years) | 808 (15.7) | 2,230 (12.2) | < 0.0001 |
| Medium (10–12 years) | 2,394 (46.6) | 7,879 (43.2) | |
| High (> 12 years) | 1,921 (37.4) | 8,076 (44.3) | |

Note: Values are n (%) or mean ± SD. Missing with < 2% was not presented.
Exposure to air pollution and autism spectrum disorders

Residential mobility during pre- and postnatal life could also contribute to the inconsistent results. Young maternal age, being unmarried, having psychiatric diseases, and low SES have been associated with residential mobility during pregnancy (Bell and Belanger 2012; Fell et al. 2004; Miller et al. 2010; Tulloch et al. 2010) and may thereby affect offspring’s ASD risk estimates (Rai et al. 2012; Roberts et al. 2013; Thomas et al. 2012). Most previous studies have not investigated the potential impact by residential mobility (Jung et al. 2013; Kalkbrenner et al. 2015; Roberts et al. 2013; Volk et al. 2013). One report from the Nurses’ Health Study II found that the positive association of PM2.5 and ASD was stronger among nonmovers, although no interaction test was performed based on moving status (Raz et al. 2015). We observed an inverse association among families that changed their residential addresses during mother’s pregnancy. The reason for this is unclear, and the influence of moving residence on the association between air pollution and ASD, which was related to SES and psychiatric disorders among the parents, should be investigated in further studies. Furthermore, misclassification of municipality at delivery among movers could contribute to the observed inverse association because we did not take into account the effect of municipalities where the mother lived before delivery.

Another explanation of the inconsistent results could be different proportions of

---

**Figure 1.** Box plot describing the distribution of NOx (white) and PM10 (gray) concentrations (μg/m³) from local traffic in study population during mother’s pregnancy and first year after child birth. The box and whiskers denote the 5th, 25th, 50th, 75th, 95th percentile and outlier values of pollutants’ distributions.

**Figure 2.** Odds ratios and 95% confidence intervals for ASD overall, ASD with or without ID by residential address-based (A) NOx (per 10-μg/m³ increase) and (B) PM10 (per 20-μg/m³ increase) levels during mother’s pregnancy and child’s first year of life. All models were conditioned on calendar year of birth and municipality of birth, as well as adjusted for sex, birth month, sibling order, maternal age, paternal age, mother’s marital status, parents’ birth countries, mother’s education, father’s education, mother’s employment, father’s employment, disposable income within household, and neighborhood deprivation.
high- and low-functioning ASD in different study settings. For example, one study in the United States reported that 40% of the ASD cases also had ID (Kalkbrenner et al. 2015), but there were only 19% of ASD cases with co-existing ID diagnosis in our study. If the positive association could only be seen in this subtype of ASD, the higher proportion of ASD without ID in our study might have resulted in diluted associations.

Residual confounding could also contribute to the inconsistent findings by socioeconomic indicators, for example. Children from higher-SES families were more likely to be diagnosed with ASD in previous studies, and the OR estimates for both air pollutants appeared slightly lower after adjusting for confounders including birth year, birth order, parental age, income, education, and ethnicity (Becerra et al. 2013; Kalkbrenner et al. 2015; Raz et al. 2015; Roberts et al. 2013; Thomas et al. 2012; Volk et al. 2013). Family and contextual SES covariates had relatively small effects on the association between air pollutants and ASD in our study. Sweden has a rather universal

Table 2. Risk of ASD overall by quartiles of modeled pollutants’ levels at different time windows among 5,136 ASD cases and 18,237 controls born in Stockholm, Sweden, between 1993 and 2007.

| Time windows and pollutants | No. of cases/controls | Models A\(^b\) OR (95% CI) | Models B\(^c\) OR (95% CI) | Models C\(^c\) OR (95% CI) |
|-----------------------------|-----------------------|----------------------------|----------------------------|----------------------------|
| Entire pregnancy NO\(_x\) | 5,112/18,192          |                            |                            |                            |
| 2nd quartile                | 1,340/4,486           | 1.01 (0.91, 1.13)          | 0.98 (0.88, 1.10)          | 0.96 (0.85, 1.07)          |
| 3rd quartile                | 1,285/4,541           | 0.94 (0.83, 1.06)          | 0.91 (0.80, 1.03)          | 0.88 (0.78, 1.00)          |
| 4th quartile                | 1,279/4,547           | 0.94 (0.82, 1.09)          | 0.91 (0.78, 1.05)          | 0.89 (0.77, 1.03)          |
| PM\(_{10}\)                 | 2nd quartile          | 1,399/4,427                | 1.03 (0.92, 1.14)          | 1.01 (0.91, 1.12)          | 0.98 (0.88, 1.09)          |
| 3rd quartile                | 1,247/4,579           | 0.92 (0.81, 1.04)          | 0.90 (0.79, 1.02)          | 0.87 (0.77, 0.99)          | 0.86 (0.75, 0.99)          |
| 4th quartile                | 1,140/4,886           | 0.93 (0.81, 1.06)          | 0.88 (0.77, 1.02)          | 0.86 (0.75, 0.99)          |
| First year of life          | 5,121/18,225          |                            |                            |                            |
| NO\(_x\)                   | 2nd quartile          | 1,321/4,515                | 1.05 (0.94, 1.18)          | 1.02 (0.91, 1.15)          | 0.98 (0.87, 1.10)          |
| 3rd quartile                | 1,328/4,509           | 1.04 (0.91, 1.19)          | 1.00 (0.87, 1.14)          | 0.95 (0.83, 1.09)          | 0.95 (0.83, 1.09)          |
| 4th quartile                | 1,329/4,539           | 1.06 (0.90, 1.25)          | 1.00 (0.85, 1.18)          | 0.98 (0.81, 1.13)          | 0.98 (0.81, 1.13)          |
| PM\(_{10}\)                | 2nd quartile          | 1,398/4,439                | 1.10 (0.99, 1.23)          | 1.08 (0.97, 1.21)          | 1.03 (0.92, 1.16)          |
| 3rd quartile                | 1,280/4,557           | 1.03 (0.90, 1.17)          | 0.98 (0.86, 1.12)          | 0.93 (0.82, 1.07)          | 0.93 (0.82, 1.07)          |
| 4th quartile                | 1,160/4,676           | 1.05 (0.90, 1.22)          | 0.97 (0.83, 1.13)          | 0.92 (0.78, 1.07)          | 0.92 (0.78, 1.07)          |

\(^a\)Models were conditioned on calendar year of birth and municipality of birth, as well as adjusted for sex and birth month.

\(^b\)Models were conditioned on calendar year of birth and municipality of birth, as well as adjusted for sex, birth month, birth order, parents’ birth countries, mother’s marital status, mother’s education, father’s education, mother’s employment, father’s employment, and disposable income within household.

\(^c\)Models were conditioned on calendar year of birth and municipality of birth, as well as adjusted for sex, birth month, birth order, parents’ birth countries, mother’s marital status, mother’s education, father’s education, mother’s employment, father’s employment, disposable income within household, and neighborhood deprivation.

Figure 3. Odds ratios and 95% confidence intervals for ASD overall by residential address-based (A) NO\(_x\) (per 10-μg/m\(^3\) increase) and (B) PM\(_{10}\) (per 20-μg/m\(^3\) increase) levels during mother’s pregnancy and child’s first year of life in stratified samples. All models were conditioned on calendar year of birth and municipality of birth, as well as adjusted for sex, birth month, sibling order, maternal age, paternal age, mother’s marital status, parents’ birth countries, mother’s education, father’s education, mother’s employment, father’s employment, disposable income within household, and neighborhood deprivation as covariates.

Note: The p-value was presented based on the Wald test for the indicated interaction term.

\(\diamond\) Crude ORs \(\mathbb{N}\) Adjusted ORs \(\mathbb{H}\) Adjusted 95% CIs
Exposure to air pollution and autism spectrum disorders

Pre- and postnatal period is not associated with ASD. The absence of positive associations in our study may be related to comparatively low air pollutant levels.

Reference

Allen JL, Liu X, Pelkowski S, Palmer B, Conrad K, Oberdörster G, et al. 2014. Early postnatal exposure to ultrafine particulate matter air pollution: persistent ventriculomegaly, neurochemical disruption, and glial activation preferentially in male mice. Environ Health Perspect 122:939–945, doi: 10.1289/ehp.1307984.

American Psychiatric Association. 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Arlington, VA:American Psychiatric Association.

Anell A, Glennärd AH, Merkur S. 2012. Health Systems in Transition: Sweden—A Health System Review 2012. Copenhagen, Denmark:World Health Organization, on behalf of the European Observatory on Health Systems and Policies. http://www.euro.who.int/__data/assets/pdf_file/0008/180469/e96455.pdf [accessed 29 November 2016].

Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, et al. 1995. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 25:63–77.

Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, et al. 2006. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet 368:210–215.

Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. 2013. Ambient air pollution and autism in Los Angeles County, California. Environ Health Perspect 121:380–386, doi: 10.1289/ehp.1205827.

Bell ML, Belanger K. 2012. Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures. J Expo Sci Environ Epidemiol 22:429–438.

Bellander T, Berglund N, Gustavsson P, Jonson T, Nyberg F, Pershagen G, et al. 2001. Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in Stockholm. Environ Health Perspect 109:633–639.

Braveman PA, Cubbin C, Egerter S, Chideya S, Marchi KS, Metzler M, et al. 2005. Socioeconomic status in health research: one size does not fit all. JAMA 294:2879–2888.

Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparén P, Cnattingius S. 2009. Can association between preterm birth and autism be explained by maternal or neonatal morbidity? Pediatrics 124:e817–e825.

Buescher AV, Civid D, Knapp M, Mandell DS. 2014. Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA Pediatr 168:721–728.

Burman L, Norman M. 2013. The Air Quality in Stockholm: Annual Report 2012 [in Swedish]. http://www.slb.nu/slb/rapporter/pdfs/lvb2013_005.pdf [accessed 7 February 2014].

CDC (Centers for Disease Control and Prevention). 2014. Prevalence of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. MMWR Surveill Summ 63(2):1–21.

Daniels JL, Forssen U, Hultman CM, Cnattingius S, Savitz DA, Feychtling M, et al. 2008. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. Pediatrics 121:1357–1392.

Durant JL, Beelen R, Eeftens M, Meliefste K, Cyrus J, Heinrich J, et al. 2014. Comparison of ambient airborne PM_{2.5} and PM_{10} absorbance and nitrogen dioxide ratios measured in 1999 and 2008 in three areas in Europe. Sci Total Environ 487:290–296.

Eneroth K, Johansson C, Bellander T. 2006. Exposure: Comparison between Measurements and Calculations Based on Dispersion Modelling (Expose). 2006:12. Stockholm Environment and Health Protection Administration. http://slb.nu/slb/rapporter/pdf8/ivr2006_012.pdf [accessed 25 November 2016].

Fell DB, Dodds L, King WD. 2004. Residential mobility during pregnancy. Paediatr Perinat Epidemiol 18:408–414.

Gardener H, Spiegelman D, Buka SL. 2011. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics 128:344–355.

Gong T, Almqvist C, Bolte S, Lichtenstein P, Ankarsäter H, Lind T, et al. 2014. Exposure to air pollution from traffic and neurevelopmental disorders in Swedish twins. Twin Res Hum Genet 17:553–562.

Grzuza O, Bellander T, Eneroth K, Kul I, Melén E, Nordling E, et al. 2012. Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. J Allergy Clin Immunol 129:240–246.

Guxens M, Ghashabian A, Gong T, Garcia-Esteban R, Porta D, Giorgis-Allemand L, et al. 2016. Air pollution exposure during pregnancy and childhood autistic traits in four European population-based cohort studies: the ESCAPE project. Environ Health Perspect 124:133–140, doi: 10.1289/ehp.1500423.

Hajat A, Diez-Roux AV, Adar SD, Aucinccinos AH, Lovasi GS, O’Neill MS, et al. 2013. Air pollution and individual and neighborhood socioeconomic status: evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). Environ Health Perspect 121:1259–1263, doi: 10.1289/ehp.1206337.

Hoekstra RA, Happé F, Baron-Cohen S, Ronald A. 2009. Association between extreme autistic traits and intellectual disability: insights from a general population twin study. Br J Psychiatry 198:531–536.

Hoekstra RA, Happé F, Baron-Cohen S, Ronald A. 2010. Limited genetic covariance between autistic traits and intelligence: findings from a longitudinal twin study. Am J Med Genet B Neuropsychiatr Genet 153B:994–1007.

Hultman CM, Sparén P, Cnattingius S. 2002. Perinatal risk factors for infantile autism. Epidemiology 13:417–423.

Idring S, Lundberg M, Sturm H, Dalman C, Grumpert C, Rai D, et al. 2015. Changes in prevalence of autism spectrum disorders in 2001–2011: findings from the Stockholm Youth Cohort. J Autism Dev Disord 45:1766–1773.

Idring S, Rai D, Dal H, Dalman C, Sturm H, Zander E, et al. 2012. Autism spectrum disorders in the Stockholm Youth Cohort design, prevalence and validity. PLoS One 7:e41280, doi:10.1371/journal.pone.0041280.

Johansson C, Andersson C, Bergström R, Kreici P. 2008. Exposure to particles due to local and non-local sources in Stockholm—estimates based on modelling and measurements 1997–2006. ITM 15:1–175. Stockholm Sweden:Stockholm University, Department of Applied Environmental Science. http://slb.nu/slb/rapporter/pdf16/itm2008_175.pdf [accessed 29 November 2016].

Jung CR, Lin YT, Hwang BF. 2013. Air pollution and newly diagnostic autism spectrum disorders: a
population-based cohort study in Taiwan. PLoS One 8:e75510, doi: 10.1371/journal.pone.0075510.

Kalkbrenner AE, Daniels JL, Chen JC, Poole C, Emch M, Morrissey J. 2010. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. Epidemiology 21:631–641.

Kalkbrenner AE, Windham GC, Serre ML, Akita Y, Wang X, Hoffman K, et al. 2015. Particulate matter exposure, prenatal and postnatal windows of susceptibility, and autism spectrum disorders. Epidemiology 26:30–42.

Lauritsen MB, Pedersen CB, Mortensen PB. 2004. The incidence and prevalence of pervasive developmental disorders: a Danish population-based study. Psychol Med 34:1329–1346.

Lee BK, Magnusson C, Gardner RM, Blomström Å, Lauritsen MB, Pedersen CB, Mortensen PB. 2003. Parental socioeconomic status and risk of offspring autism spectrum disorders in a Swedish population-based study. J Am Acad Child Adolesc Psychiatry 42:1057–1066.

Melén E, Nyberg F, Långström N, D’Onofrio B, Hallqvist J, et al. 2011. A twin study of autism symptoms in Sweden. Mol Psychiatry 16:201–213.

Nassar N, Dixon G, Bourke J, Bower C, Glasson E, de Klerk N, et al. 2009. Autism spectrum disorders in young children: effect of changes in diagnostic practices. Int J Epidemiol 38:1245–1254.

Nordling E, Berglind N, Melén E, Emens H, Hallberg J, Furu L, et al. 2008. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. Epidemiology 19:401–408.

Palmer RF, Blanchard S, Wood R. 2009. Proximity to point sources of environmental mercury release as a predictor of autism prevalence. Health Place 15:18–24.

Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C. 2013. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. BMJ 346:e2058, doi: 10.1136/bmj.e2058.

Rai D, Lewis G, Lundberg M, Araya R, Svensson A, Dalman C, et al. 2012. Parental socioeconomic status and risk of offspring autism spectrum disorders in a Swedish population-based study. J Am Acad Child Adolesc Psychiatry 51:467–476.e6.

Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. 2015. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case-control analysis within the Nurses’ Health Study II cohort. Environ Health Perspect 123:264–270, doi: 10.1289/ehp.1408133.

Ritvo ER, Jorde LB, Mason-Brothers A, Freeman BJ, Pingree C, Jones MB, et al. 1989. The UCLA-University of Utah epidemiologic survey of autism: recurrence risk estimates and genetic counseling. Am J Psychiatry 146:1032–1038.

Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, et al. 2013. Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses’ Health Study II participants. Environ Health Perspect 121:978–984, doi: 10.1289/ehp.1206187.

Ronald A, Larsson H, Anckarsäter H, Lichtenstein P. 2011. A twin study of autism symptoms in Sweden. Mol Psychiatry 16:1038–1047.

Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. 2014. The familial risk of autism. JAMA Psychiatry 71:170–177.

Sariaslan A, Långström N, D’Onofrio B, Hallqvist J, Franck J, Lichtenstein P. 2013. The impact of neighbourhood deprivation on adolescent violent criminality and substance misuse: a longitudinal, quasi-experimental study of the total Swedish population. Int J Epidemiol 42:1057–1066.

Schultz ES, Gruzieva O, Bellander T, Bottai M, Hallberg J, Kull I, et al. 2012. Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. Am J Respir Crit Care Med 186:1286–1291.

Statistics Sweden. 2006. Background Facts, Historic Population Register. http://www.scb.se/statistik/publikationer/BE9999_2006A01_BR_BER6ST0603.pdf [accessed 29 November 2016].

Statistics Sweden. 2016. Background Facts, the Longitudinal Integration Database for Health Insurance and Labor Market Studies 1990–2013 [in Swedish]. http://www.scb.se/Statistik/AM/AM9901_/dokument/AM9901_1990I13_BR_AM76BR1601.pdf [accessed 29 November 2016].

Swedish National Board of Health and Welfare. 2003. The Swedish Medical Birth Register—A Summary of Content and Quality. 2003-112-3. Stockholm, Sweden: National Board of Health and Welfare, Centre for Epidemiology. http://www.socialstyrelsen.se/NR/rdonlyres/E9BE4DDE-95EE-4E3F-A56F-36CA5125CA8C/1132/20031123.pdf [accessed 29 November 2016].

Thomas P, Zahorodyny W, Peng B, Kim S, Jani N, Halperin W, et al. 2012. The association of autism diagnosis with socioeconomic status. Autism 16:201–213.

Tulloch AD, Fearon P, Fathy T, David A. 2010. Residential mobility among individuals with severe mental illness: cohort study of UK700 participants. Soc Psychiatry Psychiatr Epidemiol 45:767–777.

Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. 2011. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect 119:873–877, doi: 10.1289/ehp.1002835.

Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. 2013. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry 70:71–77.

Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. 2006. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area. Environ Health Perspect 114:1438–1444, doi: 10.1289/ehp.9120.