Twin Research and Human Genetics
Volume 17 ▌ Number 6 ▌ pp. 553–562 ▌ © The Author(s) 2014 ▌ doi:10.1017/thg.2014.58

Exposure to Air Pollution From Traffic and Neurodevelopmental Disorders in Swedish Twins

Tong Gong,[1] Catarina Almqvist,[1,2] Sven Bölte,[3,4] Paul Lichtenstein,[1] Henrik Anckarsäter,[5] Tomas Lind,[6] Cecilia Lundholm,[1] and Göran Pershagen[6,7]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[2]Lung and Allergy Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
[3]Department of Women's and Children's Health, Center of Neurodevelopmental Disorders (KIND), Karolinska Institutet, Stockholm, Sweden
[4]Division of Child and Adolescent Psychiatry, Stockholm County Council, Stockholm, Sweden
[5]Department of Pharmacology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[6]Center for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden
[7]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Background: Recent studies have reported associations between air pollution exposure and neurodevelopmental disorders in children, but the role of pre- and postnatal exposure has not been elucidated. *Aim:* We aimed to explore the risk for autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD) among children in relation to pre- and postnatal exposure to air pollution from road traffic. *Methods:* Parents of 3,426 twins born in Stockholm during 1992–2000 were interviewed, when their children were 9 or 12 years old, for symptoms of neurodevelopmental disorders. Residence time-weighted concentrations of particulate matter with a diameter <10 μm (PM_{10}) and nitrogen oxides (NO_x) from road traffic were estimated at participants' addresses during pregnancy, the first year, and the ninth year of life using dispersion modeling, controlling for seasonal variation. Multivariate regression models were used to examine the association between air pollution exposure and neurodevelopmental outcomes, adjusting for potential confounding factors. *Results:* No clear or consistent associations were found between air pollution exposure during any of the three time windows and any of the neurodevelopmental outcomes. For example, a 5–95% difference in exposure to NO_x during pregnancy was associated with odds ratios (ORs) of 0.92 (95% confidence interval (CI): 0.44–1.96) and 0.90 (95% CI: 0.58–1.40) for ASD and ADHD respectively. A corresponding range in exposure to PM_{10} during pregnancy was related to ORs of 1.01 (95% CI: 0.52–1.96) and 1.00 (95% CI: 0.68–1.47) for ASD and ADHD. *Conclusions:* Our data do not provide support for an association between pre- or postnatal exposure to air pollution from road traffic and neurodevelopmental disorders in children.

■ **Keywords:** air pollution, PM_{10}, NO_x, autism, ADHD, twins

Neurodevelopmental disorders are relatively common and pose a substantial challenge to society (Froehlich et al., 2007; Jarbrink et al., 2003; Kogan et al., 2008; Newton, 2012). For some conditions the diagnosis rates have increased, but the reasons behind these apparent time trends remain largely unknown. Improved awareness and widened diagnostic criteria may contribute, such as for attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), but probably do not explain the whole increase. Both ADHD and ASD are childhood-onset chronic conditions of moderate to high heritability (Anckarsater et al., 2011; Martin et al., 2002; Parr et al., 2011). However, their precise etiologies remain enigmatic, and the role of environmental factors acting as triggers or contributors to general vulnerability should not be disregarded (Sandin et al., 2014).

Epidemiological and experimental studies indicate that exposure to air pollution from road traffic may induce

RECEIVED 4 April 2014; ACCEPTED 26 June 2014. First published online 17 September 2014.

ADDRESS FOR CORRESPONDENCE: Tong Gong, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-171 77 Stockholm, Sweden. E-mail: tong.gong@ki.se

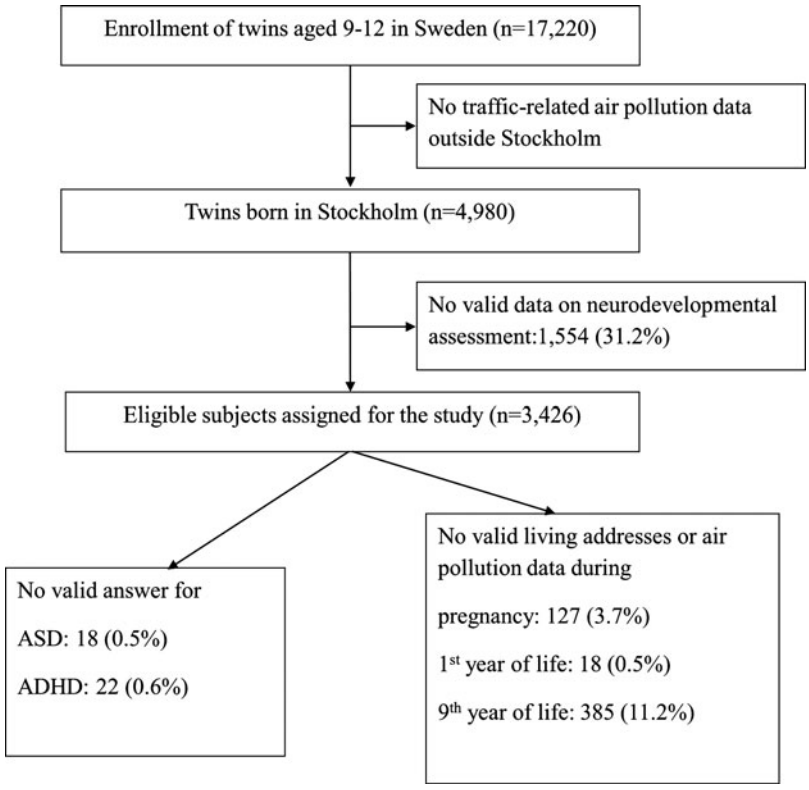

FIGURE 1
Summary of participation and response rates.

systemic inflammation and increase the risk of several diseases related to inflammation, such as asthma, allergy, and cardiovascular diseases (Mills et al., 2009; Nordling et al., 2008; Panasevich et al., 2009). Systemic inflammation can also contribute to neuronal injury and affect the development of central nervous system (Hagberg & Mallard, 2005). Recent epidemiological studies have shown associations between exposure to air pollution from road traffic or other sources and adverse neurodevelopmental effects in children (Becerra et al., 2013; Calderon-Garciduenas et al., 2011; Dix-Cooper et al., 2012; Guxens et al., 2012; Jung et al., 2013; Morales et al., 2009; Siddique et al., 2011; Volk et al., 2011, 2013; Vrijheid et al., 2012; Windham et al., 2006). However, more studies are needed to assess causality, particularly since the association may be confounded by socioeconomic and socio-demographic characteristics (Bhasin & Schendel, 2007; Flouri et al., 2012). Furthermore, it is not known whether there are specific periods of increased vulnerability.

The primary objective of this study was to investigate the relation between exposure to air pollution from road traffic and the risk of neurodevelopmental disorders in children, especially ASD and ADHD. In particular, the influence of exposure during potentially important time windows, such as the fetal and infancy periods, was in focus.

Materials and Methods

Study Population

Children from the Child and Adolescent Twin Study in Sweden (CATSS), an ongoing longitudinal cohort study that targets all twins born in Sweden since July 1, 1992, were the participants (Anckarsater et al., 2011). In this project, the twins born during 1992–2000 were included. Parents of 17,220 9-year-old twins were contacted and interviewed about their children's somatic and mental health as well as social environment (Figure 1). During the first 3 years of the study, 12-year-old twins were also included. Since the air pollution exposure assessment methodology was restricted to Stockholm County, 4,980 twins born in this area were selected and 3,426 completed neurodevelopmental assessment (response rate: 68.8%). The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Health Outcome Assessment

Children's neurodevelopmental outcomes were measured using the Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC) telephone interviews developed at the Institute of Neuroscience and Physiology, Child and Adolescent Psychiatry, Gothenburg University (Hansson et al., 2005). The A-TAC comprises 178 symptom questions from a lifetime perspective and is designed as an open-access and

https://doi.org/10.1017/thg.2014.58 Published online by Cambridge University Press

comprehensive tool for screening childhood ASD and other targeted disorders based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Response options for each question were coded as 0 for 'No,' 0.5 for 'Yes,' to some extent, and 1.0 for 'Yes'. In two previous validation studies, autistic-like traits were assessed by the sum scores of 12 items (based on the DSM-IV criteria) or 17 items (by adding one additional item from the flexibility and two additional items each from the language and social interaction modules; Larson et al., 2010; Hansson et al., 2005). In order to comprise the primary symptoms of ADHD, scores of 18 (based on the DSM-IV criteria) or 19 items (by adding one additional item from the impulsivity module) were summed. Cut-off values for the sum scores with high sensitivity and specificity from previous validation studies were used in the current study to resemble the probabilities of clinical diagnoses and severity of both diseases: ASD $\geq$ 4.5 for DSM-IV criteria and for the lower cut-off value of extended diagnostic criteria, ASD $\geq$ 8.5 for the higher cut-off value of extended diagnostic criteria, ADHD $\geq$ 8 for DSM-IV criteria, and ADHD $\geq$ 6 for the lower and ADHD $\geq$ 12.5 for the higher cut-off values of extended diagnostic criteria. Detailed information on the psychometric properties of the A-TAC is provided elsewhere (Anckarsater et al., 2011; Hansson et al., 2005; Larson et al., 2010).

Exposure Assessment

The air pollution concentrations at residential addresses during mother's pregnancy, child's first year of life, and the year before the neurodevelopmental assessment were estimated by dispersion models, described in detail elsewhere (Bellander et al., 2001; Gruzieva et al., 2012). Briefly, the residential history of the study participants was obtained from taxation authorities and geo-coded using a property register maintained by the Swedish mapping, cadastral, and land registration authority. The address information was linked with historical emission databases to obtain annual average levels of nitrogen oxides (NO_x) and particulate matter (PM) with less than 10 μm of diameter (PM_{10}). Residence time-weighted NO_x and PM_{10} concentrations related to road traffic emissions were calculated for each trimester and over the mother's pregnancy period, the child's first year, and the ninth year of life. Furthermore, daily 24-hour mean NO_x and PM_{10} levels from suburban stations were used to calculate the NO_x and PM_{10} levels during each trimester of pregnancy, which were taken into account in sensitivity analyses. Imputation for missing values of NO_x and PM_{10} in the trimester-specific analyses was performed using predictions from rooftop measurements of both pollutants from a monitoring station in the center of Stockholm.

Other Covariates

Information on gender (male/female), parity (first/second/third/fourth, or later), gestational age (<37 weeks/≥37 weeks), birth weight (<2,500 g/≥2,500 g), maternal age at birth (<25/25–29/30–34/≥35 years old), maternal smoking during pregnancy (no cigarette/1–9 cigarettes per day/≥10 cigarettes per day) was obtained from the Medical Birth Register (National Board of Health and Welfare, 2003). Using the longitudinal integration database for health insurance and labor market studies (LISA), originally from Statistics Sweden (2013), we obtained individual-level socio-economic data such as maternal marital status (married or cohabiting/single), parental education (≤9 years/10–12 years/>12 years), and family disposable income during mother's pregnancy, child's first year of life, and the ninth year of life with adjustment for inflation and family size. Furthermore, a neighborhood deprivation index was used to estimate area-based socioeconomic characteristics in the year of birth (Sariaslan et al., 2013). Neighborhood was defined by the Small-Area Market Statistics (SAMS) based on regional population density (Statistics Sweden, 2013). Data, including information from Statistics Sweden on welfare beneficiaries, unemployment, immigrants, divorce rate, income, education, residential mobility, and criminal conviction rate were linked with each SAMS unit to calculate a neighborhood deprivation index using principal component analysis. Information on comorbidity with severe chromosome abnormalities, neural tube defects, and other neurological diseases, including epilepsy and cerebral palsy (see Table S1 of the Supplementary Material), was obtained through parent-report in CATSS, as well as from the National Patient Register, according to diagnoses of hospital discharge or outpatient department visits.

Statistical Analysis

Generalized estimating equations (GEE) with exchangeable correlation structure in combination with the Huber–White sandwich estimator for standard errors to adjust for the clustering of observations within twin pairs were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for each neurodevelopmental outcome associated with the 5th to 95th percentile increase in NO_x or PM_{10} on the entire sample (Carlin et al., 2005). We used a directed acyclic graph to determine potential confounders for ORs (Greenland & Brumback, 2002). A series of models were run step-wise to assess OR changes by further adjustment for potential confounders; however, only crude and adjusted models, including all potential confounders ($p < .20$), are presented.

Cut-off values validated in two previous studies were used as outcomes in all analyses (Hansson et al., 2005; Larson et al., 2010). Furthermore, we added a general neurodevelopmental outcome, defined as scoring above any ASD- or ADHD-related cut-off values due to the high co-occurrence of both diseases. Sensitivity analyses were performed using air pollution exposure during each trimester of pregnancy and during child's ninth year of life,

https://doi.org/10.1017/thg.2014.58 Published online by Cambridge University Press

controlling for seasonal effect, and by defining cases of comorbidity with severe chromosome abnormality, neural tube defects, and other neurological diseases, including epilepsy and cerebral palsy (see Table S1). Furthermore, a subset of children whose mothers responded at the interview was analyzed to avoid reporting bias among different family members.

The statistic package STATA version 12 (Stata Corp., College Station, TX, USA) was used for all analyses.

Results

Table 1 lists characteristics of the study population. Eligible participants were, on average, aged 10.3 years; 76% of mothers did not smoke during pregnancy, and only 6% of the families had less than 9 years of education. Children with neurodevelopmental disorders were predominantly males, more likely to be born in a lower educated family with at least one parent from Scandinavian countries, exposed to maternal smoking during pregnancy, and with diagnosed comorbidity with severe chromosome abnormalities, neural tube defects, and other neurological diseases, including epilepsy and cerebral palsy. The non-responding twin parents showed some socio-demographic differences compared with those included in the analyses, such as younger maternal age, more single mothers, lower parental education and family income as well as higher neighborhood deprivation.

Figure 2 shows air pollutant levels during pregnancy, and child's first and ninth years of life. Yearly average levels of NO_x from local traffic dropped from 12.7 $\mu g/m^3$ to 5.4 $\mu g/m^3$ during the observation period, which is reflected in reduced levels from pregnancy/infancy to the ninth year of life. On the other hand, the yearly average levels of PM_{10} were relatively constant (3.3–4.2 $\mu g/m^3$). NO_x was closely correlated to PM_{10} (all p-values $< .001$, $r^2 > 0.7$) when comparing with the study period as both have local traffic as the major source of air pollution. However, there were only moderate correlations (all p-values $< .001$, $r^2 < 0.4$) between pollutants during the ninth year of life and other study periods (see Figures S1a and S1b in the Supplementary Material).

The risks of ASD and ADHD using different cut-off values were not consistently associated with exposure to NO_x or PM_{10} at any age (Figure 3 and Table 2). For example, exposure to NO_x during the first year of life was not associated with ASD (OR: 0.86, 95% CI: 0.44–1.67) or ADHD (OR: 1.06, 95% CI: 0.71–1.59) after adjusting for child gender, parity, and other relevant covariates. Similarly, exposure to PM_{10} during the first year of life was not related to ASD (OR: 0.95, 95% CI: 0.56–1.62) or ADHD (OR: 1.06, 95% CI: 0.75–1.52). A lack of association was also observed for exposure to air pollution during pregnancy. Results were similar using the dimensional outcomes for ASD and ADHD (data not shown). It should be noted that there was a substantial overlap between the diagnoses; for example, 82 of the 109 children with ASD also had ADHD.

When exposure to air pollutants for each trimester of the pregnancy controlling for seasonal effect and during the child's ninth year of life was evaluated separately, similar findings were found with no consistent associations for most neurodevelopmental outcomes related to traffic–air pollutant levels (Tables S2–S5 of the Supplementary Material). However, it is noteworthy that an inverse relation was observed between air pollution exposure during the 2nd and 3rd trimesters and ASD, as well as ADHD, using cut-off values based on the DSM-IV criteria. We also did a sensitivity analysis by redefining cases comorbid with chromosome abnormality or neurological diseases (Table S6 of the Supplementary Material). The ORs in those analyses tended to be lower, but still no statistically significant association was found. In sub-analyses, we assessed all twins whose mothers answered the telephone interview from CATSS, and similar findings were found for all outcomes (Table S7 of the Supplementary Material).

Discussion

This study did not indicate an association between exposure to NO_x or PM_{10} from traffic during pregnancy or the 1st year of life and neurodevelopmental disorders in children. For specific subgroups and diagnoses, there were some associations but no consistent patterns were evident. This also holds true for analyses related to exposure during certain time windows.

There is limited evidence on air pollution exposure and neurodevelopmental disorders in children (Becerra et al., 2013; Calderon-Garciduenas et al., 2011; Dix-Cooper et al., 2012; Guxens et al., 2012; Jung et al., 2013; Morales et al., 2009; Siddique et al., 2011; Volk et al., 2011; 2013; Vrijheid et al., 2012; Windham et al., 2006). Windham et al. (2006) reported a positive relation between the distribution of hazardous air pollutants at birth addresses and ASD among children in California. Other studies in California found that living close to freeways and traffic-related air pollution in mother's late pregnancy or child's first year of life was associated with an increased risk for autism (Volk et al., 2011, 2013). Siddique et al. (2011) compared children living in the New Delhi (India) urban area with children living in rural areas and showed that ADHD was positively correlated with current PM_{10} levels. Air pollutants may induce systematic inflammation, which could be a possible mechanism mediating these effects (Block & Calderon-Garciduenas, 2009; Calderon-Garciduenas et al., 2008).

The results of our study did not indicate that air pollution has an effect on the risk of neurodevelopmental disorders, even when time windows were considered during fetal life and infancy. The apparently discrepant results compared with some earlier studies could have several explanations. First, relatively low levels of air pollution may

https://doi.org/10.1017/thg.2014.58 Published online by Cambridge University Press

TABLE 1

Child and Family Characteristics in 9- and 12-Year-Old Twins Born in Stockholm

	Total	Healthy	ASD[a]	p^c	ADHD[a]	p^c	Non-respondents
N (%)	3,426	3,051 (89.1)	109 (3.2)		328 (9.6)		1,554
Missing in neurodevelopmental outcomes			18		22		-
Child age at interview for respondents/till year 2011 for non-respondents (mean ± *SD*)	10.3 ± 1.5	10.3 ± 1.5	10.6 ± 1.6		10.3 ± 1.5		14.7 ± 2.5
Respondent							
Biological mother	2,960 (86.4)	2,639 (86.5)	91 (83.5)	‡	281 (85.7)		–
Biological father	450 (13.1)	401 (13.1)	14 (12.8)		43 (13.1)		–
Others	16 (0.5)	11 (0.4)	4 (3.7)		4 (1.2)		–
Gender							
Male	1,756 (51.3)	1,510 (49.5)	80 (73.4)	‡	216 (65.9)	‡	733 (47.2)
Female	1,670 (48.7)	1,541 (50.5)	29 (26.6)		112 (34.2)		704 (45.3)
Parity							
First	791 (23.1)	703 (23.0)	30 (27.5)		80 (24.4)		264 (17.0)
Second	1,436 (41.9)	1,290 (42.3)	40 (36.7)		126 (38.4)		570 (36.7)
Third	845 (24.7)	755 (24.8)	24 (22.0)		80 (24.4)		408 (26.3)
Fourth or later	354 (10.3)	303 (9.9)	15 (13.8)		42 (12.8)		195 (12.5)
Zygosity							
Monozygosity	1,380 (40.3)	1,236 (40.5)	44 (40.4)		129 (39.3)		–
Dizygosity	1,742 (50.8)	1,551 (50.8)	58 (53.2)		166 (50.6)		–
Missing	304 (8.9)	264 (8.7)	7 (6.4)		33 (10.1)		–
Low gestation age (<37 weeks)							
Yes	1,360 (39.7)	1,193 (39.1)	55 (50.5)	‡	145 (44.2)	†	641 (41.2)
No	2,046 (59.7)	1,844 (60.4)	51 (46.8)		177 (54.0)		783 (50.4)
Missing	20 (0.6)	14 (0.5)	3 (2.7)		6 (1.8)		130 (8.4)
Low birth weight (<2,500 g)							
Yes	1,287 (37.6)	1,129 (37.0)	48 (44.0)		138 (42.1)		620 (39.9)
No	2,082 (60.8)	1,868 (61.2)	60 (55.1)		187 (57.0)		792 (51.0)
Missing	57 (1.7)	54 (1.8)	1 (0.9)		3 (0.9)		142 (9.1)
Maternal age (mean ± *SD*)	31.6 ± 4.6	31.6 ± 4.6	31.1 ± 5.2		31.1 ± 4.9	†	30.4 ± 5.1
<25 years	234 (6.8)	197 (6.5)	7 (6.4)	‡	34 (10.4)	†	184 (11.8)
≥25 and <30 years	838 (24.5)	737 (24.2)	39 (35.8)		89 (27.1)		418 (26.9)
≥30 and <35 years	1,392 (40.6)	1,266 (41.5)	36 (33.0)		110 (33.5)		521 (33.5)
≥35 years	962 (28.1)	851 (27.9)	27 (24.8)		95 (29.0)		314 (20.2)
Maternal smoking during pregnancy							
No	2,591 (75.6)	2,334 (76.5)	77 (70.6)		220 (67.1)	‡	1,041 (67.0)
Yes, 1–9 cigarettes/day	256 (7.5)	212 (7.0)	12 (11.0)		41 (12.5)		116 (7.5)
Yes, ≥10 cigarettes/day	164 (4.8)	132 (4.3)	8 (7.3)		29 (8.8)		77 (5.0)
Missing	415 (12.1)	373 (12.2)	12 (11.0)		38 (11.6)		320 (20.6)
Maternal marital status at birth year							
Married or cohabiting	3,140 (91.6)	2,805 (91.9)	92 (84.4)	†	297 (90.6)	†	1,258 (81.0)
Single	270 (7.9)	231 (7.6)	17 (15.6)		30 (9.2)		165 (10.6)
Missing	16 (0.5)	15 (0.5)	0		1 (0.3)		131 (8.4)
Maternal marital status during child's 9th year of life							
Married or cohabiting	2,700 (78.8)	2,431 (79.7)	78 (71.6)		238 (72.6)	†	957 (61.6)
Single	604 (17.6)	510 (16.7)	26 (23.9)		79 (24.1)		350 (22.5)
Missing	122 (3.6)	110 (3.6)	5 (4.6)		11 (3.3)		247 (15.9)
Parental ethnicity							
Either one parent from Scandinavian countries	3,168 (92.5)	2,823 (92.5)	103 (94.5)		309 (94.2)		–
Both parents from other countries	258 (7.5)	228 (7.5)	6 (5.5)		19 (5.8)		–
Highest education by either parent (pregnancy)							
Low (≤9 years)	218 (6.4)	183 (6.0)	17 (15.6)	‡	31 (9.5)	‡	179 (11.5)
Middle (10–12 years)	1,382 (40.3)	1,191 (39.0)	58 (53.2)		167 (50.9)		541 (34.8)
High(>12 years)	1,695 (49.5)	1,566 (51.3)	28 (25.7)		115 (35.1)		543 (34.9)
Missing	131 (3.8)	111 (3.6)	6 (5.5)		15 (4.6)		291 (18.7)
Highest education by either parent (1st year of life)							
Low (≤9 years)	136 (4.0)	114 (3.7)	9 (8.3)	‡	20 (6.1)	‡	145 (9.3)
Middle (10–12 years)	1,284 (37.5)	1,092 (35.8)	60 (55.1)		170 (51.8)		545 (35.1)
High(>12 years)	1,891 (55.2)	1,744 (57.2)	36 (33.0)		127 (38.7)		593 (38.2)
Missing	115 (3.4)	101 (3.3)	4 (3.7)		11 (3.4)		271 (17.4)
Highest education by either parent (9th year of life)							
Low (≤9 years)	136 (4.0)	113 (3.7)	9 (8.3)	‡	21 (6.4)	‡	160 (10.1)
Middle (10–12 years)	1,210 (35.3)	1,026 (33.6)	57 (52.3)		161 (49.1)		565 (37.9)
High(>12 years)	2,043 (59.6)	1,880 (61.6)	41 (37.6)		143 (43.6)		598 (41.2)
Missing	37 (1.1)	32 (1.1)	2 (1.8)		3 (0.9)		231 (14.9)
NPI at birth (mean ± *SD*)	-0.1 ± 1.0	-0.1 ± 1.0	0.1 ± 1.2		0.0 ± 1.1	†	0.3 ± 1.4
NPI during 9th year of life (mean ± *SD*)	-0.3 ± 0.9	-0.3 ± 0.9	-0.2 ± 1.1		-0.2 ± 0.8	†	0.1 ± 1.2
Individualized income during mother's pregnancy (mean ± *SD*, 1000 SEK)	105.0 ± 110.8	106.8 ± 116.3	86.7 ± 35.9		89.8 ± 44.3	†	89.2 ± 63.6

https://doi.org/10.1017/thg.2014.58 Published online by Cambridge University Press

TABLE 1
Continued.

	Total	Healthy	ASD[a]	p^c	ADHD[a]	p^c	Non-respondents
Individualized income during child's 9th year of life (mean ± *SD*, 1000 SEK)	162.0 ± 228.9	164.5 ± 240.6	134.5 ± 62.6		141.1 ± 88.5		149.6 ± 197.8
Comorbidity[b]							
Yes	120 (3.5)	59 (1.9)	44 (40.4)	‡	48 (14.6)	‡	75 (4.8)
No	3,306 (96.5)	2,992 (98.1)	65 (59.6)		280 (85.4)		1,479 (95.2)

Note: ASD = Autism Spectrum Disorders; ADHD = Attention Deficit/Hyperactivity Disorders; NPI = Neighborhood Deprivation Index; *SD* = standard deviation; SEK = Swedish kronor.
[a]Cut-off values of disorders from extended diagnostic criteria: ASD = 4.5 and ADHD = 6.0.
[b]Comorbidity-included co-occurrence with severe chromosome abnormalities, malformations of brain, epilepsy, cerebral palsy, and other neurological disorders. Detailed information on diagnosis codes is listed in Table S1 in supplemental materials.
[c]The *p*-values were presented comparing ASD/ADHD individuals with the ones with neither ASD nor ADHD.
†$p < .05$; ‡$p < .001$.

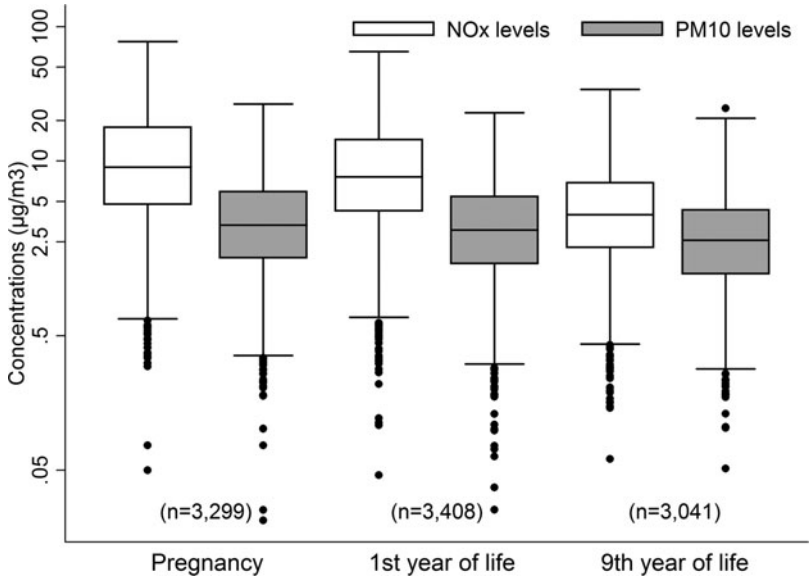

FIGURE 2
Box plot describing the distribution of log-transformed NO_x (white) and PM_{10} (gray) concentrations (µg/m^3) from local traffic in study population from mother's pregnancy to child's ninth year of life. Labels of each scale unit on concentration levels (*y*-axis) were back-transformed. The box and whiskers denoted the 5th, 25th, 50th, 75th, 95th percentile and outlier values of pollutants' distributions.

contribute to the absence of an association and make it difficult to compare with other study settings. For example, the local traffic-related PM_{10} concentrations during participants' first year of life in Stockholm was only 3.9 µg/m^3 and the long-range transported PM_{10} in this part of Sweden has a yearly average level of around 10 µg/m^3 (Gidhagen et al., 2013). The roof top levels for PM_{10} in central Stockholm have been relatively constant during 1994–2012 (Burman & Norman, 2013). However, these levels are considerably lower than in the study areas of California described above (mean value at 25 ± 7.2 µg/m^3 in one study and 36.3 ± 6.1 µg/m^3 in another study; Becerra et al., 2013; Volk et al., 2013). Furthermore, associations may exist between the socio-economic status at individual or neighborhood level and the risk for neurodevelopmental or behavioral problems (Bhasin & Schendel, 2007; Flouri et al., 2012). Maternal smoking correlates with socio-economic factors such as education and income (Kabir et al., 2011; Laaksonen et al., 2005) and may contribute to this association. The earlier studies (Calderon-Garciduenas et al., 2011; Guxens et al., 2012; Siddique et al., 2011; Volk et al., 2011; Vrijheid et al., 2012; Windham et al., 2006) did not always adjust for neighborhood deprivation as well as individual socio-economic characteristics and smoking during pregnancy, which suggests that there could be some residual confounding.

We found inconsistent associations between air pollution in late pregnancy and decreased risk of ASD and ADHD

https://doi.org/10.1017/thg.2014.58 Published online by Cambridge University Press

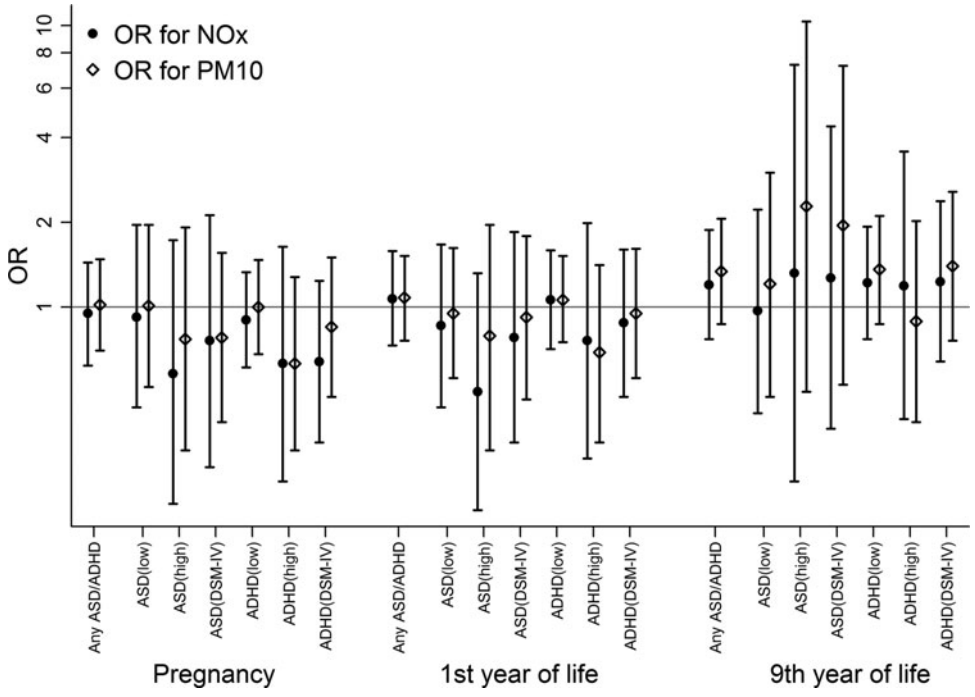

FIGURE 3

Odds ratios and 95% confidence intervals of neurodevelopmental outcomes by residential address-based NO_x (black circles) and PM_{10} (black hollow diamonds) levels. The spikes represent odds ratios for outcomes of interest and cap lines indicate 95% confidence intervals.

using cut-off values based on the DSM-IV criteria. Even though the sample size was relatively large with 3,426 participants, the number of children who scored above the cut-off values for some neurodevelopmental outcomes was low, contributing to the statistical uncertainty of risk estimates.

Strengths of the study include a population-based sample of twins and data linkage to Swedish national registries, which include baseline birth-related and socio-economic information before disease onset. Second, we investigated both ADHD and ASD because of the high degree of co-morbidity between the two conditions. Furthermore, we analyzed neurodevelopmental disorders categorically based on the DSM-IV criteria and the additional cut-off values according to previous validation studies (Hansson et al., 2005; Larson et al., 2010). Third, we included different trimesters during pregnancy, first year, and the ninth year of life using the validated dispersion modeling together with data on road traffic emissions, while previous studies reported effects from either pre- or postnatal air pollution exposures.

There are also several potential limitations of the study. One is that the occurrence of neurodevelopmental outcomes may have differed in children participating in CATSS with completed A-TAC assessment and those in the general population. Two Swedish studies found that children of immigrant parents had impaired psychological health (Gillberg et al., 1987; Magnusson et al., 2012; Van Leeuwen et al., 2012); however, the occurrence of neurodevelopmental disorders in our study was lower in families with both parents from outside of Scandinavian countries. The data linkage to other registers allowed us to acquire additional data on the CATSS non-responders, which indicated that children enrolled in the study had higher familial socio-economic status. Another possible limitation is the assessment of neurodevelopmental outcomes, which might have created some misclassification (Ragland, 1992). Earlier studies mostly attempted to evaluate outcomes as discrete scores; however, our data were highly skewed on all outcomes. Our power was limited for the analyses of sub-dimensional ASD/ADHD measures. Furthermore, for the exposure time measured during child's ninth year of life, the air pollution assessment may actually have occurred after the onset of disease.

Conclusions

We found no support for the hypothesis that traffic-related air pollution is associated with an increased risk for neurodevelopmental disorders in children. Comparatively low air pollution levels and a limited statistical power for some outcomes may contribute to explaining the results.

https://doi.org/10.1017/thg.2014.58 Published online by Cambridge University Press

TABLE 2

Crude and Adjusted ORs of Neurodevelopmental Disorders for Twins Born in Stockholm, by Exposure to NO_x and PM_{10} From Mother's Pregnancy to First Year of Life

		NO_x during pregnancy		NO_x during 1st year of life		PM_{10} during pregnancy		PM_{10} during 1st year of life	
Outcomes	Case	OR[a] (95% CI)	OR[b] (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)
ASD									
ASD_{low}	109	0.89 (0.43, 1.88)	0.92 (0.44, 1.96)	0.95 (0.50, 1.80)	0.86 (0.44, 1.67)	0.91 (0.44, 1.87)	1.01 (0.52, 1.96)	0.93 (0.53, 1.62)	0.95 (0.56, 1.62)
ASD_{high}	33	0.43 (0.16, 1.19)	0.58 (0.20, 1.73)	0.50 (0.19, 1.33)	0.50 (0.19, 1.32)	0.58 (0.23, 1.50)	0.77 (0.31, 1.92)	0.74 (0.28, 1.96)	0.79 (0.31, 1.96)
$ASD_{DSM\text{-}IV}$	47	0.68 (0.24, 1.89)	0.76 (0.27, 2.12)	0.75 (0.32, 1.80)	0.78 (0.33, 1.85)	0.74 (0.33, 1.66)	0.78 (0.39, 1.56)	0.95 (0.44, 2.05)	0.92 (0.47, 1.79)
Language	43	0.74 (0.26, 2.06)	0.84 (0.30, 2.35)	0.73 (0.29, 1.81)	0.77 (0.31, 1.90)	0.81 (0.36, 1.81)	0.97 (0.63, 1.47)	0.96 (0.43, 2.14)	0.91 (0.45, 1.82)
Flexibility	45	0.76 (0.28, 2.07)	0.83 (0.30, 2.28)	0.81 (0.34, 1.93)	0.80 (0.34, 1.92)	0.82 (0.37, 1.81)	0.82 (0.41, 1.64)	1.00 (0.46, 2.19)	0.93 (0.47, 1.82)
Social interaction	26	0.40 (0.13, 1.26)	–	0.54 (0.19, 1.52)	0.58 (0.24, 1.43)	0.42 (0.14, 1.30)	–	0.60 (0.20, 1.84)	0.64 (0.26, 1.55)
ADHD									
$ADHD_{low}$	328	0.74 (0.48, 1.14)	0.90 (0.58, 1.40)	0.90 (0.61, 1.33)	1.06 (0.71, 1.59)	0.81 (0.54, 1.21)	1.00 (0.68, 1.47)	0.88 (0.62, 1.26)	1.06 (0.75, 1.52)
$ADHD_{high}$	62	0.52 (0.18, 1.50)	0.63 (0.24, 1.64)	0.80 (0.30, 2.12)	0.76 (0.29, 1.99)	0.49 (0.21, 1.14)	0.63 (0.31, 1.28)	0.63 (0.28, 1.42)	0.69 (0.33, 1.41)
$ADHD_{DSM\text{-}IV}$	152	0.53 (0.27, 1.05)	0.64 (0.33, 1.24)	0.78 (0.43, 1.41)	0.88 (0.48, 1.60)	0.72 (0.38, 1.34)	0.85 (0.48, 1.50)	0.81 (0.46, 1.43)	0.95 (0.56, 1.61)
Impulsiveness	65	0.46 (0.14, 1.55)	0.68 (0.23, 2.06)	0.84 (0.33, 2.11)	0.91 (0.36, 2.30)	0.52 (0.18, 1.51)	0.78 (0.32, 1.90)	0.73 (0.33, 1.60)	0.84 (0.41, 1.76)
Attention	98	0.76 (0.41, 1.41)	1.01 (0.57, 1.77)	1.01 (0.56, 1.82)	1.16 (0.66, 2.02)	0.75 (0.38, 1.47)	1.02 (0.58, 1.81)	0.97 (0.52, 1.82)	1.16 (0.66, 2.04)
Any neurodevelopmental outcomes									
ASD or ADHD	355	0.79 (0.52, 1.20)	0.95 (0.62, 1.44)	0.93 (0.64, 1.35)	1.07 (0.73, 1.58)	0.84 (0.57, 1.23)	1.02 (0.70, 1.48)	0.91 (0.64, 1.28)	1.08 (0.76, 1.52)

Note: ASD = Autism Spectrum Disorders; ADHD = Attention Deficit/Hyperactivity Disorders; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders* (4th edition); OR = odds ratio; CI = confidence interval.

[a]Estimates based on crude models.

[b]Models adjusted for parity, gender, maternal age during pregnancy, maternal smoking during pregnancy, maternal marital status at birth year, parental education, family income, and neighborhood deprivation at birth year.

Acknowledgments

Financial support was provided through the Swedish Research Council for Health, Working Life and Welfare (FORTE 2012-0573), the Swedish Research Council (VR) 2011-3060, VR in partnership with FORTE, FORMAS, and VINNOVA (cross-disciplinary research program concerning children's and young people's mental health), VR through the Swedish Initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) framework, grant No. 340-2013-5867, HKH Kronprinsessan Lovisas förening för barnasjukvård, and the Strategic Research Program in Epidemiology at Karolinska Institutet.

Supplementary Material

To view the supplementary material for this article, please visit http://dx.doi.org/10.1017/thg.2014.58.

References

Anckarsater, H., Lundstrom, S., Kollberg, L., Kerekes, N., Palm, C., Carlstrom, E., ... Lichtenstein, P. (2011). The child and adolescent twin study in Sweden (CATSS). *Twin Research and Human Genetics*, *14*, 495–508.

Becerra, T. A., Wilhelm, M., Olsen, J., Cockburn, M., & Ritz, B. (2013). Ambient air pollution and autism in Los Angeles county, California. *Environmental Health Perspectives*, *121*, 380–386.

Bellander, T., Berglind, N., Gustavsson, P., Jonson, T., Nyberg, F., Pershagen, G., ... Jarup, L. (2001). Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in Stockholm. *Environmental Health Perspectives*, *109*, 633–639.

Bhasin, T. K., & Schendel, D. (2007). Socio-demographic risk factors for autism in a US metropolitan area. *Journal of Autism and Developmental Disorders*, *37*, 667–677.

Block, M. L., & Calderon-Garciduenas, L. (2009). Air pollution: Mechanisms of neuroinflammation and CNS disease. *Trends in Neurosciences*, *32*, 506–516.

Burman, L., & Norman, M. (2013). *The air quality in Stockholm: Annual report 2012*. Retrieved February 7, 2014, from http://www.slb.nu/slb/rapporter/pdf8/slb2013_005.pdf

Calderon-Garciduenas, L., Engle, R., Mora-Tiscareno, A., Styner, M., Gomez-Garza, G., Zhu, H., ... D'Angiulli, A. (2011). Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic

inflammation in clinically healthy children. *Brain and Cognition*, *77*, 345–355.

Calderon-Garciduenas, L., Solt, A. C., Henriquez-Roldan, C., Torres-Jardon, R., Nuse, B., Herritt, L., ... Reed, W. (2008). Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicologic Pathology*, *36*, 289–310.

Carlin, J. B., Gurrin, L. C., Sterne, J. A., Morley, R., & Dwyer, T. (2005). Regression models for twin studies: A critical review. *International Journal of Epidemiology*, *34*, 1089–1099.

Dix-Cooper, L., Eskenazi, B., Romero, C., Balmes, J., & Smith, K. R. (2012). Neurodevelopmental performance among school age children in rural Guatemala is associated with prenatal and postnatal exposure to carbon monoxide, a marker for exposure to woodsmoke. *Neurotoxicology*, *33*, 246–254.

Flouri, E., Mavroveli, S., & Tzavidis, N. (2012). Cognitive ability, neighborhood deprivation, and young children's emotional and behavioral problems. *Social Psychiatry and Psychiatric Epidemiology*, *47*, 985–992.

Froehlich, T. E., Lanphear, B. P., Epstein, J. N., Barbaresi, W. J., Katusic, S. K., & Kahn, R. S. (2007). Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Archives of Pediatrics & Adolescent Medicine*, *161*, 857–864.

Gidhagen, L., Omstedt, G., Pershagen, G., Willers, S., & Bellander, T. (2013). High-resolution modeling of residential outdoor particulate levels in Sweden. *Journal of Exposure Analysis and Environmental Epidemiology*, *23*, 306–314.

Gillberg, C., Steffenburg, S., Borjesson, B., & Andersson, L. (1987). Infantile autism in children of immigrant parents. A population-based study from Goteborg, Sweden. *British Journal of Psychiatry*, *150*, 856–858.

Greenland, S., & Brumback, B. (2002). An overview of relations among causal modelling methods. *International Journal of Epidemiology*, *31*, 1030–1037.

Gruzieva, O., Bellander, T., Eneroth, K., Kull, I., Melen, E., Nordling, E., ... Pershagen, G. (2012). Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. *Journal of Allergy and Clinical Immunology*, *129*, 240–246.

Guxens, M., Aguilera, I., Ballester, F., Estarlich, M., Fernandez-Somoano, A., Lertxundi, A., ... INMA Project. (2012). Prenatal exposure to residential air pollution and infant mental development: Modulation by antioxidants and detoxification factors. *Environmental Health Perspectives*, *120*, 144–149.

Hagberg, H., & Mallard, C. (2005). Effect of inflammation on central nervous system development and vulnerability. *Current Opinion in Neurology*, *18*, 117–123.

Hansson, S. L., Svanstrom Rojvall, A., Rastam, M., Gillberg, C., Gillberg, C., & Anckarsater, H. (2005). Psychiatric telephone interview with parents for screening of childhood autism — Tics, attention-deficit hyperactivity disorder and other comorbidities (A-TAC): Preliminary reliability and validity. *British Journal of Psychiatry*, *187*, 262–267.

Jarbrink, K., Fombonne, E., & Knapp, M. (2003). Measuring the parental, service and cost impacts of children with autistic spectrum disorder: A pilot study. *Journal of Autism and Developmental Disorders*, *33*, 395–402.

Jung, C. R., Lin, Y. T., & Hwang, B. F. (2013). Air pollution and newly diagnostic autism spectrum disorders: A population-based cohort study in Taiwan. *PLoS One*, *8*, e75510.

Kabir, Z., Connolly, G. N., & Alpert, H. R. (2011). Secondhand smoke exposure and neurobehavioral disorders among children in the United States. *Pediatrics*, *128*, 263–270.

Kogan, M. D., Strickland, B. B., Blumberg, S. J., Singh, G. K., Perrin, J. M., & van Dyck, P. C. (2008). A national profile of the health care experiences and family impact of autism spectrum disorder among children in the United States, 2005–2006. *Pediatrics*, *122*, e1149–e1158.

Laaksonen, M., Rahkonen, O., Karvonen, S., & Lahelma, E. (2005). Socio-economic status and smoking: Analysing inequalities with multiple indicators. *European Journal of Public Health*, *15*, 262–269.

Larson, T., Anckarsater, H., Gillberg, C., Stahlberg, O., Carlstrom, E., Kadesjo, B., ... Gillberg, C. (2010). The Autism — Tics, AD/HD and other Comorbidities Inventory (A-TAC): Further validation of a telephone interview for epidemiological research. *BMC Psychiatry*, *10*, 1.

Magnusson, C., Rai, D., Goodman, A., Lundberg, M., Idring, S., Svensson, A., ... Dalman, C. (2012). Migration and autism spectrum disorder: Population-based study. *British Journal of Psychiatry*, *201*, 109–115.

Martin, N., Scourfield, J., & McGuffin, P. (2002). Observer effects and heritability of childhood attention-deficit hyperactivity disorder symptoms. *British Journal of Psychiatry*, *180*, 260–265.

Mills, N. L., Donaldson, K., Hadoke, P. W., Boon, N. A., MacNee, W., Cassee, F. R., ... Newby, D. E. (2009). Adverse cardiovascular effects of air pollution. *Nature Clinical Practice Cardiovascular Medicine*, *6*, 36–44.

Morales, E., Julvez, J., Torrent, M., de Cid, R., Guxens, M., Bustamante, M., ... Sunyer, J. (2009). Association of early-life exposure to household gas appliances and indoor nitrogen dioxide with cognition and attention behavior in preschoolers. *American Journal of Epidemiology*, *169*, 1327–1336.

National Board of Health and Welfare. (2003). *The Swedish medical birth register: A summary of content and quality*. Retrieved January 27, 2014, from http://www.sos.se/fulltext/112/2003-112-3/2003-112-3.pdf

Newton, C. R. (2012). Neurodevelopmental disorders in low- and middle-income countries. *Developmental Medicine & Child Neurology*, *54*, 1072.

Nordling, E., Berglind, N., Melen, E., Emenius, G., Hallberg, J., Nyberg, F., ... Bellander, T. (2008). Traffic-related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology*, *19*, 401–408.

Panasevich, S., Leander, K., Rosenlund, M., Ljungman, P., Bellander, T., de Faire, U., ... Nyberg, F. (2009).

https://doi.org/10.1017/thg.2014.58 Published online by Cambridge University Press

Associations of long- and short-term air pollution exposure with markers of inflammation and coagulation in a population sample. *Occupational and Environmental Medicine*, *66*, 747–753.

Parr, J. R., Le Couteur, A., Baird, G., Rutter, M., Pickles, A., Fombonne, E., ... International Molecular Genetic Study of Autism Consortium, Members. (2011). Early developmental regression in autism spectrum disorder: Evidence from an international multiplex sample. *Journal of Autism and Developmental Disorders*, *41*, 332–340.

Ragland, D. R. (1992). Dichotomizing continuous outcome variables: Dependence of the magnitude of association and statistical power on the cutpoint. *Epidemiology*, *3*, 434–440.

Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Larsson, H., Hultman, C. M., & Reichenberg, A. (2014). The familial risk of autism. *JAMA: The Journal of the American Medical Association*, *311*, 1770–1777.

Sariaslan, A., Langstrom, 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. *International Journal of Epidemiology*, *42*, 1057–1066.

Siddique, S., Banerjee, M., Ray, M. R., & Lahiri, T. (2011). Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. *European Journal of Pediatrics*, *170*, 923–929.

Statistics Sweden. (2013). *Post codes and SAMS atlas*. Retrieved October 8, 2013, from http://www.scb.se/Pages/Standard__333368.aspx

Van Leeuwen, W., Nilsson, S., & Merlo, J. (2012). Mother's country of birth and prescription of psychotropic medication in Swedish adolescents: a life course approach. *BMJ Open*, *2*.

Volk, H. E., Hertz-Picciotto, I., Delwiche, L., Lurmann, F., & McConnell, R. (2011). Residential proximity to freeways and autism in the CHARGE study. *Environmental Health Perspectives*, *119*, 873–877.

Volk, H. E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., & McConnell, R. (2013). Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry*, *70*, 71–77.

Vrijheid, M., Martinez, D., Aguilera, I., Bustamante, M., Ballester, F., Estarlich, M., ... Project, INMA. (2012). Indoor air pollution from gas cooking and infant neurodevelopment. *Epidemiology*, *23*, 23–32.

Windham, G. C., Zhang, L., Gunier, R., Croen, L. A., & Grether, J. K. (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area. *Environmental Health Perspectives*, *114*, 1438–1444.

https://doi.org/10.1017/thg.2014.58 Published online by Cambridge University Press