



**Karolinska
Institutet**

Karolinska Institutet

<http://openarchive.ki.se>

This is a Peer Reviewed Accepted version of the following article, accepted for publication in *Twin Research and Human Genetics*.

2017-03-17

Exposure to air pollution from traffic and neurodevelopmental disorders in Swedish twins

Gong, Tong; Almqvist, Catarina; Bölte, Sven; Lichtenstein, Paul; Anckarsäter, Henrik; Lind, Tomas; Lundholm, Cecilia; Pershagen, Göran

Twin Res Hum Genet. 2014 Dec;17(6):553-62.

<http://doi.org/10.1017/thg.2014.58>

<http://hdl.handle.net/10616/45603>

If not otherwise stated by the Publisher's Terms and conditions, the manuscript is deposited under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

1 **Title page**

2

3

4 **Exposure to air pollution from traffic and neurodevelopmental**
5 **disorders in Swedish Twins**

6

7 Tong Gong¹, Catarina Almqvist^{1,2}, Sven Bölte^{3,4}, Paul Lichtenstein¹, Henrik Anckarsäter⁵,
8 Tomas Lind⁶, Cecilia Lundholm¹, Göran Pershagen^{6,7}

9

10 1 Department of Medical Epidemiology and Biostatistics

11 2 Lung and Allergy unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital

12 3 Department of Women's and Children's Health, Center of Neurodevelopmental Disorders
13 (KIND),

14 Karolinska Institutet, Stockholm, Sweden

15 4 Division of Child and Adolescent Psychiatry, Stockholm County Council, Sweden

16 5 Department of Pharmacology, Institute of Neuroscience and Physiology, Sahlgrenska
17 Academy, University of Gothenburg, Gothenburg, Sweden

18 6 Center for Occupational and Environmental Medicine, Stockholm County Council, Sweden

19 7 Institute of Environmental Medicine, Karolinska Institutet, Stockholm Sweden

20

21

22

23 ***Corresponding author:***

24 Tong Gong

25 Department of Medical Epidemiology and Biostatistics

26 Karolinska Institutet

27 SE-171 77 Stockholm, Sweden

28 T. +46 8 524 84450

29 F. +46 8 31 11 01

30 E. tong.gong@ki.se

31 ***Running title:***

32 Exposure to air pollution and neurodevelopmental disorders

33 **Abstract**

34 **Background** Recent studies have reported associations between air pollution exposure and
35 neurodevelopmental disorders in children but the role of pre- and postnatal exposure has not
36 been elucidated. **Aim** We aimed to explore the risk for autism spectrum disorders (ASD) and
37 attention-deficit hyperactivity disorder (ADHD) among children in relation to pre- and
38 postnatal exposure to air pollution from road traffic. **Method** Parents of 3,426 twins born in
39 Stockholm during 1992-2000 were interviewed when their children were 9 or 12 years old
40 regarding symptoms of neurodevelopmental disorders. Residence time weighted
41 concentrations of particulate matter with diameter < 10 μm (PM₁₀) and nitrogen oxides (NO_x)
42 from road traffic were estimated at participants' addresses during pregnancy, first year and
43 ninth year of life using dispersion modeling, controlling for seasonal variation. Multivariate
44 regression models were used to examine the association between air pollution exposure and
45 neurodevelopmental outcomes, adjusting for potential confounding factors. **Result** No clear
46 or consistent associations were found between air pollution exposure during any of the three
47 time windows and any of the neurodevelopmental outcomes. For example, a 5- 95%
48 difference in exposure to NO_x during pregnancy was associated with odds ratios (ORs) of
49 0.92 (95% confidence interval 0.44-1.96) and 0.90 (0.58-1.40) for ASD and ADHD,
50 respectively. A corresponding range in exposure to PM₁₀ during pregnancy was related to ORs
51 of 1.01 (0.52-1.96) and 1.00 (0.68-1.47) for ASD and ADHD. **Conclusion** Our data do not
52 provide support for an association between pre- or postnatal exposure to air pollution from
53 road traffic and neurodevelopmental disorders in children.

54

55 **Key words:**

56 air pollution, PM₁₀, NO_x, autism, ADHD, twins

57

58 **Abbreviations used:**

59 Attention deficit/hyperactivity disorder (ADHD); autism spectrum disorders (ASD); Autism-
60 Tics, ADHD, and other Comorbidities inventory (A-TAC); Child and Adolescent Twin Study
61 in Sweden (CATSS); confidence interval (CI); Diagnostic and Statistical Manual of Mental
62 Disorders, 4th edition (DSM-IV); generalized estimating equation (GEE); nitrogen oxides
63 (NO_x); odds ratio (OR); particulate matter (PM); small-area market statistics (SAMS).

64 **Introduction**

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

75 Epidemiological and experimental studies indicate that exposure to air pollution from road
76 traffic may induce systemic inflammation and increase the risk of several diseases related to
77 inflammation, such as asthma, allergy, and cardiovascular diseases (Mills et al., 2009;
78 Nordling et al., 2008; Panasevich et al., 2009). Systemic inflammation can also contribute to
79 neuronal injury and affect the development of central nervous system (Hagberg & Mallard,
80 2005). Recent epidemiological studies have shown associations between exposure to air
81 pollution from road traffic or other sources and adverse neurodevelopmental effects in
82 children (Becerra, Wilhelm, Olsen, Cockburn, & Ritz, 2013; Calderon-Garciduenas et al.,
83 2011; Dix-Cooper, Eskenazi, Romero, Balmes, & Smith, 2012; Guxens et al., 2012; Jung, Lin,
84 & Hwang, 2013; Morales et al., 2009; Siddique, Banerjee, Ray, & Lahiri, 2011; Windham,
85 Zhang, Gunier, Croen, & Grether, 2006; Volk, Hertz-Picciotto, Delwiche, Lurmann, &
86 McConnell, 2011; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013; Vrijheid et
87 al., 2012). However, more studies are needed to assess causality, particularly since the

88 association may be confounded by socioeconomic and sociodemographic characteristics
89 (Bhasin & Schendel, 2007; Flouri, Mavroveli, & Tzavidis, 2012). Furthermore, it is not
90 known if there are specific periods of increased vulnerability.

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

95 **Materials and methods**

96 **Study population**

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

107 [insert Figure 1 here]

108 **Health outcome assessment**

109 Children's neurodevelopmental outcomes were measured using the Autism-Tics, ADHD, and
110 other Comorbidities inventory (A-TAC) telephone interview developed at the Institute of
111 Neuroscience and Physiology, Child and Adolescent Psychiatry, Gothenburg University
112 (Hansson et al., 2005). A-TAC consists of 178 symptom questions from a lifetime perspective
113 and is designed as an open-access and comprehensive tool for screening childhood ASD and
114 other targeted disorders based on DSM-IV criteria. Response options for each question were
115 coded as 0 for "No", 0.5 for "Yes, to some extent", and 1.0 for "Yes". In two previous
116 validation studies, autistic-like traits were assessed by the sum scores of 12 items (based on
117 DSM-IV criteria) or 17 items (by adding one additional item from the flexibility and two
118 additional items each from the language and social interaction modules) (Hansson et al., 2005;

119 Larson et al., 2010). To comprise the primary symptoms of ADHD, scores of 18 (based on
120 DSM-IV criteria) or 19 items (by adding one additional item from the impulsivity module)
121 were summed up. Cut-off values for the sum scores with high sensitivity and specificity from
122 previous validation studies were used in the current study to resemble the probabilities of
123 clinical diagnoses and severity of both diseases: $ASD \geq 4.5$ for DSM-IV criteria and for the
124 lower cutoff value of extended diagnostic criteria, $ASD \geq 8.5$ for the higher cutoff value of
125 extended diagnostic criteria, $ADHD \geq 8$ for DSM-IV criteria, $ADHD \geq 6$ and $ADHD \geq 12.5$ for
126 the lower and higher cutoff values of extended diagnostic criteria. Detailed information on the
127 psychometric properties of the A-TAC is provided elsewhere (Anckarsater et al., 2011;
128 Hansson et al., 2005; Larson et al., 2010).

129 **Exposure assessment**

130 The air pollution concentrations at residential addresses during mother's pregnancy, child's
131 first year of life and the year before the neurodevelopmental assessment were estimated by
132 dispersion models, described in detail elsewhere (Bellander et al., 2001; Gruzieva et al., 2012).
133 Briefly, the residential history of the study subjects was obtained from taxation authorities and
134 geocoded using a property register maintained by the Swedish mapping, cadastral and land
135 registration authority. The address information was linked with historical emission databases
136 to obtain annual average levels of nitrogen oxides (NO_x) and particulate matter with less than
137 $10 \mu m$ of diameter (PM_{10}). Residence time weighted NO_x and PM_{10} concentrations related to
138 road traffic emissions were calculated for each trimester and over the mother's pregnancy
139 period, the child's first year and 9th year of life. Furthermore, daily 24 hour mean NO_x and
140 PM_{10} levels from suburban stations were used to calculate the NO_x and PM_{10} levels during
141 each trimester of the pregnancy, which were taken into account in sensitivity analyses.
142 Imputation for missing values of NO_x and PM_{10} in the trimester-specific analyses was

143 performed using predictions from rooftop measurements of both pollutants from a monitoring
144 station in the center of Stockholm.

145 **Other covariates**

146 Information on gender (male / female), parity (first / second / third / fourth or later),
147 gestational age (<37 weeks / ≥37weeks), birth weight (<2,500g / ≥2,500g), maternal age at
148 birth (<25 / 25-29 / 30-34 / ≥35yrs old), maternal smoking during pregnancy (no/ 1-9
149 cigarettes per day/ ≥10 cigarettes per day) was obtained from the Medical Birth Register
150 ("The Swedish Medical Birth Register: a summary of content and quality," 2003). Using the
151 Longitudinal integration database for health insurance and labor market studies (LISA),
152 originally from Statistics Sweden, we obtained individual-level socioeconomic data such as
153 maternal marital status (married or cohabiting / single), parental education (≤9yrs / 10-12yrs
154 / >12yrs) and family disposable income during mother's pregnancy, child's first year of life
155 and 9th year of life with adjustment for inflation and family size. Furthermore, a neighborhood
156 deprivation index was used to estimate area-based socioeconomic characteristics at birth year
157 (Sariaslan et al., 2013). Neighborhood was defined by the small-area market statistics (SAMS)
158 based on regional population density ("Post codes and SAMS atlas," 2013). Data including
159 information from Statistics Sweden on welfare beneficiaries, unemployment, immigrants,
160 divorce rate, income, education, residential mobility, and criminal conviction rate were linked
161 with each SAMS unit to calculate a neighborhood deprivation index using principal
162 component analysis. Information on comorbidity with severe chromosome abnormalities,
163 neural tube defects and other neurological diseases including epilepsy and cerebral palsy (see
164 Table S1) was obtained through parent-report in CATSS as well as from the National Patient
165 Register according to diagnoses from hospital discharge or outpatient department visits.

166 **Statistical analysis**

167 Generalized estimating equations (GEE) with exchangeable correlation structure in
168 combination with Huber-White sandwich estimator for the standard errors to adjust for
169 clustering of observations within twin pairs were used to estimate odds ratios (OR) and 95%
170 confidence intervals (CI) for each neurodevelopmental outcome associated with a 5th to 95th
171 percentile increase in NO_x or PM₁₀ on the entire sample (Carlin, Gurrin, Sterne, Morley, &
172 Dwyer, 2005). We used a directed acyclic graph to determine potential confounders for the
173 ORs (Greenland & Brumback, 2002). A series of models were run step-wise to assess the OR
174 changes by further adjustment for potential confounders, however, only crude and adjusted
175 models including all potential confounders (p<0.20) are presented.

176 Cutoff values validated in two previous studies were used as outcomes in all analyses
177 (Hansson et al., 2005; Larson et al., 2010). Furthermore, we added a general
178 neurodevelopmental outcome defined as scoring above any ASD or ADHD-related cutoff
179 values due to the high co-occurrence of both diseases. Sensitivity analyses were performed
180 using air pollution exposure during child's 9th year of life and during each trimester of
181 pregnancy controlling for seasonal effect, and by defining cases with comorbidity of severe
182 chromosome abnormality, neural tube defects and other neurological diseases including
183 epilepsy and cerebral palsy (See table S1). Furthermore, a subset of children whose mothers
184 responded at the interview was analyzed to avoid reporting bias among different family
185 members.

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

188 **Results**

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

199 [insert Table 1 here]

200 Figure 2 shows air pollutant levels during pregnancy, child's first and 9th years of life. Yearly
201 average levels of NO_x from local traffic dropped from 12.7μg/m³ to 5.4μg/m³ during the
202 observation period, which is reflected in reduced levels from pregnancy/infancy to the 9th year
203 of life. On the other hand, the yearly average levels of PM₁₀ were relatively constant (3.3-
204 4.2μg/m³). NO_x was closely correlated with PM₁₀ (all p-values<0.001, r²>0.7) when
205 comparing over the study period as both have local traffic as the major source. However, there
206 were only moderate correlations (all p-values<0.001, r²<0.4) between pollutants during the 9th
207 year of life and other study periods (see Figures S1a and S1b).

208 [insert Figure 2 here]

209 The risks of ASD and ADHD using different cutoff values were not consistently associated
210 with exposure to NO_x or PM₁₀ at any age (Figure 3 and Table 2). For example, exposure to

211 NO_x during the first year of life was not associated with ASD (OR 0.86, 95% CI 0.44-1.67) or
212 ADHD (OR 1.06, 95% CI 0.71-1.59), after adjusting for child gender, parity, and other
213 relevant covariates. Likewise, exposure to PM₁₀ during first year of life was not related to
214 ASD (OR 0.95, 95% CI 0.56-1.62) or ADHD (OR 1.06, 95% CI 0.75-1.52). A lack of
215 association was also observed for air pollution exposure during pregnancy. Results were
216 similar using the dimensional outcomes for ASD and ADHD (data not shown). It should be
217 noted that there was a substantial overlap between the diagnoses, e.g. 82 of the 109 children
218 with ASD also had ADHD.

219 [insert Figure 3 and table 2 here]

220 When exposure to air pollutants for each trimester of the pregnancy controlling for seasonal
221 effect and during the child's 9th year of life were evaluated separately, similar findings were
222 found with no consistent associations for most neurodevelopmental outcomes related to
223 traffic-air pollutant levels (Tables S3-S5). However, it is noteworthy that an inverse relation
224 was observed between air pollution exposure during 2nd and 3rd trimesters and ASD as well as
225 ADHD using cutoff values based on DSM-IV criteria. We also did a sensitivity analysis by
226 re-defining cases comorbid with chromosome abnormality or neurological diseases (Table S6).
227 The ORs in those analyses tended to be lower, but still no statistically significant association
228 was found. In sub-analyses we assessed all twins whose mothers answered the telephone
229 interview from CATSS and similar findings were found for all outcomes (Table S7).

230 **Discussion**

231 This study did not indicate an association between exposure to NO_x or PM₁₀ from traffic
232 during pregnancy or first year of life and neurodevelopmental disorders in children. For
233 specific subgroups and diagnoses, there were some associations but no consistent patterns
234 were evident. This also holds true for analyses related to exposure during certain time
235 windows.

236 There is limited evidence on air pollution exposure and neurodevelopmental disorders in
237 children (Becerra et al., 2013; Calderon-Garciduenas et al., 2011; Dix-Cooper et al., 2012;
238 Guxens et al., 2012; Jung et al., 2013; Morales et al., 2009; Siddique et al., 2011; Windham et
239 al., 2006; Volk et al., 2011; Volk et al., 2013; Vrijheid et al., 2012). Windham et al (2006)
240 reported a positive relation between the distribution of hazardous air pollutants at birth
241 addresses and ASD among children in California. Other studies in California found that living
242 close to freeways and traffic-related air pollution in mother's late pregnancy or child's first
243 year of life were associated with an increased risk for autism (Volk et al., 2011; Volk et al.,
244 2013). Siddique et al (2011) compared children living in New Delhi urban area with children
245 living in rural areas and showed that ADHD was positively correlated with current PM₁₀
246 levels. Air pollutants may induce systematic inflammation, which could be a possible
247 mechanism mediating these effects (Block & Calderon-Garciduenas, 2009; Calderon-
248 Garciduenas et al., 2008).

249 The results of our study did not indicate that air pollution has an effect on the risk of
250 neurodevelopmental disorders, even when time windows were considered during fetal life and
251 infancy. The apparently discrepant results compared to some earlier studies could have
252 several explanations. Firstly, relatively low levels of air pollution may contribute to the
253 absence of an association and make it difficult to compare with other study settings. For

254 example, the local traffic related PM₁₀ concentrations during participants' first year of life in
255 Stockholm was only 3.9 µg/m³ and the long-range transported PM₁₀ in this part of Sweden
256 has a yearly average level of around 10 µg/m³ (Gidhagen, Omstedt, Pershagen, Willers, &
257 Bellander, 2013). The roof top levels for PM₁₀ in central Stockholm have been relatively
258 constant during 1994-2012 (Burman & Norman, 2013). However, these levels are
259 considerably lower than in the study areas of California described above (mean value at
260 25±7.2 µg/m³ in one study and 36.3±6.1 µg/m³ in another study) (Becerra et al., 2013; Volk et
261 al., 2013). Furthermore, associations may exist between the socioeconomic status at
262 individual or neighborhood-level and the risk for neurodevelopmental or behavioral problems
263 (Bhasin & Schendel, 2007; Flouri et al., 2012). Maternal smoking correlates with
264 socioeconomic factors such as education and income (Kabir, Connolly, & Alpert, 2011;
265 Laaksonen, Rahkonen, Karvonen, & Lahelma, 2005), and may contribute to this association.
266 The earlier studies (Calderon-Garciduenas et al., 2011; Guxens et al., 2012; Siddique et al.,
267 2011; Windham et al., 2006; Volk et al., 2011; Vrijheid et al., 2012) did not always adjust for
268 neighborhood deprivation as well as individual socioeconomic characteristics and smoking
269 during pregnancy, which suggests there could be some residual confounding.

270 We found inconsistent associations between air pollution in late pregnancy and decreased risk
271 of ASD and ADHD using cutoff values based on DSM-IV criteria. Even though the sample
272 size was relatively large with 3426 subjects, the number of children who scored above the
273 cutoff values for some neurodevelopmental outcomes was low, contributing to statistical
274 uncertainty of the risk estimates.

275 Strengths of the study include a population-based sample of twins and data linkage to
276 Swedish national registries, which include baseline birth-related and socioeconomic
277 information before disease onset. Secondly, we investigated both ADHD and ASD because of
278 the high degree of comorbidity between the two conditions. Furthermore, we analyzed

279 neurodevelopmental disorders categorically based on DSM-IV criteria and the additional
280 cutoff values according to previous validation studies (Hansson et al., 2005; Larson et al.,
281 2010). Thirdly, we included different trimesters during pregnancy, first year and 9th year of
282 life using the validated dispersion modeling together with data on road traffic emissions while
283 previous studies reported effects from either prenatal or post-natal air pollution exposures.

284 There are also several potential limitations of the study. One is that the occurrence of
285 neurodevelopmental outcomes may have differed in children participating in CATSS with
286 completed A-TAC assessment and those in the general population. Two Swedish studies
287 found that children of immigrant parents had impaired psychological health (Gillberg,
288 Steffenburg, Borjesson, & Andersson, 1987; Magnusson et al., 2012; Van Leeuwen, Nilsson,
289 & Merlo, 2012), however the occurrence of neurodevelopmental disorders in our study was
290 lower in families with both parents from outside of Scandinavian countries. The data linkage
291 to other registers allowed us to acquire additional data on the CATSS non-responders, which
292 indicated that children enrolled in the study had higher familial socioeconomic status. Another
293 possible limitation is the assessment of the neurodevelopmental outcomes, which might have
294 created some misclassification (Ragland, 1992). Most earlier studies attempted to evaluate
295 outcomes as discrete scores; however, our data was highly skewed on all outcomes. Our
296 power was limited for analyses of sub-dimensional ASD/ADHD measures. Furthermore, for
297 the exposure time measured during child's 9th year of life, the air pollution assessment may
298 actually have occurred after disease onset.

299 **Conclusion**

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

304 **Financial support**

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

Reference

- 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 Res Hum Genet*, *14*(6), 495-508.
- Becerra, T. A., Wilhelm, M., Olsen, J., Cockburn, M., & Ritz, B. (2013). Ambient air pollution and autism in Los Angeles county, California. *Environ Health Perspect*, *121*(3), 380-386. doi: 10.1289/ehp.1205827
- 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. *Environ Health Perspect*, *109*(6), 633-639.
- Bhasin, T. K., & Schendel, D. (2007). Sociodemographic risk factors for autism in a US metropolitan area. *J Autism Dev Disord*, *37*(4), 667-677. doi: 10.1007/s10803-006-0194-y
- Block, M. L., & Calderon-Garciduenas, L. (2009). Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci*, *32*(9), 506-516. doi: 10.1016/j.tins.2009.05.009
- Burman, L., & Norman, M. (2013). The air quality in Stockholm: annual report 2012. Retrieved Feb 07, 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 Cogn*, *77*(3), 345-355. doi: 10.1016/j.bandc.2011.09.006
- 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. *Toxicol Pathol*, *36*(2), 289-310. doi: 10.1177/0192623307313011
- Carlin, J. B., Gurrin, L. C., Sterne, J. A., Morley, R., & Dwyer, T. (2005). Regression models for twin studies: a critical review. *Int J Epidemiol*, *34*(5), 1089-1099. doi: 10.1093/ije/dyi153
- 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*(2), 246-254. doi: 10.1016/j.neuro.2011.09.004
- Flouri, E., Mavroveli, S., & Tzavidis, N. (2012). Cognitive ability, neighborhood deprivation, and young children's emotional and behavioral problems. *Soc Psychiatry Psychiatr Epidemiol*, *47*(6), 985-992. doi: 10.1007/s00127-011-0406-4
- 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. *Arch Pediatr Adolesc Med*, *161*(9), 857-864. doi: 10.1001/archpedi.161.9.857
- Gidhagen, L., Omstedt, G., Pershagen, G., Willers, S., & Bellander, T. (2013). High-resolution modeling of residential outdoor particulate levels in Sweden. *J Expo Sci Environ Epidemiol*, *23*(3), 306-314. doi: 10.1038/jes.2012.122
- Gillberg, C., Steffenburg, S., Borjesson, B., & Andersson, L. (1987). Infantile autism in children of immigrant parents. A population-based study from Goteborg, Sweden. *Br J Psychiatry*, *150*, 856-858.
- Greenland, S., & Brumback, B. (2002). An overview of relations among causal modelling methods. *Int J Epidemiol*, *31*(5), 1030-1037.
- Gruzjeva, 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. *J Allergy Clin Immunol*, *129*(1), 240-246. doi: 10.1016/j.jaci.2011.11.001

- Guxens, M., Aguilera, I., Ballester, F., Estarlich, M., Fernandez-Somoano, A., Lertxundi, A., . . . Project, Inma. (2012). Prenatal exposure to residential air pollution and infant mental development: modulation by antioxidants and detoxification factors. *Environ Health Perspect*, *120*(1), 144-149. doi: 10.1289/ehp.1103469
- Hagberg, H., & Mallard, C. (2005). Effect of inflammation on central nervous system development and vulnerability. *Curr Opin Neurol*, *18*(2), 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. *Br J Psychiatry*, *187*, 262-267. doi: 10.1192/bjp.187.3.262
- Jarbrink, K., Fombonne, E., & Knapp, M. (2003). Measuring the parental, service and cost impacts of children with autistic spectrum disorder: a pilot study. *J Autism Dev Disord*, *33*(4), 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*(9), e75510. doi: 10.1371/journal.pone.0075510
- Kabir, Z., Connolly, G. N., & Alpert, H. R. (2011). Secondhand smoke exposure and neurobehavioral disorders among children in the United States. *Pediatrics*, *128*(2), 263-270. doi: 10.1542/peds.2011-0023
- 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*(6), e1149-1158. doi: 10.1542/peds.2008-1057
- Laaksonen, M., Rahkonen, O., Karvonen, S., & Lahelma, E. (2005). Socioeconomic status and smoking: analysing inequalities with multiple indicators. *Eur J Public Health*, *15*(3), 262-269. doi: 10.1093/eurpub/cki115
- 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. doi: 10.1186/1471-244x-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. *Br J Psychiatry*, *201*, 109-115. doi: 10.1192/bjp.bp.111.095125
- Martin, N., Scourfield, J., & McGuffin, P. (2002). Observer effects and heritability of childhood attention-deficit hyperactivity disorder symptoms. *Br J 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. *Nat Clin Pract Cardiovasc Med*, *6*(1), 36-44. doi: 10.1038/ncpcardio1399
- 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. *Am J Epidemiol*, *169*(11), 1327-1336. doi: 10.1093/aje/kwp067
- Newton, C. R. (2012). Neurodevelopmental disorders in low- and middle-income countries. *Dev Med Child Neurol*, *54*(12), 1072. doi: 10.1111/j.1469-8749.2012.04384.x
- Nordling, E., Berglund, 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*(3), 401-408. doi: 10.1097/EDE.0b013e31816a1ce3
- Panasevich, S., Leander, K., Rosenlund, M., Ljungman, P., Bellander, T., de Faire, U., . . . Nyberg, F. (2009). Associations of long- and short-term air pollution exposure with markers of inflammation and coagulation in a population sample. *Occup Environ Med*, *66*(11), 747-753. doi: 10.1136/oem.2008.043471
- 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. *J Autism Dev Disord*, 41(3), 332-340. doi: 10.1007/s10803-010-1055-2
- Post codes and SAMS atlas. (2013). Retrieved October 08, 2013, from http://www.scb.se/Pages/Standard_333368.aspx
- Ragland, D. R. (1992). Dichotomizing continuous outcome variables: dependence of the magnitude of association and statistical power on the cutpoint. *Epidemiology*, 3(5), 434-440.
- Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Larsson, H., Hultman, C. M., & Reichenberg, A. (2014). The familial risk of autism. *JAMA*, 311(17), 1770-1777. doi: 10.1001/jama.2014.4144
- 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. *Int J Epidemiol*, 42(4), 1057-1066. doi: 10.1093/ije/dyt066
- Siddique, S., Banerjee, M., Ray, M. R., & Lahiri, T. (2011). Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. *Eur J Pediatr*, 170(7), 923-929. doi: 10.1007/s00431-010-1379-0
- The Swedish Medical Birth Register: a summary of content and quality. (2003). Retrieved Jan 27, 2014, from <http://www.sos.se/fulltext/112/2003-112-3/2003-112-3.pdf>
- 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(5). doi: 10.1136/bmjopen-2012-001260
- 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. *Environ Health Perspect*, 114(9), 1438-1444.
- Volk, H. E., Hertz-Picciotto, I., Delwiche, L., Lurmann, F., & McConnell, R. (2011). Residential proximity to freeways and autism in the CHARGE study. *Environ Health Perspect*, 119(6), 873-877. doi: 10.1289/ehp.1002835
- Volk, H. E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., & McConnell, R. (2013). Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry*, 70(1), 71-77. doi: 10.1001/jamapsychiatry.2013.266
- 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(1), 23-32. doi: 10.1097/EDE.0b013e31823a4023

Tables

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)		-
Other	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)
Zygoty							
Monozygoty	1,380 (40.3)	1,236 (40.5)	44 (40.4)		129 (39.3)		-
Dizygoty	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 (<2,500g)							
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

<25yrs	234 (6.8)	197 (6.5)	7 (6.4)	34 (10.4)	184 (11.8)
≥25yrs and <30yrs	838 (24.5)	737 (24.2)	39 (35.8)	89 (27.1)	418 (26.9)
≥30yrs and <35yrs	1,392 (40.6)	1,266 (41.5)	36 (33.0)	110 (33.5)	521 (33.5)
≥35yrs	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 (≤9yrs)	218 (6.4)	183 (6.0)	17 (15.6)	31 (9.5)	179 (11.5)
Middle (10-12yrs)	1,382 (40.3)	1,191 (39.0)	58 (53.2)	167 (50.9)	541 (34.8)
High(>12yrs)	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 (1 st year of life)						
Low (≤ 9 yrs)	136 (4.0)	114 (3.7)	9 (8.3)		20 (6.1)	145 (9.3)
Middle (10-12 yrs)	1,284 (37.5)	1,092 (35.8)	60 (55.1)		170 (51.8)	545 (35.1)
High (> 12 yrs)	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 (9 th year of life)						
Low (≤ 9 yrs)	136 (4.0)	113 (3.7)	9 (8.3)		21 (6.4)	160 (10.1)
Middle (10-12 yrs)	1,210 (35.3)	1,026 (33.6)	57 (52.3)		161 (49.1)	565 (37.9)
High (> 12 yrs)	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 \pm SD)	-0.1 \pm 1.0	-0.1 \pm 1.0	0.1 \pm 1.2		0.0 \pm 1.1	† 0.3 \pm 1.4
NPI during 9 th year of life (mean \pm SD)	-0.3 \pm 0.9	-0.3 \pm 0.9	-0.2 \pm 1.1		-0.2 \pm 0.8	† 0.1 \pm 1.2
Individualized income during mother's pregnancy (mean \pm SD, 1000 SEK)	105.0 \pm 110.8	106.8 \pm 116.3	86.7 \pm 35.9		89.8 \pm 44.3	† 89.2 \pm 63.6
Individualized income during child's 9 th year of life (mean \pm SD, 1000 SEK)	162.0 \pm 228.9	164.5 \pm 240.6	134.5 \pm 62.6		141.1 \pm 88.5	149.6 \pm 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)

Definition of abbreviations: 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 was listed in Table S1 in supplemental materials.

^c The p-values were presented comparing ASD/ADHD individuals to ones with neither ASD nor ADHD. † indicates $p < 0.05$ and ‡ indicates $p < 0.001$.

Figure 1

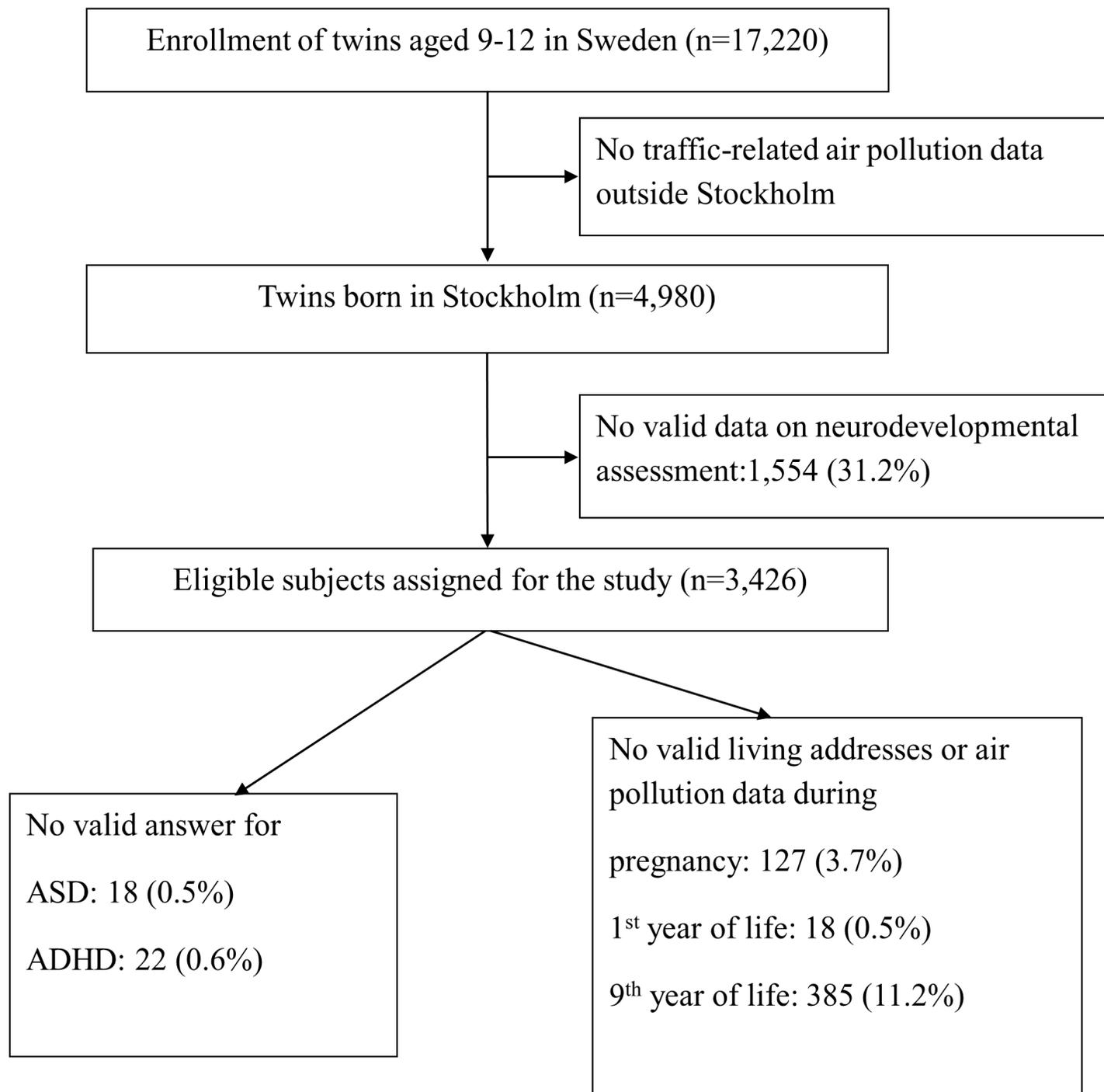


Figure 2

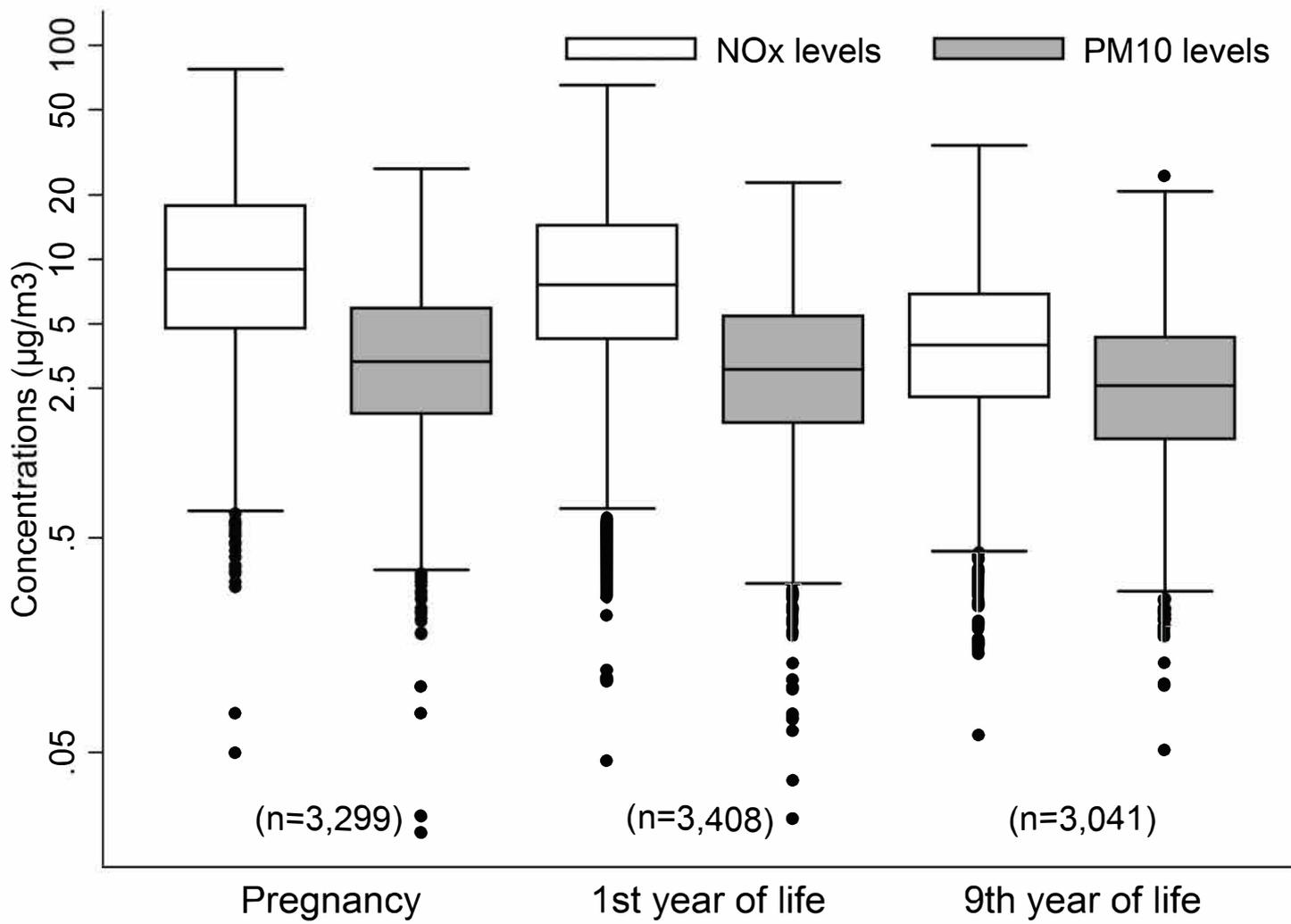


Figure 3

