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1 Title page

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

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- 32 Exposure to air pollution and neurodevelopmental disorders

33 Abstract

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

54

55 Key words:

- s6 air pollution, PM_{10} , 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
- 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

Neurodevelopmental disorders are relatively common and pose a substantial challenge to 65 society (Froehlich et al., 2007; Jarbrink, Fombonne, & Knapp, 2003; Kogan et al., 2008; 66 Newton, 2012). For some conditions the diagnosis rates have increased but the reasons behind 67 these apparent time trends remain largely unknown. Improved awareness and widened 68 diagnostic criteria may contribute, such as for attention deficit/hyperactivity disorder (ADHD) 69 and autism spectrum disorders (ASD), but probably do not explain the whole increase. Both 70 ADHD and ASD are childhood onset chronic conditions of moderate to high heritability 71 72 (Anckarsater et al., 2011; Martin, Scourfield, & McGuffin, 2002; Parr et al., 2011). However, their precise etiologies remain enigmatic, and the role of environmental factors acting as 73 triggers or contributors to general vulnerability should not be disregarded (Sandin et al., 2014). 74 Epidemiological and experimental studies indicate that exposure to air pollution from road 75 traffic may induce systemic inflammation and increase the risk of several diseases related to 76 inflammation, such as asthma, allergy, and cardiovascular diseases (Mills et al., 2009; 77 Nordling et al., 2008; Panasevich et al., 2009). Systemic inflammation can also contribute to 78 neuronal injury and affect the development of central nervous system (Hagberg & Mallard, 79 2005). Recent epidemiological studies have shown associations between exposure to air 80 pollution from road traffic or other sources and adverse neurodevelopmental effects in 81 children (Becerra, Wilhelm, Olsen, Cockburn, & Ritz, 2013; Calderon-Garciduenas et al., 82 2011; Dix-Cooper, Eskenazi, Romero, Balmes, & Smith, 2012; Guxens et al., 2012; Jung, Lin, 83 & Hwang, 2013; Morales et al., 2009; Siddique, Banerjee, Ray, & Lahiri, 2011; Windham, 84 Zhang, Gunier, Croen, & Grether, 2006; Volk, Hertz-Picciotto, Delwiche, Lurmann, & 85 McConnell, 2011; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013; Vrijheid et 86 al., 2012). However, more studies are needed to assess causality, particularly since the 87

- 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,
- 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

July 1, 1992 (Anckarsater et al., 2011). In this project the twins born 1992-2000 were

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

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

this area were selected and 3,426 completed the neurodevelopmental assessment (response

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

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

129 **Exposure assessment**

The air pollution concentrations at residential addresses during mother's pregnancy, child's 130 first year of life and the year before the neurodevelopmental assessment were estimated by 131 dispersion models, described in detail elsewhere (Bellander et al., 2001; Gruzieva et al., 2012). 132 Briefly, the residential history of the study subjects was obtained from taxation authorities and 133 geocoded using a property register maintained by the Swedish mapping, cadastral and land 134 registration authority. The address information was linked with historical emission databases 135 to obtain annual average levels of nitrogen oxides (NO_x) and particulate matter with less than 136 10 μ m of diameter (PM₁₀). Residence time weighted NO_x and PM₁₀ concentrations related to 137 road traffic emissions were calculated for each trimester and over the mother's pregnancy 138 period, the child's first year and 9th year of life. Furthermore, daily 24 hour mean NO_x and 139 PM₁₀ levels from suburban stations were used to calculate the NO_x and PM₁₀ levels during 140 each trimester of the pregnancy, which were taken into account in sensitivity analyses. 141 Imputation for missing values of NO_x and PM₁₀ in the trimester-specific analyses was 142

performed using predictions from rooftop measurements of both pollutants from a monitoringstation in the center of Stockholm.

145 **Other covariates**

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

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 5^{th} to 95^{th}
171	percentile increase in NO_x or PM_{10} 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 9 th 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.

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

188 **Results**

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

199 [insert Table 1 here]

Figure 2 shows air pollutant levels during pregnancy, child's first and 9th 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 9th 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 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

were only moderate correlations (all p-values<0.001, r^2 <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

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

219 [insert Figure 3 and table 2 here]

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

230 **Discussion**

This study did not indicate an association between exposure to NO_x or PM_{10} from traffic during pregnancy or first 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 236 children (Becerra et al., 2013; Calderon-Garciduenas et al., 2011; Dix-Cooper et al., 2012; 237 Guxens et al., 2012; Jung et al., 2013; Morales et al., 2009; Siddique et al., 2011; Windham et 238 239 al., 2006; Volk et al., 2011; Volk et al., 2013; Vrijheid et al., 2012). Windham et al (2006) reported a positive relation between the distribution of hazardous air pollutants at birth 240 addresses and ASD among children in California. Other studies in California found that living 241 close to freeways and traffic-related air pollution in mother's late pregnancy or child's first 242 year of life were associated with an increased risk for autism (Volk et al., 2011; Volk et al., 243 2013). Siddique et al (2011) compared children living in New Delhi urban area with children 244 living in rural areas and showed that ADHD was positively correlated with current PM₁₀ 245 levels. Air pollutants may induce systematic inflammation, which could be a possible 246 mechanism mediating these effects (Block & Calderon-Garciduenas, 2009; Calderon-247 Garciduenas et al., 2008). 248

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 to some earlier studies could have several explanations. Firstly, relatively low levels of air pollution may contribute to the absence of an association and make it difficult to compare with other study settings. For

example, the local traffic related PM₁₀ concentrations during participants' first year of life in 254 Stockholm was only 3.9 μ g/m³ and the long-range transported PM₁₀ in this part of Sweden 255 has a yearly average level of around 10 μ g/m³ (Gidhagen, Omstedt, Pershagen, Willers, & 256 Bellander, 2013). The roof top levels for PM_{10} in central Stockholm have been relatively 257 constant during 1994-2012 (Burman & Norman, 2013). However, these levels are 258 considerably lower than in the study areas of California described above (mean value at 259 $25\pm7.2 \,\mu\text{g/m}^3$ in one study and $36.3\pm6.1 \,\mu\text{g/m}^3$ in another study) (Becerra et al., 2013; Volk et 260 al., 2013). Furthermore, associations may exist between the socioeconomic status at 261 individual or neighborhood-level and the risk for neurodevelopmental or behavioral problems 262 (Bhasin & Schendel, 2007; Flouri et al., 2012). Maternal smoking correlates with 263 socioeconomic factors such as education and income (Kabir, Connolly, & Alpert, 2011; 264 Laaksonen, Rahkonen, Karvonen, & Lahelma, 2005), and may contribute to this association. 265 266 The earlier studies (Calderon-Garciduenas et al., 2011; Guxens et al., 2012; Siddique et al., 2011; Windham et al., 2006; Volk et al., 2011; Vrijheid et al., 2012) did not always adjust for 267 neighborhood deprivation as well as individual socioeconomic characteristics and smoking 268 during pregnancy, which suggests there could be some residual confounding. 269 We found inconsistent associations between air pollution in late pregnancy and decreased risk 270 of ASD and ADHD using cutoff values based on DSM-IV criteria. Even though the sample 271 size was relatively large with 3426 subjects, the number of children who scored above the

size was relatively large with 3426 subjects, the number of children who scored above the
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

information before disease onset. Secondly, we investigated both ADHD and ASD because of

the high degree of comorbidity between the two conditions. Furthermore, we analyzed

neurodevelopmental disorders categorically based on DSM-IV criteria and the additional 279 280 cutoff values according to previous validation studies (Hansson et al., 2005; Larson et al., 2010). Thirdly, we included different trimesters during pregnancy, first year and 9th year of 281 life using the validated dispersion modeling together with data on road traffic emissions while 282 previous studies reported effects from either prenatal or post-natal air pollution exposures. 283 There are also several potential limitations of the study. One is that the occurrence of 284 neurodevelopmental outcomes may have differed in children participating in CATSS with 285 completed A-TAC assessment and those in the general population. Two Swedish studies 286 found that children of immigrant parents had impaired psychological health (Gillberg, 287 Steffenburg, Borjesson, & Andersson, 1987; Magnusson et al., 2012; Van Leeuwen, Nilsson, 288 & Merlo, 2012), however the occurrence of neurodevelopmental disorders in our study was 289 lower in families with both parents from outside of Scandinavian countries. The data linkage 290 to other registers allowed us to acquire additional data on the CATSS non-responders, which 291 indicated that children enrolled in the study had higher familial socioeconomic status. Another 292 possible limitation is the assessment of the neurodevelopmental outcomes, which might have 293 created some misclassification (Ragland, 1992). Most earlier studies attempted to evaluate 294 outcomes as discrete scores; however, our data was highly skewed on all outcomes. Our 295 power was limited for analyses of sub-dimensional ASD/ADHD measures. Furthermore, for 296 the exposure time measured during child's 9th year of life, the air pollution assessment may 297 actually have occurred after disease onset. 298

299 Conclusion

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.

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Tables

Table 1. Child and family characteristics in 9- and 12-year-old twins born in Stockholm

							Non-
	Total	Healthy	ASD ^a	p ^c	ADHD ^a	p ^c	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) Respondent	10.3±1.5	10.3±1.5	10.6±1.6		10.3±1.5		14.7±2.5
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)	4	216 (65.9)	-	733 (47.2)
Female	1,670 (48.7)	1,541 (50.5)	29 (26.6)	Ţ	112 (34.2)	Ŧ	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)	ţ	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	Ť	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)	Ť	418 (26.9)
≥30yrs and <35yrs	1,392 (40.6)	1,266 (41.5)	36 (33.0)	Ţ	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) 29 (8.8) 38 (11.6)	*	116 (7.5)
Yes, ≥10 cigarettes/day	164 (4.8)	132 (4.3)	8 (7.3)			÷	77 (5.0)
Missing	415 (12.1)	373 (12.2)	12 (11.0)				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)	Ť	30 (9.2)	Ť	165 (10.6)
Missing	16 (0.5)	15 (0.5)	0		1 (0.3)		131 (8.4)
Maternal marital status during child's 9 th 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)	Ť	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	167 (50.9)	±	541 (34.8)
High(>12yrs)	1,695 (49.5)	1,566 (51.3)	28 (25.7)	Ţ	115 (35.1)	Ţ	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 (≤9yrs)	136 (4.0)	114 (3.7)	9 (8.3)		20 (6.1) 170 (51.8)		145 (9.3)
Middle (10-12yrs)	1,284 (37.5)	1,092 (35.8)	60 (55.1)	*		+	545 (35.1)
High(>12yrs)	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 (≤9yrs)	136 (4.0)	113 (3.7)	9 (8.3)		21 (6.4)		160 (10.1)
Middle (10-12yrs)	1,210 (35.3)	1,026 (33.6)	57 (52.3)	*	161 (49.1)	÷	565 (37.9)
High(>12yrs)	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	Ť	0.3 ±1.4
NPI during 9 th year of life (mean±SD) Individualized income during	-0.3±0.9	-0.3±0.9	-0.2±1.1		-0.2±0.8	Ť	0.1 ±1.2
mother's pregnancy (mean±SD,1000 SEK) Individualized income during	105.0±110.8	106.8±116.3	86.7±35.9		89.8±44.3	Ť	89.2±63.6
child's 9 th year of life (mean±SD,1000 SEK) Comorbidity ^b	162.0±228.9	164.5±240.6	134.5±62.6		141.1±88.5		149.6±197.8
Yes	120 (3.5)	59 (1.9)	44 (40.4)	.!-	48 (14.6)	4	75 (4.8)
No	3,306 (96.5)	2,992 (98.1)	65 (59.6)	Ţ	280 (85.4)	Ţ	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. \dagger indicates p<0.05 and \ddagger indicates p<0.001.





Figure 3

