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Title page

Parental asthma and risk of autism spectrum disorder in offspring: a population and family based case-control study

Running title: Parental asthma and offspring ASD

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Abstract

Background

Associations between parental asthma and prenatal exposure to asthma medications with offspring autism spectrum disorder (ASD) have been reported. However, the associations might be confounded by unmeasured (genetic and shared environmental) familial factors.

Objective

We investigated the association between (a) maternal/paternal asthma and offspring ASD, and (b) prenatal exposures to β 2-agonists, other asthma medications and offspring ASD using cases and controls selected from the population as well as biological relatives with different degrees of relatedness.

Methods

We included all children (N=1,579,263) born in Sweden 1992-2007. A nested case-control design was used to compare 22,894 ASD cases identified from the National Patient Register to (i) 228,940 age-, county- and sex-matched controls randomly selected from the population, (ii) their eligible full-siblings (n=1,267), (iii) half-siblings (n=1,323), (iv) full-cousins (n=11,477), and (v) half-cousins (n=3,337). Conditional logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for ASD in children differentially exposed to parental asthma or prenatal asthma medications.

Results

Maternal asthma was associated with increased risk of offspring ASD (OR 1.43, 95% CI 1.38-1.49); there was a weaker association for paternal asthma (OR 1.17, 95% CI 1.11-1.23). The risk of offspring ASD in mothers with asthma showed similar estimates when adjusting for shared familial factors among paternal half-siblings (OR 1.20, 95% CI 0.80-1.81), full-cousins (OR 1.28, 95% CI 1.16-1.41), and half-cousins (OR 1.30, 95% CI 1.10-1.54), albeit with wider confidence intervals. Prenatal exposure to asthma medications among subjects whose mothers had asthma was not associated with subsequent ASD.

Conclusions and clinical relevance

In this large observational study, parental asthma was associated with slightly elevated risk of ASD in offspring. More specifically, the increased risk by maternal asthma did not seem to be confounded by familial factors. There was no evidence of an association between asthma medications during pregnancy and offspring ASD.

Abstract

Key words: asthma; medications during pregnancy; autism spectrum disorder; nested case-control; confounding

Abbreviations:

ASD	Autism Spectrum Disorder
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body Mass Index
CI	Confidence Interval
ICD	International Classification of Diseases
LTRA	Leukotriene Receptor Antagonist
MBR	Medical Birth Register
MGR	Multi-Generation Register
NPR	National Patient Register
OR	Odds Ratio
SPDR	Swedish Prescribed Drug Register

TPR **Total Population Register**

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder defined by persistent deficits in social communication and social interaction alongside restricted, repetitive patterns of behavior, interests, or activities (1, 2). The etiology of ASD is unclear (3). In clinical care, comorbidity between maternal asthma and offspring neuropsychiatric disorders has been seen (4, 5) and several studies have examined the possible contributions of parental asthma and allergy on ASD in offspring (6-8). Nevertheless, it is yet unknown if there is a causal link between asthma in parents and ASD in offspring.

First, the association could be explained by shared environmental and/or genetic factors within the family. Previous studies have focused on the increased risk of ASD by maternal asthma, but an association with paternal asthma has not been consistently found (6-8). Furthermore, the association of parental asthma and ASD in offspring has not been investigated across samples with genetic relatedness. If the risk of ASD in offspring to

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parents with asthma diminishes or is attenuated when comparing cases with their family members, it is more likely that shared familial factors confound the association. Conversely, if the association remains, then a potential causal explanation would be more likely (9). Therefore, comparing cases with extended family members, e.g. siblings (on average sharing 50% genetic materials), half-siblings (sharing 25%), full-cousins (sharing 12.5%), half-cousins (sharing 6.25%) and biologically unrelated controls from the general population is informative to further evaluate the potential role of shared environmental and/or genetic factors (9-11).

Second, the potential association between parental asthma and offspring ASD may be due to unique environmental exposures related to asthma, such as exposure to medication use during pregnancy. Previous studies have suggested a linkage between prenatal exposure to β 2-agonists, subsequent ASD and other developmental disorders (12-15) caused by over-stimulating the β 2-adrenergic receptor during gestation and altering fetal neurodevelopment (16, 17). Furthermore, a few studies have examined short-term effects of prenatal exposure to other asthma medications, including inhaled corticosteroids, as well as leukotriene antagonists (18-21), but none has focused on long-term outcomes such as offspring ASD. Thus, there is reason to believe that the potential association between parental asthma and offspring ASD could be attributed to prenatal exposure to β 2-agonists and/or other asthma medications.

In this population-based nested case-control study, we investigated the association between parental asthma and use of asthma medication during pregnancy with the risk of ASD in offspring. First, the association between maternal/paternal asthma and offspring ASD was estimated using cases and various types of controls selected from the population and among biological relatives with different degrees of relatedness. Second, we investigated the

association between prenatal exposures to β 2-agonists, other asthma medications and offspring ASD by comparing cases with unrelated and sibling controls.

Methods

This nested case-control study was based on data linkage of several Swedish registers via unique personal identity numbers (22). Detailed information on each register and variable used are found in Table E1. Briefly, we selected a birth cohort from the Medical Birth Register (MBR) including more than 99% of all singletons born in Sweden between January 1, 1992 and December 31, 2007 (N=1,579,263) as index persons (23), and followed them until December 31, 2013 (due to in-house data availability at the time of analysis), emigration or death. Through the Multi-Generation Register (MGR), more than 95% of the index persons were linked to their biological mothers, fathers, siblings and cousins (Figure 1, for flow chart) (24).

Selection of cases

We identified ASD cases from the National Patient Register (NPR), where a primary or secondary diagnosis of ASD was recorded according to the International Classification of Diseases 9th and 10th revisions (299 for ICD-9 and all F84s for ICD-10 respectively). The National Patient Register (NPR) has complete coverage of inpatient diagnoses from 1987 and about 80% of the outpatient diagnosis from 2001 and onwards (25). In the NPR, a high positive predictive value has been noted for most diagnoses, including psychiatric ones (25). Furthermore, the ASD definitions using ICD codes have been validated in a previous study (26), where 96% of the ASD cases within Stockholm County identified from the national and regional registers could be verified by medical records.

Selection of controls

First, incidence density sampling was used to select 10 biologically unrelated controls for each ASD case. Controls were matched on birth year, sex, and county of residence, which allowed us to increase the statistical efficiency without introducing selection bias, and to balance the distribution of such characteristics in both group.

Second, half-siblings, full-cousins, and half-cousins of each case as potential controls were identified through the MGR. Controls were eligible if they had the same sex, less than 5 years of age difference to the case (in order to have complete follow-up from birth in the NPR), were singletons, and still at risk (i.e. ASD free and still under follow-up) at the age the case received an ASD diagnosis. In case of multiple eligible controls from the same extended family, we randomly selected one half-sibling, full-cousin, and half-cousin for each case.

Third, we used the MGR to identify all full-siblings of each case born from January 1995 due to the data availability on medication use. The full siblings with maternal asthma still at risk at the age the case received an ASD diagnosis were eligible as controls for the analysis on asthma medication use during pregnancy (but not for the parental asthma comparisons as they share the same exposure).

Exposure assessment

We used records from any of the three registers, i.e. MBR, NPR, and the Swedish Prescribed Drug Register (SPDR) to identify asthma ever, as an indicator of chronic disease, for biological parents of cases and controls. In MBR, a tick-box for asthma/lung diseases ever for the mother was indicated at her first antenatal visit from 1992 onwards. In NPR, we used any primary diagnosis of asthma from outpatient visits since 2001 or hospitalization records since 1961 (see Table E2 for diagnostic codes). In SPDR, we defined asthma as having ≥ 2 dispensed packages of inhaled corticosteroids (ICS), leukotriene antagonists (LTRA), fixed-

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dose β 2-ICS combinations from July 2005, or having ≥ 3 packages of ICS, LTRA, fixed-dose β 2-ICS combinations, or inhaled β 2-agonists within 12 months from July 2005 for individuals (see Table E3 for all Anatomical Therapeutic Chemical codes), based on a previous validation study (27). The reason we chose to define parental 'asthma ever' as exposure was twofold. First, the NPR does not include diagnostic information from primary health care centres whereas the SPDR allows us to identify most prevalent cases since 2005 through the validated measure (27), reducing the possibility of exposure misclassification. Second, some asthma cases can be intermittent and may have been present at an earlier age or in later adulthood. Thus, the 'asthma ever' definition of exposure would capture more intermittent asthma cases than the 'asthma before child birth' definition of exposure over the study period. Parental asthma ever was categorized as asthma from either parent (yes/no), maternal asthma (yes/no), and paternal asthma (yes/no) for analysis.

Information on asthma medication use during pregnancy was retrieved from two sources, i.e. midwife-reported medication use during pregnancy in MBR since 1995 or dispensed medications at pharmacies recorded in SPDR since July 2005. Two forms of β 2-agonists were particularly addressed in the study, as systemic β 2-agonists (i.e. oral and injection) used to be mainly administered to suppress premature labor, while inhaled β 2-agonists were primarily indicated for asthma. We categorized the exposure to asthma, β 2-agonists and other asthma medications into four mutually exclusive groups: with asthma but no medications, systemic β 2-agonists only, inhaled β 2-agonists with or without other asthma medications, and other asthma medications without any β 2-agonists.

Covariates

Socio-economic characteristics, including maternal civil status, parental country of birth, and highest education of parents by the end of the year of child birth, were retrieved from the longitudinal integration database for health insurance and labor market studies. Other background characteristics (maternal body mass index (BMI) at first antenatal visit, smoking during pregnancy and maternal age at delivery, mode of delivery, parity, gestational age, and birth weight) were retrieved from MBR. Paternal age at child birth came from the Total Population Register. Maternal diagnoses during pregnancy and delivery (pre-eclampsia, pre-gestational and gestational diabetes, premature rupture of membranes, premature contraction, placental abruption, and hemorrhage) were retrieved from MBR and NPR. Family history of psychiatric disorders was defined as any psychiatric diagnosis (yes/no) from NPR for each parent. Information on maternal asthma exacerbation history was retrieved from NPR and PDR and defined as having ≥ 1 emergency visit or hospital admission for asthma, or having dispensed ≥ 1 package of oral corticosteroid during the 12-month period prior to the pregnancy.

Statistical analyses

Statistical Analysis Software 9.4 (SAS Institute, Cary, NC) was used to conduct conditional logistic regression analyses and estimate odds ratios (OR) with 95% confidence intervals (CIs) of all analyses on parental asthma, use of asthma medication during pregnancy and offspring ASD. In addition to crude models, we also provide estimates adjusted for parity, maternal smoking, BMI, and civil status, parental age, country of birth, and education. A directed acyclic graph was used to identify potential confounders and mediators based on prior knowledge and a priori assumptions on causal relationship (Figure E1 and eMethods for

detailed information). In the analyses with the unrelated matched controls, the conditional analysis automatically gave adjustment for the matching variables (age, sex and county).

First, the association between parental asthma and offspring ASD was estimated using cases and unrelated controls. We further tested if the association was moderated by sex, county of residence, maternal smoking during pregnancy, family history of psychiatric disorders, and parental education by introducing an interaction term in the model. The independent effect and effect modification of maternal and paternal asthma were analyzed by mutual adjustment and interaction test. Sensitivity analyses were performed to explore the result robustness by gestational age, birth weight, maternal BMI, information sources of asthma, and timing of maternal asthma, i.e. before or after pregnancy (see eMethods for detailed descriptions).

Second, we performed separate analyses by comparing cases with 1) maternal half-sibling controls to estimate the effect of paternal asthma ever (i.e. case and control exposed to different biological fathers w/without asthma); 2) paternal half-sibling controls to estimate the effect of maternal asthma ever (i.e. case and control exposed to different biological mothers w/without asthma); and 3) full-cousin and half-cousin controls to estimate the effects of maternal and paternal asthma respectively. These comparisons allowed us to account for unmeasured familial confounding factors shared by cases and their relatives, as well as the measured confounders mentioned above (full-sibling controls sharing the same parental asthma ever with cases were not used here). If the association remains when comparing cases to sibling and cousin controls, this indicates that parental asthma is a potential causal risk factor for offspring ASD. In contrast, if the risk of ASD diminishes or is further attenuated, this indicates that familial factors shared between siblings and/or cousins confound the association.

Third, to investigate the association between prenatal exposures to β 2-agonists, other asthma medications during pregnancy and ASD, different subsets of cases were compared to matched unrelated and full-sibling controls if their mothers had asthma or took asthma medications during pregnancy.

The Regional Ethical Review Board in Stockholm, Sweden granted permission for the study, Dnr 2013/862-31/5, and individual information was de-identified by the register holders.

Results

Characteristics of all study populations are presented in Table E4 and Table E5 and described in eResults section of the online repository text.

Parental asthma and offspring ASD

Among 22,894 cases compared to 228,940 unrelated controls from the birth cohort, more mothers were single or with other civil status at the year of child birth (15% among cases vs. 9.3% among controls), smoked during pregnancy (19.5% vs. 13.7%), and had pregnancy- and delivery-related complications (see Table E4). Maternal asthma was associated with 43% increased odds of ASD overall when compared to unrelated controls (adjusted OR 1.43, 95% CI 1.38-1.49, Figure 2 and Table E6). In the comparisons within extended families, point estimates for the association between maternal asthma and offspring ASD were similar for half-siblings (adjusted OR 1.20, 95% CI 0.80-1.81), full-cousins (adjusted OR 1.28, 95% CI 1.16-1.41), and half-cousins (adjusted OR 1.30, 95% CI 1.10-1.54) although with wide confidence intervals and not all being statistically significant (Figure 2 and Table E7). The results were similar when mutually adjusting for paternal asthma (Table E8).

We observed an association between paternal asthma and offspring ASD (adjusted OR 1.17, 95% CI 1.11-1.23) when compared to unrelated controls (Figure 2 and Table E6). However, the estimate was attenuated in comparisons for cases and their extended family members [(adjusted OR 0.73 (95% CI 0.38-1.38) for half-siblings, OR 1.03 (95% CI 0.90-1.17) for full-cousins, and OR 1.11 (95% CI 0.87-1.42) for half-cousins, Figure 2 and Table E7]. No interaction was observed between maternal and paternal asthma (Table E8).

The estimates were similar when further adjusted for potential mediators (Table E6). Moreover, there was no evidence that these associations were modified by child sex, maternal smoking during pregnancy, county of residence, family history of psychiatric disorders, or parental education (Figure E2, all interaction p-values >0.05). Results of sensitivity analyses showed similar estimates for maternal and paternal asthma in subgroups with normal birth weight and gestational age, maternal BMI, and when asthma was identified from different information sources. When limiting the analysis to children born 2006 to 2007 (i.e. with full exposure information from all three registers), we found an association of maternal but not paternal asthma with offspring ASD. There were no differences by parental asthma identified before and after pregnancy (Tables E9 & E10).

Use of asthma medication during pregnancy and offspring ASD

Table E5 shows the characteristics of 3,507 cases and 5,350 unrelated controls eligible for the analyses of prenatal exposure to asthma medications and subsequent ASD. In comparison with the previously described characteristics of the study population, similar patterns of maternal background factors were observed among eligible cases and unrelated controls for the medication analysis. Among mothers with asthma, offspring prenatally exposed to different types of asthma medications, e.g. inhaled β_2 -agonists did not have increased risk of

subsequent ASD (adjusted OR 1.02, 95% CI 0.85-1.24) compared to offspring of asthmatic mothers without any medications. Furthermore, using full-sibling controls, adjusting for pregnancy- and delivery-related factors measured in the study, as well as for maternal exacerbation history did not seem to change the result (Table 1, E11 & E12).

Discussion

We found an increased risk of offspring ASD with maternal asthma and a weaker, but significantly increased risk with paternal asthma. The association between maternal asthma remained similar in magnitude within extended families, suggesting that genetic and environmental factors shared by half-siblings and cousins did not seem to confound the association with maternal asthma. Comparing to the maternal effect, the observed association between paternal asthma and offspring ASD, however, seem to be confounded by shared familial factors. Moreover, we did not observe any statistically significant difference in offspring ASD risk for asthmatic women medicated with β 2-agonists or other asthma medications during pregnancy compared to those without medications, which suggests a possible biological effect related to the maternal asthma, not mediated by medications.

Risk of offspring ASD by parental asthma

Our findings are consistent with the results from a case-control study by Croen et al. (6), which reported a moderately positive association between maternal asthma and ASD in offspring, particularly in asthma diagnosed prior to and during pregnancy (OR 1.6, 95% CI 1.2-2.2). However, Lyall and colleagues found no association between maternal asthma or allergies overall and offspring ASD in another case-control study (8). Characteristics of cases, study time periods, and the prevalence of maternal asthma before and after pregnancy may all contribute to differences between studies. For example, a cohort study by Langridge

et al. (7) showed a strikingly similar finding as ours for ASD without intellectual disability, with 40% increased risk with maternal asthma. Yet, they observed no association on ASD with intellectual disability, which could be due to either the relatively lower reported rates of ASD in Australia, or exclusion criteria from their cohort. Therefore, we speculate that children of mothers with asthma have increased susceptibility to develop ASD. Furthermore, Croen et al. observed more than doubled risk of offspring ASD by maternal asthma and allergies identified in early- and mid- pregnancy (6) but this was not confirmed by Lyall et al. (8). Unfortunately, we were not able to provide trimester-specific OR estimates due to limitations in exposure data regarding timing. Additional studies with proper comparisons on the timing and severity of asthma will still be required to elucidate the possibility of a causal association between maternal asthma and offspring ASD (28).

There have been few publications on the association between paternal asthma ever and offspring ASD. Two studies by Mouridsen et al. and Larsson et al. did not find any evidence of increased risk of offspring ASD neither by maternal nor paternal asthma (29, 30) although both had limited statistical power. The current result showed a difference in the effect of maternal and paternal asthma. The significant association of paternal asthma and offspring ASD was attenuated when adjusting for familial factors, potentially indicating a familial confounding between paternal asthma and ASD. However, maternal asthma had similar effect estimates on offspring ASD when comparing cases to unrelated individuals as when controlling for some degree of genetic relatedness and other measured and unmeasured familial characteristics, by comparing cases to relatives of different degrees of relatedness. Two further scenarios may be inferred: first, the association could be due to an observed differences in health seeking behaviors of asthmatic mothers compared with those of non-asthmatic mothers, i.e. an increased proportion of ASD cases were incorrectly classified as

controls among offspring of non-asthmatic mothers, however this seems unlikely since the estimates remained among biological relatives with different degrees of relatedness; second, the result can also indicate that maternal asthma is independently associated with offspring ASD, albeit the absolute risk changes related to maternal asthma being small.

Although we cannot completely rule out a genetic association via maternal inheritance of mitochondrial DNA (31), our results helped to identify a possible causal association between maternal asthma and offspring ASD. A possible biological mechanism is through immune system dysregulation during pregnancy and the ensuing development in offspring (32, 33). Recent animal studies have confirmed possible epigenetic modifications in the offspring's behavioral and cognitive abnormalities due to maternal immune activation (34, 35). Studies on immune mediators including cytokines (36), T cells (37), and auto-antibodies (38) suggest several pathways to ASD through immune dysfunction, but these findings are inconclusive. Furthermore, asthma, especially uncontrolled asthma, during pregnancy has also been associated with intermittent hypoxia (39, 40) and fetal growth restriction (41-43), which are common risk factors for several psychiatric and neurodevelopmental disorders including schizophrenia (44, 45), bipolar disorder (46, 47), ASD (48, 49), and intellectual disability (40). However, adjusting for birth weight, premature delivery, and other pregnancy and delivery-related factors as mediators, did not change the results. There may nevertheless be other potential mediators that deserve further investigation. For example, it has been proposed that asthma-associated intermittent hypoxia might be a mediator in ASD etiology (50, 51).

Risk of offspring ASD by use of asthma medication during pregnancy

Another potential mediator for the association between maternal asthma and subsequent offspring ASD is the use of asthma medication during pregnancy. A few reports on long term effects on offspring's neurodevelopmental outcomes showed inconsistent results for β 2-agonists (12, 14, 16) and no effect for corticosteroids (21, 52). Animal studies suggest a link with β 2-agonists (mainly terbutaline) to cerebellar abnormalities and behavioral impairment (14). A clinical study reported a higher ASD concordance rate in dizygotic twins in mothers treated with terbutaline due to preterm labor (16), which was partly replicated in a case-control study (12). The twin sample, strict timing, long durations and high doses of terbutaline exposure may explain the positive findings in previous studies. However, comparisons from animals to humans should also be drawn with caution. Our results did not suggest an association between prenatal exposure to asthma medication and ASD when comparing cases to unrelated and full-sibling controls. Neither is there an evidence on confounding by a history of asthma exacerbation before pregnancy. One possible explanation could be that level of asthma severity and symptom control during pregnancy confounded the association between medication use and ASD. The alternative explanation could be that a true causal effect has been diluted by a non-differential misclassification of asthma medication usage, as we observed a relatively low percentage of asthmatic women with medications during pregnancy (21-22% in cases and unrelated controls).

Strengths and limitations

In addition to the population-based nested case-control design, the comparisons within extended families helped us control for unmeasured genetic and environmental factors shared by cases and their family members (10). The study base identified from data linkage between reliable registers and up to 21 years of follow-up are advantageous for low selection bias and

no recall bias (22). The data sources for case ascertainment have been previously validated showing generally high quality (26, 53). No earlier study has investigated the association of interest using more than 20,000 ASD cases, which allowed us to report group-specific effects while accounting for measured covariates including socio-demographic characteristics and family history of psychiatric disorders.

Some limitations of this study need to be addressed. First, the coverage of some registers was incomplete during parts of the follow-up. For example, maternal asthma during pregnancy might not be identifiable in the registers if symptoms were not severe enough, because diagnostic records at primary care centers during the whole study period or mothers' medication dispensing records before pregnancy and after delivery among older children were not retrieved. Nevertheless, the prevalence of ASD and asthma in our study was similar to other publications using Swedish data (26, 54, 55) and sensitivity analyses based on children born during 2006-2007, shortly after the SPDR was initiated, verified our main findings. Second, it is difficult to draw conclusions on causal relationships and biological mechanisms from observational data, although using sibling and cousin controls allowed us to adjust for varying amounts of shared familial factors as a way of exploring the importance of confounding from such factors. Still, it is unknown whether we were able to control for all possible confounds, and there are assumptions and limitations of the family-based designs, e.g. no carry-over effect and the way of choosing discordant pairs, power issues and limited control on shared postnatal environment for half-siblings, which can influence both the internal and external validity of the results (11). Third, reverse causality cannot be ruled out as our exposure measurement was parental asthma ever. However, sensitivity analyses based on maternal asthma before child birth gave results in line with our main findings. Fourth, because no trimester-specific medication use was recorded in MBR, our risk estimates for

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medication exposures were only based on medication use anytime during pregnancy, and the proportion of asthmatic women with medications during pregnancy might be underestimated due to the incomplete information in the registers (43). Fifth, some cases not captured in the NPR could be misclassified as controls, which might have resulted in an attenuation of OR if we assume the misclassification was non-differential by their parental asthma status.

However, if cases and controls were differentially misclassified (e.g. different health-seeking behaviors among parent with or without asthma), it would be difficult to predict the direction of the estimates. Finally, results on full-siblings prenatally exposed to asthma medications may have limited power to detect an association due to the low number of asthmatic women with different asthma medication between pregnancies. Future studies are still needed to evaluate on the role of different medication uses during pregnancy.

In conclusion, we found an association between parental asthma and offspring ASD, which might be crucial for the understanding of the ASD etiology in a subgroup of cases. The association between maternal asthma could not be fully explained by measured confounders such as socioeconomic and demographic factors, mediators including pregnancy and delivery-related factors, or unmeasured familial factors such as genetics and shared environment, which indicate the importance of investigating other maternal environmental factors. For pregnant women with asthma, use of asthma medications during pregnancy did not seem to increase the risk of offspring ASD, which further highlights the importance of surveillance and monitoring of asthma in pregnancy. In comparison to the maternal effect, the association between paternal asthma and offspring ASD seemed to be confounded by unmeasured familial factors.

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Legends to Figures

Figure 1. Overall representation of the study populations. The eligibility criteria of being at risk at the age when the case was diagnosed holds for all controls. Matching on sex and less than 5 years of age difference holds for all controls in panel C.

Figure 2. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of offspring autism spectrum disorders (ASD) by parental asthma when comparing cases with unrelated controls, half-cousin, full-cousin, and maternal/paternal half-sibling controls nested in the birth cohort. Panels A and B show the estimates for maternal asthma and paternal asthma separately, after adjusting for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, and maternal body mass index at first antenatal visit. The asterisks were used to indicate statistically significant associations.

Table

Table 1. Association between use of asthma medication during pregnancy and offspring ASD.

	No. of cases/controls	OR (95% CI)	
		Model 1 ^a	Model 2 ^b
Comparing ASD cases to unrelated controls	3,507/5,350		
With asthma but no medications	2,747/4,208	Ref	Ref
Systemic β 2-agonists only	225/336	1.03 (0.85, 1.25)	0.96 (0.76, 1.22)
Inhaled β 2-agonists with or without other asthma medications	380/536	1.04 (0.89, 1.22)	1.02 (0.85, 1.24)
Other asthma medications without any type of β 2-agonists	155/270	0.84 (0.67, 1.06)	0.75 (0.57, 0.99)
		Model 3 ^a	Model 4 ^c
Comparing ASD cases to their full-sibling controls^d	1,133/1,293		
With asthma but no medications	930/1,066	Ref	Ref
Systemic β 2-agonists only	49/52	1.24 (0.75, 2.05)	0.88 (0.50, 1.55)
Inhaled β 2-agonists with or without other asthma medications	105/118	1.00 (0.70, 1.42)	1.03 (0.67, 1.58)
Other asthma medications without any type of β 2-agonists	49/57	1.01 (0.64, 1.59)	0.87 (0.50, 1.51)

Abbreviations: ASD=autism spectrum disorders; CI=confidence interval; OR=odds ratio.

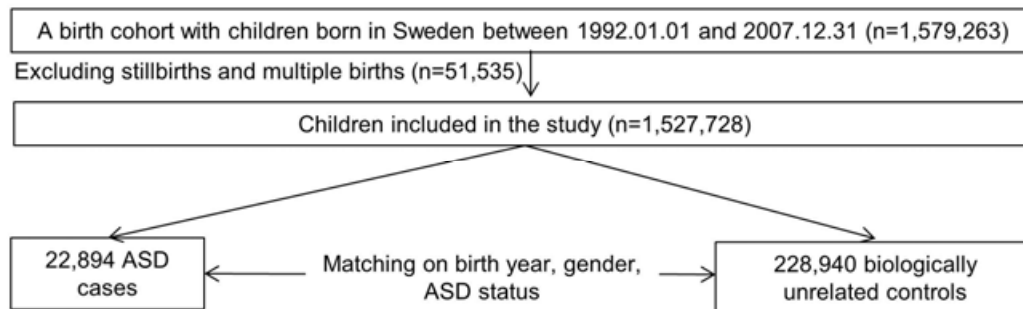
^aModel 1 and 3 did not adjust for any covariates.

^bModel 2 adjusted for birth year, parity, maternal smoking during pregnancy and civil status, country of birth and age for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

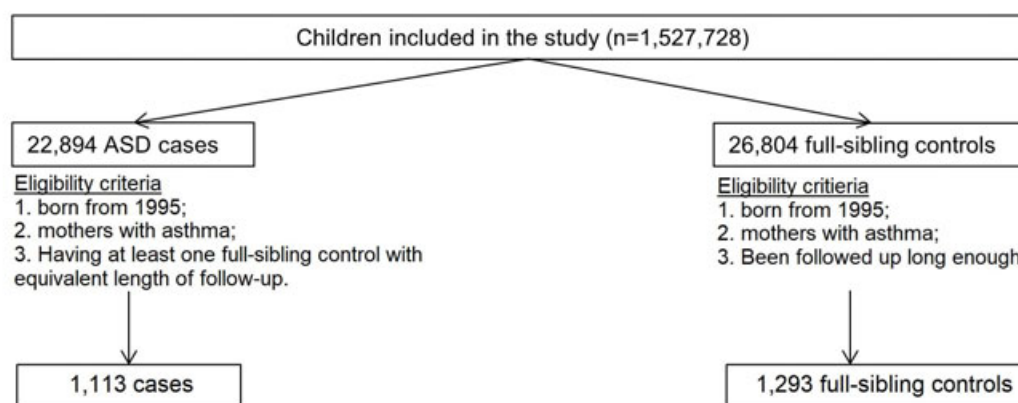
^cModel 4 adjusted for birth year, parity, maternal smoking during pregnancy, age for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

^dAnalyses using half-sibling, and cousin controls are available on request.

A. Selection of unrelated controls from the birth cohort.



B. Selections of full-siblings.



C. Selections of half-siblings, full-cousins, and half-cousins.

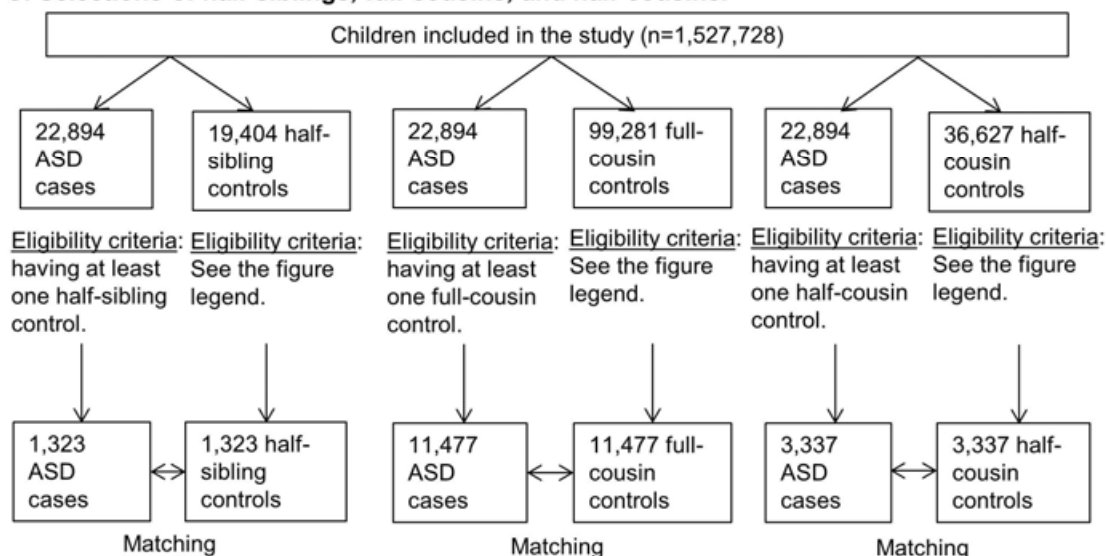
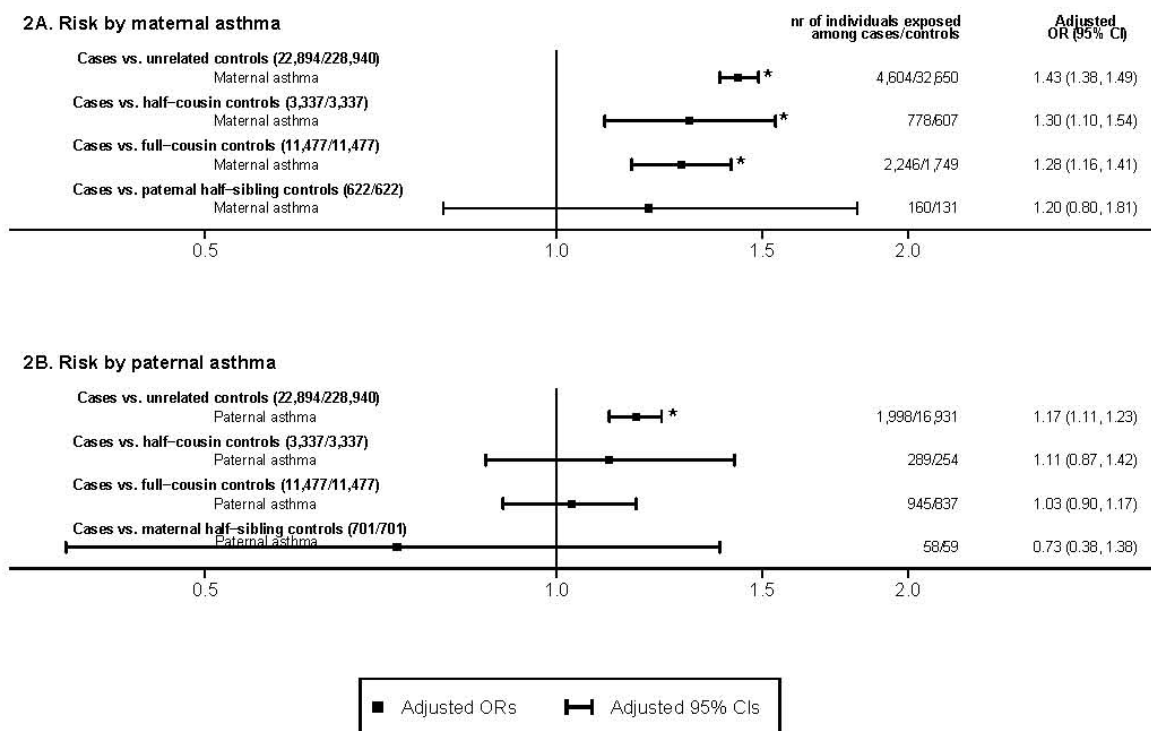


Figure 2. Risk of ASD by parental asthma among cases and various types of controls from the birth cohort



Supplementary materials to the manuscript:

**Parental asthma and risk of autism spectrum disorder in offspring:
a population and family based case-control study**

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eMethods

Statistical analysis

Directed acyclic graph (DAG) was used to identify potential confounders and mediators based on prior knowledge and a priori assumptions on causal relationship (see Figure E1). For example, it was known that birth year, parity (1), parental psychiatric diagnoses (2), parental birth countries (3), parental socioeconomic status (4), parental age (5), being a single mother (6) and having pregnancy complications (7), small for gestational age and low birth weight (5) were risk factors for ASD. Previous literature also identified risk factors for asthma such as age, smoking, socioeconomic status, country of birth, BMI etc. and potential risk of pregnancy complications due to asthma. However, the intra-linkage within these factors was combined with prior knowledge and our assumptions. For example, we supposed and presented in the DAG that the probability of having asthma in the mother depends on her education and body mass index, which also affect the offspring's risk of developing ASD. Therefore, without controlling for maternal education and early pregnancy BMI, the association between maternal asthma and offspring ASD could be confounded.

For all analyses, we also presented risk estimates from models additionally adjusted for potential mediators including pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, PROM, hemorrhage during pregnancy and after delivery, mode of delivery, gestational age, birth weight, and parity. In the presence of an association between parental asthma and offspring ASD, we also assessed whether the magnitude of associations could vary by child sex, county of residence, maternal smoking during pregnancy, parental socioeconomic background, and family history of psychiatric diseases via interaction tests.

Sensitivity analyses were performed by restricting study population to children of Sweden-born parents, conception after July 2005 when the SPDR was initiated, birth weight $\geq 2,500$ grams, and ≥ 37 weeks of gestational age respectively. We also tested if the results were confounded by maternal BMI among women with reported height and weight at first antenatal visit. To get comparable estimates for maternal and paternal asthma, we conducted analysis using asthma defined by 1) ≥ 1 diagnosis from NPR ever, or 2) dispensed medications from SPDR mentioned as above (i.e. without using midwife-reported asthma information from MBR). In order to further increase the exposure specificity, we ran the same analysis using a stricter definition for asthma by 1) having ≥ 1 diagnosis from NPR ever, or 2) having ≥ 2 dispensed packages of ICS, LTRA, and fixed-dose β_2 -ICS combinations within 12-month period. To investigate whether the association could be driven by reverse causality, we used the parental asthma definition by diagnosis, medication, or midwife-report before and after pregnancy from NPR, SPDR, and MBR, as well as the current asthma status of each parent, which was defined as either having ≥ 1 asthma diagnosis or dispensed ≥ 1 asthma controller medication (i.e. ICS, LTRA, fixed-dose β_2 -ICS combinations) 12 months prior to the date of case's first ASD diagnosis apart from being defined as "asthma ever" (see the Methods section of the manuscript). Finally, to further investigate whether the association of prenatal exposure to asthma medications and offspring ASD could be confounded by potentially uncontrolled asthma, we conducted the analysis by additionally adjusting for the 12 month history of asthma exacerbation before pregnancy.

eResults

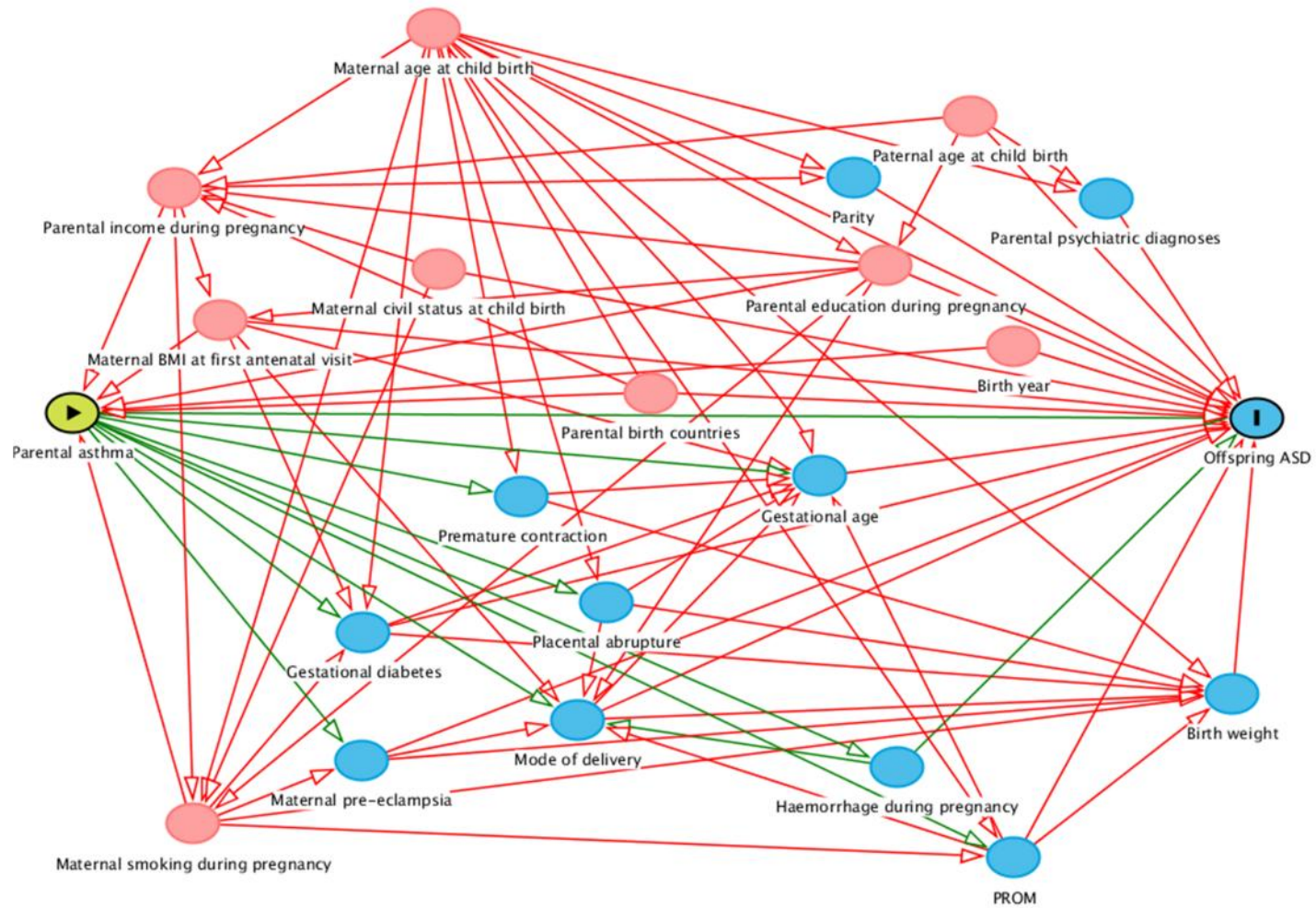
Characteristics of all study populations for the analyses on parental asthma and offspring ASD

Among cases compared to unrelated controls from the birth cohort, more mothers were single or unmarried at the year of child birth (15% among cases vs. 9.3% among controls), smoked during pregnancy (19.5% vs. 13.7%), and had pregnancy- and delivery-related complications. Among cases and controls identified from their extended family members, mothers' characteristics were similar, except higher proportions of single mothers for the cases compared to their half-sibling and half-cousin controls (Table E4).

Characteristics of study populations for the analyses on use of asthma medication during pregnancy and offspring ASD

Similar patterns of maternal background factors were observed among eligible cases and unrelated controls for the medication analysis. However, there were no major differences in characteristics between cases and full-sibling controls, except for the controls being slightly younger than the cases (Table E5).

Figure E1. Directed acyclic graph used to select covariates for model adjustment.



Note: The green-filling circle indicates the exposure and the blue-filling circle with black outline indicates the outcome. Red circles and blue circles without black outline represent confounders and mediators. Red and green lines indicate biasing and causal path respectively.

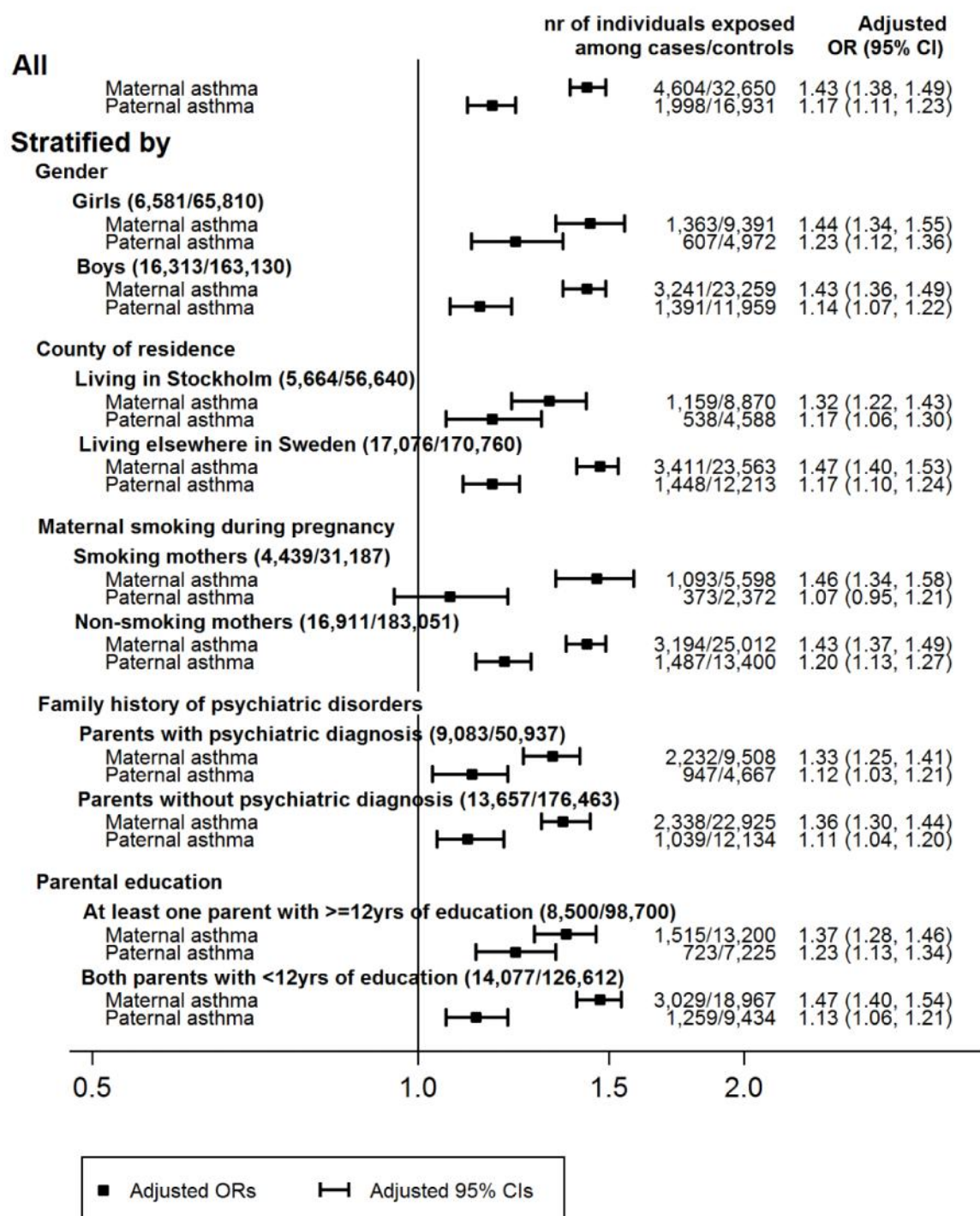
According to the directed acyclic graph, minimal sufficient adjustment sets for estimating the total effect of Parental asthma on Offspring ASD are:

- Birth year, Maternal BMI at first antenatal visit, Maternal age at child birth, Maternal civil status at child birth, Maternal smoking during pregnancy, Parental birth countries, Parental education during pregnancy, Parity, Paternal age at child birth
- Birth year, Maternal BMI at first antenatal visit, Maternal smoking during pregnancy, Parental birth countries, Parental education during pregnancy, Parental income during pregnancy

And minimal sufficient adjustment sets for estimating the direct effect of Parental asthma on Offspring ASD are:

- Birth weight, Birth year, Gestational age, Gestational diabetes, Haemorrhage during pregnancy, Maternal BMI at first antenatal visit, Maternal age at child birth, Maternal civil status at child birth, Maternal pre-eclampsia, Mode of delivery, PROM, Parental birth countries, Parental education during pregnancy, Parental income during pregnancy
- Birth weight, Birth year, Gestational age, Gestational diabetes, Haemorrhage during pregnancy, Maternal BMI at first antenatal visit, Maternal age at child birth, Maternal civil status at child birth, Maternal pre-eclampsia, Mode of delivery, PROM, Parental birth countries, Parental education during pregnancy, Parity, Paternal age at child birth
- Birth weight, Birth year, Gestational age, Gestational diabetes, Haemorrhage during pregnancy, Maternal BMI at first antenatal visit, Maternal age at child birth, Maternal pre-eclampsia, Maternal smoking during pregnancy, Mode of delivery, PROM, Parental birth countries, Parental education during pregnancy, Parental income during pregnancy
- Birth year, Gestational age, Gestational diabetes, Haemorrhage during pregnancy, Maternal BMI at first antenatal visit, Maternal age at child birth, Maternal civil status at child birth, Maternal pre-eclampsia, Maternal smoking during pregnancy, Mode of delivery, PROM, Parental birth countries, Parental education during pregnancy, Parity, Paternal age at child birth, Placental abruption, Premature contraction
- Birth year, Gestational age, Gestational diabetes, Haemorrhage during pregnancy, Maternal BMI at first antenatal visit, Maternal age at child birth, Maternal pre-eclampsia, Maternal smoking during pregnancy, Mode of delivery, PROM, Parental birth countries, Parental education during pregnancy, Parental income during pregnancy, Placental abruption, Premature contraction

Figure E2. Subgroup-specific odds ratios (OR) and 95% confidence intervals (CI) of offspring autism spectrum disorders by parental asthma.



Note: Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

Table E1. Data sources from national and regional registers for linkage until December 31, 2013.

Register name	Register managed by	Register description	Information and time points retrieved from the register for the study
Medical Birth Register (MBR)	The National Board of Health and Social Welfare	The register covers more than 99% of the birth in Sweden since 1973 (6). Diagnoses are coded according to the 7 th to 10 th versions of the International Classification of Diseases (ICD 7-10). Medications are either recorded in free text or as Anatomical Therapeutic Chemical (ATC) codes.	The basis of the birth cohort, Maternal age at child birth, Maternal asthma-ever diagnosis at first antenatal visit, Use of asthma medication during pregnancy, Maternal smoking during pregnancy (at first antenatal care visit), Gestational age, birth weight, parity, diagnoses of pre-eclampsia, pre-gestational and gestational diabetes, premature rupture of membranes, premature contraction, placental abruptions during pregnancy, haemorrhage during pregnancy and delivery.
National Patient Register (NPR)		The register covers nationwide information from 1961 on inpatient care with complete coverage since 1987 and about 80% of the visits to outpatient specialist care since 2001 (7). Diagnoses are coded according to ICD 7-10.	Lifetime maternal asthma diagnosis, Lifetime paternal asthma diagnosis, Maternal diagnosis of diseases during pregnancy and delivery mentioned above, Offspring ASD diagnoses, Lifetime parental diagnoses of any psychiatric disorders
Swedish Prescribed Drug Register (SPDR)		The register covers around 80% of dispenses of all prescribed drugs since July 2005 (8). All medications are recorded in free text and ATC codes.	Use of asthma medications during pregnancy since register starts,
Cause of Death Register (CDR)		The register covers more than 99% death in Sweden with information on primary and secondary causes of death and date of death since 1952 (9).	Children who died during follow-up.
Multi-Generation Register (MGR)		The register covers data of more than nine million individual, with >95% information on mothers and fathers of the index person born from 1932 and alive in 1961 (10).	Biological parents, half-siblings', full-cousins', half-cousins'
Total Population Register	Statistics Sweden	The register covers basic information of	Paternal age at child birth

Register name	Register managed by	Register description	Information and time points retrieved from the register for the study
(TPR) Longitudinal integration database for health insurance and labor market studies (LISA by Swedish acronym)		population composition e.g. sex, age, etc since 1968. The register covers annually updated information on employment, education, income and other socio-demographic characteristics on all individuals 16 years of age or older since 1990 (8).	Parental education levels at child birth, Country of birth for both parents, Maternal civil status at child birth

Table E2. All relevant diagnostic codes of International Classification of Diseases (ICD) used in this project.

Disorders	ICD-10 (1997-)	ICD-9 (1987-1996)	ICD-8 (1969-1986)	ICD-7 (1957-1968)
Any psychiatric disorders	F	290-315	290-319	300-326
Asthma	J45-46	493	493	241
Autism spectrum disorders (ASD)	F84	299	N/A	N/A
Pre-gestational and gestational diabetes	E11-13, O24.0-24.4	250, 648A, 648W	N/A	N/A
Haemorrhage during pregnancy	O46	641	N/A	N/A
Haemorrhage after delivery	O72	666	N/A	N/A
Placental abruptions	O45	641C	N/A	N/A
Pre-eclampsia/eclampsia	O14-15	642E-642G	N/A	N/A
Premature rupture of membranes	O42	658B	N/A	N/A
Premature contraction	O47	644	N/A	N/A

Note: N/A= Children born/mothers delivering during 1992-2007 were not in this ICD-system.

Table E3. All relevant Anatomical Therapeutic Chemical (ATC) codes for medications used in this project.

Type of medication	ATC
Inhaled β 2-agonists	R03AC
Inhaled corticosteroids (ICS)	R03BA
Fixed β 2-ICS combinations	R03AK
Oral and injection β 2-agonists	R03CC
Leukotriene receptor antagonist (LTRA)	R03DC
Oral corticosteroids	H02AB

Table E4. Study characteristics of cases and controls in this project

	Cases and unrelated controls		Cases and full-siblings born from 1995		Paternal half-sibling pairs		Maternal half-sibling pairs		Full-cousin pairs		Half-cousin pairs	
	Cases	Controls	Cases	Full-siblings	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	(n=22,894)	(n=228,940)	(n=10,204)	(n=11,112)	(n=622)	(n=622)	(n=701)	(n=701)	(n=11,477)	(n=11,477)	(n=3,337)	(n=3,337)
Age, mean±SD, yrs	15.4±4.3	15.4±4.3	13.1±3.5	11.7±4.5	16.1±4.2	16.6±5.4	16.1±4.0	16.5±5.6	15.8±4.3	16.0±5.4	15.4±4.3	15.5±5.4
Male, n (%)	16,313 (71.3)	163,130 (71.3)	7,641 (74.9)	5,801 (52.2)	428 (68.7)	428 (68.7)	478 (68.2)	478 (68.2)	8,152 (71.0)	8,152 (71.0)	2,370 (71.0)	2,370 (71.0)
Pregnancy and birth-related characteristics												
Birth year												
1992-1997	11,420 (49.9)	114,200 (49.9)	2,636 (25.8)	3,544 (31.9)	354 (56.8)	354* (56.8)	405 (57.8)	405* (57.8)	6,241 (54.4)	6,241* (54.4)	1,668 (50.0)	1,668* (50.0)
1998-2007	11,474 (50.1)	11,4740 (50.1)	7,568 (74.2)	7,568 (68.1)	268 (43.0)	268* (43.0)	296 (42.2)	296* (42.2)	5,236 (45.6)	5,236* (45.6)	1,669 (50.0)	1,669* (50.0)
Parity												
First	10,748 (47.0)	96,855 (42.3)	5,133 (50.3)	2,224 (20.0)	353 (56.7)	343 (55.1)	197 (28.1)	219 (31.2)	5,155 (44.9)	4,869 (42.4)	1,504 (45.1)	1,435 (43.0)
Not first	12,145 (53.0)	132,079 (57.7)	5,071 (49.7)	8,888 (80.0)	269 (43.2)	279 (44.8)	504 (71.9)	482 (68.8)	6,322 (55.1)	6,608 (57.6)	1,833 (54.9)	1,902 (57.0)
Maternal age at child birth												
<25 yrs	5,047 (22.0)	40,803 (17.8)	2,034 (19.9)	1,393 (12.5)	270 (43.3)	281 (45.1)	321 (45.8)	344 (49.1)	2,490 (21.7)	2,321 (20.2)	1,058 (31.7)	975 (29.2)
25-29 yrs	7,425 (32.4)	79,831 (34.9)	3,585 (35.1)	3,244 (29.2)	185 (29.7)	172 (21.6)	231 (33.0)	208 (29.7)	4,086 (35.6)	4,230 (36.9)	1,107 (33.2)	1,117 (33.5)
30-34 yrs	6,463 (28.2)	72,012 (31.4)	3,151 (30.9)	3,926 (35.3)	110 (17.7)	124 (19.9)	94 (13.4)	101 (14.4)	3,329 (29.0)	3,460 (30.1)	775 (23.2)	838 (25.1)
≥35yrs	3,959 (17.3)	36,294 (15.9)	1,434 (14.1)	2,549 (22.9)	57 (9.2)	45 (7.2)	55 (7.8)	48 (6.8)	1,572 (13.7)	1,466 (12.8)	397 (11.9)	407 (12.2)
Paternal age at child birth												

	Cases and unrelated controls		Cases and full-siblings born from 1995		Paternal half-sibling pairs		Maternal half-sibling pairs		Full-cousin pairs		Half-cousin pairs	
	Cases	Controls	Cases	Full-siblings	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	(n=22,894)	(n=228,940)	(n=10,204)	(n=11,112)	(n=622)	(n=622)	(n=701)	(n=701)	(n=11,477)	(n=11,477)	(n=3,337)	(n=3,337)
<30 yrs	11,294 (49.3)	122,193 (53.4)	5,440 (53.3)	6,450 (58.0)	246 (39.5)	232 (37.2)	221 (31.5)	224 (32.0)	5,943 (51.8)	5,921 (51.6)	1,458 (43.7)	1,522 (45.6)
30-39 yrs	2,679 (11.7)	22,992 (10.0)	1,031 (10.1)	1,662 (15.0)	42 (6.7)	33 (5.3)	49 (7.0)	48 (6.8)	852 (7.4)	778 (6.8)	262 (7.9)	260 (7.8)
40-49 yrs	8,348 (36.5)	80,137 (35.0)	3,617 (35.4)	2,824 (25.4)	333 (53.4)	356 (57.1)	425 (60.6)	421 (60.1)	4,578 (39.9)	4,676 (40.7)	1,576 (47.2)	1,533 (45.9)
≥50 yrs	358 (1.6)	2,382 (1.0)	116 (1.1)	176 (1.6)	1 (0.2)	1 (0.6)	6 (0.9)	8 (1.1)	60 (0.5)	64 (0.6)	22 (0.7)	15 (0.5)
Maternal smoking during pregnancy												
None	17,030 (74.4)	184,291 (80.5)	8,246 (80.8)	9,093 (81.8)	303 (48.6)	342 (54.9)	363 (51.8)	361 (51.5)	8,533 (74.3)	8,736 (76.1)	2,123 (63.6)	2,262 (67.8)
1-9 cigarettes/day	2,765 (12.1)	20,963 (9.2)	831 (8.1)	848 (7.6)	150 (24.1)	146 (23.4)	160 (22.8)	173 (24.7)	1,416 (12.3)	1,287 (11.2)	641 (19.2)	548 (16.4)
≥10 cigarettes/day	1,698 (7.4)	10,372 (4.5)	447 (4.4)	453 (4.1)	113 (18.1)	91 (14.6)	132 (18.8)	122 (17.4)	887 (7.7)	791 (6.9)	415 (12.4)	340 (10.2)
Missing	1,401 (6.1)	13,314 (5.8)	680 (6.7)	718 (6.5)	57 (9.1)	44 (7.1)	46 (6.6)	45 (6.4)	641 (5.6)	663 (5.8)	158 (4.7)	187 (5.6)
Maternal body mass index at first antenatal visits												
<18.5 kg/m ²	587 (2.6)	5,472 (2.4)	241 (2.4)	229 (2.1)	20 (3.2)	20 (3.2)	24 (3.4)	16 (2.3)	311 (2.7)	280 (2.4)	91 (2.7)	81 (2.4)
18.5-25 kg/m ²	10,975 (47.9)	125,877 (55.0)	4,852 (47.5)	5,123 (46.1)	289 (46.4)	260 (41.7)	337 (48.1)	314 (44.8)	5,697 (49.6)	5,599 (48.8)	1,553 (46.5)	1,529 (45.8)
>25 and <30 kg/m ²	4,787 (20.9)	43,982 (19.2)	2,210 (21.7)	2,661 (24.0)	133 (21.4)	108 (17.3)	138 (19.7)	111 (15.8)	2,360 (20.6)	2,082 (18.1)	739 (22.2)	631 (18.9)

	Cases and unrelated controls		Cases and full-siblings born from 1995		Paternal half-sibling pairs		Maternal half-sibling pairs		Full-cousin pairs		Half-cousin pairs	
	Cases	Controls	Cases	Full-siblings	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	(n=22,894)	(n=228,940)	(n=10,204)	(n=11,112)	(n=622)	(n=622)	(n=701)	(n=701)	(n=11,477)	(n=11,477)	(n=3,337)	(n=3,337)
≥30 kg/m ²	2,621 (11.5)	16,597 (7.3)	1,279 (12.5)	1,559 (14.0)	62 (9.9)	68 (10.9)	83 (11.8)	32 (11.4)	1,253 (10.9)	866 (7.6)	441 (13.2)	311 (9.3)
Missing	3,924 (17.1)	37,012 (16.2)	1,622 (15.9)	1,540 (13.9)	119 (19.1)	167 (26.8)	119 (17.0)	179 (25.5)	1,856 (16.2)	2,650 (23.1)	513 (15.4)	785 (23.5)
Pregnancy and delivery complications												
Pre-eclampsia	1,144 (5.0)	8,483 (3.7)	557 (5.5)	648 (5.8)	25 (4.0)	25 (4.0)	25 (3.6)	30 (4.3)	536 (4.7)	475 (4.1)	161 (4.8)	136 (4.1)
Pre-gestational and gestational diabetes	509 (2.2)	3,254 (1.4)	231 (2.3)	282 (2.5)	13 (2.1)	7 (1.1)	8 (1.1)	6 (0.9)	234 (2.0)	161 (1.4)	69 (2.1)	57 (1.7)
PROM	507 (2.2)	3,858 (1.7)	270 (2.6)	345 (3.1)	15 (2.4)	11 (1.8)	12 (1.7)	7 (1.0)	258 (2.3)	221 (1.9)	82 (2.5)	74 (2.2)
Premature contraction	1,788 (7.8)	13,277 (5.8)	916 (9.0)	1,317 (11.8)	66 (10.6)	50 (8.0)	79 (11.3)	85 (12.1)	851 (7.4)	749 (6.5)	339 (10.2)	254 (7.6)
Placental abruption	167 (0.7)	1,172 (0.5)	75 (0.7)	103 (0.9)	2 (0.3)	5 (0.8)	8 (1.1)	5 (0.7)	83 (0.7)	54 (0.5)	31 (0.9)	20 (0.6)
Haemorrhage during pregnancy	526 (2.3)	4,641 (2.0)	257 (2.5)	366 (3.3)	13 (2.1)	13 (2.1)	22 (3.1)	30 (4.3)	243 (2.1)	229 (2.0)	83 (2.5)	65 (2.0)
Haemorrhage after delivery	1,607 (7.0)	16,294 (7.1)	714 (7.0)	907 (8.2)	43 (6.9)	33 (5.3)	52 (7.4)	58 (8.3)	780 (6.8)	811 (7.1)	212 (6.4)	218 (6.5)
Mode of delivery												
Vaginal	17,247 (75.3)	181,243 (79.2)	7,557 (74.1)	8,629 (77.6)	481 (77.2)	481 (77.2)	589 (84.0)	578 (82.4)	8,835 (77.0)	9,091 (79.2)	2,541 (76.1)	2,619 (78.5)
Vaginal instrumental	1,742 (7.6)	16,982 (7.4)	866 (8.5)	559 (5.0)	25 (4.0)	46 (7.4)	26 (3.7)	38 (5.4)	850 (7.4)	776 (6.8)	235 (7.0)	232 (7.0)

	Cases and unrelated controls		Cases and full-siblings born from 1995		Paternal half-sibling pairs		Maternal half-sibling pairs		Full-cousin pairs		Half-cousin pairs	
	Cases	Controls	Cases	Full-siblings	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	(n=22,894)	(n=228,940)	(n=10,204)	(n=11,112)	(n=622)	(n=622)	(n=701)	(n=701)	(n=11,477)	(n=11,477)	(n=3,337)	(n=3,337)
Elective cesarean section	1,829 (8.0)	13,836 (6.0)	830 (8.1)	1,152 (10.4)	45 (7.2)	37 (5.9)	42 (6.0)	45 (6.4)	830 (7.2)	718 (6.3)	269 (8.1)	210 (6.3)
Emergency cesarean section	1,829 (8.0)	15,042 (6.6)	865 (8.5)	660 (5.9)	61 (9.8)	44 (7.1)	38 (5.4)	30 (4.3)	842 (7.3)	736 (6.4)	248 (7.4)	220 (6.6)
Birth weight												
<2,500g	1,248 (5.5)	6,539 (2.9)	532 (5.2)	415 (3.7)	40 (6.4)	29 (4.7)	34 (4.9)	24 (3.4)	580 (5.1)	456 (4.0)	184 (5.5)	146 (4.4)
2,500-2,999g	2,566 (11.2)	20,763 (9.1)	1,056 (10.3)	1,081 (9.7)	102 (16.4)	78 (12.5)	88 (12.6)	87 (12.4)	1,220 (10.6)	1,079 (9.4)	398 (11.9)	347 (10.4)
≥3,000g	18,972 (82.9)	200,960 (87.8)	8,564 (83.9)	9,580 (86.2)	477 (76.6)	515 (82.6)	575 (82.0)	588 (83.9)	9,627 (83.9)	9,911 (86.4)	2,737 (82.0)	2,838 (85.1)
Gestational age												
<34 weeks	460 (2.0)	1,912 (0.8)	198 (1.9)	138 (1.2)	15 (2.4)	8 (1.3)	14 (2.0)	7 (1.0)	197 (1.7)	136 (1.2)	62 (1.9)	36 (1.1)
34-36 weeks	1,219 (5.3)	9,079 (4.0)	543 (5.3)	513 (4.6)	37 (5.9)	31 (5.0)	38 (5.4)	34 (4.8)	620 (5.4)	551 (4.8)	193 (5.8)	196 (5.9)
≥37 weeks	21,191 (92.6)	217,698 (95.1)	9,456 (92.7)	10,450 (94.0)	568 (91.2)	582 (93.4)	649 (92.6)	659 (94.0)	10,649 (92.8)	10,777 (93.9)	3,080 (92.3)	3,102 (93.0)
Parental sociodemographic characteristics												
Maternal civil status at year of child birth												
Married or cohabiting	19,374 (84.6)	206,823 (90.3)	9,290 (91.0)	9,276 (83.5)	334 (53.6)	296 (47.5)	428 (61.1)	362 (51.6)	10,015 (87.3)	9,152 (79.7)	2,631 (78.8)	2,497 (74.8)
Other	3,444 (15.0)	21,326 (9.3)	907 (8.9)	798 (7.2)	285 (45.8)	236 (37.9)	272 (38.8)	247 (35.2)	1,460 (12.7)	989 (8.6)	704 (21.1)	470 (14.1)

	Cases and unrelated controls		Cases and full-siblings born from 1995		Paternal half-sibling pairs		Maternal half-sibling pairs		Full-cousin pairs		Half-cousin pairs	
	Cases	Controls	Cases	Full-siblings	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	(n=22,894)	(n=228,940)	(n=10,204)	(n=11,112)	(n=622)	(n=622)	(n=701)	(n=701)	(n=11,477)	(n=11,477)	(n=3,337)	(n=3,337)
Missing	76 (0.3)	791 (0.3)	7 (0.1)	1,038 (9.3)	4 (0.6)	91 (14.6)	1 (0.1)	92 (13.1)	2 (0.0)	1,336 (11.6)	2 (0.1)	370 (11.1)
Country of birth for mothers												
Sweden	19,186 (83.8)	192,260 (84.0)	8,455 (82.9)	9,215 (82.9)	546 (87.6)	551 (88.4)	636 (90.7)	636 (90.7)	10,737 (93.6)	10,750 (93.7)	3,211 (96.2)	3,199 (95.9)
Other Nordic countries	626 (2.7)	5,350 (2.3)	199 (2.0)	217 (2.0)	23 (3.7)	14 (2.3)	22 (3.1)	22 (3.1)	235 (2.0)	231 (209)	48 (1.4)	55 (1.6)
Other countries than above	3,072 (13.4)	31,278 (13.7)	1,550 (15.2)	1,678 (15.1)	54 (8.7)	58 (9.3)	43 (6.1)	43 (6.1)	505 (4.4)	496 (4.3)	78 (2.3)	83 (2.5)
Country of birth for fathers												
Sweden	18,713 (81.7)	189,577 (82.8)	8,354 (81.9)	9,090 (81.8)	495 (79.5)	495 (79.5)	615 (87.7)	597 (85.2)	10,528 (91.7)	10,561 (92.0)	3,116 (93.4)	3,160 (94.7)
Other Nordic countries	684 (3.0)	5,142 (2.3)	209 (2.1)	243 (2.2)	32 (5.1)	32 (5.1)	23 (3.3)	26 (3.7)	283 (2.5)	257 (2.2)	70 (2.1)	51 (1.5)
Other countries than above	3,275 (14.3)	32,964 (14.4)	1,639 (16.1)	1,777 (16.0)	96 (15.4)	96 (15.4)	62 (8.8)	78 (11.1)	621 (5.4)	620 (5.4)	132 (4.0)	119 (3.6)
Highest education between parents at year of child birth												
9 years	1,885 (8.2)	14,248 (6.2)	625 (6.1)	583 (5.2)	112 (18.0)	124 (19.9)	144 (20.5)	153 (21.8)	776 (6.8)	847 (7.4)	416 (12.5)	356 (10.7)
10-12 years	12,253 (53.5)	113,191 (49.4)	4,941 (48.4)	4,987 (44.9)	416 (66.8)	395 (63.4)	472 (67.3)	433 (61.8)	6,400 (55.8)	6,081 (53.0)	2,188 (65.6)	2,083 (62.4)
>12 years	8,602 (37.6)	99,404 (43.4)	4,604 (45.1)	4,483 (40.3)	92 (14.8)	79 (12.7)	85 (12.1)	84 (12.0)	4,295 (37.4)	4,236 (36.9)	729 (21.8)	786 (23.6)
Parental asthma												

	Cases and unrelated controls		Cases and full-siblings born from 1995		Paternal half-sibling pairs		Maternal half-sibling pairs		Full-cousin pairs		Half-cousin pairs	
	Cases	Controls	Cases	Full-siblings	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	(n=22,894)	(n=228,940)	(n=10,204)	(n=11,112)	(n=622)	(n=622)	(n=701)	(n=701)	(n=11,477)	(n=11,477)	(n=3,337)	(n=3,337)
Maternal asthma	4,604 (20.1)	32,650 (14.3)	1,949 (19.1)	2,119 (19.1)	160 (25.7)	131 (21.0)	190 (27.1)	190 (27.1)	2,246 (19.6)	1,749 (15.2)	778 (23.3)	607 (18.2)
Paternal asthma	1,998 (8.7)	16,931 (7.4)	898 (8.8)	978 (8.8)	58 (9.3)	58 (9.3)	58 (8.3)	59 (8.4)	945 (8.2)	837 (7.3)	289 (8.7)	254 (7.6)
Asthma from either parent	6,180 (27.0)	46,873 (20.5)	2,658 (26.1)	2,896 (26.1)	205 (32.9)	178 (28.6)	233 (33.2)	236 (33.7)	2,986 (26.0)	2,450 (21.3)	994 (29.8)	808 (24.2)
Asthma from both parents	422 (1.8)	2,708 (1.2)	189 (1.8)	201 (1.8)	13 (2.1)	11 (1.8)	15 (2.1)	13 (1.9)	205 (1.8)	136 (1.2)	73 (2.2)	53 (1.6)
Parental psychiatric disorders												
Maternal psychiatric disorders	6,588 (28.8)	32,714 (14.3)	2,554 (25.0)	2,746 (24.7)	256 (41.1)	202 (32.4)	354 (50.5)	354 (50.4)	3,098 (27.0)	1,932 (16.8)	1,248 (37.4)	720 (21.6)
Paternal psychiatric disorders	4,368 (19.1)	25,011 (10.9)	1,684 (16.5)	1,832 (16.5)	212 (34.0)	212 (34.0)	205 (29.2)	154 (22.4)	2,067 (18.0)	1,428 (12.4)	824 (24.7)	584 (17.5)
Psychiatric disorders from either parent	9,150 (40.0)	51,284 (22.4)	3,564 (34.9)	3,856 (34.7)	375 (60.2)	334 (53.6)	439 (62.6)	419 (59.8)	4,349 (37.9)	2,935 (25.6)	1,670 (50.0)	1,110 (33.3)
Psychiatric disorders from both parents	1,806 (7.9)	6,441 (2.8)	674 (6.6)	722 (6.5)	93 (14.9)	80 (12.8)	120 (17.1)	92 (13.1)	816 (7.1)	425 (3.7)	402 (12.1)	194 (5.8)

- Note:
1. *case' half-sibling, full-cousin, and half-cousin can be born during 1987-2012;
 2. We did not show the actual number of and percentage individuals with missing data if the percentage of missing values for that variable was below 1%.

Table E5. Study characteristics of cases, unrelated and full-sibling controls that were eligible for the analysis on the medication use during pregnancy and offspring ASD.

	Cases and unrelated controls born from 1995		Cases and full-siblings born from 1995	
	Cases (n=3,507)	Controls (n=5,350)	Cases (n=1,133)	Full-siblings (n=1,293)
Age, mean±SD, yrs	13.7±3.5	13.7 ±3.5	13.4±3.3	13.9±3.4
Male, n (%)	2,536 (72.3)	3,837 (71.7)	850 (75.0)	665 (51.4)
Pregnancy and birth-related characteristics				
Birth year				
1992-1997	1,139 (32.5)	1,708 (31.9)	303 (26.7)	463 (35.8)
1998-2007	2,368 (67.5)	3,642 (68.1)	830 (73.3)	830 (64.2)
Parity				
First	1,608 (45.9)	2,227 (41.6)	354 (31.2)	375 (29.0)
Not first	1,899 (54.1)	3,123 (58.4)	779 (68.8)	918 (71.0)
Maternal age at child birth				
<25 yrs	872 (24.9)	1,016 (19.0)	222 (19.6)	249 (19.3)
25-29 yrs	1,059 (30.2)	1,796 (33.6)	364 (32.1)	449 (34.7)
30-34 yrs	966 (27.5)	1,658 (31.0)	343 (30.3)	396 (30.6)
≥35yrs	610 (17.4)	880 (16.4)	204 (18.0)	199 (15.4)

	Cases and unrelated controls born from 1995		Cases and full-siblings born from 1995	
	Cases	Controls	Cases	Full-siblings
	(n=3,507)	(n=5,350)	(n=1,133)	(n=1,293)
Paternal age at child birth				
<30 yrs	1,702 (48.5)	2,858 (53.4)	598 (52.8)	677 (52.4)
30-39 yrs	387 (11.0)	516 (9.6)	133 (11.7)	139 (10.8)
40-49 yrs	1,339 (38.2)	1,903 (35.6)	390 (34.4)	465 (36.0)
≥50 yrs	47 (1.3)	53 (1.0)	12 (1.1)	12 (0.9)
Maternal smoking during pregnancy				
None	2,510 (71.6)	4,251 (79.5)	852 (75.2)	977 (75.6)
1-9 cigarettes/day	458 (13.1)	490 (9.2)	114 (10.1)	128 (9.9)
≥10 cigarettes/day	326 (9.3)	282 (5.3)	89 (7.9)	101 (7.8)
Missing	213 (6.1)	327 (6.1)	78 (6.9)	87 (6.7)
Maternal body mass index at first antenatal visits				
<18.5 kg/m ²	81 (2.3)	125 (2.3)	25 (2.2)	27 (2.1)
18.5-25 kg/m ²	1,420 (40.5)	2,630 (49.2)	448 (39.5)	507 (39.2)
>25 and <30 kg/m ²	799 (22.8)	1,167 (21.8)	256 (22.6)	315 (24.4)
≥30 kg/m ²	662 (18.9)	599 (11.2)	215 (19.0)	241 (18.6)
Missing	545 (15.5)	829 (15.5)	189 (16.7)	203 (15.7)

	Cases and unrelated controls born from 1995		Cases and full-siblings born from 1995	
	Cases	Controls	Cases	Full-siblings
	(n=3,507)	(n=5,350)	(n=1,133)	(n=1,293)
Pregnancy and delivery complications				
Pre-eclampsia	226 (6.4)	241 (4.5)	65 (5.7)	61 (4.7)
Pre-gestational and gestational diabetes	110 (2.2)	98 (1.8)	45 (4.0)	41 (3.2)
PROM	95 (2.7)	113 (2.1)	31 (2.7)	30 (2.3)
Premature contraction	433 (12.3)	481 (9.0)	144 (12.7)	179 (13.8)
Placental abruption	29 (0.8)	37 (0.7)	11 (1.0)	7 (0.5)
Haemorrhage during pregnancy	103 (2.9)	109 (2.0)	42 (3.7)	40 (3.1)
Haemorrhage after delivery	244 (7.0)	353 (6.6)	83 (7.3)	99 (7.7)
Mode of delivery				
Vaginal	2,520 (71.9)	4,059 (75.9)	853 (75.3)	995 (77.0)
Vaginal instrumental	265 (7.6)	402 (7.5)	73 (6.4)	77 (6.0)
Elective cesarean section	349 (10.0)	421 (7.9)	113 (10.0)	127 (9.8)
Emergency cesarean section	339 (9.7)	433 (8.1)	87 (7.7)	79 (6.1)
Birth weight				
<2,500g	193 (5.5)	156 (2.9)	56 (4.9)	56 (4.3)
2,500-2,999g	401 (11.4)	543 (10.2)	112 (9.9)	128 (9.9)

	Cases and unrelated controls born from 1995		Cases and full-siblings born from 1995	
	Cases	Controls	Cases	Full-siblings
	(n=3,507)	(n=5,350)	(n=1,133)	(n=1,293)
≥3,000g	2,891 (82.4)	4,628 (86.5)	960 (84.7)	1,102 (85.2)
Gestational age				
<34 weeks	84 (2.4)	41 (0.8)	20 (1.8)	13 (1.0)
34-36 weeks	202 (5.8)	225 (4.2)	63 (5.6)	82 (6.4)
≥37 weeks	3,219 (91.8)	5,078 (94.9)	1,049 (92.6)	1,198 (92.6)
Parental sociodemographic characteristics				
Maternal civil status at year of child birth				
Married or cohabiting	2,885 (82.3)	4,702 (87.9)	1,005 (88.7)	1,165 (90.1)
Other	619 (17.6)	640 (12.0)	128 (11.3)	128 (9.9)
Missing	3 (0.1)	8 (0.1)	0	0
Country of birth for mothers				
Sweden	3,065 (87.4)	4,537 (84.8)	978 (86.3)	1,120 (86.6)
Other Nordic countries	88 (2.5)	123 (2.3)	26 (2.3)	28 (2.2)
Other countries than above	353 (10.1)	690 (12.9)	129 (11.4)	145 (11.2)
Country of birth for fathers				
Sweden	2,944 (84.0)	4,436 (82.9)	963 (85.0)	1,095 (84.7)

	Cases and unrelated controls born from 1995		Cases and full-siblings born from 1995	
	Cases	Controls	Cases	Full-siblings
	(n=3,507)	(n=5,350)	(n=1,133)	(n=1,293)
Other Nordic countries	100 (2.9)	137 (2.6)	21 (1.8)	27 (2.1)
Other countries than above	431 (12.3)	756 (14.1)	149 (13.2)	171 (13.2)
Highest education between parents at year of child birth				
9 years	331 (9.4)	371 (6.9)	83 (7.3)	100 (7.7)
10-12 years	1,942 (55.4)	2,673 (50.0)	598 (52.8)	695 (53.8)
>12 years	1,222 (34.8)	2,275 (42.5)	450 (39.7)	493 (38.1)
Parental asthma				
Maternal asthma	3,391 (96.7)	5,169 (96.6)	1,130 (99.7)	1,288 (99.6)
Maternal asthma exacerbation history	44 (1.3)	35 (0.7)	3 (0.3)	13 (1.0)
Paternal asthma	322 (9.2)	460 (8.6)	111 (9.8)	121 (9.4)
Asthma from either parent	3,401 (97.0)	5,187 (97.0)	1,130 (99.7)	1,288 (99.6)
Asthma from both parents	312 (8.9)	442 (8.3)	111 (9.8)	121 (9.4)
Parental psychiatric disorders				
Maternal psychiatric disorders	1,366 (39.0)	1,099 (20.5)	413 (36.4)	455 (35.2)
Paternal psychiatric disorders	776 (22.1)	654 (12.2)	219 (19.3)	243 (18.8)
Psychiatric disorders from either parent	1,719 (49.0)	1,510 (28.2)	512 (45.2)	570 (44.1)

	Cases and unrelated controls born from 1995		Cases and full-siblings born from 1995	
	Cases	Controls	Cases	Full-siblings
	(n=3,507)	(n=5,350)	(n=1,133)	(n=1,293)
Psychiatric disorders from both parents	423 (12.1)	243 (4.5)	120 (10.6)	128 (9.9)

Table E6. Association between parental asthma and offspring autism spectrum disorders (ASD) among cases and biologically unrelated controls

	OR (95% CI)		
	Models A [†]	Models B [‡]	Models C [*]
ASD (no. of cases/controls=22,894/228,940)			
Maternal asthma	1.52 (1.47, 1.57)	1.43 (1.38, 1.49)	1.41 (1.35, 1.46)
Paternal asthma	1.20 (1.14, 1.25)	1.17 (1.11, 1.23)	1.17 (1.11, 1.24)
Asthma from either parent	1.44 (1.40, 1.48)	1.36 (1.32, 1.41)	1.35 (1.30, 1.40)

CI=confidence intervals; OR=odds ratio.

[†] Models did not adjust for any covariates other than matching criteria.

[‡] Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

^{*} Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (Pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, and mode of delivery).

Table E7. Odds ratios of offspring ASD by parental asthma among matched half-sibling, full-cousin, half-cousin pairs.

Offspring relationship	Cases		Controls		Models A [†] OR (95% CI)	Models B [‡] OR (95% CI)	Models C [*] OR (95% CI)
	Exposed	Not exposed	Exposed	Not exposed			
Paternal half-siblings (no. of cases/controls=622/622)							
Maternal asthma	160	462	131	491	1.33 (1.01, 1.74)	1.20 (0.80, 1.81)	1.21 (0.78, 1.87)
Maternal half-siblings (no. of cases/controls=701/701)							
Paternal asthma	58	643	59	642	0.94 (0.63, 1.40)	0.73 (0.38, 1.38)	0.75 (0.39, 1.43)
Full-cousins (no. of cases/controls=11,477/11,477)							
Maternal asthma	2,246	9,231	1,749	9,728	1.37 (1.27, 1.47)	1.28 (1.16, 1.41)	1.28 (1.16, 1.41)
Paternal asthma	945	10,532	837	10,640	1.17 (1.06, 1.29)	1.03 (0.90, 1.17)	1.03 (0.90, 1.18)
Half-cousins (no. of cases/controls=3,337/3,337)							
Maternal asthma	778	2,559	607	2,730	1.37 (1.22, 1.54)	1.30 (1.10, 1.54)	1.28 (1.08, 1.52)
Paternal asthma	289	3,048	254	3,083	1.17 (0.98, 1.39)	1.11 (0.87, 1.42)	1.07 (0.84, 1.38)

[†] Models did not adjust for any covariates other than matching criteria.

[‡] Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

^{*} Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (Pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, and mode of delivery) .

Table E8. Sensitivity analysis: association between parental asthma and offspring autism spectrum disorders (ASD) with mutual adjustment, and with test for interaction between maternal and paternal asthma.

OR (95% CI)				Interaction p-values [‡]
	Models A [†]	Models B [‡]	Models C [*]	
Cases vs. biologically unrelated controls (no. of cases/controls=22,894/228,940)				
Maternal asthma	1.52 (1.47, 1.57)	1.43 (1.37, 1.48)	1.41 (1.35, 1.46)	0.77
Paternal asthma	1.19 (1.13, 1.25)	1.16 (1.10, 1.23)	1.16 (1.10, 1.23)	
Paternal half-siblings (no. of cases/controls=622/622)				
Maternal asthma	1.33 (1.01, 1.74)	1.21 (0.80, 1.82)	1.21 (0.78, 1.87)	-
Maternal half-siblings (no. of cases/controls=701/701)				
Paternal asthma	0.94 (0.63, 1.40)	0.73 (0.38, 1.38)	0.75 (0.39, 1.43)	-
Full cousins (no. of cases/controls=11,477/11,477)				
Maternal asthma	1.37 (1.28, 1.47)	1.28 (1.16, 1.41)	1.28 (1.16, 1.41)	0.87
Paternal asthma	1.17 (1.06, 1.30)	1.03 (0.90, 1.18)	1.03 (0.90, 1.19)	
Half cousins (no. of cases/controls=3,337/3,337)				
Maternal asthma	1.37 (1.22, 1.55)	1.30 (1.10, 1.54)	1.28 (1.07, 1.51)	0.46
Paternal asthma	1.17 (0.98, 1.39)	1.11 (0.87, 1.41)	1.07 (0.83, 1.37)	

CI=confidence intervals; OR=odds ratio.

[†] Models did not adjust for any covariates other than matching criteria and mutual adjustment of paternal and maternal asthma.

[‡] Models adjusted mutually for maternal and paternal asthma, as well as for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

^{*} Models adjusted mutually for maternal and paternal asthma, as well as for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (Pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, and mode of delivery).

‡ Models tested for interaction term of maternal and paternal asthma, as well as adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

Table E9. Sensitivity analyses: Association between parental asthma and offspring ASD on restricted samples and asthma assessed from various sources.

	OR (95% CI)		
	Models A [†]	Models B [‡]	Models C [*]
Excluding foreign-born parents¹ (no. of cases/controls=17,228/135,389)			
Maternal asthma	1.58 (1.52, 1.64)	1.48 (1.42, 1.55)	1.46 (1.39, 1.52)
Paternal asthma	1.23 (1.16, 1.30)	1.19 (1.12, 1.26)	1.19 (1.12, 1.27)
Offspring born during 2006-2007 (no. of cases/controls=1,477/14,770)			
Maternal asthma	1.35 (1.18, 1.56)	1.35 (1.15, 1.58)	1.29 (1.10, 1.51)
Paternal asthma	0.99 (0.81, 1.22)	1.03 (0.82, 1.29)	1.06 (0.84, 1.33)
Excluding offspring born with a birth weight <2,500g² (no. of cases/controls=21,392/220,229)			
Maternal asthma	1.52 (1.47, 1.57)	1.43 (1.37, 1.49)	1.41 (1.36, 1.47)
Paternal asthma	1.19 (1.14, 1.25)	1.16 (1.10, 1.23)	1.17 (1.10, 1.23)
Excluding offspring born with a gestational age <37 weeks³ (no. of cases/controls=21,044/216,231)			
Maternal asthma	1.52 (1.47, 1.57)	1.42 (1.37, 1.48)	1.40 (1.35, 1.46)
Paternal asthma	1.19 (1.13, 1.25)	1.16 (1.10, 1.23)	1.17 (1.10, 1.23)
Excluding offspring with missing information on their maternal BMI (no. of cases/controls=18,848/190,694)			
Maternal asthma	1.53 (1.47, 1.58)	1.43 (1.38, 1.49)	1.41 (1.35, 1.46)
Paternal asthma	1.19 (1.13, 1.26)	1.17 (1.11, 1.23)	1.17 (1.11, 1.24)
With asthma information retrieved from MBR⁴ (no. of cases/controls=22,894/228,947)			
Maternal asthma ever at first antenatal visit	1.40 (1.33, 1.46)	1.35 (1.28, 1.43)	1.33 (1.26, 1.40)
With asthma information retrieved from NPR and SPDR (no. of cases/controls=22,894/228,947)			
Maternal asthma	1.49 (1.43, 1.56)	1.39 (1.32, 1.47)	1.37 (1.30, 1.45)
Paternal asthma	1.20 (1.14, 1.26)	1.17 (1.11, 1.23)	1.17 (1.11, 1.24)
With stricter asthma definitions using information from NPR and SPDR (no. of cases/controls=22,894/228,947)			
Maternal asthma	1.66 (1.58, 1.73)	1.50 (1.42, 1.58)	1.47 (1.39, 1.55)
Paternal asthma	1.23 (1.17, 1.30)	1.17 (1.10, 1.25)	1.17 (1.10, 1.25)

With current asthma information retrieved from NPR and SPDR (no. of cases/controls=22,894/228,947)

Maternal current asthma	1.62 (1.53, 1.70)	1.47 (1.39, 1.56)	1.44 (1.36, 1.53)
Paternal current asthma	1.21 (1.13, 1.29)	1.19 (1.10, 1.28)	1.19 (1.10, 1.28)

Abbreviations: CI=confidence intervals; OR=odds ratio; MBR=Medical Birth Register; NPR=National Patient Register; SPDR=Swedish Prescribed Drug Register.

[†] Models did not adjust for any covariates other than matching criteria.

^{||} Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

^{*} Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (Pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, and mode of delivery) .

Additional footnotes on model adjustment:

1 Models B-C did not adjust for country of birth for mothers and fathers.

2 Models C did not adjust for gestational age.

3 Models C did not adjust for birth weight.

4 The MBR recorded the information on maternal asthma ever at the time of first antenatal visit only.

Table E10. Sensitivity analysis: association between parental asthma identified before and after pregnancy with offspring autism spectrum disorders (ASD).

	OR (95% CI)		
	Models A [†]	Models B [‡]	Models C [*]
ASD (no. of cases/unrelated controls=22,894/228,940)			
Maternal asthma before pregnancy	1.41 (1.34, 1.47)	1.36 (1.29, 1.43)	1.33 (1.26, 1.41)
Maternal asthma since pregnancy	1.52 (1.47, 1.58)	1.40 (1.34, 1.46)	1.38 (1.32, 1.44)
Paternal asthma before pregnancy	1.29 (1.01, 1.63)	1.23 (0.94, 1.60)	1.24 (0.95, 1.63)
Paternal asthma since pregnancy	1.19 (1.14, 1.25)	1.17 (1.10, 1.23)	1.17 (1.11, 1.23)
Maternal asthma before delivery	1.47 (1.41, 1.55)	1.41 (1.34, 1.49)	1.39 (1.31, 1.46)
Maternal asthma after delivery	1.56 (1.49, 1.63)	1.45 (1.37, 1.52)	1.43 (1.36, 1.50)
Paternal asthma before delivery	1.04 (0.83, 1.29)	0.99 (0.77, 1.26)	1.02 (0.80, 1.30)
Paternal asthma after delivery	1.21 (1.15, 1.26)	1.18 (1.12, 1.25)	1.18 (1.12, 1.25)

CI=confidence intervals; OR=odds ratio.

[†] Models did not adjust for any covariates other than matching criteria.

[‡] Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, and maternal BMI at first antenatal visit.

^{*} Models adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (Pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, and mode of delivery).

Table E11. Association between use of asthma medication during pregnancy and offspring ASD with adjustment for potential confounders and mediators

	No. of cases/controls [#]	OR (95% CI) Model A [†]
Comparing ASD cases to unrelated controls	3,507/5,350	
With asthma but no medications	2,747/4,208	Ref
Systemic β 2-agonists only	225/336	0.91 (0.72, 1.17)
Inhaled β 2-agonists with or without other asthma medications	380/536	1.02 (0.84, 1.23)
Other asthma medications without any type of β 2-agonists	155/270	0.71 (0.54, 0.95)
	No. of cases/controls[#]	Model B[‡]
Comparing ASD cases to their full-siblings	1,133/1,293	
With asthma but no medications	930/1,066	Ref
Systemic β 2-agonists only	49/52	0.80 (0.45, 1.43)
Inhaled β 2-agonists with or without other asthma medications	105/118	0.94 (0.61, 1.47)
Other asthma medications without any type of β 2-agonists	49/57	0.74 (0.42, 1.31)

Abbreviations: ASD=autism spectrum disorders; CI=confidence interval; OR=odds ratio.

[#]Time-at-risk in subgroups is available on request.

[†]Model A adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, mode of delivery, and parity).

[‡]Model B adjusted for birth year, parity, maternal smoking during pregnancy, age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, and mode of delivery).

Table E12. Sensitivity analysis: association between use of asthma medication during pregnancy and offspring ASD additionally adjusting for asthma exacerbation history.

	No. of cases/controls [#]	OR (95% CI) Model A [†]
Comparing ASD cases to unrelated controls	3,507/5,350	
With asthma but no medications	2,747/4,208	Ref
Systemic β 2-agonists only	225/336	0.91 (0.71, 1.16)
Inhaled β 2-agonists with or without other asthma medications	380/536	1.01 (0.83, 1.22)
Other asthma medications without any type of β 2-agonists	155/270	0.71 (0.53, 0.93)
	No. of cases/controls[#]	Model B[‡]
Comparing ASD cases to their full-siblings	1,133/1,293	
With asthma but no medications	930/1,066	Ref
Systemic β 2-agonists only	49/52	0.82 (0.46, 1.46)
Inhaled β 2-agonists with or without other asthma medications	105/118	0.95 (0.61, 1.49)
Other asthma medications without any type of β 2-agonists	49/57	0.75 (0.42, 1.33)

Abbreviations: ASD=autism spectrum disorders; CI=confidence interval; OR=odds ratio.

[†]Model A adjusted for parity, maternal smoking during pregnancy and civil status at year of child birth, country of birth and age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, mode of delivery, and parity), as well as 12-month history of asthma exacerbation before pregnancy.

[‡]Model B adjusted for birth year, parity, maternal smoking during pregnancy, age at child birth for mothers and fathers, highest education between parents, maternal BMI at first antenatal visit, pregnancy and delivery risk factors (pre-eclampsia, pre-gestational and gestational diabetes, placental abruption, premature contraction, premature rupture of membranes, hemorrhage during pregnancy/after delivery, gestational age, birth weight, and mode of delivery), as well as 12-month history of asthma exacerbation before pregnancy.

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