

Sex differences in pregnancy complications and autism

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Abstract

Autism and pregnancy complications show sex differences in likelihood, but their interaction remains unclear. Using the Swedish Medical Birth Register, we compared sex differences in pregnancy complications among 2,413,161 singleton births (Study 1). We then examined their association with autism in a subset of the cohort, which included 59,388 diagnosed individuals (Study 2), while stratifying for co-occurring intellectual disability and sex. For both studies, we used both population-wide and sibling-controlled linear regression models. In Study 1, pregnancies of males showed greater likelihood for several complications, including placenta previa, preterm birth and birth via C-section. In Study 2, in pregnancies of autistic individuals, these sex differences in complications were absent, with autistic females being more likely to be preterm than autistic males. Within-family analyses also showed that prematurity, C-section and being born small-for-gestational-age were consistently associated with autism, independently of fetal sex or co-occurring intellectual disability. Overall, vulnerability of male pregnancies to pregnancy complications was found to mediate a small but significant fraction of the male bias in autism. Finally, modelling, based on clinical information available at birth, using an unbiased machine learning approach, revealed that fetal sex was the single most informative predictor of autism likelihood.

Keywords

Autism, pregnancy, sex, complications, environment, preterm

Background

Autism is a neurodevelopmental condition diagnosed based on difficulties with social relationships and communication alongside unusually restricted interests and repetitive behaviours, with the incidence of diagnosed cases increasing markedly in recent decades.^[1,2] Autism is a lifelong condition that can be traced back to the earliest stages of brain development and network formation, particularly during prenatal life^[3-5]. Autism likelihood is highly heritable, based on twin studies^[6], extended family studies^[7], as well as genetic studies of common and rare variants^[8]. Autism is diagnosed more often in males than females^[9]. Although this sex ratio has declined in countries such as Sweden^[10], it remains consistently skewed towards males in most populations and for diagnoses before puberty^[11]. While most of the likelihood for autism can be attributed to genetic factors (including *de novo* mutations), environmental factors, such as prenatal exposures and pregnancy complications, are estimated to determine at least a fifth of autism likelihood and to be particularly relevant as moderators of disability (e.g., for the co-occurrence of intellectual disability)^[7,12].

The placenta also shows consistent sex differences in function and dysfunction. At the genetic level, the expression of many X-linked genes in the placenta is characterised by dosage differences between males and females^[13,14], which may in turn be attributed to the rapid, clonal expansion and mosaicism of the trophoblast^[15]. In addition, differences at the protein level have also been described, with males having a faster increase in the placental growth factor (PlGF) during gestation^[16], as well as higher levels of steroidogenesis, as evidenced by differences in DHEA levels^[13]. Finally, the pregnancies with male fetuses are less likely to adapt to aspects of placental function when faced with adversity, compared to those with female fetuses^[17-19]. These processes are thought to contribute to sex differences in pregnancy complications, such as perinatal mortality, prematurity and term preeclampsia, which have been consistently shown to be more likely in pregnancies with male than with female foetuses in large studies in Scotland, Norway and Sweden^[20-22].

Interestingly, male-type patterns in all of these biological factors have been associated with increased autism likelihood or increased autistic traits in the children. These include elevated prenatal steroids (including oestrogens, 17-OH-Progesterone and DHEAS) and a faster increase of PlGF between the second and third trimester^[16,23,24]. In addition, many

of the X-linked genes that are downregulated in male placentas have been found to be either mutated in rare forms of autism or downregulated in the brains of autistic individuals (based on post-mortem studies)^[25]. Finally, a variety of placental complications have been associated with autism likelihood in multiple independent populations and meta-analyses, including gestational diabetes, preeclampsia (especially coupled with growth restriction) and premature birth^[26–28].

However, the role of sex differences in these associations has been understudied. A recent study of the Swedish population that focused on gestational duration reported an additive interaction between being male and being premature on autism likelihood^[29]. But it remains unclear if this extends to other aspects of placental dysfunction, such as preeclampsia or gestational diabetes, and if these interactions are sufficient to explain the sex bias in autism likelihood, given the higher prevalence of pregnancy complications in males. Finally, a recent assessment of many aspects of pregnancy in the Danish population replicated many of the above-mentioned associations (e.g., for prematurity, preeclampsia and gestational diabetes) but also found that many of these were no longer significant in sibling analyses, raising the prospect of familial confounding due to maternal genetics^[30]. Therefore, a larger cohort is needed, which will be sufficiently powered to test whether sex differences in placental function mediate sex differences in autism likelihood.

In the present study, we leveraged the detailed records of the Medical Birth Registry (MBR) of Sweden, linked to diagnostic data on autism and intellectual dysfunction of the children, together with demographic and diagnostic information of the parents. We conducted two studies, which respectively aimed to characterise the association of pregnancy complications with foetal sex (Study 1) and with autism likelihood in the offspring (Study 2). Both studies complemented population-wide analyses with studies of full siblings within families, to control for any familial confounding. Models predicting autism likelihood (Study 2) were stratified by co-occurring intellectual disability and further examined the role of sex by modelling interactions with pregnancy complications. Finally, machine learning was used to estimate and compare the predictive value of pregnancy characteristics, fetal sex and family history for autism likelihood in the offspring.

Results

Study 1: Sex Differences in pregnancy complications

To evaluate fetal sex differences in pregnancy complications in the general population, we included all pregnancies with available birth records in the MBR, corresponding to successful live births of singletons, between 1997 (when pregnancy records were harmonised across the country) and 2020 (the latest date based on the data release made available to researchers). Non-viable births and pregnancies with early postnatal mortality (the first month of life) were excluded (Figure 1).

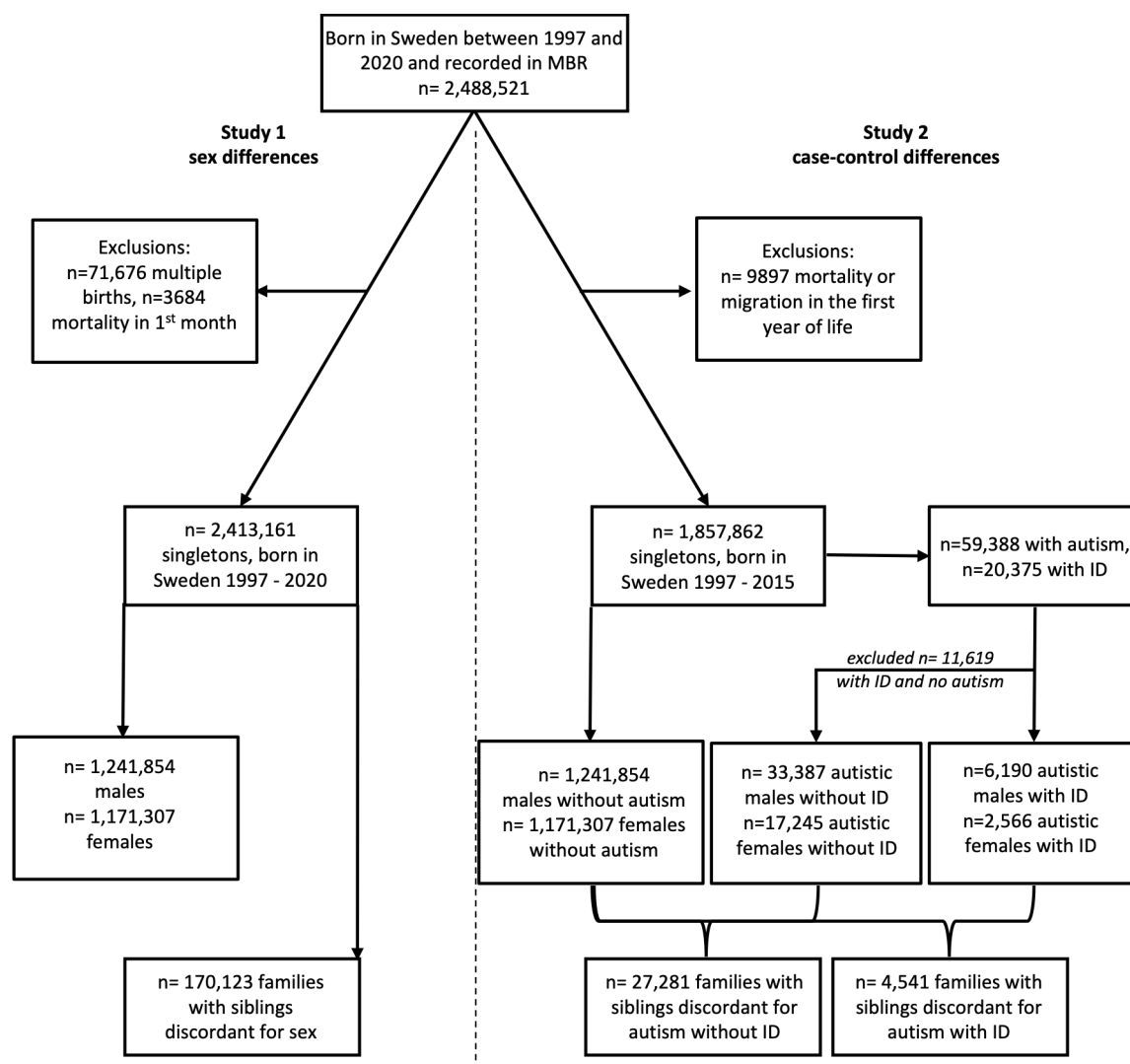


Figure 1. Flowchart outlining the population included for Study 1 (sex differences) and Study 2 (autism case-control differences), both of which included population-wide and within-family analyses.

Overall, we found that males were more likely to have placenta previa and to be born premature or via C-section (whether elective, scheduled or indicated), as well as to undergo pregnancy-induced hypertension (PIH), in two logistic regression models that adjusted for a series of demographic and parental characteristics (Model 1 adjusted for maternal age, paternal age, birth order, and birth year; Model 2 additionally adjusted for maternal smoking and income). On the contrary, females were more likely to be designated large for gestational age (LGA) at birth. No significant sex difference was observed in being born small for gestational age (SGA), although both models indicated a non-significant trend towards a female advantage (Figure 2)(Suppl. Table 1). Analyses within families with sex-discordant siblings largely confirmed these findings. Interestingly, despite the loss in statistical power, these analyses yielded significant associations between male sex and gestational diabetes, and between female sex and being born SGA, which were not significant in the population-wide models (Figure 2)(Suppl. Table 1).

Birth timing exhibited complex associations with sex. Males had higher likelihood for every deviation from term, including post-term, but there was no linear relationship. Males were more likely to be born after week 32 (moderately premature) as well as post-term (after week 42), with a much smaller sex difference for births before 32 weeks' gestation (Suppl. Figure 1A). Preeclampsia also showed heterogeneous patterns by fetal sex and birth timing, with preeclampsia being more common in males at term and in preterm females. A similar but non-significant trend was noted for gestational diabetes (Suppl. Figure 1B).

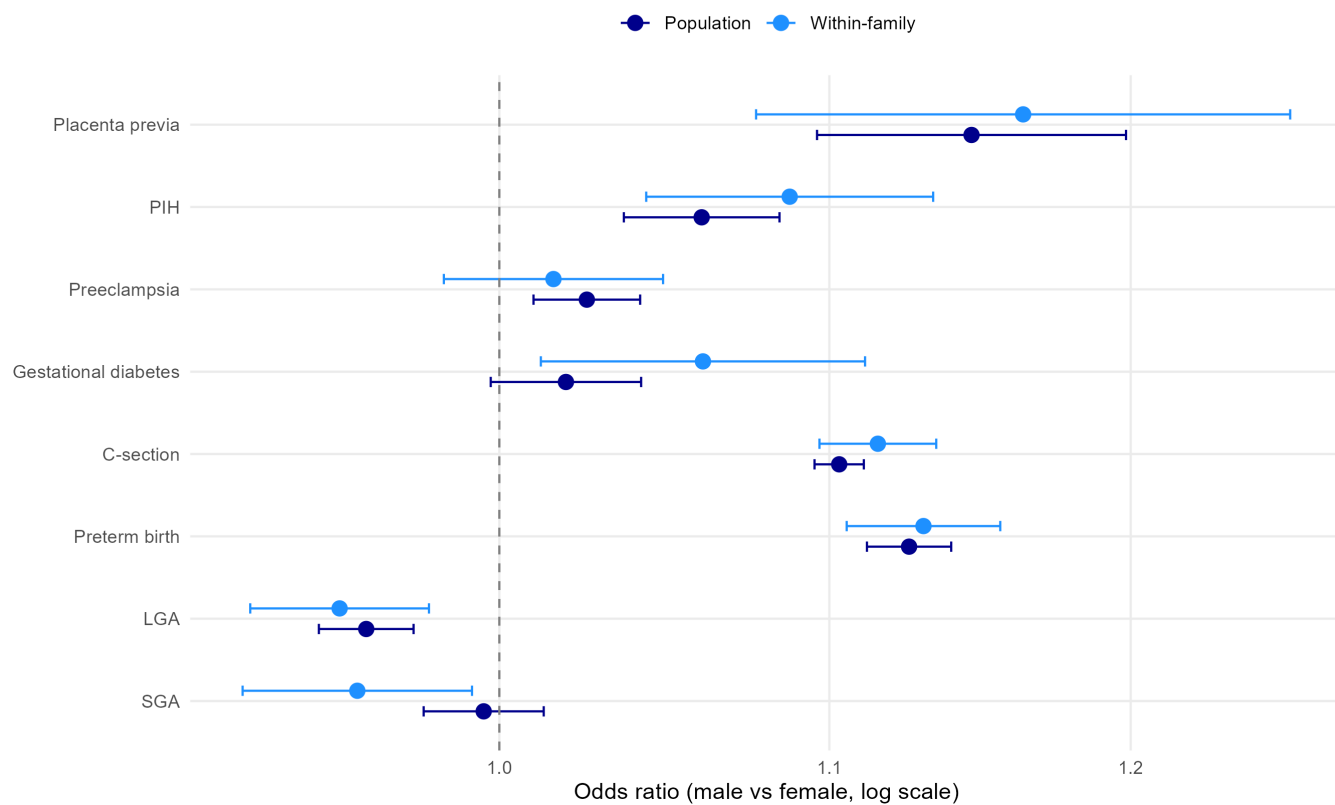


Figure 2. Sex differences in pregnancy complications. ORs denote male excess and calculated in models adjusted for maternal age, paternal age, birth order, and birth year. Within-family analyses based on families with full siblings that were discordant for both sex and the complication in question.

Study 2: Birth complications and autism: case-control differences

- Study 2 outcomes

A total of n=59,388 cases diagnosed with autism were identified in the MBR among singleton births that took place in Sweden between 1997 and 2015. Among them, n=8,756 also had a diagnosis of intellectual disability (ID). Following exclusion of individuals diagnosed only with ID, their intersection resulted into two populations (autism without ID and autism with ID), which were treated as separate groups for all subsequent comparisons to the general population, born between 1997 and 2015 and who did not have an autism or ID diagnosis (n=2,413,161) (Figure 1).

Compared to the undiagnosed population, autistic people showed small but significant differences in a variety of maternal and demographic characteristics, including birth year, parity and the parental history of neurodevelopmental and psychiatric diagnoses, with some differences in directionality for autism with ID and autism without ID (e.g., in paternal age) (Suppl. Table 2).

- Autism without ID

In logistic regression models which controlled for sex and a series of other covariates, autism without ID was associated with most pregnancy complications included in the analyses, except for placenta previa (Figure 3). The highest odds were noted for babies born SGA and for preeclampsia (Table 1). In separate sex stratified analyses using the same statistical models, these associations were consistent across both sexes, except for pregnancy-induced-hypertension (PIH), which was only significantly associated with autism without ID in pregnancies of females (Figure 3B).

In additional models which included an interaction term between each pregnancy complication and sex, only premature birth showed a significant interaction, indicating a stronger association between premature birth and autism without ID among females than males (Suppl. Table 3) consistent with sex stratified analyses (Figure 3B).

To investigate whether the associations were independent of familial confounding, the analyses were replicated using conditional logistic regression, stratified by family, in a cohort of siblings discordant for autism without ID (n=27,281). Born SGA, preeclampsia, premature birth and birth with C-section remained significantly associated with autism

without ID, whereas previously observed associations in the general population with gestational diabetes, PIH and LGA were no longer significant in the sibling analyses (Figure 3C).

- *Autism with ID*

Autism with co-occurring ID showed broadly similar association patterns with autism without ID, with significant associations for preeclampsia, born SGA, or with a C-section in models that controlled for sex (Table 1)(Suppl. Figure 2), as well as in sex-stratified models, which were adjusted for the same covariates (Suppl. Table 4). The effect sizes of the significant associations were generally larger for autism with ID than for autism without ID. Pregnancy-induced hypertension (PIH) and born LGA were exceptions to this pattern, as neither was significantly associated with autism with ID, contrary to the results for autism without ID (Table 1)(Suppl. Figure 3A). No significant interactions with sex were noted for complications in association with autism with ID (Suppl. Table 4).

Within-family analyses using conditional logistic regression among full siblings discordant for autism with ID (n=4,541) showed that being born with C-section, being premature and being born SGA were significantly associated with autism with ID (Table 1). However, contrary to the results in the general population, gestational diabetes and preeclampsia were no longer associated with increased likelihood for autism with ID, when only comparing siblings discordant for the condition (Suppl. Figure 2C).

Table 1. Association of pregnancy complications with autism (without or with ID). N shows the number of families with complete data and siblings that were discordant for both autism and each complication.

Model 1 adjusted for: sex, maternal age, paternal age, birth order, and birth year. Model 2 additionally adjusted for maternal smoking during pregnancy and family income (in quintiles). SGA: small for gestational age, LGA: large for gestational age, PIH: pregnancy-induced hypertension

Complication	Population				Within-family (full siblings)				
	Model 1 OR (95% CI)	FDR p	Model 2 OR (95% CI)	FDR p	Model 1 OR (95% CI)	FDR p	Model 2 OR (95% CI)	FDR p	N
Autism without ID									
Placenta previa	0.95 (0.81–1.13)	0.572	0.93 (0.78–1.10)	0.388	0.89 (0.64–1.25)	0.575	0.89 (0.64–1.25)	0.574	168
PIH	1.20 (1.11–1.31)	1.8×10^{-5}	1.23 (1.13–1.33)	2.1×10^{-6}	1.03 (0.87–1.24)	0.708	1.03 (0.86–1.23)	0.724	593
Preeclampsia	1.43 (1.36–1.49)	3.2×10^{-16}	1.44 (1.37–1.50)	3.2×10^{-16}	1.20 (1.07–1.34)	0.004	1.20 (1.07–1.34)	0.003	1,484
Gestational diabetes	1.32 (1.22–1.44)	1.3×10^{-11}	1.22 (1.13–1.32)	1.9×10^{-6}	1.10 (0.90–1.35)	0.488	1.09 (0.89–1.34)	0.517	447
C-section	1.29 (1.26–1.32)	3.2×10^{-16}	1.27 (1.24–1.30)	3.2×10^{-16}	1.14 (1.06–1.21)	4.8×10^{-4}	1.14 (1.06–1.21)	4.8×10^{-4}	4,133
Preterm birth	1.40 (1.35–1.46)	3.2×10^{-16}	1.38 (1.33–1.43)	3.2×10^{-16}	1.25 (1.15–1.35)	2.6×10^{-6}	1.25 (1.15–1.35)	2.6×10^{-6}	2,642
LGA	1.31 (1.25–1.37)	3.2×10^{-16}	1.33 (1.27–1.39)	3.2×10^{-16}	1.07 (0.97–1.17)	0.272	1.07 (0.97–1.17)	0.274	2,440
SGA	1.45 (1.37–1.52)	3.2×10^{-16}	1.34 (1.27–1.41)	3.2×10^{-16}	1.37 (1.21–1.56)	6.0×10^{-6}	1.37 (1.21–1.56)	6.1×10^{-6}	1,326
Autism with ID									
Placenta previa	1.12 (0.78–1.60)	0.540	1.09 (0.76–1.57)	0.629	0.85 (0.42–1.71)	0.747	0.86 (0.43–1.72)	0.739	38
PIH	1.07 (0.87–1.31)	0.540	1.11 (0.90–1.36)	0.378	0.94 (0.59–1.48)	0.784	0.93 (0.59–1.46)	0.739	86
Preeclampsia	1.60 (1.44–1.77)	3.2×10^{-16}	1.60 (1.44–1.77)	4.0×10^{-16}	1.12 (0.86–1.46)	0.678	1.12 (0.86–1.46)	0.739	256

Complication	Population				Within-family (full siblings)				
	Model 1 OR (95% CI)	FDR p	Model 2 OR (95% CI)	FDR p	Model 1 OR (95% CI)	FDR p	Model 2 OR (95% CI)	FDR p	N
Gestational diabetes	2.09 (1.80–2.42)	3.2×10^{-16}	1.80 (1.55–2.10)	1.7×10^{-14}	1.11 (0.77–1.59)	0.747	1.09 (0.75–1.56)	0.739	143
C-section	1.61 (1.53–1.70)	3.2×10^{-16}	1.58 (1.50–1.66)	4.0×10^{-16}	1.41 (1.22–1.64)	1.7×10^{-5}	1.41 (1.22–1.64)	1.6×10^{-5}	814
Preterm birth	2.28 (2.13–2.45)	3.2×10^{-16}	2.22 (2.07–2.38)	4.0×10^{-16}	2.12 (1.76–2.54)	2.5×10^{-15}	2.14 (1.79–2.57)	1.0×10^{-15}	589
LGA	1.11 (0.99–1.23)	0.097	1.14 (1.02–1.27)	0.028	0.91 (0.72–1.15)	0.678	0.92 (0.72–1.16)	0.739	388
SGA	3.29 (3.02–3.59)	3.2×10^{-16}	2.97 (2.73–3.24)	4.0×10^{-16}	2.98 (2.36–3.76)	1.6×10^{-15}	2.99 (2.37–3.77)	1.0×10^{-15}	440

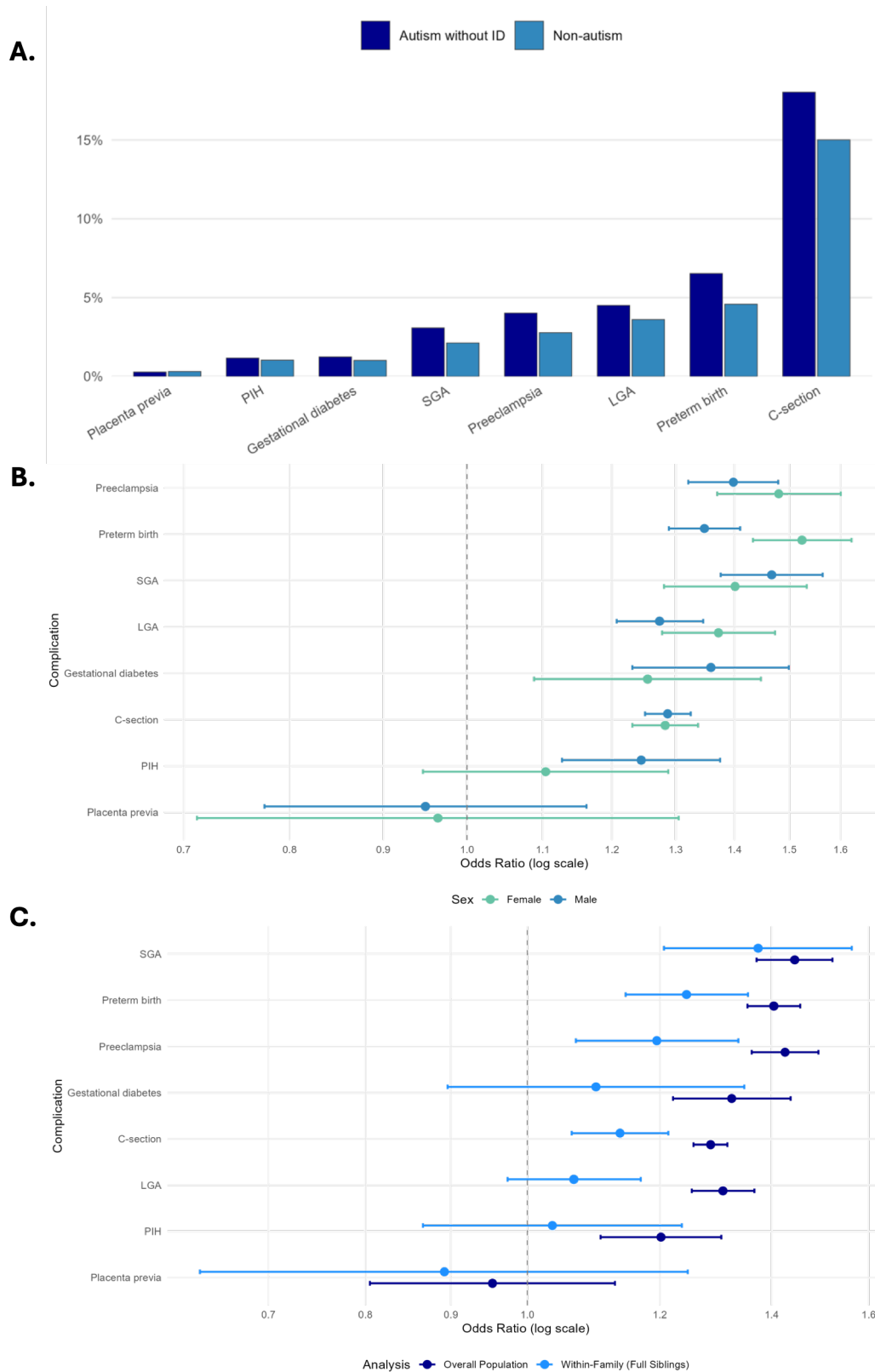


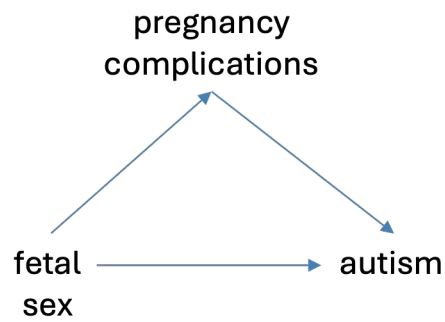
Figure 3. Autism without ID in association with pregnancy complications. A) absolute count differences for each complication. B) population-wide sex-stratified analyses and C) analyses combining and adjusting for sex in both population-wide and within-family cohorts. Values are from separate models for each complication and adjusted for maternal age, paternal age, birth order, and birth year (Model 1). SGA: small for gestational age, LGA: large for gestational age, PIH: pregnancy-induced hypertension.

- *Mediation analyses*

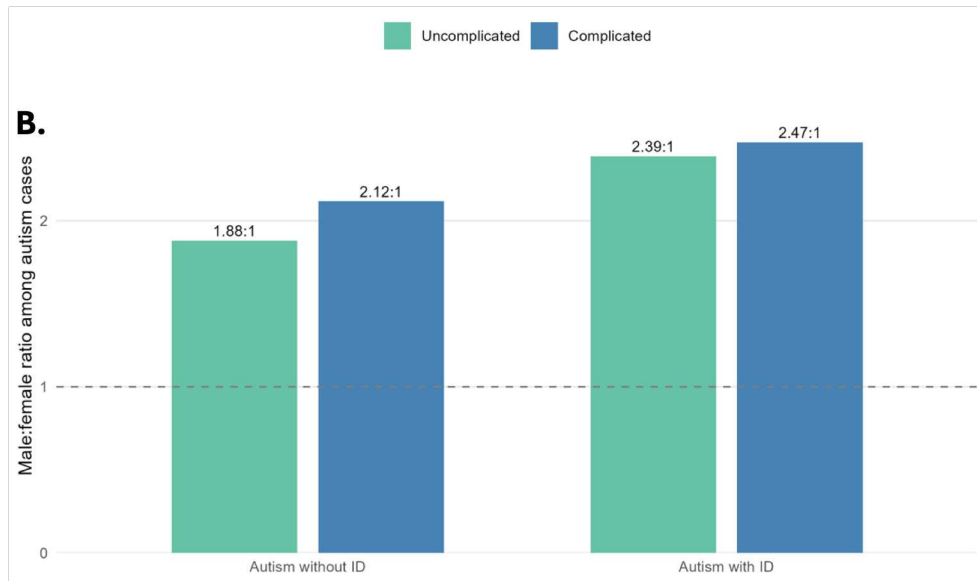
Given the co-occurrence of many pregnancy complications (Suppl Figure 3B-C), we tested the extent to which birth outcomes, such as prematurity or C-section, mediated the effect of placental dysfunction (as evident in preeclampsia, gestational diabetes or PIH) on autism with and autism without ID, using a subset of the population-wide cohort. These mediation models found that prematurity and C-section were significant mediators for all types of placental dysfunction on the likelihood of autism with, as well as without ID (Suppl. Table 5).

Mediation analyses were further conducted to test whether the male bias in autism likelihood was partly mediated by male vulnerabilities to pregnancy complications (Figure 4A). To better capture the cumulative effect of prenatal male vulnerability, we also created a composite variable, grouping all complications showing a male bias in the population-wide analyses of the general population (Figure 2)(Suppl. Table 1). These complications and specifically C-section, prematurity and preeclampsia were found to be significant mediators of the male excess in the likelihood of autism without ID (Figure 4C)(Suppl. Table 6). While significant, these effects accounted for less than 1% of the sex difference in autism without ID. This small but significant statistical effect was consistent with the sex ratio reduction observed in the raw prevalence data: in uncomplicated pregnancies, the sex ratio was decreased by 11.3% in autism without ID and by 3.2% for autism with ID, when comparing them to complicated pregnancies (Figure 4B).

A.



B.



C.

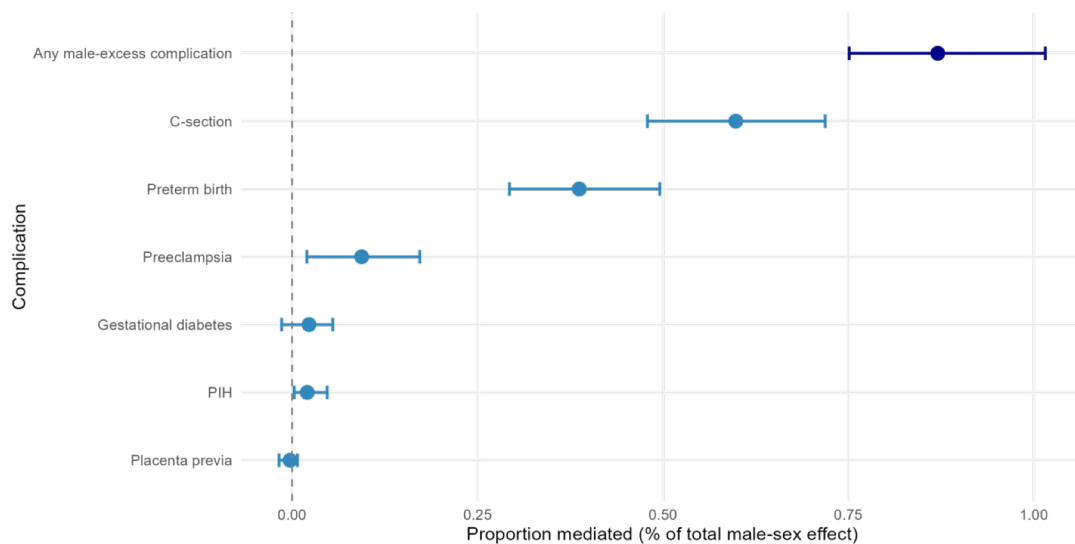


Figure 4. A) Sex differences in autism likelihood as mediated by sex differences in pregnancy complications. B) Reduced sex ratio for autism in individuals without pregnancy complications, particularly for autism without ID. C) Percentage of sex differences in autism (without ID) that is mediated by each complication, in a subset of the Study 2 population. PIH: pregnancy-induced hypertension. “Any male-excess” includes all complications below.

- *Prediction of autism likelihood*

To complement the association analyses, we conducted an exploratory assessment for the predictability of autism (with and without ID, total n=59,388) based on information available at birth, and the relative contribution of foetal sex in this regard. We compared three nested gradient-boosted models: family history and demographics (M1); the addition of pregnancy and birth parameters and complications (M2); and the further addition of foetal sex (M3). Overall discrimination was modest and increased only slightly across the three models. Adding pregnancy and birth information produced limited improvement (AUC 0.663 to 0.667), whereas adding foetal sex produced the largest gain (AUC 0.667 to 0.688), accompanied by a corresponding increase in specificity from 0.38 to 0.43 at a fixed sensitivity rate of 80% (Figure 5A-B).

For this combined model, analysis of variable importance based on SHAP values showed that foetal sex was the single most influential predictor, followed by maternal psychiatric history, while more rare conditions such as pregnancy and birth complications contributed the least (Figure 5C).

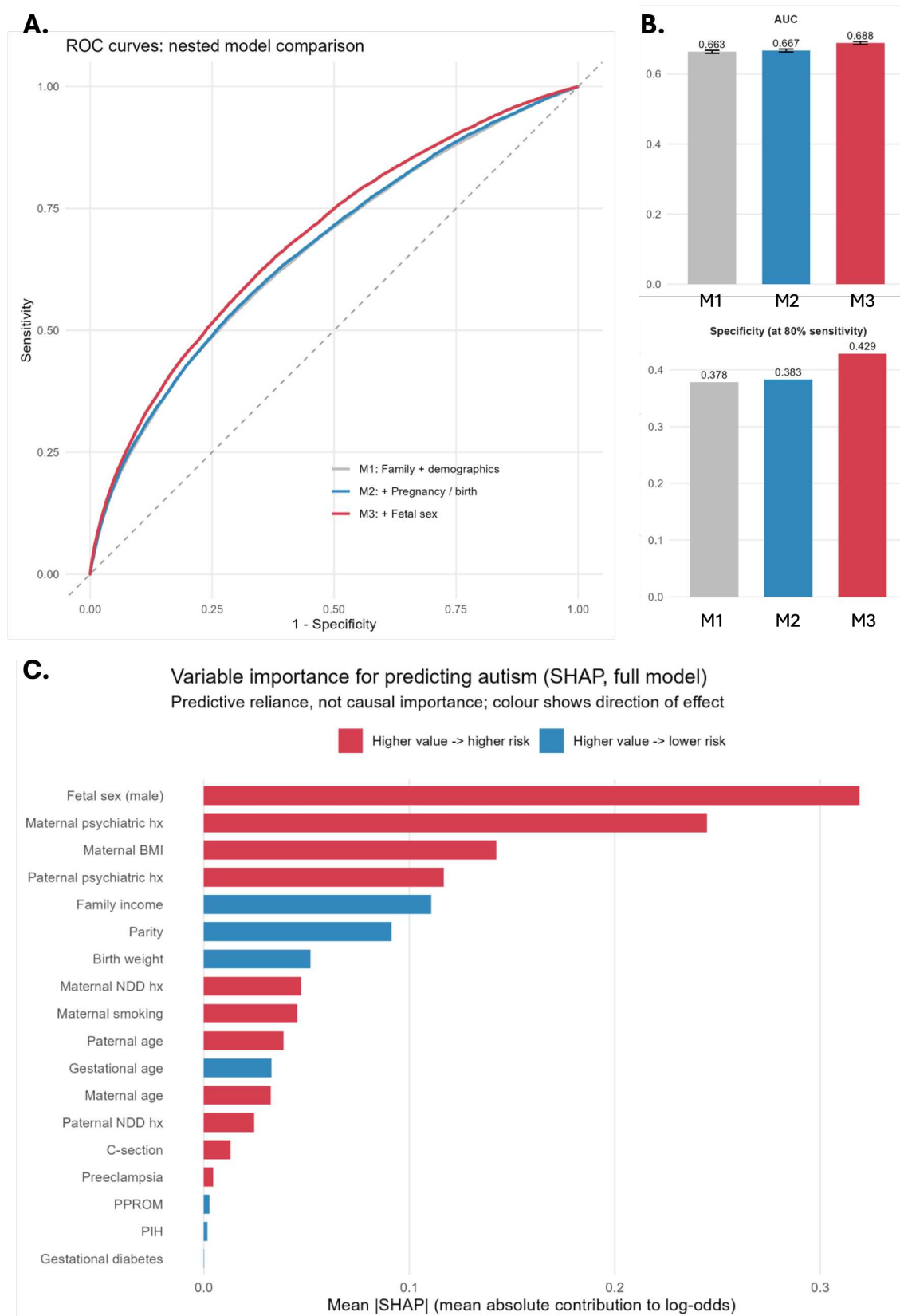


Figure 5: A. Predictive metrics of three models trained on a wider set of data available in the MBR with nested gradient boosting. B. For Model M3, the addition of sex improved both area under the curve (AUC) and specificity at a set 80% sensitivity. C. Variables included in M3 sorted based on mean absolute SHAP values.

Discussion

This study reviewed data in the national birth and patient registries of Sweden to examine the associations of pregnancy complications with sex (Study 1) and with autism likelihood in the children, stratified by co-occurring ID and an emphasis on the role of sex (Study 2). In addition, mediation analyses examined if the male excess in autism with or without ID could be attributed to male excess in birth complications. Finally, machine-learning was utilised to estimate the combined predictive potential of these variables for autism likelihood.

First, in Study 1, we observed a general vulnerability in pregnancies of male fetuses compared to female fetuses, both in the general population and in within-family analyses of sex-discordant siblings. This vulnerability was particularly evident for birth outcomes, such as C-section and prematurity (28 weeks to 36 weeks gestation), rather than overt placental dysfunction diagnoses, such as preeclampsia, gestational diabetes and pregnancy-induced hypertension, which showed limited ($OR < 1.1$) or non-significant sex differences in the general population. On the other hand, birth weight variability was more evident in females, who were more likely than males to be born small or large for gestational age, in within-family analyses. These patterns are consistent with previous reports, indicating that on-average female foetuses may adjust their body weight, more readily than males, who instead may have a greater likelihood for placental dysfunction and prematurity, possibly due to a greater prioritisation of energy uptake from the mother [17–19]. This combination was more evident after 32 weeks of gestation, indicating a role for emergent sex differences, such as those linked to hormone effects or overall body size. Interestingly, the largest sex difference was noted for placenta previa, which was more frequent in pregnancies of male, compared to female, foetuses. This has been reported before [31–33] and could be attributed to sex differences in earlier processes, such as in implantation and in the viability of embryos positioned lower on the womb.

In Study 2, autism likelihood was linked to a variety of pregnancy complications, but sex differences were attenuated or largely absent. Most pregnancy complications (SGA, C-section, preeclampsia, preterm birth, gestational diabetes) were found to be significantly associated with autism (both with and without co-occurring ID) in the population-wide models. Highest effect sizes were noted for being born SGA, or for having preeclampsia

and gestational diabetes, consistently with previous reports in population-wide analyses in Sweden, the UK, Denmark and Norway [21,27,30].

We also tested if the effects of these complications differed by sex of the child. The only significant interaction effect was noted for preterm birth, which showed a stronger effect on autism likelihood in females, irrespective of co-occurring ID. This has been reported before in a different subset of the same population[29]. The observed interaction may reflect overlapping contributions of male sex and preterm birth to autism likelihood, resulting in different relative effects in males and in females. Interestingly, we found that this interaction was largely specific to preterm births after gestational week 32, indicating the developmental window of late pregnancy may be particularly relevant for the pathophysiology of autism in both males and females. This period coincides with rapid maturation of thalamocortical connectivity, increasingly coordinated cortical activity, and with the transition from a large pre-myelinating oligodendrocyte population into active cerebral myelination[34–36].

When comparing pregnancies according to autism status and co-occurring ID in the offspring, associations with pregnancy complications showed larger effect sizes among offsprings with ID, than those without. Pregnancy-induced hypertension (PIH) and being born large for gestational age (LGA) were the exceptions to this trend, showing greatly attenuated or non-significant associations in autism with ID. This may indicate that their effect is more specific to autism than ID, or that they can be attributed to compensatory mechanisms, which are absent in autism with ID. Both PIH and LGA may also be linked to weight gain during pregnancy, which has also been found to be associated with autism likelihood in a previous population study [37] and may be part of compensatory mechanism that warrants further research.

Consistently with our hypothesis, we also found that the male excess in pregnancy complications partly mediated the male excess in autism likelihood. The effect was driven by complications, such as prematurity and C-section. Yet, it is important to note that the mediation was overall small, accounting for less than 2% of the sex difference in autism likelihood, and an approximately 11% higher sex ratio in complicated pregnancies, compared with uncomplicated pregnancies, for autism without ID. This study could only capture differences based on overt clinical diagnoses, rather than subclinical variations in placental function, such as those regarding PlGF or steroid hormone production, which

have been found to mediate sex differences in autism-linked outcomes in smaller, clinical cohorts^[16,23]. Subclinical gene-environment interactions may also be contributing to the skewed sex ratio, given the abundance of neurodevelopmental genes on the X-chromosome (including genes mutated in autism) and X-linked transcriptome differences in the brain and in the placenta^[25,38,39].

The importance of heritable factors is also indicated by our findings in analyses within families. While complications such as C-section, SGA and prematurity remained significant when comparing autism-discordant siblings that share a mother and father, the association was no longer significant for LGA, PIH and gestational diabetes, with mixed findings for preeclampsia (significant only for autism without co-occurring ID). This could indicate the presence of familial confounding in the associations of these conditions with autism in the general population, as reported before^[30]. But the null finding within families may be also due to more limited power, or the presence of additive maternal effects. Interestingly, the complications which were no longer significant within-families (LGA, PIH and gestational diabetes) are also associated with high BMI and metabolic dysfunction in the mothers^[40,41]. Therefore, it is plausible that maternal metabolic imbalance could be acting additively to autism likelihood, but independently to the child's own genetics.

Given the epidemiological nature of this study, our findings are correlational and population-specific and should not be used for clinical decision-making on the individual level. Placental dysfunction could not be profiled beyond clinically apparent conditions, with diagnostic codes that were contained in the records and specifically the medical birth registry of Sweden^[42]. As such, subclinical variations could not be studied or included in the machine learning component that compared different likelihood factors. In addition, it is important to note that the findings are specific to the population and healthcare system of Sweden. Furthermore, while the diagnostic codes used for autism remained consistent and analyses were controlled for birth year, the definition and nature of autism as a diagnostic category have shifted over time, particularly as awareness for the condition and for the specific behavioural patterns of girls and women has improved^[43]. For this reason, our observations regarding sex differences within autism, may not necessarily extend to the future, as the diagnostic rate in Sweden is approaching gender parity^[10].

In conclusion, we find that pregnancy complications are more frequent in pregnancies with male, compared to female, fetuses and that this sex difference mediates a small part of the male bias in autism likelihood. Future research ought to consider subclinical aspects of placental function, as well as other sources of sex differences during prenatal development, such as steroid hormone levels and genetics, which may interact to increase autism likelihood, in both boys and girls.

Methods

Study design

We conducted nationwide population-based cohort studies using data from several Swedish population-based registers to facilitate linkage between pregnancy-related variables and later, postnatal diagnoses in the children. Two related studies were conducted drawing on partially overlapping cohorts. Study 1 examined whether a series of pregnancy complications differ in frequency by fetal sex. Study 2 examined associations between the same pregnancy complications and an autism diagnosis in the children, stratified by co-occurring ID. For both studies, we compared outcome likelihood in both the general population, as well as within families with outcome-discordant siblings.

Data sources

The primary data source was the Swedish Medical Birth Register (MBR). Established in 1973 and maintained by the National Board of Health and Welfare, the MBR records approximately 98% of all births in Sweden and has, since 1982, been based on prospectively recorded information from standardized antenatal, obstetric, and neonatal records. Using the unique personal identification number assigned to all Swedish residents upon birth or migration to Sweden, we linked the MBR to multiple nationwide registers. Diagnostic information on autism, intellectual disability (ID) and parental psychiatric or neurodevelopmental disorders was obtained from the National Patient Register (NPR), which includes data on in-patient care at public and private hospitals since the 1960s, with nationwide coverage since 1987, and specialized outpatient care since 2001. Diagnoses are recorded according to the International Classification of Diseases (ICD). Sociodemographic information, including parental education and income, was retrieved from the Longitudinal Integrated Database for Health Insurance and

Labour Market Studies (LISA). Information on migration dates was obtained from the Total Population Register (TPR), and data on mortality, including dates of death, were obtained from the National Cause of Death Register (CDR). To identify family relationships and sibling structures, we used the Swedish Multigeneration Register (MGR), which links individuals to their biological parents.

Main study populations

For Study 1, we included all live, singleton births recorded in the MBR from 1997 to 2020, excluding instances of multiple gestation and mortality in the first month of life (main Study 1 population, n=2,413,161). For Study 2, the main population was further subset to births between 1997 and 2015, allowing a minimum of 6 years for autism and intellectual disability diagnoses through 2021, at which point data was provided for research (main Study 2 population, n=1,857,862)(Figure 1).

Study 1 outcomes - Pregnancy complications

For both studies, we examined eight pregnancy complications spanning placental dysfunction (i.e., placenta previa, pregnancy-induced hypertension (PIH), preeclampsia, gestational diabetes) and birth-related outcomes (i.e., C-section, preterm birth, large-for-gestational-age (LGA) birth, and small-for-gestational-age (SGA) birth. Each was modelled as a binary, categorical variable. Small- and large-for-gestational-age status had previously been defined in the MBR using the sex-specific Swedish reference curve for normal foetal growth, with SGA and LGA defined as a birth weight of more than 2 standard deviations below and above, respectively, the sex- and gestational-age-specific mean^[44]. Gestational age at birth in the MBR is determined primarily from second-trimester ultrasound, performed in approximately 95% of Swedish pregnancies, with the date of the last menstrual period used when ultrasound dating was unavailable. The variable concerning C-section in this analysis, included both scheduled and emergency C-sections. For analyses of gestational age at birth, the variable was further refined in additional analyses based on the following categories: term (37 to <41 weeks), late-term (41 to <42 weeks), and post-term (≥ 42 weeks) delivery, late preterm (34 to <37 weeks), moderate preterm (32 to <34 weeks), very preterm (28 to <32 weeks), and extremely preterm (<28 weeks).

These pregnancy complications were used as outcomes for Study 1 (sex differences) and as predictors for Study 2 (autism differences).

Study 2 outcomes - Autism and intellectual disability (ID)

Autism was ascertained based on any recorded diagnosis in the NPR under the F84 ICD-10 code, including childhood autism, atypical, Asperger syndrome, Rett syndrome and other/unspecified developmental disorders (ICD-10 codes: F840, F841, F842, F843, F844, F845, F848, F849). The majority of autism cases (>50%) corresponded to a diagnosis of 'childhood autism', followed by 'Asperger's syndrome' and 'atypical autism'. Intellectual disability was ascertained based on ICD-10 codes F70-F79 inclusive. The outcomes of 'autism without ID' and 'autism with ID' were defined based on their intersection and used as separate categories in further analyses.

Covariates

Both studies included additional information ascertained via the MBR on parental ages at the point of pregnancy, the year of birth and birth order, based on the history of previous pregnancies. Study 2 also included information on the income of both parents and the history of smoking of the mother, based on their self-report.

Statistical analyses

Study 1 - Sex differences in pregnancy and birth complications

In this study, the exposure of interest was fetal sex, and the outcome was pregnancy complications. For each complication, we fitted a logistic regression with the binary complication as the dependent variable and foetal sex as the primary exposure, using females as the reference group. Two models were specified; Model 1 adjusted for maternal age, paternal age, birth order, and birth year; Model 2 additionally adjusted for maternal smoking and income. We report the association as the odds ratio for male versus female infants, such that an odds ratio above one indicates a higher likelihood of the complication in males. P-values were corrected across the eight complications within each model, using the Benjamini–Hochberg false discovery rate (FDR).

- *Sex differences in complications by gestational timing*

We additionally examined sex differences across the gestational-age spectrum in two ways. First, for each gestational-age category we estimated the odds of membership in that category for male versus female infants, under both adjustment sets, with term delivery as the implicit reference. Second, to assess whether the sex difference in each complication varied by gestational timing, we computed, within each gestational-age category, the relative risk of each complication for male versus female infants, presented on the log scale as a heatmap with the corresponding category-specific test of association. Statistical comparisons between the sexes for these binary combinations were conducted via chi-square tests of the corresponding contingency tables. Significance across all category-by-complication cells was FDR-corrected.

- *Sibling analyses for Study 1*

To account for confounding by stable, unmeasured familial factors, we conducted sibling-comparison analyses using conditional logistic regression stratified by family. Full siblings were defined as children sharing both biological parents, and only families with at least two eligible children contributed; the majority of families (approximately 70%) had exactly two siblings meeting this definition. In Study 1, fetal sex was the exposure and each complication the outcome, so the analysis draws information from families discordant on foetal sex ($n = 170,123$). We fitted models under both adjustment sets (Model 1 and Model 2) and, for every complication separately. Of the children with at least one full sibling, the number of informative families varied by complication according to its frequency, being largest for common outcomes such as C-section and preterm birth and smallest for rare conditions such as placenta previa.

Study 2 – Birth complications and autism: case-control analyses

We compared each autism group versus the total control group, using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables.

For each complication and each autism outcome (without and with co-occurring ID), we estimated the association with autism using logistic regression, fitting a separate model for each complication so that every reported odds ratio derives from a model in which that complication was the sole exposure of interest. All models adjusted for covariates ascertained at or before birth. Model 1 adjusted for fetal sex, maternal age, paternal age,

birth order, and birth year in grouped intervals. Model 2 additionally adjusted for maternal smoking during pregnancy and family income (modelled in income quintiles). P-values were FDR-corrected for multiple comparisons across the eight complications.

- *Choice of regression method*

Throughout, we modelled the binary occurrence of each outcome using logistic regression rather than modelling time to diagnosis with Cox proportional-hazards regression. A time-to-event model, such as Cox, estimates the rate at which a diagnosis is recorded, which in the case of autism may be shaped by non-biological determinants of when, and whether, a child reaches diagnostic services, including referral patterns, diagnostic capacity, parental help-seeking, and documented gender biases in recognition, whereby girls in particular are diagnosed later or missed. Modelling time to diagnosis would risk conflating biological sex differences in liability with social and clinical differences in detection, particularly in the case of autistic women. We therefore framed the question as one of cumulative likelihood of autism over the follow-up period rather than timing of diagnosis.

- *Sibling analyses for Study 2*

We also conducted sibling-comparison analyses using conditional logistic regression stratified by family, to account for confounding by familial factors, including shared maternal genetic background, chronic maternal health conditions, and persistent socioeconomic and environmental circumstances. Siblings were identified within the main Study 2 population (born between 1997 and 2015) and included in this analysis if they shared both biological parents and were discordant for autism. Analyses were conducted separately for autism without ID (n=27,281 families) and for autism with ID (n=4,541 families), using the same adjustment covariates as the analysis in the main population (Model 1: foetal sex, maternal age, paternal age, birth order, and birth year, Model 2: as Model 1 with the addition of maternal smoking and family income in quintiles). Across both outcomes approximately 70% of these families comprised exactly two children, with the remainder distributed across larger sibships. Because conditional logistic regression additionally requires discordance on the complication, the number of families informing any individual complication's estimate is a subset of these totals and

varies by complication. For this reason, we report, for every within-family estimate, the number of informative families and the number of cases among them.

- *Assessment of sex differences in Study 2*

Given the marked male preponderance of autism, we further characterised the role of sex within the Study 2 population in three complementary ways. First, for each complication and outcome, we fitted the same logistic regression models as in the main analysis, with the addition of a multiplicative interaction term between the occurrence of a complication and foetal sex, in order to test for effect modification based on the latter. Second, we fitted sex-stratified models, applying the Model 1 specification separately within males and females and presenting the sex-specific odds ratios side by side. Third, we conducted separate mediation analyses in a subset of the main population to estimate whether, and to what extent, sex differences in pregnancy complications contribute to sex differences in autism likelihood.

- *Mediation analyses*

To evaluate whether the elevated autism risk associated with male sex operates partly through pregnancy and birth complications, we conducted causal mediation analyses with male sex as the exposure, each complication as a candidate mediator, and autism as the outcome. We restricted candidate mediators to the six complications more frequent among males (placenta previa, pregnancy-induced hypertension, preeclampsia, gestational diabetes, C-section, and preterm birth), since a mediator must be differentially distributed by the exposure to transmit any portion of its effect. In addition to evaluating each complication individually, we constructed a composite mediator indicating the presence of any of these six complications, testing the broader hypothesis that male sex confers a generalised susceptibility to perinatal adversity that in turn elevates autism risk. Mediator and outcome models were logistic regressions adjusted for the Model 1 covariate set. We estimated the average causal mediation (indirect) effect, the average direct effect, the total effect, and the proportion of the total effect mediated, using the quasi-Bayesian Monte Carlo approximation with 500 simulations. To render the procedure computationally tractable in a cohort of this size with a relatively rare outcome, mediation models were fitted on a case-cohort subsample comprising all autism cases and a randomly selected set of controls at a 10:1 control-to-case ratio. Mediation

analyses were performed separately for autism with ID and autism without ID, using controls that had neither autism nor ID. Causal mediation rests on an assumption of no unmeasured confounding of the mediator–outcome relationship, which cannot be guaranteed in observational data. We assessed robustness using E-values, which quantify the minimum strength of association, on the odds-ratio scale, that an unmeasured confounder would need to fully explain away the observed association. We report the E-value for each point estimate and for the confidence-interval bound nearest the null, with larger values indicating greater robustness.

- *Exploratory prediction analysis*

As an exploratory analysis, we assessed how much of the variation in autism is predictable from information available at or around birth, and the relative contribution of foetal sex. We compared three nested gradient-boosted models (LightGBM), each adding a block of variables to the previous. Model 1 comprised family history and demographic factors: maternal and paternal age, maternal and paternal history of psychiatric conditions, maternal and paternal history of neurodevelopmental conditions, maternal smoking, family income, parity, and maternal body mass index. Model 2 added pregnancy and birth parameters and complications: birth weight, gestational age, C-section, pregnancy-induced hypertension, preeclampsia, gestational diabetes, and preterm premature rupture of membranes (PPROM). Model 3 added fetal sex. The outcome was any autism diagnosis against clean controls. Models were trained and evaluated on separate partitions of the cohort, with discrimination summarised by the area under the receiver-operating-characteristic curve (AUC) and, given the rarity of autism, the area under the precision-recall curve and the specificity at a fixed 80% sensitivity. Variable importance was quantified using SHAP values. This analysis is exploratory and not intended as a clinical screening or risk-prediction tool.

Software

All analyses were conducted in RStudio. Logistic regression used base R; conditional logistic regression for sibling comparisons used the survival package; causal mediation analyses used the mediation package; sensitivity analyses used the EValue package; the exploratory prediction analysis used the lightgbm, pROC, and PRROC packages; and figures and tables were produced with ggplot2, flextable, and officer.

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