

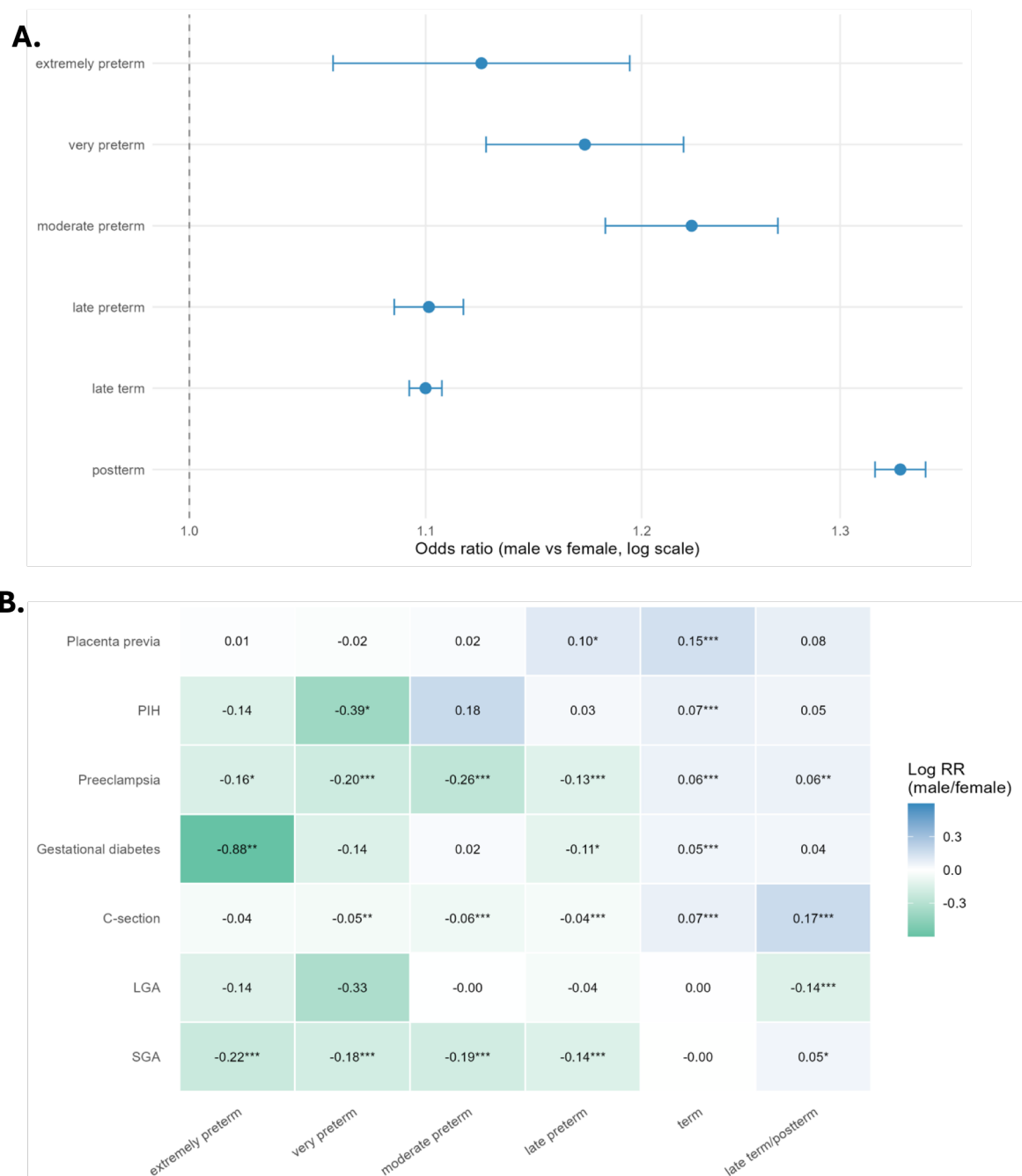
Supplementary Information for: “Sex differences in pregnancy complications and autism”

Supplementary Table 1

Sex differences in pregnancy complications, as assessed with logistic regression models, adjusted for maternal age, paternal age, birth order, and birth year. Within-family analyses included families that included full siblings that were discordant for both sex and the complication in question.

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- Families
Placenta previa	1.15 (1.10–1.20)	5.6×10^{-9}	1.15 (1.10–1.20)	6.8×10^{-9}	1.16 (1.08–1.26)	2.4×10^{-4}	1.16 (1.08–1.26)	2.3×10^{-4}	2,902
PIH	1.06 (1.04–1.08)	5.6×10^{-7}	1.06 (1.04–1.08)	6.1×10^{-7}	1.09 (1.04–1.13)	1.9×10^{-4}	1.09 (1.04–1.13)	2.1×10^{-4}	9,632
Preeclampsia	1.03 (1.01–1.04)	0.002	1.03 (1.01–1.04)	0.002	1.02 (0.98–1.05)	0.333	1.02 (0.98–1.05)	0.340	19,390
Gestational diabetes	1.02 (1.00–1.04)	0.094	1.02 (1.00–1.04)	0.098	1.06 (1.01–1.11)	0.017	1.06 (1.01–1.11)	0.017	8,960
C-section	1.10 (1.10–1.11)	$<2 \times 10^{-16}$	1.10 (1.10–1.11)	$<2 \times 10^{-16}$	1.12 (1.10–1.13)	$<2 \times 10^{-16}$	1.12 (1.10–1.13)	$<2 \times 10^{-16}$	57,472
Preterm birth	1.13 (1.11–1.14)	$<2 \times 10^{-16}$	1.13 (1.11–1.14)	$<2 \times 10^{-16}$	1.13 (1.11–1.16)	$<2 \times 10^{-16}$	1.13 (1.11–1.16)	$<2 \times 10^{-16}$	33,984
LGA	0.96 (0.95–0.98)	7.2×10^{-8}	0.96 (0.95–0.98)	4.9×10^{-8}	0.95 (0.93–0.98)	7.4×10^{-4}	0.95 (0.93–0.98)	5.6×10^{-4}	30,275
SGA	1.00 (0.98–1.01)	0.609	1.00 (0.98–1.01)	0.590	0.96 (0.93–0.99)	0.017	0.96 (0.93–0.99)	0.015	18,813

Supplementary Figure 1



Supplementary Figure 1 (A) Sex differences in birth timing based on logistic regression models, adjusted for maternal age, paternal age, birth order, and birth year. **(B)** Sex differences in absolute counts of complicated preterm births, according to each complication in the study.

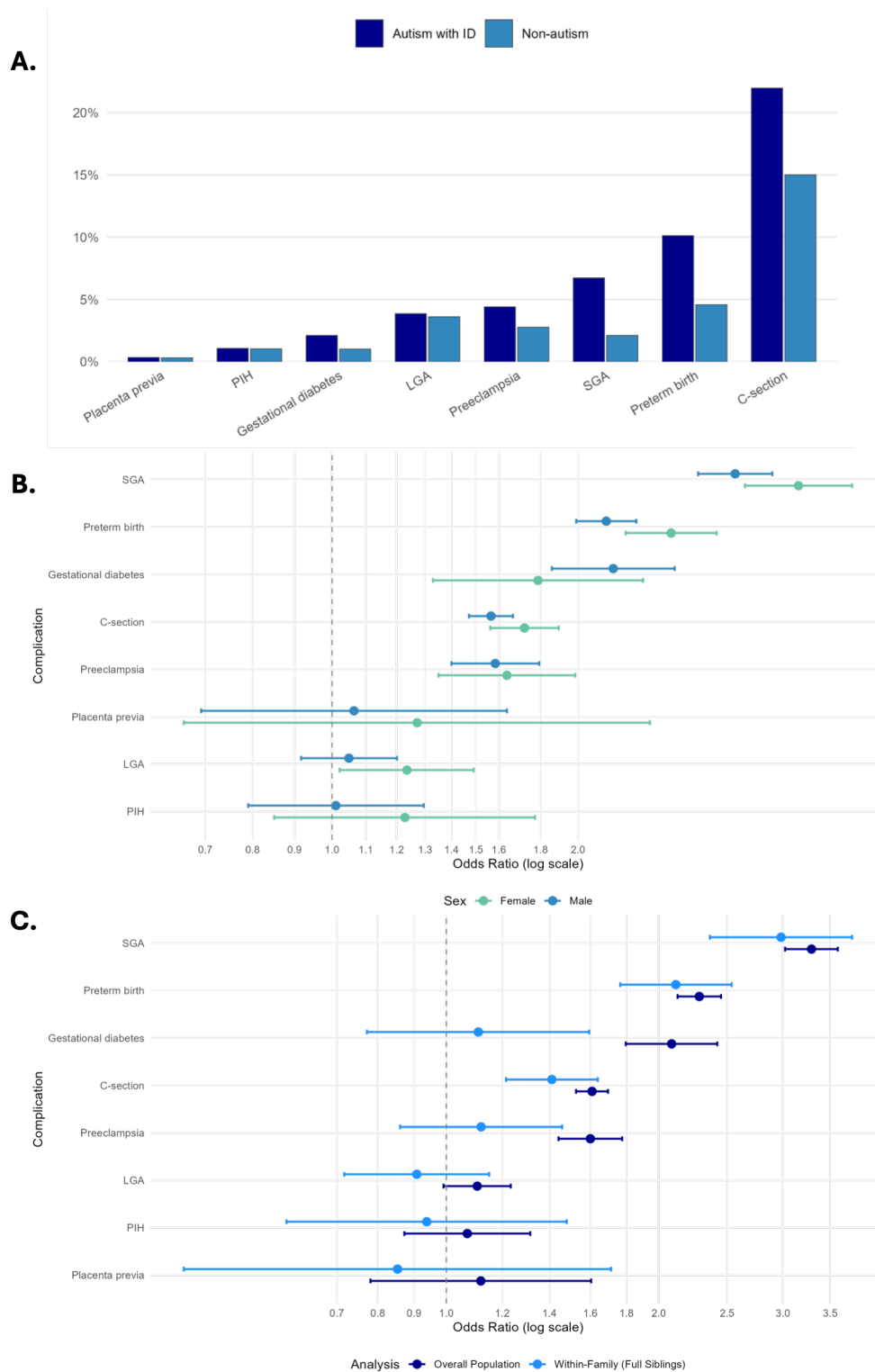
Significance was assessed based on chi-square tests of the contingency tables. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Supplementary Table 2

Case-control differences in demographic and family characteristics, further stratified by sex and co-occurring ID for autism. † P-value for the difference between male and female controls (Wilcoxon rank-sum for continuous; chi-square for categorical).‡ P-value for the difference between the ASD group and the total control group.

Variable	Controls (total)	Controls (male)	Controls (female)	P†	Autism without ID	P‡	Autism with ID	P‡
N	1,786,855	910,144	876,711		50,632		8,756	
Maternal age, years	30.09 (5.14)	30.09 (5.13)	30.09 (5.14)	0.31	29.59 (5.52)	<1e-16	29.91 (5.68)	0.00078
Paternal age, years	32.98 (6.17)	32.97 (6.16)	32.98 (6.18)	0.504	32.60 (6.62)	<1e-16	33.61 (6.98)	2.27e-13
Birth order	1.55 (0.75)	1.55 (0.75)	1.55 (0.75)	0.157	1.43 (0.69)	<1e-16	1.50 (0.77)	<1e-16
Family income (quintile)	3.01 (1.41)	3.01 (1.41)	3.00 (1.41)	0.00065	2.70 (1.39)	<1e-16	2.46 (1.38)	<1e-16
Birth year								
1997-2001	237,318 (13.3%)	120,891 (13.3%)	116,427 (13.3%)	0.166	8,376 (16.5%)	<1e-16	1,344 (15.3%)	<1e-16
2002-2006	428,001 (24.0%)	218,466 (24.0%)	209,535 (23.9%)		17,613 (34.8%)		2,478 (28.3%)	
2007-2011	484,753 (27.1%)	246,310 (27.1%)	238,443 (27.2%)		15,433 (30.5%)		2,328 (26.6%)	
2012-2015	636,783 (35.6%)	324,477 (35.7%)	312,306 (35.6%)		9,210 (18.2%)		2,606 (29.8%)	
Maternal smoking								
No	1,646,398 (92.1%)	839,133 (92.2%)	807,265 (92.1%)	0.00315	43,400 (85.7%)	<1e-16	7,742 (88.4%)	<1e-16
Yes	140,457 (7.9%)	71,011 (7.8%)	69,446 (7.9%)		7,232 (14.3%)		1,014 (11.6%)	
Maternal psychiatric history								
No	1,401,149 (78.4%)	714,395 (78.5%)	686,754 (78.3%)	0.00962	29,646 (58.6%)	<1e-16	5,719 (65.3%)	<1e-16
Yes	385,706 (21.6%)	195,749 (21.5%)	189,957 (21.7%)		20,986 (41.4%)		3,037 (34.7%)	
Maternal neurodevelopmental history								
No	1,733,558 (97.0%)	883,184 (97.0%)	850,374 (97.0%)	0.101	44,221 (87.3%)	<1e-16	7,975 (91.1%)	<1e-16
Yes	53,297 (3.0%)	26,960 (3.0%)	26,337 (3.0%)		6,411 (12.7%)		781 (8.9%)	
Paternal psychiatric history								
No	1,504,086 (84.2%)	766,925 (84.3%)	737,161 (84.1%)	0.00089	36,431 (72.0%)	<1e-16	6,444 (73.6%)	<1e-16
Yes	282,769 (15.8%)	143,219 (15.7%)	139,550 (15.9%)		14,201 (28.0%)		2,312 (26.4%)	
Paternal neurodevelopmental history								
No	1,741,215 (97.4%)	887,025 (97.5%)	854,190 (97.4%)	0.227	46,455 (91.8%)	<1e-16	8,172 (93.3%)	<1e-16
Yes	45,640 (2.6%)	23,119 (2.5%)	22,521 (2.6%)		4,177 (8.2%)		584 (6.7%)	

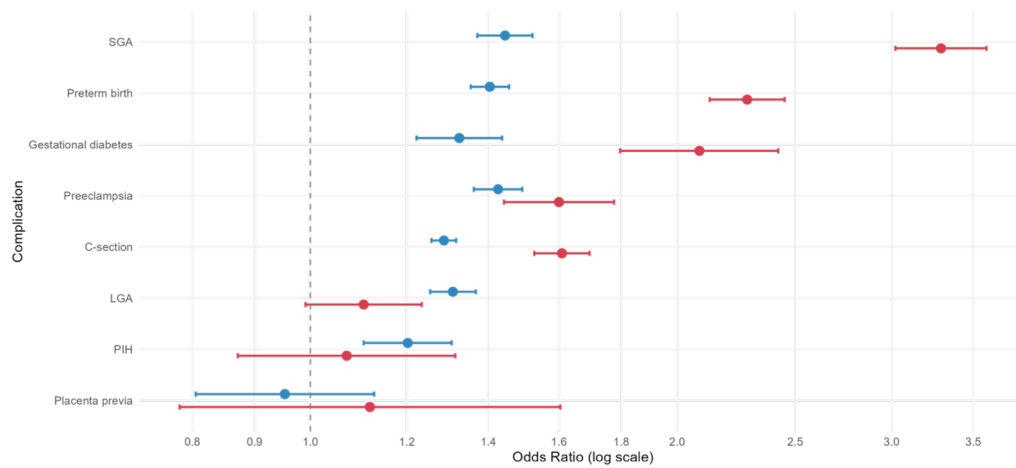
Supplementary Figure 2



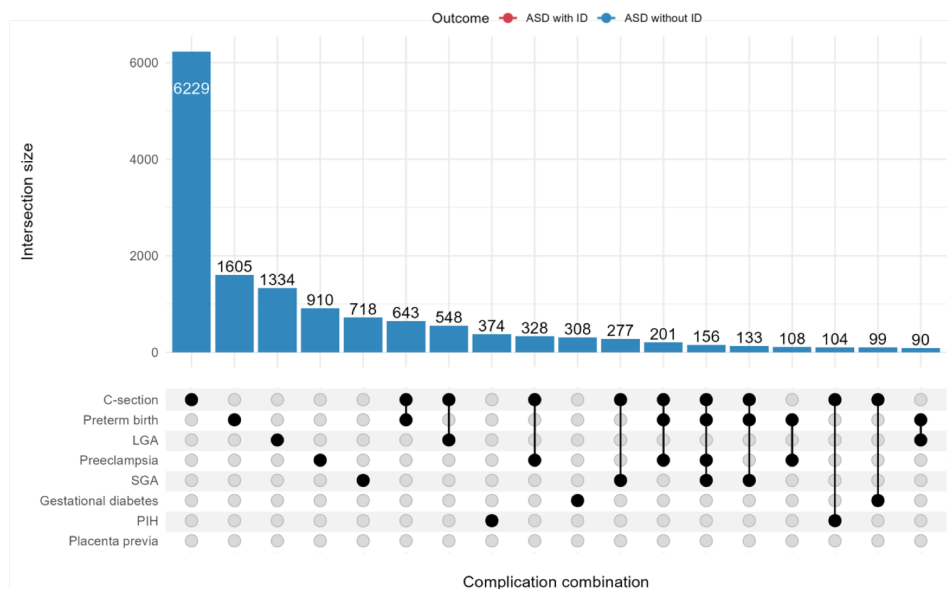
Supplementary Figure 2. Autism with ID in association with pregnancy complications. (A) absolute count differences for each complication. (B) sex-stratified (C) population-wide and within-family association analyses for each complication based on Model 1, adjusted for foetal sex, maternal age, paternal age, birth order, and birth year. SGA: small for gestational age, LGA: large for gestational age, PIH: pregnancy-induced hypertension.

Supplementary Figure 3

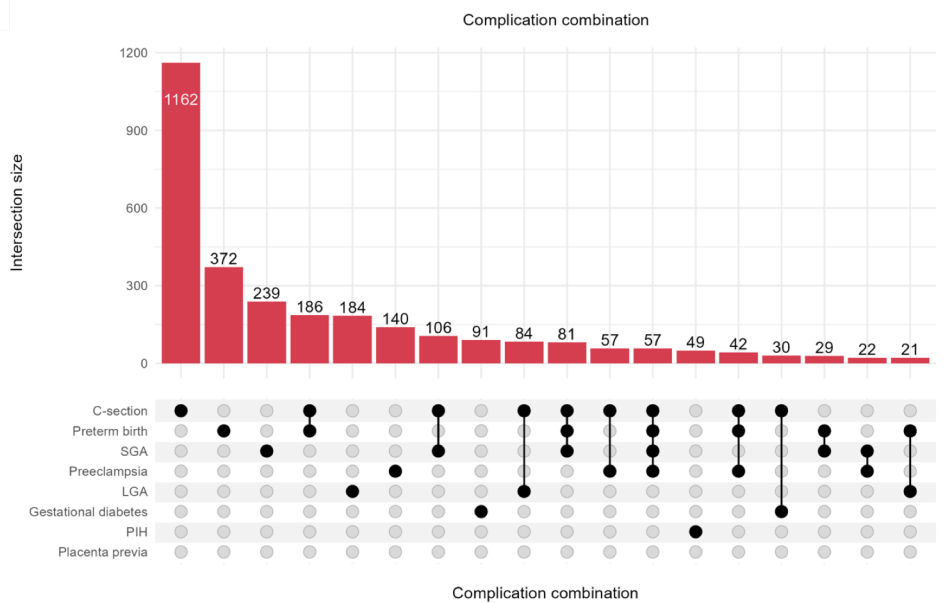
A.



B.



C.



Supplementary Figure 3 (A) Comparison of Model 1 results between autism with and autism without ID. (B) Combinations of pregnancy complications for autism without ID, and (C) for autism with ID, with a minimum count number of 18.

Supplementary Table 3

Logistic regression of autism without intellectual disability with a sex interaction term

Model 1 adjusts for maternal and paternal age, birth order, and birth year. Model 2 additionally adjusts for maternal smoking and family income. † Interaction p-values are FDR-adjusted (Benjamini–Hochberg) within each model; main-effect p-values are unadjusted.

Term	Model 1		Model 2	
	OR (95% CI)	p	OR (95% CI)	p
Placenta previa				
Complication	0.95 (0.78–1.17)	0.651	0.93 (0.76–1.14)	0.493
Sex (female vs male)	0.54 (0.53–0.55)	2.0×10^{-16}	0.53 (0.52–0.54)	2.0×10^{-16}
Complication × sex †	0.99 (0.69–1.43)	0.976	0.99 (0.69–1.43)	0.956
PIH				
Complication	1.27 (1.15–1.41)	2.0×10^{-6}	1.30 (1.18–1.44)	2.8×10^{-7}
Sex (female vs male)	0.54 (0.53–0.55)	2.0×10^{-16}	0.54 (0.53–0.55)	2.0×10^{-16}
Complication × sex †	0.83 (0.69–1.00)	0.134	0.83 (0.69–1.00)	0.129
Preeclampsia				
Complication	1.41 (1.33–1.49)	2.0×10^{-16}	1.42 (1.34–1.50)	2.0×10^{-16}
Sex (female vs male)	0.53 (0.52–0.55)	2.0×10^{-16}	0.53 (0.52–0.54)	2.0×10^{-16}
Complication × sex †	1.04 (0.95–1.15)	0.453	1.04 (0.95–1.15)	0.440
Gestational diabetes				
Complication	1.37 (1.24–1.52)	3.0×10^{-10}	1.27 (1.15–1.40)	2.8×10^{-6}
Sex (female vs male)	0.54 (0.53–0.55)	2.0×10^{-16}	0.54 (0.53–0.55)	2.0×10^{-16}
Complication × sex †	0.90 (0.76–1.07)	0.305	0.90 (0.76–1.07)	0.292
C-section				
Complication	1.30 (1.27–1.34)	2.0×10^{-16}	1.28 (1.25–1.32)	2.0×10^{-16}
Sex (female vs male)	0.54 (0.53–0.55)	2.0×10^{-16}	0.54 (0.53–0.55)	2.0×10^{-16}
Complication × sex †	0.96 (0.92–1.01)	0.248	0.96 (0.92–1.01)	0.274
Preterm birth				
Complication	1.35 (1.29–1.41)	2.0×10^{-16}	1.32 (1.26–1.38)	2.0×10^{-16}
Sex (female vs male)	0.53 (0.52–0.54)	2.0×10^{-16}	0.53 (0.52–0.54)	2.0×10^{-16}
Complication × sex †	1.13 (1.04–1.22)	0.018	1.13 (1.04–1.22)	0.017
LGA				
Complication	1.26 (1.19–1.33)	2.0×10^{-16}	1.28 (1.21–1.35)	2.0×10^{-16}
Sex (female vs male)	0.53 (0.52–0.54)	2.0×10^{-16}	0.53 (0.52–0.54)	2.0×10^{-16}
Complication × sex †	1.11 (1.02–1.22)	0.075	1.11 (1.02–1.22)	0.073
SGA				
Complication	1.48 (1.39–1.58)	2.0×10^{-16}	1.37 (1.29–1.46)	2.0×10^{-16}
Sex (female vs male)	0.54 (0.53–0.55)	2.0×10^{-16}	0.54 (0.53–0.55)	2.0×10^{-16}
Complication × sex †	0.93 (0.84–1.04)	0.305	0.93 (0.83–1.04)	0.291

Supplementary Table 4

Logistic regression of autism with intellectual disability with a sex interaction term. †
Interaction *p*-values are FDR-adjusted (Benjamini–Hochberg) within each model; main-effect *p*-values are unadjusted.

Term	Model 1		Model 2	
	OR (95% CI)	p	OR (95% CI)	p
Placenta previa				
Complication	1.06 (0.69–1.64)	0.773	1.04 (0.68–1.61)	0.845
Sex (female vs male)	0.43 (0.41–0.45)	2.0×10^{-16}	0.43 (0.41–0.45)	2.0×10^{-16}
Complication × sex †	1.19 (0.54–2.61)	0.759	1.17 (0.54–2.57)	0.787
PIH				
Complication	1.02 (0.80–1.31)	0.850	1.06 (0.83–1.36)	0.647
Sex (female vs male)	0.43 (0.41–0.45)	2.0×10^{-16}	0.43 (0.41–0.45)	2.0×10^{-16}
Complication × sex †	1.16 (0.75–1.81)	0.675	1.16 (0.74–1.80)	0.683
Preeclampsia				
Complication	1.60 (1.41–1.81)	9.8×10^{-14}	1.59 (1.41–1.80)	1.4×10^{-13}
Sex (female vs male)	0.43 (0.41–0.45)	2.0×10^{-16}	0.43 (0.41–0.45)	2.0×10^{-16}
Complication × sex †	1.00 (0.80–1.26)	0.984	1.01 (0.80–1.26)	0.960
Gestational diabetes				
Complication	2.21 (1.86–2.63)	2.0×10^{-16}	1.92 (1.61–2.28)	1.8×10^{-13}
Sex (female vs male)	0.43 (0.41–0.45)	2.0×10^{-16}	0.43 (0.41–0.45)	2.0×10^{-16}
Complication × sex †	0.81 (0.57–1.14)	0.368	0.80 (0.57–1.13)	0.381
C-section				
Complication	1.58 (1.48–1.68)	2.0×10^{-16}	1.55 (1.46–1.65)	2.0×10^{-16}
Sex (female vs male)	0.43 (0.41–0.45)	2.0×10^{-16}	0.43 (0.40–0.45)	2.0×10^{-16}
Complication × sex †	1.07 (0.96–1.20)	0.368	1.07 (0.96–1.20)	0.381
Preterm birth				
Complication	2.17 (2.00–2.36)	2.0×10^{-16}	2.11 (1.94–2.30)	2.0×10^{-16}
Sex (female vs male)	0.42 (0.40–0.45)	2.0×10^{-16}	0.42 (0.40–0.45)	2.0×10^{-16}
Complication × sex †	1.19 (1.02–1.39)	0.224	1.19 (1.02–1.38)	0.237
LGA				
Complication	1.04 (0.91–1.19)	0.595	1.07 (0.93–1.22)	0.346
Sex (female vs male)	0.42 (0.40–0.44)	2.0×10^{-16}	0.42 (0.40–0.44)	2.0×10^{-16}
Complication × sex †	1.22 (0.97–1.54)	0.317	1.22 (0.97–1.54)	0.360
SGA				
Complication	3.15 (2.83–3.49)	2.0×10^{-16}	2.85 (2.56–3.16)	2.0×10^{-16}
Sex (female vs male)	0.42 (0.40–0.44)	2.0×10^{-16}	0.42 (0.40–0.44)	2.0×10^{-16}
Complication × sex †	1.16 (0.96–1.39)	0.317	1.15 (0.95–1.38)	0.376

Supplementary Table 5

Causal mediation analysis decomposing the effect of two birth outcomes (C-section and preterm birth) on autism, stratified by co-occurring ID. Mediator and outcome models adjusted for sex, maternal and paternal age, birth order, and birth year (Model 1 covariate set). Analyses use a 10:1 case-cohort subsample. 'Mediator → autism' OR is the conditional association between the birth outcome and autism after adjustment. The E-value (CI bound) reports the minimum strength of an unmeasured confounder needed to explain the mediator-outcome association (larger values indicate greater robustness). Proportion mediated is the share of the total effect of each listed pregnancy complication operating through the listed birth outcome (C-section or preterm birth).

Exposure / mediator	Mediator → autism OR (95% CI)	E-value (CI bound)	Proportion mediated (95% CI)	p
Autism without intellectual disability				
Mediator: Preterm birth				
Preeclampsia	1.37 (1.31–1.42)	1.55	16.99% (14.10–21.03)	<2e-16
PIH	1.42 (1.36–1.47)	1.61	1.18% (0.02–2.93)	0.04
Gestational diabetes	1.41 (1.36–1.47)	1.60	5.28% (3.88–7.86)	<2e-16
Mediator: C-section				
Preeclampsia	1.26 (1.23–1.29)	1.45	13.92% (11.78–16.51)	<2e-16
PIH	1.28 (1.25–1.31)	1.48	4.78% (2.76–10.65)	<2e-16
Gestational diabetes	1.27 (1.24–1.31)	1.47	7.43% (5.25–10.62)	<2e-16
Autism with intellectual disability				
Mediator: Preterm birth				
Preeclampsia	2.22 (2.05–2.41)	2.22	40.59% (30.70–54.75)	<2e-16
PIH	2.29 (2.12–2.48)	2.27	3.34% (-73.87–106.32)	0.71
Gestational diabetes	2.27 (2.10–2.46)	2.26	7.55% (4.77–11.35)	<2e-16
Mediator: C-section				
Preeclampsia	1.57 (1.49–1.67)	1.74	23.93% (17.89–31.03)	<2e-16
PIH	1.60 (1.52–1.70)	1.76	15.20% (-327.49–276.81)	0.57
Gestational diabetes	1.59 (1.51–1.68)	1.76	6.33% (4.19–9.04)	<2e-16

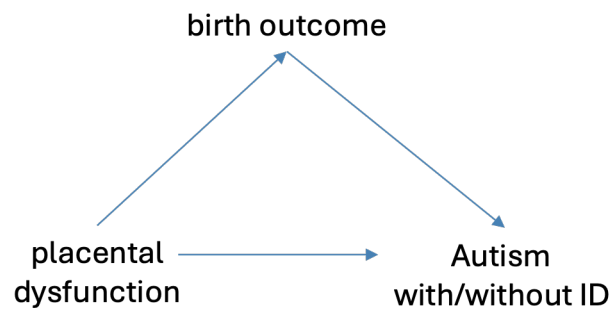
Supplementary Table 6

Causal mediation analysis decomposing the effect of male sex on autism stratified by co-occurring ID. Mediator and outcome models adjusted for maternal and paternal age, birth order, and birth year (Model 1 covariate set). Analyses use a 10:1 case-cohort subsample. 'Mediator → autism' OR is the conditional association between the complication and autism after adjustment. The E-value (CI bound) reports the minimum strength of an unmeasured confounder needed to explain the mediator-outcome association (larger values indicate greater robustness). Proportion mediated is the share of the total male-sex effect operating through the listed complication. 'Any male-excess' included the complications below.

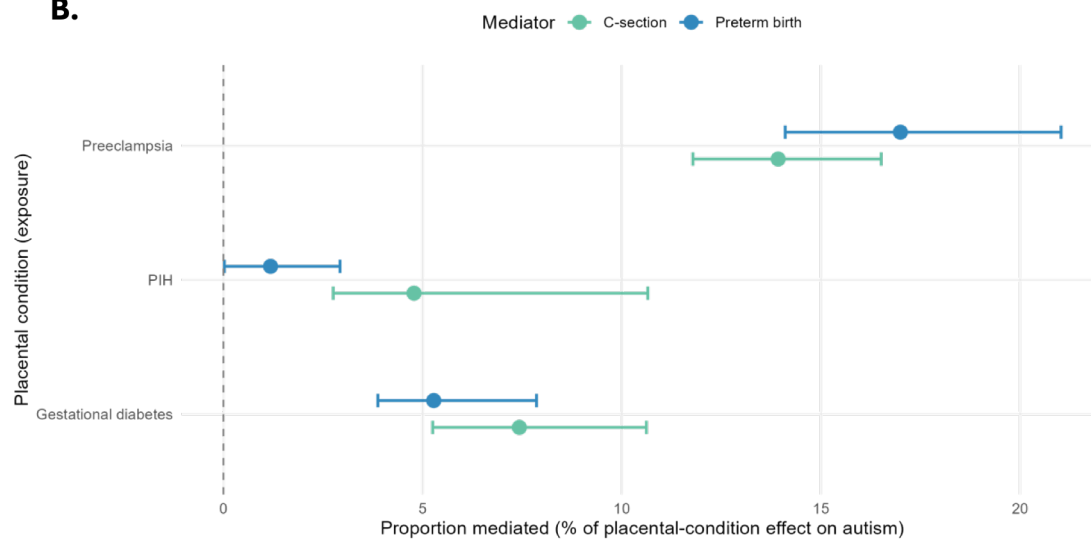
Complication (mediator)	Mediator → autism OR (95% CI)	E-value (CI bound)	Proportion mediated (95% CI)	p
Autism without intellectual disability				
Any male-excess complication	1.32 (1.30–1.35)	1.54	0.87% (0.75–1.02)	<0.001
Placenta previa	0.93 (0.78–1.11)	—	-0.00% (-0.02–0.01)	0.424
PIH	1.20 (1.09–1.30)	1.27	0.02% (0.00–0.05)	0.02
Preeclampsia	1.44 (1.37–1.51)	1.61	0.09% (0.02–0.17)	0.016
Gestational diabetes	1.38 (1.27–1.50)	1.50	0.02% (-0.01–0.05)	0.2
C-section	1.30 (1.27–1.33)	1.50	0.60% (0.48–0.72)	<0.001
Preterm birth	1.40 (1.35–1.46)	1.59	0.39% (0.29–0.50)	<0.001
Autism with intellectual disability				
Any male-excess complication	1.73 (1.65–1.82)	1.89	1.76% (1.31–2.22)	<0.001
Placenta previa	1.04 (0.71–1.52)	—	0.00% (-0.02–0.03)	0.98
PIH	1.00 (0.80–1.24)	—	-0.00% (-0.03–0.04)	0.96
Preeclampsia	1.64 (1.47–1.84)	1.72	0.14% (-0.05–0.34)	0.14
Gestational diabetes	2.26 (1.91–2.67)	2.11	0.22% (0.01–0.47)	0.044
C-section	1.63 (1.54–1.72)	1.79	1.21% (0.80–1.63)	<0.001
Preterm birth	2.29 (2.12–2.48)	2.27	1.06% (0.63–1.59)	<0.001

Supplementary Figure 4

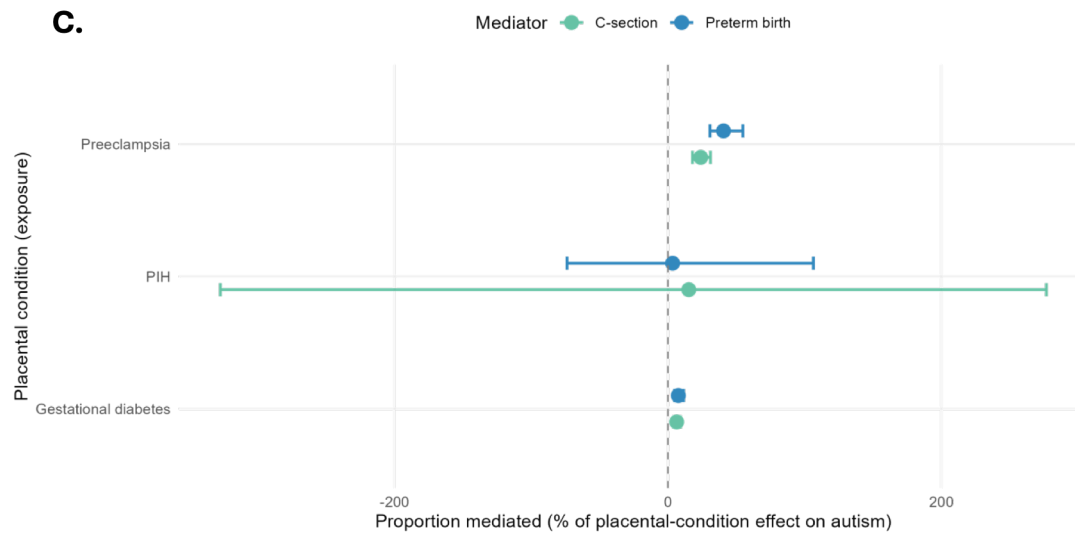
A.



B.



C.



Supplementary Figure 4: A. Causal mediation analysis for birth outcomes (C-section and preterm birth) on the effect of pregnancy complications on autism. Proportion of effect for each listed complication on autism, mediated by either birth outcome, for B. autism without ID, C. autism with ID.

