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Labor Induction and Offspring Risk of Autism Spectrum Disorders

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Induction of Labor • Autism Spectrum Disorders • Family studies • Sibling comparison
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ABSTRACT

Importance: Induction of labor is a frequently performed obstetrical intervention. It would thus be of great concern if reported associations between labor induction and offspring risk of autism spectrum disorders (ASD) reflected causal influence.

Objective: To assess the associations of labor induction with ASD, comparing differentially exposed relatives (siblings and cousins discordant for induction).

Design: Register-based follow-up of a nation-wide birth cohort

Setting: Swedish Medical Birth Register linked to population registers of familial relations, in- and out-patient visits and education.

Participants: All live births in Sweden between 1992-2005

Exposures for Observational Studies: Induction of labor

Main outcomes and Measures: Autism Spectrum Disorder (ASD) identified by diagnoses from inpatient and outpatient records between 2001 and 2013. Hazard Ratios (HRs) quantified the association between labor induction and offspring ASD. In addition to considering a wide range of measured confounders, comparison of exposure-discordant births to the same woman allowed additional control for all unmeasured factors shared by siblings.

Results: The full cohort included 1,362,950 births, of which 22,077 were diagnosed with ASD (1.6%) by ages 8-21. In conventional models of the full cohort, associations between labor induction and offspring ASD were attenuated but remained statistically significant after adjustment for measured potential confounders (HR, 1.19; 95% CI, 1.13-1.24). When comparison was made within siblings whose births were discordant with respect to induction, thus accounting for all environmental and genetic factors shared by siblings, labor induction was no longer associated with offspring ASD (HR, 0.99; 95% CI, 0.88-1.10).

Conclusions and Relevance: In this nationwide sample of live births we observed no association between induction of labor and offspring ASD in within sibling comparison. Our findings suggest that concern for ASD should not factor into the clinical decision about whether to induce labor.

INTRODUCTION

Autism spectrum disorders (ASD) are a group of permanent developmental disabilities characterized by impairments in social interaction, language development, along with stereotyped and repetitive behaviors; they are estimated to affect approximately 1 in 90 children in the United States.[1] Both genetic and environmental factors in early life are thought to be of importance in neurodevelopment.[2] Recently, a large, population-based study suggested an independent association between induction and augmentation of labor and risk of offspring ASD.[3] The study linked information on 625, 042 live births from the North Carolina Detailed Birth Record and the Education Research databases (which included information on approximately 5500 children with a documented exceptionality designation for ASD). After control for confounding variables, the odds ratio for development of ASD following exposure to labor induction and augmentation was 1.27 (95% confidence interval 1.05 to 1.52).

While not the first study to link induction of labor to offspring neurodevelopment,[4-6] this population-based study gained widespread media attention and sparked a vivid debate among clinicians and researchers. Causal speculation has largely focused on the potential role of oxytocin, which is administered to stimulate uterine contractions (in all augmentations and a majority of inductions). Oxytocin is a neurotransmitter involved in social function and cognition,[7] and it has been hypothesized that pre-delivery exposure could predispose to ASD due to a down-regulation of oxytocin receptors.[8] Alternatively, it may not be the method but the intervention per se that increases risk of offspring ASD, by setting off downstream complications with negative influence on neurodevelopment (e.g., fetal distress and hypoxia, uterine rupture, emergency cesarean delivery etc.). Importantly, many have also argued for non-causal explanations to the findings,[9-11]

including the possibility that dysfunctional labor and ASD neuropathology share genetic origin (calcium homeostasis).[12]

Understanding whether induction of labor truly confers increased risk of neuro-psychiatric disorders in the offspring is important to clinicians and patients in weighing the risks and benefits of this therapeutic intervention. Here, we study the association of labor induction with ASD in a nation-wide register-based birth cohort, with ability to identify differentially exposed relatives (siblings and cousins that are discordant with respect to whether their births occurred after induction of labor) and follow them with respect to diagnosis of ASD. The richness of information available through linkage of Swedish population registers allows for thorough individual confounder adjustment, while the identification of differentially exposed relatives (e.g., siblings born to same mother, one who was induced for one pregnancy, but not the other) allows additional adjustment for unmeasured factors shared in families.[13]

METHODS

Data Source and Study Cohort

All residents in Sweden are assigned a unique civic registration number, through which individuals can be tracked and linked in national population registries of health and demographics.[14] The Multi-Generation Register (MGR)[15] links all Swedish residents to their parents, adoptive or biological, thereby allowing for the identification of full and half-siblings, as well as more complex family structures. The Medical Birth Register (MBR)[16] contains medical records from antenatal visits, the delivery and pediatric examination of the newborn on 96-99% of all live births in Sweden since 1973. Women are routinely enrolled in antenatal care during week 8-12, and the midwife uses a standardized form to record information such as the mother's weight and height, socio-

demographics (e.g. age and cohabitation status), reproductive history, use of tobacco smoke, and current and previous illnesses. Standardized charts are also used at the time of delivery to record information including length of gestation, fetal presentation, onset and mode of delivery. After the delivery, all relevant diagnoses and procedures up to the point of discharge are recorded using the WHO's International Classification of Diseases (ICD).[17] This study also made use of the National Patient Register (NPR),[18] which includes data from all psychiatric inpatient visits since 1973, all hospital admissions since 1987, and all specialized outpatient care since 2001. Finally the Education Register at Statistics Sweden allowed assessment of the mothers' highest attained level of education.

Labor induction was introduced as a yes/no indicator on the standardized delivery charts during 1991, and since 1997 it has been further possible to document through procedure coding on the discharge record. Checkbox indicators on charts are generally considered to have high reliability, as they are less likely missed and/or prone to error than manual recording of codes.[19,20] Cases of ASD were identified based on the recording of ICD10-codes (F84: Pervasive Developmental Disorders) in NPR records from 2001 and onward. These diagnoses are set by specialized (i.e. not general practice) physicians, and case reviews have shown high agreement with DSM-IV criteria.[21,22] Further face validity may be drawn from finding prevalence estimates of ASD based on this type of identification consistent with a large-scale detailed assessment from the same period.[23]

To allow exposure (from 1991) and outcome (up to 2013) identification, the study base consisted of the birth cohorts between 1992 and 2005. All live births in the period were followed with respect to neuropsychiatric diagnosis (event), emigration from Sweden or death (right censoring) up until the end of 2013 (ages 8-21 years). Missing information

predominantly occurred for maternal early pregnancy body mass index (BMI: 16%), and smoking (6%). Deletion of individuals with missing information on any of the final covariates of interest (mother's country of origin, education, BMI and smoking) yielded a sample of N=1,117, 220 (82%) available for complete case analysis. Among these we further identified N=694,612 siblings (bound by mothers) and N=323,436 cousins (bound by sisters).

Statistical Analysis

First we assessed the association between labor induction and ASD graphically, plotting for induced and not induced respectively, the cumulative risk of ASD with age using Kaplan-Meier estimation. The influence of induction was then modeled in Cox proportional hazard regression, with age as the underlying time scale and allowing censoring due to emigration or death. To account for clustering arising from the inclusion of more than one offspring/birth per woman (siblings), robust standard error estimation was used. With follow up beginning in 2001, some in the earlier born cohorts may be subject to left censoring (with incident diagnosis occurring before 2001). Since the majority of (and all severe) cases are expected to be frequent consumers of psychiatric and medical care, they are very likely identified as cases during follow-up, just not capturing the true incident age at diagnosis. To account for this, and any concern for birth cohort effects (due to a concomitant rising prevalence of induction and diagnoses of neuropsychiatric disorders with time), all analyses were adjusted for birth year. All analyses were performed in SAS statistical software version 9.4.

To evaluate the influence of covariates on the association between induction and offspring ASD, we performed complete case analysis following an a priori defined modeling strategy to sequentially increase the degree of confounder adjustment. The

baseline model including birth year, parity and maternal age, was expanded with measured stable maternal covariates (not likely to vary between consecutive births) such as education and country of origin. Covariates specific to each birth were further added, including smoking and BMI in early pregnancy, multiple gestation, gestational diabetes, gestational hypertension, preeclampsia, chorioamnionitis, urogenital infection, premature rupture of membranes, and prolonged or high-risk pregnancy. These covariates were selected based on known or plausible association with both labor induction and offspring ASD. After fitting each of these population-based models (i.e., M1, M2 and M3), we tested the proportional hazards assumption explicitly by evaluating the scaled Schoenfeld residuals for non-zero slope and found no evidence that the induction parameter violated the assumption in any of these. In a final model we then included a fixed effect to allow the underlying hazard to vary between mothers, making the contrast within siblings only, while maintaining adjustment for individual-level covariates (unique to each birth).

To explore the influence of potential bias we performed a series of sensitivity analyses. First, we repeated all analyses restricted to the later born cohort (infants born 1999-2005), in whom left censoring was less likely. Because the selection to the sibling comparison could affect generalizability (representativeness of the population) we assessed whether the cohort estimates (model 1-3) were different when the sample was restricted to individuals who had at least one sibling in the cohort. We also compared occurrence of ASD in maternal first cousins (offspring of sisters) differentially exposed to labor induction, avoiding the requirement of at least two births to the same woman. The comparison accounts for all factors shared by children of sisters, including some genetic and maternal environmental factors. The use of cousins in the fixed-effects contrast further allowed us to assess all models (1-4) in first-born individuals only, to completely

exclude any confounding influence of birth order. We also performed all analyses after excluding the 6% delivered through elective Cesarean, which restricts the contrast to reflect those with and without indication to induce (comparison being spontaneous start of labor). Lastly, since a majority of missingness was due to mother's BMI, we performed a complete case analysis without consideration of BMI (including 94% of the study base).

Finally it is important to note that the comparison of relatives will rely solely on the pairs (of siblings or cousins) that are discordant with respect to exposure status. In our sample, 15.2% of all maternal sibling pairs and 18.2% of all maternal cousin pairs were discordant for labor induction. With an overall induction prevalence of 12% in this sample, a random match of unrelated individuals should produce on average 21% discordance for this obstetric intervention. The lower discordance seen among relatives could be due to familial factors that make relatives more similar (concordant). In siblings, this could also be counteracted by a potential influence of birth order (making siblings different).

RESULTS

Of the N=1,362,950 individuals, N=22,077 were diagnosed with ASD during follow-up. Overall, 11% of all live births in Sweden between 1992-2005 were preceded by labor induction (with a slight increase over time). Table 1 shows the maternal and pregnancy characteristics of the study base overall, and stratified by induction status. Comparing distributions, the induced deliveries were more likely to occur in later years of the cohort and to women who were primiparous, of older age, and of higher BMI than in the general population. Mother's education, country of origin and smoking in early pregnancy did not differ substantially across exposure groups (induced and not induced). Labor induction however occurred more commonly in association with a number of pregnancy

complications, including gestational diabetes, gestational hypertension and pre-eclampsia. Nearly a fourth (23%) of all induced pregnancies were postterm (42+ weeks of gestation), 15% had pre-eclampsia, and 7% had intrauterine growth restriction (Table 1).

The occurrence of ASD in the complete case sample, and its relation to labor induction is shown graphically in Figure 1, where the cumulative risks of ASD are plotted as a function of age, stratified by exposure to induction. An exponential increase in the cumulative risk of ASD reflects the increased rate (slope) of discovery/diagnosis with age. By the age of 20 years, just over 2.5% of the study population had been diagnosed with ASD (3.5% among the induced and 2.5% among the non-induced).

The main analysis exploring the association between labor induction and ASD is presented in Table 2. In the baseline model, labor induction was statistically significantly associated with ASD in the full cohort (HR 1.32; 95% CI, 1.27-1.38). Adjustment for stable maternal characteristic including maternal education level and country of origin (Model 2) did not substantially change the risk estimate (HR 1.31, 95% CI 1.26-1.37). After adjustment for all measured factors including stable maternal characteristics and birth-specific characteristics (Model 3), the association was still statistically significant, albeit somewhat attenuated (HR, 1.19; 95% CI, 1.13-1.24). However, when further adjustment was made using fixed-effects models – comparing discordant siblings to each other to account for all factors they share (Model 4) – labor induction was no longer associated with ASD (HR 0.99; 95% CI, 0.88-1.10).

A series of sensitivity analyses were performed to test the robustness of the findings from the main analysis (Table 3). Refitting the models in samples restricted to the later born

cohorts or to individuals with one or more siblings respectively produced very similar estimates as in the full population. Comparison of exposure discordant maternal cousins showed attenuation from the fully adjusted cohort model (M3) although the point estimate did not go completely to null as in the sibling analysis . Restriction to first-born individuals showed slight attenuation of all estimates, but with an intact pattern of statistically significant positive associations in the cohort further attenuated within cousins. The exclusion of elective Cesarean deliveries, while leading to slightly stronger cohort associations, still showed complete attenuation (no association) in the sibling comparison. Lastly, and reassuringly, the complete case analysis excluding only 6% (re-introducing those only missing BMI, and not adjusting for this covariate) was nearly identical to the main complete case analysis (which excluded 18% of the cohort for missing data; Table 3).

DISCUSSION

In this large, population-based study from Sweden, using a family comparison design, we observed no relationship between induction of labor and offspring ASD. Our findings suggest that concern about ASD after induced labor should not factor into the clinical decision about whether to induce labor. The results also provide reassurance to parturients, that undergoing this common obstetrical intervention will not increase their child's risk of developing this condition.

Consistent with recent prior studies,[3,6] we observed a significant crude association between induction of labor and the risk for ASD that persisted also after adjustment for measured maternal factors and pregnancy conditions that were pre-specified as potential confounders. However, when we applied a fixed-effects model to compare induction-discordant siblings to each other (i.e., siblings born to same mother, in one the labor was

induced and in the other it was not), this association was no longer present. The method allowed further control for all shared maternal factors (present across all pregnancies) that are unmeasured in registries but appear to confound the association between labor induction and neurodevelopmental disorders in the offspring. These unmeasured characteristics are likely to have also been present in prior studies that observed an association between induction and ASD. Through the use of this rich data and innovative, family-based design, we were able to account for factors that are not possible to capture using traditional approaches.

Exactly what constitutes the unmeasured factors that lead to residual confounding in traditional approaches cannot be directly deduced from our data. The source would have to be a common cause of the exposure (labor induction) and outcome (ASD), and further a factor that is present across all pregnancies to the same woman. This points to genetic and/or environmental factors that are shared by siblings and confer risk of both labor induction and adverse neurodevelopmental outcome. A previous commentary have for example pointed to genes involved in cellular calcium homeostasis, which may play a role in the initiation and progression of labor, as well as in neurodevelopment.[12] A shared environmental factor could, speculatively, involve the characteristics of the healthcare setting where women and their offspring are treated; if cared for in a higher-intensity medical system it is possible that a woman would be more likely to be induced and her child more likely to be diagnosed with a neurodevelopmental disorder than a woman and child treated in a lower-intensity system. Since Sweden has a decentralized government-funded health care system with universal access, the potential for such differences might, if anything, arise from local variation in health care practice.

Our study has a number of important strengths. The source population for the analysis encompasses nearly all births that occur in Sweden ensuring that the study is free from any selection bias. The large size also allows for precise estimates of the association between induction of labor and the neurodevelopmental outcomes. The study benefits from the multiple database linkages, including information from the Medical Birth Register and the Multi-Generation Register that allow for the sibling- and cousin-based designs, and the National Patient Register, which allows for the long-term follow-up of offspring for the development of neurodevelopmental problems. It uses an innovative analytic approach that does not rely solely on measured covariates to account for common causes.[24-26] The exposure was identified based on a combination of both codes and checkboxes in the delivery records, ensuring that it is captured with both sensitivity and specificity. Likewise, the approach to identify the outcome of ASD has been shown to correlate well with DSM-4 criteria.

The study is also subject to certain limitations inherent in its data and design. Similar to the earlier large population-based study reporting an association between induction and ASD[3] our exposure information did not include specification of the *type of method* used, and contrary to this study we did not have information on labor augmentation. From this follows that our findings pertain to the risks associated with induction per se and not the method/medication used, hence not specifically testing the proposed biological pathway through oxytocin exposure. While not specifically coded in the delivery charts, given contemporary obstetric practice it is likely that a majority of induced women were exposed to oxytocin (for either induction or augmentation, or both), but we also note that a proportion of the women with spontaneous start of labor in the comparison group will also have been exposed to oxytocin through augmentation. A more important potential limitation is that the within-family comparison validity relies on the selection

of discordant family members. While the analysis of discordant relatives allows for the control for all the factors they share, it also means that the discordance has to be caused by something other than the shared factors. If for example due to the influence of unmeasured birth-specific confounders or misclassification of the exposure, this will bias the within-relative comparison. However, since induction is a common obstetric intervention and its recording is facilitated by a checkbox indicator on the delivery chart, it is likely captured with high fidelity. Concern about confounding from unmeasured individual factors should further be ameliorated by the fact that combined adjustment for shared factors and an extensive list of measured birth-specific (individual) confounders (e.g., preeclampsia, chorioamnionitis, urogenital infection, premature rupture of membranes, prolonged and high risk pregnancy) achieved complete attenuation of the within-sibling comparison.

CONCLUSION

Using a design that incorporates the comparison of exposure discordant relatives, the findings of this study provide no support for a causal association between induction of labor and offspring development of ASD.

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REFERENCES

1. Autism, Developmental Disabilities Monitoring Network Surveillance Year Principal I, Centers for Disease C, Prevention. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill Summ.* 2012;61(3):1-19.
2. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. *Pediatrics.* 2011;128(2):344-355.
3. Gregory SG, Anthopolos R, Osgood CE, Grotegut CA, Miranda ML. Association of autism with induced or augmented childbirth in North Carolina Birth Record (1990-1998) and Education Research (1997-2007) databases. *JAMA Pediatr.* 2013;167(10):959-966.
4. Juul-Dam N, Townsend J, Courchesne E. Prenatal, Perinatal, and Neonatal Factors in Autism, Pervasive Developmental Disorder-Not Otherwise Specified, and the General Population. *Pediatrics.* 2001;107(4):e63.
5. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. *Arch Gen Psychiatry.* 2004;61(6):618-627.
6. Dodds L, Fell DB, Shea S, Armson BA, Allen AC, Bryson S. The role of prenatal, obstetric and neonatal factors in the development of autism. *J Autism Dev Disord.* 2011;41(7):891-902.
7. Stavropoulos KK, Carver LJ. Research review: Social motivation and oxytocin in autism--implications for joint attention development and intervention. *J Child Psychol Psychiatry.* 2013;54(6):603-618.
8. Wahl RU. Could oxytocin administration during labor contribute to autism and related behavioral disorders?--A look at the literature. *Med Hypotheses.* 2004;63(3):456-460.
9. Vintzileos AM, Ananth CV. Induction or augmentation of labor and autism. *JAMA Pediatr.* 2014;168(2):190.

10. Stitely ML. Induction or augmentation of labor and autism. *JAMA Pediatr.* 2014;168(2):189-190.

11. Saade GR, Sibai BM, Silver R. Induction or augmentation of labor and autism. *JAMA Pediatr.* 2014;168(2):190-191.

12. Barnabei VM, Rasmusson RL, Bett GC. Autism and Induced Labor: Is Calcium a Potential Mechanistic Link? *Am J Obstet Gynecol.* 2014.

13. D'Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. The critical need for family-based, quasi-experimental research in integrating genetic and social science research. *American Journal of Public Health.* 2013;103:S46-S55.

14. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol.* 2009;24(11):659-667.

15. Statistics Sweden. *Multi-Generation Register 2009 - A Description of Contents and Quality.* Örebro, Sweden: Statistics Sweden; 2010. 2010:13.

16. National Board of Health and Welfare. *The Swedish Medical Birth Register - A Summary of Content and Quality.* Stockholm: National Board of Health and Welfare; 2003.

17. WHO. *International Classification of Diseases, World Health Organization WHO.* Geneva1992.

18. National Board of Health and Welfare. *Quality and Content in the Patient Register - Inpatient care discharges 1964-2007 and outpatient (specialized care) visits 1997-2007 [in Swedish].* Stockholm: National Board of Health and Welfare; 2009. 2009-125-15.

19. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scand J Soc Med.* 1990;18(2):143-148.

20. Frost F, Starzyk P, George S, McLaughlin JF. Birth complication reporting: the effect of birth certificate design. *Am J Public Health.* 1984;74(5):505-506.

21. Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. *Mol Psychiatry.* 2011;16(12):1203-1212.

22. Sullivan PF, Magnusson C, Reichenberg A, et al. Family History of Schizophrenia and Bipolar Disorder as Risk Factors for AutismFamily History of Psychosis as Risk Factor for ASD. *Arch Gen Psychiatry*. 2012:1-5.

23. Idring S, Rai D, Dal H, et al. Autism Spectrum Disorders in the Stockholm Youth Cohort: Design, Prevalence and Validity. *PLOS One.* 2012;7:e41280.

24. Academy of Medical Sciences Working Group. *Identifying the environmental causes of disease: How should we decide what to believe and when to take action?* London: Academy of Medical Sciences; 2007.

25. D'Onofrio B, Class QA, Lahey BB, Larsson H. Testing the Developmental Origins of Health and Disease Hypothesis for Psychopathology Using Family-Based, Quasi-Experimental Designs. *Child Development Perspectives.* 2014;8(3):151-157.

26. Donovan SJ, Susser E. Commentary: Advent of sibling designs. *International Journal of Epidemiology.* 2011;40:345-349.

Figure title:

Figure 1 | Relationship between labor induction and Autism Spectrum Disorders

Figure legend:

Figure 1 | Cumulative risk of being diagnosed with Autism Spectrum Disorders (ASD) as a function of age (years), shown separately for individuals exposed to labor induction (blue) and unexposed (black). Dotted lines outline the point-wise 95% confidence band on the failure proportion.

Table 1 | Maternal and pregnancy characteristics for the N=1,362,950 live births in the study period (1992-2005), according to induction status

		All	No induction	Induction
Mother's characteristics		N (%)	N (%)	N (%)
Highest education	missing	5764 (0.42)	5201 (0.43)	563 (0.39)
	< 9 years	25144 (1.84)	22744 (1.87)	2400 (1.67)
	completed 9 years	95857 (7.03)	85160 (6.98)	10697 (7.44)
	upper secondary 2-3 years	637136 (46.75)	569567 (46.71)	67569 (47.02)
	post secondary (any)	599049 (43.95)	536577 (44.01)	62472 (43.47)
Country of birth	missing	78 (0.01)	74 (0.01)	4 (0.00)
	Sweden	1130129 (82.92)	1009877 (82.83)	120252 (83.68)
Civil status	missing	87888 (6.45)	79037 (6.48)	8851 (6.16)
	married/co-habitating	1209316 (88.73)	1082297 (88.77)	1270190 (88.39)
	living alone	65746 (4.82)	57915 (4.75)	7831 (5.45)
Pregnancy characteristics				
Age at delivery, years	<20	26562 (1.95)	24279 (1.99)	2283 (1.59)
	20-29	687062 (50.41)	621784 (51.00)	65278 (45.43)
	30-39	615668 (45.17)	544646 (44.67)	71022 (49.42)
	>40	33658 (2.47)	28540 (2.34)	5118 (3.56)
Birth year	1992-1996	713078 (52.32)	649591 (53.28)	63487 (44.18)
	1997-2001	649872 (47.68)	569658 (46.72)	80214 (55.82)
Parity	1	569187 (41.76)	503166 (41.27)	66021 (45.94)
	2	500192 (36.70)	457945 (37.56)	42247 (29.40)
	3	202305 (14.84)	179822 (14.75)	22483 (15.65)
	≥4	91266 (6.70)	78316 (6.42)	12950 (9.01)
Early pregnancy BMI	missing	215553 (15.82)	193213 (15.85)	22340 (15.55)
	<18.5	30845 (2.26)	28596 (2.35)	2249 (1.57)
	18.5-24	746215 (54.75)	678584 (55.66)	67631 (47.06)
	25-29	267211 (19.61)	233514 (19.15)	33697 (23.45)
	30-34	75955 (5.57)	63599 (5.22)	12356 (8.60)
	>35	27171 (1.99)	21743 (1.78)	5428 (3.78)
Smoking	missing	77074 (5.65)	68758 (5.64)	8316 (5.79)
	No smoking	1101565 (80.82)	985515 (80.83)	116050 (80.76)
	1-10 /day	122412 (8.98)	109538 (8.98)	12874 (8.96)
	≥10/ day	61899 (4.54)	55438 (4.55)	6461 (4.50)
Gestational diabetes		9521 (0.70)	7118 (0.58)	2403 (1.67)
Gestational hypertension		12229 (0.90)	8284 (0.68)	3945 (2.75)
Pre-eclampsia		42672 (3.13)	20919 (1.72)	21753 (15.14)
Chorioamnionitis		2867 (0.21)	2188 (0.18)	679 (0.47)
Urogenital infection		151464 (11.11)	133435 (10.94)	18029 (12.55)

High-risk pregnancy	4 307 (0.32)	3132 (0.26)	1175 (0.82)
Premature rupture of membranes	20 723 (1.52)	17472 (1.43)	3 251 (2.26)
Postterm gestation	81 254 (5.96)	47889 (3.93)	33 365 (23.22)
Intrauterine growth restriction	38 929 (2.86)	28628 (2.35)	10301 (7.17)
Multiple gestation	126 660 (9.29)	112571 (9.23)	14089 (9.80)
Female offspring	662 941 (48.64)	597813 (49.03)	65128 (45.32)

Table 2 | Association between labor induction and offspring ASD (complete case)

		Model 1:	**Model 2:**	**Model 3:**	**Model 4:**
		Baseline	**+Stable maternal**	**+ Birth-specific**	**Within siblings**
Sample:	N	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Complete case	1117220	1.32 (1.27, 1.38)	1.31 (1.26, 1.37)	1.19 (1.13, 1.24)	0.99 (0.88, 1.10)
NOTE: HR is hazard ratio, CI is confidence interval					
M1 [Baseline]: adjusting for birth year, parity and maternal age at birth					
M2 [Stable maternal]: adding maternal education and country of origin					
M3 [Birth-specific]: adding smoking and BMI in early pregnancy, gestational diabetes or hypertension, pre-eclampsia, chorioamnionitis, urogenital infection, IUGR, PROM, postterm gestation, multiple gestation, and high-risk pregnancy					
M4 [Within siblings]: adjusting for all factors shared by maternal siblings, and all measured birth-specific covariates					

Table 3 | Sensitivity analysis of association between labor induction and offspring ASD

		Model 1:	Model 2:	Model 3:	Model 4:	Model 5:
		Baseline	+Stable maternal	+Birth-specific	Within siblings	Within cousins
Type of analysis	N	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
1. 1999 – 2005 only	545500	1.35 (1.27, 1.44)	1.34 (1.26, 1.43)	1.21 (1.13, 1.29)	1.07 (0.87, 1.33)	
2. Siblings only	694612	1.32 (1.25, 1.40)	1.31 (1.24, 1.38)	1.20 (1.13, 1.28)	0.99 (0.88, 1.10)	
3. Complete case	1117220	1.32 (1.27, 1.38)	1.31(1.26, 1.37)	1.19 (1.13, 1.24)	0.99 (0.88, 1.10)	1.08 (0.98, 1.19)
4. First-born only	466805	1.26 (1.19, 1.34)	1.26 (1.18, 1.34)	1.12 (1.04, 1.20)	-	1.02 (0.83, 1.26)
5. Excl. Cesarean	959303	1.36 (1.30, 1.43)	1.35 (1.29, 1.42)	1.24 (1.17, 1.30)	0.98 (0.86, 1.12)	-
6. Incl. missing BMI	1280928	1.32 (1.27, 1.37)	1.31 (1.26, 1.36)	1.21 (1.15, 1.26)	1.02 (0.93, 1.13)	
NOTE: HR is hazard ratio; CI is confidence interval; Models 1-4 are the same as in Table 2						
M5 [Within cousins]: adjusting for all factors shared by maternal first cousins, and all measured birth-specific covariates						
Row 1: Restriction to the later born cohort, for which follow-up began when offspring were 0 - 4 years of age						
Row 2: Restriction to the sample of individuals with at least one sibling to the same mother also in the cohort						
Row 3: Original complete case analysis (from Table 2) adding Model 5 to compare the offspring of sisters (maternal first cousins)						
Row 4: Restriction to all first born individuals (hence not possible to compare siblings)						
Row 5: Excluding all elective Cesareans, comparing induction to when labor began spontaneously						
Row 6: Complete case analysis without adjusting for BMI (so that only 6% of study base is excluded due to missing data)						