Labor epidural analgesia and subsequent risk of offspring autism spectrum disorder and attention-deficit/hyperactivity disorder: A cross-national cohort study of 4.5 million individuals and their siblings

Tor-Arne Hegvik, MD, PhD, Kari Klungsøyr, MD, PhD, Ralf Kuja-halkola, PhD, Hanna Remes, PhD, Jan Haavik, MD, PhD, Brian M. D'onofrio, PhD, Niina Metsä-simola, PhD, Anders Engeland, PhD, Seena Fazel, MD, Paul Lichtenstein, PhD, Pekka Martikainen, PhD, Henrik Larsson, PhD, Amir Sariaslan, PhD

PII: S0002-9378(22)00650-0

DOI: https://doi.org/10.1016/j.ajog.2022.08.016

Reference: YMOB 14680

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 4 May 2022

Revised Date: 31 July 2022

Accepted Date: 1 August 2022

Please cite this article as: Hegvik T-A, Klungsøyr K, Kuja-halkola R, Remes H, Haavik J, D'onofrio BM, Metsä-simola N, Engeland A, Fazel S, Lichtenstein P, Martikainen P, Larsson H, Sariaslan A, Labor epidural analgesia and subsequent risk of offspring autism spectrum disorder and attention-deficit/hyperactivity disorder: A cross-national cohort study of 4.5 million individuals and their siblings, *American Journal of Obstetrics and Gynecology* (2022), doi: https://doi.org/10.1016/j.ajog.2022.08.016.

Manuscript word count: 3443
Tables and figures: 5 (3 tables and 2 figures)
References: 61
Abstract: 331
AJOG at a glance: 228

Labor epidural analgesia and subsequent risk of offspring autism spectrum disorder and attention-deficit/hyperactivity disorder: A cross-national cohort study of 4.5 million individuals and their siblings

Tor-Arne HEGVIK[1,2], MD, PhD; Kari KLUNGSØYR[3,4], MD, PhD; Ralf KUJA-HALKOLA[5], PhD; Hanna REMES[6], PhD; Jan HAAVIK[2,7], MD, PhD; Brian M. D'ONOFRIO[8], PhD; Niina METSÄ-SIMOLA[6], PhD; Anders ENGELAND[3,4], PhD; Seena FAZEL[9], MD; Paul LICHTENSTEIN[5], PhD; Pekka MARTIKAINEN[6,10,11], PhD; Henrik LARSSON[5,12], PhD; Amir SARIASLAN[9], PhD

[1] Department of Biomedicine, University of Bergen, Bergen, Norway
[2] Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
[3] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[4] Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway
[5] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[6] Population Research Unit, Faculty of Social Sciences, University of Helsinki, Helsinki, Finland
[7] Bergen Center for Brain Plasticity, Division of Psychiatry, Haukeland University Hospital, Bergen, Norway
[8] Department of Psychological and Brain Sciences, Indiana University, Bloomington, United States
[9] Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, United Kingdom
[10] Centre for Health Equity Studies (CHESS), Stockholm University and Karolinska Institutet, Stockholm, Sweden
[11] Max Planck Institute for Demographic Research, Rostock, Germany
[12] School of Medical Sciences, Örebro University, Örebro, Sweden

All correspondence should be sent to: Dr Amir Sariaslan, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, United Kingdom. E-mail: amir.sariaslan@psych.ox.ac.uk.

Acknowledgements
The study was supported by the Academy of Finland (#308247, #294861), University of Bergen, NevSom – Oslo University Hospital, the Swedish Initiative for Research on Microdata in the Social And Medical Sciences (SIMSAM) framework (#340-2013-5867), the Swedish Research Council (#2014-3831), and the National Institute on Drug Abuse (R01DA048042). AS and SF are supported by the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215-20005). SF is further funded by the Wellcome Trust as part of a Senior Research Fellowship in Clinical Science

(#202836/Z/16/Z). PM has received funding from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement No 101019329), and the NordForsk grant for the project WELLIFE (#83540). JH has been a speaker for Medice, Shire/Takeda and Biocodex. HL reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals and Evolan Pharma AB, all outside the submitted work. The remaining authors declare that they have no conflicts of interest. The funders were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The study was approved by the Ethics Board of Statistics Finland (TK-53-1121-18), the Regional Committees for Medical Research Ethics in Norway (2020/75421) and the Regional Ethical Review Board in Stockholm, Sweden (2013/862-31/5).

Author contributions

Dr Sariaslan and Dr Hegvik had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Sariaslan, Hegvik

Acquisition, analysis, or interpretation of data: Sariaslan, Hegvik, Haavik, Engeland, Klungsøyr, Larsson, Lichtenstein, Martikainen, Kuja-Halkola

Drafting of the manuscript: Sariaslan, Hegvik

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Sariaslan, Hegvik

Obtained funding: Haavik, Klungsøyr, Larsson, Lichtenstein, Martikainen

Administrative, technical, or material support: Sariaslan, Haavik, Engeland, Klungsøyr, Larsson, Lichtenstein, Martikainen

Supervision: Sariaslan

Keywords

Labor epidural analgesia, autism-spectrum disorder, attention-deficit/hyperactivity disorder, family-based designs, causal inference

CONDENSATION PAGE

Condensation: Labor epidural analgesia is not associated with offspring autism spectrum disorder or attention-deficit/hyperactivity disorder after accounting for familial factors

Short title: Labor epidural analgesia and subsequent risk of offspring autism spectrum disorder and attention-deficit/hyperactivity disorder

AJOG at a glance

Why was this study conducted?

One previous study has reported an association between labor epidural analgesia and offspring autism-spectrum disorder (ASD), but the causal nature of this association remains unclear. It is possible that elevated depressive and anxiety symptoms in mothers who choose labor epidural analgesia are genetically associated with the ASD risk of their offspring and, as a result, may confound the association between labor epidural analgesia and offspring ASD risk.

Key findings

In this multi-national cohort study of 4,498,462 children and using unexposed siblings as controls to account for shared familial risks (e.g., genetic differences and early-life environments) in addition to measured individual-level confounders, there were no associations between labor epidural analgesia during delivery and offspring ASD or attention-deficit/hyperactivity disorder (ADHD).

What does this add to what is known?

In the largest study of its kind, using total population data derived from three different countries, we did not find support for the hypothesis that exposure to labor epidural analgesia causes an increased risk of either offspring ASD or ADHD. In contrast to previous replication efforts, the current study was able to explicitly account for shared familial risks whilst being sufficiently large to estimate the associations with a high degree of precision. As the decision to use epidural analgesia in labor is unlikely to cause offspring neurodevelopmental disorders, there is no need to revise current clinical guidelines.

Abstract

Background

A recent study has suggested that labor epidural analgesia may be associated with increased rates of offspring autism spectrum disorder (ASD). Subsequent replication attempts have lacked sufficient power to confidently exclude the possibility of a small effect and the causal nature of this association remains unknown.

Objective

To investigate the extent to which exposure to labor epidural analgesia is associated with offspring ASD and attention-deficit/hyperactivity disorder (ADHD) following adjustments for unmeasured familial confounding.

Study design

We identified 4,498,462 singletons and their parents using the Medical Birth Registers in Finland (cohorts born 1987-2005), Norway (1999-2015), and Sweden (1987-2011), linked with population and patient registries. These cohorts were followed from birth until they either had the outcomes of interest, emigrated, died, or reached the end of the follow-up (at mean ages 13.6-16.8 years), whichever occurred first. Cox regression models were used to estimate country-specific associations between labor epidural analgesia recorded at birth and outcomes (e.g., at least one secondary care diagnosis of ASD and ADHD or at least one dispensed prescription of medication used for the treatment of ADHD). The models were adjusted for sex, birth year, birth order, and unmeasured familial confounders via sibling-comparisons. Pooled estimates across all three countries were estimated using inverse variance weighted fixed-effects meta-analysis models.

Results

A total of 4,498,462 individuals (48.7% female) were included, 1,091,846 (24.3%) of which were exposed to labor epidural analgesia. Of these, 1.2% were diagnosed with ASD and 4.0% with ADHD. On the population level, pooled estimates showed that labor epidural analgesia was associated with increased risk of offspring ASD (adjusted hazard ratio, aHR=1.12; 95% CI: 1.10-1.14, absolute risks: 1.20% vs. 1.07%) and ADHD (aHR=1.20; 1.19-1.21; 3.95% vs. 3.32%). However, when comparing full-siblings who were differentially exposed to labor epidural analgesia, the associations were fully attenuated for both conditions, with narrow confidence intervals (aHR_{ASD}=0.98; 0.93-1.03; aHR_{ADHD}=0.99; 0.96-1.02).

Conclusion

In this large cross-national study, we found no support for the hypothesis that exposure to labor epidural analgesia causes either offspring ASD or ADHD.

Introduction

Labor epidural analgesia is commonly used worldwide to provide pain relief to women in labor, as it is effective and considered safe.[1–4] The most common side effects for mothers are typically temporary and relatively mild (e.g., urinary retention and maternal fever),[1,2] whilst more serious side effects (e.g., epidural hematoma and deep infections) remain extremely rare.[5,6] However, few studies have examined long-term outcomes in offspring exposed to labor epidural analgesia.[2] A recent cohort study[7] of nearly 148,000 children in the US reported that labor epidural analgesia may be associated with up to 37% increased risk of offspring autism spectrum disorder (ASD). Criticism of the study, including from several medical societies,[8–10] have raised concerns about the methodological limitations of the study, the lack of biological plausibility of the proposed association, and the possible clinical implications that an implied causal inference might have.[11–13]

A key limitation of this and other observational studies is that unmeasured genetic confounders that may simultaneously increase the likelihood of the exposure (i.e., labor epidural analgesia) as well as the outcome (i.e., offspring ASD) have not been adequately accounted for. This is important for two reasons. First, it has been demonstrated that women who elect to give birth using labor epidural analgesia tend to have elevated anxiety and depressive symptoms,[14,15] which are moderately heritable traits.[16,17] Second, twin and family-based pedigree studies have consistently found that genetic influences account for approximately 80% of the individual risk differences in ASD,[18–20] which partly overlap with those explaining individual differences in anxiety and depressive symptoms.[21–23] It has therefore been recommended that investigations of possible pre- and perinatal risk factors for neurodevelopmental disorders should adopt family-based research designs to account for unmeasured familial confounding (e.g., genetic and early-life environmental risks shared within families).[24]

To our knowledge, there are currently four published replication attempts of the original study,[7] which have used population-based data from Canada[25,26] and Denmark,[27,28] in combination with the genetically informative 'within-mother' design, where risks of offspring ASD were compared between maternal siblings who were differentially exposed to labor epidural analgesia.[29] This approach allowed the researchers to account for a portion of the genetic differences shared between siblings.[30] Although these studies have consistently demonstrated that population-wide associations between labor epidural analgesia and offspring ASD (odds/hazard ratio range: 1.05-1.32), were fully attenuated in the adjusted within-mother models, they have lacked sufficient statistical power to confidently exclude the possibility of a small and potentially causal association.

To address these limitations in previous research and to assess the long-term safety of labor epidural analgesia in relation to ASD risk, we used nationwide register data from three Nordic countries (Finland, Norway, and Sweden) to examine the associations between labor epidural analgesia on subsequent risk of offspring ASD across 4.5 million singletons. On the basis of the previous replication studies,[25–28] we hypothesized that this association would be fully explained by unmeasured familial confounders. We also investigated attention-deficit/hyperactivity disorder (ADHD) as an outcome as it is a more prevalent neurodevelopmental disorder that shares some of its genetic etiology with autism spectrum disorder.[21,31,32] Importantly, to account for unmeasured familial confounders, we combined statistical methods that accounted for measured covariates with a research design that compared outcome rates between biological full siblings who were differentially exposed to labor epidural analgesia. We were able to estimate these associations with greater precision than in previous studies by pooling associations from all three countries and weighting them according to their population sizes using meta-analytic models.

Methods

Study population

We linked several Nordic nationwide population registry data to generate country-specific samples. All residents in Nordic countries are assigned a personal identification number, which is used in respective nationwide registers, and provides accurate linkage.[33] We were granted permission to use pseudonymized data following approvals from the Ethics Board of Statistics Finland (TK-53-1121-18), the Regional Committees for Medical Research Ethics in Norway (2020/75421) and the Regional Ethical Review Board in Stockholm, Sweden (2013/862-31/5). We conducted the data analyses separately on secure servers located in each country. The output, which included the magnitude of the associations and their uncertainties (i.e., standard errors), was then used as input data for a meta-analytical model that estimated the pooled associations across all three countries while accounting for their population size differences. Informed consent is not required for register-based studies in Nordic countries.

We initially identified all singleton children born in Finland 1987-2005 (n=1,125,424), Norway 1999-2015 (n=965,882), and Sweden 1987-2011 (n=2,512,569) using the population-wide Medical Birth Registers in each country,[34] which also provided data on labor epidural analgesia use, offspring gestational age, the mode of delivery, and the maternal age at delivery. The sample thus included a combined total of 4,603,875 children. We then prospectively identified individuals who had ever been diagnosed with ASD and ADHD in the Finnish Care Register for Health Care, which included all inpatient care episodes 1987-2017 and specialist outpatient care visits 1998-2017 according to the ninth and tenth revisions of the International Classification of Diseases (ICD-9 and ICD-10).[35] We similarly identified the same patient groups in the Norwegian Patient Register (inpatient and outpatient care 2008-19, ICD-10),[36] and the Swedish Patient Register (inpatient care: 1987-2013;

outpatient care: 2001-13, ICD-9-and ICD-10).[37] Data on ADHD medications were gathered from the prescribed drug registers in Finland (1995-2018), Norway (2004-19), and Sweden (2005-14).[38] Migration and mortality dates were retrieved from the population registers in Finland and Norway, and the Migration and Causes of Death registers in Sweden. The average age at the end of follow-up was 15.9 years.

We constructed our analytical sample by excluding individuals who could not be linked to both of their biological parents (n=56,846 [1.2%]), had missing data on gestational age at birth (n=14,846 [0.3%]) and their mode of delivery (n=897 [0.02%]). We further removed those who had either migrated (n=21,383 [0.5%]) or died (n=11441 [0.3%]) before reaching their first birthday in Finland and Sweden, and prior to their fifth birthday in Norway (due to the outcome data being available at a later date). Our analytical sample consequently retained 97.7% of the targeted sample (n=4,498,462). For country-specific sample sizes, see eTable 1.

Exposures and outcomes

Labor epidural analgesia was defined as a binary measure derived from the Medical Birth Registries in each country, where midwives attending birth had recorded the type of, if any, analgesia that the mothers had received in labor. There were no data available on the solution types or dosages used.

We defined individuals who had been diagnosed with ASD (ICD-9: 299, ICD-10: F84) on at least one occasion to have ASD and identified the first observed diagnosis date.[19] Similarly, we defined individuals who had received at least one diagnosis of ADHD (ICD-9: 314, ICD-10 F90) or who at least once dispensed a prescription of medications used nearly exclusively in the treatment of ADHD (Anatomical Therapeutic Chemical codes: N06BA01, N0BA02, N06BA04, N06BA09,

N06BA12) to have ADHD, and identified the first observed diagnosis date or date for first prescription. Single-episode diagnoses of ASD and ADHD in the national healthcare registers have been found to have excellent validity (i.e., positive predictive values varying between 88% and 96%) across Finland,[39,40] Norway,[41] and Sweden.[42,43]

Analytical approach

We quantified the crude population-wide associations between labor epidural analgesia and subsequent risks for offspring ASD and ADHD, expressed as adjusted hazard ratios (aHRs), using Cox proportional hazards regression models. The underlying time scale was defined as time from birth to the first of any of the following events: having the outcome of interest, emigration, death, or reaching the end of the follow up (Finland: 31 December 2017 for ASD and 31 December 2018 for ADHD; Norway: 31 December 2019; Sweden: 31 December 2013 for ASD and 31 December 2014 for ADHD). These models were adjusted for sex, birth year (each year as a separate category), and birth order (categorized into 1, 2, 3 and 4+). To further account for time-stable unmeasured familial confounding shared between full-siblings (i.e., their shared early-life environments and an average of half of their co-segregating genes),[30] we fitted analogous stratified Cox regression models, which allowed for the baseline hazards to vary across families, thus implying that the risk comparisons were made within families and between differentially exposed full-siblings.[30,44] To increase the precision of the estimates, we subsequently pooled the country-specific estimates using the inverse variance weighted fixed-effects meta-analytic model, which weighs the estimates from each country by their relative sample size.[45]

In complementary sensitivity analyses, we excluded offspring born by cesarean section; those born prematurely (gestational age <37 weeks); and defined individuals as having ASD or ADHD only if

they had been diagnosed with each condition (or dispensed ADHD medications) at two separate instances. We additionally examined ADHD as outcome using only the patient data. The sibling-comparison design assumes that the siblings are generalizable to the full population, and the absence of any birth order or carry-over effects, namely that the exposure and outcome of a given sibling in a family do not influence the exposures and outcomes of their co-siblings. To test for these assumptions, we initially fitted the population-wide models on a subset of all siblings. We then re-examined the associations in a subset of all first-born cousins in Finland and Sweden who were differentially exposed to labor epidural analgesia (n=155,299).

Results

We examined a total of 4,498,462 individuals born in Finland (n=1,097,266), Norway (n=929,560) and Sweden (n=2,471,636) between 1987 and 2015, of which 1,091,846 (24.3%) were exposed to labor epidural analgesia (**Table 1**). There was considerable variation in the rates of labor epidural analgesia across time, ranging from approximately 10% at the baseline of the study to approximately 35%-40% at the end of the follow-ups, with relatively small between-country differences (**Figure 1**). Crude absolute risks of the outcomes were marginally elevated among individuals who were exposed to labor epidural analgesia when compared to unexposed individuals (ASD: 1.20% vs. 1.07%; ADHD: 3.95% vs. 3.32%; **Table 2**).

After pooling estimates across all three countries, we found that labor epidural analgesia was associated with an approximately 12% increased risk of ASD (adjusted hazard ratio, aHR=1.12; 95% CI: 1.10-1.14) and 20% increased risk of ADHD (aHR=1.20; 1.19-1.21) following adjustments for sex, birth year and birth order (**Figure 2**). To further account for shared, unmeasured familial confounders (e.g., genetic risks and early life environmental factors), we subsequently compared the hazards of the outcomes between 985,444 full siblings who were differentially exposed to labor

epidural analgesia, of which 24,516 had later developed ASD and 68,991 ADHD (**Table 3**). We found that those who had been exposed to labor epidural analgesia were no more likely than their unexposed siblings to be diagnosed with either ASD (aHR=0.98; 0.93-1.03) or ADHD (aHR=0.99; 0.96-1.02; **Figure 2**).

In the complementary sensitivity analyses, we obtained similar estimates as in the main sibling-comparison models when we excluded cesarean deliveries (aHR_{ASD}=1.02; 0.96-1.08; aHR_{ADHD}=1.01; 0.98-1.05) and those born prematurely (aHR_{ASD}=1.00; 0.95-1.06; aHR_{ADHD}=1.01; 0.98-1.04). We further found commensurate results when we used stricter definitions by requiring at least two diagnoses or ADHD medication purchases on separate occasions (aHR_{ASD}=1.01; 0.95-1.07; aHR_{ADHD}=1.00; 0.97-1.03) or by excluding ADHD medication purchases (aHR_{ADHD}=0.98; 0.94-1.02). To test for the generalizability of the sibling-comparison estimates, we initially ran the population-wide models in the sibling subsets and found similar results (aHR_{ASD}=1.12; 1.09-1.15; aHR_{ADHD}=1.20; 1.18-1.22). We subsequently tested for the potential impact of carry-over effects by examining within-extended family associations using first-born cousins who were differentially exposed to labor epidural analgesia. The within-extended family association between labor epidural analgesia and ASD was completely attenuated (aHR=1.02; 0.92-1.12), and the equivalent association with ADHD was attenuated by 35% (aHR=1.13; 1.06-1.20).

Comment

Principal findings

In our cohort study of 4.5 million singleton births in Finland, Norway, and Sweden, including over 985,000 siblings who were differentially exposed to labor epidural analgesia, we did not find support

for the hypothesis that labor epidural analgesia causes subsequent increased risks of offspring ASD or ADHD.

Results in context

First, in our initial population-wide analyses, we found that labor epidural analgesia was associated with 12 percent increased risk of developing ASD and 20 percent increased risk of developing ADHD. These results are broadly consistent with earlier reports focusing on the population-wide association between labor epidural analgesia and offspring ASD in Denmark,[27,28] Canada,[25,26] and the US,[7] although the magnitude of the reported estimates have varied widely across studies (odds/hazard ratio range: 1.05-1.37). Whilst these variations could arise from country and temporal factors, they could be attributed to different methods (e.g., using administrative register data vs. private health insurance data, matching procedures, and statistical model selection).

Second, we found that the associations between labor epidural analgesia and offspring risks of ASD and ADHD were entirely attenuated once we accounted for unmeasured familial confounders (i.e., genetic and early-life environmental influences) shared between biological full siblings who were differentially exposed to labor epidural analgesia. Inconsistent with a causal interpretation, we found that the siblings who were exposed to labor epidural analgesia were no more likely than their unexposed co-siblings to develop either ASD or ADHD. These findings could not be attributed to limited within-family variation in either the exposure or the outcomes, the inclusion of cesarean deliveries and those born pre-term, or stricter outcome definitions.

These findings are in keeping with recent population-based Canadian[25,26] and Danish[27,28] studies that used a within-mother design to examine the association between labor epidural analgesia and ASD

whilst accounting for unmeasured familial confounding. The earlier work had primarily stratified their models across clusters of mothers, instead of both biological parents, which implies that their sibling-comparisons included a combination of both full siblings and maternal half-siblings. Such an approach boosts the statistical power by increasing the number of differentially exposed siblings, but this comes with the limitation of lower internal validity (i.e., poorer adjustments for unmeasured genetic confounding as maternal half-siblings share, on average, a quarter of their co-segregating genes). Although this earlier work did not find that siblings who were exposed to epidural analgesia during labor were more likely than their unexposed siblings to develop ASD, estimates lacked statistical power, which resulted in wide confidence intervals. These previous studies could therefore not exclude the possibility of a moderately sized association, given that upper bounds of the confidence intervals were consistent with a risk increase ranging between 21%[25] and 31%.[26]

Our third main finding is that our pooled sibling-comparison estimate of the same labor epidural analgesia-ASD association, which was based on a nearly three-fold larger population sample than the previous studies combined, enabled us to exclude the possibility of non-precise estimation because the upper bound of its confidence interval was consistent with a negligible maximum risk increase of 2%. Our study therefore adds to the accumulated evidence that does not support a causal interpretation of the associations between labor epidural analgesia with offspring neurodevelopmental disorders. Moreover, our findings are consistent with the literature reporting that a broader set of pre- and perinatal risk markers (e.g., cesarean section deliveries,[46] labor induction,[47,48] maternal infections,[49] and smoking during pregnancy[50–52]) are not associated with offspring neurodevelopmental disorders once unmeasured familial confounders have been adequately accounted for.

Clinical implications

Our findings suggest that current clinical guidelines[53–55] do not need to revise their recommendation to informing and complying with the requests of pregnant women for labor epidural analgesia, as we have demonstrated that the risks of offspring developing ASD or ADHD as a result of such exposure are, if anything, negligible and not clinically significant.

Research implications

Our findings further demonstrate that, while sibling comparison designs are effective at accounting for unmeasured familial confounding, they frequently require very large sample sizes to be sufficiently powered to be informative about null results. The latter is because the design is driven by the number of siblings who are differentially exposed to the risk factor of interest and who have different outcomes than their co-siblings.[30] As a result, if either the risk factor or the outcomes are uncommon in a given study, the sibling comparisons will be based on much smaller sample sizes. In the present study, we had three population samples totaling 4.5 million individuals, but our effective sibling sample sizes (i.e., siblings who were differentially exposed to labor epidural analgesia and the neurodevelopmental outcomes) were less than 2% of that (n_{ASD}=24,516; n_{ADHD}=68,991). We have shown that it is possible for studies in reproductive epidemiology to harmonize data across different population registers into a common pipeline and pool the associations using meta-analytical techniques to improve on the statistical power of the analyses and thereby increase the precision of the estimates. International collaborations of this nature may therefore be necessary in the future to address etiological research questions with significant clinical implications that require very large sample sizes.

Strengths and limitations

Our study had several important strengths. The combination of nationwide registry data from three Nordic countries, all with universal and accessible high-quality healthcare, enabled us to study 4.5 million individuals whilst keeping selection biases to a minimum. We were able to test for the associations between labor epidural analgesia and externally validated diagnoses of ASD in the offspring. Additionally, we considered offspring ADHD as an outcome due to its clinical significance, common etiology with ASD, and higher prevalence.[31,32]. The inclusion of both conditions contributed to an improvement of the generalizability of our findings. Importantly, we adopted the sibling-comparison design to account for unmeasured familial confounding between biological full-siblings who share their early-life environmental influences and an average of half of their co-segregating genes. The consistency of the risk estimates between the three countries further added to the generalizability of our findings.

Our study had some important limitations. First, we did not have access to outpatient care and prescription drug data across the entire follow-up period for the older cohorts. Additionally, we did not have access to inpatient care data in Norway prior to 2008. We may have consequently overestimated the age at which the conditions were first identified in the older cohorts. However, despite these differences in data availability, the findings remained similar across all three countries, and in the case of ADHD, we also found commensurate results when we excluded medication data. Second, the sibling-comparison design requires very large sample sizes and assumes that the siblings are generalizable to the general population and that no birth order or sibling carry-over effects exist (e.g., exposure of labor epidural analgesia in older siblings affecting the exposure and outcome in their younger co-siblings).[56] We rigorously tested for these assumptions in complementary sensitivity analyses and did not find any evidence that they were violated. Third, while the sibling-comparison design is an effective method for accounting for time-stable unmeasured familial confounders that

are shared between siblings, it requires that non-shared confounders are included as measured covariates in the statistical models.[30] In the present study, we adjusted for a subset of potential non-shared confounders (i.e., gender, birth year, and birth order), but not all. For instance, as a result of being born in different years, some of the siblings were exposed to different early-life environmental risks compared to their co-siblings, including relative family income poverty[57,58] and residing in socioeconomically deprived neighborhoods.[59] Parental separation may have further caused some of the siblings to grow up in different households. However, the inclusion of the latter non-shared confounders would unlikely have altered our findings as the sibling-comparison models yielded null results, indicating that there were no residual associations left to be explained by the adjustment for additional confounders. Fourth, we were unable to assess any potential dose-response effects as we did not have access to data on the duration of labor epidural analgesia exposure. Although this remains an empirical question that could be addressed in future studies, a recent nationwide Danish study[28] was not able to replicate the dose-response pattern of associations that had been previously reported.[7]

In relation to generalizability, our estimated prevalence rates of ASD[60] and ADHD[61] were similar to rates in other high-income countries. Labor epidural analgesia use increased considerably throughout the follow-up period across the all three countries that we examined with relatively small between country-differences, suggesting that the findings are generalizable across the Nordic countries. Given that our findings were consistent with within-mother associations in Canada,[25,26] where the rates of labor epidural analgesia use have been consistently high throughout the same time period, suggests that our findings may also be generalizable to other high-income countries.

Conclusions

In the largest study to date examining the associations between labor epidural analgesia and subsequent risks of offspring ASD and ADHD, we found that the associations were entirely attenuated once we accounted for unmeasured familial confounders shared between exposure-discordant full-siblings. In contrast to previous sibling-comparison studies examining these associations, we had sufficient statistical power to confidently exclude the possibility of a larger than negligible association. We conclude that it is unlikely that labor epidural analgesia causes an increased risk of either offspring ASD or ADHD. Pregnant women have therefore no reason to fear that their decision to use epidural analgesia during labor will have any meaningful impact on their offspring's risk of developing neurodevelopmental disorders, such as ASD or ADHD.

References

1. Anim-Somuah M, Smyth RMD, Cyna AM, Cuthbert A. Epidural versus non-epidural or no analgesia for pain management in labour. *Cochrane Database Syst Rev*. 2018;2018(5).
2. Lim G, Facco FL, Nathan N, Waters JH, Wong CA, Eltzschig HK. A review of the impact of obstetric anesthesia on maternal and neonatal outcomes. *Anesthesiology*. 2018;129(1):192-215.
3. Hillyard SG, Bate TE, Corcoran TB, Paech MJ, O'Sullivan G. Extending epidural analgesia for emergency Caesarean section: a meta-analysis. *Br J Anaesth*. 2011;107(5):668-678.
4. Seijmonsbergen-Schermers AE, van den Akker T, Rydahl E, et al. Variations in use of childbirth interventions in 13 high-income countries: A multinational cross-sectional study. Stock SJ, ed. *PLoS Med*. 2020;17(5):e1003103.
5. Ruppen W, Derry S, McQuay H, Moore RA. Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. *Anesthesiology*. 2006;105(2):394-399.
6. Pitkänen MT, Aromaa U, Cozanitis DA, Förster JG. Serious complications associated with spinal and epidural anaesthesia in Finland from 2000 to 2009. *Acta Anaesthesiol Scand*. 2013;57(5):553-564.
7. Qiu C, Lin JC, Shi JM, et al. Association Between Epidural Analgesia During Labor and Risk of Autism Spectrum Disorders in Offspring. *JAMA Pediatr*. 2020;174(12):1168.
8. American Society of Anesthesiologists. Labor Epidurals Do Not Cause Autism; Safe for Mothers and Infants, Say Anesthesiology, Obstetrics, and Pediatric Medical Societies. Published online 2020. Accessed March 17, 2021. https://www.asahq.org/about-asa/newsroom/news-releases/2020/10/labor-epidurals-and-auti sm-joint-statement.
9. McKeen DM, Zaphiratos V. Lack of evidence that epidural pain relief during labour causes autism spectrum disorder: a position statement of the Canadian Anesthesiologists' Society. *Can J Anesth*. 2021;68(2):180-182.
10. Royal College of Anaesthetists. No evidence that labour epidurals cause autism. Published online 2020. Accessed March 17, 2021. https://rcoa.ac.uk/news/no-evidence-labour-epidurals-cause-autism
11. Kern-Goldberger AR, Burris HH, Levine LD. Methodologic Concerns With Concluding a Link Between Epidural and Autism Spectrum Disorder. *JAMA Pediatr*. Published online 2021. doi:10.1001/jamapediatrics.2020.6692
12. Lee A, Guglielminotti J, Landau R. Methodologic Concerns With Concluding a Link Between Epidural and Autism Spectrum Disorder. *JAMA Pediatr*. Published online 2021. doi:10.1001/jamapediatrics.2020.6686
13. Carrier FM, Lavoie A, Zaphiratos V. Epidural analgesia during labour and autism risk: getting lost on the causal path. *Can J Anesth*. 2021;68(3):277-284.
14. Alder J, Fink N, Bitzer J, Hösli I, Holzgreve W. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. *J Matern Fetal Neonatal Med*. 2007;20(3):189-209.
15. Smorti M, Ponti L, Tani F. The effect of maternal depression and anxiety on labour and the well-being of the newborn. *J Obstet Gynaecol*. 2019;39(4):492-497.
16. Meier SM, Deckert J. Genetics of Anxiety Disorders. *Curr Psychiatry Rep*. 2019;21(3):16.

17. McIntosh AM, Sullivan PF, Lewis CM. Uncovering the Genetic Architecture of Major Depression. *Neuron*. 2019;102(1):91-103.
18. Lichtenstein P, Carlström E, Råstam M, Gillberg C, Anckarsäter H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiatry*. 2010;167(11):1357-1363.
19. Sandin S, Lichtenstein P, Kuja-Halkola R, Hultman C, Larsson H, Reichenberg A. The heritability of autism spectrum disorder. *JAMA*. 2017;318(12):1182-1184.
20. Bai D, Yip BHK, Windham GC, et al. Association of Genetic and Environmental Factors with Autism in a 5-Country Cohort. *JAMA Psychiatry*. 2019;76(10):1035-1043.
21. Wang K, Gaitsch H, Poon H, Cox NJ, Rzhetsky A. Classification of common human diseases derived from shared genetic and environmental determinants. *Nat Genet*. 2017;49(9):1319-1325.
22. Grove J, Ripke S, Als TD, et al. Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet*. 2019;51(3):431-444.
23. Ghirardi L, Kuja-Halkola R, Butwicka A, et al. Familial and genetic associations between autism spectrum disorder and other neurodevelopmental and psychiatric disorders. *J Child Psychol Psychiatry*. 2021;62(11):1274-1284.
24. D'Onofrio BM, Sjölander A, Lahey BB, Lichtenstein P, Öberg AS. Accounting for Confounding in Observational Studies. *Annu Rev Clin Psychol*. 2020;16:25-48.
25. Wall-Wieler E, Bateman BT, Hanlon-Dearman A, Roos LL, Butwick AJ. Association of Epidural Labor Analgesia With Offspring Risk of Autism Spectrum Disorders. *JAMA Pediatr*. 2021;175(7):698-705.
26. Hanley GE, Bickford C, Ip A, et al. Association of Epidural Analgesia During Labor and Delivery With Autism Spectrum Disorder in Offspring. *JAMA*. 2021;326(12):1178-1185.
27. Mikkelsen AP, Greiber IK, Scheller NM, Lidegaard Ø. Association of Labor Epidural Analgesia With Autism Spectrum Disorder in Children. *JAMA*. 2021;326(12):1170-1177.
28. Ren T, Zhang J, Yu Y, et al. Association of labour epidural analgesia with neurodevelopmental disorders in offspring: a Danish population-based cohort study. *Br J Anaesth*. Published online December 7, 2021. doi:10.1016/j.bja.2021.10.042
29. Hammad IA, Meeks H, Fraser A, et al. Risks of cause-specific mortality in offspring of pregnancies complicated by hypertensive disease of pregnancy. *Am J Obstet Gynecol*. 2020;222(1):75.e1-75.e9.
30. Sjölander A, Frisell T, Öberg S. Sibling Comparison Studies. *Annu Rev Stat Its Appl*. 9(1):2022. doi:10.1146/annurev-statistics-040120-024521
31. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Primer*. 2015;1.
32. Ghirardi L, Brikell I, Kuja-Halkola R, et al. The familial co-aggregation of ASD and ADHD: A register-based cohort study. *Mol Psychiatry*. 2018;23(2):257-262.
33. Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: Possibilities and pitfalls when combining Nordic registry data. *Scand J Public Health*. 2017;45(17_suppl):14-19.
34. Langhoff-Roos J, Krebs L, Klungsøyr K, et al. The Nordic medical birth registers – a potential goldmine for clinical research. *Acta Obstet Gynecol Scand*. 2014;93(2):132-137.
35. Finnish Institute for Health and Welfare. Trends in access to specialised health

care. Published online 2015. Accessed February 13, 2021. https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/quality-descriptions/trends-in-access-tospecialised-%0Dhealth-care

36. Bakken IJ, Ariansen AMS, Knudsen GP, Johansen KI, Vollset SE. The Norwegian Patient Registry and the Norwegian Registry for Primary Health Care: Research potential of two nationwide health-care registries. *Scand J Public Health*. 2020;48(1):49-55.

37. Ludvigsson J, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11(1):450.

38. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol*. 2010;106(2):86-94.

39. Lampi K, Sourander A, Gissler M, et al. Brief report: validity of Finnish registry-based diagnoses of autism with the ADI-R. *Acta Paediatr*. 2010;99(9):1425-1428.

40. Joelsson P, Chudal R, Gyllenberg D, et al. Demographic Characteristics and Psychiatric Comorbidity of Children and Adolescents Diagnosed with ADHD in Specialized Healthcare. *Child Psychiatry Hum Dev*. 2016;47(4):574-582.

41. Surén P, Havdahl A, Øyen AS, et al. Diagnostisering av autismespekterforstyrrelser hos barn i Norge [Diagnosing autism spectrum disorder among children in Norway]. *Tidsskr Nor Laegeforen*. 2019;139(14).

42. Idring S, Rai D, Dal H, et al. Autism spectrum disorders in the Stockholm youth cohort: Design, prevalence and validity. *PLoS One*. 2012;7(7).

43. Larsson H, Rydén E, Boman M, Långström N, Lichtenstein P, Landén M. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. *Br J Psychiatry*. 2013;203(2):103-106.

44. Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Diseases in children born to mothers with preeclampsia: a population-based sibling cohort study. *Am J Obstet Gynecol*. 2011;204(2):157.e1-157.e5.

45. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw*. 2010;36:1-48. doi:10.18637/jss.v036.i03

46. Zhang T, Brander G, Mantel Ä, et al. Assessment of Cesarean Delivery and Neurodevelopmental and Psychiatric Disorders in the Children of a Population-Based Swedish Birth Cohort. *JAMA Netw Open*. 2021;4(3):e210837.

47. Oberg AS, D'Onofrio BM, Rickert ME, et al. Association of Labor Induction With Offspring Risk of Autism Spectrum Disorders. *JAMA Pediatr*. 2016;170(9):e160965.

48. Wiggs KK, Rickert ME, Hernandez-Diaz S, et al. A Family-Based Study of the Association Between Labor Induction and Offspring Attention-Deficit Hyperactivity Disorder and Low Academic Achievement. *Behav Genet*. 2017;47(4):383-393.

49. Ginsberg Y, D'Onofrio BM, Rickert ME, et al. Maternal infection requiring hospitalization during pregnancy and attention-deficit hyperactivity disorder in offspring: a quasi-experimental family-based study. *J Child Psychol Psychiatry*. 2019;60(2):160-168.

50. Skoglund C, Chen Q, D'Onofrio BM, Lichtenstein P, Larsson H. Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. *J Child Psychol Psychiatry*. 2014;55(1):61-68.

51. Kalkbrenner AE, Meier SM, Madley-Dowd P, et al. Familial confounding of the association between maternal smoking in pregnancy and autism spectrum disorder in offspring. *Autism Res*. 2020;13(1):134-144.

602 52. Arrhenius B, Sariaslan A, Suominen A, Sourander A, Gyllenberg D. Familial
603 confounding affected the associations between maternal smoking during pregnancy and offspring
604 speech and language, scholastic and coordination disorders. *Acta Paediatr*. 2021;110(12):3275-
605 3283.
606 53. American College of Obstetricians and Gynecologists' Committee on Practice
607 Bulletins—Obstetrics. ACOG Practice Bulletin No. 209: Obstetric Analgesia and Anesthesia.
608 *Obstet Gynecol*. 2019;133(3):e208-e225.
609 54. Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American
610 Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric
611 Anesthesia and Perinatology. *Anesthesiology*. 2016;124(2):270-300.
612 55. National Institute for Health and Care Excellence (NICE). *2019 Surveillance of*
613 *Intrapartum Care for Healthy Women and Babies (NICE Guideline CG190)*. National Institute
614 for Health and Care Excellence (NICE); 2019.
615 56. D'Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. Critical need for family-
616 based, quasi-experimental designs in integrating genetic and social science research. *Am J Public*
617 *Health*. 2013;103 Suppl(Suppl 1):S46-55.
618 57. Larsson H, Sariaslan A, Långström N, D'Onofrio B, Lichtenstein P. Family income
619 in early childhood and subsequent attention deficit/hyperactivity disorder: A quasi-experimental
620 study. *J Child Psychol Psychiatry*. 2013;55:428-435.
621 58. Sariaslan A, Mikkonen J, Hiilamo H, Aaltonen M, Martikainen P, Fazel S. No
622 causal associations between childhood family income and subsequent psychiatric disorders,
623 substance misuse and violent crime arrests: a nationwide Finnish study of >650 000 individuals
624 and their siblings. *Int J Epidemiol*. 2021;50(5):1628-1638.
625 59. Sariaslan A, Larsson H, D'Onofrio B, Långström N, Fazel S, Lichtenstein P. Does
626 population density and neighborhood deprivation predict schizophrenia? A nationwide Swedish
627 family-based study of 2.4 million individuals. *Schizophr Bull*. 2015;41(2):494-502.
628 60. Anorson N, Male I, Farr W, Memon A. Prevalence of autism in Europe, North
629 America and Oceania, 2000-2020: A systematic review. *Eur J Public Health*.
630 2021;31(Supplement_3):ckab164.786.
631 61. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual Research
632 Review: A meta-analysis of the worldwide prevalence of mental disorders in children and
633 adolescents. *J Child Psychol Psychiatry*. 2015;56(3):345-365.
634
635

Table 1. Baseline demographic characteristics

Figure 1. Proportion of births with labor epidural analgesia in Finland, Norway, and Sweden between 1987 and 2015

Table 2. Person-time at risk, number of patients, prevalence rates and incident rates per 1000 person-years for autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD), stratified across individuals exposed to labor epidural analgesia (LEA)

Figure 2. Population-wide and within-family (e.g., sibling-comparison) associations between labor epidural analgesia and later risks of offspring autism-spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in Finland, Norway, Sweden, and their pooled estimates

Notes: All models were adjusted for sex, birth year and birth order. The sibling-comparison models further accounted for unmeasured familial confounders shared between full siblings.

Table 3. The number of siblings who were differentially exposed to labor epidural analgesia, had different outcomes or were both differentially exposed and had different outcomes

Notes: ASD refers to autism-spectrum disorder and ADHD to attention-deficit/hyperactivity disorder.

eTable 1. Inclusion criteria for the nationwide samples

	Finland	Norway	Sweden	Pooled	Excluded
All individuals in the targeted cohorts	1,125,424	965,882	2,512,569	4,603,875	-
Could be linked to both biological parents	1,112,142	947,128	2,487,759	4,547,029	56,846
Not missing data on gestational age at birth	1,104,992	941,993	2,485,198	4,532,183	14,846
Not missing data on cesarean delivery	1,104,095	941,993	2,485,198	4,531,286	897
Did not migrate before age 1y or 5y*	1,099,580	931,408	2,478,915	4,509,903	21,383
Did not die before age 1y or 5y*	1,097,266	929,560	2,471,636	4,498,462	11,441

* The prescription drugs register started in 2004 in Norway when the oldest cohort were 5 years of age. The Norwegian National Patient Register had a later start in 2008. We therefore excluded all children who were right-censored before reaching the age of 5 years in the Norwegian sample.

Table 1. Baseline demographic characteristics

	Finland (n=1,097,266)		Norway (n=929,560)		Sweden (n=2,471,636)		Pooled (n=4,498,462)	
	Unexposed to LEAs	**Exposed to LEAs**	**Unexposed to LEAs**	**Exposed to LEAs**	**Unexposed to LEAs**	**Exposed to LEAs**	**Unexposed to LEAs**	**Exposed to LEAs**
Total	829,526 (76.6%)	267,740 (24.4%)	670,362 (72.1%)	259,198 (27.9%)	1,906,728 (77.1%)	564,908 (22.9%)	3,406,616 (75.7%)	1,091,846 (24.3%)
Sex								
Female	407,420 (49.1%)	128,938 (48.2%)	329,084 (49.1%)	123,247 (47.5%)	934,371 (49.0%)	267,530 (47.4%)	1,670,875 (49.0%)	519,715 (47.6%)
Male	422,106 (50.9%)	138,802 (51.8%)	341,278 (50.9%)	135,951 (52.5%)	972,357 (51.0%)	297,378 (52.6%)	1,735,741 (51.0%)	572,131 (52.4%)
Birth year								
1987-1989	162,751 (19.6%)	14,295 (5.3%)	-	-	274,463 (14.4%)	41,631 (7.4%)	437,214 (12.8%)	55,926 (5.1%)
1990-1994	262,623 (31.7%)	48,744 (18.2%)	-	-	483,557 (25.4%)	82,529 (14.6%)	746,180 (21.9%)	131,273 (12.0%)
1995-1999	206,376 (24.9%)	77,136 (28.8%)	43,057 (6.4%)	12,475 (4.8%)	321,423 (16.9%)	111,164 (19.7%)	570,856 (16.8%)	200,775 (18.4%)
2000-2004	163,917 (19.8%)	106,024 (39.6%)	202,123 (30.2%)	64,575 (24.9%)	326,265 (17.1%)	120,099 (21.3%)	692,305 (20.3%)	290,698 (26.6%)
2005-2009	33,859 (4.1%)	21,541 (8.0%)	200,993 (30.0%)	75,982 (29.4%)	355,373 (18.6%)	143,164 (25.3%)	590,225 (17.3%)	240,687 (22.0%)
2010-2014	-	-	189,376 (28.2%)	87,293 (33.6%)	145,647 (7.6%)	66,321 (11.7%)	335,023 (9.8%)	153,614 (14.1%)
2015	-	-	34,813 (5.2%)	18,873 (7.3%)	-	-	34,813 (1.0%)	18,873 (1.7%)
Birth order								
1st	329,778 (39.8%)	128,311 (47.9%)	221,631 (33.1%)	161,803 (62.4%)	666,705 (35.0%)	392,480 (69.5%)	1,218,114 (35.8%)	682,594 (62.5%)
2nd	279,418 (33.7%)	92,320 (34.5%)	268,228 (40.0%)	68,201 (26.3%)	769,382 (40.4%)	128,147 (22.7%)	1,317,028 (38.7%)	288,668 (26.4%)
3rd	136,290 (16.4%)	33,027 (12.3%)	127,765 (19.1%)	21,578 (8.3%)	326,346 (17.1%)	33,094 (5.9%)	590,401 (17.3%)	87,699 (8.0%)
4th or higher	84,040 (10.1%)	14,082 (5.3%)	52,738 (7.9%)	7616 (2.9%)	144,295 (7.6%)	11,187 (2.0%)	281,073 (8.3%)	32,885 (3.0%)
Mother born abroad								
No	799,363 (96.4%)	254,457 (95.0%)	535,853 (79.9%)	207,405 (80.0%)	1,577,108 (82.7%)	472,723 (83.7%)	2,912,324 (85.5%)	934,585 (85.6%)
Yes	30,163 (3.6%)	13,283 (5.0%)	124,724 (18.6%)	48,855 (18.8%)	329,620 (17.3%)	92,185 (16.3%)	484,507 (14.2%)	154,323 (14.1%)
Missing	-	-	9785 (1.5%)	2938 (1.1%)	-	-	9785 (0.3%)	2938 (0.3%)
Maternal age at delivery (years)								
≤17	1752 (0.2%)	1362 (0.5%)	1999 (0.3%)	1474 (0.6%)	6112 (0.3%)	3580 (0.6%)	9863 (0.3%)	6416 (0.6%)
18-19	10,365 (1.2%)	7136 (2.7%)	9229 (1.4%)	6348 (2.4%)	27,493 (1.4%)	13,986 (2.5%)	47,087 (1.4%)	27,470 (2.5%)

20-24	117,093 (14.1%)	53,392 (19.9%)	87,975 (13.1%)	45,800 (17.7%)	303,664 (15.9%)	112,526 (19.9%)	508,732 (14.9%)	211,718 (19.4%)
25-29	275,765 (33.2%)	94,249 (35.2%)	215,421 (32.1%)	87,862 (33.9%)	641,771 (33.7%)	195,374 (34.6%)	1,132,957 (33.3%)	377,485 (34.6%)
30-34	262,769 (31.7%)	73,961 (27.6%)	229,982 (34.3%)	79,430 (30.6%)	602,510 (31.6%)	163,932 (29.0%)	1,095,261 (32.2%)	317,323 (29.1%)
35-39	128,677 (15.5%)	30,906 (11.5%)	106,436 (15.9%)	32,634 (12.6%)	271,564 (14.2%)	64,291 (11.4%)	506,677 (14.9%)	127,831 (11.7%)
40-44	31,201 (3.8%)	6404 (2.4%)	18,556 (2.8%)	5458 (2.1%)	51,514 (2.7%)	10,854 (1.9%)	101,271 (3.0%)	22,716 (2.1%)
≥45	1904 (0.2%)	330 (0.1%)	764 (0.1%)	192 (0.1%)	2100 (0.1%)	365 (0.1%)	4768 (0.1%)	887 (0.1%)

Table 2. Person-time at risk, number of patients, prevalence rates and incident rates per 1000 person-years for autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD), stratified across individuals exposed to labor epidural analgesia (LEA)

Country	LEAs	Population size	Person-years at risk		Number of patients	Prevalence rate [95% CI]	Incidence rate per 1000 person-years [95% CI]
			Total	Mean (SD)			
Finland							
ASD							
	No	829,526 (75.6%)	18,409,039	22.2 (5.7)	8520	1.03% [1.01%; 1.05%]	0.5 [0.5; 0.5]
	Yes	267,740 (24.4%)	5,017,184	18.7 (5.2)	3743	1.40% [1.35%; 1.44%]	0.7 [0.7; 0.8]
ADHD							
	No	829,526 (75.6%)	1,906,4091	23.0 (6.0)	26,744	3.22% [3.19%; 3.26%]	1.4 [1.4; 1.4]
	Yes	267,740 (24.4%)	5,214,454	19.5 (5.5)	12,344	4.61% [4.53%; 4.69%]	2.4 [2.3; 2.4]
Norway							
ASD							
	No	670,362 (72.1%)	8,130,884	12.1 (4.9)	4331	0.65% [0.63%; 0.67%]	0.5 [0.5; 0.5]
	Yes	259,198 (27.9%)	2,918,292	11.3 (4.9)	1813	0.70% [0.67%; 0.73%]	0.6 [0.6; 0.7]
ADHD							
	No	670,362 (72.1%)	8,045,820	12.0 (4.8)	21,802	3.25% [3.21%; 3.30%]	2.7 [2.7; 2.7]
	Yes	259,198 (27.9%)	2,883,688	11.1 (4.8)	9347	3.61% [3.53%; 3.68%]	3.2 [3.2; 3.3]
Sweden							
ASD							
	No	1,906,728 (77.1%)	28,507,860	15.0 (7.5)	23,751	1.25% [1.23%; 1.26%]	0.8 [0.8; 0.8]
	Yes	564,908 (22.9%)	69,727,41	12.3 (7.0)	7516	1.33% [1.30%; 1.36%]	1.1 [1.1; 1.1]
ADHD							
	No	1,906,728 (77.1%)	30,137,810	15.8 (7.5)	64,720	3.39% [3.37%; 3.42%]	2.1 [2.1; 2.2]
	Yes	564,908 (22.9%)	7,456,083	13.2 (7.0)	21,397	3.79% [3.74%; 3.84%]	2.9 [2.8; 2.9]
Pooled							
ASD							
	No	3,406,616 (75.7%)	55,047,783	16.2 (7.5)	36,602	1.07% [1.06%; 1.09%]	0.7 [0.7; 0.7]
	Yes	1,091,846 (24.3%)	14,908,217	13.6 (6.8)	13,072	1.20% [1.18%; 1.22%]	0.9 [0.9; 0.9]
ADHD							
	No	3,406,616 (75.7%)	57,247,721	16.8 (7.7)	113,266	3.32% [3.31%; 3.34%]	2.0 [2.0; 2.0]
	Yes	1,091,846 (24.3%)	15,554,225	14.2 (6.9)	43,088	3.95% [3.91%; 3.98%]	2.8 [2.7; 2.8]

Table 3. The number of siblings who were differentially exposed to labor epidural analgesia, had different outcomes or were both differentially exposed and had different outcomes

	Number of siblings discordant on:		
	Labor epidural analgesia	**Outcome**	**Both labor epidural analgesia and outcome**
Finland			
ASD	248,132	18,975	6609
ADHD	248,132	54,502	19,521
Norway			
ASD	205,053	8080	2698
ADHD	205,053	35,379	12,424
Sweden			
ASD	532,259	48,167	15,209
ADHD	532,259	116,264	37,046
Pooled			
ASD	985,444	75,222	24,516
ADHD	985,444	206,145	68,991

Notes: ASD refers to autism-spectrum disorder and ADHD to attention-deficit/hyperactivity disorder.