Tartu University Hospital
Anaesthesiology and Intensive Care Clinic

UNIVERSITY OF TARTU
Institute of Clinical Medicine

Autism and epidural analgesia

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Autism spectrum disorder (ASD)

- A heterogeneous neurodevelopmental disorder characterized by
  - deficits in social communication and social interaction
  - the presence of restricted, repetitive behaviors
- Worldwide prevalence 1%. It means 70 mln persons
- Factors associated with ASD
  - Genetics, 50-80%. Inherited variations and *de novo* mutations
  - Enviromental factors
    - Parental age
    - Maternal conditions
    - Toxins
    - Perinatal factors – about 0.3% (asphyxia, breech, pre-eclampsia, cesarean delivery epidural analgesia in labour)

Labor epidural analgeesia (LEA)

- Most powerful analgesia method for labour pain
- Use increases, being up to 75% in some populations
  - Estonia – 25% LEA rate >> 3500 newborns exposed
- Mothers can ask a question about ASD during consent
- Local anaesthetics are neurotoxins at clinical concentrations in animal studies

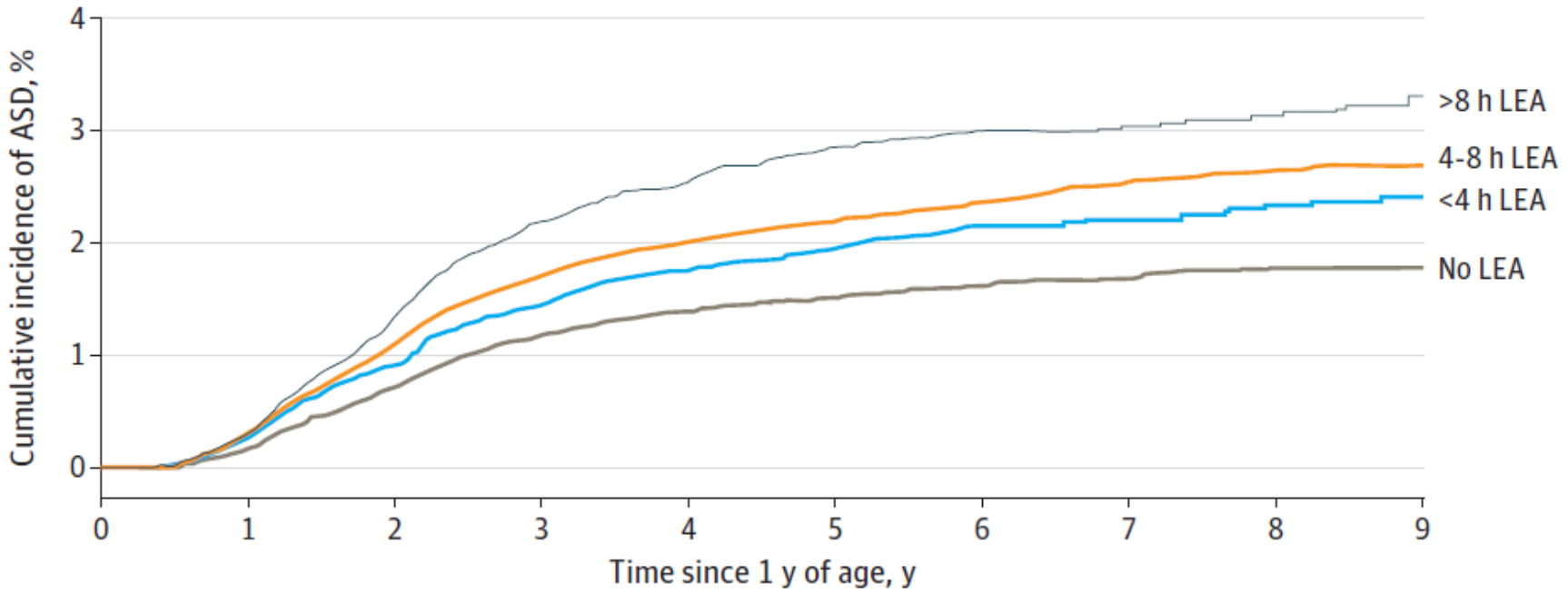
JAMA Pediatrics | Original Investigation 2020 174 (12): 1168-1175

Association Between Epidural Analgesia During Labor and Risk of Autism Spectrum Disorders in Offspring

Chunyuan Qiu, MD, MS; Jane C. Lin, MS; Jiaxiao M. Shi, PhD; Ting Chow, MPH; Vimal N. Desai, MD; Vu T. Nguyen, MD; Robert J. Riewerts, MD; R. Klara Feldman, MD; Scott Segal, MD, MHCM; Anny H. Xiang, PhD

- 2008…2015 KPSC hospitals, VD at 28 – 44 weeks
- 147 895 children, 50.3% boys
- LEA duration
- Mother fever 38°C
- Covariates
  - Social demographic characteristics (age, parity, educational level, race, income)
  - Co-morbidties
  - Obesity
  - DM
  - Preeclampsia
  - Smoking
  - Newborn covariates (gestational age, gender, weight)

Figure 2. Unadjusted Cumulative Incidence of Autism Spectrum Disorder (ASD) by Duration of Labor Epidural Anesthesia (LEA)



No. at risk										
No LEA	38176	34965	31723	25426	20296	16268	12889	9882	6964	4079
<4 h LEA	32433	29658	26841	21315	16715	12883	9472	6578	3984	1645
4-8 h LEA	50248	45628	41260	32259	24746	18676	13487	9087	5411	2233
>8 h LEA	27038	24646	22165	16689	12437	9028	6299	4092	2393	1003

Qiu C et al. JAMA Pediatrics 2020 174 (12): 1168-1175

Table 2. Associations Between Labor Epidural Analgesia Use at Delivery and Risk of ASD in Offspring

Characteristic	No. with ASDs/total No.	Hazard ratio (95% CI)	
		Bivariable[a]	Adjusting for covariates[b]
Labor epidural analgesia			
No	485/38 176	1 [Reference]	1 [Reference]
Yes	2039/109 719	1.48 (1.34-1.65)	1.37 (1.23-1.53)
Duration of labor epidural analgesia			
No labor epidural analgesia	485/38 176	1 [Reference]	1 [Reference]
<4 h	527/32 433	1.28 (1.12-1.46)	1.33 (1.17-1.53)
4-8 h	911/50 248	1.46 (1.29-1.64)	1.35 (1.20-1.53)
>8 h	601/27 038	1.78 (1.57-2.03)	1.46 (1.27-1.69)
Linear trend (per 4 h)[c]	2039/109 719	1.11 (1.07-1.15)	1.05 (1.01-1.09)

Abbreviation: ASD, autism spectrum disorder.

[a] Labor epidural analgesia was analyzed individually where only birth year was adjusted in the model.

[b] Covariates included birth year, maternal age at delivery, parity, race/ethnicity, educational level, household income, history of comorbidity, diabetes during pregnancy, smoking during pregnancy, preeclampsia or eclampsia, prepregnancy body mass index, gestational weight gain, gestational age at delivery, birth weight, and medical center.

[c] Linear trend is defined as the duration of labor epidural analgesia as a continuous variable within the labor epidural analgesia group.

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Association of Epidural Analgesia During Labor and Delivery With Autism Spectrum Disorder in Offspring

Gillian E. Hanley, PhD; Celeste Bickford, BSc; Angie Ip, MD; Nancy Lanphear, MD; Bruce Lanphear, MD, MPH; Whitney Weikum, PhD; Lonnie Zwaigenbaum, MD, MSc; Tim F. Oberlander, MD

- 2000…2014 VD, singleton, term, British Colombia in Canada
- ASD assessment not before 2 y of age
- 388 254 VD
  - LEA exposed 111 480 (28.7%)
  - 6246 siblings with diferent AD status
- Covariates
  - Social demographic characteristics (age, parity, educational level, race, income)
  - Co-morbidties: obesity, DM, smoking, PIH, preeclampsia
  - Labor characteristics (age, duration, augmentation, AB use)
  - Newborn (gestational age, gender, weight, anomalies)

10 new ASD cases per year

Table 2. Association of Epidural Analgesia Use During Labor and Delivery With Risk of Autism Spectrum Disorder (ASD) in Offspring

	Epidural analgesia during labor and delivery, No. (%)		Absolute RD, % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]		
	Exposed	Not exposed			Model 1[b]	Model 2[c]	Model 3[d]
No. of deliveries	111 480	276 774	388 254	388 254	358 709	358 699	358 690
ASD	1710 (1.53)	3482 (1.26)	0.28 (0.19-0.36)	1.32 (1.24-1.40)	1.30 (1.22-1.38)	1.12 (1.05-1.20)	1.09 (1.00-1.15)

Abbreviations: HR, hazard ratio; RD, risk difference.

[a] Missing data for body mass index were imputed using multiple imputation. The missing data for other variables were not imputed and were assumed missing at random.

[b] Adjusted for year of birth, maternal and co-parent age, neighborhood income quintile, and community size.

[c] Adjusted for items in model 1 plus gestational diabetes, preexisting diabetes, pregnancy-induced hypertension, other hypertension, parity, smoking during pregnancy, and body mass index.

[d] Adjusted for items in models 1 and 2 plus induction of labor, gestational age, sex, small or large for gestational age, and congenital anomaly.

Hanley GE et al. JAMA 2021;326(12):1178-1185. doi:10.1001/jama.2021.14986

Table 3. Association of Epidural Analgesia Use During Labor and Delivery With Risk of Autism Spectrum Disorder (ASD) in Unmatched and Matched Sibling Cohorts

	Epidural analgesia during labor and delivery, No. (%)		Absolute RD, % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]		
	Exposed	Not exposed			Model 1[b]	Model 2[c]	Model 3[d]
Unmatched analysis in sibling cohort[e]							
No. of deliveries	59 033	174 449	233 482	233 482	218 132	218 128	218 124
ASD	938 (1.59)	2140 (1.23)	0.36 (0.25-0.48)	1.30 (1.20-1.41)	1.29 (1.18-1.40)	1.12 (1.03-1.22)	1.10 (0.99-1.20)
Matched analysis in sibling cohort[f]							
No. of deliveries	1659	4587	6246	6246	5465	5465	5462
ASD	839 (50.6)	1905 (41.5)	9.04 (6.25-11.84)	1.57 (1.36-1.81)	1.29 (1.10-1.52)	1.05 (0.89-1.24)	1.07 (0.87-1.30)

Abbreviations: HR, hazard ratio; RD, risk difference.

[a] Missing data for body mass index were imputed using multiple imputation. The missing data for other variables were not imputed and were assumed missing at random.

[b] Adjusted for year of birth, maternal and co-parent age, neighborhood income quintile, and community size.

[c] Adjusted for items in model 1 plus gestational diabetes, preexisting diabetes, pregnancy-induced hypertension, other hypertension, parity, smoking during pregnancy, and body mass index.

[d] Adjusted for items in models 1 and 2 plus induction of labor, gestational age, sex, small or large for gestational age, and congenital anomaly.

[e] Logistic regression models were run comparing deliveries among the cohort of deliveries born to mothers with 2 or more deliveries during the study period.

[f] Conditional logistic regression models were run matching a woman to herself and comparing across her deliveries. These models only make use of offspring that were discordant in ASD status born to the same woman. Siblings may have had different biological fathers.

Hanley GE et al. JAMA 2021;326(12):1178-1185. doi:10.1001/jama.2021.14986

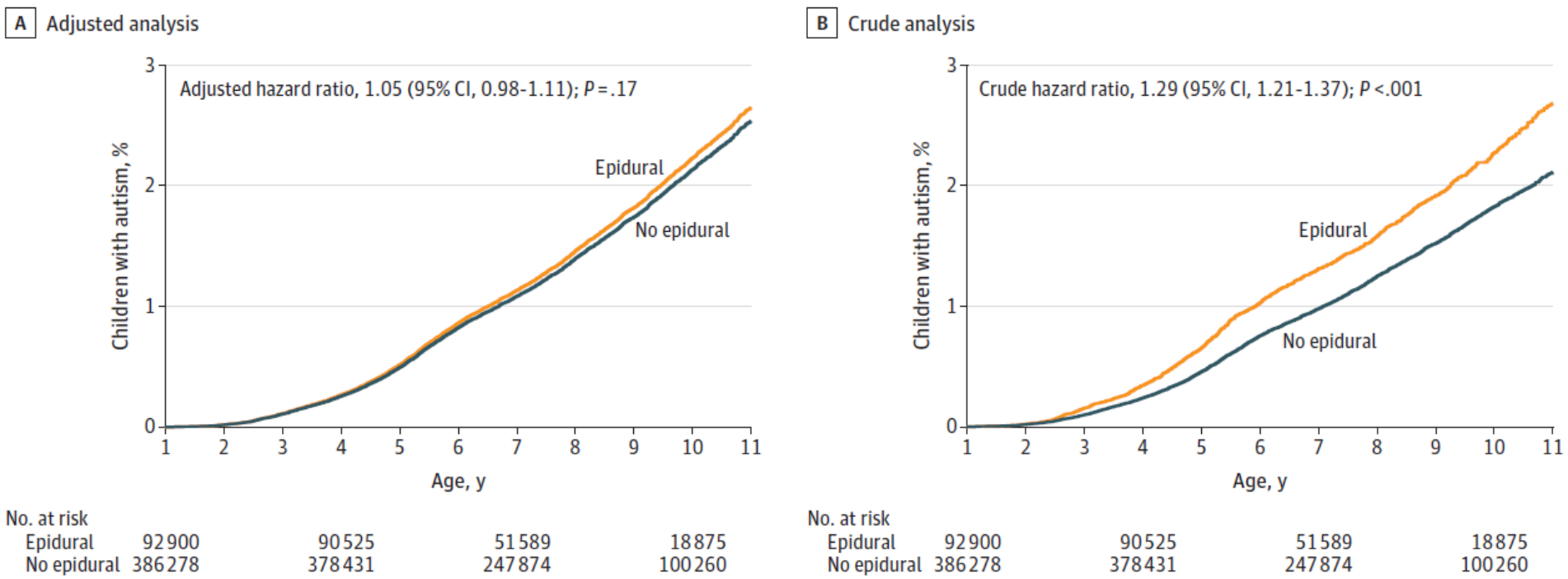
JAMA | Original Investigation 2021;326(12):1170-1177. doi:10.1001/jama.2021.14986

Association of Labor Epidural Analgesia With Autism Spectrum Disorder in Children

Anders Pretzmann Mikkelsen, MD; Iben Katinka Greiber, MD; Nikolai Madrid Scheller, MD; Øjvind Lidegaard, MD, DMSc

- Nationwide, Dannish cohort
- 2006…2013 all deliveries
- Additionally, to previous studies
  - ASD in first degree relatives
  - Psychiatric disorders, psychotropic drugs and medical-seeking behaviour of mother
- 485 093
  - LEA exposed 92 900 (19%)
  - Within-mother analysis 59 154 with different, at least one exposed and one unexposed child

Figure 2. Association of Labor Epidural Analgesia With Autism Spectrum Disorder in Children



Adjusted vs crude probability of autism spectrum disorder by exposure to labor epidural analgesia in a Danish cohort of 479 178 children. A, Adjusted for delivery year, maternal age, age of listed father, gestational age at birth, child's sex, firstborn child, multiple birth, elective cesarean delivery, child small for gestational age, induction of labor, maternal diabetes, maternal hypertensive disorder of pregnancy, body mass index ≥30, smoking status, education, employment status, geography of delivery, family history of autism, history of psychiatric disorder, psychotropic medication use, and medical-seeking behavior. The adjusted survival plot was based on the first of the 20 imputed data sets and used conditional balancing. The *P* value is for the covariate of labor epidural. B, Crude probability of autism spectrum disorder. The log-rank test was used to estimate the *P* value. The median observation time in children exposed to labor epidural analgesia was 6.4 (IQR, 4.6-8.6) years and in children not exposed to labor epidural analgesia was 7.1 (IQR, 5.1-9.1) years.

Mikkelsen AP et al. JAMA 2021;326(12):1170-1177. doi:10.1001/jama.2021.14986

Table 3. Primary and Secondary Analyses of the Association Between Exposure to Labor Epidural Analgesia and Outcome of Autism Diagnosis

Analysis	With labor epidural		Without labor epidural		Unadjusted absolute difference, % (95% CI)	Adjusted hazard ratio (95% CI)[b]
	No. with outcome/total (%)	Incidence rate per 10 000 person-years[a]	No. with outcome/total (%)	Incidence rate per 10 000 person-years[a]		
Primary analysis	1409/92 900 (1.5)	23.1	5019/386 278 (1.3)	18.5	0.2 (0.1 to 0.3)	1.05 (0.98-1.11)
Secondary analyses						
Within-mother analysis[c]	442/28 617 (1.5)	20.8	322/30 537 (1.1)	17.1	0.5 (0.3 to 0.7)	1.05 (0.90-1.21)
Numeric variables modeled using penalized splines[d]	1409/92 900 (1.5)	23.1	5019/386 278 (1.3)	18.5	0.2 (0.1 to 0.3)	1.04 (0.98-1.11)
Outcome of 2 separate autism diagnoses[e]	744/92 900 (0.8)	12.1	2599/386 278 (0.7)	9.5	0.1 (0.1 to 0.2)	1.05 (0.96-1.14)
Stratified by child's sex						
Female	273/44 083 (0.6)	9.4	1053/189 322 (0.6)	7.9	0.1 (0.0 to 0.1)	1.05 (0.91-1.20)
Male	1136/48 817 (2.3)	35.6	3966/196 956 (2.0)	28.7	0.3 (0.2 to 0.5)	1.04 (0.97-1.11)
Stratified by gestational age at birth, wk						
<37	91/4103 (2.2)	33.3	542/26 772 (2.0)	28.8	0.2 (−0.3 to 0.7)	1.10 (0.87-1.33)
≥37	1318/88 797 (1.5)	22.6	4477/359 506 (1.2)	17.7	0.2 (0.2 to 0.3)	1.05 (0.98-1.12)

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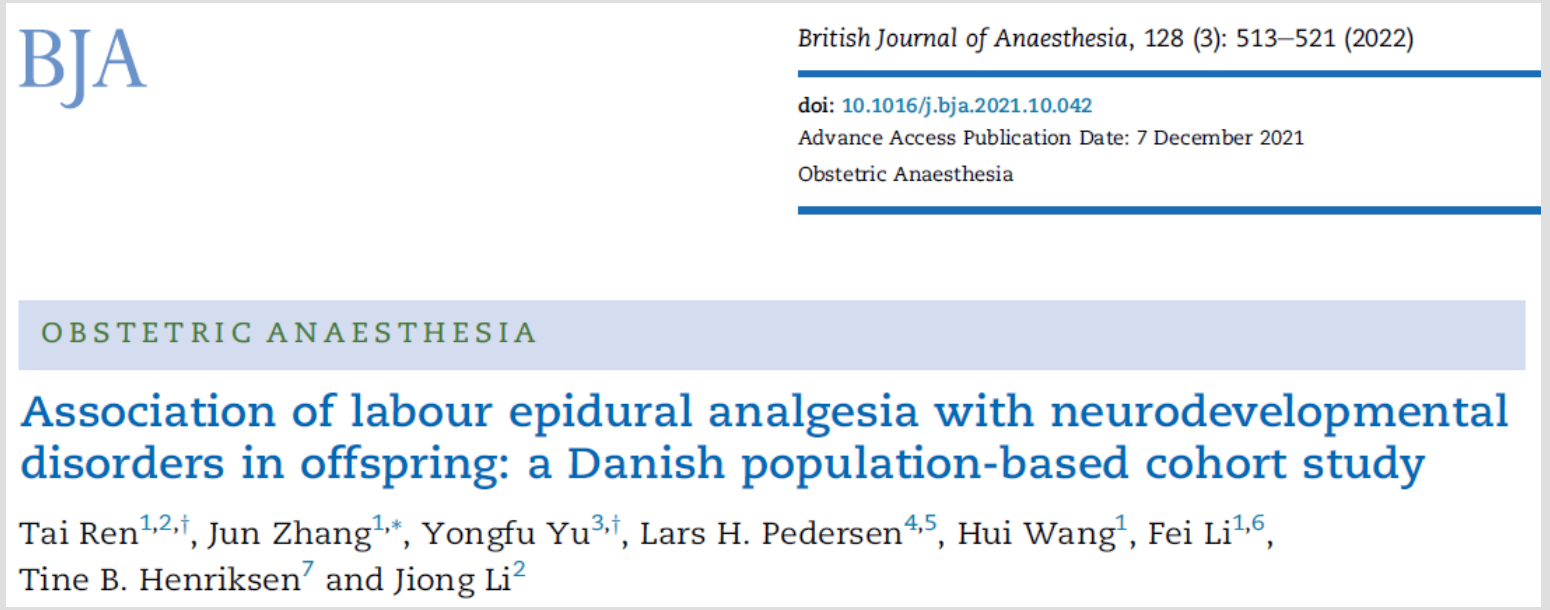

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OBSTETRIC ANAESTHESIA

Association of labour epidural analgesia with neurodevelopmental disorders in offspring: a Danish population-based cohort study

Tai Ren[1,2,†], Jun Zhang[1,*], Yongfu Yu[3,†], Lars H. Pedersen[4,5], Hui Wang[1], Fei Li[1,6], Tine B. Henriksen[7] and Jiong Li[2]

- Nationwide, Dannish cohort
- 2005…2016 intended to deliver vaginally, singleton
- Additionally, to previous Dannish cohort study
  - LEA duration < 4h, 4-8 h and > 8 hours
- 624 952 intended, 56 239 intrapartum CD
  - LEA exposed 116 296 (18.1%)
  - Within-mother analysis 59 154 with different, at least one exposed and one unexposed child

Table 2 Associations between maternal labour epidural analgesia and risk of autism spectrum disorder in offspring born in Denmark, 2005–16. aHR, adjusted hazard ratio; ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio; LEA, labour epidural analgesia. *Covariates include parity, maternal age, maternal education level, maternal cohabitation, calendar year, maternal smoking during pregnancy, maternal BMI before pregnancy, paternal age, any parental history of psychiatric disorder before pregnancy, gestational hypertension, gestational diabetes mellitus, abruptio placenta, induction of labour, augmentation of labour, fetal distress, labour dystocia, macrosomia, and gestational age.

Exposure	Number of offspring with ASD (%)	Incidence per 1000 person-years	Crude HR (95% CI)	aHR (95% CI)*
Full cohort				
No LEA	6023 (1.2)	1.6	1.0 (reference)	1.0 (reference)
LEA	1648 (1.4)	2.2	1.38 (1.31–1.46)	1.11 (1.04–1.18)
Duration of LEA (h)				
<4	372 (1.3)	2.1	1.32 (1.19–1.47)	1.10 (0.98–1.22)
4–8	451 (1.3)	2.1	1.40 (1.27–1.54)	1.09 (0.98–1.20)
>8	285 (1.1)	2.0	1.35 (1.20–1.52)	0.99 (0.87–1.12)
Missing	540 (2.1)	2.4	1.42 (1.30–1.55)	1.20 (1.10–1.32)
Sibling analysis				
No LEA	412 (1.0)	1.6	1.0 (reference)	1.0 (reference)
LEA	539 (1.4)	1.9	1.09 (0.92–1.29)	1.03 (0.84–1.27)

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EDITORIALS

Epidural labour analgesia and autism spectrum disorder: is the current evidence sufficient to dismiss an association?

Alexander J. Butwick[1,*], Daniel A. Abrams[2] and Cynthia A. Wong[3]

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leagues,[35] we believe that there is now sufficiently robust, high-quality epidemiological data to support the assertion that there is no meaningful association between epidural labour analgesia and autism spectrum disorder. Cumulatively, these studies answered the appropriate call by Qui and colleagues[12] for further research to confirm their findings, but with results that instead refuted their original finding of a positive association between epidural labour analgesia and offspring autism spectrum disorder risk. The findings of the