



# Is there any impact of association between labor neuraxial analgesia and autism spectrum disorders in offspring at the population level?

Kairavi Desai<sup>1,2</sup> · Makoto Sumie<sup>1,3,4,5</sup> · Alan Yang<sup>1</sup> · Marina Englesakis<sup>6</sup> · Jason T. Maynes<sup>1,7</sup> · Kazuyoshi Aoyama<sup>1,3</sup>

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To the Editor:

Labor neuraxial analgesia (LNA) has been a widely used and effective method for providing pain relief during childbirth and includes techniques such as epidurals and spinal blocks. In Canada, the rate of epidural use for all deliveries was 54% from 2021 to 2022 [1], with similar rates seen in the United States of 64.4% for multiparous and 78.8% for nulliparous American women in 2013 [2]. However, with the widespread adoption of LNA, concerns have arisen regarding its potential association with increasing the risk of development of autism spectrum disorders (ASD) in offspring [3]. Autism spectrum disorders encompass a range of neurodevelopmental disorders, characterized by deficits in social interactions, limited interests, and behaviors, and are influenced by genetic and environmental factors to varying amounts [4].

Numerous epidemiological and observational studies have examined the association between LNA and ASD and have revealed contradicting conclusions regarding the relationship, demonstrating that it is a complex and contentious subject that demands rigorous investigation. It is paramount to critically examine the available evidence to ensure the safety of both the mother and children as LNA continues to be the gold standard and is growing in popularity. In the current letter, we aimed to identify existing literature of population-based studies exploring the association between LNA and ASD by a comprehensive literature search and present a pooled risk of the association by a pair-wise meta-analysis.

## Methods

A comprehensive literature search was conducted using the MEDLINE All database with the search limited to studies published from inception to July 29th, 2023. The search strategy included the concepts of: [(epidural and autism) or (pregnancy or partum) and (anesthesia and population)]. The full details of the search strategy are available in the online supplement 1.

The inclusion criteria were population-based observational studies involving children diagnosed with autism spectrum disorders before the age of 18, with a sample size of more than 10 000. The exposure of interest was LNA that was administered during the process of childbirth. The main outcome of interest was the occurrence of autism spectrum disorders, diagnosed using standardized diagnostic criteria such as DSM-5, ICD-9, or ICD-10.

Two independent reviewers (K.D., M.S.) screened titles and abstracts to identify potentially eligible studies, and the full-text articles were assessed for eligibility based on predefined criteria. Discrepancies were resolved by a third reviewer (K.A.). Data extraction included study

✉ Kazuyoshi Aoyama  
kazu.aoyama@utoronto.ca

<sup>1</sup> Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, 555 University Ave, #2211, Toronto, ON M5G 1X8, Canada

<sup>2</sup> Michael G. DeGroot School of Medicine, McMaster University, Hamilton, ON, Canada

<sup>3</sup> Program in Child Health Evaluative Sciences, SickKids Research Institute, Toronto, ON, Canada

<sup>4</sup> Department of Anesthesiology, St. Mary's Hospital, Fukuoka, Japan

<sup>5</sup> Department of Anesthesiology and Critical Care Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

<sup>6</sup> Library and Information Services, University Health Network, Toronto, ON, Canada

<sup>7</sup> Program in Molecular Medicine, SickKids Research Institute, Toronto, ON, Canada

characteristics, patient demographics, individual study definitions of ASD, and the primary outcome of the prevalence of ASD diagnosis. The data extraction was performed using a standardized form.

From the extracted data, unadjusted relative risks reported in eligible studies were used to calculate the pooled relative risk with a 95% confidence interval (CI) by a pair-wise meta-analysis with random effects. Heterogeneity was examined using the  $I_2$  statistic. The extracted data were inputted into the software, ReviewManager (Review Manager 2020; Copenhagen, Denmark), which allowed for the meta-analysis of the data [5]. The software computed the relative risks which were used for further calculations. The population attributable fraction (PAF) was also calculated using the pooled relative risk that was initially determined [6, 7].

### Results

A total of 188 records were identified through the initial database search. After conducting title and abstract screening and assessing for eligibility with the inclusion and exclusion criteria, 9 studies met the inclusion criteria and were included in the analysis. The evaluation of the studies is demonstrated in the PRISMA flow diagram (online supplement 2).

The nine included studies were conducted across various geographic regions, including North America and Europe [8–16]. All the studies were published within the past 5 years, reflecting recent interest in the potential association between LNA and ASD. Most of the studies used ICD-9 or ICD-10 for defining autism spectrum disorders. One study used the Autism Diagnostic Observation Schedule and Autism Diagnostic Interview-Revised to define the outcome of interest [11]. Two studies by the same author had

overlapping study participants; however, the results were published separately [13, 14]. The most recent study was included and used for further analysis [14].

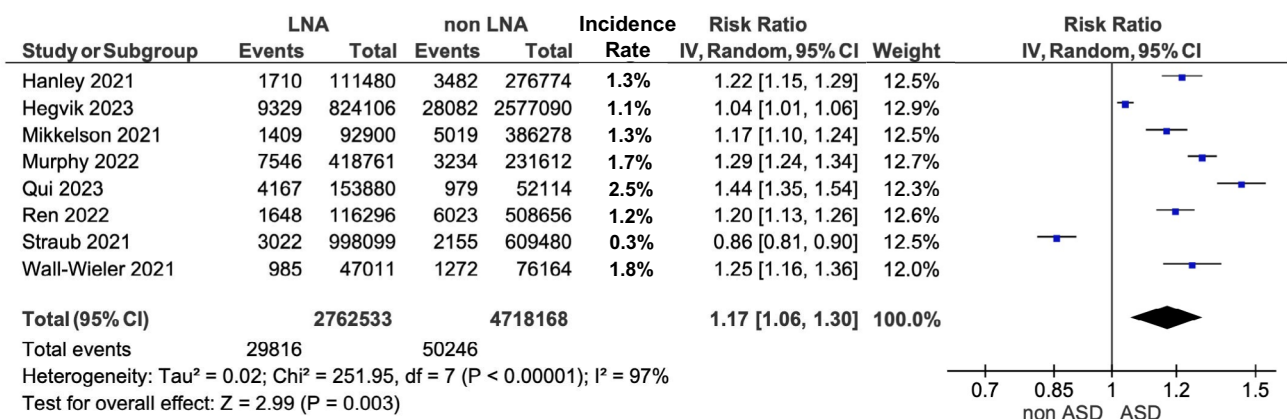
The incidence rate was between 0.3% and 2.5% (Fig. 1). The pooled risk ratio was 1.17 (95% CI 1.06–1.30). The heterogeneity calculated using the  $I_2$  statistic was 97%. The population attributable fraction was 5.9% (95% CI 1.9–10.0).

### Discussion

The potential association between LNA and the risk of the offspring developing ASD has been a topic of interest among healthcare providers and parents. The objective of this research letter was to conduct a thorough literature search to locate population-based studies that examined the relationship between LNA and ASD and perform a pair-wise meta-analysis to demonstrate the pooled risk of the association.

There are two main conclusions that can be drawn from the evidence. First, the pooled risk ratio suggests that there is a slightly increased likelihood of offspring exposed to labor epidural analgesia to develop autism spectrum disorders. Second, the population attributable fraction shows that the risk of developing ASD would be reduced by a limited proportion if women did not receive labor epidural analgesia.

It is critical to consider the methodological limitations when evaluating the current findings. First, the accuracy of exposure assessment was variable as many studies did not report details regarding the duration or dose of analgesia provided. Second, a high heterogeneity was calculated due to various risks of the association observed among eligible studies. The genetic risk and other number of environmental factors could explain the heterogeneity among the studies. Another limitation is that the included studies did not assess genetic risk factors for autism spectrum disorders which may lead to an overinflated PAF.



**Fig. 1** Forest plot of the incidence of the development of autism spectrum disorders in exposed and unexposed children to labor neuraxial analgesia (LNA)

The five studies suggested the possibility of misclassification of ASD or LEA due to misidentification, and the four other studies suggested the possibility of residual confounding due to unmeasured covariates as the limitations of the study. Lastly, the analysis employed crude ratios instead of adjusted ratios, resulting in the potential for confounding variables to affect the association that was determined.

In conclusion, the evidence presented in this study does not provide a clear basis for altering clinical practice. While the evidence may be limited by its weaknesses, the findings contribute to the ongoing conversation of the potential association. It is critical to analyze the evidence examining the relationship between neuraxial analgesia and ASD to ensure that expectant mothers are aware of the risks and benefits with the procedure. The use of epidural analgesia during labor continues to be a crucial technique for reducing pain and supporting the health of the mother during childbirth [17, 18], and clinicians should continue to make well-informed decisions regarding its use. We recommend that anesthesiologists continue to make informed decisions supported by evidence-demonstrated risks and benefits. Future research should include rigorous exposure assessment and the evaluation of other non-genetic risk factors, such as advanced maternal age and gestational hypertension, to ultimately compare the effect of various risk factors in developing ASD at population level.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00540-024-03343-3>.

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**Author contribution** KA conceived this paper. KD, MS, and ME conducted a literature search. KD, MS, AY, JTM, and KA conducted analyses. KD and KA wrote the initial and subsequent draft of the manuscript, which MS, AY, ME, and JTM commented and edited. All authors approved the final version.

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## Declarations

**Conflict of interest** The authors declare that they have no competing interest related to this publication.

## References

- Canadian Institute for Health Information. Epidural Rate for Vaginal Deliveries. Accessed August 30, 2023.
- Seijmonsbergen-Schermer AE, van den Akker T, Rydahl E, Beeckman K, Bogaerts A, Binfa L, Frith L, Gross MM, Missetwitz B, Halfdansson B, Daly D, Corcoran P, Calleja-Agius J, Calleja N, Gatt M, Nilsen ABV, Declercq E, Gissler M, Heino A, et al. Variations in use of childbirth interventions in 13 high-income countries: a multinational cross-sectional study. *PLoS Med.* 2020. <https://doi.org/10.1371/journal.pmed.1003103>.
- Sumie M, Yamaura K, Aoyama K. Association of labor neuraxial analgesia with autism spectrum disorders in offspring. In *Journal of Anesthesia* (Vol. 37, Issue 2, pp. 327–329). 2023. Springer. <https://doi.org/10.1007/s00540-023-03162-y>.
- Hodges H, Fealko C, Soares N. Autism spectrum disorder: Definition, epidemiology, causes, and clinical evaluation. In *Translational Pediatrics* (Vol. 9, pp. S55–S65). AME Publishing Company. 2020. <https://doi.org/10.21037/tp.2019.09.09>.
- Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020. Available at [revman.cochrane.org](http://revman.cochrane.org).
- Zapata-Diomedes B, Barendregt JJ, Veerman JL. Population attributable fraction: names, types and issues with incorrect interpretation of relative risks. *Br J Sports Med.* 2018;52(4):212. <https://doi.org/10.1136/bjsports-2015-095531>.
- Bartsch E, Medcalf KE, Park AL, Ray JG, Al-Rubaie ZTA, Askie LM, Berger H, Blake J, Graves L, Kingdom JC, Lebovic G, Lord SJ, Maguire JL, Mamdani MM, Meloche J, Urquia ML, van Wagner V. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *The BMJ.* 2016. <https://doi.org/10.1136/bmj.i1753>.
- Murphy MSQ, Ducharme R, Hawken S, Corsi DJ, Petrcich W, El-Chaar D, Bisnaire L, McIsaac DI, Fell DB, Wen SW, Walker MC. Exposure to intrapartum epidural analgesia and risk of autism spectrum disorder in offspring. *JAMA Netw Open.* 2022;5(5):E2214273. <https://doi.org/10.1001/jamanetworkopen.2022.14273>.
- Straub L, Huybrechts KF, Mogun H, Bateman BT. Association of neuraxial labor analgesia for vaginal childbirth with risk of autism spectrum disorder. *JAMA Netw Open.* 2021. <https://doi.org/10.1001/jamanetworkopen.2021.40458>.
- Mikkelsen AP, Greiber IK, Scheller NM, Lidgaard Ø. Association of labor epidural analgesia with autism spectrum disorder in children. *JAMA J Am Med Assoc.* 2021;326(12):1170–7. <https://doi.org/10.1001/jama.2021.12655>.
- Hanley GE, Bickford C, Ip A, Lanphear N, Lanphear B, Weikum W, Zwaigenbaum L, Oberlander TF. Association of epidural analgesia during labor and delivery with autism spectrum disorder in offspring. *JAMA J Am Med Assoc.* 2021;326(12):1178–85. <https://doi.org/10.1001/jama.2021.14986>.
- 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. <https://doi.org/10.1001/jamapediatrics.2021.0376>.
- Qiu C, Lin JC, Shi JM, Chow T, Desai VN, Nguyen VT, Riewerts RJ, Feldman RK, Segal S, Xiang AH. Association between epidural analgesia during labor and risk of autism spectrum disorders in offspring. *JAMA Pediatr.* 2020;174(12):1168–75. <https://doi.org/10.1001/jamapediatrics.2020.3231>.
- Qiu C, Carter SA, Lin JC, Shi JM, Chow T, Desai VN, Nguyen VT, Spitzer J, Feldman RK, Xiang AH. Association of labor epidural analgesia, oxytocin exposure, and risk of autism spectrum disorders in children. *JAMA Netw Open.* 2023;6(7):e2324630. <https://doi.org/10.1001/jamanetworkopen.2023.24630>.
- Hegvik TA, 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. *Am J Obstet Gynecol.* 2023;228(2):233.e1-233.e12. <https://doi.org/10.1016/j.ajog.2022.08.016>.
16. Ren T, Zhang J, Yu Y, Pedersen LH, Wang H, Li F, Henriksen TB, Li J. Association of labour epidural analgesia with neurodevelopmental disorders in offspring: a Danish population-based cohort study. *Br J Anaesthesia.* 2022;128(3):513–21. <https://doi.org/10.1016/j.bja.2021.10.042>.
17. Guglielminotti J, Landau R, Daw J, Friedman AM, Chihuri S, Li G. Use of labor neuraxial analgesia for vaginal delivery and severe maternal morbidity. *JAMA Netw Open.* 2022. <https://doi.org/10.1001/jamanetworkopen.2022.0137>.
18. Pankiv E, Yang A, Aoyama K. Neuraxial labor analgesia for vaginal delivery and severe maternal morbidity. *JAMA Netw Open.* 2022;5:6. <https://doi.org/10.1001/jamanetworkopen.2022.0142>.

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