http:// ijp.mums.ac.ir
Original Article (Pages: 13309-13317)

Is There an Association between Fetal Distress and Autism Spectrum Disorders (ASD) among Children? A Systematic Review and Meta-Analysis

Ensiyeh Jenabi[1], Erfan Ayubi[2, 3], *Mahsa Naemi[4]

[1]Autism Spectrum Disorders Research Center, Hamadan University of Medical Sciences, Hamadan, Iran. [2]Department of Community Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.

[3]Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.

[4]Assistant Professor, Department of Obstetrics and Gynecology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Background

Evidence regarding the relation between fetal distress and development of autism spectrum disorders (ASD) among children is rare. Therefore, this systematic review and systematic review and meta-analysis was conducted to assess the relation between fetal distress and ASD among children with stronger evidence.

Materials and Methods: In this systematic review and meta-analysis, Medline, Scopus, Web of Science and Google Scholar were searched using the relevant keywords on observational studies from inception to October 2020 without any language restriction by two independent authors. The pooled odds ratios (OR), and 95% confidence intervals (CI) were calculated from eligible studies used as random effect estimates of association among included studies. The inconsistency across results of studies was quantified using I^2 statistic. Data were analyzed using Stata software version 13.0.

Results: From 341 identified studies, eight studies (684,262 individuals) were included in the meta-analysis. The pooled estimates of OR did not show a significant association between fetal distress and the risk of ASD among children, respectively (OR = 1.27, 95% CI = 0.88 to 1.67). There was medium heterogeneity among included studies (I^2=50.4%, P=0.049).

Conclusion

Our findings showed that fetal distress was not a risk factor for ASD among children. In a comparison to the previous meta-analysis, this study provides the most up-to-date evidence supporting a lack of significant association between fetal distress and ASD. Here, the association between fetal distress and ASD is still under discussion so that, further researches and umbrella reviews are needed.

Key Words: Autism spectrum disorder, Children, Fetal distress, Systematic Review.

*Please cite this article as: Jenabi E, Ayubi E, Naemi M. Is There an Association between Fetal Distress and Autism Spectrum Disorders (ASD) among Children? A Systematic Review and Meta-Analysis. Int J Pediatr 2021; 9(4): 1795-1802. DOI: **10.22038/IJP.2021.55739.4391**

Corresponding Author:

Mahsa Naemi (MD), Assistant Professor, Department of Obstetrics and Gynecology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Email: naemi.m2018@gmail.com

Received date: Nov.22, 2020; Accepted date: Feb. 22, 2021

1- INTRODUCTION

Autism spectrum disorder (ASD) is a complex disease of neurodevelopment. ASD is one of the most common childhood diseases. In terms of clinical symptoms, the disease ranges from mild to severe. The global prevalence of the disease is estimated to be 0.62% (1). The financial burden that the disease imposes on the health system, along with insufficient knowledge of the epidemiology, etiology and natural history of the disease, has complicated the situation (2). The causal mechanism of ASD is still not well understood. ASD is a multifactorial disorder that is caused by genetic and environmental factors (3). According to the literature, 35 to 40 percent of autism is related to genetic factors, and the remaining 60 to 65 percent is probably due to other factors, such as environmental factors in prenatal, perinatal, and postnatal conditions (4, 5).

The results of studies show that high parental age, gestational hypertension, risk of miscarriage, fetal failure, cesarean delivery and low birth weight are associated with an increased risk of ASD (6-8). There have been several studies on the association of fetal distress with autism with conflicting results (9-16). These contradictory results can be explained by different study methods, not comparable comparison groups, race and region, differences in study sample size and exposure assessment method. Therefore, conducting a meta-analysis is necessary to pool inconsistent data from these studies and to reach a more definitive conclusion.

The association between some explanatory variables with the increased risk of ASD has been shown previously through systematic-review and meta-analysis studies (17-20); although the previous meta-analysis (7) showed that fetal distress is associated significantly with a 52% increase in the risk of ASD, in this meta-analysis only four studies were included which had potential impact on the overall effect estimates. Therefore, we performed this meta-analysis to assess the association between fetal distress and ASD among children with stronger evidence.

2- MATERIALS AND METHODS

A systematic review study was performed using published Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist (21).

2-1. Inclusion criteria

All observational studies that have examined the association between fetal distress and the risk of autism were included.

2-2. Exclusion criteria

The case series, animal studies, letter to editor, medical hypotheses, randomized clinical trial studies and studies of unrelated exposures were excluded.

2-3. Study selection

The Medline (via PubMed), Scopus, Web of Science and Google Scholar were searched using the key words "autism or autism spectrum disorder or ASD" in combination with "fetal distress" limited to peer-reviewed studies published in any language until October 2020. The literature search sought to identify all observational studies that have examined the association between fetal distress and the risk of autism. A total of 48 additional potential studies were identified after screening the reference lists of studies.

2-4. Data collection process

The method of data collection, abstraction and quality control of articles has been reported in previous studies (22-24). The following data for each study was recorded: (a) study design (cohort or case control); (b) sample size; (c) comparison group description (e.g., control subjects, healthy versus abnormal control subjects,

and diagnosis of abnormal control subjects); (d) autism diagnostic criteria and mode of reporting (e.g., Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV), International Classification of Diseases, 9th Revision, International Classification of Diseases, 10th Revision, medical record review, physician assessment, and diagnostic measures used); (e) covariates in multivariate models; and (f) study results, including indicators of statistical significance, prevalence of exposures among case and control neonates, rates or risks of autism across exposure levels, relative risks (RRs), and 95% confidence intervals (CIs). These stages were conducted by two authors (EJ and SK). Any disagreement was resolved by discussion between the two authors.

2-5. Risk of bias in individual studies

The studies were divided into two categories based on the quality of reporting using Newcastle-Ottawa Scale (NOS) (25) with items as follows by two authors: (a) scores of the studies were categorized into low quality (<7 points), and (b) high quality (≥7 points).

2-6. Synthesis of results

The pooled odds ratios (OR), and 95% confidence intervals (CI) were calculated from eligible studies used as random effect estimates of association among included studies. Output was reported as overall odds ratio (OR) with 95% confidence interval (95% CI).The statistical heterogeneity was performed using the Chi-square test at the 5% significance level ($P < 0.05$). We quantified the inconsistency across results of studies using I^2 statistic. We quantified the inconsistency across results of studies using I^2 statistic. Since the studies were homogenous ($I^2<50\%$), a fixed effect model was used, otherwise, random effect model was employed for the analyses. Publication bias was assessed to examine the association between study size and fetal distress exposure by conducting two tests, Begg and Egger (26). The p-value <0.05 was considered significant for publication bias. The current meta-analysis was conducted using Stata software version 13 (Stata Corp, College Station, TX, USA).

3- RESULTS

3-1. Description of studies

In total, 341 studies were identified in the initial search through database searching and other sources. Among these, 56 duplicate articles were excluded. In total, 270 studies were excluded after reviewing the studies by title and abstract and 7 studies after reviewing the full paper were excluded. Eventually, eight studies (total samples= 684,262) were included in the present analysis (**Figure.1**). The included studies were the four studies cohort (9-12), three studies case-control (13-15) and one study cross-sectional (16). The confounder variables of the association between fetal distress and the risk of ASD among children were maternal age at delivery, gender, birth year, mode of delivery and gestational age.

3-2. Synthesis of results

The forest plot in **Figure.2** shows the association between fetal distress and the risk of ASD among children. The pooled estimates of OR did notshow a significant association between fetal distress and the risk of ASD among children, respectively (OR = 1.27, 95% CI = 0.88 to 1.67). There was medium heterogeneity among included studies ($I^2=50.4\%$, P=0.049). There was not publication bias among studies based on Begg's and Egger's tests. The P- value for Begg's and Egger's regression were 0.322 and 0.301, respectively.

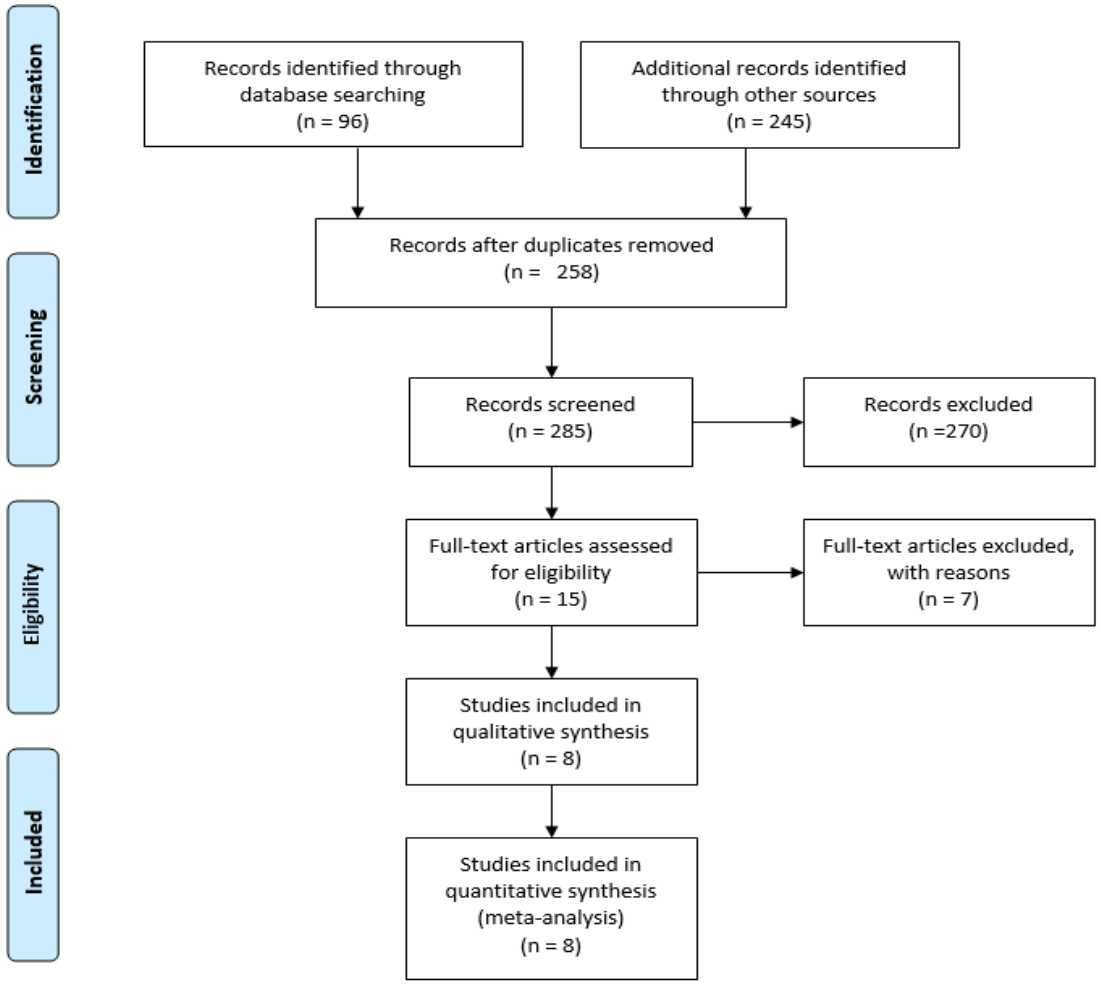

Fig.1: Diagram of studies through the different phases of the systematic review.

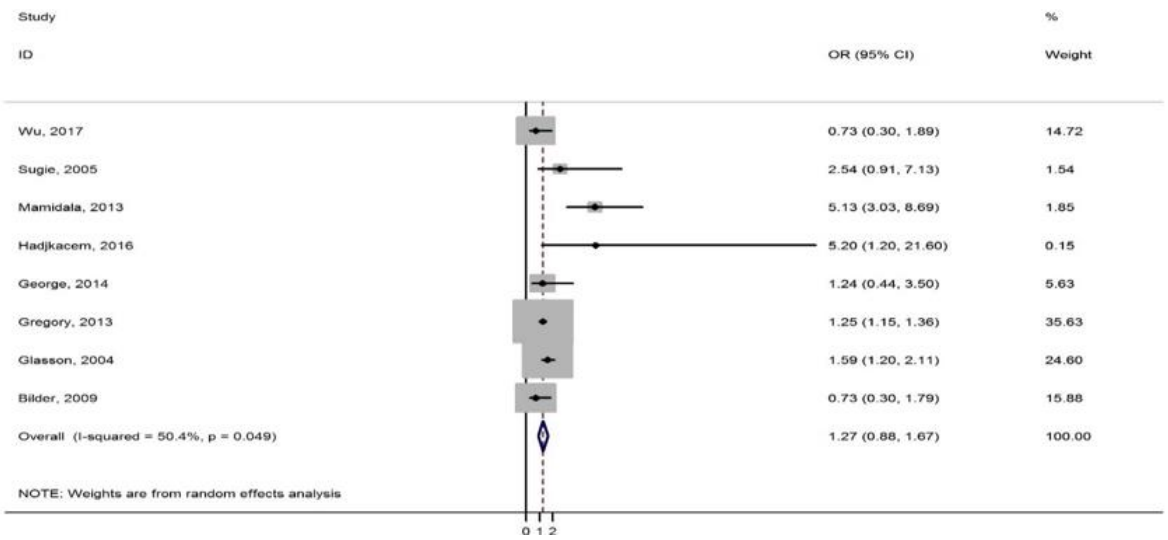

Fig.2: Forest plot of the association between fetal distress and ASD.

ASD: Autism spectrum disorder.

3-3. Sensitivity analysis

There was evidence of medium heterogeneity among the included studies to investigate the association between fetal distress and the risk of ASD (I^2 = 50.4%). Therefore, we performed the sensitivity analysis based on the sequential algorithm to obtain homogeneity among studies. We obtained the minimum desired I^2 threshold (50%) by omitting one study from the meta-analysis. By removing a study (11), heterogeneity reached 0.13%. (OR= 1.24; 95% CI: 1.03–1.45; I^2 = 0. 5%, P=0.33).

3-4. Quality of the studies

The quality of the studies in the present meta-analysis was categorized into seven studies with high quality and one study with low quality according to the NOS Scale (25) (**Table.1, 2**).

Table-1: Summary results of the included studies

1st Author, Year	Country	Design	Sample size	Estimate	Adjustment	Age, year /mean	Autism criteria	Quality
George, 2014	India	Case-control	343	OR	Crude	2-6	CARS	Low
Gregory, 2013	USA	Cohort	625042	OR	Adjusted	No data	No criteria	High
Glasson, 2004	Australia	Cohort	1774	OR	Adjusted	<3	DSM-IV	High
Bilder, 2009	USA	Case-control	26315	OR	Adjusted	8	ICD-9	High
Hadjkacem, 2016	Tunisia	Cross-sectional	101	OR	Adjusted	3-12	DSM-IV	High
Wu, 2017	China	Cohort	27940	OR	Crude	3	DSM-IV	High
Sugie, 2005	Japan	Case-control	1805	OR	Crude	≥3	DSM-IV	High
Mamidala, 2013	India	Cohort	942	OR	Adjusted	2-10	ICD-10	High

Table-2: Quality of studies based on the Newcastle Ottawa Scale (NOS) (25).

First author, Year	Selection	Comparability	Exposure	Total quality score
George, 2014	3	1	2	6
Gregory, 2013	3	2	3	8
Glasson, 2004	3	2	3	8
Bilder, 2009	4	2	3	9
Hadjkacem, 2016	3	2	3	8
Wu, 2017	3	1	3	7
Sugie, 2005	4	1	2	7
Mamidala, 2013	4	2	2	8

Low quality (<7 points), and high quality (≥7 points).

3-5. Subgroup analysis

The subgroup analyses were performed based on the adjusted form. The OR in crude and adjusted studies was reported 0.92 (0.23, 1.61), and 1.37 (0.86, 1.81), respectively. The significant association was not found in the adjusted and crude studies (**Table.3**).

Table-3: Results of subgroup analysis of fetal distress and autism spectrum disorders (ASD).

Subgroups	Studies		
	No. of studies	OR (95% CI)	I^2
Adjusted form			
Crude analysis	3	0.92 (0.23, 1.61)	0.0%
Adjusted analysis	5	1.37 (0.86, 1.81)	66.0%

OR: Odds ratio, CI: Confidence interval, I2: I square, ASD: Autism spectrum disorder.

4- DISCUSSION

This systematic review and meta-analysis evaluated the relationship between fetal distress and ASD. Results of the study indicate fetal distress may be associated with a 37% increase in the risk of ASD, although there was not enough evidence to conclude a statistically significant association. Potential mechanism of the effect of fetal distress on ASD could be explained in several ways. Regardless of the direct effect of fetal distress and hypoxia on early brain development, fetal distress can be considered as a mediator variable that lies between the risk factors and ASD in a causal pathway. For example, there is a positive association between maternal diabetes and fetal distress (27), so maternal diabetes may result in fetal oxidative stress at first and developing fetal distress may positively influence the later risk of ASD. Etiology of autism is a constellation of genetic and environmental factors (28-31). Some of the most important environmental factors are prenatal, perinatal and postnatal factors that have been investigated in recent years (9, 16). In a comprehensive meta-analysis by Gardener et al. (32), several perinatal and neonatal risk factors are introduced as risk factors for ASD. In the previous meta-analysis including 4 articles, fetal distress was indicated to be associated significantly with a 52% increase in the risk of ASD. We performed an updated meta-analysis of published studies involving 8 articles with a total of 684,262 participants and in contrast, a non-significant positive association was found between fetal distress and ASD. Although the quality assessment in our study has demonstrated that the majority of included studies are good in quality, results from a meta-analysis of observational studies should be interpreted with caution because such studies are prone to several biases such as selection bias, information bias and confounding (33). For example, in one study included in this meta-analysis e.g., Glasson et al. (9), all potential confounders e.g., socioeconomic status (34) or maternal smoking during pregnancy (35), were not considered in the multivariable analysis. In another included case control study by George et al. (14) in which data about antenatal, natal and postnatal risk factors were obtained using an interview with mothers, it was suggested that this can induce the risk of interviewer bias and information bias in the results. Heterogeneity in the adjusted effect estimates across studies was high (I^2>0.50)

(36). Here, possible explanations of observed heterogeneity in the meta-analysis needs to be investigated using subgroup analysis and meta-regression. Addressing the heterogeneity in this meta-analysis was not performed due to a limited number of studies included when defining subgroups. Therefore, the effect of fetal distress on the ASD needs to be further examined according to important covariates such as other pregnancy complications. Our study was an updated meta-analysis on published studies about the association between fetal distress and ASD involving a large number of participants, however, several limitations should be considered. Although the publication bias was statistically insignificant, the chance of selection bias due to missing potential studies should be considered because some databases such as EMBASE and Cochrane library as well as grey literature were not considered for searching. Generalizability of the results is limited because the effect measures from studies conducted in the have contributed the most in the estimation of merged OR.

5- CONCLUSION

Our findings showed that fetal distress was not a risk factor for ASD among children. In a comparison of the previous meta-analysis (32), this work provides the most up-to-date evidence supporting a lack of significant association between fetal distress and ASD. Here, the association between fetal distress and ASD is still being debated so that, further researches and umbrella reviews are needed.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, et al. Global prevalence of autism and other pervasive developmental disorders. Autism research. 2012;5(3):160-79.

2. Gomes PT, Lima LH, Bueno MK, Araújo LA, Souza NM. Autism in Brazil: a systematic review of family challenges and coping strategies. Jornal de Pediatria (Versão em Português). 2015;91(2):111-21.

3. Wang C, Geng H, Liu W, Zhang G. Prenatal, perinatal, and postnatal factors associated with autism: a meta-analysis. Medicine. 2017;96(18): e6696.

4. Froehlich-Santino W, Tobon AL, Cleveland S, Torres A, Phillips J, Cohen B, et al. Prenatal and perinatal risk factors in a twin study of autism spectrum disorders. Journal of psychiatric research. 2014;54:100-8.

5. Tchaconas A, Adesman A. Autism spectrum disorders: a pediatric overview and update. Current opinion in pediatrics. 2013;25(1):130-43.

6. Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, et al. Advancing paternal age and autism. Archives of general psychiatry. 2006;63(9):1026-32.

7. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics. 2011;128(2):344-55.

8. Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. Archives of pediatrics & adolescent medicine. 2007;161(4):326-33.

9. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. Archives of general Psychiatry. 2004;61(6):618-27.

10. 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 pediatrics. 2013;167(10):959-66.

11. Mamidala MP, Polinedi A, PTV PK, Rajesh N, Vallamkonda OR, Udani V, et al. Prenatal, perinatal and neonatal risk factors of Autism Spectrum Disorder: a comprehensive epidemiological assessment from India.

Research in developmental disabilities. 2013;34(9):3004-13.

12. Wu DM, Wen X, Han XR, Wang S, Wang YJ, Shen M, et al. Relationship between neonatal vitamin D at birth and risk of autism spectrum disorders: the NBSIB study. Journal of Bone and Mineral Research. 2018;33(3):458-66.

13. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics. 2009;123(5):1293-300.

14. George B, Padmam MR, Nair M, Leena M, Russell PSS. CDC Kerala 13: antenatal, Natal and postnatal factors among children (2–6 y) with autism–a case control study. The Indian Journal of Pediatrics. 2014;81(2):133-7.

15. Sugie Y, Sugie H, Fukuda T, Ito M. Neonatal factors in infants with autistic disorder and typically developing infants. Autism : the international journal of research and practice. 2005;9(5):487-94.

16. Hadjkacem I, Ayadi H, Turki M, Yaich S, Khemekhem K, Walha A, et al. Prenatal, perinatal and postnatal factors associated with autism spectrum disorder. Jornal de pediatria. 2016;92(6):595-601.

17. Jenabi E, Bashirian S, Asali Z, Seyedi M, Street F. Association between small for gestational age and risk of autism spectrum disorders: a meta-analysis. Clinical and Experimental Pediatrics. 2021.

18. Mehri F, Bashirian S, Jenabi E. Association between pesticide and PCB exposure during pregnancy and autism spectrum disorder among children: a meta-analysis. Journal of the Korean Pediatric Society. 2020. DOI: https://doi.org/10.3345/cep.2020.00864.

19. Jenabi E, Karami M, Khazaei S, Bashirian S. The association between preeclampsia and autism spectrum disorders among children: a meta-analysis. Korean journal of pediatrics. 2019;62(4):126.

20. Jenabi E, Bashirian S, Khazaei S. Is breech presentation associated with autism spectrum disorders among children: a meta-analysis. Advances in Human Biology. 2019;9(1):12.

21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41.

22. Fazel M, Khari S, Gubari MI, Ataei N, Yousefifard M, Hosseini M. The Efficacy of Paricalcitol Administration for Management of Pediatric Chronic Kidney Disease: A Systematic Review and Meta-analysis. International Journal of Pediatrics. 2020;8(2):10951-9.

23. Aryanpur M, Yousefifard M, Hosseini M, Oraii A, Heydari G, Kazempour-Dizaji M, et al. Effect of Active and Passive Exposure to Cigarette Smoke on Lipid Profile of Children and Adolescents; A Systematic Review and Meta-Analysis. International Journal of Pediatrics. 2018;6(5):7575-88.

24. Saei Ghare Naz M, Ghasemi V, Kiani Z, Rashidi Fakari F, Ozgoli G. The effect of breastfeeding duration on bone mineral density (BMD): a systematic review and meta-analysis. International Journal of Pediatrics. 2019;7(1):8831-43.

25. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses2009 Septamber 15, 2017. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ : British Medical Journal. 1997;315(7109):629-34.

27. Castelijn B, Hollander K, Hensbergen JF, RG IJ, Valkenburg-van den Berg AW, Twisk J, et al. Peripartum fetal distress in diabetic women: a retrospective case-cohort study. BMC Pregnancy Childbirth. 2018;18(1):228.

28. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, et al. Autism as a strongly genetic disorder: evidence from a British twin study. Psychological medicine. 1995;25(1):63-77.

29. Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. Acta obstetricia et gynecologica Scandinavica. 2012;91(3):287-300.

30. Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Molecular autism. 2017;8:13.

31. Risch N, Spiker D, Lotspeich L, Nouri N, Hinds D, Hallmayer J, et al. A genomic screen of autism: evidence for a multilocus etiology. Am J Hum Genet. 1999;65(2):493-507.

32. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics. 2011;128(2):344-55.

33. Szklo M, Nieto FJ. Epidemiology: beyond the basics: Jones & Bartlett Publishers; 2014. Available at: https://shmu.ac.ir/file/download/news/1564213580-epidemiology-beyod.pdf

34. He P, Guo C, Wang Z, Chen G, Li N, Zheng X. Socioeconomic status and childhood autism: A population-based study in China. Psychiatry research. 2018;259:27-31.

35. Caramaschi D, Taylor AE, Richmond RC, Havdahl KA, Golding J, Relton CL, et al. Maternal smoking during pregnancy and autism: using causal inference methods in a birth cohort study. Translational psychiatry. 2018;8(1):262.

36. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.