

Not breastfeeding and risk of autism spectrum disorders among children: a meta-analysis

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Background: To our knowledge, this is the first meta-analysis of the association of not breastfeeding and the risk of autism spectrum disorder (ASD) based on observational studies.

Purpose: This meta-analysis aimed to evaluate of the association of not breastfeeding and the risk of ASD.

Methods: Three databases (PubMed, Web of Science, and Scopus) were systematically searched until December 2021. Heterogeneity was determined using the chi-square test and its quantity was measured using the I^2 statistic. The Begg line regression test was used to assess publication bias. A random-effects model was used to analyze the data. Seven studies were included in this meta-analysis.

Results: The total study population included 3,270 individuals. According to the random-effects model, the estimated odds ratio of the risk of ASD associated with not breastfeeding was 1.81 (95% confidence interval, 1.35–2.27; $I^2=0\%$).

Conclusion: The results of the included studies were homogeneous. Our findings showed that not breastfeeding is a risk factor for ASD. These results suggest the importance of breastfeeding in decreasing the risk of ASD in children.

Key words: Autism spectrum disorders, Breastfeeding, Child, Meta-analysis

Key message

This study aimed to determine whether there is an association between not breastfeeding (versus breastfeeding) and the risk of autism spectrum disorders (ASD) among children. We found that the risk of ASD associated with not breastfeeding had an odds ratio of 1.81 (95% confidence interval, 1.35–2.27; $I^2=0\%$). These findings suggest the importance of breastfeeding in decreasing the risk of ASD among children.

Introduction

Autism spectrum disorders (ASD) among children are characterized by impaired social interactions, communication deviance,

and the presence of restrictive and repetitive behavior patterns.¹⁾ Previous reviews reported that ASD is predominantly genetic. Genetic factors alone account for 20%–30% of ASD cases, whereas the remaining 70%–80% are due to a complex interaction between environmental risk factors and genetics.²⁾ Recent meta-analyses have identified the role of advanced parent age, gestational infections, low birth weight, fetal distress, intrauterine growth retardation, small for gestational age, neonatal icterus, preterm labor, cesarean section, preeclampsia, and labor complications in the pathogenesis of ASD.^{3–5)}

Some researchers have suggested that breastfeeding may protect against ASD,^{6–8)} while another study did not show this association.⁹⁾ A meta-analysis by Tseng et al.¹⁰⁾ found that children with ASD were significantly less likely to be breastfed than those without ASD. However, they assessed the prevalence of breastfeeding (less versus more breastfeeding) and different breastfeeding durations in children with versus without ASD. Therefore, the present meta-analysis evaluated not breastfeeding versus breastfeeding and the risk of ASD among children based on epidemiological studies.

Methods

We performed the meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews) criteria.

1. Eligibility criteria

The exposure variable was not breastfeeding, while the outcome of interest was ASD in children aged ≤ 18 years. Observational studies included cohort, cross-sectional, and case-control studies irrespective of language; publication date; and participant nationality, race, and age. The exclusion criteria were systematic reviews and meta-analyses, case reports and series, controlled trials, letters to the editor, and studies lacking complete data.

2. Information sources and search

We systematically searched the PubMed, Web of Science, and

Scopus databases for articles published through December 2021. The search terms were applied in combination: (not breastfeeding, not breastfed, no breast milk, lactation, breastfeeding, breastfed, artificial milk-fed) and (ASD, autism spectrum disorders, or autism). The reference lists of the retrieved articles were manually searched to identify any further studies. We contacted the authors of the included studies for additional data.

3. Study selection

We used EndNote reference management software (Chicago Manual of Style, USA) to merge the results from different databases. Duplicate studies were subsequently excluded. In addition, 2 researchers independently extracted all data, and disagreements between the 2 researchers were resolved by discussion.

4. Data extraction

Data from the included studies were extracted using a data sheet in Stata ver. 13 (StataCorp LLC, College Station, TX, USA). The following data were included: first author, year of publication, country, study design, sample size, control for confounding variables (adjusted, unadjusted), age range, and ASD diagnostic method.

5. Methodological quality

We evaluated study quality using the Newcastle Ottawa Scale (NOS).¹¹⁾ Any study could achieve a maximum of 9 NOS stars: 4 for selection quality, 2 for comparability, and 3 for exposure quality. A score ≥ 7 indicated high quality.

6. Heterogeneity and reporting biases

Interstudy heterogeneity was assessed using the chi-square test¹²⁾ and the I^2 statistic,¹³⁾ while publication bias was assessed using Begg¹⁴⁾ line regression test.

7. Summary measures

The association between breastfeeding and the risk of ASD was assessed using odds ratios (ORs) and 95% confidence intervals (CIs). We used fully adjusted ORs to control for potentially confounding factors. A random-effects model was used to analyze the data.¹⁵⁾ Stata ver. 13 was used for the analysis, with a significance level of 0.05.

Results

1. Description of studies

According to our search strategy, 766 references were identified until December 20, 2021. Of them, 189 were duplicates and 566 were excluded by the title and abstract screening. Eleven studies were subjected to full-text review, which eliminated 4 full papers. Therefore, 7 studies were ultimately included in the present meta-analysis (Fig. 1A): 5 with a case-control design^{6-9,16)} and 2 with a cross-sectional design.^{17,18)} The total study population was 3,270 individuals. All studies were published in English (Table 1).

2. Effects of exposure

Fig. 1B assessed the association between not breastfeeding and the risk of ASD. According to the random-effects model, the estimated OR of the risk of ASD associated with not breastfeeding was 1.81 (95% CI, 1.35–2.27; $I^2=0\%$) (Fig. 1B). The results of the included studies were homogenous.

3. Publication bias

Publication bias was assessed using Begg test. The P value for Begg regression among the children with ASD was 0.176. No evidence of publication bias was found among studies reporting an association between breastfeeding and the risk of ASD.

4. Subgroup analysis

We performed a subgroup analysis of the quality of the studies and designs. The pooled results of the cross-sectional and case-control designs were OR=1.62 (95% CI, 1.12–2.13) and 2.65 (95% CI, 1.57–3.73), respectively. There was no significant association in studies with a low-quality OR (2.98; 95% CI, 0.91–5.05; Table 2).

5. Study quality

In the evaluation of study quality based on the NOS scale, 6 studies were of high quality and one was of low quality (Table 1).

Discussion

To our knowledge, this is the first meta-analysis based on epidemiologic studies of the association between not breastfeeding versus breastfeeding and the risk of ASD. Our results showed that not breastfeeding was a risk factor for ASD. No heterogeneity was detected among the studies that reported an association between breastfeeding and the risk of ASD. The mechanisms underlying the association between breastfeeding and ASD risk are unclear and warrant further research. Different findings have been reported regarding ASD with different biological factors.

An inadequate intake of “beneficial” omega-3 and omega-6 polyunsaturated fatty acids (PUFA) derived from the mother during pregnancy or lactation may also play an important role in ASD. However, omega-3 and omega-6 PUFA deficiencies have been identified in children with ASD, while the relationship between poor breastfeeding and the risk of ASD has been investigated. Fatty acids are abundant in the colostrum secreted during the first 2–3 days after birth. Breast milk is a rich source of long-chain polyunsaturated omega-3 and omega-6 fatty acids considered important in the development of the cognitive, social, and language abilities of children aged 6 months to 3.5 years.^{19,20)} Other studies reported that the elevated oxytocin levels experienced during infant sucking may protect against the development of ASD.^{21,22)}

A meta-analysis by Ghozy et al.²³⁾ in 2018 showed that breastfeeding decreased the risk of ASD by 58%, while exclusive

breastfeeding decreased the risk by 76%. Breastfeeding for 12–24 months resulted in the most significant reduction in the risk of ASD.

Another meta-analysis by Tseng et al.¹⁰⁾ reported that children with ASD (clinical diagnosis or self-reported) were significantly less likely to be breastfed than those without ASD (OR, 0.61; 95% CI, 0.45–0.83; $P=0.002$). However, they assessed the prevalence (less versus more) and durations in children with

ASD versus without ASD. The present meta-analysis evaluated not breastfeeding versus breastfeeding as a risk factor for ASD in children.

This study has some limitations. First, to control for known risk factors for ASD, we used an adjusted form. However, other studies have reported only the unadjusted OR. This may have introduced bias into our study. Second, the sample sizes of the included studies were small. Despite these limitations, our results

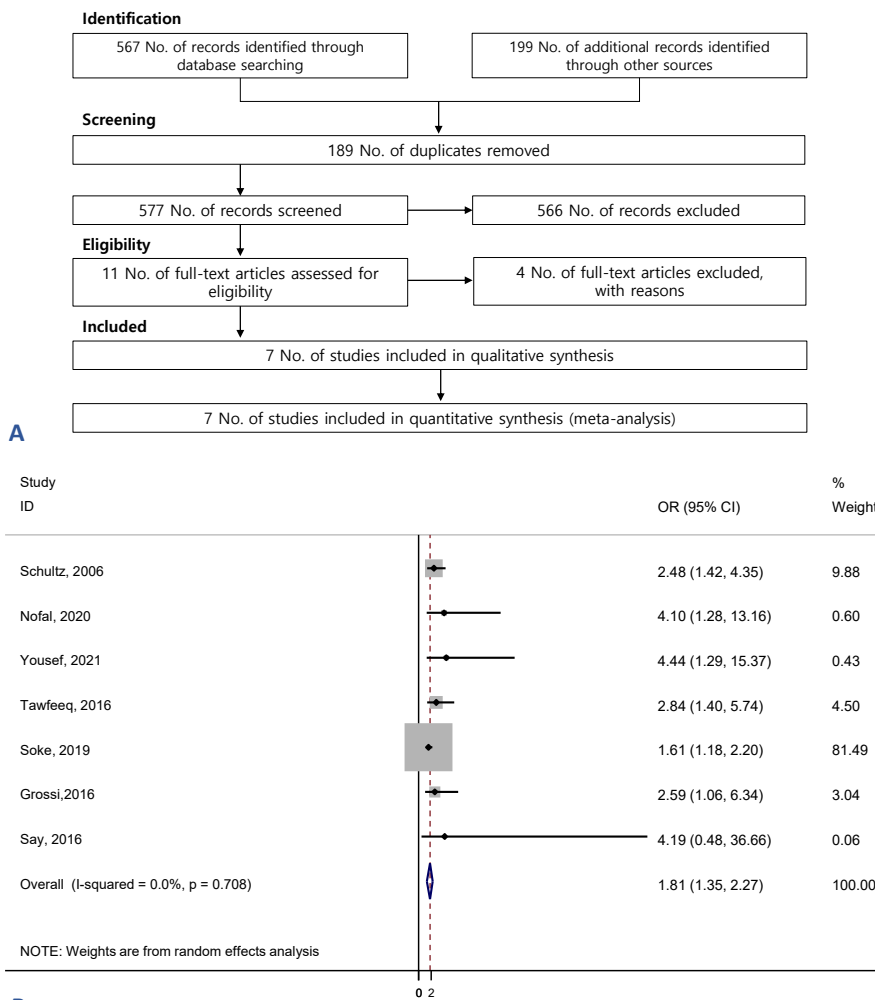


Fig. 1. Flow of information through the different phases of the systematic review. (A) Flow of information through the different phases of the systematic review. (B) Forest plot of not breastfeeding and the risk of autism spectrum disorders. OR, odds ratio; CI, confidence interval.

Table 1. Characteristics of the studies in the present meta-analysis

Study	Country	Design	Sample	Diagnose method	Child age (mean or range based on year or month)	Estimate	Adjustment	Quality
Schultz et al., ⁸⁾ 2006	USA	Case-control	984	Self-report	2–18 Year	OR	Adjust	High
Nofal et al., ¹⁶⁾ 2020	Egypt	Case-control	144	DSM	2–16 Year	OR	Crude	High
Yousef et al., ¹⁸⁾ 2021	Egypt	Cross-sectional	104	DSM-IV/CARS	2–5 Year	OR	Crude	Low
Tawfeeq et al., ⁶⁾ 2016	Iraq	Case-control	200	Not reported	3–15 Year	OR	Crude	Low
Soke et al., ¹⁷⁾ 2019	USA	Cross-sectional	1,549	DSM-IV-TR	30–68 Months	OR	Adjust	High
Grossi et al., ⁷⁾ 2016	Italy	Case-control	113	DSM-IV	12.88 Year in case 9.13 Year in control	OR	Crude	High
Say et al., ⁹⁾ 2016	Turkey	Case-control	176	DSM-IV	3–18 Year	OR	Crude	High

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; CARS, Childhood Autism Rating Scale; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Text-Revised; OR, odds ratio.

Table 2. Results of subgroup analysis of not breastfeeding and autism spectrum disorders

Subgroups	Studies		
	No. of studies	Odds ratio (95% CI)	<i>I</i> ²
Study design			
Case-control	5	2.65 (1.57, 3.73)	0%
Cross-sectional	2	1.62 (1.12, 2.13)	0%
Quality of the study			
Low	2	2.98 (0.91, 5.05)	0%
High	5	1.75(1.28, 2.22)	0%

CI, confidence interval.

suggested that not breastfeeding is a risk factor for ASD. Therefore, breastfeeding is necessary to decrease the risk of ASD in children.

In conclusion, our results showed that not breastfeeding was a risk factor for ASD. Therefore, breastfeeding is necessary to reduce the risk of ASD in children. Our findings suggest that the possible association between ASD and not breastfeeding should be added to the list of reasons to provide breastfeeding support.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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