

The Effects of 6-Month Exclusive Breastfeeding on Febrile Seizure: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: Prior research investigating the variance in febrile seizure (FS) incidence between 6-month-old exclusively breastfed (EBF) and partially breastfed children has yielded inconsistent findings. To fill this void, this study conducted a systematic review and meta-analysis.

Materials & Methods: This study performed a search across electronic databases, including PubMed, Scopus, the Cochrane Library, and Google Scholar without any restrictions, from the year 2000 up to January 2024.

Results: Thirteen studies were reviewed. Regarding six articles (data number=1876753) used in the meta-analysis, EBF (OR=0.65, 95% CI: 0.50, 0.85) and partial breastfeeding (OR=0.92, 96% CI: 0.91, 94) were both significantly associated with lower risks of FS. However, the association in the EBF group was stronger.

Conclusion: Breastfeeding positively affects lowering the risk of FS. Encouraging mothers to breastfeed and implementing preventive strategies can be beneficial for health policymakers in reducing the incidence of FS.

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Introduction

A febrile seizure (FS) is a convulsion in a child triggered by a fever in the absence of a central nervous system infection (1).

The incidence of FS is 2-5% in Europe and North America (2, 3). In Asia, the approximate prevalence ranges from 8.3 to 9.9% (2), from 6 to 9% in Japan (4), 11% in Korea, and 14% in Guam (5). Boys are more sensitive to FS (2, 5-7). FS generally occurs in children 6-60 months of age (2, 8).

FS is the most common cause of status epilepticus, particularly in children aged less than three years. Therefore, identifying the risk factors is crucial for the timely prevention and treatment of FS.

Formula feeding (5, 6, 9), male sex (2, 5-7), increased fever episodes (10), degree of temperature (7, 10), history of prematurity, genetic factors (11, 12), infectious factors (13), any bacterial/viral diseases, and environmental factors are more candidates for FS. The presence of a close family history of FS is the most identified risk factor for FS (14).

Exclusive breastfeeding (BF) is recommended for up to six months of age to achieve optimal growth (World Health Organization). It is recommended to continue BF with the appropriate complementary foods until the age of two or beyond. The percentage of children under six months who were exclusively breastfed is below 50% in most countries (15).

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Seemingly, we need to modify BF support strategies to specific patterns.

BF is the most natural means of feeding and the best source of infant nutrition, offering benefits to both mothers and infants. It diminishes the incidence of many diseases, such as infections, by developing an early immune system. Reducing the risk factors associated with FS is crucial for subsequent monitoring and treatment. The effectiveness of BF in reducing FS is still unclear (10), and prior research shows inconsistent results. According to some studies, children who were breastfed had a lower risk of FS (2, 5, 6, 8, 9, 14, 16, 17). However, another study showed a negative association or no significant relation between BF and the incidence of FS (10, 18).

Managing the risk factors linked to FS in children is crucial given their high prevalence (10). This systematic review and meta-analysis study aims to determine the effect of 6-month exclusive BF on preventing FS in children.

Materials & Methods

This systematic review and meta-analysis study was carried out to investigate published data for identifying the BF and FS association among children aged from six months to seven years. It was logged in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number.

Searches were conducted in the following databases in January 2024: Scopus (n=154), Google Scholar (n=6220), ProQuest (n=20), PubMed (n=50), and Cochrane Library (n=1).

The searched terms for BF were breastfeeding, breast feeding, breastfed, breast feed, lactation, human milk, breast milk, infant feeding, bottle fed, bottle feeding, bottle feed, formula fed, formula milk, formula feed, and weaning. The present study combined the BF terms with the following outcomes keywords: FS; febrile convulsion; simple FS; complex FS.

This study employed the terms found within the titles, abstracts, and keywords of notable articles, along with the key terms and Medical Subject Headings (MeSH) utilized for indexing these articles, to construct the comprehensive search approach for this review. This research used the conjunctions “AND” and “OR” to merge the key terms.

The present study conducted a manual search of references to identify any supplementary studies that could be incorporated into this review. The following outcomes were investigated in each manuscript: FS: Odds ratio comparing breastfed and non-breastfed individuals.

To report the number of studies included and excluded in every phase of the selection and screening process, this study employed a PRISMA flow diagram. The flow charts for selecting studies in the update of systematic reviews are depicted in Figure 1.

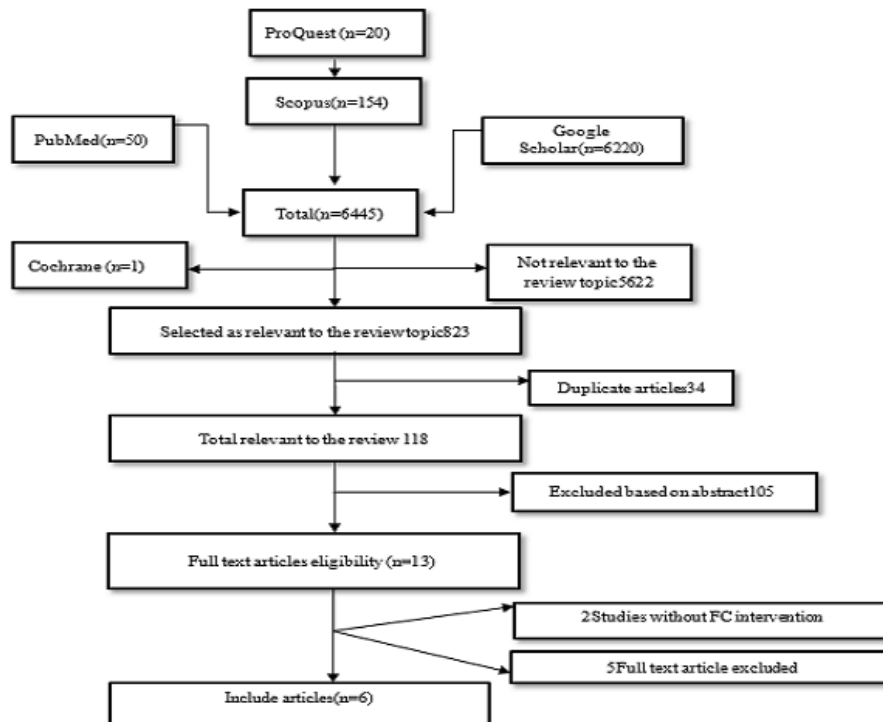


Figure 1: Flow diagram of study selection

Two researchers independently evaluated each paper to determine its inclusion or exclusion based on predefined criteria. Studies meeting the following criteria were included, independent of race, geographical location, or socioeconomic status:

- 1) A study that reported the relation between FS as an exposure and BF.
- 2) Published journals between 2000 and 2024.
- 3) Observational studies employing different study designs considered eligible to be included: Case-control studies, prospective cohort studies, and retrospective cohort studies.

Exclusion criteria

- 1) Animal studies and all other BF research that were not included in the inclusion criteria.
- 2) Studies with patients who have comorbid diseases that affect the study variables.
- 3) Studies not available in English.

Study selection

The selection process involved three stages, independently carried out by two authors—the initial stage involved screening titles, followed by abstracts in the second stage. Finally, full texts of the remaining articles were screened according to the inclusion criteria. A third author was responsible for resolving any disagreements that were not resolved during the selection process. A PRISMA flow diagram was utilized to provide information regarding the number of studies included and excluded at every phase of the selection procedure.

Data extraction

Details extracted from the selected papers contained the following information: The name of the first author, the name of the country, the age of participants, the aim of the study, the design of the study, sample size, duration of study, and outcome.

Quality assessment

Two independent reviewers used the Joanna Briggs Institute (JBI) critical appraisal checklist to assess the methodological quality of the included studies (19), a valid and reliable quality index for the appraisal of observational studies. If needed, a third reviewer participated in discussing and resolving discrepancies. JBI critical appraisal checklists consist of standardized sets of questions, categorized into three versions tailored for case-control and cohort (20) studies, each comprising ten and 11 questions, respectively, concentrating on various components of bias in the study design, conduct, and analysis. Each question is evaluated for bias using a judgment of yes, no, unclear,

or not applicable answers. In advance, the scoring system and cut-off for study inclusion will be determined, and all the reviewers participating must agree before the critical appraisal begins (20). All reviewers agreed that studies with two or more negative responses, suggesting low methodological quality, must be excluded.

Statistical analysis

BF effects were determined by conducting odds ratios (ORs). The inverse of the variance was used to calculate study weights for each study. Weighted averages and 95% confidence intervals were pooled utilizing a random effects model. The I² statistic, representing the percentage of total variation across studies attributed to heterogeneity, was computed to evaluate the statistical heterogeneity between studies. Subgroup analyses were conducted across different levels of qualitative confounders to elucidate potential sources of heterogeneity. The metareg command in STATA was utilized to conduct a meta-regression analysis (21) to assess the relationship between age and ORs. Publication bias was evaluated through funnel plots and Egger's tests. Statistical analysis was performed using STATA version 17 (StataCorp LP, College Station, TX, USA) software. Two-tailed significant probability is considered less than 0.05.

Statistical analysis

ORs and 95% confidence intervals (CI) regarding the relationship of BF with the risk of FS in each study were extracted. The effect sizes were pooled using random effects meta-analysis and the DerSimonian–Laird approach. Meta-analyses were performed for both crude and adjusted effect sizes. The I² statistic was used to assess the heterogeneity of studies. Subgroup analyses based on the type of BF (six months exclusive BF or partial BF) compared to formula were investigated. This study evaluated the risk of publication bias overall via evaluating a funnel plot, including for asymmetry, and Egger's test. In the presence of publication bias, this study performed a trim-and-fill analysis. All statistical analyses were performed by using Stata version 17.0 (StataCorp, College Station, TX), and a 2-sided 0.05 level of significance was used in all cases.

Results

Study characteristics

Following the exclusion of irrelevant or duplicated articles, the extensive primary literature search found 6445 citations. After screening for title and abstract, 13 citations remained. Ultimately, six studies met the

inclusion criteria (Fig. 1). Of the included studies, nine were case-control (2, 6-10, 14, 16, 18), and two were prospective cohort studies (5, 17). Selected articles and study characteristics are listed in Table 2. Studies assessed subjects aged between six months and seven years. The “Population,” “Intervention,” “Comparison,” “Outcome”, and “Study design” (PICOS) were defined: P (Children aged between six months and seven years old, regardless of sex or race). I and C (BF, BF duration or exclusive BF, formula feeding), O (FS), and S (Case-control, cohort studies).

Included studies were published within the last 15 years, and interestingly, all studies were conducted in Asia.

Quality assessment

Each study was evaluated based on 11 items for cohort studies and ten items for case-control studies, and received a score of 0-1. Six out of eleven articles received at least seven “YES” answers and were included in the meta-analysis (Table 1). The mean corresponding and criteria scores for all studies were 75.5%

Table 1: The quality measures of studies

corresponding and criteria scores													
Author	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	Total	%
Yoona	1	1	1	0	0	0	1	1	1	0	1	7	63.5%
Peng	1	1	1	1	1	1	0	1	1	1	-	9	90%
Herman	1	1	1	1	1	0	0	1	0	1	-	7	70%
Amena	1	1	1	1	1	0	0	1	0	1	-	7	70%
Yu Chen	1	1	1	1	1	1	0	1	0	1	-	8	80%
Mitsuda	1	0	1	1	1	1	1	1	0	1	-	8	80%

NB: 1 indicates that the article meets the specified criteria and 0 indicates the article does not meet the stated criteria

Systematic review results

While nonexclusive BF (2, 5, 14), exclusive BF (8), BF duration (7), BF in the first 4-6 months (17), and until two years old (16) showed protective effects against the incidence of FS, the study by Chen et al.

indicated that the risk of FS increased with longer BF duration. Akhundi et al. did not find any significant correlation between FS and EBF in the first six months. In two other studies, formula feeding was identified as a risk factor for FS (6, 9).

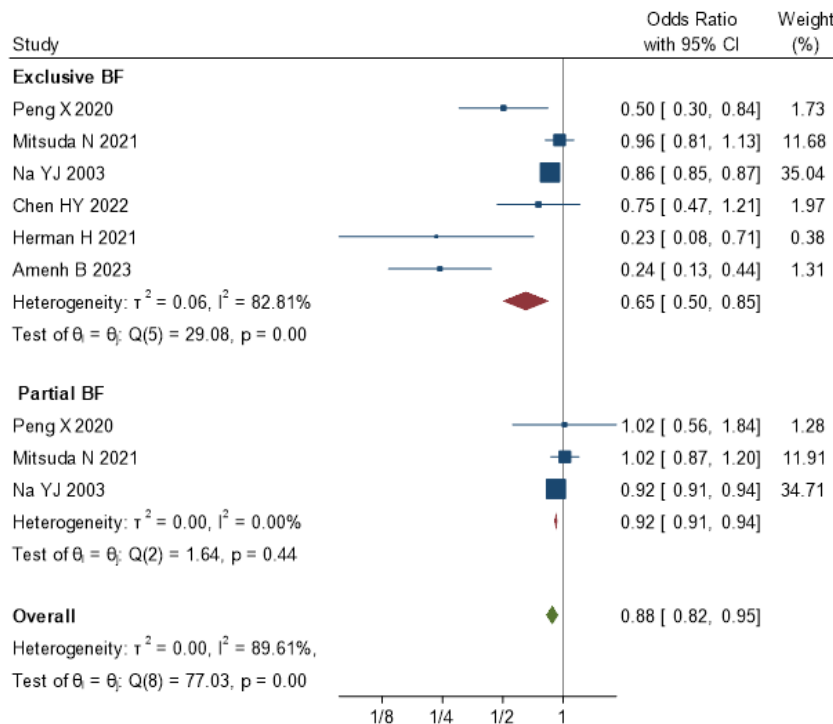


Figure 2: Foerst plot showing the association of exclusive an partial breastfeeding with the risk of FS across studies.

Meta-analysis results

The meta-analysis of crude ORs showed a protective effect of BF on FS (Figure 2). Overall, BF compared to the formula was associated with a lower risk of FS (OR=0.88, 95% CI: 0.82, 0.95). Heterogeneity between studies was considerable (I²=89.0%). In a subgroup analysis, this study investigated the association of six months of exclusive BF and partial BF versus formula. Both exclusive BF

(OR=0.65, 95% CI: 0.50, 0.85) and partial BF (OR=0.92, 96% CI: 0.91, 94) were significantly associated with lower risks of FS, with a stronger association observed in the exclusive BF group.

Egger’s test and funnel plot confirmed the existence of publication bias (Egger’s p<0.001). In a trim-fill analysis conducted to adjust the effect of publication bias, the overall effect did not change substantially (OR=0.90, 95% CI: 0.84, 0.94).

Table 2. Forest plot of crude odds ratios regarding the association between breastfeeding (six months exclusive or partial vs. formula) and febrile seizure. (FS: febrile seizure, BF: breastfeeding, EBF: exclusive breastfeeding, FSE: febrile status epilepticus).

author	country	Age	Aim of study	Design	Number of participants	Duration of study	Outcome
AbolfaziMahyar(7)	Iran (2010)	9 months - 5 years	Recognizing the risk factors for FS among Iranian children.	Case-control study	80 cases 80 controls	2007	The occurrence of the first FS is influenced by BF duration and body temperature.
Amenh B. Yousifa(14)	Egypt (2017)	6–60 months	To discover and quantify the risk factors for FS in Libyan children.	Case control study	100 cases 100 controls	2016-2017	Nonexclusive breast-feeding is risk factors for FS
sharafi R(6)	Iran (2019)	6 – 60 months	To explore the risk factors of FSE in children.	Case-control study	756with FSE EBF=226	2007-2014	Formula feeding, can be identified as risk factors of FSE.
Akhondian(18)	Iran (2006)	6 months - 6 years	To compare the rate of EBF in children with and without FC.	Case-control study	148Cases 100 controls.	2000	There is no significant effect between FS and EBF in the first 6 months, but it may have a protective role for complex FS which is a predisposing factor for epilepsy.
Herman(2)	Indonesia (2021)	3 – 5 years	Investigate the relationship between EBF and the incidence of FS in children.	Observational study with a case-control	30 cases 30controls	January to Mei 2016	EBF is related to the incidence of FS in children
Riyadh Abdulatif Al-Obeidi(9)	Iraq (2021)	6 months - 5 years	To find the risk factors of the first simple FS among children	Case-control	120 cases 120 controls	from January to May 2020	Significant relation was noted between young age, family history, and bottle feeding
Ju Hee Kim(17)	Korea (2021)	6–7 years	To identify the relation between BF in the first 4 - 6 months and subsequent development of childhood diseases between 6 months and 10 years of age.	cohort	188,052 children	Participants were born in 2008 and followed up till 10 years of age	The risk of febrile convulsion decreased with BF compared to formula feeding.
Xia Peng(8)	China (2020)	Case=27.63 month Control=27.43month	To examine the connection between BF during the first 6 months of life and the occurrence of FS	Case control study	336 cases 336 controls	2017-2019	Independently reducing the occurrence of FS can be achieved through EBF
Naomi Mitsuda(16)	Japan (2021)	2-3 years	.To investigate the association between BF and FS during the initial first 3 years of life.	Case-control study	6264 cases,78057 controls	2011-2014	BF until 2 years old, which is the most susceptible age for FS, had a slight but protective effect on FS
Jae Yoon Naa,(5)	Korea (2023)	4 months - 6 years	To determine the protective impact of BF against FS	Cohort study	203492 cases 1587843 controls	2008-2014	BF has a beneficial effect on FS in the most common age range (0 to 2.5 years). Only EBF had a protective effect throughout the entire age period of interest.
Hsi-Yu Chen(10)	Taiwan (2020)	Children younger than 5 years (Children born from 2005–2019)	To investigate the relationship between BF and FS, and to examine the influence of different BF durations	Case-control study	55 cases 110 control	2010 - 2019	The risk of FS increased with longer BF duration

Discussion

This review aimed to examine the effect of BF on FS systematically. A large-scale birth cohort study in Japan realized a negative association between BF and FS (16). In Herman et al.’s research, exclusive BF practices were known to be the risk factors for FS (2). Two studies showed no significant effect on the incidence of FS regarding gender (6, 9, 22).

A study by Chen et al. found that the duration of BF was significant concerning the incidence of FS. They indicated that longer BF duration is associated with an increased risk of FS (10). Exclusive BF refers to the practice of feeding infants solely with breast milk from their mother, a wet nurse, or expressed breast milk, excluding intake of other liquids or solids except drops or syrups consisting of vitamins, mineral supplements, or medicines.

A dose-response relationship was found between the protective effect and the most prevalent time of FS. For instance, partial BF provided less protective effect compared to exclusive BF, and the protection did not sustain through the age of five years. Yoon et al. reported that exclusive BF had a significant protective effect against FS in the first 12 months (aOR: 0.65, 95% CI: 0.42-0.99). However, this effect was not sustained beyond the age of three years (risk ratio 1.04, 95% CI: 0.841.27) (5). Kim et al. showed that this protective effect lasted up to the age of ten years (17). Both Iranian and Japanese studies showed that the shorter duration of BF leads to a higher incidence of FS (7, 16). Japanese studies have shown that BF decreased the FS incidence during the initial year of life. Moreover, with a longer duration, BF has been observed to provide a protective effect against FS (7).

Peng et al. found that BF shows a positive correlation with decreased FS incidence, independent of various potential confounding factors, including birth weight, gender, and delivery mode (8). Mahyar et al.'s study revealed that children who experienced their first FS had a notably shorter mean duration of BF compared to healthy children (7).

Several studies have observed that the majority of FS occur during the second year of life (between 13 and over 25 months), with the peak age being at 18 months (23-25). This is a unique age, more sensitive to fever due to increased neuronal excitability as the brain develops normally (26).

According to the American Academy of Pediatrics, FS are more frequent in children under two years old (27). These children's brain development is more responsive to fever and is predisposed to experiencing seizure attacks at a low threshold level (9).

Breast milk contains anti-inflammatory, antimicrobial, and immunomodulatory factors that protect infants from infections and other diseases (28). These factors play essential roles in shaping and activating the immune system, in addition to influencing the composition of microbiota (5).

Several possibilities and mechanisms are available for the protective effect of breast milk on FS. Firstly, breast milk contains natural taurine, long-chain polyunsaturated fatty acids, and lactose, all of which support white matter growth and nerve myelin formation. Secondly, breast milk contains immunoglobulin A, promoting the child's resistance to infectious diseases. Thus, the chances of fever decrease, which in turn lowers the chances of convulsions. Thirdly, it has been suggested that the three long-chain polyunsaturated fatty acids found in breast milk play a significant role in reducing neuronal excitability and preventing seizures (29). Polyunsaturated fatty acids like docosahexaenoic acid (DHA), arachidonic acid (AA), cholesterol, and sialic acid significantly influence the developing brain and neuronal membranes stabilization through the neuroprotective mechanism (30).

In Conclusion

BF has a positive effect on lowering the risk of FS. Encouraging mothers to breastfeed and implementing preventive strategies can be beneficial for health policymakers in reducing the incidence of FS.

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Limitations and strengths

The strength of this systematic review and meta-analysis lies in its thorough search of all original published studies reporting the effect of BF on FS.

The health impacts of BF may vary depending on income levels. A limitation of this systematic review and meta-analysis is that the findings may not be generalized, as the included studies were conducted in a middle-income country.

Additionally, large sample sizes in two cohort studies can pose a problem. Despite the clinically minor differences observed, the significant differences were detectable due to the expansive sample sizes.

Furthermore, no studies were found assessing the quality of breast milk and complementary foods.

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Authors' Contribution

Bahareh Vard conceptualization; Zahra Akbarzadeh resources; Zahra Akbarzadeh. and Maryam Yazdi data curation; Maryam Yazdi formal analysis; Bahareh Vard and R.K. supervision; Maryam Yazdi validation; Zahra Akbarzadeh. investigation; Bahareh Vard visualization; Maryam Yazdi and Zahra Akbarzadeh. methodology; Zahra Akbarzadeh writing-original draft; Bahareh Vard and Roya Kelishadi project administration; Roya Kelishadi Maryam Yazdi Zahra Akbarzadeh writing-review and editing. All authors reviewed and approved the final manuscript.

Conflicts of Interest

The authors declare that this manuscript has been written without any involvement of influence from governmental support or external resources. furthermore, there are no financial or personal relationships with individuals or organizations that could potentially impact or bias the integrity

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