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Review Article

Association of Iron Deficiency Anemia and Febrile Seizure in Asia: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Current findings suggest that iron deficiency anemia (IDA) may be a predisposing factor for febrile seizure (FS), while some studies show the lower prevalence of IDA in the children with FS. The present systematic review and meta-analysis aimed to elucidate the association between IDA and FS.

Methods: A comprehensive search was performed using MeSH keywords in databases such as PubMed, Scopus, Embase, ScienceDirect, Web of Science, and Google Scholar without time limit until 2017. Cochrane test and I^2 index were used for the evaluation of heterogeneity among the retrieved studies. Data analysis was performed in Comprehensive Meta-Analysis (CMA) software version 2.

Results: In total, 38 studies conducted on 3,738 cases and 3,720 controls were reviewed in this meta-analysis. Considering the significant heterogeneity (I^2=87.981; P<0.001), the odds ratio (OR) was combined using the random effects model. The pooled results indicated that IDA significantly increased the risk of FS (OR=2.36; 95% confidence interval [CI]: 1.72-3.24; P<0.0001). Meta-analysis was performed based on the simple febrile convulsion (FC) and first febrile convulsion (FFC), and OR was estimated at 2.98 (95% CI: 1.67-5.31; P<0.001) and 2.23 (95% CI: 1.33-3.73; P<0.001), respectively. In the subgroup analysis of the studies conducted in Iran, India, and Pakistan, OR was determined at 1.06 (95% CI: 0.71-1.58), 4.21 (95% CI: 2.97-5.97), and 2.22 (95% CI: 1.70-2.90), respectively, which revealed significant differences in this regard (P<0.001).

Conclusion: According to the results, IDA is a predisposing factor for FC. Therefore, children with FS must be examined for the risk of IDA.

Keywords: Anemia, Asia, Febrile seizure, Iron-deficiency, Meta-analysis

Introduction

Febrile seizure (FS) is the most common seizure affecting children with the incidence rate of 2-5% (1, 2), which mainly occurs in children aged six months to five years (3). The exact etiology of FS remains unidentified, while the current findings confirm the role of several genetic and environmental factors in this regard (4, 5). Furthermore, several studies have suggested that iron deficiency anemia (IDA) may be a predisposing factor for FS (6-8).

Iron deficiency is the most common nutritional deficiency in infants and children (9-11). Iron is an important micronutrient that affects the function of neurotransmitters and several enzymes of the nervous system. Since iron is essential for myelination, it could be associated with the occurrence of seizures (12, 13). Impaired motor function, sensory system performance, and cognitive development are among the other consequences of iron deficiency (14).

The peak incidence of IDA has been reported in the children aged 9-24 months (15, 16). Evidence suggests an association between age and the maximum incidence of IDA and FS (17). Several studies have been conducted worldwide to evaluate the correlation of IDA and FS although the results are controversial. For instance, the study by Kamalammal et al. showed no strong

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association between IDA and FS (18). Similarly, Amirsalari et al. observed no significant differences in the hemoglobin (Hb), mean corpuscular volume (MCV), and plasma ferritin between the patient with FS and control subjects (19). In this regard, Derakhshanfar et al. reported the lower risk of FS in anemic children (4), while Momen et al. claimed that iron deficiency is more common among the children with the first episode of FS (20).

On the other hand, Waheed et al. stated that iron concentration is not associated with the occurrence of FS (21). Kumar et al. reported the higher susceptibility to FS in the cases with iron deficiency (22), which is consistent with the results obtained by Kankane and Sreenivasa (23, 24). However, the level of serum ferritin was not associated with FS in the case-control study by Talebian (25). In another research, Ghasemi and Valizadeh considered IDA to be a risk factor that might be involved in FS (26, 27). In the study by Hartfield, the findings showed the higher rate of iron deficiency in the cases with FS compared to healthy controls (6). In addition, in the research by Miri-Aliabad et al., 44% of the cases and 36% of the controls were diagnosed with IDA (28).

Objectives

A meta-analysis involves the use of specific statistical methods to summarize the results of independent studies in order to find the most accurate correlations between the studied variables. These statistical methods help review the data of various articles without the effect of personal comments on the process (29-32).

Several studies focusing on the association of IDA and FS have suggested that IDA is a risk factor for FS. Nevertheless, there is no concordance between the research findings in this regard, and some studies have denoted the lower risk of FS in the patients with IDA.

Considering the discrepancy in the current findings, the present study aimed to combine the results of various studies to reach a conclusion.

Methods

Data sources

This systematic review and meta-analysis was conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (32). A third author resolved the disagreement between the two independent researchers regarding all the research procedures.

A comprehensive search was conducted in databases such as Scopus, PubMed, Science Direct, Embase, Web of Science, Google Scholar and reference lists of the retrieved publications in order to identify the epidemiologic studies relating to IDA and FS with no time limit until September 2017. Literature search strategies were developed for each database through combinations of keywords, including “Anemia, Iron-Deficiency" [MeSH], "Seizures, Febrile" [MeSH], "Iron Deficiency", "Seizures" [MeSH], and "Asia" [MeSH].

Inclusion and exclusion criteria

Inclusion criteria of the review were the epidemiological case-control studies and cross-sectional or cohort studies published in English until September 2017, which investigated the association of IDA and FS. Exclusion criteria were as follows: 1) duplicate studies; 2) irrelevant studies; 3) articles with missing or insufficient data (e.g., not investigating the impact of IDA on FS by odds ratio (OR) and 4) letters to editor, case reports, and review articles.

Quality assessment

The selected articles were evaluated by two authors using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (33), and the lowest acceptable score was considered to be 8. STROBE consists of 22 sections, each of which is scored with the range of 0-1. In terms of quality, the retrieved studies were classified as low-quality (score: <8), average-quality (score: 8-16), and high-quality (score: >16). High- and average-quality studies were selected for the meta-analysis.

Data extraction

Data of the selected articles were extracted, including the first author, country, year of study, study design, journal’s name, characteristics of the case and control samples (gender, mean age, sample size), IDA diagnostic criteria, OR with 95% confidence interval (CI), and positive/negative IDA in the case and control groups.

Meta-analysis

In the current review, OR was used to determine the effect of IDA on FS, and OR with 95% CI was estimated in the selected studies. In addition, Cochran's Q test and I^2 index were used to evaluate the heterogeneity of the articles (34, 35). Due to the high heterogeneity, the random effects model was employed to combine the

retrieved studies. Sensitivity analysis was performed by removing one study to investigate the stability of data, and cumulative analysis was carried out based on the year of publication. To find a source of heterogeneity, a subgroup analysis was conducted based on the country. Begg and Egger's tests were also used to assess publication bias. Data analysis was performed in the Comprehensive Meta-Analysis (CMA) software version 2.

Results

Literature search results

In total, 560 articles were retrieved from the related databases in the present study, 280 of which were excluded due to duplication. Additionally, the abstracts of the remaining 280 articles were reviewed, and 221 irrelevant articles were excluded from further evaluation. The full texts of the remaining articles were reviewed, and 21 articles were excluded (Figure 1). Finally, 38 studies, which were conducted on 3,738 cases and 3,720 controls, were reviewed and analyzed (Table 1). Mean age of the case and control groups in the selected studies was 23.80 months (95% CI: 21.27-26.32) and 23.77 months (95% CI: 21.03-26.52), respectively.

Overall association of IDA and FS

In the present review, the selected studies had high heterogeneity (I^2=87.98; P<0.001). The pooled results were indicative of a significant overall association between IDA and FS (OR=2.36; 95% CI: 1.72-3.24; P<0.001) (Figure 2).

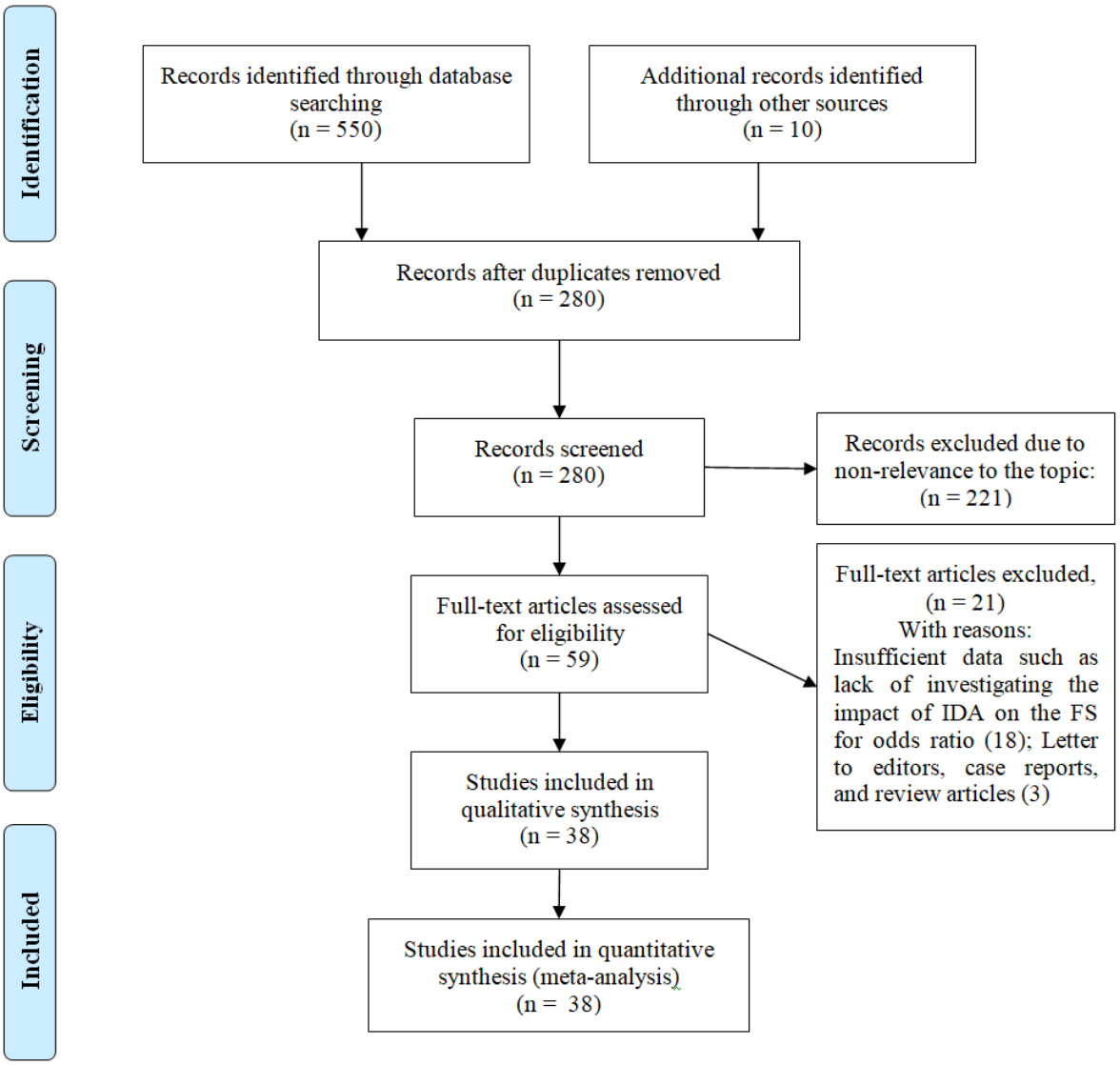
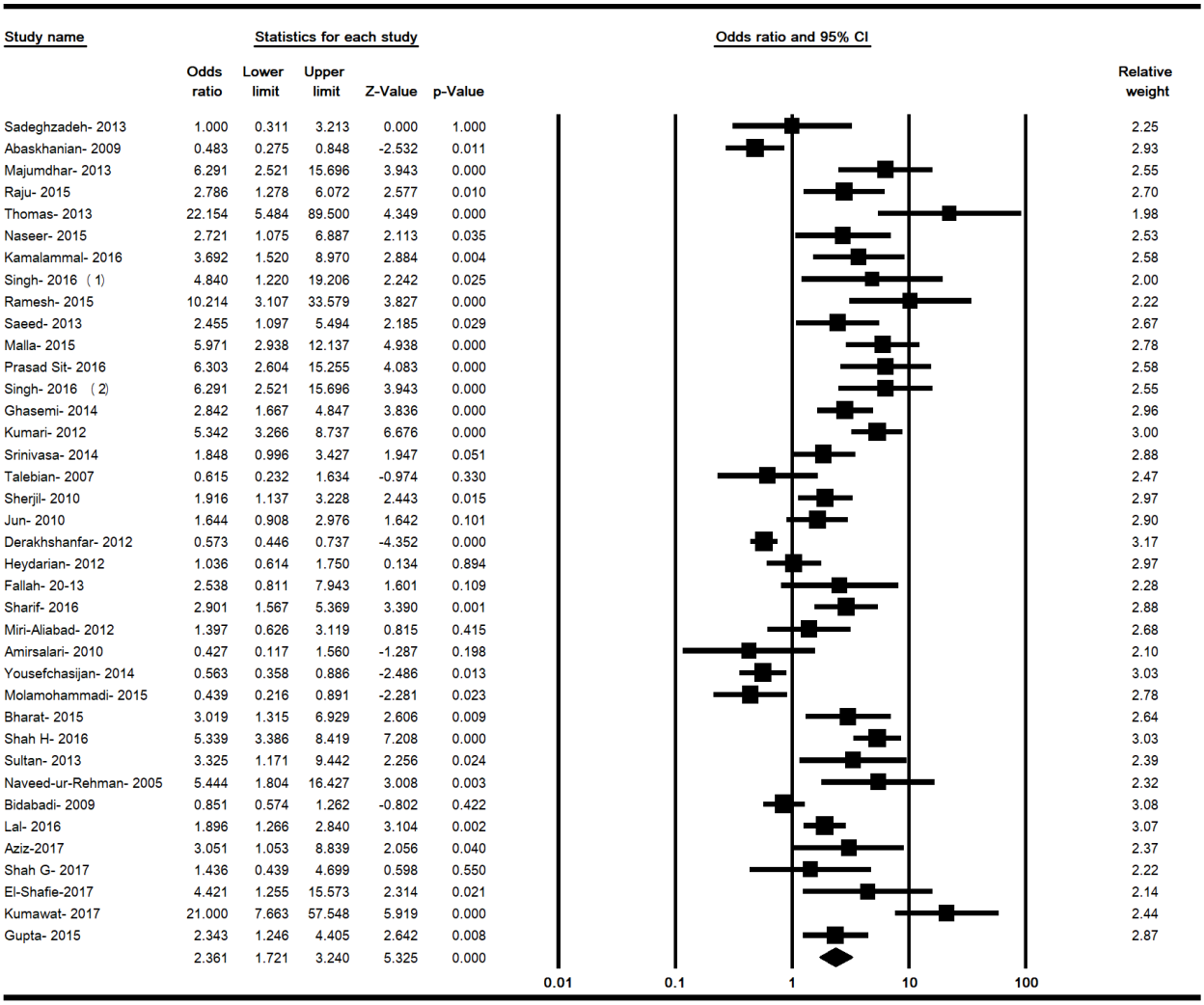


Figure 1. PRISMA Flow Diagram

Table 1. Data Obtained from Reviewed Studies on Association of Iron Deficiency Anemia (IDA) and Febrile Seizure (FS)

Author	Year	Country	Case		Control		Diagnostic Criteria
			Total	Positive IDA	Total	Positive IDA	
Sadeghzadeh (38)	2013	Iran	100	6	100	6	Hb<10.5 g% serum iron to TIBC ratio of <12%, MCV<70 fl
Abaskhanian (39)	2009	Iran	100	42	100	60	Hb and Hct<2 SD of normal values for age
Majumdhar (7)	2013	India	50	29	50	9	Hb<11g/dl, MCV<70 fl, MCH<27 pg, plasma ferritin<12 µgm/dl; serum iron<60 µg/dl, TIBC>450 µg/dl, transferrin<250 mg/dl
Raju (40)	2015	India	75	63	75	49	Hb≤11 gm/dl, serum ferritin≤30 ng/ml
Thomas (41)	2013	India	75	72	13	25	Hb<2 SD of normal value for age
Naseer (42)	2015	India	100	17	100	7	Hb<11 g/dl, MCV<70 fl, MCH<27 pg, plasma ferritin<12 µgm/dl
Kamalammal (18)	2016	India	24	50	10	50	Hb<11 g/dl, MCV<73 fl, MCHC<24 pg/dl
Singh (8)	2016	India	11	36	3	36	Hb<11.5 g/dl, MCV<72 fl, MCHC<23, serum ferritin<30 µgm/dl, RDW>15%
Ramesh (43)	2015	Iran	43	22	43	4	Hb<11 g/dl, MCV<70 fl, MCH<25, serum ferritin <20 µgm/dl
Saeed (44)	2013	Pakistan	50	32	50	21	Low serum ferritin level
Malla (45)	2015	Nepal	92	57	70	15	Hb<2 SD of normal value for age
Prasad Sit (46)	2016	West Bengal	50	32	50	11	Hb<11 g/dl, MCV<70 fl, MCH<27 pg, serum ferritin<25-50 µg/Dl
Singh (47)	2016	India	50	29	50	9	Hb<11 g/dl, MCV<70 fl, MCH<27 pg, plasma ferritin<12 gµgm/dl
Ghasemi (27)	2014	Iran	100	40	200	38	Hb<10.5 g/dl, hematocrit (Hct)<33%, MCV<70 fl, MCH<23 pg, MCHC<30 g/dl, RBC<3.7×106 cell/mm^3 In children aged 2-5 years, IDA was defined as Hb<11.5 g/dl, Hct<34%, MCV<75 fl, and MCH<24 pg.
Kumari (48)	2012	India	154	98	154	38	Hb<11 g%, red cell distribution width>15%, serum ferritin value<12 ng/ml
Srinivasa (49)	2014	India	108	37	100	22	Hb<11 g%, serum ferritin<12 ng/ml, RDW>15%
Talebian (50)	2007	Iran	60	8	60	12	Hb<2 SD of normal value for age
Sherjil (17)	2010	Pakistan	157	50	153	30	Hb<9 g/dl, serum ferritin<7, MCV<65, MCHC<28
Jun (51)	2010	Korea	100	39	100	28	Hb<10.5
Derakhshanfar (4)	2012	Iran	500	223	500	292	Hb<2 SD of normal value for age
Heydarian (52)	2012	Iran	120	45	120	44	Hb<10.5 g/dl
Fallah (26)	2013	Iran	50	11	50	5	Serum ferritin<12 ng/ml if CRP was negative or 1+, ferritin<30 ng/ml if CRP was ≥2+, or serum iron<22 µg/dl or transferrin saturation<16%
Sharif (53)	2016	Iran	100	45	100	22	Hb< 10.5 g/dl for children aged six months-two year, Hb<11.5 g/dl for children aged 2-5 years
Miri Aliabad (28)	2012	Iran	50	22	50	18	Hb<11 g/dl in age range of 6-48 months, Hb<11.5 g/dl in age range of 48-72 months
Amirsalari (19)	2010	Iran	132	4	88	6	Hb<10.5 mg/dl, plasma ferritin<12 ng/dl, MCV<70 fl
Yousefchaijan (54)	2014	Iran	191	43	191	65	

Continuous of Table 1.							
Molamohammadi (55)	2015	Iran	65	22	65	35	Hb<2 SD of normal value for age
Bharat (56)	2015	India	50	27	50	14	
Shah H. (57)	2016	India	180	114	180	44	Hgb<11, RDW<15%, Frrt<30
Sultan (58)	2013	Pakistan	31	21	31	12	Hb<11 g/dl
Naveed-ur-Rehman (59)	2005	Pakistan	30	21	30	9	
Bidabadi (60)	2009	Iran	200	88	200	96	Hb and Hct <2 SD of normal value for age
Lal (61)	2016	Pakistan	255	82	255	51	
Aziz (62)	2017	Pakistan	30	21	30	13	Hb<11.5 g/dl
Shah G (63)	2017	India	34	8	34	6	Hb<11 g/dl, RDW>15.6%, MCV<70 fl
El-Shafie (64)	2017	Egypt	40	21	20	4	Hb<11 g/dl, Hct<33%, MCV<74 fl, MCH<24 pg, MCHC<32%, SI<50 µg/dl, SF<12 µg/dl, TIBC>400 µg/dl, transferring saturation<15%
Kumawat (65)	2017	India	60	54	60	18	
Gupta (66)	2015	India	70	46	100	45	Hb<11 g%, serum ferritin<12 ng/ml



Meta Analysis

Figure 2. Meta-Analysis of Studies on Association of FS and IDA (mean point of each segment shows the estimated OR, and the length of each segment shows 95% CI in each study; the diamond mark shows the OR in each study.)

Cumulative and sensitivity analysis

Cumulative analysis of the association between FS and IDA is depicted in Figure 3. Accordingly, a significant association was reported between FS and IDA in 2014. In addition, a sensitivity analysis

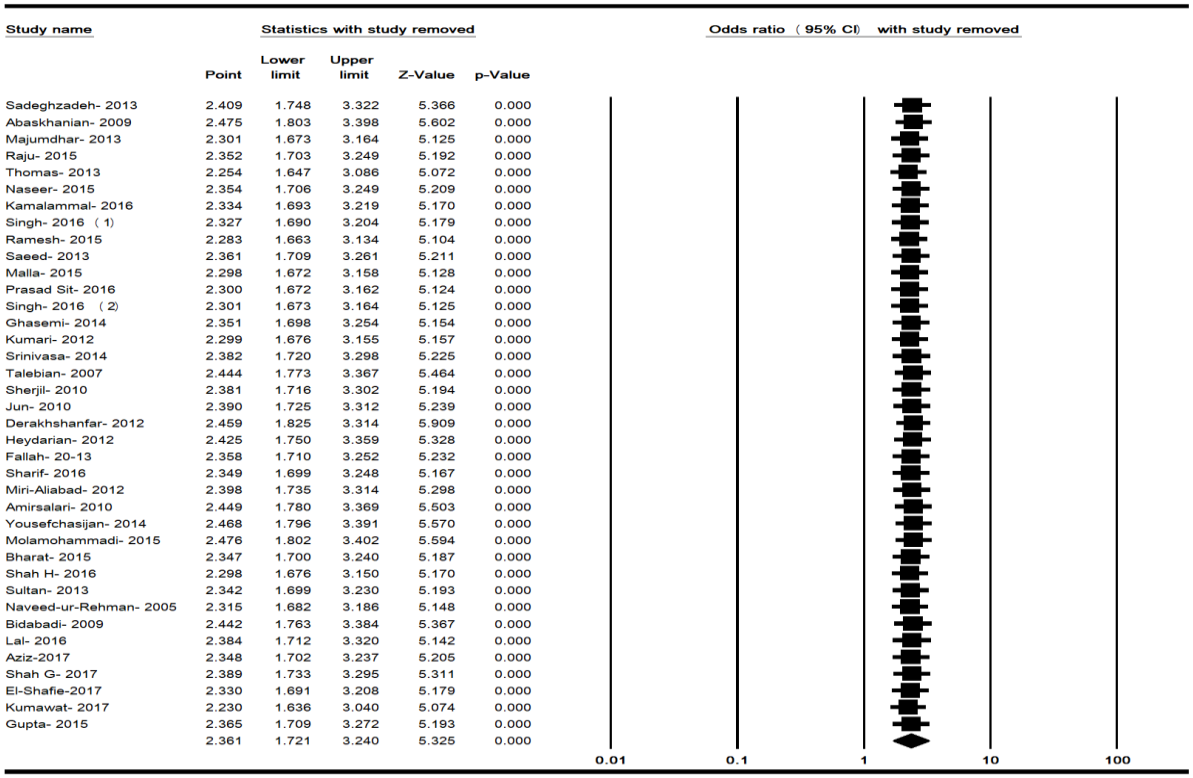


Figure 3. Cumulative Analysis (A) and Sensitivity Analysis (B) in Meta-Analysis on Association of IDA and FS

was performed by removing one study, which indicated good stability (Figure 3).

Association of IDA and FS based on seizure type

Meta-analysis was conducted based on the simple febrile convulsion (FC) and first febrile convulsion (FFC), and OR was estimated at 2.98 (95% CI: 1.67-5.31; P<0.001) and 2.23 (95% CI: 1.33-3.73; P<0.001), respectively (Figure 4). Moreover, a sensitivity analysis was performed by removing one study, which indicated good stability.

Subgroup analysis based on country

The results of subgroup analysis showed that the association of IDA and FS was not significant in 14 studies conducted in Iran on 1,811 cases and 1,868 controls (OR=1.06; 95% CI: 0.71-1.58; P=0.76). On the other hand, the association was considered significant in 14 studies performed on 1,092 cases and 1,064 controls in India (OR=4.21; 95% CI: 2.97-5.97; P<0.001). Furthermore, test results regarding the differences in the subgroup analysis were significant (P<0.001) (Table 2).

Publication bias

In the Egger and Begg tests, P-value was estimated at <0.001 and 0.11, respectively (Figure 5).

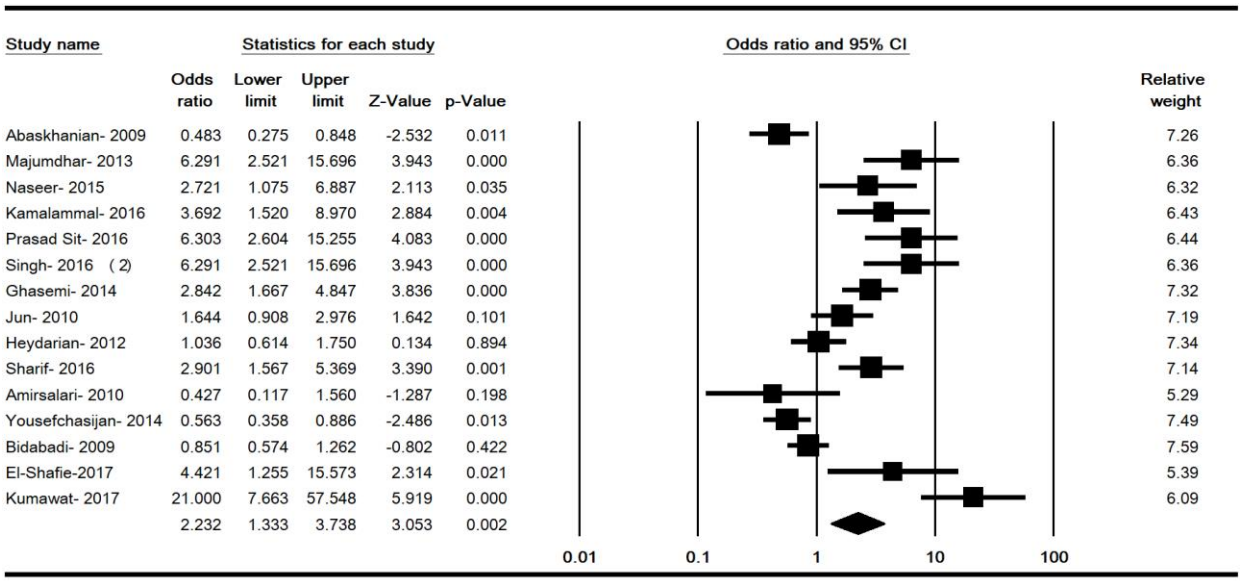


Figure 4. Meta-Analysis of Studies on Associations of SF (A), FFC (B), and IDA

Table 2. Subgroup Analysis of Association between IDA and FS Based on Country

Type of Seizure	Studies (N[a])	Case/Control (N)	Heterogeneity		OR[b]	95% CI[c]	P-value (significant)
			I^2	P-value			
Iran	14	1811/1867	83.47	<0.001	1.063	0.71-1.58	0.30
India	14	1092/1064	62.34	0.001	4.213	2.97-5.97	<0.001
Pakistan	6	553/549	0	0.49	2.225	1.70-2.90	<0.001
Nepal	1	92/70	-	-	5.97	2.93-12.13	<0.001
West Bengal	1	50/50	-	-	6.30	2.60-15.25	<0.001
Korea	1	100/100	-	-	1.64	0.90-2.97	<0.001
Egypt	1	40/20	-	-	4.42	1.25-15.57	<0.001

Test for difference in subgroup analysis: Q-Value: 39.64; df(Q): 6; P<0.001
a: Number, odds ratio, b: odds ratio c: confidence interval

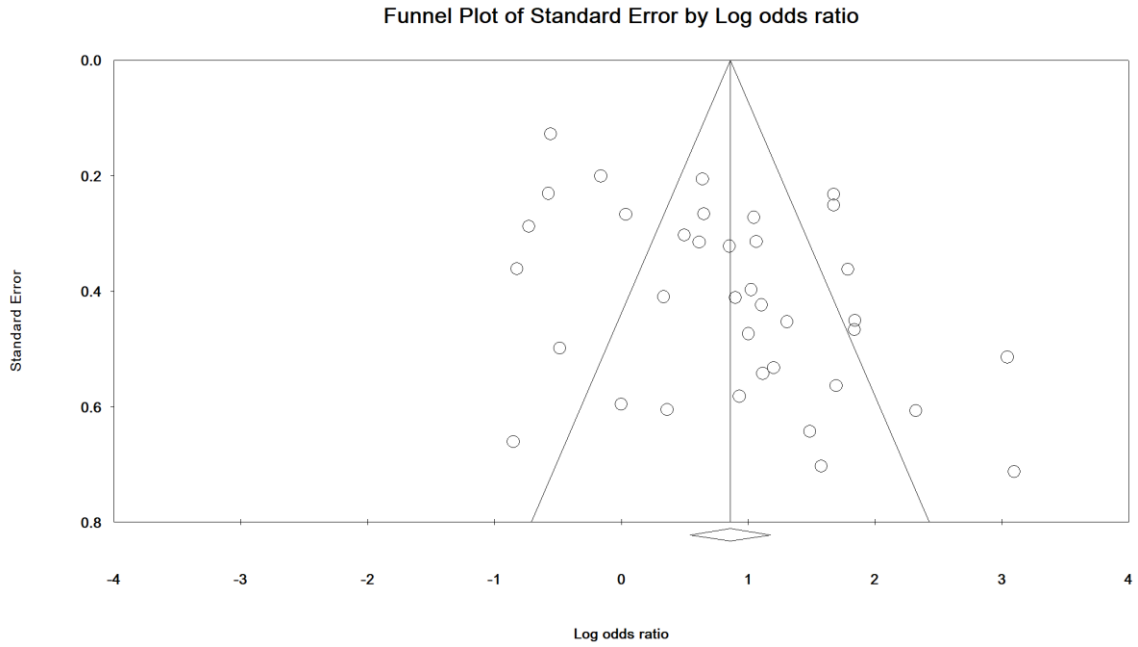


Figure 5. Publication Bias in Meta-Analysis of Studies on Association of FS and IDA

Discussion

After searching in the related databases, article selection, and quality assessment, 38 studies were considered suitable for the final analysis in the present study, which resulted in the OR of 2.36 (95% CI: 1.72- 3.24; P<0.001). In most of the selected studies, OR was significant, which suggested that IDA is a significant risk factor for FS. Moreover, the rate of heterogeneity was high (I^2=87.981; P<0.001), and therefore, the random effects model was employed, and subgroup analysis was performed based on the seizure type and country. Our findings are in line with the systematic review and meta-analysis conducted by Nasehi et al., which analyzed 11 studies that were conducted on FC patients and control groups, and IDA was reported to be a risk factor for FC with the overall OR of 1.27 (CI 95%: 1.03-1.56) (36).

In another systematic review and meta-analysis, IDA was observed to be more common in the febrile convulsion group compared to the control group with the combined OR of 1.52 (95% CI: 1.03-2.25), introducing IDA as a risk factor for FC (37). Iron deficiency and IDA could induce seizures through the mechanism of hypoxemia, alteration of neurons and brain metabolism, changes in the gamma-butyric acid metabolism and reduction of this neurotransmitter, myelination impairment, and decreasing the level of enzymes such as aldehyde oxidase (66-69).

One of the limitations of the current review was that most of the collected studies were conducted in Asia, which affects the generalizability of the findings. Moreover, types of the seizures were not mentioned in some articles. The main strength of our study was the review of various articles and performing subgroup analysis based on different variables.

Conclusion

According to the results, there is a strong association between IDA and FS. Therefore, it is recommended that children with FS be screened for iron deficiency in order to reduce the risk of FS. Appropriate and timely detection and management of IDA in children could effectively prevent FS and its neurological consequences. Further investigations must be conducted on larger sample sizes in diverse geographical regions so as to enhance the accuracy of the findings in this regard.

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Conflicts of interests

None declared.

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