Original Article

Breastfeeding and early childhood caries: a meta-analysis of observational studies

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Background and Objectives: The associations of breastfeeding and early childhood caries (ECC) risk have been evaluated in several epidemiological studies with conflicting results. We performed an update meta-analysis to estimate the association of feeding patterns, breastfeeding durations and ECC risk. **Methods and Study Design:** Studies were identified through searching Pubmed, Web of Science, and Embase from January 1990 to December 2015. **Results:** Thirty-five studies involving 73,401 participants aged 0-71 months were included. The overall analysis showed children ever breastfed had a reduced risk of ECC compared with those never breastfed (OR=0.77, 95% CI: 0.61-0.97, p=0.026). Subgroup analysis revealed ever breastfeeding significantly reduced ECC risk for the studies with 3-6 years old children (OR=0.70, 95% CI: 0.54-0.90, p=0.005), with sample size >500 subjects (OR=0.63, 95% CI: 0.46-0.87, p=0.004), with Newcastle-Ottawa Scale (NOS) score ≥6 (OR=0.66, 95% CI: 0.46-0.94, p=0.023), published after 2010 (OR=0.50, 95% CI: 0.30-0.82, p=0.006), with adjusted OR (OR=0.40, 95% CI: 0.18-0.88, p=0.023). Exclusive breastfeeding did not significantly decrease ECC risk compared with bottle feeding (OR=0.68, 95% CI: 0.35-1.31, p=0.248). The children breastfed ≥12 months significantly increased ECC risk compared with those breastfed <12 months (OR=1.86, 95% CI: 1.37-2.52, p<0.001). Whereas, children breastfed ≥6 months did not significantly increase ECC risk compared with those breastfed <6 months (OR=1.13, 95% CI: 0.83-1.53, p=0.428). **Conclusions:** Our analysis suggests ever breastfeeding may protect children from ECC, and breastfeeding duration ≥12 months is associated with higher ECC risk. Additional large cohort studies are required to illustrate the relationship in further study.

Key Words: breastfeeding, feeding pattern, early childhood caries, meta-analysis, association

INTRODUCTION

Early childhood caries (ECC) is defined as the presence of one or more decayed teeth (with non-cavitated or cavitated lesions), missing teeth (due to caries), or a filled surface on any primary tooth in a child aged 71 months or younger.[1] ECC is the most common infection related disease in young children worldwide.[2,3] Its initiation and progression is also associated with cultural, social, behavioral, nutritional and biological risk factor.[4,5] Children experiencing caries as infants or toddlers have a much greater probability of subsequent caries in both the primary and the permanent teeth.[6] Not only does ECC affect the dental health, but it also leads other health consequences (e.g. pain, infection, altered eating habits or sleep disturbances), childhood development (e.g., altered cognitive development, reduced speech development or reduced growth involving low body weight and height), and psychological outcomes for both children and their families (e.g., altered wellbeing and quality of life, poor self-esteem or altered concentration).[5,7,8] These observations underscore the critical importance of elucidation of the causes and etiology of this disease.

The latest publication[9] conducted a rudimentary systematic review and meta-analysis including only five studies and found reduced risk of dental caries in children breastfed more versus less up to 12 months of age. The another systematic review and meta-analysis including only 2 cross-sectional studies[10] found breastfed children were less affected by dental caries than bottle fed children. The latest large scale study has investigated the association between breastfeeding duration and the risk of ECC from the age of 30 to 66 months in Japan including 43,383 infants, which found an association between breast feeding for at least 6 or 7 months and elevated risk of dental caries at age 30 months and the association became attenuated as children grew older.[11] Therefore, it still needs a comprehensive, thorough and deeper

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meta-analysis for the associations between breastfeeding and ECC involving more studies.

To comprehensively summarize the current evidence for the association between breastfeeding and ECC, we conducted an updated meta-analysis focusing on the infancy feeding patterns and duration of breastfeeding including 35 studies consisting of 73,401 children aged 0-71 months.

METHODS

Data sources and search strategy

A comprehensive literature search was conducted to identify the association between breastfeeding and ECC. Published papers were identified from three electronic databases: Pubmed (www.pubmed. gov), Web of Science (http://www.isiknowledge.com), and Embase (http://store.elsevier.com/embase), from January 1990 to December 2015. The following search terms were used: "breastfeeding" OR "breast feed" OR "breast fed" OR "lactation" OR "feeding pattern" combined with "dental caries" OR "early childhood caries" OR "tooth decay". Besides, the references of the original literatures and the related articles were also searched for potential complements, especially the reviews and meta-analysis.[9,12]

Inclusion criteria and exclusion criterion

The following inclusion criteria were used for the present meta-analysis: 1) original articles about the association between infant feeding patterns and early dental caries; 2) birth cohort, case-control and cross-sectional study design; 3) studies providing infant feeding patterns in detail including breastfeeding, bottle feeding and mix feeding, or duration of breastfeeding; 4) studies with sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); 5) published in English.

Accordingly, the following exclusion criteria were also considered: 1) abstracts, reviews, letters to the editor, case report and repeated publications; 2) studies without sufficient data for estimating the OR with 95% CI; 3) studies without specific feeding pattern; 4) published in other languages.

Data extraction

Two authors extracted data independently (Lingling Cui and Yalan Tian), and discrepancies were resolved through discussion. The following information was extracted from the selected literatures: name of first author, year of publication, study design, country where the study was performed, ethnicity of the population, age range of children, number of children, ECC case number in each feeding group, diagnostic criteria of ECC and OR adjusted. If the same study participants were used by more than one publication, the data were only collected from the largest sample size or more authoritative scientific journal, which have higher impact factor.

Additionally, assessment of quality for the included studies were conducted independently by two researchers (Lingling Cui and Yalan Tian) using the Newcastle-Ottawa Scale (NOS).[13] The scores of the quality were calculated to evaluate the quality of the included studies (Supplementary table 1-3).

Statistical analysis

The combined ORs together with their corresponding 95% CIs were used to calculate and assess the strength of association between the breastfeeding and ECC. For observational studies, we synthesized ORs comparing the extreme categories of feeding pattern of infants (ever breastfed vs never breastfed, exclusive breastfeeding vs bottle feeding, as defined within each study) or the duration categories of breastfeeding (breastfeeding ≥12 months vs. breastfeeding <12 months, breastfeeding ≥6 months vs. breastfeeding <6 months), respectively. To reveal the possible confounding factors which might affect the results of the published reports, we performed further analysis by subgroup analysis based on age, economic level, sample size, study design, NOS score, ethnicity, published year, adjusted OR and diagnose criteria.

Heterogeneity assumption was examined by the chi-square based on Q-test. The pooled OR estimation of each study was calculated with a random-effect model using the DerSimonian and Laird method when $p<0.05$, otherwise with a fixed-effect model using the Mantel–Haenszel method.[14] Publication bias was evaluated through the Begg's test, the Egger's Asymmetry test, and visual inspection of funnel plots, in which the standard error was plotted against the Log (OR) to form a simple scatter plot. The sensitivity analysis was performed by omitting one study at a time to assess the stability of the meta-analysis results. The unchanged pooled OR implied the stable result.

The statistical analyses were performed using STATA version 11.0 (Stata Corporation, College Station, TX). All the p values were for a two-tailed test and $p<0.05$ was considered as statistically significant.

RESULTS

Literature search, study characteristics and quality assessment

A total of 344 studies on the association of breastfeeding and ECC were identified and screened for data retrieval. First, 63 potential reports were screened through reviewing the titles and abstracts. Second, 15 papers were excluded for reviews, without specific data, other dental disease and repeated publication. Third, 13 papers were excluded without exact data, irregular cutting point and RCTs.[15-18] Finally, 35 studies from 35 original articles were qualified for the meta-analysis, including 11 birth cohort studies, 3 case-control studies and 21 cross-sectional studies with 73,401 children aged 0-71 months. The study selection process is presented in Figure 1.

Tables 1 and 2 present the primary characteristics and the main outcomes of 22 studies on the association of different feeding pattern and ECC, including 6 birth cohorts,[19-24] 3 case-control studies[24-26] and 13 cross-sectional studies[27-39] with 52,389 children younger than 66 months. Of these 21 original reports, 10 studies provided the detail information about ECC prevalence in breastfeeding, bottle feeding and mix feeding groups,[19-21,24,27-31] and 12 studies provided the data on ever breastfeeding and never breastfeeding.[22,23,25,26,32-39] Exclusive breastfeeding and mixed feeding were combined and considered as ever breastfeeding. Table 3 shows the characteristics and summarized outcomes of 15 studies focused

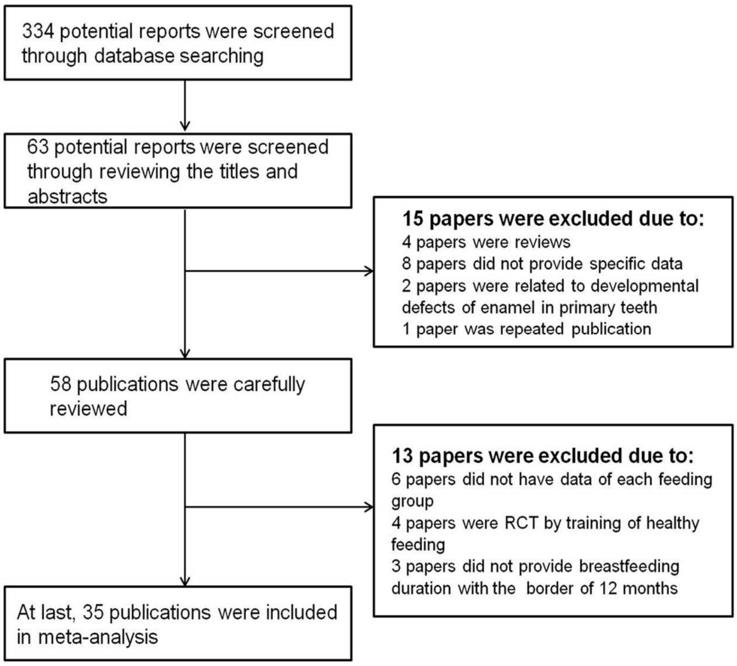

Figure 1. A flow diagram for the selection of studies and specific reasons for exclusion in this meta-analysis

on the association of different duration of breastfeeding and ECC, including 5 birth cohorts[40-44] and 10 cross-sectional studies[34,35,45-52] containing 23,696 participants aged 8-71 months.

The quality scores of included studies ranged from 1 to 9 based on the NOS score system. There were 13 studies considered as high quality ones (NOS score ≥6), including 9 birth cohort studies, 3 case-control studies and one cross-sectional study. Whereas 22 studies were low quality studies (NOS score <6), including 1 birth cohort study and 21 cross-sectional studies.

Feeding patterns and risk of ECC

Twenty-two studies including 52,389 children younger than 66 months were pooled to estimate the risk of ECC for ever breastfeeding compared with never breastfeeding. Overall, children ever breastfed had a reduced risk of ECC compared with those never breastfed (OR=0.77, 95% CI: 0.61-0.97, p=0.026, Figure 2A), with high evidence of heterogeneity (I^2=85.6%, p<0.001). To search the possible influencing factors on the overall results, we performed a further analysis on data stratified by age, economic level, sample size, study design, NOS score, ethnicity, year of publication, OR adjusted, diagnose criteria (Table 4). The only finding in the subgroup analysis was that ever breastfeeding significantly decreased the risk of ECC for the studies with children aged 3-6 years (OR=0.70, 95% CI: 0.54-0.90, p=0.005), the studies with sample ≥500 subjects (OR=0.63, 95% CI: 0.46-0.87, p=0.004), the studies with NOS score ≥6 (OR=0.66, 95% CI: 0.46-0.94, p=0.023), the studies published after 2010 (OR=0.50, 95% CI: 0.30-0.82, p=0.006), the studies with adjusted OR (OR=0.40, 95% CI: 0.18-0.88, p=0.023). However, we did not find any significant association between breastfeeding and ECC risk in the studies with children aged 0-3 years old, with sample size <500 subjects, with NOS score <6, published before 2010 and with unadjusted OR. We did not detect any significant difference between breastfeeding and ECC in the subgroup analysis stratified by economic level, study design, ethnicity, and diagnosed criteria. The heterogeneity was weakened significantly both in the stratified analysis by ethnicity and publication date.

To assess whether each individual study would affect the final results, sensitivity analysis was performed by excluding one study at a time. In this way, three studies[11,33,37] were postulated to affect the result slightly and no association was detected after the three studies were excluded, respectively (Supplementary figure 1, Supplementary table 4). Neither the Begg's test nor Egger's test provided any obvious evidence of publication bias (Z=0.23, p=0.822; t=-0.79, p=0.438). The shapes of the funnel plots appeared to be symmetrical (Figure 3A).

Additionally, the association for exclusive breastfeeding on the risk of ECC compared with bottle-feeding was estimated involving 10 studies including 13,075 children. The overall meta-analysis showed exclusive breastfeeding did not significantly decrease the risk of ECC relative to bottle feeding (OR=0.68, 95% CI: 0.35-1.31, p=0.248) (Figure 2B).

Breastfeeding duration and risk of ECC

Fourteen studies involving 15,029 children were pooled to estimate the effect of duration of breastfeeding on the risk of ECC. Overall, breastfeeding ≥12 months could increase the risk of ECC compared with breastfeeding <12 months (OR=1.86, 95% CI: 1.37-2.52, p<0.001) with high evidence of heterogeneity (I^2=90.5%, p<0.001) (Figure 2C, Table 5). To search for the possible influencing factors on the results, we performed a further analysis by stratification of economic level, sample size, study design, ethnicity, year of publication, classification of caries and diagnose criteria. Subgroup analysis showed that breastfeeding ≥12 months significantly increased the risk of

Table 1. Characteristic of studies included in the Meta-analysis of feeding patterns and ECC

First author, year	Study design	Age (months)	Country	Diagnostic criteria of ECC	Sample size	Breastfeeding		Mix feeding		Bottle feeding		NOS score
						ECC	ECC- free	ECC	ECC- free	ECC	ECC- free	
Kato, 2015[11]	BC	66	Japan	No reported	35754	3042	5124	9253	16350	743	1242	7
Majorana, 2014[19]	BC	24-30	Italy	ICDAS score	2395	348	240	1055	214	533	5	9
Prakash, 2012 [27]	CS	8-48	India	WHO 1997 (dmft)	1500	133	317	233	626	47	144	4
Retnakumari, 2012[20]	BC	12-36	India	WHO (defs)	350	78	113	98	59	1	1	8
Seow, 2009[24]	CC	0-48	Australia	AAPD	619	44	100	85	313	27	50	8
Mohebbi, 2008[28]	CS	12-36	Iran	WHO (dmft)	478	49	224	NR	NR	27	178	5
Livny, 2007[29]	CS	12-36	Palestine	WHO (dmft)	102	5	33	11	48	2	3	3
Yonezu, 2006[21]	BC	36	Japan	No reported	90	14	28	NR	NR	8	40	5
Olmez, 2003[30]	CS	9-57	Turkey	WHO (dft)	92	22	9	8	2	35	16	2
Dini, 2000[31]	CS	36-48	Brazil	WHO (dmft)	245	8	5	83	112	21	16	4

BC: birth cohort; CC: case-control study; CS: cross-sectional study; dft: decayed, filling teeth; dmft: decayed, missing and filled teeth; ICDAS: International Caries Detection and Assessment System; AAPD: The American Academy of Pediatric Dentistry.

Table 2. Characteristic of studies included in the Meta-analysis of ever breastfed compared with never breastfed and ECC

First author, year	Study design	Age (months)	Country	Diagnostic criteria of ECC	Sample size	Ever breastfeeding		Never breastfeeding		NOS score
						ECC	ECC-free	ECC	ECC-free	
Peltzer, 2015[23]	BC	3 y	Thailand	WHO (Dmft)	597	117	183	145	150	
Perera, 2014[32]	CS	36-60	USA	WHO (deft)	285	89	88	48	60	4
Nunes, 2012[22]	BC	18-42	Brazil (low income)	dmft	241	11	38	65	127	6
Qadri, 2012[33]	CS	3-5 y	Syria	WHO (Dmft)	400	OR=0.27, 95% CI: 0.18-0.41[2]				4
Sankeshwari, 2012[34]	CS	3-5 y	India	WHO 1997 (Dmft)	1116	680	406	25	5	3
Werneck, 2008[25]	CC	32	Canada	dmft	104	48	36	4	16	8
Qin, 2008[26]	CC	<48	China	WHO 1997 (Dmft, dmfs, dt, ds)	246	65	65	52	64	6
Iida, 2007[35†]	CS	2-5 y	USA	AAPD (Dfs)	1568	234	705	203	426	5
Sayegh, 2005[36]	CS	48-60	Jordan	WHO (dmft)	1075	678	330	38	29	5
Dye, 2004[37]	CS	2-5 y	USA	No reported	4228	401	1490	624	1713	6
Rosenblatt, 2004[38]	CS	12-36	Brazil	dmft	478	32	66	111	269	2
Du, 2000[39]	CS	24-48	China	WHO (Dmft)	426	136	256	17	17	4

BC: birth cohort; CC: case-control study; CS: cross-sectional study; dmft: decayed, missing and filled teeth; AAPD: The American Academy of Pediatric Dentistry.

OR was adjusted by age and sex.

[†]OR and 95% CI: 0.97(0.63-1.49) was adjusted by birth weight, age, race and time since last dental visit.

Table 3. Characteristic of studies included in the Meta-analysis of breastfeeding duration and ECC

First author, year	Study design	Age	Country	Diagnostic criteria of ECC	Sample size	ECC/Total				NOS score
						≤6 m	6-11 m	12-17 m	≥18 m	
Chaffee, 2014[40]	BC	38 m	Brazil	WHO	537	50/216	38/100	20/65	70/156	8
Nobile, 2014[45]	CS	36-71 m	Italy	WHO (dmft)	487	43/245	14/115	13/62	20/65	4
Prakasha Shrutha, 2013[46]	CS	8-48 m	India	WHO 1997 (Dmft)	2000	66/206	193/473	468/934	233/387	3
Tanaka, 2013[41]	BC	41-50 m	Japan	No reported	315	17/69	15/82	19/95	23/69	8
Tanaka, 2012[47]	CS	3 y	Japan	No reported	2056	85/416	74/498	90/583	176/559	5
Iida, 2007[35]	CS	2-5	USA	AAPD (Dfs)	1562	309/1072	56/274	71/216		5
Sankeshwari, 2012[34]	CS	3-5 y	India	WHO 1997 (Dmft)	1086	79/117	245/393	356/576		3
Hong, 2014[44]	BC	5 y	USA	No reported	509	89/359	29/150			7
van Palenstein, 2006[42]	BC	25-30 m	Myanmar	No reported	998	0/11		4/34	10/46	6
Slabsinskiene, 2010[48]	CS	3 y	Lithuania	WHO (dmft/dmfts)	531	46/503		16/28		3
Feldens, 2010[43]	BC	4 y	Brazil	NIH	3340	46/164		80/176		10
Campus, 2009[49]	CS	4 y	Italy	WHO (dmfs)	5312	238/1006		891/4306		4
Tiano, 2009[50]	CS	8-36 m	Brazil	ADA (dmfs)	661	17/47		6/14		4
Tyagi, 2008[51]	CS	2-6 y	India	NR	3312	42/156		114/156		1
Azevedo, 2005[52]	CS	36-71 m	Brazil	WHO	990	40/150		91/202		5

BC: birth cohort; CC: case-control study; CS: cross-sectional study; ADA: American Dental Association; AAPD: The American Academy of Pediatric Dentistry.

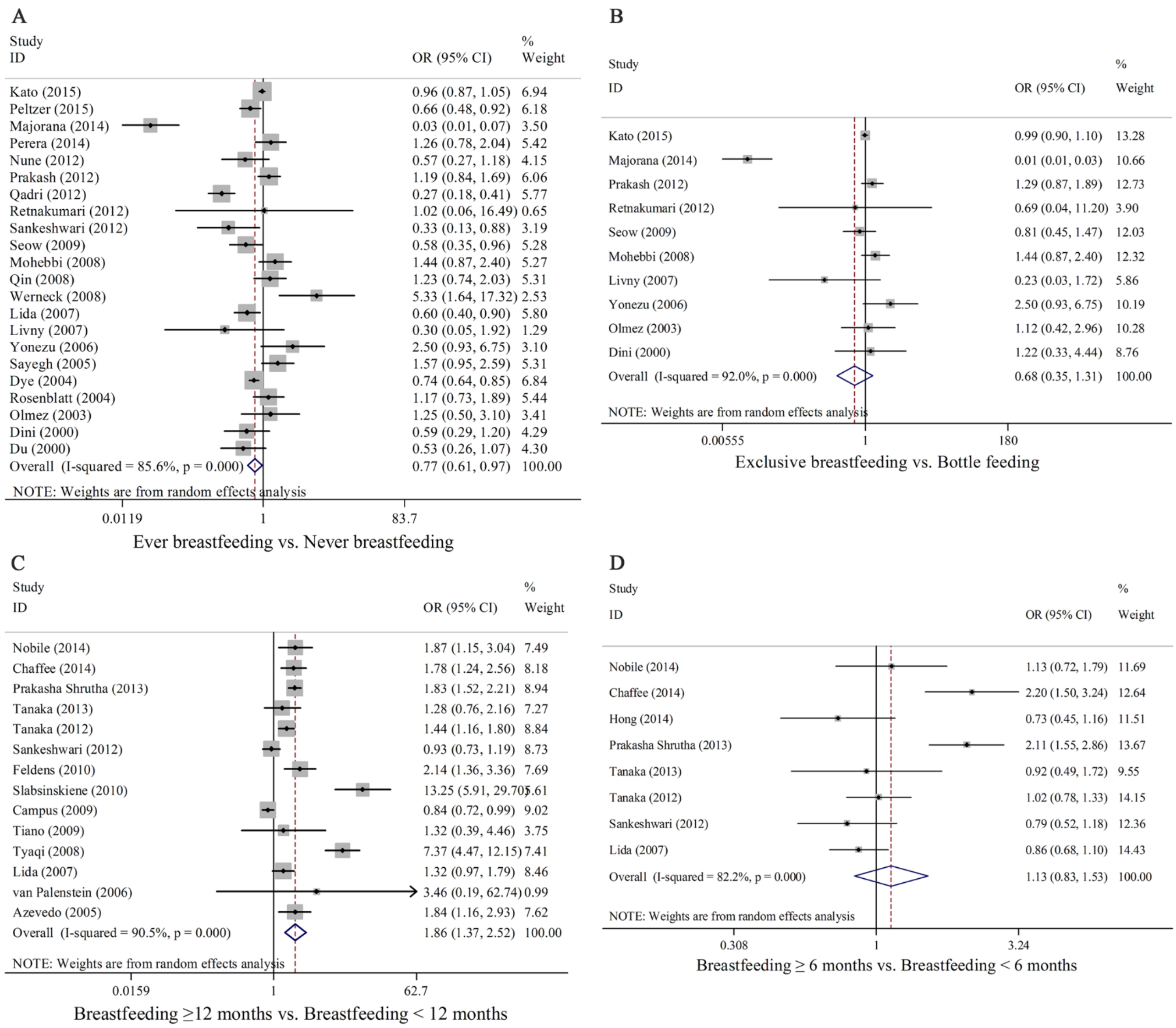

Figure 2. Forest plots for the association between feeding patterns and feeding duration and ECC risk

ECC compared with breastfeeding <12 months in all the studies except for the studies published before 2010 (OR=1.88, 95% CI: 0.93-3.77, p=0.077) (Table 5). The heterogeneity was weakened significantly both in the stratified analysis by study design, NOS score, and ethnicity.

Sensitivity analysis found that no study might affect the overall results (Supplementary figure 2, Supplementary table 5). Marginal publication bias was found through Egger's test (t=2.15, p=0.053) and no evidence provided by the Begg's test (Z=0.99, p=0.324). The shapes of the funnel plots appeared to be symmetrical (Figure 3B). Additionally, 8 studies including 8552 children presented dental caries by the cut point of 6 months. The overall meta-analysis showed that breastfeeding ≥6 months did not significantly increase the risk of ECC compared with breastfeeding <6 months (OR=1.13, 95% CI: 0.83-1.53, p=0.428) (Figure 2D).

DISCUSSION

To clarify the association between breastfeeding and the risk of ECC, we analyzed the effect of different feeding patterns (ever breastfeeding and never breastfeeding) and varied duration of breastfeeding on the risk of ECC, respectively. Overall, a significant inverse association was found for ever breastfeeding and the risk of ECC compared with never breastfeeding including 52,389 children in 22 studies. The latest publication of meta-analysis9 including only 5 studies also found reduced risk of dental caries in children breastfed more versus less up to 12 months, which was basically similar with our results. However, subgroup analysis found that ever breastfeeding could only decrease the risk of ECC for children aged 3-6 years old. Epidemiological data focusing on ECC prevalence in toddlers are scarce.[53] The epidemiological studies[54] have found that the prevalence of ECC was positively correlated with age in preschool children. Higher incidence for 3-6 years old children than 0-3 years old might explain why ever breastfeeding was the protective factor of ECC for 3-6 years old children only. Although subgroup analysis did not detect the variation of study designs, wherever ever breastfeeding as the protective factor was revealed from the studies with high qualities (NOS score ≥6, sample size ≥500). Interestingly, the protective effect was only seen in the studies published after 2010. As time goes on, increasing health awareness and economic level might diminish or eliminate the confounding factors for ECC protection, such as tooth brushing habit,

Table 4. Summary estimates of the association between ever breastfeeding compared with never breastfeeding and the risk of ECC

Subgroup analysis	Number of study populations	OR (95% CI)	Between-group differences, *p*-value	Heterogeneity test		
				Q	*p*	I^2 (%)
All studies	22	0.77 (0.61-0.97)	0.026	146	<0.001	85.6
Age (years)						
0~3	12	0.85 (0.49-1.48)	0.569	84.7	<0.001	87.0
3~6	10	0.70 (0.54-0.90)	0.005	59.3	<0.001	84.8
Economic level						
Middle/ low	12	0.77 (0.52-1.13)	0.178	55.2	<0.001	80.1
High	10	0.76 (0.54-1.06)	0.103	89.6	<0.001	90.0
Sample size						
<500	13	0.96 (0.62-1.48)	0.865	60.1	<0.001	80.0
≥500	9	0.63 (0.46-0.87)	0.004	85.7	<0.001	90.7
Study design						
Cohort	6	0.52 (0.25-1.10)	0.086	68.3	<0.001	92.7
Case-control	3	1.35 (0.52-3.53)	0.538	12.9	<0.001	84.5
Cross-sectional	13	0.80 (0.59-1.06)	0.215	59.7	<0.001	79.9
NOS score						
<6	13	0.85 (0.59-1.23)	0.515	63.2	<0.001	81.0
≥6	9	0.66 (0.46-0.94)	0.023	82.7	<0.001	90.3
Ethnicity						
Caucasian	17	0.71 (0.49-1.03)	0.074	122	<0.001	87.7
Non-caucasian	5	0.85 (0.63-1.14)	0.604	15.3	0.009	67.4
Year of publication						
Before 2010	13	0.98 (0.75-1.29)	0.905	40.7	<0.001	70.5
After 2010	9	0.50 (0.30-0.82)	0.006	105	<0.001	92.4
Adjusted OR						
Yes	2	0.40 (0.18-0.88)	0.023	7.34	<0.001	86.4
No	20	0.84 (0.66-1.06)	0.135	112	<0.001	83.0
Diagnose criteria						
WHO	13	0.81 (0.56-1.15)	0.241	58.3	<0.001	79.4
Others	9	0.71 (0.49-1.02)	0.061	84.5	<0.001	90.8

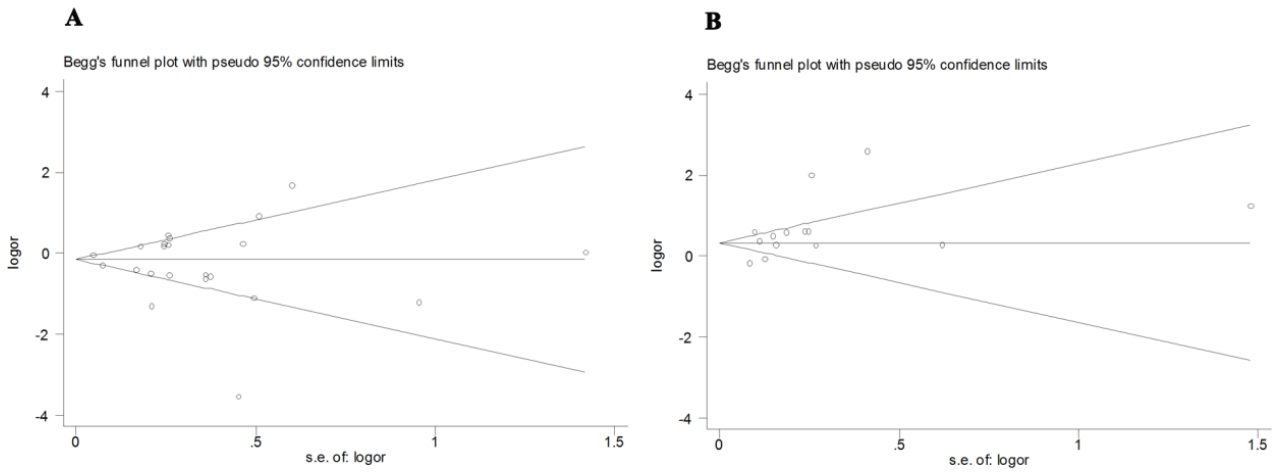

Figure 3. Funnel plots for feeding patterns (A) and feeding duration (B) for ECC risk

and making breastfeeding prominent. An in vitro study showed that plain and sweetened packaged cow milk supported greater bacterial growth and caused more fermentation than human breast milk.[55] The cariogenicity of human breast milk has not been extensively examined *in vivo*; however animal studies suggested that human breast milk has greater cariogenicity compared with cow's milk but less than infant formula, at high frequency exposures.[56,57] Therefore, ever breastfeeding might be protective factor of ECC for children compared with never breastfeeding. The association between breastfeeding and ECC is potentially susceptible to confounding by other factors such as nocturnal breastfeeding, tooth brushing habit, frequency of sweets, and parents' education level. Of the 22 studies, only 2 studies[33,35] found ever breastfed children had a decreased risk of ECC compared with never breastfed children with adjusted OR.

Furthermore, only 10 studies provided the detail of exclusive breastfeeding and bottle feeding and overall analysis showed that exclusive breastfeeding decreased the risk of ECC relative to bottle-feeding without statistical significance. On the other hand, the latest systematic review and meta-analysis found breastfed children were less affected by dental caries than bottle fed children including only 2 cross-sectional studies.[10] Exclusive breastfeeding means that an infant receives only breast milk

Table 5. Summary estimates of the association between breastfeeding duration ≥12 months compared with <12 months and the risk of ECC

Subgroup analysis	Number of study populations	OR (95% CI)	Between-group differences, *p*-value	Heterogeneity test		
				Q	*p*	I^2 (%)
All studies	14	1.86 (1.37-2.52)	<0.001	136	<0.001	90.5
Economic level						
Middle/low	7	2.04 (1.25-3.32)	0.002	58.1	<0.001	89.7
High	7	1.72 (1.15-2.57)	0.009	61.7	<0.001	90.3
Sample size						
<500	7	2.24 (1.35-3.71)	0.002	28.2	<0.001	78.7
≥500	7	1.59 (1.11-2.28)	0.011	82.1	<0.001	92.7
Study design						
Cohort	4	1.76 (1.37-2.25)	<0.001	2.34	0.505	0
Cross-sectional	10	1.91 (1.32-2.77)	<0.001	130	<0.001	93.1
NOS score						
<6	10	1.91 (1.32-2.77)	0.001	130	<0.001	93.1
≥6	4	1.76 (1.39-2.25)	<0.001	2.34	0.505	0
Ethnicity						
Caucasian	12	1.98 (1.37-2.88)	<0.001	136	<0.001	92.6
Non-caucasian	3	1.42 (1.16-1.74)	0.001	0.53	0.767	0
Year of publication						
Before 2010	6	1.88 (0.93-3.77)	0.077	72.4	<0.001	93.1
After 2010[†]	8	1.83 (1.33-2.51)	<0.001	50.7	<0.001	86.2
Classification						
ECC	11	1.59 (1.16-2.17)	0.004	99.6	<0.001	90.0
S-ECC	3	3.51 (1.33-9.24)	0.011	23.2	<0.001	89.3
Diagnose criteria						
WHO	7	1.78 (1.17-2.71)	0.007	85.7	<0.001	93.0
Others	7	1.98 (1.23-3.18)	0.005	40.4	<0.001	85.1

[†]Studies published in 2010 were also divided into group "after 2010".

with no additional foods or liquids, not even water for at least 6 months. Actually most children were fed both by breastfeeding and formula feeding in the included studies. The negative association between exclusive feeding and ECC risk might be caused by the small sample size and larger sample size studies are needed to clarify the effect.

Both the overall and subgroup analysis found breastfeeding ≥12 months could increase the risk of ECC compared with breastfeeding <12 months with high heterogeneity, which was consistent with the previous meta-analysis[9] which included only 7 studies. Subgroup analysis showed that breastfeeding ≥12 months could increase the risk of ECC compared with breastfeeding <12 months for the studies published only after 2010 with moderate heterogeneity. Further analysis, we found that the NOS score of studies published before 2010 was lower than those published after 2010. Due to relatively poor quality of the studies published before 2010, we failed to detect the association of breastfeeding length and ECC. Breastfeeding ≥12 months had 1.64 fold increased risk of ECC and 3.14 fold increased risk of S-ECC compared with <12 months. The heterogeneity was weakened significantly both in the stratified analysis by study design, NOS score and ethnicity, which might be the source of the heterogeneity.

This meta-analysis still has several limitations. First, to examine the influence of breastfeeding on ECC, all the observational studies were included in the meta-analysis, containing birth cohort studies, case-control studies, and cross-sectional studies. The cross-sectional studies with poor NOS score may introduce recall bias and selection bias. Second, we did not include the randomized controlled trials (RCTs), which have been published,[15-18] providing the training of healthy feeding guidelines to pregnant or lactating women. It is not ethical to conduct randomized trials assigning participants breastfed or bottle fed in order to definitively assess the association between infant feeding patterns and early dental caries. However, not all the infants have been breastfed in the intervention groups, and the training also included other possible factors of dental caries, such as feeding habits and tooth brushing, in addition to the feeding patterns. Therefore, RCTs were excluded for the meta-analysis. Third, we did not conduct the dose-response relationship for the breastfeeding length and ECC risk because of the irregularity data of feeding duration in our analysis.

In conclusion, this meta-analysis suggests that ever breastfeeding may protect against ECC, and breastfeeding length ≥12 months is associated with higher risks of ECC. Six months of exclusive breastfeeding and continued partial breastfeeding until two years of age is then recommended according to WHO recommendations. To prevent ECC, we should maintain good dietary and health habits for children breastfed after 12 months. Additionally, higher quality research studies are needed to estimate the effect after adjustment for other possible confounding factors.

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AUTHOR DISCLOSURES

The authors declare that there are no conflicts of interest.

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Supplementary table 1. The details of the NOS score for the birth cohort studies

First author, year	Representativeness	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest not present at start	Comparability	Assessment of outcome	Adequate follow up time	Adequate follow up of cohorts	Score/10
Kato, 2015[11]	*	*	*	*	*		*	*	7
Peltzer, 2015[23]	*	*	*	*	*	**	*	*	9
Majorana, 2014[19]	*	*	*	*	*	**	*	*	9
Chaffee, 2014[40]	*	*	*	*	*	*	*	*	8
Hong, 2014[44]	*	*	*	*	*		*	*	7
Tanaka, 2013[41]	*	*		*	**	**	*		8
Retnakumari, 2012[20]	*	*	*	*	*	*	*	*	8
Nunes, 2012[22]		*		*	*	**		*	6
Feldens, 2010[43]	*	*	*	*	**	**	*	*	10
Yonezu, 2006[21]			*			**	*	*	5
van Palenstein, 2006[42]			*	*		**	*	*	6

Supplementary table 2. The details of the NOS score for the case-control studies

First author, year	Adequate case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Method of ascertainment	Nonresponse rate	Score/10
Seow, 2009[24]	*	*	*	*	**		*	*	8
Werneck, 2008[25]	*	*	*	*	**		*	*	8
Qin, 2008[26]	*	*		*	*		*	*	6

Supplementary table 3. The details of the NOS score for the cross-sectional studies

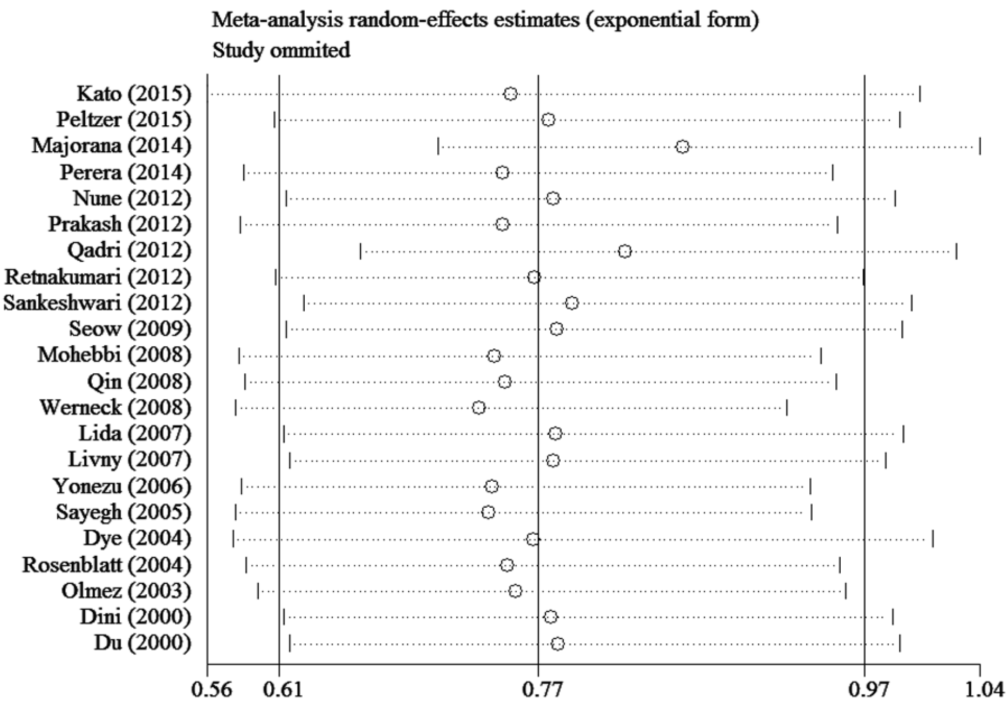
First author, year	Representativeness	Selection of nonexposed cohort	Ascertainment of exposure	Comparability	Assessment of outcome	Score/7
Nobile, 2014[45]	*	*		*	*	4
Perera, 2014[32]		*	*		*	4
Prakasha Shrutha, 2013[46]	*	*			*	3
Prakash, 2012[27]	*	*	*		*	4
Qadri, 2012[33]	*	*	*		*	4
Sankeshwari, 2012[34]	*	*			*	3
Tanaka, 2012[47]	*	*		*	**	5
Slabsinskiene, 2010[48]	*	*			*	3
Campus, 2009[49]	*	*		*	*	4
Tiano, 2009[50]		*	*		*	4
Mohebbi, 2008[53]	*	*		**	*	5
Tyagi, 2008[51]					*	1
Iida, 2007[35]	*	*	*	*	*	5
Livny, 2007[29]		*	*		*	3
Sayegh, 2005[36]	*	*		*	**	5
Dye, 2004[37]	*	*		**	**	6
Rosenblatt, 2004[38]		*			*	2
Olmez, 2003[30]		*			*	2
Dini, 2000[31]	*	*		*	*	4
Du, 2000[39]		*		*	*	3

Supplementary table 4. Sensitivity analyses by omitting one study at a time for the association between ever breast-feeding compared with never breastfeeding and the risk of ECC

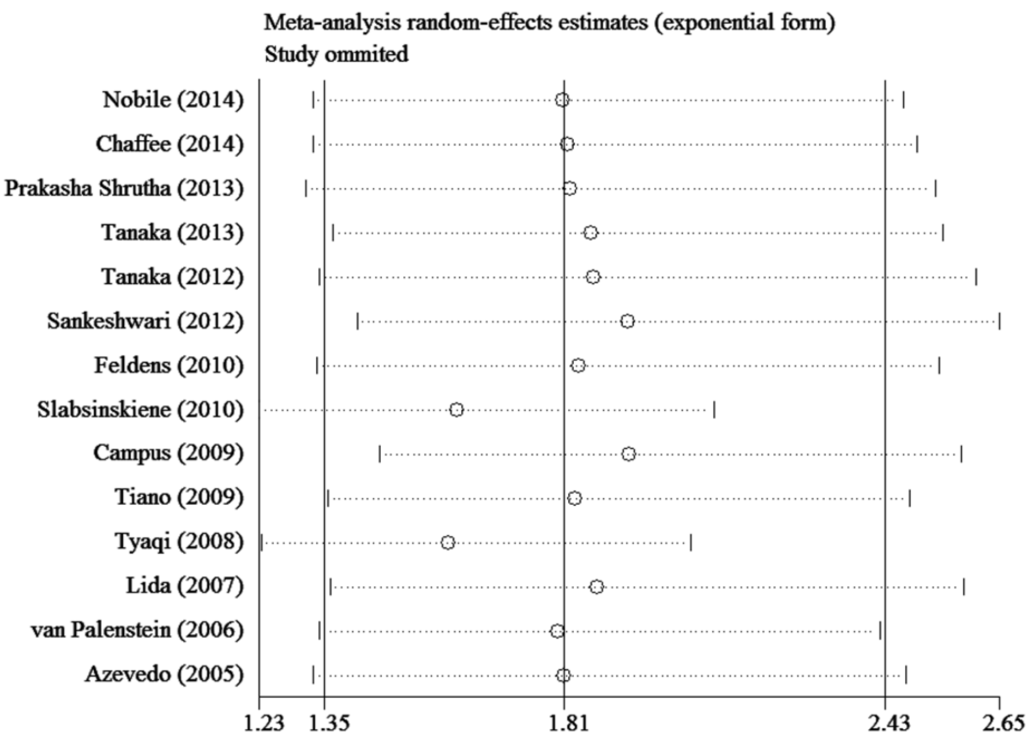
The omitted study	*p*	OR (95% CI)	Heterogeneity test		
			Q	I^2 (%)	*p*
Total	0.026	0.77 (0.61-0.97)	145.84	85.6	<0.001
Kato (2015)	0.052	0.75 (0.56-1.00)	134.11	85.1	<0.001
Peltzer (2015)	0.042	0.77 (0.60-0.99)	143.41	86.1	<0.001
Majorana (2014)	0.118	0.86 (0.70-1.04)	89.7	77.7	<0.001
Perera (2014）	0.017	0.74 (0.58-0.95)	143.21	86.0	<0.001
Nune (2012）	0.039	0.78 (0.61-0.99)	144.64	86.2	<0.001
Prakash (2012)	0.019	0.74 (0.58-0.95)	142.26	85.9	<0.001
Qadri (2012)	0.082	0.82 (0.66-1.03)	115.07	82.6	<0.001
Retnakumari (2012)	0.026	0.76 (0.60-0.97)	145.83	86.3	<0.001
Sankeshwari (2012)	0.048	0.79 (0.62-1.00)	142.25	85.9	<0.001
Seow (2009)	0.043	0.78 (0.61-0.99)	143.57	86.1	<0.001
Mohebbi (2028)	0.014	0.74 (0.58-0.94)	141.68	85.9	<0.001
Qin (2008)	0.018	0.75 (0.58-0.95)	143.75	86.1	<0.001
Werneck (2008)	0.008	0.73 (0.58-0.92)	136.51	85.3	<0.001
Lida (2007)	0.043	0.78 (0.61-0.99)	142.88	86.0	<0.001
Livny (2007)	0.035	0.78 (0.61-0.98)	144.61	86.2	<0.001
Yonezu (2006)	0.012	0.74 (0.58-0.93)	141.32	85.8	<0.001
Sayegh (2005)	0.012	0.74 (0.58-0.94)	140.06	85.7	<0.001
Dye (2004)	0.059	0.76 (0.58-1.01)	140.97	85.8	<0.001
Rosenblatt (2004)	0.019	0.75 (0.59-0.95)	144.07	86.1	<0.001
Olmez (2003)	0.020	0.75 (0.59-0.96)	145.17	86.2	<0.001
Dini (2000)	0.038	0.77 (0.60-0.99)	144.82	86.2	<0.001
Du (2000)	0.042	0.78 (0.61-0.99)	144.09	86.1	<0.001

Supplementary table 5. Sensitivity analyses by omitting one study at a time for the association between breastfeeding duration ≥12 months compared with <12 months and the risk of ECC

The omitted study	*p*	OR (95% CI)	Heterogeneity test		
			Q	I^2 (%)	*p*
Total	<0.001	1.86 (1.37-2.52)	136.26	90.05	<0.001
Nobile (2014)	<0.001	1.86 (1.35-2.57)	134.74	91.1	<0.001
Chaffee (2014)	<0.001	1.87 (1.35-2.60)	134.27	91.1	<0.001
Prakasha Shrutha (2013)	<0.001	1.88 (1.33-2.64)	125.43	90.4	<0.001
Tanaka (2013)	<0.001	1.92 (1.39-2.65)	136.18	91.2	<0.001
Tanaka (2012)	<0.001	1.92 (1.36-2.72)	136.08	91.2	<0.001
Sankeshwari (2012)	<0.001	1.99 (1.44-2.77)	125.11	90.4	<0.001
Feldens (2010)	<0.001	1.84 (1.34-2.54)	132.52	90.9	<0.001
Slabsinskiene (2010)	0.001	1.65 (1.24-2.18)	105.83	88.7	<0.001
Campus (2009)	<0.001	2.00 (1.48-2.69)	88.66	86.5	<0.001
Tiano (2009)	<0.001	1.89 (1.38-2.58)	136.25	91.25	<0.001
Tyaqi (2008)	<0.001	1.88 (1.36-2.58)	141.68	85.9	<0.001
Lida (2007)	<0.001	1.93 (1.38-2.69)	136.16	91.2	<0.001
van Palenstein (2006)	<0.001	1.85 (1.36-2.51)	135.87	91.2	<0.001
Azevedo (2005)	<0.001	1.86 (1.35-2.57)	134.70	91.1	<0.001



Supplementary figure 1. Sensitivity analysis for the overall association between feeding patterns (ever and never) and ECC risk in 22 studies.



Supplementary figure 2. Sensitivity analysis for the overall association between duration of breastfeeding (≥12 months vs <12 months) and ECC risk in 14 studies.