SYSTEMATIC REVIEW AND META-ANALYSIS

Risk Factors for Early Childhood Caries: A Systematic Review and Meta-Analysis of Case Control and Cohort Studies

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Abstract: ***Purpose:*** *The purpose of this study was to perform a systematic review to assess current evidence for association between various risk factors and the prevalence or incidence of early childhood caries (ECC).* ***Methods:*** *Two reviewers searched various databases until January 2019. The Newcastle-Ottawa scale was used to perform risk of bias assessment.The included studies were categorized according to the World Bank classification. Data were summarized in a meta-analysis using fixed and random effects inverse-generic meta-analyses.* ***Results:*** *A total of 7,034 records involving 89 studies that evaluated 1,352,097 individuals were included; 23 were high, 46 were moderate, and 20 were of low quality. A total of 123 risk factors were found. Meta-analysis revealed that the strongest risk factors found in the high-income countries were presence of dentinal caries (dmft greater than zero; odds ratio [OR] equals 4.21 [2.18 to 8.16]) and high levels of mutans streptococci (OR equals 3.83 [1.81 to 8.09]). In upper-middle-income countries, presence of enamel defects (OR equals 14.62 [6.10 to 35.03]) was found to be the strongest risk factor.* ***Conclusion:*** *The strongest risk factors associated with early childhood caries was the presence of enamel defects, presence of dentinal caries and high levels of mutans streptococci.* *(Pediatr Dent 2019;41(2):95-106.E18-E23) Received September 11, 2018 / Last Revision January 31, 2019 / Accepted February 4, 2019*

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Early Childhood Caries (**ECC**) remains the most prevalent chronic disease in children, with significant impact on society.[1,2] Numerous studies have observed the increasingly skewed distribution of carious lesions.[3-6] Most carious lesions or restorations are found in a small number of disadvantaged individuals. ECC is disproportionately found in certain segments of the childhood population.[7,8] Although the key factors causing dental caries in adults and children are similar, there are certain unique risk factors present in young children, probably because oral microbial flora and host defense mechanisms are in the developing stage. Also, newly erupted tooth surfaces may have hypoplastic defects associated with higher risk for caries. In addition, parents must understand the dietary changes from liquids to solids through breastfeeding/bottle feeding.

Several studies have evaluated and categorized the risk factors of ECC, such as sociodemographic factors, dietary factors, oral hygiene factors, and factors related to oral bacterial flora and breastfeeding/bottle feeding.[1,2,6,8,9] However, the degree to which different risk factors are associated with ECC remains unclear.

Significant gaps have been observed in the collective evidence on risk factors known to cause ECC. Until now, only two systematic reviews have examined the evidence on multiple risk factors associated with ECC. Harris et al. in 2004[9] systematically reviewed the literature and identified 106 risk factors associated with ECC. Nevertheless, more than 50 percent of the included studies were cross-sectional, thereby lacking robustness for the evaluation of risk factors and for conclusions to be drawn. In addition, there were few studies of a high quality, defined as those using validated and standardized measures for oral hygiene and dietary habits. The other systematic review[10] studied risk factors for ECC only in the first year of life and suggested further clarification to identify and quantify the main risk factors. Neither of the two systematic reviews presented a quantitative analysis. Furthermore, recently reported risk factors—namely, increased body mass index, maternal cognitive disorders, increased enamel permeability, enamel composition, and the influence of parental attitudes, were not included. Finally, the search for the review by Harris[8] was conducted over a decade ago, in 2004; hence, an update is indicated.

Therefore, the purpose of this study was to conduct a systematic review and a meta-analysis of cohort and case control studies for possible associations between various risk factors and early childhood caries.

Methods

Guidelines from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were followed in the present review, which was registered at PROSPERO before the initial screening stage. We deviated from the original protocol by adding a category of included studies based on the World Bank Classification. In addition, we also searched for another database—LILACS—which was not mentioned in the original protocol.

Search strategy. The identification of included studies, which began on July 1, 2016 and was updated until January 2019, was based on a search strategy performed for each electronic database: MEDLINE; EMBASE; Cochrane Central Database; Cochrane Oral Health Group's Specialised Register; CINAHL via EBSCO; LILACS; and IndMED. The MeSH terms used were "dental caries," "preschool child," "infant,"

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and "risk factors." The following strategy was used to search MEDLINE: ("dental caries"[MeSH terms] OR ("dental"[all fields] AND "caries"[all fields]) OR "dental caries"[all fields]) AND (("infant"[MeSH terms] OR "infant"[all fields]) OR (("child"[MeSH terms] OR "child"[all fields]) AND preschool [all fields]) OR ("child"[MeSH terms] OR "child"[all fields] OR "children"[all fields])) AND ("risk factors"[MeSH terms] OR ("risk"[all fields] AND "factors"[all fields]) OR "risk factors"[all fields] OR ("risk"[all fields] AND "factor"[all fields]) OR "risk factor"[all fields]). The search strategies for CENTRAL (Cochrane *Central* Register of Controlled Trials), EMBASE, EBSCO, LILACS, and IndMED were comparable to those used in the MEDLINE search. We identified and synthesized all relevant studies, up to June 2016, to reduce selection bias. In addition, the reference lists of existing systematic and narrative reviews and of all included studies were reviewed for studies that might have been missed. We hand searched some key journals in this field (from 2005)—such as *Community Dental Health, International Journal of Paediatric Dentistry, Journal of Public Health Dentistry, Community Dentistry and Oral Epidemiology, Pediatrics, Pediatric Dentistry, European Archives of Pediatric Dentistry, European Journal of Pediatric Dentistry, Pediatric Dental Journal, Journal of Dentistry for Children, Journal of Clinical Pediatric Dentistry,* and *International Journal of Clinical Pediatric Dentistry*—to identify those publications that could have been missed from the electronic database and searches of the reference lists.[10] Hand searches were performed from 2005 to June 2016. This was because there was already an update on hand searches by Harris et al.[9] until 2004. This has further been updated to January 2019. This also helped us identify very recent articles. Attempts to obtain grey literature were performed by screening a national database for dissertation abstracts (i.e., SHODHGANGA).

Selection of studies. A reference management system (Mendeley Desktop 1.17.13, Elsevier, Atlanta, Ga., USA) was used to upload all the potentially eligible studies and remove duplicate studies. Two trained reviewers independently assessed for inclusion of all the eligible studies on the basis of the title, abstract, and keywords. Full texts of papers or reports, for those studies that required more information to determine relevance or in cases where abstracts were unclear/unavailable, were obtained through electronic mail or communication through Research Gate. In addition, the full text of each study considered for inclusion was also obtained. Blinding of the articles was not performed regarding the journals published, authors, or institutions. Disagreements among the reviewers were resolved by discussion. Where agreement could not be reached, a third reviewer arbitrated to reach consensus. All excluded studies at this stage were documented in an Excel spreadsheet (Excel 10, Microsoft Corp., Redwood City, Calif., USA), along with the reasons for exclusion.

Selection criteria. We included prospective cohort, retrospective cohort, and case control studies that investigated the association between risk factors and ECC prevalence, experience, or incidence. Case series, case reports, and cross-sectional studies were excluded. Randomized controlled trials (**RCTs**) were also excluded because an interventional study is not the ideal study design in which to evaluate the association between the risk factor and disease occurrence. Our study followed the PECO format.

All preschool children, regardless of gender, race, health status, geographical location, or socioeconomic status (**SES**), from birth until six years of age (less than 72 months old) were included. Children with special health care needs were excluded. Exposure included socio demographic factors, dietary factors, factors related to oral hygiene, factors related to breastfeeding and bottle feeding, and other factors. In case control studies, individuals without ECC are the matched control group. Presence of ECC was the outcome. However, any method of assessment of the outcome (ECC) was considered.

Data extraction and quality assessment. For all studies that met the inclusion criteria, data extraction was performed independently by two reviewers using piloted electronic Excel 10 spreadsheets. Wherever possible, appropriate translators were used for data extraction from papers in languages not known by the review authors. Review authors discussed disagreements in data extraction. A third review author resolved discrepancies, and lead authors of the respective studies were contacted to obtain missing data, if necessary. Data were recorded in accordance with the guidelines outlined by the Cochrane Collaboration and categorized as study characteristics, participant characteristics, adjusted effects, and absolute effects estimates.

The Newcastle-Ottawa scale (**NOS**), modified for observational studies,[12] was used to perform the risk of bias assessment of the included studies. The domains of the scale include selection of cases and controls, comparability of the groups, and measurement of exposure and outcomes. The scale has two parts, one pertinent to case control studies and one for cohort studies. Studies were categorized as having low, moderate, and high methodological quality, according to NOS scores under five, from five to seven, and above seven, respectively. This quality assessment was used only for the descriptive part and not for statistical evaluation.

Data synthesis and analysis. Although there is a need for controlling confounders in observational studies, we used unadjusted measures as the primary effect estimates when they were provided. Odds ratio (**OR**) is considered an appropriate

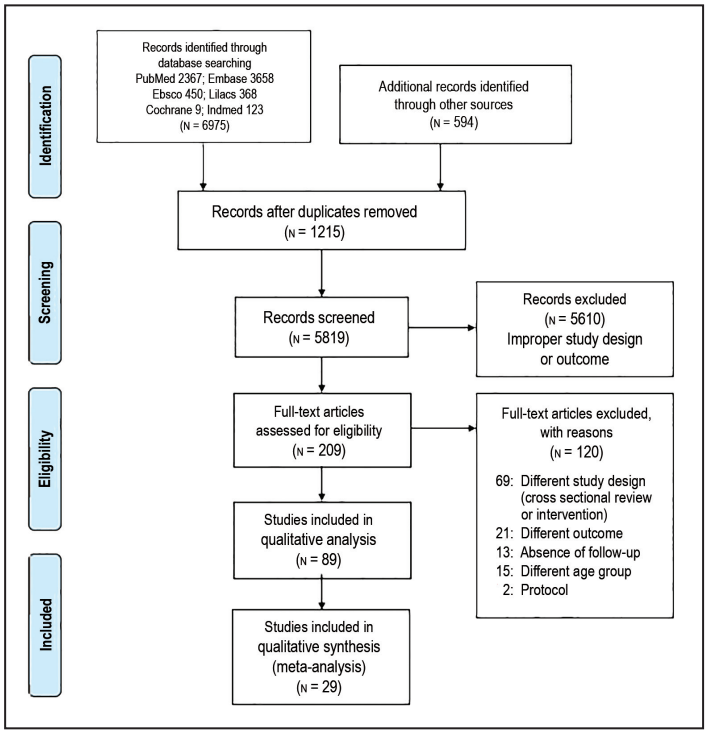

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram.

effect estimate for cohort and case control studies. Only those studies that reported or allowed the calculation of OR and error estimates (*P*-values, confidence intervals [**CIs**], and standard deviation) were used for quantitative data synthesis. When investigators used multivariate models to adjust for potential confounders, we did not consider the measures, since they would usually involve adjusted ORs. If unadjusted measures were not given as a part of the primary analysis, we calculated the same wherever possible.

The results of the included studies were evaluated Review Manager 2012 statistical software (Revman 5.3, The Cochrane Collaboration, London, UK). Forest plots were used to visualize the estimate effect sizes and 95 percent (95%) CIs of individual studies. Inverse-variance weighted averages and 95% CIs were used to represent the summary estimates for the entire sample. Data were summarized in a meta-analysis when they were sufficiently homogeneous. We combined data from studies if they had comparable risk factors, follow-ups, and outcome measures and organized the results by the particular type of exposure examined in the study. For ease of categorization, the studies retrieved were categorized according to the World Bank classification into lower-income (**LI**), lower-middle-income (**LMI**), upper-middle-income (**UMI**), and high-income (**HI**) countries.

We assessed clinical heterogeneity (e.g., participant characteristics, risk factors, and study settings) by investigating the pertinent criteria. The chi-square and I-square tests were used for the assessment of heterogeneity.[13] An I-square value between 50 percent and 100 percent was considered for statistical heterogeneity to be present. A random-effects model for meta-analysis was used if there was evidence of substantial or considerable heterogeneity. To estimate effect sizes and their 95% CIs, both random and fixed-effects generalized linear models were used.

Results

Study selection and characteristics. The search revealed that 7,034 studies were relevant to the present systematic review. Following the removal of 1,215 duplicates, 5,819 records were screened based on the title, abstract, and keywords. Of these, 5,610 records were eliminated based on improper study design or outcome. The remaining 209 papers were assessed for complete examination. The reason for exclusion of the 120 articles at this stage was different study design— including review, cross sectional or interventional-based studies, outcomes other than dental caries, or the absence of follow-up, as described in Figure 1. After a full text review, 89 studies[1,2,14-101] with a 1,352,097 total participants, were included in the present

Table 1. QUALITY OF EVIDENCE OF INCLUDED STUDIES BASED ON THE NEWCASTLE-OTTAWA SCALE

Studies graded with high methodological quality	Studies graded with moderate methodological quality		Studies graded with low methodological quality
Peltzer and Mongkochali (2015)[51]	Ostberg et al. (2016)[2]	Nelson et al. (2005)[84]	Ghazal et al. (2015)[29]
Yokomichi H et al. (2015)[52]	Shantinath et al. (1996)[86]	Warren et al. (2016)[1]	Zaror et al. (2014)[14]
Winter et al. (2015)[53]	Mahesh et al. (2013)[28]	Tanaka et al. (2015)[40]	Gao et al. (2014)[55]
Peltzer et al. (2014)[27]	Tanaka et al. (2015)[88]	Watanabe et al. (2014)[54]	Almeida et al. (2012)[60]
Majorana et al. (2014)[15]	Campus et al. (2007)[85]	Hong et al. (2014)[56]	Mattila et al. (1998)[70]
Zhou et al. (2012)[31]	Schroth et al. (2014)[76]	Moimaz et al. (2014)[57]	Sanders and Slade (2010)[33]
Kay et al. (2010)[17]	Law and Seow (2006)[39]	Tanaka et al. (2013)[58]	Ismail et al. (2009)[23]
Hong et al. (2009)[47]	Wigen and Wang (2011)[77]	Kato et al. (2015)[34]	Yonezu and Yakushiji (2008)[21]
Teanpaisan et al. (2007)[18]	Peretz and Kafka (1997)[78]	Tanaka et al. (2013)[59]	Lim et al. (2008)[66]
Oliveira et al. (2006)[19]	Slade et al. (2006)[83]	Chankanka et al. (2015)[25]	Yonezu et al. (2006)[67]
Van Palenstein Henderman et al. (2006)[41]	Nunes et al. (2012)[16]	Tanaka et al. (2012)[32]	Yonezu et al. (2006)[46]
Ansai et al. (2000)[45]	Grytten et al. (1988)[75]	Grindefjord et al. (1996)[73]	Tada et al. (1999)[35]
Lai et al. (1997)[20]	Levy et al. (2003)[68]	Bankel et al. (2011)[61]	O' Sullivan et al. (1996)[44]
Wendt et al. (1996)[72]	Rodrigues and Sheiham (2000)[69]	Parisoto et al. (2011)[62]	Al Mendalwi and Karam (2014)[24]
Wendt et al. (1995)[74]	Ollila et al. (1998)[37]	Targino et al. (2011)[49]	Seow et al. (2009)[48]
Aaltonen et al. (1994)[43]	Thibodeau and O' Sullivan (1996)[71]	Wigen et al. (2011)[63]	Yu et al. (2015)[79]
Menon et al. (2013)[26]	Meruman and Pienihakkihen (2010)[30]	Ismail et al. (2008)[65]	Evans et al. (2013)[81]
Dantas Cabral de Melo et al. (2015)[80]	Warren et al. (2009)[42]	Feldens et al. (2010)[64]	Del Rosario Garcia et al. (2011)[82]
Melo et al. (2011)[22]	Nishide et al. (2018)[89]	Peres et al. (2017)[94]	Lulic Dukic et al. (2001)[38]
Qin et al. (2008)[87]	Cabral et al. (2017)[91]	Bernabe et al. (2017)	Marino et al. (1989)[36]
Boustedt et al. (2018)[90]	Jean et al. (2018)[92]	Fan et al. (2016)[98]	
Birungi et al. (2017)[95]	Feldens et al. (2018)[93]	Paglia et al. (2016)[99]	
Nirunsittirat (2016)[97]	Dabawala et al. (2017)[100]	Roberts et al. (1994)[101]	

review. Of these, five articles were translated to English by Google Translate. Further, six authors were contacted requesting full texts through Research G or electronic mail. Figure 1 summarizes the study identification process in the form of PRISMA flow diagram. The study participants' ages ranged from birth to six years. Publication years of included studies ranged from 1981 to Jan 2019. Among the included studies, 64 were prospective cohort,[1,2,17-21,23,25,27,29-35,37,39-47,49,51-77,89-91,93-97] four were retrospective cohort,[14,15,16,92] and 21 were case control.[22,24,26,28,36,38,48,78-87,98-101] Among the 68 cohort studies, 50 studies[1,2,14,15,17,20,21,23,25,29,30,32-35,37,40,42-47,52-56,58,59,61,63,65-77,88-90,92,97] belonged to the HI category, 16[16,18,19,27,31,49,51,57,60,62,64,69,91,93,94,96] studies belonged to the UMI category, one study[41] belonged to the LMI category, and one study[95] belonged to the LI category. Among the 21 case control studies, 10 studies[36,38,48,78,81,83-86,99] belonged to the HI category, eight studies[22,24,79,80,82,87,98,101] belonged to the UMI category, three belonged to the LMI category[26,28,100] and no studies were present in the LI category.

Risk of bias in included studies. The NOS was used for the quality assessment of included studies (Table 1). This is a star rating system, with eight questions, that assigns a maximum of nine stars within three domains: selection (four stars); comparability (two stars); and measurement of exposure (risk factor) in case control studies or outcome (dental caries) in cohort studies (three stars). A high risk of bias was considered for those studies with less than five stars. Quality varied greatly among studies, with 20 studies of low quality, 46 studies showing moderate quality, and 23 studies demonstrating high quality. Overall, five studies were rated with low risk of bias and high methodological quality in all three NOS risk of bias categories (i.e., four prospective cohort studies and one case control study. All four cohort studies studied different risk factors and were conducted in various parts of the world, including England (HI),[17] Brazil (UMI),[18] Thailand (UMI),[19] and the United States (HI).[20] The study by Lai et al.[20] was a case-controlled prospective study conducted in the United States (HI) to learn if the enamel hypoplasia seen in very low birthweight children predisposed them to increased dental caries risk; it concluded that no significant association existed. Studies with a high risk of bias and low methodological quality in all three NOS risk of bias categories included one case control[82] and three cohort studies,[21,46,67] as seen in Table 1. Three of the four studies were based on the same cohort in Japanese preschool children (HI country), with data collected prospectively.[21,46,67] The fourth study was a retrospective study in which risk factors—namely consumption of cariogenic food, oral hygiene habits, topical application of fluoride, and annual oral evaluation—were studied.[82]

Assessment of the outcome. Most studies evaluated dental caries using the decayed, filled, and missing primary teeth (**dmft**) index and decayed, filled, and missing primary surfaces (dmfs) index, according to the World Health Organization[23]; a few studies determined both noncavitated and cavitated teeth and surfaces, according to the International Caries Detection and Assessment System (ICDAS). Only one study used a five-grade caries diagnostic system, from the most superficial (grade one) to the most profound (grade five). Grades one and two constituted enamel carious lesions (initial caries), and grades three to five were diagnosed when the carious lesions had reached the dentin (manifest caries). Initial and/or manifest carious lesions (grades one to five) constituted all carious lesions of different depths.[2]

Narrative review. Most of the included studies examined a wide range of exposures. Information about these exposures was obtained predominantly from parents through interviews,[28,30]

Table 2. FACTORS RELATED TO THE PREVALENCE AND/OR INCIDENCE OF PRIMARY TEETH CARIES IN CHILDREN AGE 6 YEARS AND YOUNGER

Sociodemographic factors	Dietary factors	Oral hygiene
Gender (male)[27,51,52,81]	Daily sweet snacks[17,54]	Daily frequency of toothbrushing at <1 year old[24,27,33,53,87]
Residence (urban) [24]	High sugar foods >1x/day[15,29,74,101]	No daily toothbrushing by parents[2,54]
Age[65,79,81]	Cariostat 3 or more[54]	Age brushing started >1[2,33,38,53]
Non-Hispanic Caucasian[81]	Daily consumption of fruit juice[79]	Visible plaque[31,39,42,48,89]
Low socioeconomic status[2,26,85,101]	Added sugar beverage intake[1,42]	Parental indulgence while toothbrushing[2]
Low education of the caregiver[22]	Consumption of beverages/ carbonated drinks daily[54]	Lack of fluoride toothpaste[28,49,53,101]
Low parental education[24,81,56]	Sweet food index >24[53]	Poor oral hygiene exam at 18 months[26,46]
No schooling of mother[51]	Presweetened cereal consumption at meals [25]	Low Oral Hygiene Index score[84]
Low maternal education[1,22]	No milk consumption at meals [25]	Trouble with toothbrushing[48]
Greater household size [1,22,81]	Use of thirst quenchers other than water[30]	Visible plaque index[79]
Young maternal age[1,63]	Added sugar[22,30]	
Birth order (3 or more)[33,54,80,101]	High density of sugar at 12 months[64]	
Drinking water in household[1,33]	Very frequent sugar consumption[75]	
Ethnicity[30,33,84]	Cariogenic food consumption[82]	
Mother unemployed[28,48]	Sweet drinks[1,87,100]	
Single mother[27]	Regular exposure to sweet drinks in the first 6 months[83]	
Low household income [27,33,40,48,51]	Nighttime consumption of sweet beverages after 24 months[38]	
Single parenting household[36]	Eating sweets several times a day[87]	
First born child[28]	Added sugar at snacks[25]	
	Pre-chewed food[87]	
	Juice in bottle during day-time[86]	
	Snack more than 3x/day[28]	
	Solid sugar consumption[79]	
	Consumption of sweets between meals[80]	
	Low levels of Vitamin D during pregnancy[32,76]	
	Low levels of calcium during pregnancy[32]	
	Low levels of dairy products during pregnancy[32]	
	Low levels of curd during pregnancy[32]	
	Low levels of cheese during pregnancy[32]	

self-reports,[14,24,52] or questionnaires.[1,2,15,22,27,29,40,51,53-55-60] In total, the number of risk factors found to be associated with ECC among the 76 included studies were 123. These could be grouped as 19 sociodemographic factors, 28 factors related to diet, 10 factors related to oral hygiene habits, 10 factors related to breastfeeding, 15 related to bottle feeding, three related to oral bacteria flora, and 38 related to other factors such as genetic mutation and parental smoking (Table 2). The results of the studies, according to each category (sociodemographic factors, dietary factors, factors related to oral hygiene, factors related to breastfeeding and bottle feeding, and other factors), are summarized next.

Sociodemographic factors. Of the 19 sociodemographic factors, gender (male) and low household income were found to be frequently implicated in most studies.[27,33,40,48,51,52,81] Factors such as low SES, low maternal education, and unemployed mother have been investigated and were found to be significant in only a few studies.[1,2,26-28,48] The reason for the inconsistent results with the SES factor could be the different scales used in different studies, based either on only household income[24] or mother's education at recruitment and family income,[25] per capita monthly income,[26] or based on the parent's occupation status, with social class level based on the higher occupation status of the father or mother[85]. The factors studied in a single study were residence of the child (urban/rural),[24] low education of the caregiver,[22] presence of a single mother,[27] and the child being firstborn.[28]

Dietary factors. There were many dietary factors associated with ECC. Most of these factors were related either to the frequency, amount, or timing of sugar consumption.[17,29,30] Among all the dietary factors, the most commonly investigated risk factor was frequency of eating foods high in sugar more than once per day. Although this factor was found to have a significant association in some studies,[5,29,74] one study reported[31] that this association was not significant when adjusted for confounders (unadjusted OR equals 2.5; 95% CI equals 1.2 to 5.2; adjusted ORs not provided). Another study[32] was conducted on the association between calcium intake and dairy

Table 2. CONTINUED

Factors related to breastfeeding/bottle feeding		Oral bacterial flora	Other factors*
Breastfeeding	**Bottle feeding**		
Duration of breastfeeding <6 months[56]	Sleep with bottle at 30 months 1-6x/week[51]	Presence of *Streptococcus mutans*[48]	Presence of enamel defects[19,31,48,47,49]
No breastfeeding[15,54]	Nocturnal bottle feeding[64]	Increased baseline salivary *S. mutans* levels[30,31,42-45,71]	Smoking by family members[27,54]
Prolonged breastfeeding >12 months[14,46,64,101]	Nighttime bottle use at 2 months[64]	Presence of LB[37,55]	1 parent born abroad[2]
Breastfeeding at least 6 months[34]	Bottle feeding[38,84,85]		2 parents born abroad[2,73]
Nocturnal breastfeeding[30,31,46]	Slept at night with bottle containing sweet drink[33,101]		Parent's dental attendance[2]
Breastfeeding[35]	Feeding to help them sleep[86]		Parent's negative attitude[2]
Daily breastfeeding frequency at 12 months[64]	On-demand feeding[86]		High chance locus of control[2]
>15 minutes/feeding at night[41]	Feeding associated with nap time[86]		Drinking water in household/home water fluoride level[27,28,56]
>2 nocturnal breastfeeding[41]	Age of weaning from bottle[36,86]		Low birthweight[56,96]
Breastfeeding ≥24 months[94]	Formula in bottle at night[86]		History of previous dental visit at age 3 years[29]
	Child held bottle while falling asleep (propping)[86]		Previous dental experience[14]
	Prolonged bottle feeding, especially at night[36,93]		Regular dental check ups <5[53]
	Added sugar in bottle[48]		Late bedtime[36,54]
	Sleeping while feeding after 12 months[87]		Low body mass index[31]
	Feeding habits before 6 months[87]		One or both parents of non-western origin[63]
			Blue collar occupation of caretaker[30]
			Reported poor oral health of father[30,33]
			Teeth erupted at 18 months >6[33]
			Low Apgar score[33]
			High density of lipids at 12 months[64]
			Soda consumption 2-6x/day[65]
			Mother missing teeth[75]
			Incidence of caries (DMFT>0)[48,70]
			Parental stress[26]
			Reason for dental visits[84,101]
			Complication during pregnancy[78]
			Delivery (instrument/Caesarean)[78,90]
			Tantrums/strong temper[36]
			Parental smoking[24,96]
			Ear infection[84]
			No previous dental visit[28]
			Day care person[28]
			Visible abscess[48]
			Mutation in the locus[79]
			Inappropriate fluoride supplementation[36]
			Mothers knowledge of when to clean the child's mouth and brush the child's teeth[48]
			Oral thrush[92]

* DMFT= decayed, filled, and missing permanent teeth.

Table 3. OVERVIEW OF THE META-ANALYSIS OF THE INCLUDED COHORT STUDIES CATEGORIZED AS UPPER-MIDDLE-INCOME AND UPPER-INCOME COUNTRIES*

Risk factor	N	K	Pooled odds ratio (95% CI)	Chi-square² value	I² value
Upper-middle-income countries					
Low birthweight[31,51]	822	2	0.83 (0.49, 1.41)	1.83	45
Increased baseline salivary levels of *Streptococcus mutans*[18,31]	394	2	9.21 (4.97, 17.07)	0.22	0
Presence of enamel defects[19,31]	453	2	14.62 (6.10, 35.03)	0.00	0
Night bottle feeding[49,64]	564	2	0.62 (0.49, 0.78)	1.91	48
Night breastfeeding[31,49]	449	2	1.28 (1.11, 1.47)	1.54	35
Gender (male)[51,64]	937	2	1.26 (0.85, 1.88)	3.45	71
Toothbrushing at least once a day[31,49]	449	2	1.36 (1.08, 1.72)	0.60	0
Brushing with fluoride toothpaste[51,64]	937	2	1.03 (0.75, 1.42)	0.47	0
Sugar snacks at least once a day[31,49]	449	2	0.69 (0.16, 3.00)	0.95	84
Low maternal age (<25 years)[31,51]	822	2	0.65 (0.45, 0.94)	1.75	43
High-income countries					
Low maternal education (≤9 years)[2,17,56,63,66,70,75]	5,885	8	1.84 (1.14, 2.08)	31.49	78
Low birthweight (<2,500 g)[56,63]	1,857	2	1.70 (0.89, 3.23)	0.00	0
Smoking during pregnancy[1,63]	1,580	2	1.33 (0.74, 2.39)	2.53	60
Increased baseline salivary levels of *S. mutans*[30,42,45,55,73]	2,812	5	3.83 (1.81, 8.09)	47.96	92
Increased consumption of soda pop[25,56]	886	2	1.12 (1.03, 1.23)	0.18	0
Maternal age (<25 years)[1,17,63]	2,565	3	1.26 (0.65, 2.45)	17.43	89
Toothbrushing at least once a day[2,25,66,67]	2,328	4	0.91 (0.55, 1.51)	6.69	55
Visible plaque present[42,70,72]	1,106	3	3.1 (2.00, 4.80)	0.52	0
Poor oral hygiene[67,72]	394	2	3.12 (1.77, 5.49)	0.28	0
Night bottle feeding[37,42,58]	592	3	1.15 (0.44, 3.04)	14.91	87
Age at dental exam >1 year[2,25,66,67]	2,328	2	1.68(1.06, 2.66)	0.78	0
Liquids in bottle other than milk[58,68]	421	2	1.27 (0.83, 1.94)	2.04	51
Presence of lactobacilli[37,55]	1,728	2	2.18 (2.03, 2.34)	1.13	11
Gestational age <37 weeks[29,63]	1,445	2	0.67 (0.14, 3.12)	3.50	71
Gender (males)[17,30,39,63]	2,727	4	0.98 (0.80, 1.19)	2.01	0
Age started brushing ≥1[2,53]	836	2	2.12 (1.49, 3.01)	0.00	0
Brushing <1x/day[17,53,54,75]	32,984	4	1.08 (0.61, 1.92)	12.39	76
Dentinal caries (dmft >0)[66,70]	2,268	2	4.21 (2.18, 8.16)	0.42	0
No topical fluoride application[53,54]	31,768	2	1.50 (1.39, 1.63)	1.22	18
Frequent consumption of sweetened foods[2,54]	31,472	2	3.14 (0.89, 11.04)	3.01	67
Intake of sugar snacks daily[2,30,54]	31,831	3	1.56 (1.42, 1.71)	0.68	0
Intake of sugar beverages[2,42,67,68,73]	1,298	5	1.67 (0.25, 3.92)	46.18	91
Socioeconomic status[25,39]	412	2	0.46 (0.28, 0.74)	0.05	0

* N=number of participants; K=number of studies; dmft=decayed, filled, and missing primary teeth.

products during pregnancy and dental caries in children; it concluded that the increased maternal intake of cheese during pregnancy may significantly decrease the risk of developing dental caries in children (P=0.001). Weaning after 18 months as a risk factor was assessed in another study[33] and found to be not significant (P=0.291).

Factors related to breastfeeding/bottle feeding. The number of included studies that investigated breastfeeding and bottle feeding as a risk factor are 15 and 13, respectively. According to Kato et al. in 2015,[34] breastfeeding for six to seven months or more might increase dental caries risk due to simultaneous events that occur during the same period, such as the eruption of primary teeth. The same study reported breastfeeding and bottle feeding as risk factors for ECC; in that study, breastfeeding was specifically associated with caries in maxillary anterior teeth and bottle feeding was associated with caries in molars.[34] That study also mentioned that this association became attenuated through the follow-up period and was no longer statistically significant beyond the age of 42 months for the partially breastfed group and beyond the age of 54 months for the exclusively breastfed group. Another case control study involving South African children compared a group with nursing caries to those without it. They found no statistically significant differences for feeding patterns between the groups in relation to the prevalence of nursing caries.[101] Most studies counted on parental recall in the form of questionnaires or interviews,[14,23,31,35-40] and very few studies used standardized validated questions or previous dental records, which are more reliable.[14,41]

Factors related to oral hygiene. Past studies collected data by means of self-reports or more directly via the use of a plaque or oral hygiene index for oral hygiene habits. It is interesting to note that, in one of the included studies, parental indulgence (when parents neglected to help the child brush twice daily or when they did not have the time to brush) was reported as one of the most important risk factors for ECC.[2] Among all the factors studied, visible plaque[42,48] and toothbrushing less than once daily[24,27,33,53,87] were the two most important oral hygiene factors related to ECC. The other less important factors are age at which toothbrushing was started,[3,38] not having teeth brushed at bedtime, using nonfluoridated toothpaste,[28,49] and parental supervision of toothbrushing.[2]

Factors related to oral bacteria flora. *Streptococcus mutans* is known to be the main bacterium in the aetiology of dental caries. An association between ECC and the colonization of mutans streptococci (MS) in saliva or plaque has been demonstrated. The age at which MS is detectable in a child's oral cavity is said to be

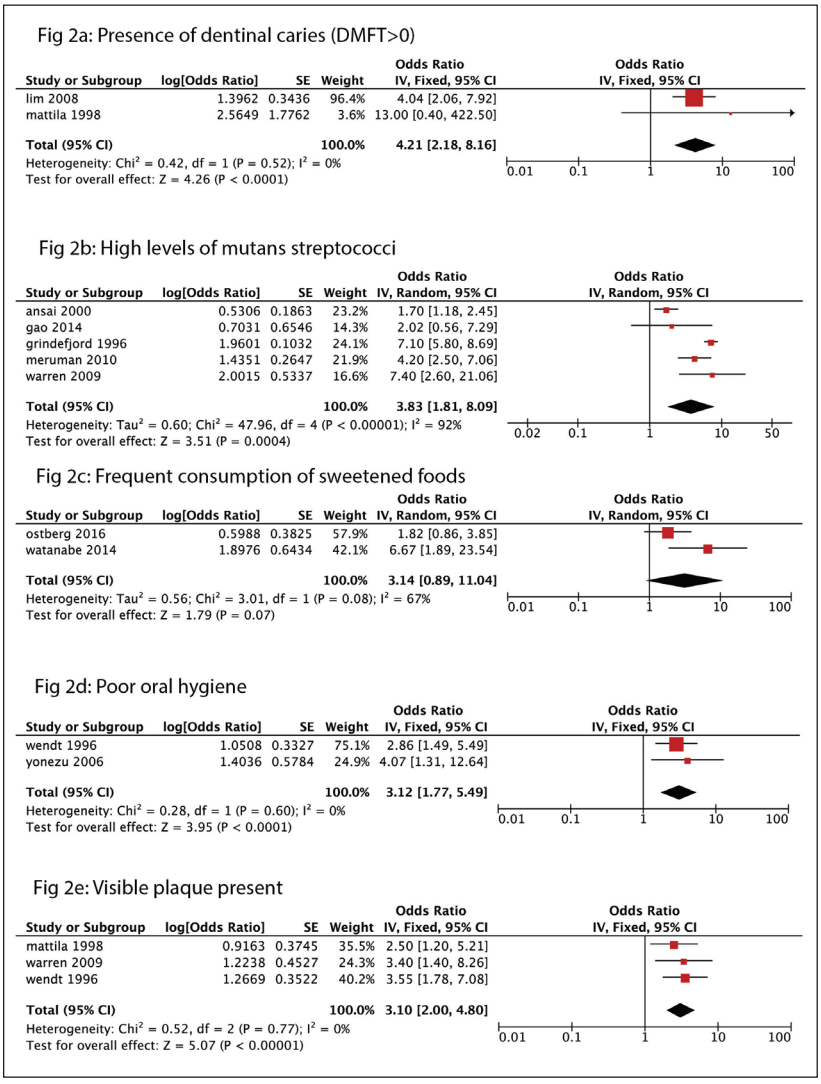

Figure 2. Risk factors found in the high-income category. (a) Forest plot showing presence of dentinal caries (decayed, filled, and missing primary teeth [dmft] index score greater than zero) as a risk factor for early childhood caries. (b) Forest plot showing presence of mutans streptococci as a risk factor for ECC. (c) Forest plot showing frequent consumption of sweetened foods as a risk factor for ECC. (d) Forest plot showing poor oral hygiene as a risk factor for ECC. (e) Forest plot showing visible plaque present as a risk factor for ECC.

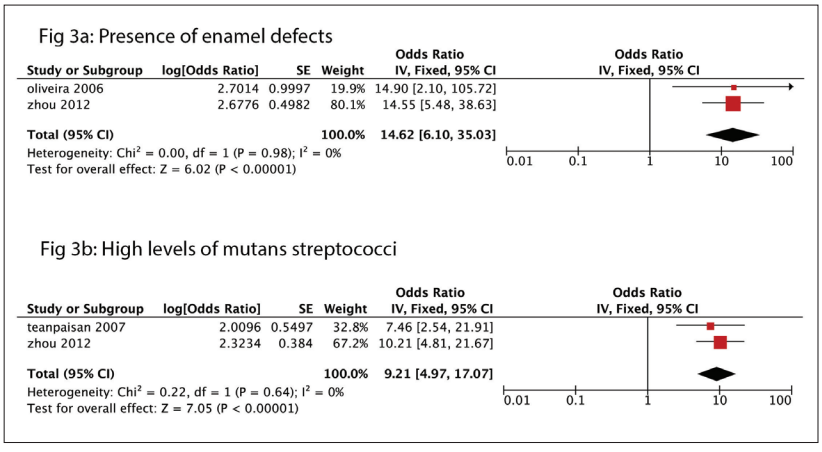

Figure 3. Risk factors found in the upper-middle-income category. (a) Forest plot showing presence of enamel defects as a risk factor for ECC. (b) Forest plot showing presence of mutans streptococci as a risk factor for ECC.

an important indicator of caries risk, although it may not be detectable in the infant's mouth prior to tooth eruption (Table 2). One study[31] suggested that the earlier *S. mutans* colonizes in a child, the greater the risk of developing caries. Another study[18] observed MS in 1.78 percent of predentate infants as young as three months and studied the presence of dental caries in nine- and 24-month-old children. Most studies assessed how the individual's baseline caries risk influenced the development of caries in children aged six months to six years. Almost all the studies in this area observed an increase in the caries experience, with increased salivary MS levels at baseline.[30,42-46] However, whatever the ethnic group may be, if MS is present in the oral cavity, it appears to be an important indicator of caries risk. Ethnic differences in the prevalence of dental caries can, to an extent, be explained by differences in the acquisition of cariogenic bacteria.

Other factors. There were 38 factors which belonged to this category. Among them, enamel hypoplasia was the most commonly studied. All studies that included the presence of enamel hypoplasia as a potential risk factor for ECC concluded that the risk of developing dental caries was significantly increased.[19,31,47-49] One study[19] observed a total of 224 children, with enamel defects from the age of 12 to 54 months, for the presence of ECC. At 12 months, none of the infants showed the presence of dental caries. At 42 months, 9.2 percent of children presented with carious teeth; at 54 months, 48.4 percent of the children with dental caries showed the presence of enamel defects. The study also concluded that enamel hypoplasia was the most common category of enamel defect associated with dental caries. On the contrary, another study[47] concluded that the type of enamel defect with the most frequently associated risk factor with dental caries in children aged 36 months was opacity with enamel hypoplasia (42.7 percent), followed by hypoplasia (42.7 percent) and diffuse opacity (6.4 percent).

A recent study assessed whether there is an association between oral thrush or other Candida-related conditions in infancy and ECC diagnosed by pediatricians. The study design was a retrospective cohort using electronic health records from six national children's hospitals. There were 1,012,668 children included in the study, with one visit at ages one to 12 months and another visit at ages 13 to 71 months. This study concluded that oral thrush may be a risk factor for ECC.[92]

Quantitative analysis. Among the 89 included studies, 68 are cohort studies and 21 are case control studies. Of the 68 cohort studies 50 studies[1,2,14,15,17,20,21,23,25,29,30,32-35,37,40,42-47,52-56,58,59,61,63,65-77,88-90,92,97] belonged to the HI category, 16 studies[16,18,19,27,31,49,51,57,60,62,64,69,91,93,94,96] fit in the UMI category, one study[41] was categorized as LMI, one study[95] belonged to the LI category. From the 68 cohort studies, only 29 studies contributed for quantitative analysis. Among these 29 studies, 23 studies[1,2,17,25,29,30,37,39,42,45,53-56,58,63,66-68,70,72,73,75] fit within the HI category and six studies[18,19,31,49,51,64] belonged to the UMI category. No

studies from the LMI and the LI category were included. The remaining 30 studies[14-16,20,21,23,27,32-35,40,41,43,44,46,47,52,57,59,60-62,65,69,71,74,76,77,88-97] were excluded, either because the data were missing or heterogeneous.

None of the risk factors among the 21 case control studies[22,24,26,28,36,38,48,78,79,80-87,98-101] was eligible for quantitative analysis. Either the factors could not be combined, due to missing data, or they belonged to a different country classification based on income.

Figures 2 and 3 show the significant risk factors found in the HI and UMI categories, respectively. The forest plots represent only those with an OR greater than three (Figures 2 and 3). Figures 4 to 9 represent the re-maining risk factor forest plots (see **Electronic Appendix**). Table 3 shows an overview of the meta-analysis of the included cohort studies, categorized as UMI and HI countries.

The important risk factors (OR greater than one) amid HI countries were: low maternal education; low birth weight (less than 2,500 g); smoking during pregnancy; the presence of MS; increased daily soda pop intake; maternal age younger than 25 years; visible plaque present; bad oral hygiene; night bottle feeding; age at first dental examination younger than one year; liquids other than milk in bottles; the presence of lactobacilli; tooth brushing less than once daily; age when brushing began at one year of age or older; negative parental attitudes; the presence of dentinal caries (dmft greater than zero); topical fluoride application; frequent consumption of sweetened foods; daily intake of sugary snacks; and intake of sugary beverages. The strongest risk factors associated were the: presence of dentinal caries (dmft greater than zero; OR equals 4.21 [2.18 to 8.16]); high levels of MS (OR equals 3.83 [1.81 to 8.09]); frequent consumption of sweetened foods (OR equals 3.14 [0.89 to 11.04]); poor oral hygiene (OR equals 3.12 [1.77 to 5.49]); and visible plaque present (OR equals 3.10 [2.0 to 4.80]; Figure 2).

Among the studies grouped under UMI countries, the factors found to have a positive association with ECC (OR greater than one) were high levels of MS counts, the presence of enamel defects, nighttime breastfeeding, gender (male), brushing with fluoride toothpaste, and brushing at least once a day. The strongest risk factors associated with ECC, among the studies, were the presence of enamel defects (OR equals 14.62 [6.10 to 35.03]) and high levels of MS (OR equals 9.21 [4.97 to 17.07]; Figure 3).

Discussion

To the best of our knowledge, this study is the first systematic review and meta-analysis, including case control and cohort studies, examining possible associations between various risk factors and ECC. The objective of a systematic review is to identify, evaluate, and synthesize evidence from previously conducted studies to provide informative empirical answers to unanswered research questions. The key question of the present review is, what are the main risk factors for early childhood caries?

To answer this, we undertook a structured approach to identify pertinent literature and to minimize bias in the selected studies.[9] The only way to understand the relationship between etiological factors and disease in the population is through observational studies, since randomization is impossible. Nevertheless, the confounding factors may mask the exact association between a risk factor and ECC, in the absence of randomization. The description of a risk factor clearly indicates that the exposure has occurred prior to the outcome. Hence, longitudinal studies are needed to study risk factors. In a cross-sectional study, an exposure associated with an outcome can be considered a risk indicator only. Hence, we included only cohort and case control studies in the present systematic review, which is the ideal study design to examine risk factors.[50] This evidence can have key implications for the development of prevention strategies for common risk factors associated with ECC.

The present review used the NOS to assess risk of bias of individual studies. Modification of this scale for two questions was needed to suit the present research question. First, in the rating system for ascertainment of exposure, one star was allocated not only for the structured interview (as in the original scale) but also for questionnaire or medical records. This item was modified for both the cohort and case control studies. Second, under the rating of comparability for cases and controls, it was not possible to determine the main confounder, as the present systematic review studied the role of multiple etiological factors. Therefore, it was decided to give two stars if the study adjusted for confounders using multiple logistic regression analysis and one star if the study controlled for at least one potential confounder (e.g., age, gender, income, or SES). In the present systematic review, 76 out of the 89 studies adjusted for at least one of the confounding variables, which can be considered a major strength of the included studies.

However, the present review used only the studies that provided unadjusted ORs for the meta-analysis, since there was no standardization of confounders adjusted in various studies. This probably led to the fewer number of studies included under each risk factor category.

Limitations. Overall, there are three major limitations with the included studies of risk factors for ECC. The first is the absence of adjustment for confounding factors. A known constraint of observational studies is the ability of confounding factors to exaggerate or diminish the significance of some factors, since randomization is not possible. This is usually compensated by using multiple logistic regression analysis, which is almost compulsory in these studies. This analysis depends on the use of dichotomized data, which means that the categorizations used in each study may be as significant as the numbers of exposures tested. For example, one study[22] might investigate toothbrushing frequency by comparing once, twice, or thrice daily versus less than once daily, whereas another study might compare one or more times daily[53] and reach different conclusions. Although most studies performed some form of adjustment for confounders, this was often poorly reported or not described. Moreover, the values—namely, adjusted or unadjusted *P*-values and odds ratios were not provided. Furthermore, 11 included studies in this review did not perform any method to account for the confounding factors.

The ideal selection of a confounder in the present study is based on existing evidence of an accepted association with the risk factor studied (exposure) and ECC (outcome). The second is the lack of consistency and detail among the categories of risk factors studied, which restricts comparison between and among the studies. Also, it is possible that the mothers of the study participants, who completed questionnaires regarding their children's various risk factors, were provided with some basic information regarding the same. Hence, the accuracy of their answers could be questionable. This could be explained by the wide range of risk factors evaluated across the included studies. However, specific definitions of risk factors studied are necessary to ensure the accuracy of the data collected. Further

Table 4. OVERVIEW OF THE SOCIOECONOMIC STATUS (SES) OF THE POPULATION STUDIED IN EACH STUDY IN THE META-ANALYSIS, BASED ON WORLD BANK CLASSIFICATION

High-income countries				Upper-middle-income countries		Lower-middle-income countries	Lower-income countries
Low SES (N=3)	High SES (N=1)	Not mentioned (N=18)	All SES profiles (N=1)	Low SES (N=4)	Not mentioned (N=2)	—	—
Lim et al. (2008)[66]; Warren et al.(2009)[42]; Ghazal et al. (2015)[29]	Hong et al. (2014)[56]	Gao et al. (2014)[55]; Watanabe et al. (2014)[54]; Wigen and Wang (2011)[77]; Tanaka et al. (2013)[58]; Levy et al. (2003)[68]; Kay et al. (2010)[17]; Yonezu T et al. (2006)[67]; Ansai et al. (2000)[45]; Mattila et al. (1998)[70]; Ollila et al. (1998)[37]; Wendt et al. (1996)[72]; Grindefjord et al. (1996)[73]; Grytten et al. (1988)[75]; Law and Seow (2006)[39]; Gao et al. (2014)[55]; Watanabe et al. (2014)[54]; Wigen and Wang (2011)[77]; Levy et al. (2003)[68]	Warren et al. (2016)[1]	Feldens et al. (2010)[64]; Oliveira et al. (2006)[19]; Teanpaisan et al. (2007)[18]; Targino et al. (2011)[49]	Peltzer and Mongkochali (2015)[51]; Zhou et al. (2012)[31]		

standardization among the studies to measure oral health outcomes (dental caries) and the risk factors in children is required to facilitate a more accurate knowledge base of the risk factors for ECC. In addition to the shortcomings of the included studies, our statistical analysis has caveats, as we pooled estimates from various study designs, detection cutoffs, caries measures, and statistical models. The third limitation of the included studies was that, among the 89 included studies, quality varied greatly among studies—with 20 studies of low quality, 46 studies showing moderate quality, and 23 studies demonstrating high quality. Overall, only five studies were rated high in all three categories. These findings carry implications for future research.

Among the 89 included studies, using World Bank classification for categorizing the countries: 60 studies (10 case control studies, 50 cohort studies) were from the HI category; 24 studies (eight case control studies, 16 cohort studies) were categorized as UMI; four studies (three case control studies, one cohort study) fell into the LMI category; and one study was categorized as LI. Of the 76 studies only 29 cohort studies contributed for quantitative analysis. Evaluation of the population studied in the 29 cohort studies (HI equals 23; UMI equals six; LMI equals zero; LI equals zero) showed that various SES children were included in each study. Among the 23 studies in the HI category, SES profiles of the population studied were low, high, all profiles, and not mentioned in three, one, one, and 18 studies, respectively. In the six UMI categorized studies, the SES profiles were low in four studies and not mentioned in two studies. As low SES is associated with greater risk of acquiring ECC, it is imperative that future studies should mention the population studied for better understanding of this association. The categorization further revealed that only one study was performed in the LMI category (Myanmar)[41] and one study was performed in the LI category (Uganda).[95] Therefore, future studies are required mainly in LMI and LI country category groups, using standardized data collection and outcome measures with appropriate adjustment of potential confounders.

Meta-analysis of UI countries showed that presence of dentinal caries, high levels of MS, frequent consumption of sweetened foods, poor oral hygiene, and visible plaque present are major risk factors (each with an OR above three) associated with ECC. In UMI countries, high levels of MS and presence of enamel defects were the major risk factors. However, the readers are advised to interpret these findings with caution, because the population studied might belong to a low, moderate, or high SES in UI or UMI countries, as previously discussed (Table 4). Further studies in HI, UMI, LMI, and LI countries, including all SES populations, are needed to better understand the various risk factors associated with ECC in different countries and among people from different SES.

Regardless of the heterogeneous nature of the included studies, when it comes to study design and the statistical tests used, the accuracy and magnitude of our estimates strongly support the presence of an association between certain risk factors and ECC. In the HI category, the presence of dentinal caries, high levels of MS, frequent consumption of sweetened foods, poor oral hygiene, and the presence of visible plaque were the significant risk factors. This can be attributed to the fact that sugar consumption is usually higher and more equally distributed in HI countries versus LI countries. In UMI countries, the presence of enamel defects and high levels of MS were found to be significant. This may be because malnutrition and increased rates of infection in early life are more prevalent in these countries and are predisposing factors for enamel defects. It is noteworthy that no longitudinal study was found that evaluated host factors, such as enamel permeability, enamel composition, contact areas, and types of pits and fissures, as risk factors for ECC. Their role in the etiology of ECC remains unclear and requires further investigation.

Conclusions

Based on this study's results, the following conclusions can be made:

1. The two strongest risk factors associated with early childhood caries in high- or upper-middle-income categories were: (a) the presence of enamel defects; and (b) high levels of mutans streptococci.
2. Significant secondary risk factors in the high-income category were the presence of dentinal caries, frequent consumption of sweetened foods, poor oral hygiene, and the presence of visible plaque.

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Electronic Appendix

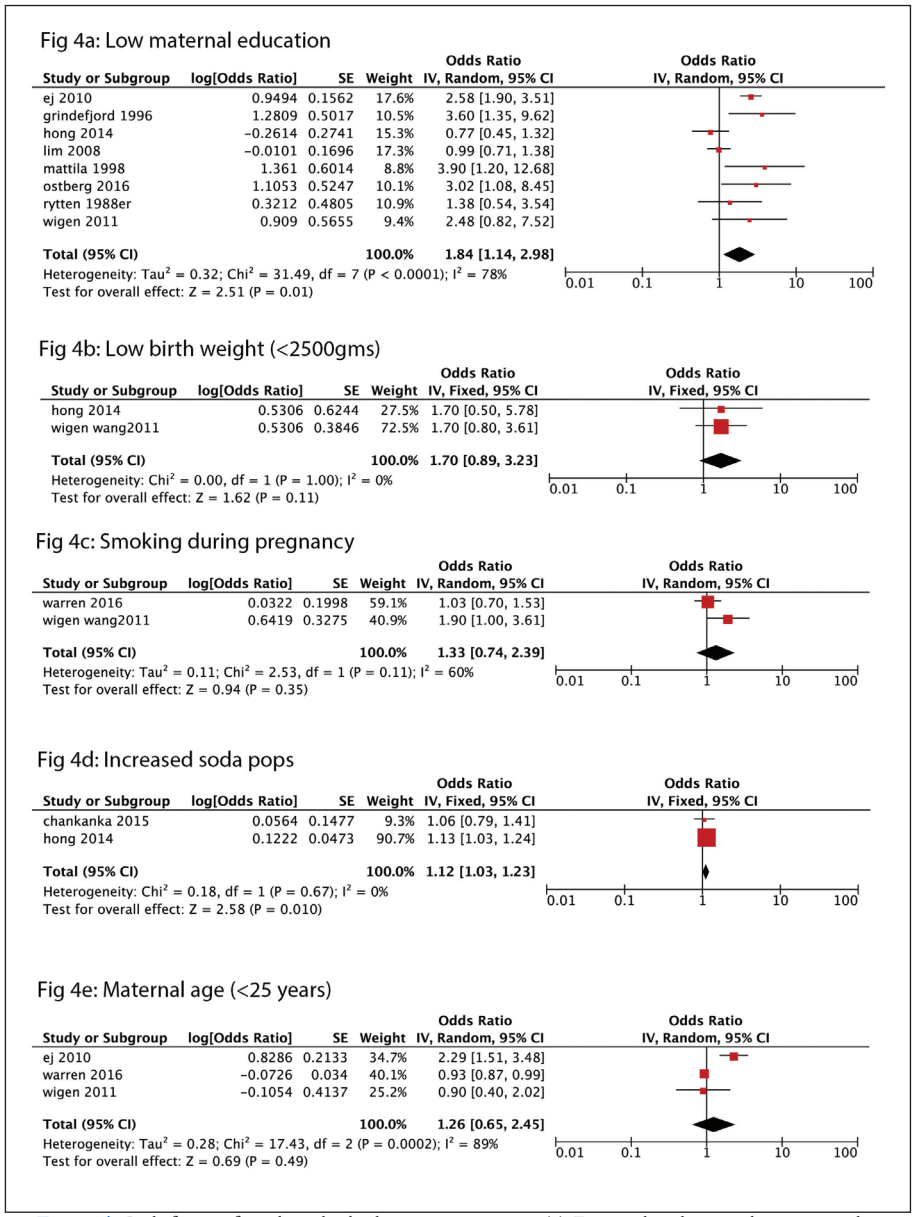

Figure 4. Risk factors found in the high-income category. (a) Forest plot showing low maternal education as a risk factor for ECC. (b) Forest plot showing low birthweight (less than 2,500 g) as a risk factor for early childhood caries. (c) Forest plot showing smoking during pregnancy as a risk factor for ECC. (d) Forest plot showing increased consumption of soda pop as a risk factor for ECC. (e) Forest plot showing maternal age (younger than 25 years) as a risk factor for ECC.

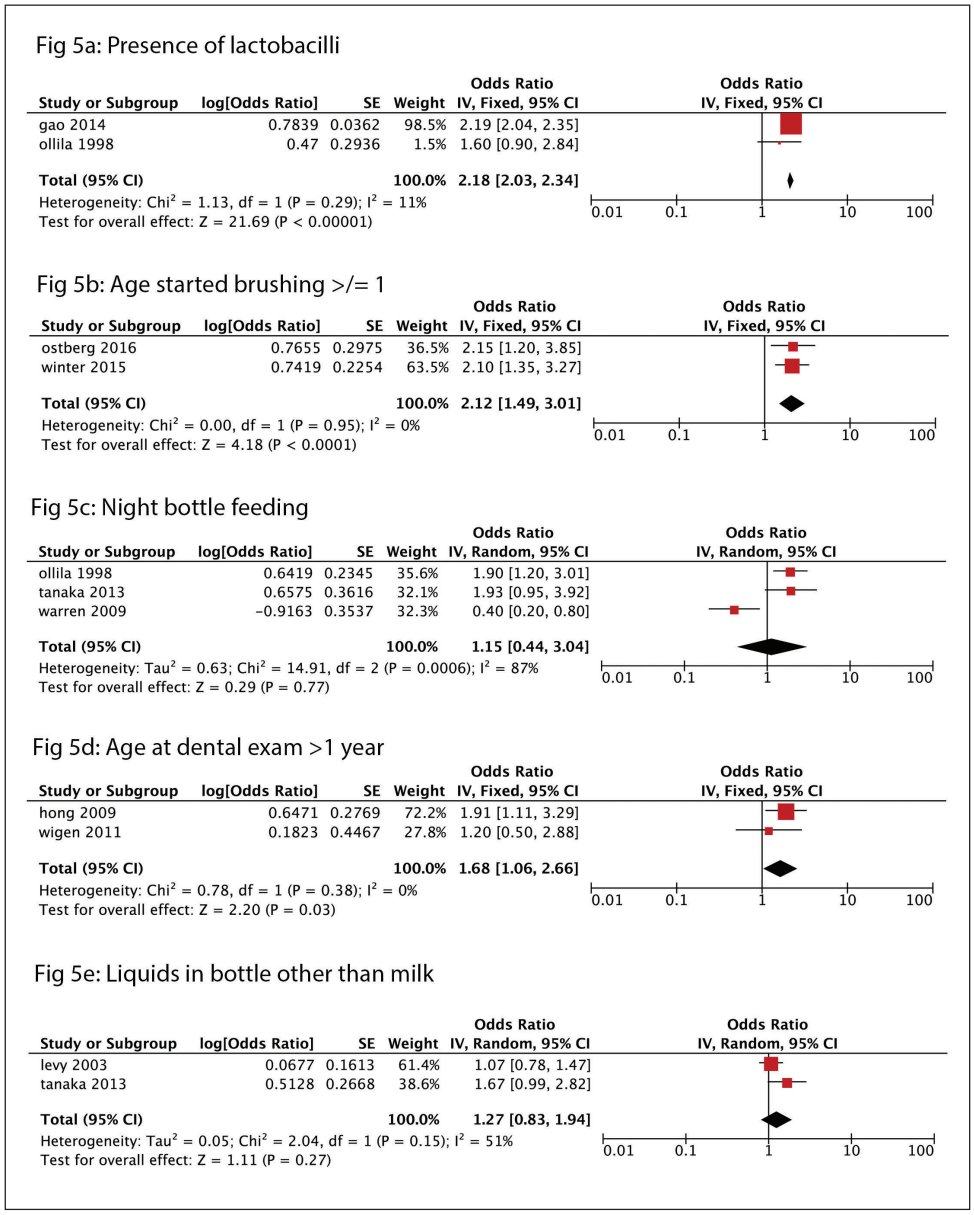

Figure 5. Risk factors found in the high-income category. (a) Forest plot showing presence of lactobacillus as a risk factor for early childhood caries. (b) Forest plot showing age when brushing started at least by one year as a risk factor for ECC. (c) Forest plot showing night bottle feeding as a risk factor for ECC. (d) Forest plot showing age at dental exam older than one year of age as a risk factor for ECC. (e) Forest plot showing liquids in bottle other than milk as a risk factor for ECC.

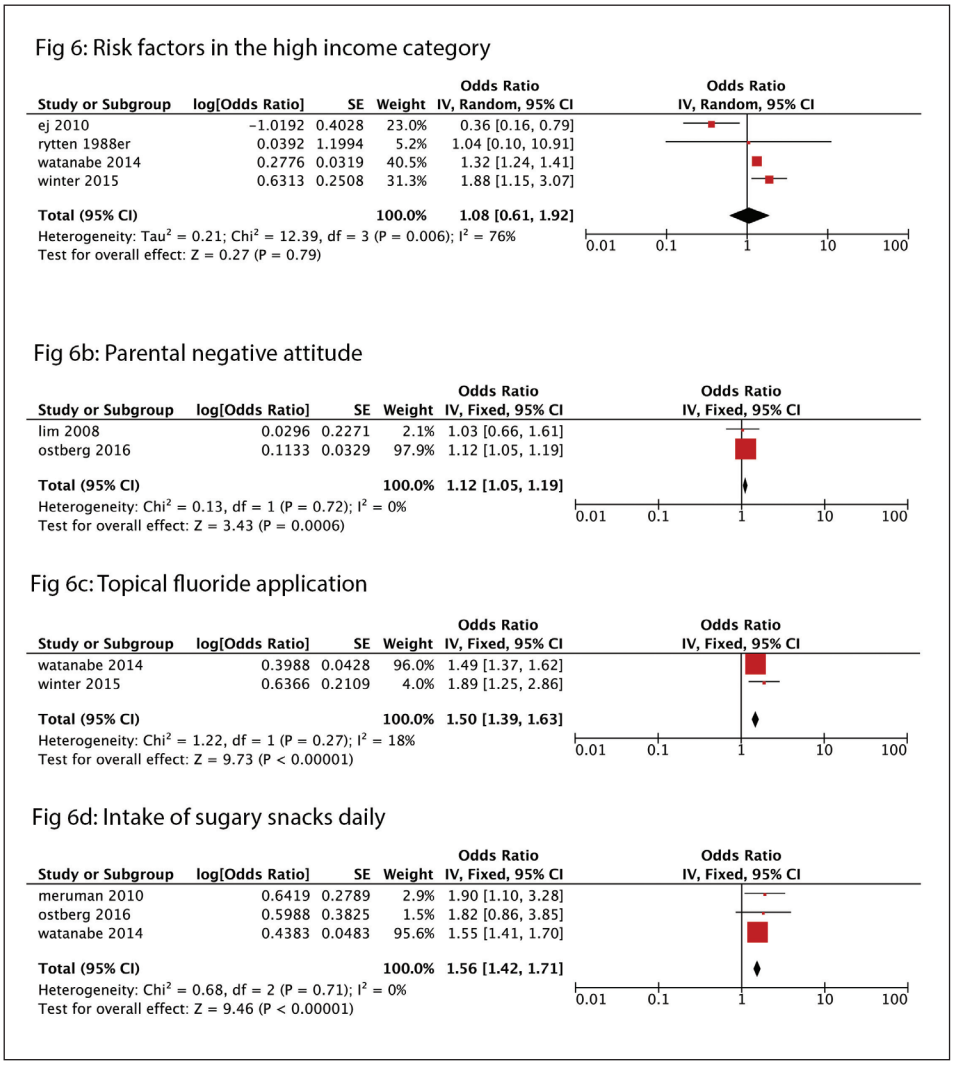

Figure 6. Risk factors found in the high-income category. (a) Forest plot showing toothbrushing less than once a day as a risk factor for early childhood caries. (b) Forest plot showing parental negative attitude as a risk factor for ECC. (c) Forest plot showing topical fluoride application as a risk factor for ECC. (d) Forest plot showing intake of sugary snacks daily as a risk factor for ECC.

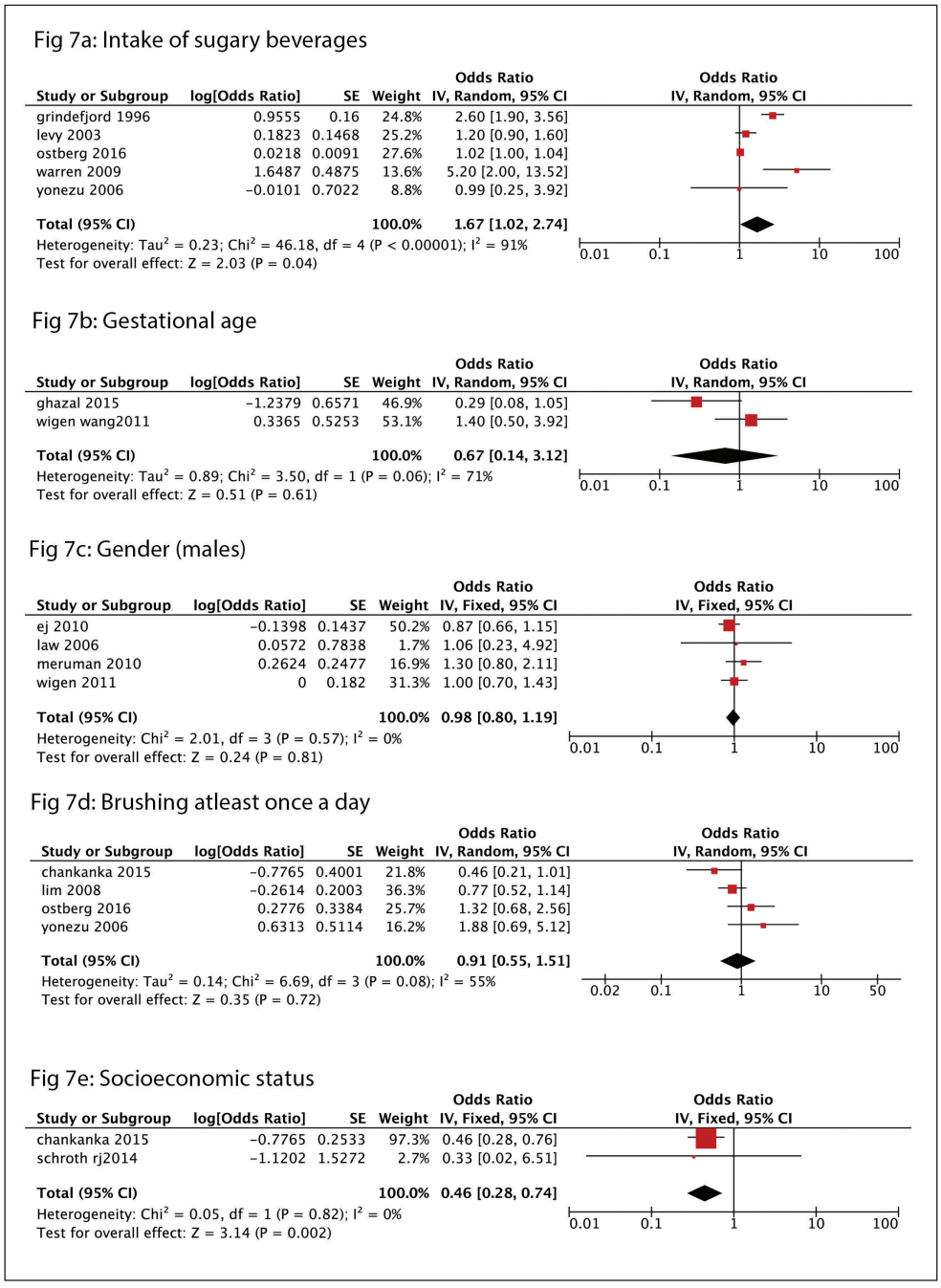

Figure 7. Risk factors found in the high-income category. (a) Forest plot showing intake of sugary beverages as a risk factor for early childhood caries. (b) Forest plot showing gestational age as a risk factor for ECC. (c) Forest plot showing gender (males) as a risk factor for ECC. (d) Forest plot showing brushing at least once a day as a risk factor for ECC. (e) Forest plot showing socioeconomic status (SES) as a risk factor for ECC.

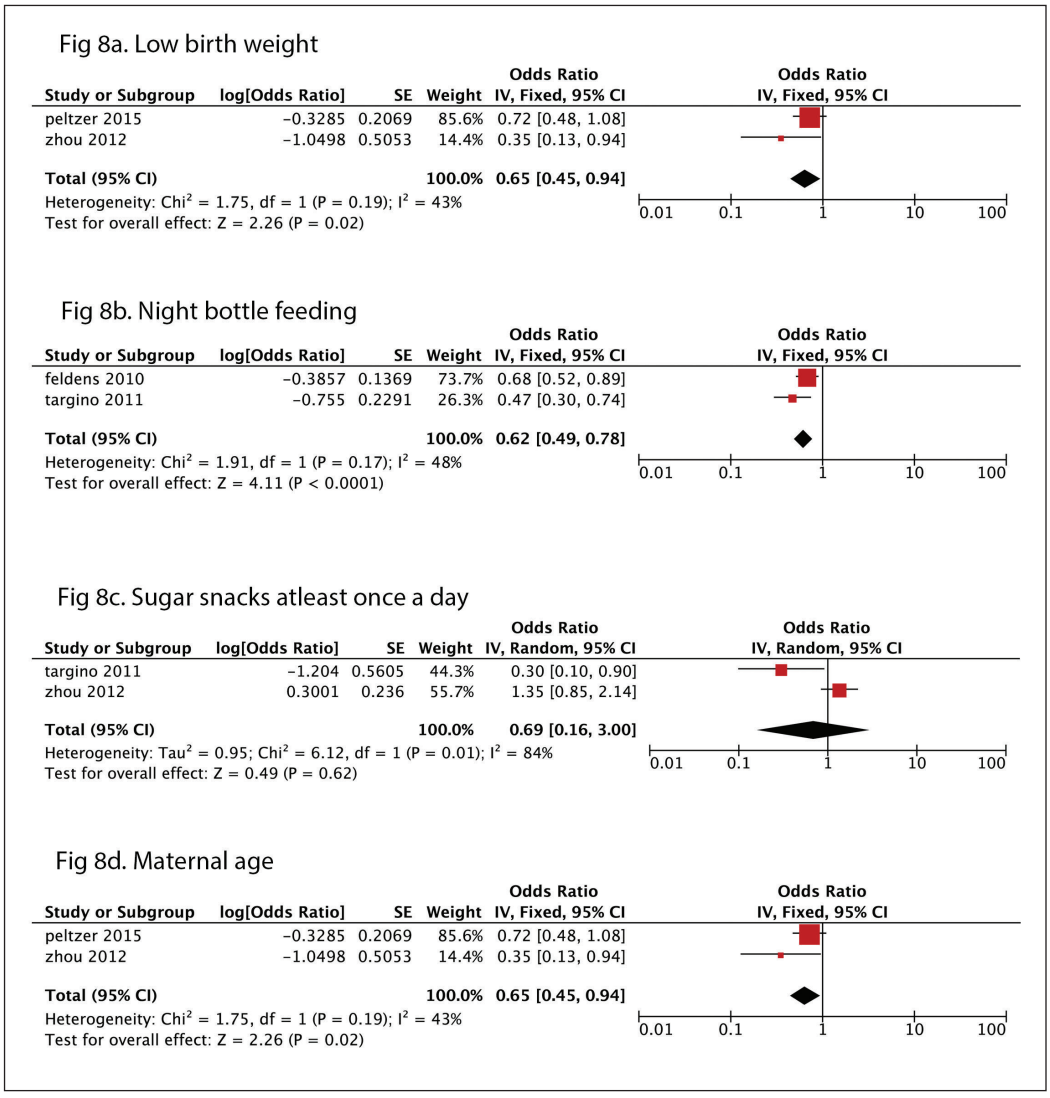

Figure 8. Risk factors found in the upper-middle-income category. (a) Forest plot showing low birthweight as a risk factor for early childhood caries. (b) Forest plot showing night bottle feeding as a risk factor for ECC. (c) Forest plot showing sugar snacks at least once a day as a risk factor for ECC. (d) Forest plot showing maternal age as a risk factor for ECC.

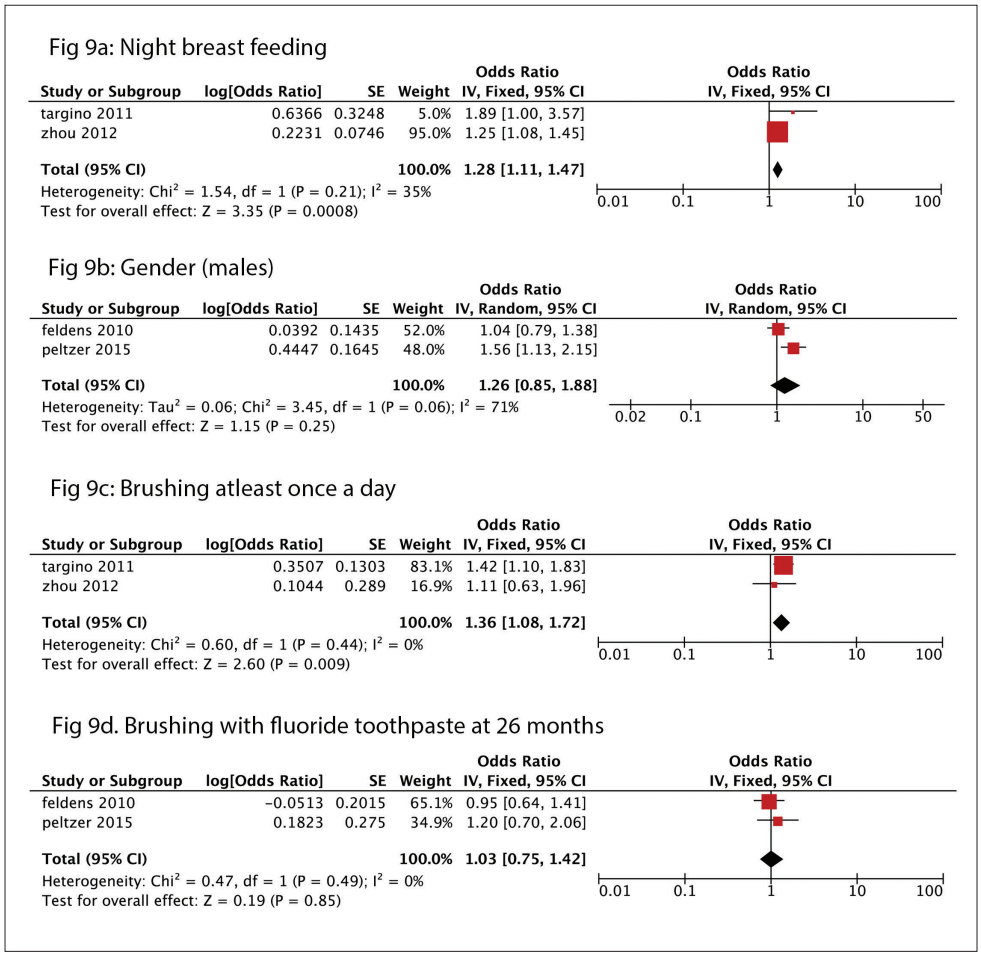

Figure 9. Risk factors found in the upper-middle-income category. (a) Forest plot showing night breastfeeding as a risk factor for early childhood caries. (b) Forest plot showing gender (males) as a risk factor for ECC. (c) Forest plot showing brushing at least once a day as a risk factor for ECC. (d) Forest plot showing brushing with fluoride toothpaste at 26 months as a risk factor for ECC.