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META-ANALYSIS

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Does dental caries play a role on the asthma development?—systematic review and meta-analysis

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Abstract

Asthma and dental caries are the two most common diseases in children, and the relationship between them has been a focus of research. Whether dental caries affects the development of asthma has long been controversial. The aim of this study was to conduct a systematic review of the literature to assess the effect of dental caries on the development of asthma and provide new ideas for the pathogenesis and promoting factors of asthma. For a systematic review and meta-analysis, we systematically searched three databases (PubMed, Web of Science, and Embase) for studies published from database inception to 22 May 2022. We included observational studies that investigated the effect of dental caries on the development of asthma. Studies were critically appraised and a meta-analysis was performed to estimate a pooled effect. From the 845 studies initially identified, 7 of these were included in the meta-analysis. Included studies originated from America (n = 5) and Asia (n = 2). A meta-analysis of data from seven selected studies suggested that dental caries was positively associated with the risk of asthma development (The odds ratio for the pooled effect was 1.06, 95% confidence interval: 1.01, 1.10). In addition, the effect of dental caries on asthma risk varied in different geographic locations according to subgroup analyses. This study suggests that dental caries may affect the development of asthma and emphasizes the importance of increased awareness of dental care and caries prevention in patients with asthma.

Keywords

Dental caries; Asthma; Meta-Analysis

1. Introduction

Asthma is a chronic inflammatory disease of the airway, characterized by reversible airflow obstruction and airway hyperresponsiveness. It is one of the most common chronic diseases in children [1]. Dental caries is a chronic progressive destructive disease that occurs in tooth hard tissue under the influence of various factors, mainly bacteria [2]. In 2016, Lancet released the Global Burden of Disease Study, showing that the incidence rate of dental caries in the world was ranked second among all diseases, while that of deciduous teeth was ranked fifth. Therefore, dental caries and asthma are two of the most common childhood diseases, and their similar early incidence, chronic inflammatory characteristics, and of several common risk factors suggest that there is a certain association between the two diseases.

Current studies and meta-analyses on the relationship between dental caries and asthma have focused on whether asthma affects the occurrence of dental caries [3–5]. Some studies have linked children with asthma to a higher risk of dental caries, depending on their condition and the effects of medications [6, 7]. However, there are few reports about the effect of dental caries on asthma development. As the starting site of the human digestive tract, the oral cavity contains a large number of microorganisms [8]. The imbalance of oral microorganisms may be closely related to dental caries and other oral diseases and plays a role in the occurrence and development of systemic diseases, such as inflammatory bowel disease, Alzheimer's disease, diabetes, rheumatoid arthritis, and cardiovascular disease [9]. The lung microbiome of healthy people closely resembles the microbiome in the mouth, and the mouth may be the main source of bacteria in the lungs [10]. Several epidemiological studies have confirmed that poor oral hygiene may increase the occurrence of pneumonia and chronic obstructive pulmonary disease (COPD) [11], but the effect on asthma is not clear.

Whether dental caries affects the development of asthma has long been controversial. Even in studies that consider caries to affect asthma development, the conclusions are inconsistent. Some studies have suggested that dental caries increases the risk of asthma: asthma is considered to be a disease driven by immune cells [12], and the oropharynx is the source of tracheobronchial microbiota, most likely through microaspiration [13]. It is reasonable to speculate that the imbalance of oral microbiota may regulate the immune responses and thus promote the development of asthma. Other, in the aetiology of asthma, the "hygiene hypothesis" holds that infection may

TABLE 1. Search strategies used for initial screening.

Database	Commands used	Manuscripts found
PubMed	((((((((((((((((((Dental Caries) OR (Dental Decay)) OR (Decay, Dental)) OR (Carious Lesions)) OR (Carious Lesion)) OR (Lesion, Carious)) OR (Lesions, Carious)) OR (Caries, Dental)) OR (Carious Dentin)) OR (Carious Dentins)) OR (Dentin, Carious)) OR (Dentins, Carious)) OR (Dental White Spot)) OR (Spot, Dental White)) OR (Spots, Dental White)) OR (White Spot, Dental)) OR (White Spots, Dental)) OR (Dental White Spots)) AND ((((Asthma) OR (Asthmas)) OR (Bronchial Asthma)) OR (Asthma, Bronchial))	178
Web of Science (ISI)	TS = (Dental Caries OR Dental Decay OR Decay, Dental OR Carious Lesions OR Carious Lesion OR Lesion, Carious OR Lesions, Carious OR Caries, Dental OR Carious Dentin OR Carious Dentins OR Dentin, Carious OR Dentins, Carious OR Dental White Spot OR Spot, Dental White OR Spots, Dental White OR White Spot, Dental OR White Spots, Dental OR Dental White Spots) AND TS = (Asthma OR Asthmas OR Bronchial Asthma OR Asthma, Bronchial) #1 AND #2	330
Embase	#1: 'dental caries' OR (dental AND decay) OR (decay, AND dental) OR (carious AND lesions) OR (carious AND lesion) OR (lesion, AND carious) OR (lesions, AND carious) OR (caries, AND dental) OR (carious AND dentin) OR (carious AND dentin) OR (dentin, AND carious) OR (dentin, AND carious) OR (dental AND white AND spot) OR (spot, AND dental AND white) OR (spots, AND dental AND white) OR (white AND spot, AND dental) OR (white AND spots, AND dental) OR (dental AND white AND spots) #2: asthma OR asthma OR (bronchial AND asthma) OR (asthma, AND bronchial)	337

TS: topic sentence.

help prevent the development of asthma [14]. According to this theory, growing up in a more hygienic environment with less microbial contact may increase the risk of asthma for patients [15]. However, epidemiological studies attempting to link infection with allergic diseases have yielded conflicting results [16]. Ectopic colonization of flora and immune response regulators may be the common factors that underline the relationship between asthma and dental caries [17]. Some data indicate that the microbiota may play a role in asthma development, and the response of asthmatics to antibiotics confirms the importance of bacteria in the pathogenesis of the disease [18]. Thus, the influence of the microbiota on the pathogenesis and development of asthma cannot be ruled out.

According to our literature search, there have been no previous meta-analyses on the impact of dental caries on asthma development. To study the relationship between dental caries and the development of asthma, we conducted a systematic review and meta-analysis. Our results suggested that oral hygiene and dental status might be influence factors affecting the development of asthma.

2. Materials and method

The protocol of systematic review was accomplished using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (**Supplementary material**) based on the following review questions: "Does dental caries play a role in asthma development?" The exposure of interest was dental caries. The outcome measure was asthma. This review was not registered.

2.1 Study selection and screening

References were managed using the software EndNote (version X9, Thomson Reuters, New York, NY, USA) Duplicate records were excluded in the first step. Before retrieving full-text papers, titles and abstracts were independently screened by two reviewers (YZ and LG) according to the inclusion criteria. The screening results of the two reviewers were compared, and the differences were resolved by consensus. If there was still no agreed conclusion, the corresponding author (GY) was contacted to decide the inclusion or exclusion of the article.

2.2 Inclusion and exclusion criteria

The inclusion criteria included: the definition of asthma was well-described; dental caries was diagnosed through clinical examination; no age restriction; applicable quantitative information on the relation between asthma and dental caries was provided.

The exclusion criteria included: animal studies; studies conducted in samples with systemic diseases other than asthma; reviews; case reports; in vitro and in situ studies; comments or conference abstracts; studies on the effect of asthma on the incidence of dental caries; studies in languages other than English.

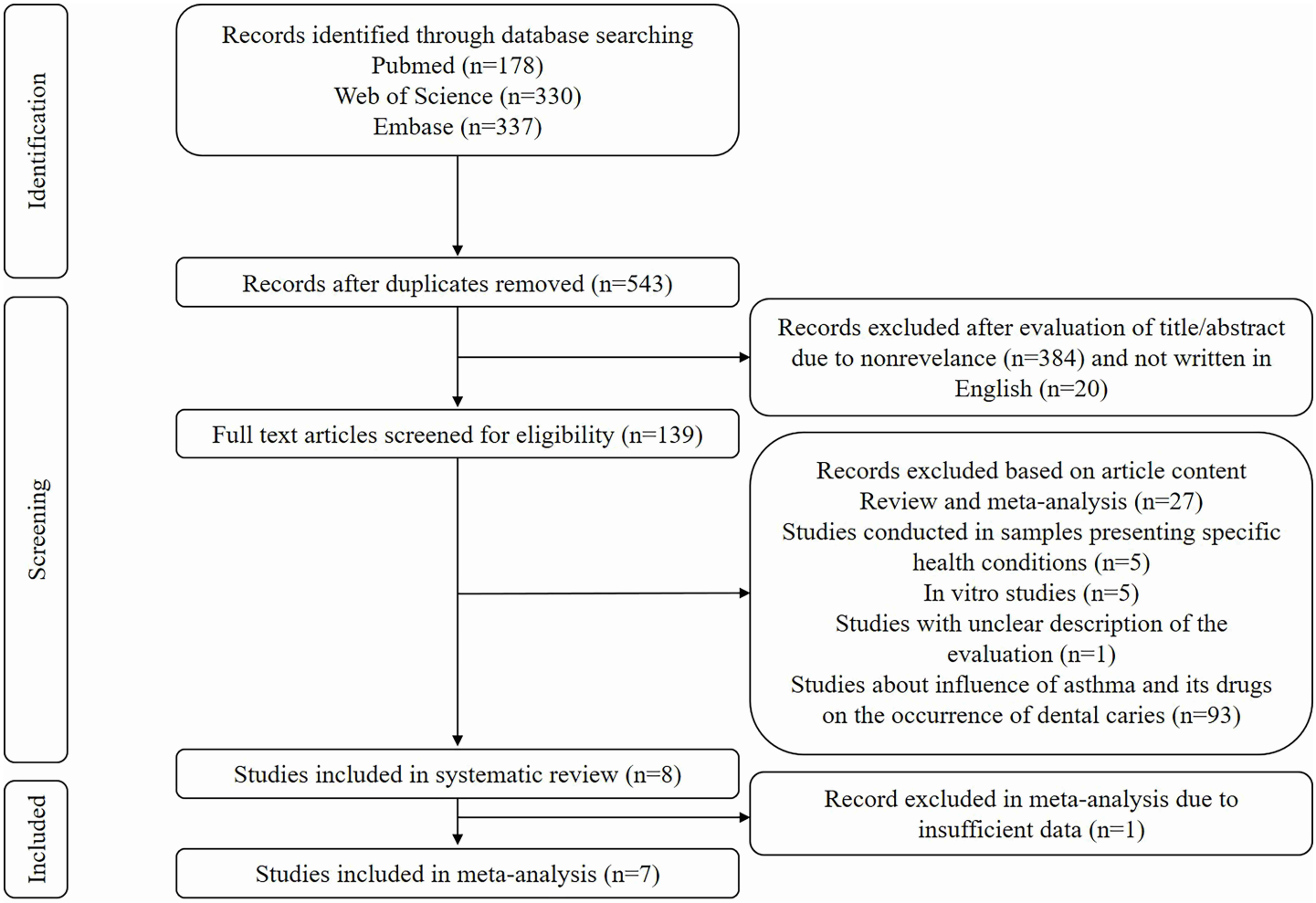

FIGURE 1. Flowchart of the study selection process for the systematic review and meta-analysis of dental caries effect on the asthma development. initial time limitation was applied to 22 May 2022.

2.3 Search strategy

We conducted a systematic literature search in three different databases: PubMed, Web of Science and Embase, with no initial date restriction until 22 May 2022. Keywords comprised MeSH and free terms. Table 1 presents the different combinations for each database.

2.4 Data extraction

Data on each subject's age range, study design, sample size, geographic location of the study, dental caries and asthma definition were recorded. To ensure the reliability of data, two reviewers (YZ and LG) performed the data extraction independently. For any ambiguous answers or doubts about methodological aspects and the results in the included articles, judgment was made by the corresponding author (GY). If articles provided multiple dental caries measurements, we analyzed the data separately to obtain as much information as possible.

2.5 Critical appraisal

As all the studies included were cross-sectional studies, we thus adopted the Critical Appraisal Checklist recommended by the Joanna Briggs Institute (JBI) to assess the quality of the studies included in this research. The checklist evaluated methodological aspects through questions answered as "YES", "NO" or "UNCLEAR". The two reviewers (YZ and LG) assessed each study independently. The percentage of "YES" answers was assessed to compare different study designs. Disagreements were resolved by contacting the corresponding author (GY).

2.6 Statistical analyses

A meta-analysis was conducted to explore the impact of dental caries on the development of asthma. Data were summarized using the odds ratio (OR) with a 95% confidence interval (CI). We estimated using random effect models because of the heterogeneity (I^2 >50%) [19]. A sensitivity analysis was performed to assess the influence of each study on the overall estimate by excluding one study at a time. Possible publication bias was evaluated by visual inspection of funnel plots and more objectively through Egger's test. In addition, we performed subgroup analyses to investigate potential sources of between-study variability. The statistical analysis was performed using Review Manager (version 5.3, Nordic Cochrane Centre (Cochrane Collaboration), Copenhagen, Denmark) and STATA (version 14.0, StataCorp, Texas, USA).

TABLE 2. Characteristics of the studies included in the systematic review.

First Author, Year	Subjects' age range (average)	Study Design	Sample size	Location	Dental caries definition	Asthma definition	OR (95% CI) for dental caries in relation to asthma	*p*	JBI critical Appraisal*
J.D. Shulman [20], 2001	11.0–16.0	Cross-sectional study	2670	USA	DMFT DMFS	Self-report	1.3000 (1.1556, 1.4544) 1.2800 (1.1292, 1.4593)	<0.0001 <0.0001	85%
Keiko Tanaka [15], 2008	6.0–15.0	Cross-sectional study	21,792	Japan	One or more teeth had decayed and/or had been filled	Self-report	0.9900 (0.8700, 1.1400)		70%
Ida Anjomshoaa [21], 2009	17.0–84.0 (41.7)	Cross-sectional study	318	USA	DMFT DMFS	Self-report	1.0500 (1.0100, 1.1000) 1.0100 (0.9900, 1.1000)	0.0200 0.0800	70%
Eliza M Vázquez [22], 2011	4.0–5.0 (4.5)	Cross-sectional study	1160	Mexico	DMFT and DMFS	Self-report	1.2400 (0.8400–1.8100)	0.2640	80%
Lindsay Johnston [17], 2014	6.0–94.0 (47.7)	Cross-sectional study	1281	USA	DMFT and DMFS	Self-report	**		85%
Mario H. Vargas [12], 2014	14.0–24.0	Cross-sectional study	329,780	Mexico	Decayed tooth Missing teeth	Self-report	0.9650 (0.9570–0.9720) 1.0330 (1.0140–1.0520)	<0.0010 0.0010	70%
S. Y. Kim [23], 2017	4.0–15.0	Cross-sectional study	3703	Korea	Clinical examination	Self-report	0.5500 (0.3300–0.9000)	0.0170	95%
Parth D. Shah [24], 2021	18.0–(46.5)	Cross-sectional study	13,135	USA	Decayed and filled teeth Decayed teeth	Self-report	1.3700 (1.1300–1.6600) 1.3800 (1.1000–1.7300)		95%

**Proportion of "yes" answers in Joanna Briggs Critical Appraisal Checklist for the specific study design.*
***Without sufficient information for OR, the article was not included in the meta-analysis.*
OR: odds ratio; CI: confidence interval; JBI: Joanna Briggs Institute; DMFT: decayed, missing, filled teeth; DMFS: decayed, missing, filled surfaces.

3. Results

3.1 Studies identified in the searches

The study selection process is shown in Fig. 1. The systematic literature search produced 845 articles, and 302 articles were removed due to duplication. Screening of the titles and abstracts of these articles led to the exclusion of 404 studies that lacked relevance and were not written in English. The full texts of the remaining 139 articles were screened, and 8 articles were included in the systematic review. The 8 articles were as follows: J.D. Shulman, 2001 [20]; Keiko Tanaka, 2008 [15]; Ida Anjomshoaa, 2009 [21]; Eliza M Vázquez, 2011 [22]; Lindsay Johnston, 2014 [17]; Mario H. Vargas, 2014 [12]; S. Y. Kim, 2017 [23]; Parth D. Shah, 2021 [24]. The study characteristics and critical appraisal are shown in Table 2. Due to the lack of sufficient data for 1 article, only 7 articles were finally included in the meta-analysis.

3.2 Meta-analysis

The summary OR for asthma risk in studies on the relationship between dental caries and asthma was 1.06 (95% CI: 1.01, 1.10) (shown in Fig. 2). Both visual inspection of the forest plot and quantitative data (I^2 = 91%) revealed substantial heterogeneity between the study-specific estimates, and the random-effects model was therefore considered to obtain a more appropriate estimate.

3.3 Sensitivity analysis

Sensitivity analysis demonstrated that the omission of any study would not significantly change the results (shown in Table 3).

3.4 Potential publication bias

Fig. 3 shows the possibility of publication bias, which was assessed with funnel plots. The funnel plot was symmetrical at the top but indicated some asymmetry in the middle and at the bottom. Egger's test value was 0.028, which indicated the presence of publication bias.

3.5 Subgroup analysis

Fig. 4 shows the results of the subgroup analysis according to geographical location. The summary OR for the Asian studies was 0.78 (95% CI: 0.44, 1.37), indicating that dental caries experience was a protective factor against asthma. However, the summary OR for the American studies was 1.07 (95% CI: 1.02, 1.12), indicating that dental caries increased the risk of asthma.

Fig. 5 shows the results of the subgroup analysis according to average age. The summary OR for the studies in which the average age <17 was 1.04 (95% CI: 0.98, 1.11) and in which the average age >17 was 1.09 (95% CI: 1.01, 1.18). The results suggested that the effect of dental caries on asthma risk was not significantly different in the two age groups.

4. Discussion

The effect of dental caries on the development of asthma is controversial. In this study, we conducted a comprehensive and updated systematic review to assess the association between asthma and dental caries. A total of 7 manuscripts were included in the meta-analysis under well-defined criteria allowing its reproducibility and undertaking a quality assessment of the included studies. We found that individuals with dental caries had 1.06 times higher odds of asthma development by adopting a random-effect model due to the large heterogeneity. It indicates that the presence of bacterial biofilms in dental caries might lead to dysbacteriosis and the development of asthma. In the sensitivity analysis, the omission of any study would not significantly change the results. In the subgroup analysis, estimates in subjects whose average age was greater than 17 and below 17 reported no significant difference. It shows that age may not affect the impact of caries on the development of asthma.

Moreover, we found that studies conducted in America reported larger estimates than those conducted in Asia. The presence of bacterial biofilms in dental caries may contribute to the maturation of the immune system and has a protective effect on asthma development in Asia. This may be related to geographical differences and there are various types of research on the prevalence or severity of asthma, which may be related to the difference between the populations studied and local geographic factors [25]. Some research confirmed that sensitization towards the dominant allergens, such as a microbe, was facilitated by demographic characteristics such as a genetic predisposition to atopic diseases, living in urban areas, and peculiarities of geographical regions [26, 27].

Substantial heterogeneity was observed in the meta-analysis and subgroup analysis. The possible reason may be (1) different outcome measurements: The definition of dental caries varies among studies. Even if DMFT and/or DMFS are used to define dental caries, they still cannot show the real situation. Only "decayed" really refers to the current progress of caries, and the latter two variables refer to the occurrence of dental caries in the past. These three conditions correspond to different oral flora states, which makes the research results deviate; (2) Although we performed a subgroup analysis of age, we did not distinguish between primary dentition and permanent dentition. The differences between primary dentition and permanent dentition, such as pathogenic bacteria, will increase the heterogeneity of the results [4, 28, 29]; (3) No distinction about symptoms and types of asthma: Asthma is a multifactorial disease and is thus associated with genetic and environmental factors. Dental caries may be more closely related to a certain type of asthma. For example, in the research of Eliza *et al.* [22], a significant association was found between nocturnal asthma symptoms and dental caries.

In this study, individuals with dental caries had higher odds of asthma development. The possible reason is that oral bacteria enter the lung tissue through micro-respiration, affecting the immune and inflammatory reaction, thus aggravating the development of asthma. Bacterial infection is associated with asthma symptoms and the asthma pathogenesis. *Haemophilus influenzae*, *Moraxella catarrhalis*, *Strepto-*

TABLE 3. Sensitivity analysis.

Excluded study	Effect size			
	OR	95% CI	I^2	*p*
J.D. Shulman [20], 2001	1.03	0.99, 1.08	91%	<0.00001
Keiko Tanaka [15], 2008	1.06	1.01, 1.11	92%	<0.00001
Ida Anjomshoaa [21], 2009	1.09	1.02, 1.16	91%	<0.00001
Eliza M Vázquez [22], 2011	1.05	1.01, 1.10	92%	<0.00001
Mario H. Vargas [12], 2014	1.11	1.03, 1.20	80%	<0.00001
S. Y. Kim [23], 2017	1.06	1.01, 1.11	92%	<0.00001
Parth D. Shah [24], 2021	1.03	0.99, 1.08	91%	<0.00001

OR: odds ratio; CI: confidence interval.

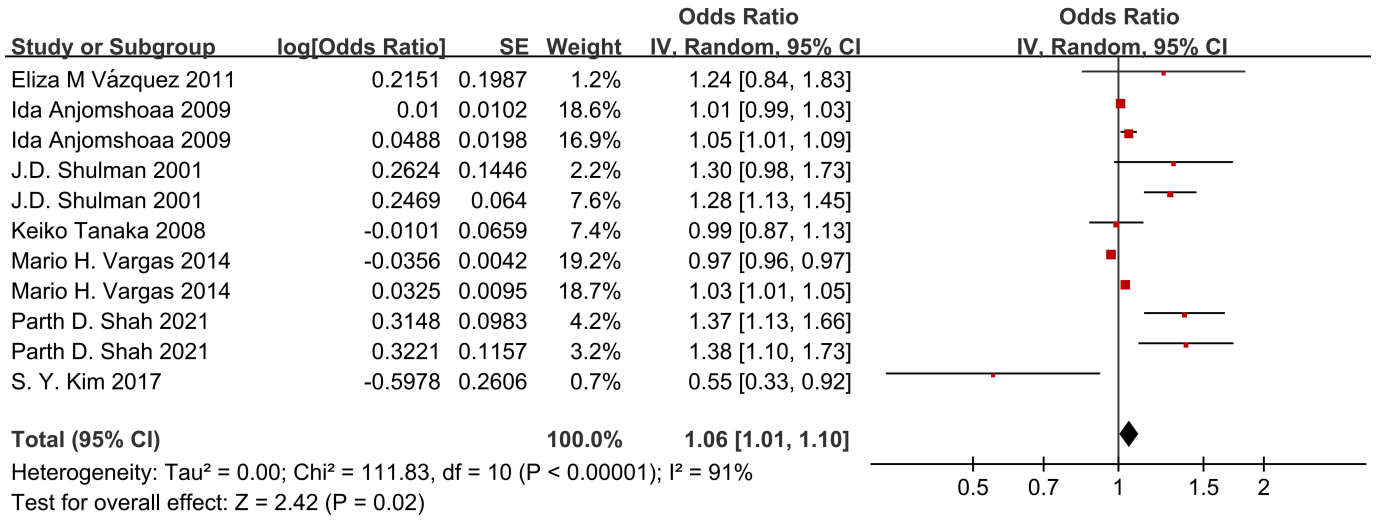

FIGURE 2. Study-specific and summary effect estimates OR and 95% CI for asthma risk in studies on the relationship between dental caries and asthma. CI: confidence interval; SE: standard errors.

coccus pneumoniae, *Veillonella spp.*, *Faecalibacterium spp.*, *Lachnospira spp., Rothia spp.*, *Staphylococcus spp.* and *Neisseria spp.* found in the lungs of asthmatic patients are closely related to increased asthma risk [30]. Among them, *Veillonella spp.* [31], *Rothia spp.* [32] and *Staphylococcus spp.* [33] are also important pathogens causing infections associated with dental caries. Oral microbial immigration seems to be an important source of pulmonary microbiome. Bassis *et al.* [10] showed that the most dominant bacterial operational taxonomic units in the oral cavity and lungs were classified as two different Streptococcus species, an unclassified member of the family Pasteurellaceae, a Fusobacterium species, and a Neisseria species. Thus, the bacterial communities of the healthy lungs shared similar membership with the oral cavity, and the upper aerodigestive tract might be factors that formed the pulmonary microbial community in health and disease condition. Cherkasov *et al.* [34] suggested that the teeth of children with asthma were colonized by opportunistic bacteria with a high pathogenic capacity, for example, *Streptococcus*, *Neisseria*, *Veillonella*, *Prevotella*, *Haemophilus*, *Fusobacterium* and *Porphyromonas*, which might be associated with the pathogenesis of both caries and asthma. These bacteria may stimulate the underlying antigen presenting cells and induce an immune response that results in an influx of eosinophilic or neutrophilic cells into the airway and further mediates development of asthma [30].

There are many deficiencies in this study. As all reports are cross-sectional studies, the current study could not explain the effect of dental caries treatment on the asthma development. Most studies have defined asthma based on self-reports, and most of the caries diagnoses were based on clinical examinations without X-ray examinations, which may have led to deviations in the diagnosis and affected the results.

Through this study, we can understand the possible relationship between dental caries and systemic diseases, especially allergic diseases. However, the relationship between dental caries and asthma is affected by various factors, including but not limited to different types of asthma, the time of asthma onset, and the genetic susceptibility of patients. In future research, we will increase the number of articles and conduct more accurate subgroup analysis to further clarify the pathogenic effect of dental caries on asthma. In addition, the pathogenic mechanism of dental caries on asthma needs further study to clarify the aetiology of asthma and provide a theoretical basis for oral health care.

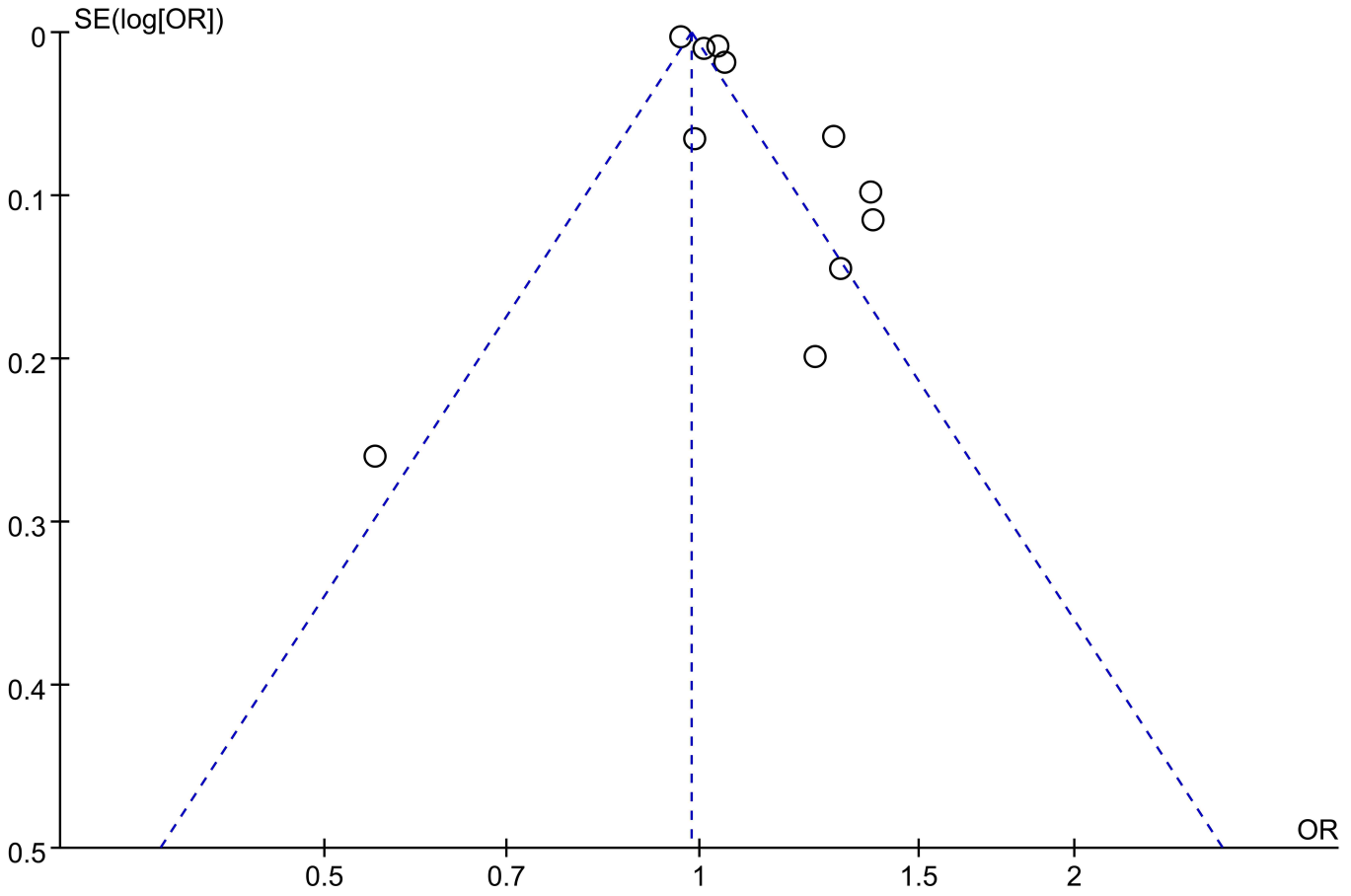

FIGURE 3. Funnel-plots to identify possible publication bias. OR: odds ratio; SE: standard errors.

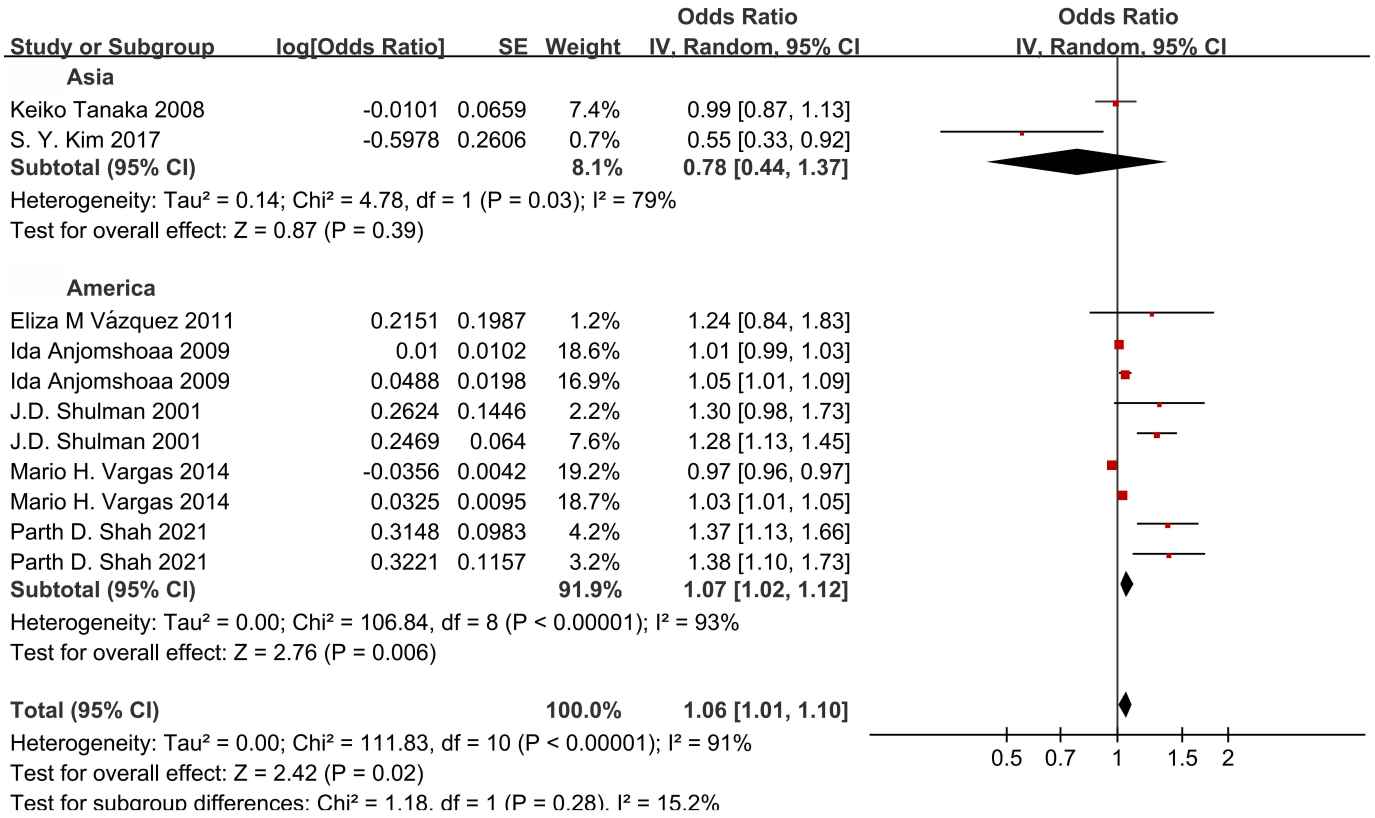

FIGURE 4. Subgroup meta-analysis according to geographic location. CI: confidence interval; SE: standard errors.

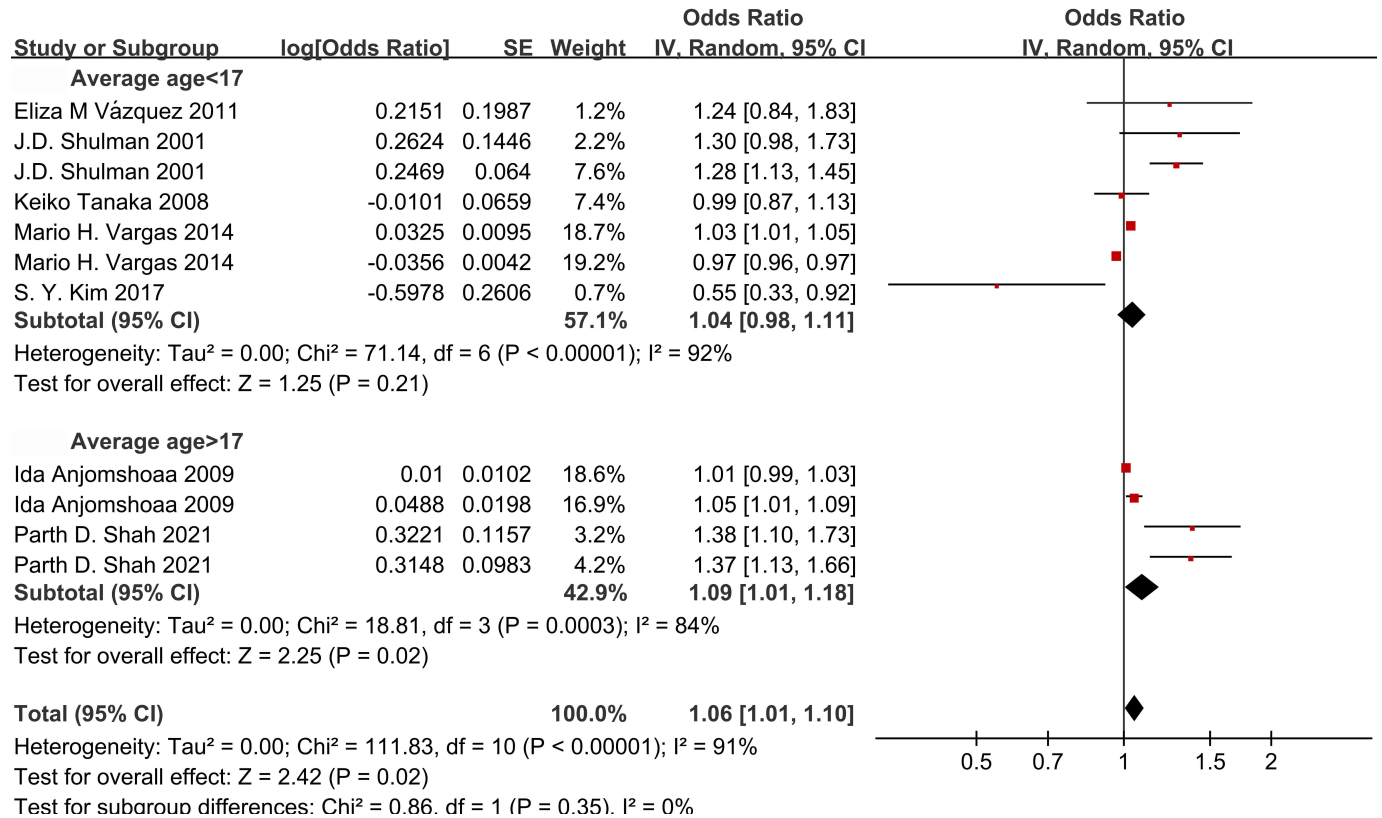

FIGURE 5. Subgroup meta-analysis according to average age. CI: confidence interval; SE: standard errors.

5. Conclusion

This meta-analysis provides evidence that dental caries is a risk factor for asthma. However, the results may vary in different geographical location.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article (and supplementary material).

AUTHOR CONTRIBUTIONS

GY—designed the research study. YZ and LG—performed the research and analyzed the data. YZ—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/1675758646219161600/attachment/Supplementary%20material.docx.

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