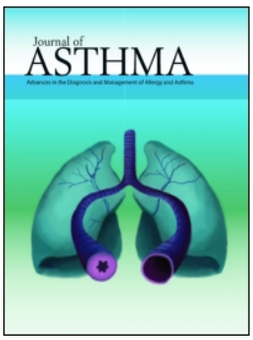

Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: http://www.tandfonline.com/loi/ijas20

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To cite this article: Bernardo Antonio Agostini, Kaue Farias Collares, Francine dos Santos Costa, Marcos Britto Correa & Flavio Fernando Demarco (2018): The role of asthma in caries occurrence – meta-analysis and meta-regression , Journal of Asthma, DOI: 10.1080/02770903.2018.1493602

To link to this article: https://doi.org/10.1080/02770903.2018.1493602

Accepted author version posted online: 04 Jul 2018.

The role of asthma in caries occurrence – meta-analysis and meta-regression

Short Title: Asthma and caries: a review and meta-regression

Key-words: Asthma. Dental caries. Chronic inflammatory disease. Antiasthmatic drugs. Wheezing.

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Abstract:
Objective: We aimed to conduct a systematic review of the literature regarding the association between asthma and caries, assess the effect of asthma on the occurrence of

caries in primary and permanent dentitions, and determine factors that could affect the estimates of this association. *Data Source*: We used the following databases: PubMed, Web of Science, SCOPUS, and LILACS/BVS, for the literature review. *Study Selection*: We included observational studies that investigated the association between asthma and dental caries, excluding studies with syndromic patients, literature reviews, case reports, and *in vitro* and *in situ* studies. A meta-analysis was performed to estimate a pooled effect, and meta-regression was conducted to determine study factors that could affect the estimates. *Results*: From 674 studies initially identified, 40 fulfilled the inclusion criteria, and 36 of these were used in the meta-analysis. Odds ratio (OR) for the pooled effect was 1.45 (95% confidence interval (CI): 1.22–1.72; I^2, 71.8%; $P < 0.001$) and 1.52 (95% CI: 1.34–1.73; I^2, 83.1%; $P < 0.001$) for primary and permanent dentitions, respectively. In addition, a small proportion of the heterogeneity was attributed to included factors in the meta-regression (primary dentition, 10.7%; and permanent dentition, 3.1%). *Conclusions*: This study provides reliable and robust evidence that emphasizes the impact of asthma on the occurrence of dental caries in both, primary and permanent, dentitions. The findings provide useful data for recommending that dentists and physicians collaborate to establish the control for both diseases in a multidisciplinary manner.

Introduction

Dental caries is a progressive disease, accounting for the loss of tooth structure, resulting in several functional and aesthetics complications, and thereby, affecting the individuals' quality of life [1,2]. According to the Global Burden of Disease 2010, untreated caries of permanent teeth is the most prevalent condition in the world, affecting more than 35% of the population [3,4] and it is the primary reason for tooth loss in young and adults [5]. Likewise, asthma is a chronic disease affecting 300 million people worldwide, resulting from a complex process of chronic inflammation in the airways; it is the highest prevalent chronic disease of childhood, accounting for several years of life lost (YLLs)[6]. Given the high prevalence of both conditions and their negative impacts on the lives of the individuals, both are considered public health problems.

The similar occurrence of asthma and caries in early ages, their chronic characteristics, and some shared risk factors have highlighted the interest for investigating the association between these conditions since the 1980s [7,8] to date [9,10]. Some studies have assessed the effects of antiasthmatic drugs, such as salivary flow reduction, a decline in oral pH, and higher consumption of sugary beverages by asthmatic individuals, intending to elucidate the effects of asthma on the occurrence of caries. Although several studies using different designs have been conducted, no consensus has been attained to date. The inconclusive results could be attributed to several limitations associated to methodological aspects and definitions of asthma and dental caries.

Although some reviews were conducted to summarize the knowledge about the association between asthma and caries [11-14], just one conducted a meta-analysis [14]. Based on this late study, the risk of caries occurrence in asthmatic patients is two times higher than in healthy subjects. Despite this effect demonstrated, the authors raised several queries regarding methodological designs that affected the estimate because of the high heterogeneity detected. In addition, Matthews et al. [15], criticized the meta-analysis regarding the exclusion of several studies, the heterogeneous definition of the exposure, and the lack of explanation about the possible reasons for the association observed. The previous meta-analysis also highlighted the need for future high-quality

prospective studies to elucidate the association between asthma and the occurrence of caries along with possible causal pathways [14]. Furthermore, earlier reviews have suggested that the observed association could be related to the antiasthmatic medication regimes, oral breathing, psychological aspects in consequence of the disease, or even to the adoption of unhealthy behaviors [12,13]. All of these factors could be mediators of the association between asthma and caries.

After the meta-analyses published in 2011, several other studies appeared in literature [9-10,16-22]; however, some of these could not establish an association between the two chronic conditions [10,16, 18, 19-21]. In addition, the pathways responsible for the relationship remain unclear. A better understanding of this association could enable the prevention of the caries occurrence in individuals affected by asthma. Hence, this study aimed to conduct an extensive, updated, and critical systematic review of the literature regarding the association of asthma and caries. Moreover, the study aimed to estimate the effect of asthma on the occurrence of caries and determine study factors that could affect the estimates. We hypothesized that asthmatic subjects are at an increased risk of dental caries, and methodological aspects of the studies can affect the estimates.

Methods

This systematic review was conducted in accordance with the PRISMA guidelines based on the following review questions: "What is the influence of asthma on the occurrence of caries?" and "Are there any methodological aspects affecting this relationship?"

Eligibility Criteria

We included original observational studies that investigated the association between asthma diagnosis, asthma symptoms, wheezing, or people using antiasthmatic drugs and dental caries. The inclusion criteria comprised the following: well described definition of asthma or asthma-related exposure (i.e., persistent wheezing or use of anti-asthmatic drugs), evaluated independently of other respiratory diseases; caries detection must have been diagnosed through clinical examination, describing the criteria used. Of

note, no age restriction was applied. In contrast, we excluded the following: animal studies; studies conducted in samples presenting specific health conditions, such as cancer, paralysis or syndromes and similar convenience samples; literature reviews; case reports; anthropological studies; *in vitro* and *in situ* studies; comments or conference abstracts; and studies in languages other than English, Spanish or Portuguese.

Search strategy

We conducted an Electronic search in four different databases: PubMed, Web of Science, SCOPUS, and LILACS/BVS, with no initial date restriction until December 2017. Keywords comprised MeSH and free terms, which were combined using Boolean operators with different tags, specific to each base. All of the independent searches used "asthma", "wheezing", and "breathlessness" to determine the exposure of interest and "dental caries", "caries", and "tooth decay" for the outcome. Table 1 presents different combinations for each database.

References were managed using the software EndNote X7.4 (Thomson Reuters, New York, NY, USA). First, duplicate records were excluded. Then, titles and abstracts were independently screened by two reviewers based on the aforementioned criteria (BAA and KFC). Next, the screened lists were compared and differences were discussed and resolved by consensus. In the absence of consensus, a third examiner intervened to determine the inclusion or exclusion of the article in question. Full-text articles were screened by the same two observers. Reference lists of the eligible papers were reviewed according to the eligibility criteria.

Critical appraisal

We adopted the Critical Appraisal Checklist recommended by the Joanna Briggs Institute (JBI) (23) to assess the quality of the studies included in this review. The checklist evaluates methodological aspects through questions answered as "YES", "NO", or "UNCLEAR". Same reviewers assessed each study independently. The appraisal used for each study was selected matching the study design to its corresponding appraisal checklist. As the total number of questions differed among the instruments (i.e., JBI Critical Appraisal checklist for cohort studies is composed by 11 questions while there

are just 9 questions in the prevalence studies checklist), we adopted the percentage of "yes" answers in the instrument to compare different study designs. Disagreements were resolved by reaching consensus through discussion.

Data extraction and Statistical analysis

Data about sample size, geographic location of the study, income of the country (according to the World Bank income level classification) [24], study design, age of the study population, exposure definition, criteria used for assessing the outcome and, adjustment in the analysis matched for socioeconomic background, and the effect size were collected. Two reviewers (BAA and KFC) performed the data extraction independently. Structured data collection worksheets were used for the assessment of each publication. For any unclear answer or doubts about methodological aspects and the results presented by the included articles, contacting the corresponding authors was attempted.

A meta-analysis was conducted to address the impact of asthma on the occurrence of caries in primary and permanent dentitions. The combined results for both dentitions were presented as a pooled odds ratio (OR). We estimated using fixed- and random-effect models. In the event of the heterogeneity (P <0.05, *chi square* or I^2 >50%), we preferred the random-effect model [25]. In addition, other effect estimates presented, as relative risk were appropriately converted to ORs when necessary [26]. Moreover, when articles presented only results based on the mean differences for the exposed (asthmatics) and unexposed (healthy subjects) groups, those values were converted to ORs and standard error. We performed the conversions using the formulas presented in Borenstein et al. [27]. When more than one measurement of caries was presented in the assessed study, we selected data from tooth estimates (dmt, DMFT) rather than those from the surface because the classification of missing teeth in surfaces index (dms, DMFS) could overestimate the real caries experience due to missing components [28].

To assess any potential publication bias, we used the funnel plot and the Egger test. In addition, we performed meta-regression and subgroups analyses to investigate potential sources of between-study variability. Methodological characteristics were included in a multivariable meta-regression model using a backward stepwise approach.

Variables with a P <0.20 remained in the final model, and adjusted R^2 was used to assess the explained heterogeneity of the final model. Furthermore, sensitivity analyses were conducted to estimate the impact of each study on the pooled effect. The statistical analysis was performed using the STATA 14.2 software (StataCorp, College Station, TX, USA).

Results

The electronic search identified 674 studies, of which 294 were duplicates and thus, excluded. Overall, 353 articles were submitted to title and abstract screening. Of these, 55 studies were included for full-text evaluation, resulting in 16 of this being excluded and one being included after manual search in references list of the included studies. Thus, 40 articles fulfilled the inclusion criteria; however, four of them do not provide any effect measure or adequate data for necessary conversions. Hence, the final number of articles available for the statistical analysis considering, at least, one dentition, was 36 (Figure 1). Table 2 summarizes the main characteristics of the included studies. Since 2011 to the end of database search (December 2017), 20 new studies were published; two of them were not being included in any meta-analysis due to the lack of information to estimate effect size. Considering all studies included, 13 do not fulfil > 50% of the JBI Critical Appraisal checklist specific for the study design, and only nine answered >70% of positive answers in the checklists.

The meta-analysis for primary and permanent dentition was performed separately. The OR of the pooled effect for primary dentition was 1.45 (95% confidence interval (CI): 1.22–1.72), with significant heterogeneity between studies (I^2 = 71.8% %; *chi square* p-value <0.001; Figure 2). Similarly, the OR of the pooled effect for permanent dentition was 1.52 (95% CI: 1.34–1.73), with high heterogeneity between studies (I^2, 83.1%; *chi square* P <0.001; Figure 3). The Egger test revealed the presence of publication bias for primary (P = 0.003) and permanent dentition (P < 0.001), which was confirmed by the meta-funnel analysis for both dentitions (Figure 4). Furthermore, sensitivity analysis demonstrated that the omission of any study would not significantly modify the effect for both dentitions (Figure 5).

Table 3 presents the subgroup analysis for primary and permanent dentition and the results from the final adjusted meta-regression models for each dentition. In the final meta-regression analysis for permanent dentition, just 3% of the heterogeneity was explained and none of the variables included to assess heterogeneity were statistically related ($P < 0.05$). However, some variables with $P \leq 0.20$ must be highlighted. The type of dentition assessed by the study ($P = 0.090$) and the sample size ($P = 0.113$) remaining in the final model and are considered important factors that must be included in further analysis. In addition, the results of meta-regression for primary dentition did not exhibit the same pattern and explained 10.7% of the total heterogeneity from 16 included studies. Country income (based on the World Bank income classification) and the sample size of the studies were associated in the adjusted meta-regression ($P = 0.045$ and 0.001, respectively). Besides its no statistical significance, the use of medication ($P = 0.056$) and the quality of the study ($P = 0.085$) remained in the adjusted meta-regression model because these improved the explained heterogeneity. Although few variables in the meta-analysis provided statistical evidence, Table 3 presents all the factors tested. Despite the absence of statistical significance, estimates were higher in the low-quality studies (<70% of positive answers in the JBI critical appraisal) for both dentitions.

Discussion

Asthma has been suggested as a potential factor enhancing the occurrence of dental caries; however, this association has not been well-understood, especially because of several methodological aspects from different studies. In this study, we conducted an comprehensive updated systematic review to assess the relationship between asthma and dental caries and possible methodological aspects that could result in biased estimates. We included 36 manuscripts in the meta-analysis, under well-defined criteria allowing its reproducibility, amplifying the statistical power and undertaking an additional quality assessment of studies included. Thus, it provided a robust source of evidence with more reliable results, strengthening a previous idea of the effect of asthma in dental caries [14]. By adopting a random-effect model due to a large heterogeneity, we determined that individuals with asthma had nearly 1.5 times higher odds of the occurrence of dental caries for both primary and permanent dentitions. In addition, publication bias was

present for primary and permanent dentition, being high in the permanent one. Although this fact does not invalidate the findings, it could overestimate the effect size; hence, some caution must be considered in the interpretation of data.

Even with high heterogeneity, the similar effects size for both dentitions suggest that mechanisms underlying this association could be the same for primary and permanent dentitions; thus, prevention or management strategies could be useful for both dentitions. The meta-regression identified methodological aspects that explained the heterogeneity and affected the pooled effect as statistically significant only for primary dentition. In addition, studies conducted in lower-middle income countries reported larger estimates compared with high-income countries; this result could be attributed to better resources and quality of data collection in high income countries. However, only one study assessed primary dentition in lower-middle-income countries and all the estimates for such groups were based on a single measure. More than just location, sample size explained some source of heterogeneity in primary dentition ($P < 0.001$), and was included in the final model in permanent dentition ($P < 0.20$), small studies ($n < 200$) reported higher effect-size. Conversely, studies with > 1,000 participants reported no effect of asthma on the occurrence of caries for both dentitions, suggesting that population-based studies exhibited lower difference, or even no difference, questioning the real impact of this association in public health and demonstrating that the present findings may be more useful in clinical practice than supporting the planning public health policies because the effect exist but could be readily observed in specific populations, as observed in clinical environments.

Despite no association in meta-regression, studies with the utilization of anti-asthmatic drugs seem to show high estimates, suggesting some effect of medication intake on the relationship between asthma and caries. This could favor the continuous effort in the investigation of the consequences of anti-asthmatic medication and justify further medication development with less harmful effects. This meta-analysis did not aim to verify the mechanisms of the association between dental caries and asthma; however, our systematic review reported a lack of methodologically high-quality studies addressing such association. More than just prospective studies, new statistical approaches, such as structural equation modeling or pathway analysis approaches, verifying possible

mediators or effect modifiers are warranted. Assumedly, such approaches would provide robust evidence based on the impact of asthma on dental caries and a possible critical period to develop more efficient actions preventing, or even intervening, the hazardous effects.

Although the study design used in the included articles does not affect the estimates, we should highlight the existence of few cohort studies for both dentitions, and also that just three of them presented good quality in the checklist used (> 70% of "yes" answers in the JBI Critical Appraisal Checklist for Cohort studies). The need for prospective and high-quality studies to investigate the association is still holds relevance, as stated previously [14]. Even after seven years of a previous meta-analysis, and the inclusion of a large number of new studies, the design adopted by these new studies, essentially cross-sectional, fails to provide strong evidence about the causality of this association. Thus, randomized control trials could be a good alternative as well, cohort studies, as already stated, will help in further elucidation.

The findings of this study are in accordance with a previous meta-analysis [14], revealing increased odds to develop caries in asthmatic patients for both dentitions compared to healthier patients. We observed the same direction in the association between asthma and dental caries but with small effect. However, we believe that our findings could be easier to reproduce and provide a more reliable result because the criteria adopted. Although the inclusion criteria of Alavaikko et al. were suitable to evaluate a real effect estimate, it was not clearly stated. Moreover, there is no specification which was considered adequate definition of the exposure and outcome, as well as, the proper conversions performed to achieve a single effect estimate (i.e., odds ratio) for each study. Considering the included studies, from those included in the Alavaikko et al., just three did not fulfil all the inclusion criteria because of methodological concerns: (a) Arnrup et al., 1993, assessed estimates for medically compromised children; Kankaala et al. 1993, did not use a reliable index for outcome measurement and; Reddy et al. 2003, did not use a healthy control group. These questions were considered exclusion criteria since they could lead to an inappropriate estimate.

Moreover, some differences in the OR values of the same studies included by Alavaikko et al., could have occurred because of different outcome measurements used.

In this study, we made the necessary conversions using mean and standard deviation obtained for teeth (DMF-T/dmf-t) not surfaces (DMF-S/dmf-s) as in the former meta-analysis. We adopted such criteria because surface measure could overestimate the disease impact due to misclassification of missing components [28]. Another reason is that most studies showed dmft/DMFT values, but not always dmfs/DMFS ones. Furthermore, we united different groups of asthmatic patients into one standard mean using the formulas for combining groups proposed by Cochrane [59] for each study instead of using one specific category, when only different definitions of asthma were shown, creating a reliable measure for further comparisons.

There are some limitations in our study that should be considered. First, most studies included in the review were of low methodological quality, attaining small proportions of positive answers in the critical checklists, which may have affected the pooled estimate. However, meta-regression analysis revealed no impact of methodological quality on the variability between studies. Second, even including several aspects that could affect estimates variability, sources of heterogeneity persist, which could be because of different aspects in data collection or even the conditions as the studies were performed, as well as individuals' characteristics that could not be adequately considered. We believe that the standardization of exposure and outcome measurements, based on validated indexes and guidelines will be helpful for further studies allowing a better comparison. We adopted a quality assessment, through JBI checklists, as used in previous studies. Besides, some aspects could not be evaluated in the checklist; thus, the use of different checklists to assess the quality of the method could be an alternative for further studies.

In addition, meta-regression conducted in few studies could fail to identify some effects of heterogeneity because of the lack of statistical power, which might not have happened even in the permanent dentition analysis because none of the variables showed $P < 0.05$ in the final model, and we included all the possible studies and used recommended statistical approach for data analysis. Furthermore, the Egger test and the funnel plot revealed publication bias; in an attempt to reduce this bias, we adopted some strategies, such as a manual search in the references list of all studies included and the performance of a sensitivity analysis. Next, the language restriction to English, Spanish

and Portuguese is another limitation, along with no inclusion of important language studies, such as Chinese. We believe that all essential studies about the topic were published in English, which were all included in our data-base search. Therewithal, articles in languages other than those selected could increase, even more, the heterogeneity found, thus it would compromise the interpretability of the data due to the difficulty in translating the results. Finally, we used estimates based on a conversion of the mean standard difference as proposed by Borenstein et al. 2009 (27), and such conversion methods could provide different effect sizes as those based on regression models from original individual data from the participants of the studies. However, such conversion methods were already used before and are a reliable and recommended option to summarize different measures of association.

Regarding the strengths, we applied no time restrictions and used a great variety of search terms trying to create reliable search strategy. Furthermore, we adopted several criteria for study inclusion, focusing on determining possible sources of bias in the real estimates. Moreover, we conducted careful data extraction and conversion calculations, providing genuinely comparable estimates even with high heterogeneity. Finally, this up-to-date review and meta-analysis summarize all reliable results providing a robust critical evidence of the association between asthma and dental caries.

Conclusion

This meta-analysis and meta-regression provide reliable and robust evidence that emphasizes and validate the previously stated effect of asthma on the occurrence of caries in both primary and permanent dentitions. Although the risk of occurrence of caries because of asthma is stated, the mechanisms underlying this relation must be well described. Hence, further research evaluating mediation effect and possible effect modifiers, such as the role of anti-asthmatic drugs or mouth breathing, must be conducted. Furthermore, prospective cohort studies are highly recommended, providing further knowledge to stablish a causal relation between asthma and dental caries.

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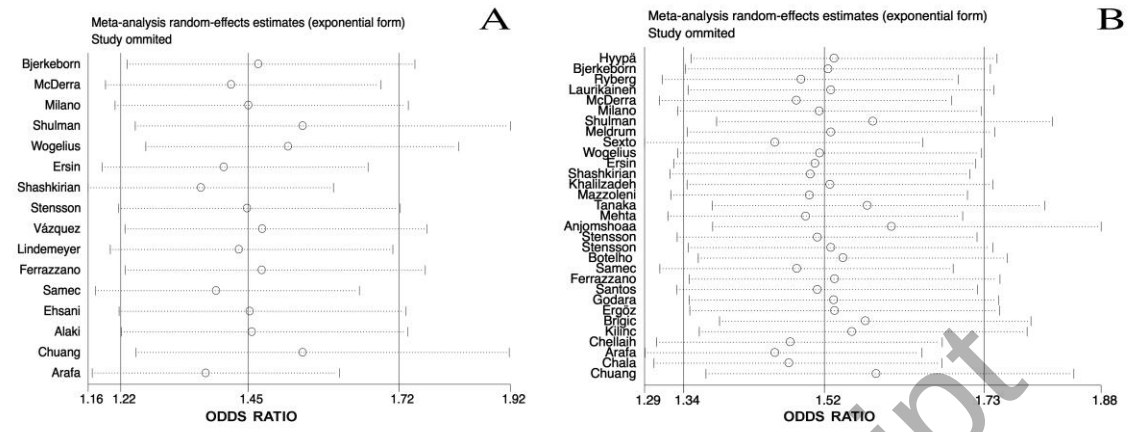
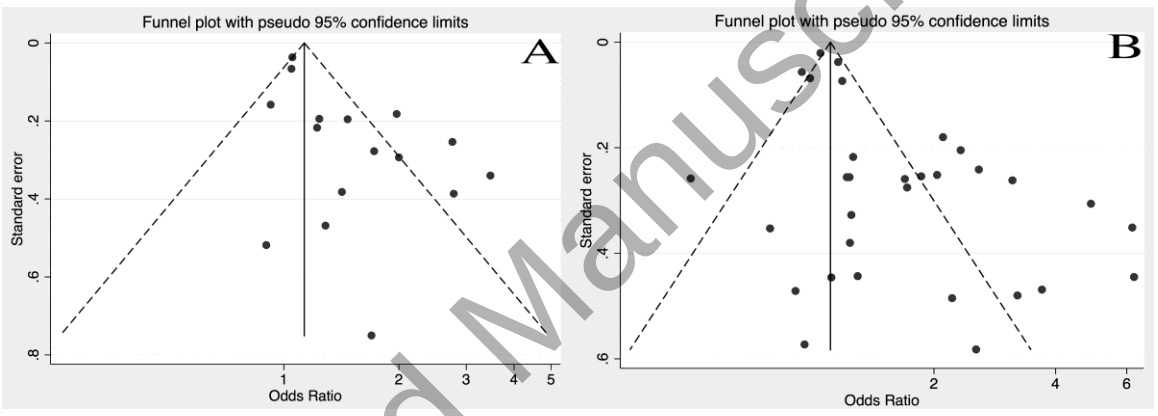
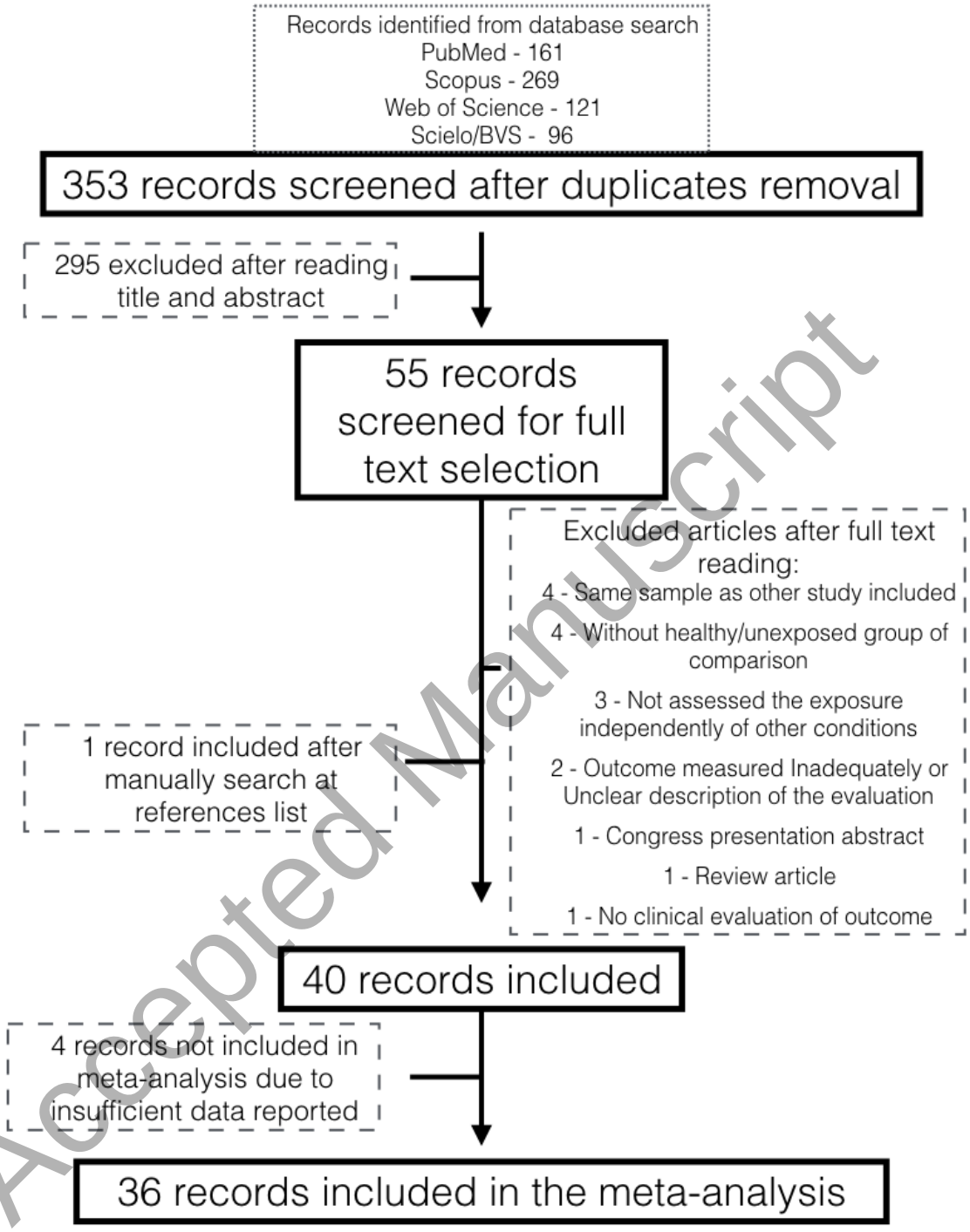
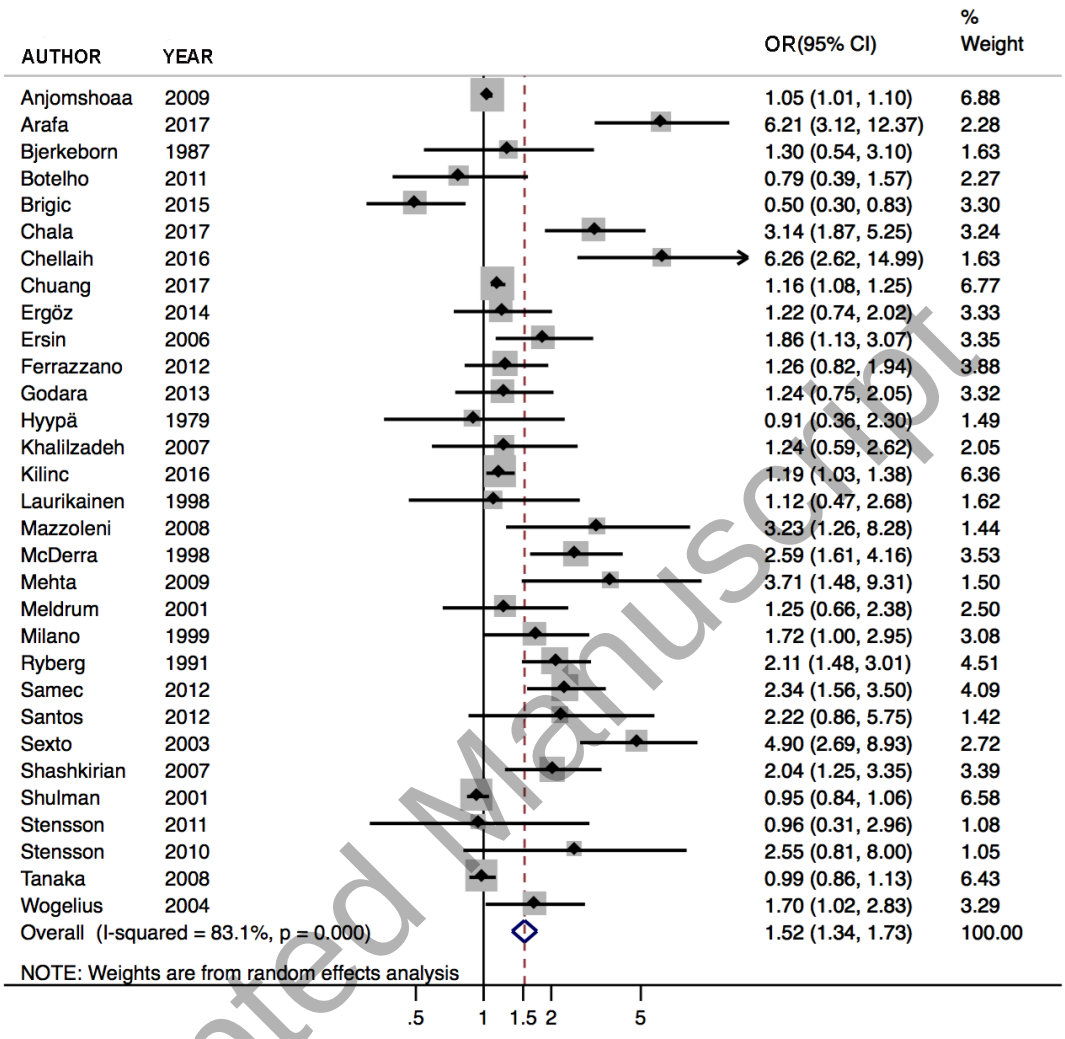
Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.









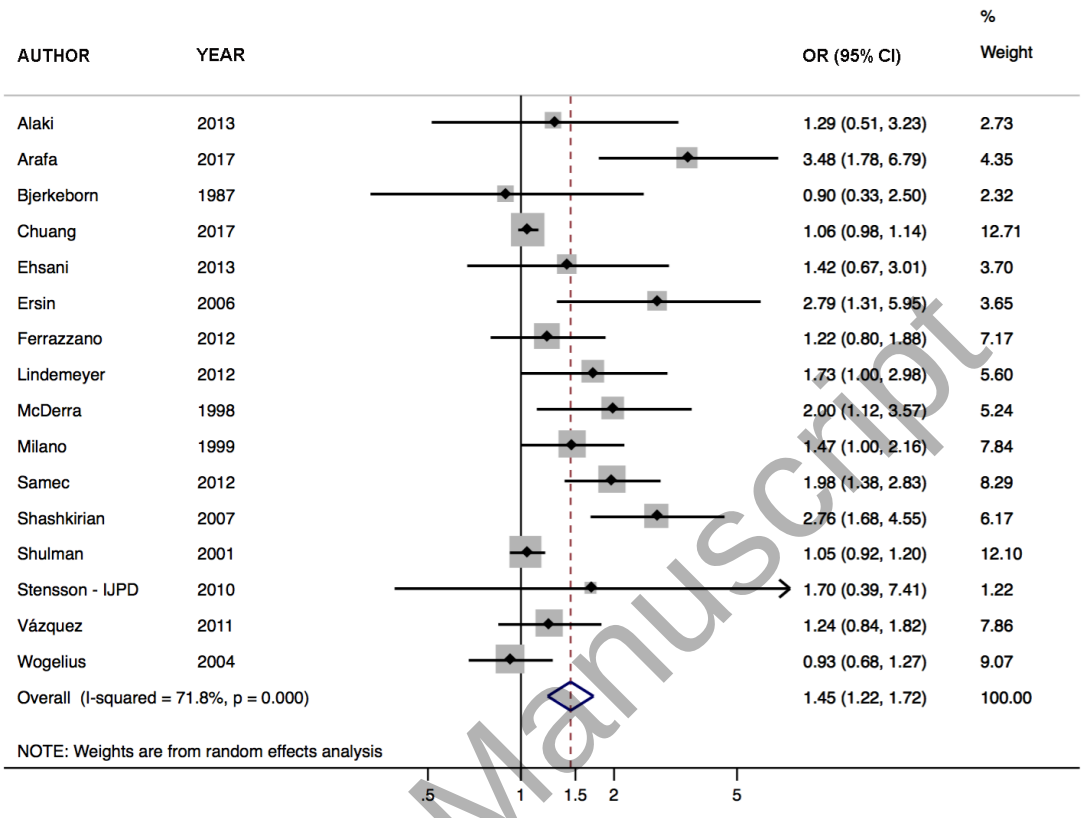


Table 1 – Search strategies used for initial screening.

Database	Commands used	Manuscripts found
PubMed	(((((("Asthma"[Mesh]) OR asthma) OR wheezing) OR breathlessness)) AND (((caries) OR "dental caries") OR "tooth decay")	161
Scopus	(TITLE-ABS-KEY (asthma OR wheezing OR breathlessness) AND TITLE-ABS-KEY (caries OR "dental caries" OR "tooth decay"))	269
Web of Science (ISI)	TS=(asthma OR wheezing OR breathlessness) AND TS=(caries OR "dental caries" OR "tooth decay")	121
LILACS	(tw:(caries)) OR (tw:(carie)) AND (tw:((tw:(asma)) OR (tw:(asthma)) OR (tw:(wheezing)) OR (tw:(chiado))))	96

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

First Author; Year (# ref.)	Subjects' age range (average)	tudy Design	Sample size	Location	Asthma definition	Caries definition	Meta-analysis Primary dentition	Meta-analysis Permanent dentition	JBI critical Appraisal*
							OR (95% CI)	OR (95% CI)	
Alaki. 2013 (19)	5-13	ross-sectional with comparison group	60	Saudi Arabia	Physician diagnosis	DMF/dmf index WHO criteria	1.29 (0.51-3.23)	--	62.5%
Anjomshoaa. 2009 (29)	17-84 (41.7)	ross-sectional	318	USA	Self-report	DMF/dmf index WHO criteria	--	1.05 (1.01-1.10)	25%
Arafa. 2017 (30)	4-12	ross-sectional with comparison group	180	Saudi Arabia	Physician diagnosis	DMF/dmf index WHO criteria	3.48 (1.78-6.79)	6.21 (3.12-12.37)	62.5%
Bjerkeborn. 1987 (7)	5-18	ross-sectional with comparison group	116	Sweden	Phsysician diagnosis	Koch criteria	0.90 (0.33-2.50)	1.30 (0.54-3.10)	50%
Boskabady. 2012 (31)	(27)	ross-sectional with comparison group	80	Iran	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	**	**	62.5%
Botelho. 2011 (18)	3-15	ross-sectional with comparison group	160	Brazil	Using anti-asthmatic medication	DMF/dmf index WHO criteria	--	0.79 (0.39-1.57)	87.5%
Brigic. 2015 (22)	7-15	ross-sectional with comparison group	200	Bosnia and Herzegovina	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	--	0.50 (0.30-0.83)	50%
Chala. 2017 (9)	>18 (36.3)	ross-sectional with comparison	200	Morocco	Self-report	DMF/dmf index WHO	--	3.14 (1.87-5.25)	100%

		group				criteria			
Chellaih. 2016 (32)	6-14	ross-sectional with comparison group	110	India	Physician diagnosis and under treatment	DMF index Klein. Palmer Criteria	--	6.26 (2.62-14.99)	62.5%
Chuang. 2017 (10)	9	Cohort	9038	Taiwan	Physician diagnosis	ICD-9-CM code 521.0	1.06 (0.98-1.14)	1.16 (1.08-1.25)	82%
Ehsani.2013 (20)	3-6	ross-sectional with comparison group	90	Iran	Physician diagnosis excluding severe asthma	DMF/dmf index WHO criteria	1.42 (0.67-3.01)	--	62.5%
Ergöz. 2014 (33)	6-12	ross-sectional with comparison group	200	Turkey	Physician diagnosis and spirometry	DMF/dmf index WHO criteria	--	1.22 (0.74-2.02)	62.5%
Ersin. 2006 (34)	6-19	ross-sectional with comparison group	206	Turkey	Using anti-asthmatic medication	DMF/dmf index WHO criteria	2.79 (1.31-5.95)	1.86 (1.13-3.07)	62.5%
Ferrazzano. 2012 (35)	(8.95)	ross-sectional with comparison group	280	Italy	Physician diagnosis	DMF/dmf index WHO criteria	1.22 (0.80-1.88)	1.26 (0.82-1.94)	62.5%
Ghapanchi. 2015 (21)	12-83	ross-sectional	200	Iran	Physician diagnosis	DMF/dmf index WHO criteria	**	**	37.5%
Godara. 2013 (36)	10-45	ross-sectional with comparison group	200	India	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	--	1.24 (0.75-2.05)	62.5%
Hyyppä. 1979 (37)	10-12	ross-sectional with comparison	60	Finland	Physician diagn	DMF/dmf index WHO	--	0.91 (0.36-2.30)	50%

		group			osis	criteria			
Johnston. 2014 (38)	6-94 (47.7)	ross-sectional	1281	USA	Self-Report	DMF/dmf index WHO criteria	**	**	75%
Khalilzadeh. 2007 (39)	5-15 (11)	ross-sectional with comparison group	91	Iran	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	--	1.24 (0.59-2.62)	25%
Kilinc. 2016 (40)	4-16 (11)	Cohort	102	Turkey	Physician diagnosis and under treatment	ICDAS classified according to DMF-T (ICDAS 3-6 as decayed)	--	1.19 (1.03-1.38)	75%
Laurikainen. 1998 (41)	25-50	ross-sectional with comparison group	66	Finland	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	--	1.12 (0.47-2.68)	62.5%
Lindemeyer. 2012 (42)	0-6	ross-sectional with comparison group	172	USA	Physician diagnosis	DMF/dmf index WHO criteria	1.73 (1.00-2.98)	--	50%
Mazzoleni. 2008 (43)	6-12	ross-sectional with comparison group	60	Italy	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	--	3.23 (1.26-8.28)	62.5%
McDerra. 1998 (44)	4 -1 6	ross-sectional with comparison group	249	UK	Physician diagnosis and under treatment	BASCD analyzed according DMF/dmf index values	2.00 (1.12-3.57)	2.59 (1.61-4.16)	50%
Mehta. 2009 (45)	11-25	ross-sectional with	160	India	Physician	DMF index	--	3.71 (1.48-	62.5%

		comparison group			diagnosis and under treatment	Klein and Palmer criteria		9.31)	
Meldrum. 2001 (46)	15-18	Cohort	242	New Zealand	History of persistent wheezing and the use of medication	DMF/dmf index WHO criteria	--	1.25 (0.66-2.38)	62.5%
Milano. 1999 (47)	2-13	ross-sectional with comparison group	344	USA	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	1.47 (1.00-2.16)	1.72 (1.00-2.95)	62.5%
Ryberg. 1991 (48)	14-24 (19.6)	Cohort	42	Sweden	Physician diagnosis and under treatment	Lenox and Kopczyk criteria	--	2.11 (1.48-3.01)	63.6%
Samec. 2012 (49)	2-17 (8.5)	ross-sectional with comparison group	440	Slovenia	Physician diagnosis and under treatment	Measured by ICDAS classified according to DMF-S	1.98 (1.38-2.83)	2.34 (1.56-3.50)	100%
Santos. 2012 (50)	10-18 (14)	ross-sectional with comparison group	80	Brazil	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	--	2.22 (0.86-5.75)	62.5%
Sexto-Delgado. 2003 (51)	6-15	ross-sectional with comparison group	200	Cuba	Unclear	DMF/dmf index WHO criteria	--	4.90 (2.69-8.93)	37.5%

Shashkirian. 2007 (52)	6-14	Cohort	211	India	Using medication for asthma	DMF/dmf index WHO criteria	2.76 (1.68-4.55)	2.04 (1.25-3.35)	36.3%
Shulman. 2001 (53)	4-16	ross-sectional	6938	USA	Parents' report of Physician diagnosis	DMF/dmf index WHO criteria	1.05 (0.92-1.20)	0.95 (0.84-1.06)	100%
Stensson. 2011 (17)	18-24	ross-sectional with comparison group	40	Sweden	Physician diagnosis and under treatment	Koch criteria	--	0.96 (0.31-2.96)	25%
Stensson. 2010 (54)	12-16	ross-sectional with comparison group	40	Sweden	Physician diagnosis and medication use for at least 4 years	Koch criteria	--	2.55 (0.81-8.00)	50%
Stensson. 2010 (55)	3-6	Cohort	114	Sweden	Physician diagnosis for asthma and parents report for contrl group	DMF/dmf index WHO criteria	1.70 (0.39-7.41)	--	73%
Tanaka. 2008 (56)	6-15	ross-sectional	21792	Japan	Self-report of asthma and wheezing in	Decay and Filled tooth	--	0.99 (0.86-1.13)	87.5%

					the last 12 months				
Vázquez. 2011 (16)	4-5	ross-sectional nested in a cohort study	1160	Mexico	Parents report of medical diagnosis or asthma symptoms	DMF/dmf index WHO criteria	1.24 (0.84-1.82)	--	100%
Wierchola. 2006 (57)	3-15	ross-sectional with comparison group	652	Poland	Physician diagnosis and under treatment	DMF/dmf index WHO criteria	**	**	37.5%
Wogelius. 2004 (58)	4-7	Cohort	4920	Denmark	Anti-asmatic drug prescription	DMF/dmf index WHO criteria	1.45 (1.22-1.72)	1.70 (1.02-2.83)	63.6%

*Proportion of "yes" answers in Joanna Briggs Critical Appraisal Checklist for the specific study design.
**Without sufficient information for effect size calculation, the article was not included in the meta-analysis.

Table 3. Subgroup meta-analysis and meta-regression between asthma and dental caries (DMF-T) according to covariates.

Methodological characteristics	Primary dentition			Permanent Dentition		
	N	Pooled OR (95%CI)	p-value [a]	N	Pooled OR (95%CI)	p-value [a]
Main Analysis	16	1.45 (1.22-1.72)		31	1.63 (1.41-1.87)	
Location			--			--
Europe	7	1.49 (1.06-2.10)		15	1.49 (1.17-1.89)	
Asia/Africa/Oceania	5	1.78 (1.01-3.14)		10	1.30 (1.02-1.67)	
America	4	1.24 (0.99-1.55)		6	1.86 (1.40-2.47)	
Income[b]			*0.045*			--
Lower-middle	1	2.76 (1.68-4.55)		5	2.62 (1.57-4.37)	
Upper-middle	3	1.57 (0.99-2.50)		8	1.36 (0.91-2.04)	
High	12	1.33 (1.12-1.58)		18	1.40 (1.22-1.61)	
Sample Size			*0.001*			*0.113*
< 200	6	1.73 (1.19-2.51)		14	1.87 (1.33-2.65)	
200-1000	6	1.85 (1.43-2.38)		13	1.64 (1.23-2.20)	
> 1000	4	1.05 (0.99-1.12)		4	1.07 (0.92-1.28)	
Year			--			--
<2000	3	1.53 (1.13-2.08)		6	1.80 (1.36-2.38)	
2000-2010	5	1.51 (0.98-2.32)		12	1.44 (1.20-1.73)	
≥2011	8	1.49 (1.13-1.97)		13	1.54 (1.20-1.96)	
Dentition assessed			--			*0.090*
Only one	5	1.13 (0.98-1.31)		14	1.22 (1.06-1.42)	
Both	11	1.59 (1.21-2.08)		17	1.91 (1.48-2.46)	
Use of medication			*0.056*			--
Stated	10	1.20 (1.03-1.40)		11	1.32 (1.13-1.54)	
Non-stated/unclear	6	1.77 (1.23-2.56)		20	1.67 (1.33-2.09)	
Definition of asthma			--			--
Physician diagnosis	13	1.53 (1.21-1.94)		25	1.70 (1.40-2.06)	
Self/Parents' Reports	3	1.32 (1.22-1.72)		6	1.52 (0.98-1.73)	
Design			--			--
Cohort	4	1.32 (0.88-1.99)		6	1.41 (1.17-1.71)	
Cross-sectional	12	1.55 (1.23-1.94)		25	1.60 (1.34-1.90)	
Critical Appraisal [c]			*0.085*			--
0-69%	11	1.64 (1.25-2.16)		24	1.76 (1.39-2.24)	
≥70%	5	1.19 (1.22-1.76)		7	1.23 (1.03-1.47)	
Heterogeneity Explained primary (R^2): 10.74 %						
Heterogeneity Explained permanent (R^2): 3.06 %						

[a] p-value of the variable in the final adjusted meta-regression model. [b]according to world bank atlas method classification by income. [c]according to % of agreement in the Joanna Briggs Critical Appraisal for each study design.