

Systematic Reviews and Meta- and Pooled Analyses

Asthma and Caries: A Systematic Review and Meta-Analysis

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There is inconclusive evidence suggesting a possible association of asthma with increased risk of caries. The authors conducted a systematic review and meta-analysis to synthesize the evidence on the relation between asthma and caries. They performed an Ovid Medline (US National Library of Medicine) database search of literature published from 1950 through May 2010 using the Medical Subject Headings “asthma” and “caries.” Summary effect estimates were calculated with fixed- and random-effects models, and determinants of heterogeneity were studied in meta-regression analysis. The meta-analysis was based on 11 articles providing estimates of the effect of asthma on primary dentition and 14 articles on permanent dentition. Summary effect estimates for the relation between asthma and caries from the random-effects models were 2.73 (95% confidence interval: 1.61, 4.64) and 2.04 (95% confidence interval: 1.44, 2.89), respectively. Factors identified as determinants of heterogeneity were geographic region for primary dentition and publication year, sample size, asthma definition, and information on the use of asthma medication for permanent dentition. Evidence from this analysis suggests that asthma doubles the risk of caries in both primary and permanent dentition. Publication bias diagnostics and simulation suggested possible overestimation of the summary odds ratio for permanent dentition but not for primary dentition. Physicians and dentists should recommend preventive measures against caries for persons with asthma.

asthma; dental caries; meta-analysis; review

Abbreviations: CI, confidence interval; dfs, number of decayed and filled surfaces in primary dentition; dft, number of decayed and filled teeth in primary dentition; dmf, number of decayed, missing (due to caries), and filled teeth or surfaces in primary dentition; DMF, number of decayed, missing (due to caries), and filled teeth or surfaces in permanent dentition; dmfs, number of decayed, missing, and filled surfaces in primary dentition; DMFS, number of decayed, missing, and filled surfaces in permanent dentition; dmft, number of decayed, missing, and filled teeth in primary dentition; DMFT, number of decayed, missing, and filled teeth in permanent dentition; NOS, Newcastle-Ottawa Quality Assessment Scale; OR, odds ratio.

Asthma is the most common chronic disease in childhood and is also a major public health problem in adult populations. The basic mechanism of asthma is an inflammatory process in the airways (1). The airway inflammation and airflow limitation cause various symptoms according to the severity of the asthma, which determines the need for asthma medication. Caries is a progressive disease affecting teeth and causing several complications. The prevalence of caries is still high, even in developed countries, and caries is the most common chronic health problem affecting children in the United States. In addition to affecting the quality of life, its treatment is expensive and is needed for the rest of the

patient's life (2). Thus, prevention of caries is an important public health issue with the potential of substantial economic gains.

The role of asthma as a potential determinant of caries risk was first studied in the late 1970s. Since then, several studies have evaluated the effect of asthma severity on caries prevalence (3–12), and some studies have evaluated the possible cariogenic mechanisms related to use of asthma medications (3–6, 13–18). Most of the studies published to date have provided inconclusive results, mainly because of limitations related to the size of the study population. To throw light on potential mechanisms by which asthma could affect caries,

some investigators have measured parameters such as saliva flow, composition, and pH in persons with asthma (3, 5, 13–15, 19–21). All of these factors might be influenced by asthma medications or the disease itself and may lead to an increased risk of caries (2).

According to an Ovid Medline database (US National Library of Medicine) literature search, there have been no previous meta-analyses on the association between asthma and caries. To investigate the relation between asthma and occurrence of caries, as well as factors potentially contributing to such a relation, we conducted a systematic review and meta-analysis. Because several articles provided effect estimates of the relation between asthma and caries for both primary and permanent dentition, these results were analyzed separately. We also conducted stratified meta-analyses and meta-regression in order to analyze potential sources of heterogeneity between the study-specific effect estimates, and we constructed funnel plots to address the possibility of publication bias.

MATERIALS AND METHODS

Search strategy

We conducted a systematic literature search of the Ovid Medline database from 1950 through May 2010 by using the Medical Subject Headings “asthma” and “caries.” To ensure that we identified all of the relevant articles, we also conducted a PubMed search with the text terms “asthma” and “caries” in the title or abstract. Government reports and conference proceedings were also searched, but information relevant to this meta-analysis was not found in those sources.

Inclusion criteria

There were 5 criteria for inclusion of a study in this meta-analysis: The study 1) provided relevant and applicable quantitative information on the relation between asthma and caries; 2) was an original study that had an independent study population; 3) was a case-control, cohort, or cross-sectional study; 4) had an adequate definition of asthma; and 5) had an adequate definition and measurement of caries.

Data extraction

The studies fulfilling the inclusion criteria were independently examined and their main characteristics were recorded by two of the authors (S. A., J. J.). The data were collected according to a pilot-tested form including factors such as authors, year of publication, study objective, study design, study population, geographic region, sample size, subjects' average birth year, definition of asthma, measurements of oral health, effect estimates, variables adjusted for, and factors matched for.

If articles provided multiple caries measurements, we preferred those referring to tooth surfaces (dfs, DMFS) over those referring to teeth (dft, DMFT), in an attempt to have as much information about the amount of caries as possible. If the article had caries measurements for both primary and per-

manent dentition, we obtained results for both in order to evaluate the risk of caries in both types of dentition by conducting separate analyses.

Assessment of study quality

Articles that met the eligibility criteria were further assessed for quality by means of the Newcastle-Ottawa Quality Assessment Scale (NOS) (22). A study could receive 1 point per item for 1) selection of the study population (0–4 items), 2) comparability of subjects (0–2 items), and 3) outcome for cohort and cross-sectional studies (0–3 items). For selection, the items included the representativeness of the exposed cohort, selection of the unexposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study. For comparability, the items included comparability for core factors and comparability for additional factors. For outcome, the items included assessment of outcome, sufficient duration of follow-up for the outcome to occur, and adequacy of follow-up of cohorts. The maximum number of points that any study could receive was 9 (i.e., 4 + 3 + 2). In the main analyses, the quality of the study was classified as high if it had received at least 7 points. This cutpoint was chosen to achieve approximately similar number of studies for each group (i.e., high vs. low). However, we conducted sensitivity analyses with different cutpoints for study quality to determine whether the choice would influence the results.

Statistical methods

Since most of the articles fulfilling the inclusion criteria presented results as mean values and standard deviations for caries measurements in asthmatics (forming the exposed group) and healthy subjects (forming a reference group), we first used these mean values and standard deviations to calculate odds ratios and 95% confidence intervals. The conversions were made according to formulas presented by Borenstein et al. (23). The final summary effect estimates were calculated with Stata 9.2 (StataCorp LP, College Station, Texas), using the commands “meta” and “metareg.” Both fixed- and random-effects models were used for the main analyses and the stratified analyses. Heterogeneity was examined using the *Q* statistic and the distribution of study-specific effect estimates and assessing the results of stratified analyses. Possible publication bias was evaluated by visual inspection of funnel plots and application of both Begg's test and Egger's test with Stata. The influence of potential publication bias was further evaluated by implementing the Duval and Tweedie nonparametric “trim-and-fill” method (23). This method simulates an unbiased database by imputing “missing” effect estimates (Stata “metatrim” command) and provides new simulated estimates.

RESULTS

Studies identified in the searches

Figure 1 shows the study selection process. The systematic literature search of the Ovid Medline database from

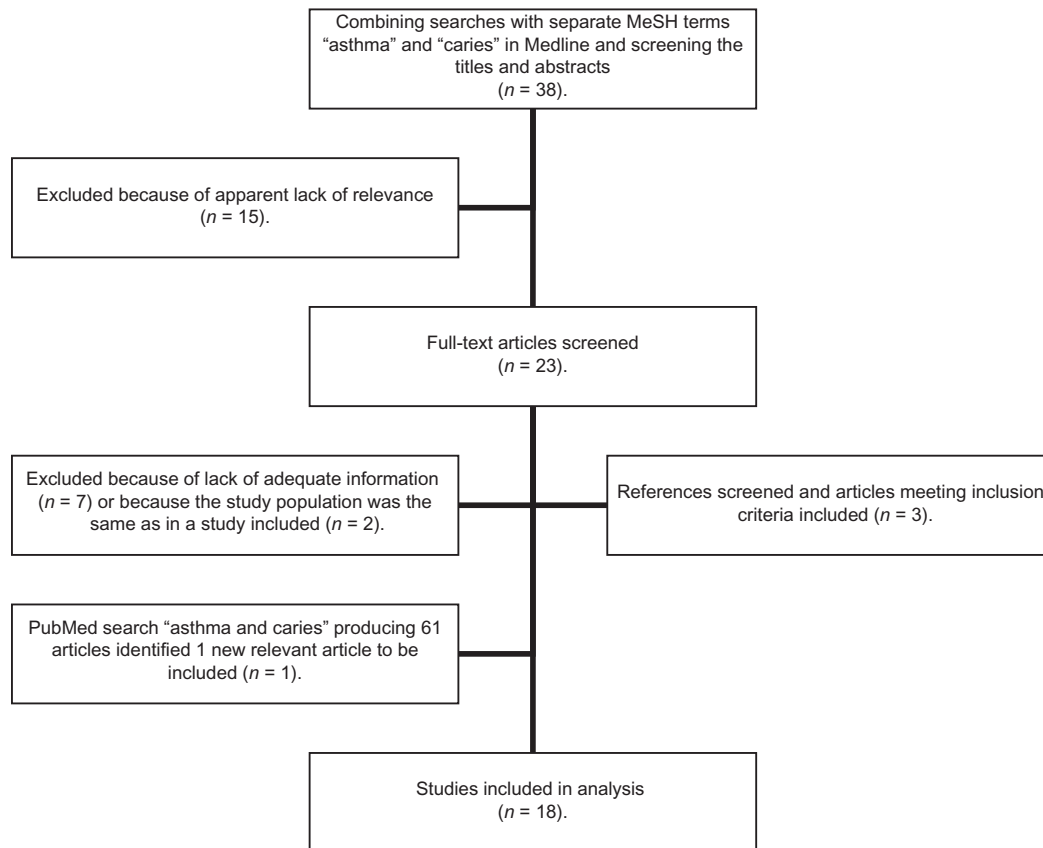


Figure 1. Process used to select published studies for a systematic review and meta-analysis of the relation between asthma and caries, 1950–May 2010. MeSH, Medical Subject Headings.

1950 to May 2010 produced 38 articles with the Medical Subject Headings “asthma” and “caries.” Screening of the titles and abstracts of these articles led to the exclusion of 15 studies with an apparent lack of relevance. The full texts of the remaining 23 articles were screened. Seven more articles were excluded because of a lack of adequate information, and 2 additional articles were excluded because of use of the same study population as another study that was included. In the latter cases, a longitudinal study was preferred over a cross-sectional one. Reference lists of the 14 articles included were screened, and another 3 articles fulfilling the eligibility criteria were also included.

The text search command “asthma and caries” was applied to the PubMed database to ensure identification of every relevant article. One additional relevant article was found among the 61 articles that this search produced. No additional relevant articles were identified by screening the reference list of this article.

Overall, we identified 18 articles, of which 11 provided information on primary dentition and 15 on permanent dentition. However, 1 article (8) presented a very discrepant effect estimate (odds ratio (OR) = 0.025) on the permanent dentition and was excluded from the final analyses, since we suspected that there were errors in the published data. We conducted sensitivity analyses based on the remaining 14 articles.

Study characteristics and effect estimates

The main study characteristics and study-specific effect estimates for both primary- and permanent-dentition articles are shown in Table 1. From the 11 articles on primary dentition, 6 were published in 2000–2010 and 5 before 2000. In the group of permanent-dentition studies, 8 were published in 2000–2010 and 6 before 2000.

Asthma and caries assessments

Asthma was defined as a physician-diagnosed condition in 9 articles in the primary-dentition group and in 10 articles in the permanent-dentition group. In 2 articles in the primary-dentition group and in 4 articles in the permanent-dentition group, the definition of asthma was based on asthma symptoms or use of asthma medication only.

Caries was expressed as several different indices of decayed or missing teeth and the presence of teeth or surfaces with fillings (dmf, DMF), indicating the number of teeth or surfaces that caries had affected. Small letters are used in dentistry when referring to primary dentition (dmft, dmfs) and capital letters when referring to permanent dentition (DMFT, DMFS). The studies' information on the amount of caries was based on dental records.

Table 1. Selected Design Characteristics of Studies Included in an Analysis of the Relation between Asthma and Caries, 1950–May 2010

First Author, Year (Reference No.)	Study Design	Size of Study Population	Subjects' Average Birth Year	Geographic Region	Asthma Definition	Meta-Analysis of Primary Dentition		Meta-Analysis of Permanent Dentition	
						OR	95% CI	OR	95% CI
Amrup, 1993 (18)	Cross-sectional	269	1981	Örebro, Sweden	Physician diagnosis	2.89	1.36, 6.13		
Bjerkeborn, 1987 (3)	Cross-sectional	116	1975	Huddinge, Sweden	Physician diagnosis	0.90	0.33, 2.50	1.30	0.54, 3.10
Ersin, 2006 (5)	Cross-sectional	206	1992	Izmir, Turkey	Physician diagnosis and use of asthma medication	2.79	1.32, 5.91	4.31	2.57, 7.21
Hyypä, 1979 (19)	Cross-sectional	60	1967	Finland	Physician diagnosis			0.91	0.36, 2.29
Kankaala, 1998 (17)	Cohort	153	1985	Merijärvi, Oulainen, and Vihanti, Finland	Physician diagnosis and use of asthma medication	2.57	1.33, 4.94		
Laurikainen, 1998 (13)	Cross-sectional	66	1960	Tampere, Finland	Physician diagnosis			1.58	0.66, 3.80
Mazzoleni, 2008 (14)	Cross-sectional	60	1998	Padua, Italy	Physician diagnosis and use of asthma medication			3.23	1.26, 8.28
McDerra, 1998 (11)	Cross-sectional	249	1985	Guiseley, Leeds, and Yeadon, United Kingdom	Physician diagnosis and use of asthma medication	0.33	0.18, 0.58	4.75	2.92, 7.73
Mehta, 2009 (6)	Cross-sectional	160	1990	Mangalore, India	Physician diagnosis and use of asthma medication			3.71	1.48, 9.33
Meldrum, 2001 (9)	Cohort	242	1973	Dunedin, New Zealand	Use of asthma medication and asthma symptoms			1.25	0.66, 2.38
Milano, 1999 (10)	Cross-sectional	344	1991	Houston, Texas, United States	Physician diagnosis and use of asthma medication	3.45	1.48, 8.03	1.66	0.95, 2.90
Reddy, 2003 (7)	Cross-sectional	205	1992	Mangalore, India	Physician diagnosis and use of asthma medication	4.50	0.75, 26.93	3.31	1.51, 7.23
Ryberg, 1991 (20)	Cohort	42	1971	Umeå, Sweden	Physician diagnosis and use of asthma medication			1.99	0.66, 5.97
Shashikiran, 2007 (15)	Cohort	211	1996	India	Use of asthma medication	8.66	5.09, 14.7	2.06	1.26, 3.38
Shulman, 2001 (8)	Cross-sectional	6,938	1978	United States	Physician diagnosis	4.11	3.55, 4.76	0.025 ^a	0.020, 0.032
Stensson, 2010 (21)	Cohort	144	2001	Jönköping, Sweden	Physician diagnosis	1.7	1.1, 2.6		
Tanaka, 2008 (12)	Cross-sectional	21,792	1994	Nago and Naha, Japan	Asthma symptoms			0.99	0.87, 1.14
Wogelius, 2004 (16)	Cohort	3,325	1993	North Jutland, Denmark	Use of asthma medication	0.96	0.80, 1.15	1.62	1.03, 2.56

Abbreviations: CI, confidence interval; OR, odds ratio.

^a The estimate was not included in the meta-analysis.

Asthma and caries in primary dentition

Figure 2 shows a forest plot for the studies on primary dentition. Both visual inspection of the forest plot and quantitative data (given in Table 2) revealed substantial heterogeneity between the study-specific estimates, and hence the random-effects model was considered to obtain a more appropriate estimate, since it allows for heterogeneity. The summary odds ratio for the relation between asthma and caries from the random-effects models was 2.73 (95% confidence interval (CI): 1.61, 4.64). The sources of heterogeneity were elaborated in both stratified analyses (Table 2) and meta-regression. In general, the stratum-specific effect estimates

were consistently elevated and, with a few exceptions, statistically significant.

In the analysis stratified by study design, 7 rather homogeneous effect estimates from cross-sectional studies produce a summary odds ratio of 3.86 (95% CI: 3.37, 4.41) in the fixed-effects model. The study-specific effect estimates from the 4 cohort studies were heterogeneous (Q statistic: $P < 0.001$), and the random-effects model produced a summary odds ratio of 2.50 (95% CI: 0.90, 6.96). The 4 smallest studies generated a rather homogeneous summary odds ratio of 1.97 (95% CI: 1.30, 2.98), whereas the effect estimates from the 7 medium-sized and large studies were heterogeneous, with a summary odds ratio of 3.15 (95% CI: 1.60, 6.20) in

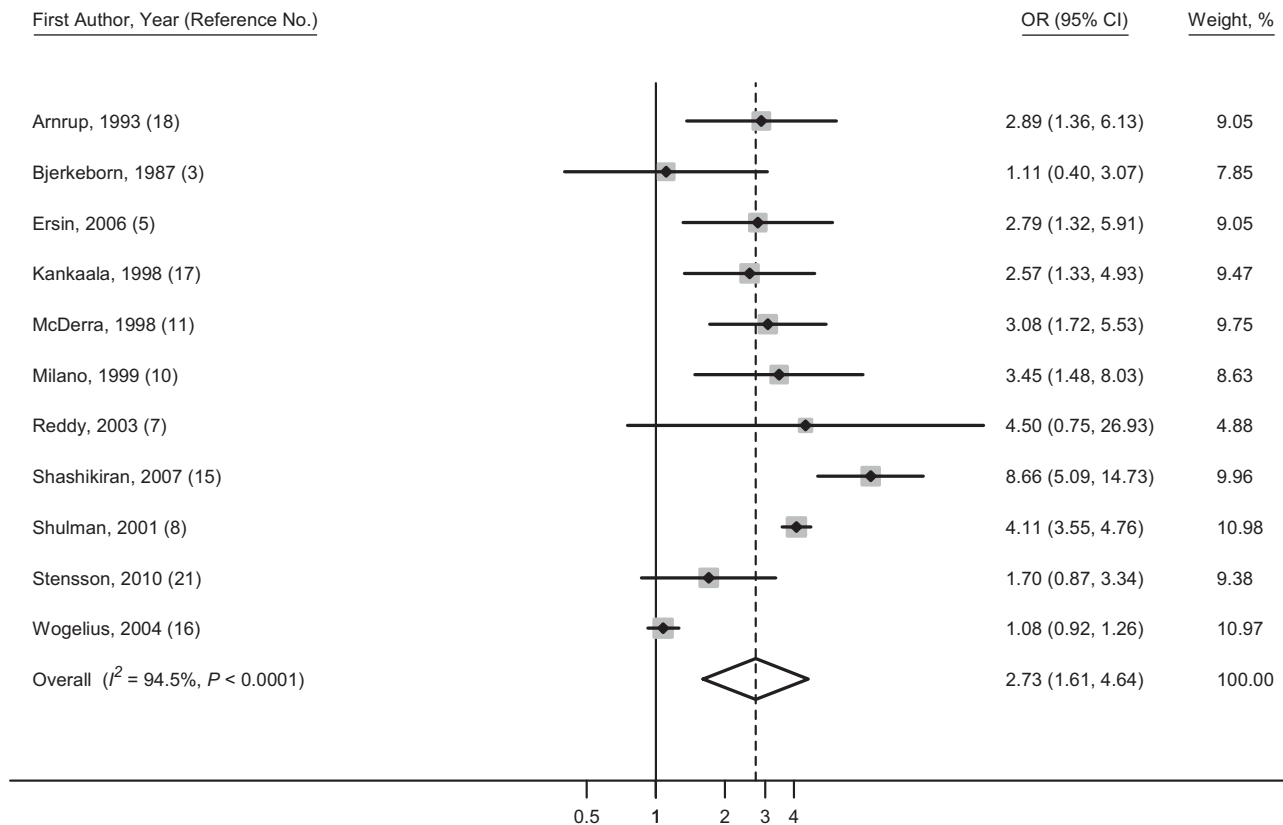


Figure 2. Study-specific and summary effect estimates (log odds ratio (OR) and 95% confidence interval (CI)) for caries risk in studies on the relation between asthma and caries in primary dentition, 1950–May 2010.

the random-effects model. The summary odds ratio from the 7 European studies was smaller (OR = 1.98, 95% CI: 1.25, 3.11) than that from the 4 non-European studies (OR = 4.99, 95% CI: 3.14, 7.92). The summary odds ratio for the higher-quality studies was 1.56 (95% CI: 0.89, 2.73) when including studies with an NOS score of 8–9, 1.78 (95% CI: 1.03, 3.06) when including studies with an NOS score of 7–9, and 2.64 (95% CI: 1.47, 4.72) when including studies with an NOS score of 6–9. The corresponding odds ratios for lower-quality studies were 3.62 (95% CI: 2.58, 5.10) for NOS score 0–7, 3.72 (95% CI: 2.55, 5.44) for NOS score 0–6, and 3.09 (95% CI: 1.55, 6.18) for NOS score 0–5. Publication year, the mean birth year of the study population, and asthma definition had little effect on the summary odds ratio.

In the meta-regression analysis of studies on primary dentition, the only statistically significant determinant of heterogeneity was geographic region (regression coefficient (β) = -0.961 , 95% CI: -1.526 , -0.397 ; $P = 0.001$) in bivariate analysis, while in multivariate analysis taking into account the influence of other factors simultaneously, no significant factor explaining heterogeneity was observed.

Asthma and caries in permanent dentition

Figure 3 shows a forest plot for the studies on permanent dentition. The study-specific effect estimates exhibited sub-

stantial heterogeneity, and the summary odds ratio from the random-effects model was 2.04 (95% CI: 1.44, 2.89). Table 3 also shows summary odds ratios from the stratified analyses. The summary odds ratio was higher for cross-sectional studies (OR = 2.21, 95% CI: 1.32, 3.70) than for cohort studies (OR = 1.66, 95% CI: 1.33, 2.08). The summary odds ratio from studies applying a physician-diagnosed definition of asthma was substantially higher (OR = 2.52, 95% CI: 1.76, 3.60) than that for the remaining studies (OR = 1.39, 95% CI: 0.96, 2.02). The summary odds ratio for the higher-quality studies was 1.64 (95% CI: 1.25, 2.15) when including studies with an NOS score of 8–9, 2.42 (95% CI: 1.53, 3.81) when including studies with an NOS score of 7–9, and 2.16 (95% CI: 1.59, 2.94) when including studies with an NOS score of 6–9. The corresponding odds ratios for lower-quality studies were 2.09 (95% CI: 1.36, 3.21) for NOS score 0–7, 1.80 (95% CI: 1.10, 2.95) for NOS score 0–6, and 1.70 (95% CI: 0.52, 5.50) for NOS score 0–5. Publication year, the mean birth year of the study population, and geographic region had little effect on the summary odds ratio.

In the meta-regression analysis of the 14 studies on permanent dentition, statistically significant determinants of heterogeneity in the most parsimonious multivariate model were publication year ($\beta = 0.686$, 95% CI: 0.188, 1.183; $P = 0.007$), sample size ($\beta = 0.540$, 95% CI: 0.0464, 1.035; $P = 0.032$), asthma definition ($\beta = 1.103$, 95% CI: 0.514,

Table 2. Summary Odds Ratios From Main and Stratified Meta-Analyses of the Relation between Asthma and Caries in Studies of Primary Dentition, 1950–May 2010

Stratification	Fixed-Effects Model		Random-Effects Model		Heterogeneity		
	OR	95% CI	OR	95% CI	<i>Q</i>	No. of Studies	<i>P</i> Value
Main analysis	2.34	2.12, 2.58	2.73	1.61, 4.64	182.5	11	<0.0001
Simulated main analysis adjusting for potential publication bias	2.29	2.02, 2.45	2.30	1.38, 3.81	209.1	13	<0.0001
Stratified analyses							
Study design							
Cross-sectional	3.86	3.37, 4.41	3.29	2.49, 4.34	8.5	7	0.207
Cohort	1.33	1.16, 1.53	2.50	0.90, 6.96	59.2	4	<0.0001
Publication year							
<2000	2.66	1.92, 3.69	2.66	1.92, 3.69	3.5	5	0.478
≥2000	2.31	2.09, 2.56	2.95	1.35, 6.44	178.3	6	<0.0001
Sample size							
<200	1.98	1.30, 2.98	1.97	1.30, 2.98	2.9	4	0.415
≥200	2.36	2.14, 2.61	3.15	1.60, 6.20	178.9	7	<0.0001
Mean birth year of study population							
<1990	3.85	3.35, 4.39	2.97	2.04, 4.31	9.1	5	0.058
≥1990	1.37	1.19, 1.58	2.85	1.21, 6.70	65.5	6	<0.0001
Geographic region							
Europe	1.29	1.13, 1.48	1.98	1.25, 3.11	27.0	7	<0.0001
Other	4.32	3.75, 4.95	4.99	3.14, 7.92	7.3	4	0.063
Outcome (i.e., asthma) definition							
Physician's diagnosis	3.68	3.24, 4.19	2.86	2.14, 3.83	15.1	9	0.057
Other	1.27	1.10, 1.47	3.01	0.39, 23.15	54.4	2	<0.0001
Asthma medication							
Use was stated	1.55	1.25, 1.91	2.14	0.87, 5.26	87.6	7	<0.0001
Use was not stated	3.86	3.37, 4.42	2.85	1.79, 4.55	10.2	4	0.017
Assessment of study quality ^a							
Higher (7–9 points)	1.19	1.03, 1.38	1.78	1.03, 3.06	12.8	4	0.005
Lower (0–6 points)	4.09	3.59, 4.67	3.72	2.55, 5.44	15.9	7	0.014

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Studies were assessed for quality by means of the Newcastle-Ottawa Quality Assessment Scale (22). A study could receive 1 point per item for 1) selection of the study population (0–4 items), 2) comparability of subjects (0–2 items), and 3) outcome for cohort and cross-sectional studies (0–3 items).

1.692; $P < 0.0001$), and use of asthma medication ($\beta = 0.531$, 95% CI: 0.0713, 0.990; $P = 0.024$).

Potential publication bias

The possibility of publication bias was assessed with funnel plots (Figures 4 and 5). In the absence of publication bias, the studies are distributed symmetrically around the summary odds ratio. In the presence of publication bias, the studies are expected to be symmetrical around the line representing the summary odds ratio at the top (large studies), with a few studies missing on the left side in the middle and more studies missing near the bottom (small studies).

The funnel plot for primary dentition (Figure 4) appears symmetrical at the top despite substantial heterogeneity. However, there seems to be slight asymmetry in the middle and for the

smallest studies. Still, the visual impression does not conform with the presence of publication bias. The impression is supported by Egger's test ($P = 0.688$) and Begg's test ($P = 0.484$), which do not indicate any publication bias. The "trim-and-fill" method added 2 studies and reduced the effect estimates only slightly, from 2.34 to 2.29 in the fixed-effects model and from 2.73 to 2.30 in the random-effects model (Table 2).

The funnel plot for permanent dentition (Figure 5) was symmetrical at the top but indicated some asymmetry in the middle and at the bottom. Begg's test ($P = 0.484$) did not indicate publication bias, but Egger's test ($P = 0.014$), based on regression, suggested a possibility of publication bias. The "trim-and-fill" method suggested 7 additional studies to achieve a symmetrical funnel plot. The simulated effect estimate changed from 1.41 to 1.13 in the fixed-effects model and from 2.04 to 1.19 in the random-effects model (Table 3).

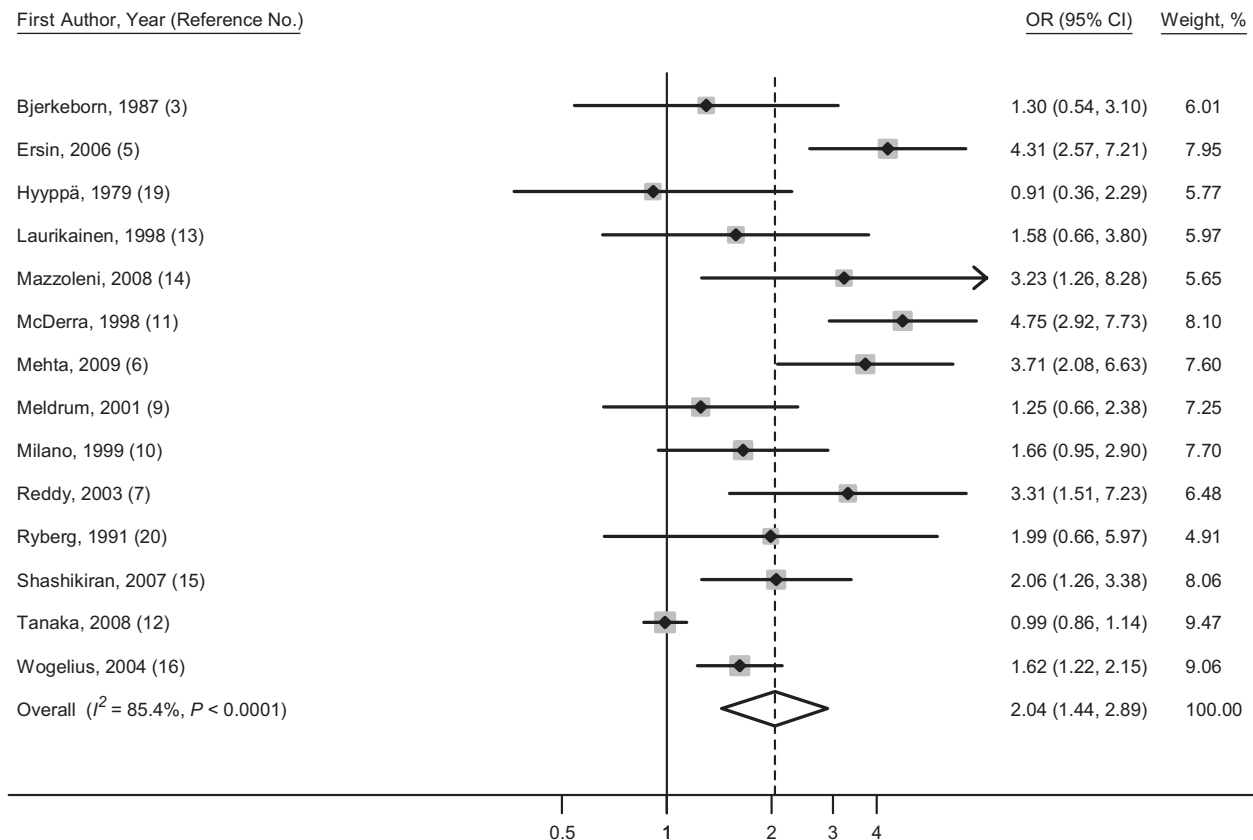


Figure 3. Study-specific and summary effect estimates (log odds ratio (OR) and 95% confidence interval (CI)) for caries risk in studies on the relation between asthma and caries in permanent dentition, 1950–May 2010.

DISCUSSION

Asthma and the use of asthma medication have long been suggested to potentially increase the risk of caries, but the results of individual studies have been inconclusive. Asthma is a common chronic disease in children and adults; thus, it would be important to identify such a link so that preventive measures could be implemented. To assess whether asthma is related to the risk of caries, we conducted a systematic review and meta-analysis based on studies fulfilling a priori set inclusion criteria. Altogether, 11 studies on primary dentition and 14 studies on permanent dentition were identified as relevant and included in the analyses. Random-effects models showed a significant association between asthma and caries for both primary and permanent dentition, the odds ratios being 2.73 (95% CI: 1.61, 4.64) and 2.04 (95% CI: 1.44, 2.89), respectively. Publication bias was an unlikely explanation for primary dentition, but it could have produced overestimation of the summary odds ratio for permanent dentition.

Analyses stratified by factors related to study characteristics showed an increased risk of caries related to asthma across all strata. Heterogeneity between individual studies was observed among both primary and permanent dentition studies, the effect estimates being higher in cross-sectional

studies and more recent publications. In addition, in analyses of studies on permanent dentition, the definition of asthma (i.e., physician's diagnosis or another method) and the use of asthma medication seemed to make significant contributions to heterogeneity. Among studies on permanent dentition, a higher quality score was related to a higher effect estimate, while among studies on primary dentition, a higher effect estimate was detected in relation to a lower quality score.

Validity of results

Many individual studies included in the meta-analyses were small, resulting in broad confidence intervals and inconclusive results. The majority of the studies were cross-sectional in design, comparing the risk of caries in asthmatics with that in nonasthmatics. Fewer studies were cohort studies that estimated the occurrence of caries among asthmatics and nonasthmatics during a defined follow-up period. The populations of most studies were derived from medical records during a particular time period according to specified criteria. The definition of asthma varied between the studies, but most investigators defined asthma as a physician-diagnosed condition. A few studies considered patients using asthma medication or experiencing asthma symptoms to be asthmatic. A more specific definition of asthma was associated with

Table 3. Summary Odds Ratios From Main and Stratified Meta-Analyses of the Relation between Asthma and Caries in Studies of Permanent Dentition, 1950–May 2010

Stratification	Fixed-Effects Model		Random-Effects Model		Heterogeneity		
	OR	95% CI	OR	95% CI	<i>Q</i>	No. of Studies	<i>P</i> Value
Main analysis	1.41	1.27, 1.57	2.04	1.44, 2.89	89.4	14	<0.0001
Simulated main analysis adjusting for potential publication bias	1.13	1.02, 1.24	1.19	0.83, 1.69	202.0	21	<0.0001
Stratified analyses							
Study design							
Cross-sectional	1.35	1.20, 1.52	2.21	1.32, 3.70	85.1	10	<0.0001
Cohort	1.66	1.33, 2.08	1.66	1.33, 2.08	1.6	4	0.657
Publication year							
<2000	2.22	1.66, 2.96	1.85	1.07, 3.22	16.1	6	0.007
≥2000	1.32	1.18, 1.48	2.17	1.39, 3.38	62.4	8	<0.0001
Sample size							
<200	2.29	1.68, 3.12	2.15	1.42, 3.27	10.3	7	0.114
≥200	1.33	1.19, 1.48	2.00	1.25, 3.21	68.6	7	<0.0001
Mean birth year of study population							
<1990	2.13	1.58, 2.87	1.74	0.96, 3.18	18.1	6	0.003
≥1990	1.33	1.19, 1.49	2.24	1.44, 3.47	63.0	8	<0.0001
Geographic region							
Europe	2.21	1.82, 2.68	2.22	1.42, 3.48	27.0	8	<0.0001
Other	1.18	1.04, 1.33	1.86	1.13, 3.05	34.0	6	<0.0001
Outcome (i.e., asthma) definition							
Physician's diagnosis	2.81	2.27, 3.49	2.52	1.76, 3.60	22.5	10	0.007
Other	1.14	1.01, 1.29	1.39	0.96, 2.02	15.5	4	0.001
Asthma medication							
Use was stated	2.61	2.16, 3.15	2.57	1.89, 3.51	22.8	10	0.007
Use was not stated	1.01	0.88, 1.15	1.01	0.88, 1.15	1.4	4	0.699
Assessment of study quality ^a							
Higher (7–9 points)	2.13	1.73, 2.61	2.42	1.53, 3.81	17.7	6	0.003
Lower (0–6 points)	1.22	1.08, 1.38	1.80	1.10, 2.95	50.9	8	<0.0001

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Studies were assessed for quality by means of the Newcastle-Ottawa Quality Assessment Scale (22). A study could receive 1 point per item for 1) selection of the study population (0–4 items), 2) comparability of subjects (0–2 items), and 3) outcome for cohort and cross-sectional studies (0–3 items).

a higher effect estimate. The definition of caries was based on dental records expressing the amount of caries in the form of an index calculated on the basis of decayed or missing teeth and the presence of teeth or surfaces with fillings. In summary, by selecting asthmatics and controls according to specified criteria, by adjusting for potential confounders, and by clearly defining asthma and caries, most of the studies controlled adequately for potential bias.

The results of the meta-analyses showed that the risk of caries was approximately doubled in relation to asthma. However, there seemed to be heterogeneity between the study-specific estimates. Factors potentially explaining such heterogeneity were explored further through stratified and meta-regression analyses. A higher effect estimate was

detected among higher-quality articles on permanent dentition, suggesting that the higher risk estimate for permanent dentition is more reliable. The overall summary estimates from the random-effects models were very similar for both primary and permanent dentition studies, which gives us some assurance that our estimates are valid and suggests that the mechanisms underlying the link between asthma and caries may be similar for primary and permanent dentition.

The funnel plot and statistical tests for primary dentition did not indicate any obvious influence of publication bias, whereas for permanent dentition, publication bias was suggested. Based on “trim-and-fill” analysis assuming symmetric funnel plots, the effect estimates would have been 1.13 (95% CI: 1.02, 1.24) in the fixed-effects model and

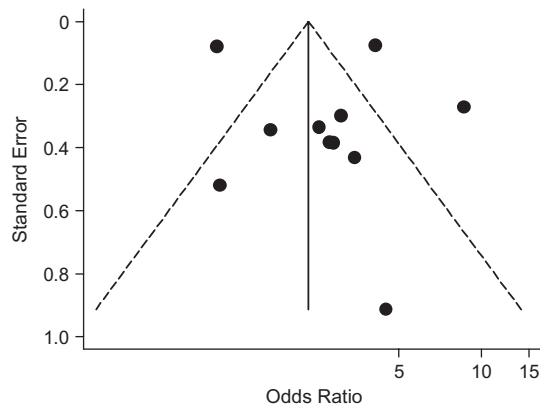


Figure 4. Log odds ratio for caries according to the standard error of the log odds ratio in studies on the relation between asthma and caries in primary dentition, 1950–May 2010.

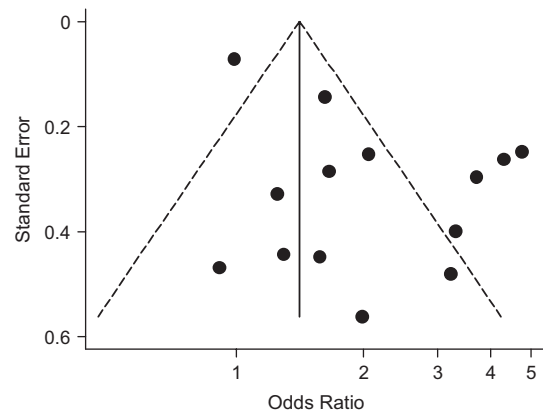


Figure 5. Log odds ratio for caries according to the standard error of the log odds ratio in studies on the relation between asthma and caries in permanent dentition, 1950–May 2010.

1.19 (95% CI: 0.83, 1.69) in the random-effects model. The simulated effect estimates showed what the estimate might look like if positive results did not influence publication.

Synthesis with previous knowledge

Two reviews on asthma and caries were published after the end of our data collection period. Thomas et al. (24) reviewed the possible mechanisms that may increase the risk of caries and other oral health conditions in asthmatics and presented results from some epidemiologic studies on the association between asthma and caries. For their review, Maupomé et al. (25) conducted a systematic Medline search (1976–March 2010) and identified 27 studies described in 29 articles. Maupomé et al. decided not to conduct a formal meta-analysis because of the heterogeneity of variables, measurements, and statistical approaches (25). However, we concluded that meta-analyses were both feasible and useful and provided added value over the systematic review. The body of evidence included several, mainly small, inconclusive studies in which effect estimates were elevated but not always statistically significant. Further, both the determinant of interest (asthma) and the outcome (caries) were satisfactorily defined (asthma) or quantified (caries) in the majority of studies, and there was information on relevant effect estimates or sufficient information to calculate such estimates. The characteristics and effect estimates of the studies were heterogeneous, but there was a possibility of assessing the factors influencing heterogeneity by applying stratified analyses and meta-regression.

Maupomé et al. concluded that there was no strong evidence suggesting a causal link between asthma and dental caries (25). In the present study, we identified 27 of the 29 articles identified by Maupomé et al., but our inclusion criteria aiming at meta-analyses were more strict, leading to exclusion of the studies by Storhaug (26) (inclusion criteria 1 and 3), Ryberg et al. (27) (redundant data with another study by Ryberg et al. (20)), Eloit et al. (4) (inclusion criteria 1 and 3), Bimstein et al. (28) (inclusion criterion 1; apparent

error in effect estimates), Wierchola et al. (29) (inclusion criterion 1), and Anjomshoa et al. (30) (inclusion criterion 1). Our search did not identify the article by Herrström and Högsted (31) or Khalilzadeh et al. (32). Herrström and Högsted (31) reported on a case series, and their article would have been excluded from our meta-analysis because it did not provide sufficient data for an effect estimate. Khalilzadeh et al. (32) studied 45 asthmatic children and 47 healthy children and found that asthmatics had higher DMFT scores than healthy controls. Based on means and standard deviations reported by Khalilzadeh et al. (32), the odds ratio was estimated to be 1.10 (95% CI: 0.52, 2.31). Because this study was not included in our primary search or identified in the references, it was not from a methodological perspective that was eligible for the meta-analysis. However, it can be deduced that given the magnitude of the odds ratio and the broad confidence interval, the effect estimate would not have had any impact on the summary odds ratio.

In our meta-analysis, the quantitative summary odds ratios suggested a strong association between asthma and the risk of caries, although the study-specific effect estimates were heterogeneous. The majority of the individual studies had found an association between asthma and caries, so the summary estimates from the meta-analyses were consistent with the results of individual studies. In addition, the quantitative estimates of the association between asthma and caries were very similar for both primary and permanent dentition.

Although the association between asthma and caries was found to be significant, the mechanisms underlying this association are still inadequately understood and warrant future research. The role of asthma medication is likely to be a contributing factor and has been investigated in several studies (3–5, 14, 33). Overall, persons with asthma have been found to have a significantly decreased saliva secretion rate, which is known to predispose people to caries (34). One-month treatment with an inhaled β_2 -agonist and corticosteroid leads to a significantly decreased saliva secretion rate and an increased dental plaque index (35). Moreover,

asthmatics treated with β_2 -agonists have a significantly lower saliva secretion rate and higher *Streptococcus mutans* counts in saliva than healthy controls (27). Inhalant medications also decrease salivary pH (36). Hence, our results showing an association between asthma and caries are plausible, because decreased salivary flow rate and lower pH are known to lead to decreased buffer capacity and remineralization and increased caries (37). Thus, it is not surprising that the amount of asthma medication used is associated with the prevalence of caries (33) and that patients using inhalers (β_2 -agonists or corticosteroids) have more caries than healthy controls or asthmatics using β_2 -agonists as tablets (15).

Pathways other than use of asthma medication that potentially explain the detected association include asthma per se's increasing the risk of caries, perhaps through mechanisms related to the inflammatory state observed in asthmatics. In our literature search, we were not able to identify any studies that had investigated caries as a potential risk factor for asthma. However, one potential pathway is the possibility of some common genetic or environmental determinant predisposing to both asthma and caries. The content of secretory immunoglobulin A in saliva might be one such shared determinant, as it plays an essential role in the immune system (38). Both excess (39–41) and lack (42) of secretory immunoglobulin A have been related to the prevalence of caries. Immunoglobulin A has also been linked to asthma (43, 44). We recommend that a large prospective study investigating potential mechanisms underlying the relation of asthma to caries be conducted in the future.

Conclusions

This meta-analysis provides evidence that asthma significantly increases the risk of caries. Possible contributing factors include asthma medication's predisposing people to dental caries through its effects on saliva secretion and the content of secretory immunoglobulin A's contributing to both asthma and caries, but the underlying mechanisms need more research. In the future, special attention should be given to the oral health of patients with asthma. Because fluoride has been shown to significantly reduce the rate of caries, regular use of fluoride products (e.g., in toothpaste) is recommended for asthmatics (45, 46). Because of the possible contribution of medication, physicians should recommend that persons with asthma be especially attentive to oral hygiene after using asthma medication. In addition, healthy dietary habits could prevent the development of caries (47, 48). Dentists should also pay extra attention to the oral status of asthmatic patients, since they are more susceptible to caries and its progression. In this way, several painful and harmful complications and the huge economic expenses due to caries could be reduced among persons with asthma.

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