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How Common is Dry Mouth? Systematic Review and Meta-Regression Analysis of Prevalence Estimates

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The aim of this paper is to systematically review the literature to estimate the overall prevalence of xerostomia/hyposalivation in epidemiological studies. An electronic search was carried out up to February 2018 with no language restrictions. A total of 5760 titles were screened and just twenty-nine papers were included in review and the meta-analysis after a two independently reviewers applied the selection criteria. Data were extracted from PubMed and Web of Science databases. Eligibility criteria included original investigations from observational population-based studies that reported the prevalence of xerostomia or data that allowed the calculation of prevalence of xerostomia and/or hyposalivation. Studies conducted in samples with specific health conditions, literature reviews, case reports and anthropological studies, as conferences or comments were excluded. Sample size, geographic location of the study, study design, age of the studied population, diagnosis methods, and evaluation criteria used to determine xerostomia e/or hyposalivation were extracted for meta-analysis and meta-regression. Multivariate meta-regression analysis was performed to explore heterogeneity among studies. The overall estimated prevalence of dry mouth was 22.0% (95%CI 17.0-26.0%). Higher prevalence of xerostomia was observed in studies conducted only with elderly people. Despite diverse approaches to the condition's measurement, just over one in four people suffer from xerostomia, with higher rates observed among older people. Moreover, the measurement methods used currently may over- or underestimate xerostomia. These findings highlight the need for further work on existing and new clinical measure and will be useful to determine which one is more reliable in clinical and epidemiological perspectives.

Key Words: xerostomia, dry mouth, hyposalivation, global prevalence, salivary function.

Introduction

Xerostomia and hyposalivation are two distinct and independent phenomena, which may manifest alone or in combination (1). Xerostomia is defined as the subjective sensation of dry mouth and it is diagnosed through self-report (2). On the other hand, hyposalivation refers to an objectively measured low salivary flow (3). Either dry mouth situations may negatively affect oral health-related quality of life (4,5) and may cause oral health problems such as halitosis, impaired chewing and swallowing, and difficulties in prosthesis retention (6). There is evidence that lower salivary flow increases the risk of dental caries, due to an absence of the physical cleaning action and buffering capacity of saliva (7). This increasing risk is not exclusive of elderly and can occur in early age, specially in asthmatic patients under treatment.

Epidemiological studies of dry mouth situations from the last two decades have shown prevalence estimates ranging from 1% (8) to 62% (1). The high variability in estimates has been attributed to variations in measurement methods, populations investigated, sample representativeness, study design, and the age of individuals evaluated (9). Despite the research effort, much remains unanswered about the epidemiology of dry mouth. Even xerostomia that is measured through self-report (2,10), there are methodological differences, whereby some studies report only the presence or absence of dry mouth (7,11,12) and others investigate the frequency of such a sensation (5,13,14). New approaches use scales, such as the Xerostomia Inventory (XI) developed and tested by Thomson et al. (15), which includes a battery of seven xerostomia questions used by Locker (16) or a nine-item battery of questions on dry mouth-related symptoms and behaviors (17).

Hyposalivation is diagnosed through the assessment of salivary flow, which may be evaluated by collecting the fluid from individual salivary glands (or pairs of glands) and; also, total salivary flow may be evaluated by collecting whole saliva. The latter method is more common (9). However, there is a lack of consensus in the literature about which salivary flow rate indicates hyposalivation, ranging from less than 0.1mL/min unstimulated saliva (15) to 0.8 mL/min stimulated saliva (18).

There is evidence of health conditions and risk behavior being determinants of xerostomia and hyposalivation.

Increasing age has been reported as a risk marker for xerostomia (11,19). Chronic diseases such as diabetes, autoimmune diseases, especially Sjögren's Syndrome (12), and polypharmacy (10,20,21) are recognized as major dry mouth associations. Not only polypharmacy, but specific medicines favor the occurrence of xerostomia and hyposalivation, especially inhaled antiastmatic drugs (22). The action of such medicines, even in early ages can significantly affect salivary flow. Considering the widespread occurrence of asthma since childhood (23) and the impact of its therapy in dry mouth, the effects of it therapy in a long-term are not clear and it must be considered in all ages as well.

A previous systematic review evaluating the prevalence of xerostomia in population samples was published in 2006 (24). However, that study included only estimates for xerostomia. Moreover, the study did not use a meta-analysis, so it was unable to obtain an overall prevalence estimate for xerostomia. Many epidemiological studies on dry mouth have been published since then.

This paper presents a systematic review of the literature on the prevalence of xerostomia and hyposalivation in order to obtain a global combined prevalence estimate for dry mouth, and to determine the factors behind the considerable variability in prevalence estimates.

Material and Methods

This systematic review was organized using the PRISMA statement and it was based on the following review question: "What is the estimated worldwide prevalence of xerostomia/hyposalivation?"

Eligibility Criteria

Original investigations from observational studies that reported the prevalence of xerostomia were included. Only population-based studies with representative samples, according to the Critical Appraisal Checklist for prevalence studies recommended by the Joanna Briggs Institute, were considered for this review. As a qualifying condition, all selected studies should have clearly reported the prevalence of xerostomia and/or hyposalivation or have included data allowing its calculation.

Studies conducted in samples with specific health conditions (asthma, cancer, depression, paralysis, syndromes - including Sjögren's Syndrome, and similar convenience samples) were excluded, as were literature reviews, case-control studies, retrospective studies, case reports, anthropological studies, in vitro and in situ studies, and comments or conference abstracts. Articles in other languages than English, Spanish, Portuguese, French or German were excluded.

Search Strategy

An electronic search was performed in the PubMed and Web of Science databases, with no initial date and language restrictions. Keywords included the following MeSH and free terms: (Xerostomia(Mesh)) OR (Xerostomia (all)) OR (Dry Mouth(all)) OR (Mouth Dryness(all)) OR (Hyposalivation(all)) AND Epidemiologic Studies(Mesh)) AND (Cross-Sectional Studies(Mesh)) AND (Longitudinal Studies(Mesh)) AND (Cohort Studies(Mesh)), which are presented in Table 1 in several combinations.

Reports were managed using the EndNote X7.4 software (Thomson Reuters, New York, NY, USA). Duplicate reports were excluded. Two reviewers (GOC and ERS) independently screened titles and abstracts, based on the aforementioned criteria. The screened lists were compared and differences were discussed and resolved by consensus. If there was no consensus, a third examiner was asked to decide on the inclusion or exclusion of the study. The same two reviewers also screened full text manuscripts. Reference lists from the eligible papers were reviewed according to the eligibility criteria. Gray Literature was not screened.

Critical Appraisal

The Critical Appraisal Checklist for prevalence and

Table 1. Search strategy

PubMed (((((“Xerostomia”(Mesh)) OR “Xerostomia”(all)) OR “Dry Mouth”(all) OR “Mouth Dryness”(all) OR “Hyposalivation”(all))) AND ((((((((((((((((((((((((“Epidemiological Studies”) OR “Epidemiological Study”) OR “Cross Sectional Study”) OR “Cross Sectional Studies”) OR “Cross-Sectional Study”) OR “Cross-Sectional Studies”) OR “Studies, Cross-Sectional”) OR “Study, Cross-Sectional”) OR “Prevalence Studies”) OR “Prevalence Study”) OR “Studies, Prevalence”) OR “Study, Prevalence”) OR “Cohort Study”) OR “Cohort Studies”) OR “Incidence Study”) OR “Incidence Studies”) OR “Studies, Incidence”) OR “Study, Incidence”) OR “Follow up Studies”) OR “Follow-up Studies”) OR “Follow up Study”) OR “Follow-up Study”) OR “Prevalence”) OR “Incidence”))
Web of Science ((((“Xerostomia” OR “Dry Mouth”) OR “Mouth Dryness”) OR “hypersalivation”) AND ((((((((((((((((((((((“Epidemiological Studies” OR “Epidemiological Study”) OR “Cross Sectional Study”) OR “Cross Sectional Studies”) OR “Cross-Sectional Study”) OR “Cross-Sectional Studies”) OR “Studies, Cross-Sectional”) OR “Study, Cross-Sectional”) OR “Prevalence Studies”) OR “Prevalence Study”) OR “Studies, Prevalence”) OR “Study, Prevalence”) OR “Cohort Study”) OR “Cohort Studies”) OR “Incidence Study”) OR “Incidence Studies”) OR “Studies, Incidence”) OR “Study, Incidence”) OR “Follow up Studies”) OR “Follow-up Studies”) OR “Follow up Study”) OR “Follow-up Study”) OR “Prevalence”) OR “Incidence”))

incidence studies recommended by the Joanna Briggs Institute was employed. The same reviewers independently evaluated each study and answered 'Yes', 'No', or 'Unclear' for each of the 9 items of the instrument. Disagreements were resolved by reaching consensus through discussion.

Data Extraction and Data Analysis

Information extracted from the studies included sample size, geographic location, study design, age of the studied population, diagnosis methods, and evaluation criteria used to define xerostomia and/or hyposalivation. Prevalence rates for xerostomia/hyposalivation were also collected (or calculated, if necessary). In case of missing data, the authors were contacted up by e-mail. When more than one method for measuring dry mouth was employed, prevalence rate of hyposalivation was included in the meta-analysis for dry mouth. Prevalence rates were categorized according to the age of the participants (adults or elders), when more than one available, the highest was used; however, when such information was not available, studies were grouped into mixed population (adults and elders). Considering that cohort studies could showed prevalences of xerostomia or hyposalivation in more than 1 time, it was established the use of the most recent values of prevalences.

The estimated global prevalence of dry mouth was calculated using fixed- and random-effect models. When heterogeneity was present (I2>50% or chi-square p value<0.05), the random-effect model was favored (25). The same criteria were adopted for individual meta-analysis of xerostomia and hyposalivation information of each study. Additionally, meta-regression and subgroup analyses were conducted to investigate sources of between-study variability for each criterion. Characteristics were included in a multivariate meta-regression model. Variable selection was performed using the backward stepwise approach. Variables with p value<0.20 remained in the final model, but only those with p value<0.05 were considered significant in the final adjusted model. Explained heterogeneity was obtained from the adjusted R2 of the final model. Subgroup analysis was also conducted for each methodological variable included in the final meta-regression model. Sensitivity analyses were conducted to estimate the influence of each study on the pooled results. Funnel plot and the Egger test were used to test for any potential publication bias (17). All analyses were performed using the Stata 14.1 software (StataCorp, College Station, TX, USA).

Results

Electronic searches revealed 5760 studies. From those, 1346 were excluded for being duplicates. A total of 4414 articles were submitted to title and abstract screening and 114 of them remained for full-text evaluation, from which 85 were excluded after appraisal (Fig. 1, Table 2). A total of 29 articles met the inclusion criteria, among these articles, 26 reported the prevalence of xerostomia or data on it and 14 reported the prevalence of hyposalivation

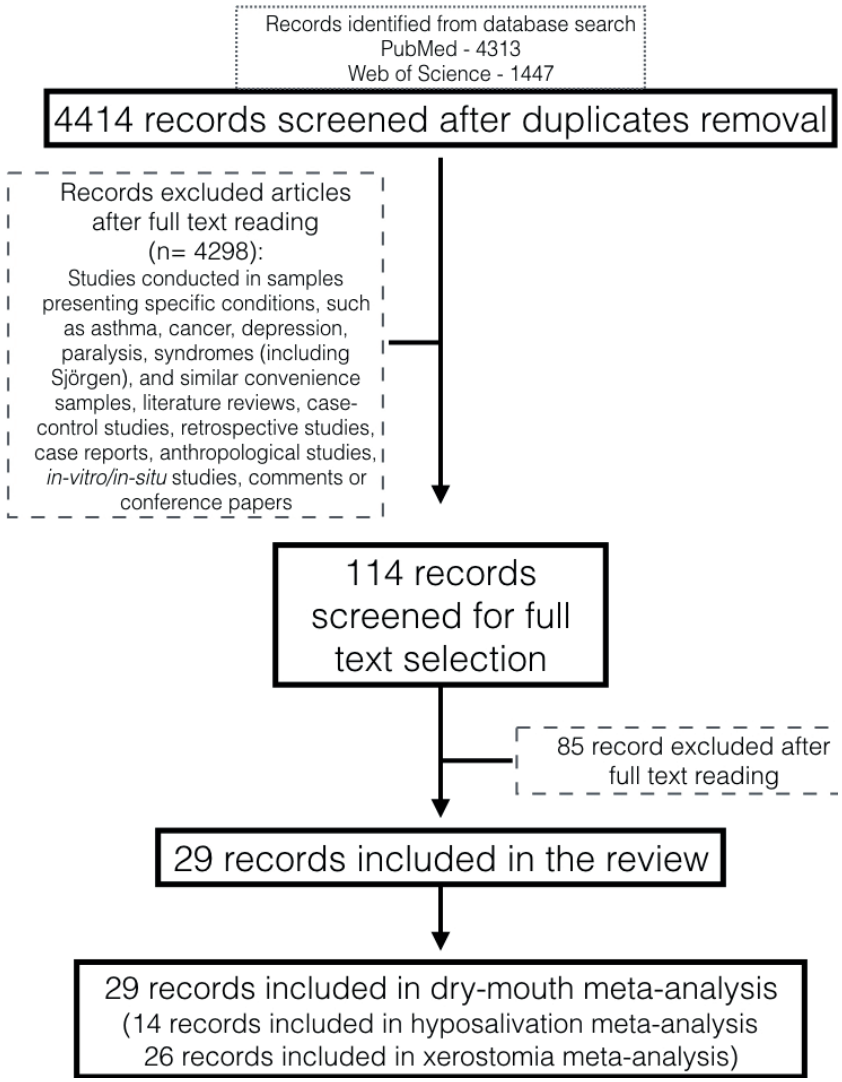

Figure 1. Flowchart selection process for studies included in this systematic review.

or data on it. One study was included twice in the meta-analysis, because it presented separate data for different populations under study (14).

The overall prevalence of xerostomia was estimated to be 23.0% (95%CI 18.0-28.0%), with high heterogeneity among studies (I2 99.8%; chi square p value<0.001; Fig. 2). The overall prevalence of hyposalivation was estimated to be 20.0% (95%CI 15.0 – 25.0%) with high heterogeneity among studies (I2 99.4%; chi square p value<0.001; Fig. 3). The overall prevalence of dry mouth (xerostomia or hyposalivation) was estimated to be 22.0% (95%CI 17.0-26.0%), also with high heterogeneity among studies (I2 99.8%; chi square p-value<0.001; Fig. 4).

The final meta-regression analysis explained about 16% of the between-study variability.

Table 3 presents the main characteristics of the included studies. Some studies presented weaknesses under critical appraisal (Table 4), as follows: two studies (12,26) did not use an adequate sample frame for the target population, two studies (7,27) did not have an adequate sample size or were unclear, one study (3) did not describe their participants and the setting in detail, one study (28) did not conduct the data analysis with sufficient coverage of the identified sample did not avoid coverage bias in data analysis, one

Table 2. Excluded studies and reasons for exclusion

Author and year	Reason for exclusion
Abdullah 2015	Convenience/specific sample
Acevedo et al. 1996	Comments/abstracts of conferences
Allen and Locker 1997	No prevalence data
Almas et al. 2003	Convenience/specific sample
Almstahl et al. 2012	Convenience/specific sample
Anusavice 2002	No access to full text
Arcury et al. 2009	Convenience/specific sample
Atchinson et al. 1993	Convenience/specific sample
Bai and Lin 2006	Full text in Chinese
Barbagli et al. 2014	No prevalence data
Benaryeh et al. 1985	Convenience/specific sample
Bergdahl 2000	Convenience/specific sample
Bergdahl and Bergdahl 2001	Convenience/specific sample
Bergdahl and Bergdahl 2002	Convenience/specific sample
Bhattacharyya and Kenpes 2015	Prevalence data not clear
Billings 1993	Review
Billings et al. 1996	Convenience/specific sample
Cabrera et al. 2007	Convenience/specific sample
Castrejon-Perez et al. 2017	Convenience/specific sample
Chopra et al. 2015	Convenience/specific sample
Coccia et al. 2015	No access to full text
El Osta et al. 2014	Convenience/specific sample
Elishoov et al. 2005	Full text in Hebrew
Enoki et al. 2014	Convenience/specific sample
Evans et al. 2000	Prevalence data not clear
Farah et al. 2008	Convenience/specific sample
Field et al. 2000	Convenience/specific sample
Field et al. 2001	Convenience/specific sample
Field et al. 2001	No access to full text
Flink 2007	No access to full text
Flink et al. 2008	Convenience/specific sample
Flink et al. 2000	Convenience/specific sample
Foerster et al. 1998	Convenience/specific sample
Fure 1998	Non-representative sample
Fure 2003	Non-representative sample
Gerdin et al. 2005	Convenience/specific sample
Ghezzi and Ship 2003	Non-representative sample
Gilbert et al. 1993b	Same sample of an included study
Goaz et al. 1994	Comments/abstracts of conferences
Gois et al. 2018	Convenience/specific sample
Guignon and Novy 2015	Comments/abstracts of conferences
Hahnel et al. 2014	Convenience/specific sample
Hassel et al. 2010	Non-representative sample
Ichikawa et al. 2011	No prevalence data
Ikebe et al. 2011	Convenience/specific sample
Ikebe et al. 2006	Convenience/specific sample
Ikebe et al. 2007	Convenience/specific sample
Ikebe et al. 2006	Convenience/specific sample
Ikebe et al. 2001	Convenience/specific sample
Ikebe et al. 2002	Convenience/specific sample
Imazato et al. 2006	Convenience/specific sample
Inoue et al. 2006	Convenience/specific sample
Iwabuchi et al. 2012	Convenience/specific sample
Johanson et al. 2015	Same sample of an included study
Johanson et al. 2009	Same sample of an included study
Khalifa et al. 2012	Convenience/specific sample
Kreher et al. 1987	Convenience/specific sample
Kreher et al. 1991	Convenience/specific sample
Lee et al. 2014	Convenience/specific sample
Leung et al. 2016	Convenience/specific sample
Lewis et al. 1993	No prevalence data
Locker 1997	Same sample of an included study
Marino et al. 2015	No prevalence data
Mizutani et al. 2015	Convenience/specific sample
Nally 1990	Editorial
Narhi 1994	Same sample of a study already included
Navazesh et al. 1996	Convenience/specific sample
Ohara et al. 2015	Same sample of a study already included
Ohara et al. 2011	Convenience/specific sample
Pedersen et al. 2015	No prevalence data
Porter 2010	Review
Pujol et al. 1998	Convenience/specific sample
Ramsay et al. 2015	Convenience/specific sample
Ramsay et al. 2015	Convenience/specific sample
Ramsay et al. 2018	Convenience/specific sample
Russell and O'Grady 1990	Full text in Hungarian
Salako and Farsi 2000	Comments/abstracts of conferences
Schein et al. 1999	Convenience/specific sample
Sorensen et al. 2018	Convenience/specific sample
Sreebny and Valdini 1988	Convenience/specific sample
Thomson et al. 1999	Same sample of an included study
Thomson et al. 2000	No prevalence data
Thomson et al. 2006	Same sample of a study already included
van Eijk et al. 2013	Letter to editor
Villa and Abati 2011	Convenience/specific sample

study (12) did not use an appropriate statistical analysis, and one study (7) did not have a sufficient participation rate.

Tables 5 and 6 shows the subgroup analysis according to the variables retained in the final adjusted meta-

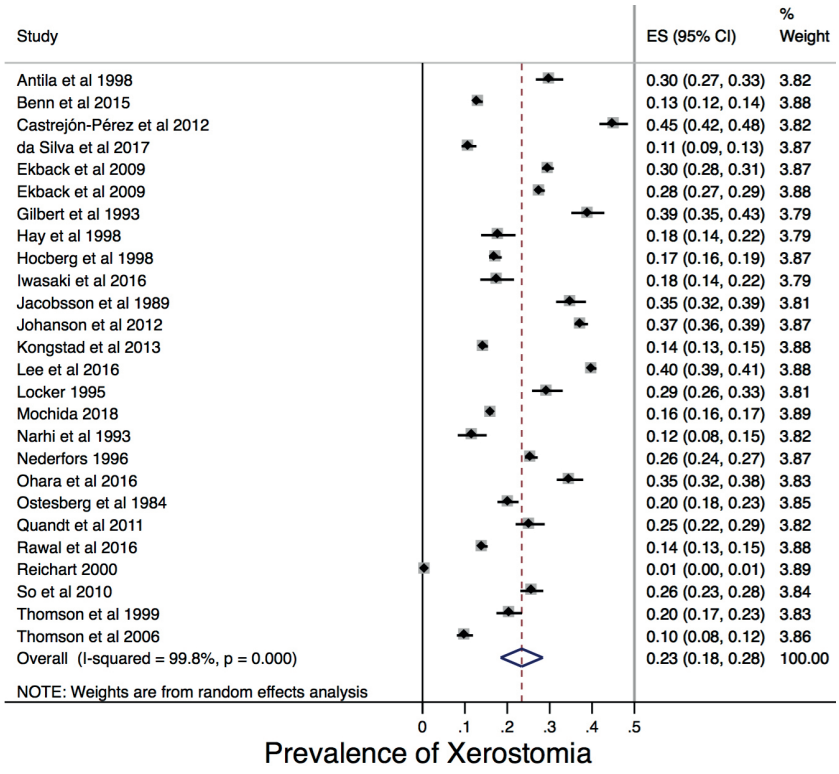

Figure 2. The overall prevalence of xerostomia.

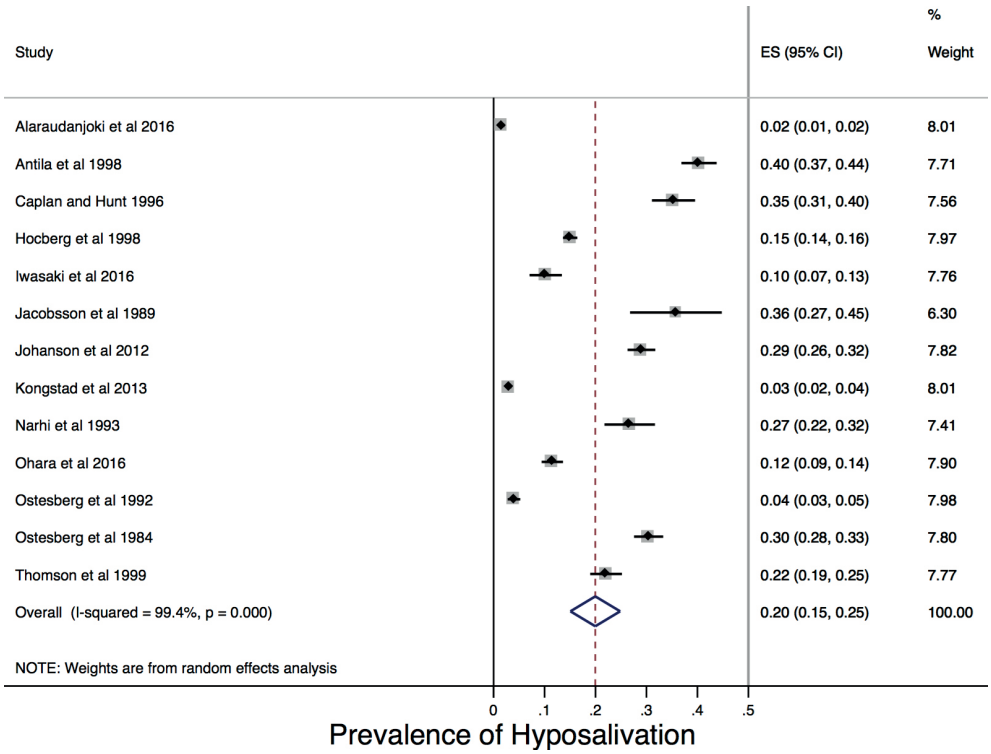

Figure 3. The overall prevalence of hyposalivation.

Table 3. Main characteristics of included studies

Author and year (# ref)	Country	Participants	Age of participants	Study design	Xerostomia/ Hyposslivation assessment	Xerostomia/ Hyposalivation criteria	Cases of Xerostomia/ Hyposalivation	Total Sample	Prevalence
Alaraudanjoki et al. 2016 (3)	Finland	Adults	46	Cohort	Unstimulated salivary flow rate	Unstimulated salivary flow rate <0.1 mL/min	31	1,944	0.2*
Antila et al. 1998 (13)	Finland	Adults	55	Cross-sectional	Self-reported	Frequency ('Sometimes' 'Often')	232	774	30.0
		Adults	55	Cross-sectional	Stimulated salivary flow rate	Stimulated salivary flow rate <0.7 mL/min	312	774	40.3*
		Adults	55	Cross-sectional	Unstimulated salivary flow rate	Unstimulated salivary flow rate <0.1 mL/min	123	772	15.9
Benn et al. 2015 (5)	New Zealand	Adults/Elderly	>18	Cross-sectional	Self-reported	Frequency ('Always' 'Frequently)	455	3475	13.1*
Caplan and Hunt 1996 (28)	United States of America	Elderly	>65	Cross-sectional	Stimulated salivary flow rate	Stimulated salivary flow rate < 1 mL/min	173	490	35.3*
Castrejón-Pérez et al. 2012 (2)	Mexico	Elderly	>70	Cohort	Self-reported	Presence/Absence	378	838	45.1*
da Silva et al. 2017 (35)	Brazil	Adults	20-59	Cohort	Self-reported	Frequency ('Regular' "Irregular') according to "Frequently" or "Always" answers to the question 'How often do you experience dry mouth?' in 2009 and 2012.	134	1222	11.0*
Ekback et al. 2009 (14)	Norway	Elderly	65	Cross-sectional	Self-reported	Frequency ('Sometimes' 'Often' 'Seldom')	1,201	4,062	29.6*
	Sweden	Elderly	65	Cross-sectional	Self-reported	Frequency ('Sometimes' 'Often' 'Seldom')	1,685	6,078	27.7*
Gilbert et al. 1993 (10)	United States of America	Elderly	>65	Cross-sectional	Self-reported	Presence/Absence	234	600	39.0*
Hay et al. 1998 (26)	United States of America	Adults/Elderly	18-75	Cross-sectional	Self-reported	Classification based on 3 questions: Does your mouth feel dry every day? Have you had recurrent or persistent swelling of your salivary glands as an adult? Do you frequently have to take a drink in order to swallow?	61	341	17.9*
Hocberg et al. 1998 (11)	England	Elderly	65-84	Cohort	Self-reported	Classification based on 2 questions: Does your mouth usually feel dry? Do you wake at night feeling so dry in your mouth that you need to drink fluids?	427	2,482	17.2
	England	Elderly	65-84	Cohort	Stimulated salivary flow rate	Stimulated salivary flow rate < 1 mL/min	373	2,482	15.0*
Iwasaki et al. 2016 (7)	Japan	Elderly	80	Cohort	Self-reported	Presence/Absence	62	352	17.6
		Elderly	80	Cohort	Stimulated salivary flow rate	Stimulated salivary flow rate <0.5 mL/min	36	352	10.2*
Jacobsson et al. 1989 (12)	Sweden	Adults	52-72	Cohort	Self-reported	Classification based on 2 questions: Do you often feel a gritty or sandy sensation in your eyes? Do you wake up at night feeling so dry in the mouth that you need to drink water?	247	705	35.0
		Adults	52-72	Cohort	Unstimulated salivary flow rate	Unstimulated salivary flow rate <0.1 mL/min	39	109	35.8*

Overall prevalence of dry mouth

Johanson et al. 2012 (1)	Sweden	Elderly	75	Cohort	Self-reported	Frequency ('Sometimes' 'Often' 'Seldom')	1,325	3,539	37.4
		Elderly	75	Cohort	Self-reported	Frequency ('Sometimes' 'Often' 'Seldom')	2,064	3,591	57.5
		Elderly	75	Cohort	Self-reported	Frequency ('Sometimes' 'Often' 'Seldom')	2,249	3,611	62.3
		Elderly	75	Cohort	Stimulated salivary flow rate	Stimulated salivary flow rate <0.7 mL/min	311	1072	29.0*
Kongstad et al. 2013 (19)	Denmark	Adults/Elderly	18-96	Cross-sectional	Self-reported	Frequency ('Sometimes' 'Often' 'Seldom')	634	4,402	14.4
		Adults/Elderly	18-96	Cross-sectional	Stimulated salivary flow rate	Stimulated salivary flow rate <0.5 mL/min	132	4,402	3.0*
Lee et al. 2016 (29)	Korea	Elderly	>65	Cross-sectional	Self-reported	Presence/Absence	3,943	9,84	40.1*
Locker 1995 (34)	Canada	Adults	>50	Cross-sectional	Self-reported	Presence/Absence	180	611	29.5*
Mochida et al. 2018 (41)	Japan	Elderly	>65	Cohort	Self-reported	Presence/Absence	6256	38529	16.2*
Narhi et al. 1993 (18)	Finland	Elderly	>75	Cohort	Self-Reported	Presence/Absence	40	341	11.7
		Elderly	>75	Cohort	Unstimulated salivary flow rate	Unstimulated salivary flow rate <0.1 mL/min	143	306	46.7
		Elderly	>75	Cohort	Stimulated salivary flow rate	Stimulated salivary flow rate <0.8 mL/min	82	307	26.7*
Nederfors 1996 (37)	Sweden	Adults	20-80	Cross-sectional	Self-reported	Presence/Absence	851	3,313	25.7*
Ohara et al. 2016 (27)	Japan	Elderly	>65	Cross-sectional	Self-reported	Presence/Absence	311	894	34.8
		Elderly	>65	Cross-sectional	Unstimulated salivary flow rate	Weight <0,1 g	103	894	11.5*
Ostesberg et al. 1992 (20) Ostesberg et al. 1984 (40)	Sweden	Elderly	>70	Cohort	Stimulated salivary flow rate	Stimulated salivary flow rate <0.2 mL/min	39	975	4.0*
		Elderly	>70	Cohort	Self-reported	Presence/Absence	201	996	20.2
		Elderly	>70	Cohort	Stimulated salivary flow rate	Stimulated salivary flow rate <0.1 mL/min	303	996	30.4*
Quandt et al. 2011 (36)	United States of America	Elderly	>60	Cross-sectional	Self-reported	Frequency ('Always' 'Frequently)	158	622	25.4*
Rawal et al. 2016 (33)	United States of America	Adults	>40	Cross-sectional	Self-reported	Presence/Absence	513	3,603	14.2*
Reichart 2000 (8)	Germany	Adults	>35	Cross-sectional	Self-reported	Presence/Absence	7	1,367	0.1*
So et al. 2010 (17)	Korea	Elderly	>55	Cross-sectional	Self-reported	Classification based on 9 questions.	261	1,012	25.8*
Thomson et al. 1999 (15)	Australia	Elderly	75	Cohort	Self-reported	Frequency ('Always' 'Frequently)	140	684	20.5
		Elderly	75	Cohort	Unstimulated salivary flow rate	Unstimulated salivary flow rate <0.1 mL/min	151	684	22.1*
Thomson et al. 2006 (4)	New Zealand	Adults/Elderly	26 and 32	Cohort	Self-reported	Frequency ('Always' 'Frequently)	95	950	10.0*

*Values included in the meta-analysis of overall prevalence of dry-mouth (xerostomia or hyposalivation) of the studies with more than one measure of salivary conditions.

regression models. A higher prevalence estimate for dry mouth was noted in studies conducted with older people only and in studies conduceted in Americas (Table 5). Table 6 presents overall prevalence estimates for xerostomia and hyposalivation separately. Considerating age group, the higher prevalence values were 27.2% for xerostomia in studies conducted with older people only; and 26.0% for hyposalivation in studies considering adults people only. The heterogeneity of the studies for each outcome was higher than 99.0%.

The Egger test revealed the presence of publication bias (p-value=0.007), which was confirmed by the metafunnel analysis (Fig. 5). Sensitivity analysis demonstrated that the omission of any study would not significantly modify the estimated prevalence of dry mouth (Fig. 6).

Table 4. Evaluation of included studies according to Joanna Brings Institute Critical Appraisal Checklist

	Checklist item								
	1	2	3	4	5	6	7	8	9
Alaraudanjoki et al. 2016 (3)	yes	yes	yes	no	yes	yes	yes	yes	yes
Antila et al. 1998 (13)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Benn et al. 2015 (5)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Caplan and Hunt 1996 (28)	yes	yes	yes	yes	no	yes	yes	yes	yes
Castrejon-Perez et al. 2012 (2)	yes	yes	yes	yes	yes	yes	yes	yes	yes
da Silva et al. 2017 (35)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Eckback et al. 2009 (14)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Gilbert et al. 1993 (10)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Hay et al. 1998 (26)	unclear	yes	yes	yes	yes	yes	yes	yes	yes
Hocberg et al. 1998 (11)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Iwasaki et al. 2016 (7)	yes	yes	no	yes	yes	yes	yes	yes	no
Jacobsson et al. 1989 (12)	unclear	yes	yes	yes	yes	yes	yes	no	yes
Johanson et al. 2012 (1)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Kongstad et al. 2013 (19)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Lee et al. 2016 (29)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Locker 1995 (34)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Mochida 2018 (41)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Narhi et al. 1993 (18)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Nederfors 1996 (37)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Ohara et al. 2016 (27)	yes	yes	unclear	yes	yes	yes	yes	yes	yes
Ostesberg et al. 1992 (20)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Ostesberg et al. 1984 (40)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Quandt et al. 2011 (36)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Rawal et al. 2016 (33)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Reichart 2000 (8)	yes	yes	yes	yes	yes	yes	yes	yes	yes
So et al. 2010 (17)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Thomson et al. 1999 (15)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Thomson et al. 2006 (4)	yes	yes	yes	yes	yes	yes	yes	yes	yes

1- Was the sample frame appropriate to address the target population?; 2- Were study participants sampled in an appropriate way?; 3- Was the sample size adequate?; 4- Were the study subjects and the setting described in detail?; 5- Was the data analysis conducted with sufficient coverage of the identified sample?; 6- Were valid methods used for the identification of the condition?; 7- Was the condition measured in a standard, reliable way for all participants?; 8- Was there appropriate statistical analysis? 9- Was the response rate adequate, and if not, was the low response rate managed appropriately?

Discussion

This meta-analysis of findings from epidemiological studies on dry mouth has found the overall estimated prevalence of dry-mouth from population-based studies tov be 22.0% (95%CI 17.0-26.0). Xerostomia and hyposalivation are two phenomena that may negatively affect the oral health of individuals and their quality of life (4,5,13). Dry mouth impairs oral function, chewing, and swallowing (29). Considering oral diseases, evidences from different study designs researches highlight the impact of salivary problems in caries experience (30,31). Moreover, a recent study showed that dry mouth could influence the occurrence of halitosis and consequently affect oral health-related quality of life (32). Besides oral manifestations, these problems may result in more general effects, including loss of appetite, malnutrition, impaired interpersonal communication and social interactions, and perhaps even depression, thereby negatively affecting the daily lives of sufferers (4,5).

When only xerostomia was considered the overall prevalence in the studies considered in this review ranged from 0.01% (8) to

45% (2). For hyposalivation, the prevalence rate ranged from 0.02% (3) to 40% (13). For both situations, ageing seems to be determinant of its occurrence, studies have shown what appears to be an increase in the prevalence of dry mouth with increasing age. Diverse factors have been investigated to clarify the potential association of age with such oral conditions. However, most studies were conducted in samples of older people and no population-based studies were conducted in children or adolescents sample. Moreover, a few studies conducted in both populations of young adults and older adults have found prevalence differences between them. Thomson et al. (15) found a prevalence of 20% of xerostomia in an older population and 10% in an adult population (4). Similar findings were observed by Benn et al. (5) in a nationally representative sample, in which the prevalence of xerostomia was 5% in the 18-24 age group and 26% in those aged 75 years or older, but there was not a consistent age gradient. These findings provide further evidence that xerostomia, even in divergent proportions, could not affect only older people, and that perhaps the lack of knowledge of its occurrence by young adults is because younger age groups have become aware of it only over the last decade or so. Hence, it is difficult to establish age-standardized population prevalences of dry mouth and what kind factors really modify salivary conditions in young population.

There is evidence that the association with age is not just due to the aging process itself. Aging is associated with increases in comorbid chronic medical conditions, which consequently increases the use of medications. Many of the drugs taken are associated with lower salivary flow (10,11,17,27,33). In this context, an interesting observation was the association between the number of medications taken and the prevalence of xerostomia (34-36). The prevalence of xerostomia is usually higher in individuals who take more than one medication (4,37). Factors such as changes in saliva quality, underlying diseases, and medications should be

Table 5. Meta-regression of dry mouth and subgroup analysis according to methodological characteristics.

Methodological characteristics	Prevalence % (95%CI)	p value[a]	Heterogeneity Explained (R^2)
Age of the participants		0.259	10.52%
Only adults	19.3 (12.8-25.7)		
Only elders	25.4 (20.0-30.9)		
Adults and Elders	10.8 (4.2-17.5)		
Geographic location		0.187	2.79%
Europe	20.4(14.7-26.2)		
Australasia	18.6(10.6-26.7)		
Americas	27.1 (18.7-35.5)		
Heterogeneity Explained by final model (R^2) [b]: 15.81%			

a p value of the variable in the final meta-regression model. b including both variables in adjusted meta-regression.

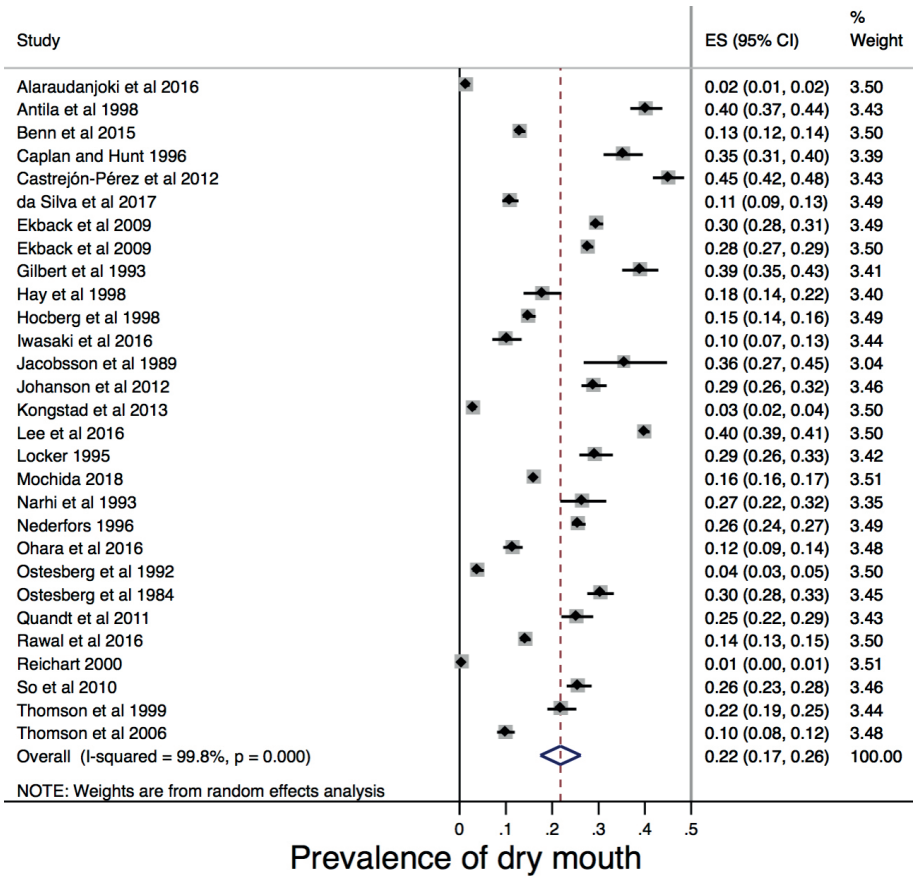

Figure 4. The overall prevalence of dry mouth (xerostomia or hyposalivation).

considered as the cause of higher subjective perception of dry mouth with aging (16). Not only polypharmacy but specific drugs present salivary flow and quality adverse effects. Antiasthmatic drugs were suggested as the main mediator of high risk of dental caries in asthmatic children and adolescent due to its high impact on salivary

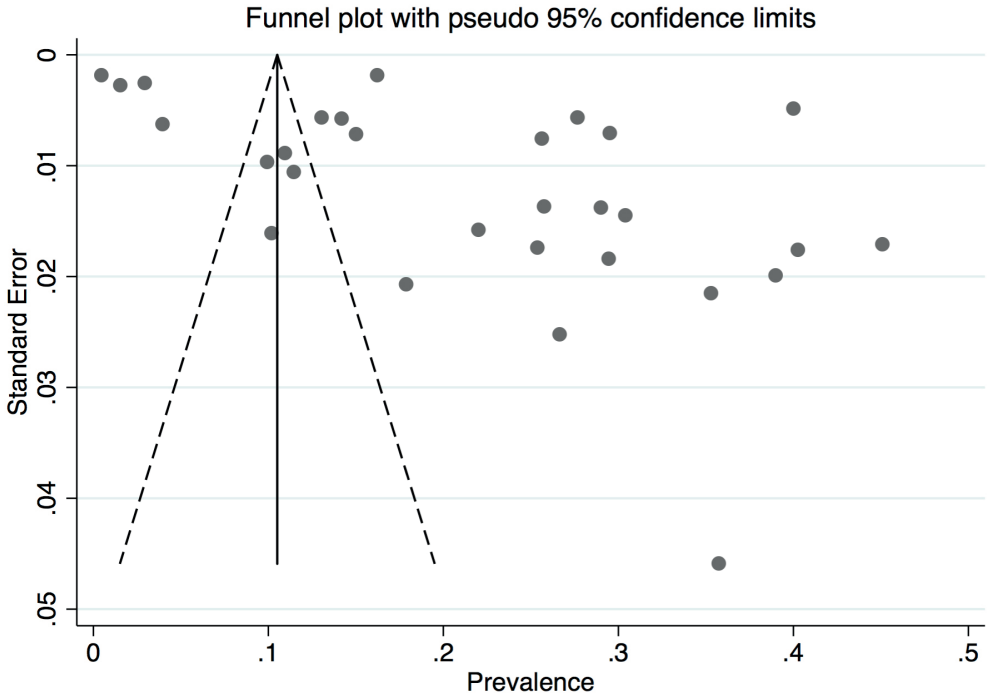

Figure 5. Funnel plot of the studies included in metaregression analysis.

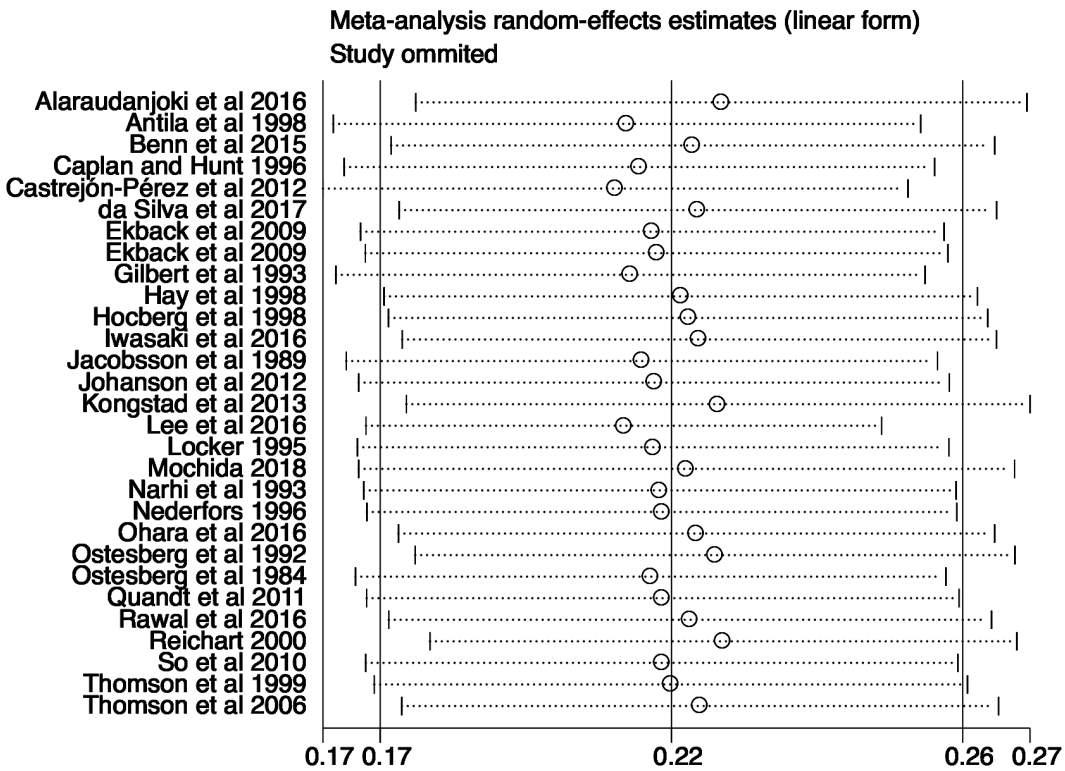

Figure 6. Estimated prevalence of dry mouth and confidence interval with random effect after the omission of the study.

conditions. Even few months using inhaled β2-agonist and corticosteroids could decrease significantly the salivary flow rate, increase dental plaque index, and decrease salivary pH (38-40), all of these consequences favor dental caries. Finally, the long-term effect of this group of medicines in salivary aspects is not known, and identify asthmatic population that used inhaled medicines in the past could be an alternative to understand life-course effects of medication on salivary flow rate.

This study has several strengths that should be considered. The first one is the inclusion of population-based studies only, excluding studies that investigated clinical or other biased samples, then the common occurrence of dry mouth in general population could be evaluated. Secondly, the analytical approach used, including the meta-analysis, allowed estimating the global prevalence of xerostomia. Such methodology has already been used to estimate the global prevalence of halitosis (32) and its use here by regarding dry mouth highlights the importance of the approach for obtaining global estimates of the impact of major oral conditions. The high heterogeneity found in all meta-regressions conducted evidence the lack of a standard criteria for population-based studies aiming to assess salivary conditions. However, we used meta-regression as a tool to explain heterogeneity in prevalence among studies. Although there was no statistical association, a considerable amount of heterogeneity were explained after considering age-groups and geographic location of the studies as potential sources of heterogeneity. Finally, the studies included showed high quality, since just six studies of all included do not fulfill all items as "yes" in the JBI critical appraisal checklist.

Besides the strengths stated, our findings should be interpreted with caution. Firstly, the Egger test and the funnel plot revealed publication bias, although the main databases for the outcome had been searched and an extensive search had been conducted this could suggest a lack of information of unpublished studies or grey literature. Even though, a great variety of studies were screened (4,414 articles). Moreover, the chosen databases included the main peer reviewed journals of the field and probably all high-quality population-based salivary studies were included in our research. Secondly, even adopting strategies to collect detailed information of all studies, as send e-mail to authors, eight potential articles were excluded due not provide prevalence data, and it is not clear their influence on the overall result. Moreover, language restriction was applied and some specific countries prevalences were not considered, but only three articles were excluded by such reason, being in Hebrew, Chinese and Hungarian. Finally, we cannot fully explain the heterogeneity found based on the included variables. Hence we encourage the development of further studies addressing other potential sources of heterogeneity in salivary research.

Table 6. Overall prevalence of Xerostomia and Hyposalivation and subgroup analysis according to methodological characteristics

Methodological characteristics	Xerostomia	p[a]	Hyposalivation	p[a]
	Prevalence % (95%CI)		Prevalence % (95%CI)	
Age of the participants		0.469		0.220
Only adults	20.8(10.6-30.9)		26.0(-0.5-56.0)	
Only elders	27.2(21.4-33.0)		20.0(13.0-27.0)	
Adults and elders	13.4(11.3-15.5)		3.0(2.0-4.0)	
Geographic location		0.327		
Europe	22.7(13.2-32.2)		20.0(14.0-26.0)	0.238
Australasia	22.3(14.0-30.6)		15.0(8.0-21.0)	
Americas 25.9(17.2-34.7) 35.0(31.0-40.0)				
Heterogeneity (I^2):	99.8%		99.4%	
Heterogeneity Explained (R^2)[b]:	13.82%		9.15%	

[a] p-value of the variable in the final meta-regression model. [b] including both variables in adjusted meta-regression.

The studies included were conducted mostly in high-income countries, except for one study in Mexico. Considering that the occurrence of chronic diseases and aging are rather socially determined, and social inequality manifests differently and perhaps more acutely in poorer countries, it is possible that the overall dry mouth prevalence estimate may have been different had more data from those countries been available. It is also important to emphasize the need for more information from prospective cohort studies, including from younger populations (34) and consider the high presence of specific chronic diseases, such asthma that could influence xerostomia through medicines, in order to better understand the history of dry mouth and its effects (9).

Another important factor to consider is that the estimated prevalence rate highly depends on the method used to measure dry mouth. Xerostomia is not necessarily accompanied by lower salivary flow rate (7,10,13). In this context, Thomson et al. (15) reported that xerostomia and hyposalivation occurred together in only 6% of their overall sample, and that this was equivalent to only one in six of the 36% of individuals who had either condition. The measurement methods used may over- or underestimate xerostomia, a fact widely discussed by Thomson et al. (21). These findings emphasize the need for further work on existing and new clinical measures, including the most recent ones working with scales for epidemiological use to measure the prevalence of xerostomia. Alternatively, researchers may be required to reach a consensus on which of the many currently available measures should be used.

There is still much to find out about dry mouth and its associations (41). Despite diverse approaches to the condition's measurement, just over one in four people in adult age or older suffer from xerostomia, with higher rates observed among elderly.

Resumo

O objetivo do estudo é revisar sistematicamente a literatura afim de estimar a prevalência global de xerostomia/hiposalivação em estudos epidemiológicos. Uma busca eletrônica foi conduzida até Fevereiro de 2018 sem restrições de linguagem. Um total de 5760 títulos foram inicialmente identificados e somente vinte e nove artigos foram incluídos na revisão e meta-análise após dois revisores independentes aplicarem os critérios de seleção. Os artigos foram extraídos das bases de dados PubMed/Medline e Web of Science. Os critérios de elegibilidade incluíram investigações originais de estudos observacionais de base populacional os quais reportaram a prevalência de xerostomia ou dados que permitissem o cálculo da prevalência de xerostomia e/ou hiposalivação. Estudos realizados em populações com condições de saúde específicas, revisões de literatura, relato de casos e estudos antropológicos, assim como, conferências ou comentários foram excluídos. Tamanho amostral, localização geográfica aonde foi realizado o estudo, desenho do estudo, idade da população estudada, métodos de diagnóstico e o critério de avaliação para determiner xerostomia e/ou hiposalivação foram extraídos para a meta-análise e metaregressão. Análise de meta-regressão multípla foi realizada para explorar a heterogeneidade entre os estudos. A prevalência global estimada de boca seca foi de 22.0% (95%IC 17.0-26.0%). Uma maior prevalência de xerostomia foi observada em estudos realizados exclusivamente em populações idosas. Apesar de diferentes abordagens utilizadas para mensurar as condições de interesse, cerca de uma em quatro pessoas é acometida por xerostomia, com taxas mais elevadas sendo observadas na população idosa. Além disso, os métodos de mensuração podem ter super- ou subestimado os valores de xerostomia. Os achados do presente estudo salientam a necessidade de mais estudos acerca das existentes e novas formas de avaliação clínica, os quais serão úteis para determinar qual é a mais confiável para as perspectivas clínicas e epidemiológicas.

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