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REVIEW

Is depression associated with oral health outcomes in adults and elders? A systematic review and meta-analysis

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Abstract

Objectives To systematically review the literature in order to investigate association between depression and oral diseases.

Material and methods Electronic searches were performed in five databases. Studies testing associations between depression and oral diseases as either exposure or outcome were included. Oral disease variable included any tooth loss or edentulism, periodontal disease, and dental caries.

Results A total of 2504 articles were identified in the electronic database search. Sixteen studies were included in this systematic review being 14 included in the meta-analyses. Eleven studies considered oral health as outcome, whereas three studies considered depression as an outcome variable. Depression was associated to dental caries, tooth loss, and edentulism. Pooled estimates showed that depression increased the odds of dental caries (OR 1.27; 95% CI 1.13–1.44), tooth loss (OR 1.31; 95% CI 1.24–1.37), and edentulism (OR 1.17; 95% CI 1.02–1.34), respectively. When the oral diseases were tested as independent variable and depression as outcome, associations with both edentulism (OR 1.28; 95% CI 1.06–1.55) and periodontal disease (HR 1.73; 95% CI 1.58–1.89) were found.

Conclusions The results of our systematic review and meta-analyses show a positive association between depression and oral diseases, specifically dental caries, tooth loss, and edentulism, in adults and elders. More longitudinal studies are required to test causal and temporal relationship between depression and oral health status.

Clinical relevance Mental and oral health are among the main disabilities worldwide. This article helps to understand more about the relationship between both conditions, highlighting the importance for both clinicians and policy makers of considering individual's psychological status in management of oral health.

Keywords Depression · Oral health · Dental caries · Periodontitis · Periodontal diseases · Tooth loss

Introduction

Depression is among the most prevalent chronic diseases in worldwide. In 2015, this mental disorder was classified as the third main cause of global disability [1]. Depression is a well-established and important risk factor for many systemic conditions, including obesity, sleep disturbance, and chronic diseases [2–4]. In addition to the general health conditions, oral diseases have also been associated with depression [5–11].

Nowadays, oral diseases are still considered a public health problem with substantial economic burden. A study published in 2018 estimated an average of 4.6% of global health expenditures related to treatment expenditures costs of dental diseases [12]. Kassebaum and coworkers [13–16], through a systematic review about global burden of the most prevalent chronic diseases, observed a worldwide prevalence of 34.1%, 7.4%, and 4.1% for untreated dental caries, severe periodontitis, and tooth loss, respectively. Specifically, untreated dental caries presented a prevalence of 41.5% (15–49 years of age), 37.8% (50–69 years of age), and 35.1% (more than 70 years of age) for adults and seniors, respectively. In these same age groups, prevalence of 6.6%, 18%, and 15.1% were identified for severe periodontal disease. In relation to tooth loss, 1.4%, 10.1%, and 23.7% of prevalence were observed for age groups aforementioned [16].

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The association between mental and oral health has been discussed through biological and behavioral mechanisms. In relation to behavioral component, a positive contribution of depression to poor oral health by acquisition and maintenance of harmful oral habits [6, 17, 18], poor dental health [19], and dental attendance pattern [6] has been discussed. The biological component seems to play an important role related to changes in the salivary immunity [20]. In addition, a positive association between the growth of lactobacilli and use of antidepressant medication when dental caries was considered as oral health outcome have been found [21].

In the last years, most studies have drawn attention to a contribution of depression to poor oral health status [5, 6, 8–10, 22–28]. Conversely, there are researchers investigating a possible influence of oral health conditions on depression [11, 17, 29, 30], suggesting a bi-directional relationship between oral health and mental disorders. In view of the relevance of depression and oral health, and the lack of consensus about the association between these conditions, a study that summarizes the literature is of great importance.

Thus, the aim of this study was to perform a systematic review of the literature and meta-analysis in order to investigate an association between depression and oral health.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed for this systematic review [31].

Review questions

The following review question was performed for this systematic review:

– Is there an association between depression and oral health conditions (dental caries, periodontal disease, and tooth loss) in adults and elders?

The strategy of search was carried out based on the prespecified question with use of relevant MeSH terms following the PICO model: (a) P: representative population-based studies; (b) I: individuals with major depression disorder; (c) C: individuals without depression; (d) O: dental caries/periodontal disease/tooth loss (including edentulism). Detailed search in each specific database can be found in the Table 1.

Inclusion and exclusion criteria

Original cross-sectional and longitudinal prospective and retrospective observational studies were included. Studies should have investigated an association between major depression disorder and oral health conditions (dental caries and/or periodontal disease and/or tooth loss). In order to ensure adequate power to detect statistical significance and the representativeness of the sample, the study should present details regarding sample selection, or the study should clearly describe the representativeness the sample (e.g., representative subsample of a national survey).

Studies of specific sample, such as psychiatric populations, individuals with periodontitis, children or adolescents, and populations comprised only by pregnant women, and sample of people with learning disability were not included. Studies that described sample as convenience were excluded. Additionally, case-control studies, reviews, technical reports, case reports and series, abstracts from conferences, letters to the editor, animal studies, in vitro studies, and qualitative studies were not considered.

Definitions/criteria considered for a diagnosis of depression or anxiety

As criteria for a diagnosis of depression, studies with a primary diagnosis of depression, including clinical diagnoses or diagnostic criteria through validate tools, were selected. When measures of lifetime and current diagnoses were presented, a preference was given for current diagnoses using validate tools. Other mental disorders and dental phobias were not included.

Definitions/criteria considered for a diagnosis of oral diseases

In relation to oral diseases, only those considered as public health problem with a global burden were included. Therefore, studies that presented dental caries, periodontal disease, or tooth loss as outcome or as exposure were considered. As inclusion criteria, oral health should have been evaluated by self-reported measures or clinical diagnoses. When measures of self-report or clinical diagnoses were presented, a preference was given for clinical diagnoses. In addition, when more than one category of oral disease was presented; the most severe was chosen. Tooth loss and edentulism were considered separately. Studies that explored other oral diseases including erosion, dysfunction temporomandibular, or xerostomia were not included. Studies of qualitative measures related to dental outcomes such as poor oral health were also excluded.

Search strategy, data collection and quality assessment

An electronic search was conducted in PsychInfo, PubMed, Scielo, Scopus, and Web of Science, without language restrictions and with no initial date restriction until 20 April 2018.

Table 1 Search strategies used according to specific databases. 2018

Database	Key words
PsycInfo	("Depression" OR "depressive disorder not otherwise specified") AND ("Dental Caries" OR "Periodontal Diseases" OR "Periodontitis" OR "Tooth Loss" OR "Edentulism" OR "Dental Status" OR "Oral Health")
Pubmed	((("Depression"[all]) OR ("Depressive Disorder"[all])) AND (("Dental Caries"[all]) OR ("Periodontal Diseases"[all]) OR ("Periodontitis"[all]) OR ("Tooth Loss"[all]) OR ("Edentulism") OR ("Dental Status"[all]) OR ("Oral Health"[all]))
Scielo	("Depression" OR "Depressive Disorder") AND ("Dental Caries" OR "Periodontal Diseases" OR "Periodontitis" OR "Tooth Loss" OR "Edentulism" OR "Dental Care" OR "Dental Status" OR "Oral Health")
Scopus	TITLE-ABS-KEY ("Depression" OR "Depressive Disorder") AND TITLE-ABS-KEY ("Dental Caries" OR "Periodontal Diseases" OR "Periodontitis" OR "Tooth Loss" OR "Edentulism" OR "Dental Care" OR "Dental Status" OR "Dental Health")
Web of Science	TS = ("Depression" OR "Depressive Disorder") AND TS = ("Dental Caries" OR "Periodontal Diseases" OR "Periodontitis" OR "Tooth Loss" OR "Edentulism" OR "Dental Care" OR "Dental Status" OR "Oral Health")

The strategies of search for specific databases are presented in Table 1. All references were managed in the software EndNote X7 (Thomson Reuters, New York, NY, USA). Duplicate references were identified and excluded. Based on the inclusion and exclusion criteria, two reviewers independently (MGC and MTG) screened titles and abstracts. In case of disagreement, a consensus was determined by discussion after a comparison of the lists of the included studies. In the next step, the same two reviewers read the full texts of the articles, reviewing according to the inclusion and exclusion criteria. Both articles excluded and reasons for the exclusion were recorded (Table 2). After this, the reviewers also performed a hand search in the reference list of the included studies.

In order to perform the data collection, predefined worksheets were employed independently by the two reviewers. Data related to study identification (first author's name and year of publication), location, sample characteristics, study's design, and information regarding exposure and outcomes variables were extracted. Statistical method and effect measures used, adjustments performed, and confounding factors considered were recorded. When necessary, authors where contacted and questions about the study were clarified.

The methodological quality assessment of the included studies was performed using the Critical Appraisal Checklist for observational studies referred by The Joanna Briggs Institute (JBI) [58]. The checklist is comprised of ten items, which should be answered with "Yes," "No," or "Unclear" by reviewers. The sum of the number of "Yes" answers defined the overall score for each study, ranging from 0 to 10. Studies were classified as follows: low quality (0–3 scores); medium quality (4–6 scores); and high quality (7–10 scores). The data extraction and the quality assessment process were performed by the same two reviewers independently, who matched the information collected and discussed cases of disagreement.

Statistical analysis

For each oral disease, distinct meta-analyses were performed, considering the direction of association presented in the study. If a study presented two or more variables of interest, data were also analyzed independently. If a study presented more than one category for the variable of interest, it was considered the most severe category. For meta-analysis, preferably adjusted results were included. When it was not possible, crude result estimates were considered or calculated. Odds ratio (OR) was used to measure effect size with 95% confidence interval (CI). Relative risk measures presented in studies were converted to ORs [59]. Fixed- and random-effects models were used to estimate pooled OR. The random-effects model was chosen in the presence of heterogeneity [60]. Heterogeneity was evaluated with the I2 statistic and considered when I2 was more than 50%. Sensitivity analyses were used to observe the effect of each study on the pooled results. Data were analyzed using the software Stata 12.0 (Stata Corp, College Station, TX, USA).

Results

The searches performed in the electronic database presented 2504 potential articles, of which 1127 were duplicates. A first screening was performed for title and abstract in 1377 articles, including 44 studies. In the second screening, the studies received full-text reading, and 28 publications were excluded (Table 2). Therefore, 16 studies were included in this systematic review and 15 studies were included in this meta-analysis. The reason for not including the meta-analysis of one study was missing data for the estimate of effect measures [60]. Figure 1 presents the flow chart of study inclusion process according to recommended by PRISMA statement. Main characteristics of all studies included in the systematic review are presented in Tables 3 and 4, considering the direction of association presented in the studies.

Twelve studies explored the association considering depression as an exposure variable to oral disease. Of these, 11 were included in the meta-analysis. Four studies tested the association considering oral disease as an exposure variable

Table 2 Excluded articles and main reason for exclusion. 2018

Study	Setting	Reason for exclusion
Ababneh et al. 2010a [32]	Jordan	Case-control design
Ababneh et al. 2010b [33]	Jordan	Without sample calculation
Alkan et al. 2015 [34]	Turkey	Without sample calculation
Almomani et al. 2017 [35]	Jordan	Qualitative measures of oral health
Bertoldi et al. 2018 [36]	Italy	Specific sample (patients with periodontal disease)
Coles et al. 2011 [37]	Scotland	Without sample calculation
D'Avila et al. 2017 [38]	Brazil	Only root caries
Dirik et al. 2006 [39]	Turkey	Convenience sample
Ehrenthal et al. 2016 [40]	Germany	Specific sample (patients with periodontal disease)
Hayashi et al. 2001 [41]	Japan	Convenience sample
Johannsen et al. 2006 [42]	Sweden	Case-control design
Kim et al. 2017 [43]	Korea	Qualitative measures of oral health
Kjellström et al. 2017 [44]	Sweden	Case-control design
Koyanagi et al. 2016 [45]	47 low- and middle-income countries	Data presented by a previous study
Kumar et al. 2015 [46]	India	Without sample calculation
Li et al. 2011 [47]	China	Chinese language
Marques-Vidal et al. 2006 [48]	Portugal	Convenience sample
Mendes et al. 2013 [49]	Brazil	Without sample calculation
Moghadam et al. 2016 [50]	Iran	Case-control design
Monteiro da Silva et al. 1996 [51]	London	Convenience sample
Ng and Leung 2006 [52]	China	Convenience sample
O'Neil et al. 2014 [19]	USA	Qualitative measures of oral health
Roohafza et al. 2015 [7]	Iran	Convenience sample
Rosania et al. 2009 [53]	USA	Specific sample (patients with periodontal disease)
Shah et al. 2015 [54]	India	Specific sample (patient under dental treatment)
Solis et al. 2004 [55]	Brazil	Case-control design
Sundararajan et al. 2015 [56]	India	Case-control design
Takiguchi et al. 2016 [57]	Japan	Without sample calculation

to depression, being three included in the meta-analysis. Results are presented below according to each oral disease.

Dental caries versus depression Two studies [5, 22] assessing association between dental caries and depression were included in this systematic review. All included studies in this systematic review tested this association considering depression as an exposure variable and oral health as an outcome variable. The studies were published between 2012 and 2015, with sample sizes ranging from 390 to 4667 individuals with a high methodological quality [5, 22]. Delgado-Angulo et al.'s [22] study was conducted in high-income country (Finland), and Hugo et al.'s [5] study was conducted in middle-income country (Brazil). Both included studies had a cross-sectional design and assessed depression as a current measure through validated scales, Beck's Depression Inventory (BDI) [22] and Geriatric Depression Scale (GDS) [5]. In relation to oral health measure, both studies used clinical examination. Delgado-Angulo et al. [22] considered number of decayed teeth as a count variable, and Hugo et al. [5] used the DMFT index as a dichotomous variable (decayed teeth > 0) (Table 3).

According to pooled estimate, depression was associated with dental caries (OR 1.27; 95% CI 1.13–1.44) (Fig. 2). Both included studies statistically controlled their analyses for potential confounders, as described in Table 3. Heterogeneity among studies in the final model was not observed. Sensitivity analysis and publication bias analysis were not performed due to the low number of included studies.

Periodontal disease versus depression Five studies testing the association between periodontal disease and depression were included in this systematic review. Of these, four considered depression as exposure and periodontitis as outcome in their analyses [22–24, 27]. These four studies had a cross-sectional design, were conducted in high-income countries (Finland, the USA, Korea), and were published between 2003 and 2015. The sample sizes ranging from 701 to 63,540 individuals. Depression was

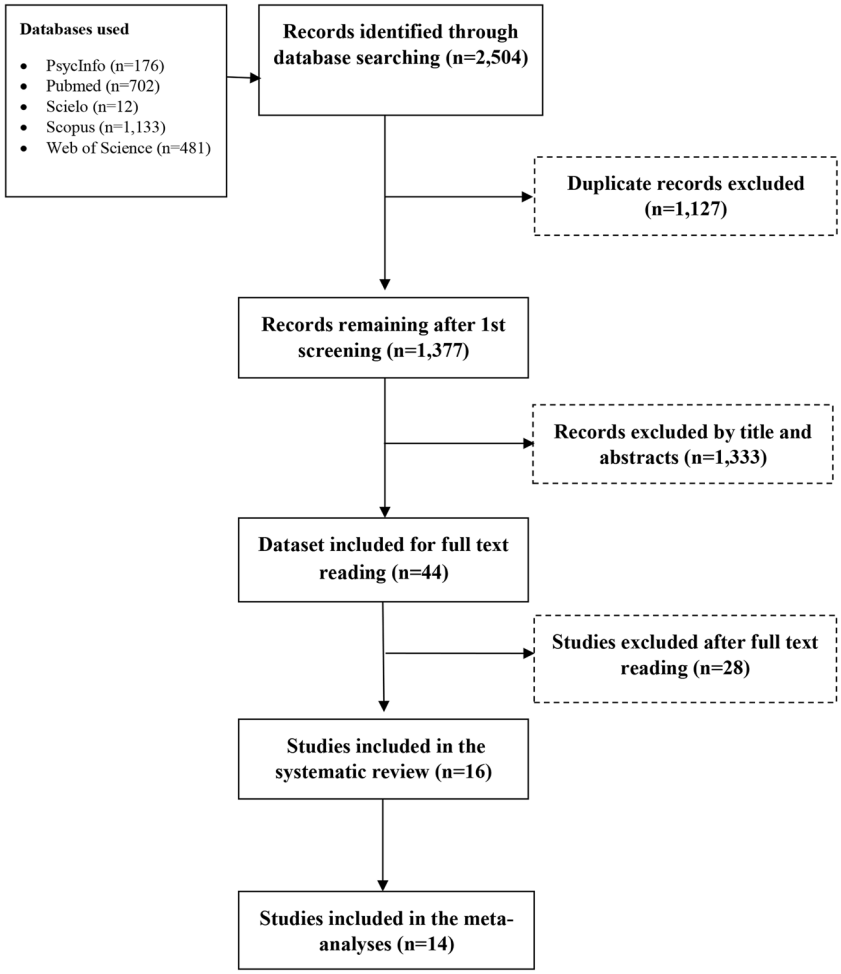

Fig. 1 Flow chart of studies selection according to PRISMA statement

measured using validated scales, specifically the BDI, the GDS, and the World Health Organization Composite International Diagnostic Interview, auto version 2.1 (CIDI-Auto). Park et al. [27] assessed lifetime diagnosis of depression through self-report. Periodontal disease was assessed with clinical examination considering periodontal pocket depth ≥ 4 mm [22], clinical attachment loss ≥ 4 mm [23], periodontitis severity using the Community Periodontal Index, and horizontal bone loss > 0 mm using panoramic radiographs [24]. Regarding the methodological assessment, three studies presented a high quality [22, 23, 27] and one study presented moderate quality [24]. In the meta-analysis, the pooled estimate does not show an association (OR 0.96; 95% CI 0.84–1.10) between depression and periodontal disease (Fig. 3). All included studies statistically controlled their analyses for potential confounders, as described in Table 3. Heterogeneity among studies was not found (0%). Sensitivity analysis showed that omission of any study would not become positive the association as presented in Fig. 4. Due to the low number of included studies, meta-regression, Funnel plot, and Egger test were not performed.

Only one study, conducted in Taiwan (a high-income country), investigated periodontitis as a risk factor for depression employing a longitudinal design, with a high methodological quality and more than 60,000 participants [29]. This study assessed both oral and mental health trough medical diagnoses using the International Classification of Diseases (ICD). After a 10-year follow-up period, Hsu and coworkers [29] observed that periodontitis increased the risk of subsequent depression (HR 1.73; 95% CI 1.58–1.89) (Table 4).

Tooth loss versus depression Five studies [6, 8, 9, 25, 26] investigated the association between tooth loss and depression. All included studies in this systematic review tested this association considering depression as an exposure variable for tooth loss. Four studies were conducted in high-income countries [6, 8, 9, 26], specifically in the USA and in Chile, and one study was conducted in Latin American and Caribbean cities including high- and middle-income countries [25]. The studies were published between 2012 and 2015, with sample sizes ranging from 1553 to 5,419,019 individuals. All studies presented a high methodological quality [6, 8, 9, 26], with the exception of Singh' study [25] which was classified as

Table 3 Main characteristics of the studies selected for the systematic review and meta-analysis with oral health as outcome. 2018

Author/year	Country/study design	Sample characteristics	Measure of Depression (cutoff)	Measure of oral health (cutoff)	Statistical analysis (effect measure)	Adjustment variables	Results	Quality of the evidence
Dental caries								
Delgado-Angulo et al. 2015 [22]	Finland/cross-sectional	4667 subjects (≥30 years)	21-item modification of the BDI (≥10 points)	Clinical examination: Number of decayed teeth (count variable)	Negative binomial regression (rate ratio)	Sex, age, marital status, education, monthly income, sugar consumption, tooth brushing frequency, dental attendance, smoking status, diabetes, antidepressant medication use	Positive association (RR 1.25; 95% CI 1.07–1.45)	High
Hugo et al. 2012 [5]	Brazil/cross-sectional	390 subjects (≥60 years)	GDS (≥6 points)	Clinical examination: DMFT index (decayed teeth >0)	Multivariate Poisson regression (prevalence ratio)	Sex, age, education, monthly income, geographic location, marital status, oral hygiene care, medication use, smoking, biofilm, saliva flow, number of teeth	Positive association (PR 1.31; 95% CI 1.07–1.60)	High
Periodontal disease								
Delgado-Angulo et al. 2015 [22]	Finland/cross-sectional	4673 subjects (≥30 years)	21-item modification of the BDI (≥10 points)	Clinical examination: PPD ≥4 mm (count variable)	Negative binomial regression (ate ratio)	Sex, age, marital status, education, monthly income, dental attendance, plaque accumulation, smoking status, coronary heart disease, diabetes, antidepressant medication use	Positive association (RR 0.96; 95% CI 0.88–1.05)	High
Khambaty and Stewart 2013 [23]	USA cross-sectional	1979 subjects (20–-39 years)	CIDI-auto (cutoff not specified)	Clinical examination: one or more tooth sites with loss of attachment ≥4 mm	Logistic regression analysis (odds ratio)	Age, sex, race–ethnicity, education, diabetes, pregnancy	Depression was not associated with periodontal disease (OR 0.92; 95% CI 0.42–2.02)	High
Park et al. 2014 [27]	Korea/cross-sectional	6139 subjects (≥19 years)	Self-report: lifetime diagnosis of a depressive disorder	Clinical examination: CPI—severity (periodontal bleeding, calculus, shallow periodontal pocket, deep periodontal pocket	Logistic regression analysis (odds ratio)	Age, sex, marital status, education, monthly household income, employment status, national health insurance status, private health insurance plan, smoking status	Positive association with maxillary periodontal bleeding category only (right and left maxillary periodontal status)	High
Persson et al. 2003 [24]	USA/cross-sectional	701 subjects (60–-75 years)	GDS (≥8 points) and history of depression disorder	Clinical examination: panoramic radiographs (horizontal bone loss >0 mm) and full-mouth periodontal pocket probing (proportional distribution of sites with pocket probing depths ≥5.0 mm)	Binary stepwise logistic regression analysis (odds ratio)	Not specified	Depression was not associated with periodontitis (OR 1.37; 95% CI 0.86–2.18)	Moderate
Tooth loss								
Okoro et al. 2012 [6]	USA/cross-sectional	80,486 subjects (≥18 years)	PHQ-8 (≥10 points) and lifetime depression	Self-report: no tooth loss, 1–5 missing teeth, 6–31 missing teeth (category included in this meta-analysis), and full tooth loss	Multinomial logistic regression (odds ratio)	Age, race/ethnicity, marital status, employment status, dental visit, smoking status, alcohol consumption, body mass index, angina pectoris, myocardial infarction, stroke, diabetes, asthma, use of assistive technology, perceived social support	Positive association between tooth loss and current depression (OR 1.83; 95% CI 1.51–2.22) and lifetime depression (OR 1.27; 95% CI 1.10–1.47)	High
Saman et al. 2014 [8]	USA/cross-sectional	5,419,019 subjects (partial	PHQ-8 (≥10 points)	Self-report: number of teeth removed because of tooth decay or gum disease	Logistic regression	Age, socioeconomic status, chronic disease, race/ethnicity, smoking status, health service deficits,	Positive association between depression and partial	High

Table 3 (continued)

Author/year	Country/study design	Sample characteristics	Measure of Depression (cutoff)	Measure of oral health (cutoff)	Statistical analysis (effect measure)	Adjustment variables	Results	Quality of the evidence
		tooth loss) (18–-99 years).			analysis (odds ratio)	employment, self-defined health status, heavy drinker, smoking status, marital status, children at home, chronic disease index, geographic locale, feel supported emotionally	tooth loss (OR 1.315; 95% CI 1.311–1.318)	
Singh et al. 2015 [25]	Latin American and Caribbean cities/cross--sectional	10,902 subjects (≥60 years)	GDS (cutoff not specified)	Self-report: Number of teeth missing. It was categorized as Yes/No.	Descriptive statistics. For this meta-analysis, crude association was calculated (odds ratio).	It was not considered	Overall, depression was not associated with tooth loss (OR 1.31; 95% CI 0.9–1.89). In descriptive analysis, only in the Mexico City, a positive association was observed.	Moderate
Urzua et al. 2012 [9]	Chile/cross-sectional	1553 subjects (35–-74 years)	Self-report: presence of depression (Yes/No)	Clinical examination: DMFT index: presence of less than 21 teeth in the mouth	Logistic regression analyses stratified for age groups: 35–44 years and 65–74 years (odds ratio).	Education, familiar income, personal income, diabetes, obesity	Positive association only in the 35–44-year group (OR 1.93; 95% CI 1.24–3.0). In the 65–74-year group, as association was not observed (OR 1.12; 95% CI 0.63–2.0)	High
Wiener et al. 2015 [26]	USA/cross-sectional	76,292 subjects (≥18 years)	Self-report: medical diagnoses of depression (Yes/No)	Self-report: more than 6 teeth removed because of tooth decay or gum disease (not all)	Multivariable logistic regression (odds ratio)	Age, sex, race/ethnicity, education, income, dental visit within the year, smoking, physical activity, diabetes, and obesity	Positive association (OR 1.23; 95% CI 1.10–1.37)	High
Edentulism								
Hybels et al. 2016 [28]*	USA/longitudinal (10 years)	943 subjects (≥65 years)	CES-D (cutoff not specified)	Self-report: no teeth in the mouth and one or more teeth	Logistic regression analysis (odds ratio)	Age, race, ethnicity, sex, education, income, health conditions, functional difficulties, self-reported physical health, cognition	Depression trajectory and edentulism was not associated. Having neither low ($p = 0.5290$) nor moderate ($p = 0.7985$) depressive symptoms was associated with dentate status.	Moderate
Okoro et al. 2012 [6]	USA/cross-sectional	80,486 subjects (≥18 years)	PHQ-8 (≥10 points) and lifetime depres-sion	Self-report: no tooth loss, 1–5 missing teeth, 6–31 missing teeth, and full tooth loss (category included in this meta-analysis)	Multinomial logistic regression (odds ratio)	Age, race/ethnicity, marital status, employment status, dental visit, smoking status, alcohol consumption, body mass index, angina pectoris, myocardial infarction, stroke, diabetes, asthma, use of assistive technology, perceived social support	Positive association between edentulism and current depression (OR 1.44; 95% CI 1.11–1.86), nut not with lifetime depression (OR 0.93; 95% CI 0.76–1.13)	High
Ren et al. 2016 [10]	China/cross-sectional		CES-D (cutoff	Self-report: having lost all of one's natural teeth (Yes/No)	Multivariate logistic	Age, sex, place of residence, education, marital status, income level,	Positive association (OR 1.21; 95% CI 1.02–1.43).	High

Table 3 (continued)

Author/year	Country/study design	Sample characteristics	Measure of Depression (cutoff)	Measure of oral health (cutoff)	Statistical analysis (effect measure)	Adjustment variables	Results	Quality of the evidence
		17,167 subjects (≥ 45 years)	≥ 10 points)		regression (odds ratio)	diabetes, hypertension, cardiovascular disease, stroke, chronic pulmonary disease, chronic kidney disease, asthma, arthritis, cognition, physical function, subjective health rating, smoking, body mass index, serum cholesterol, CRP level	When serum cholesterol, CRP level variables were considered; this association was vanished (OR 1.20; 95% CI 0.98–1.48).	
Wiener et al. 2015 [26]	USA/cross-sectional	76,292 subjects (≥ 18 years)	Self-report: medical diagnoses of depression (Yes/No)	Self-report: edentulism (any teeth present)	Multivariable logistic regression (odds ratio)	Age, sex, education, income, dental visit within the year, smoking, physical activity, diabetes, and obesity	Positive association (OR 0.95; 95% CI 0.82–1.09)	High

*Study not included in the meta-analysis. *BDI*, Beck's Depression Inventory; *CES-D*, Center for Epidemiological Studies-Depression Scale; *CID-Auto*, World Health Organization Composite International Diagnostic Interview, auto version 2.1; *CPI*, Community Periodontal Index; *GDS*, Geriatric Depression Scale; *PHQ-8*, Patient Health Questionnaire 8; *PPD*, periodontal pocket depth

moderate quality. Depression was assessed using the PHQ-8 [6, 8], the GDS [25], and self-reported measures [9, 26]. Most of the studies assessed oral health through self-reported measures inquiring about number of missing teeth or removed because of tooth decay or gum disease [6, 8, 25, 26]. Urzua and coworkers [9] assessed tooth loss through clinical examination using the DMFT index (presence of less than 21 teeth in the mouth).

In the meta-analysis, the Urzua et al.'s [9] study was included twice because the sample was stratified by age. The pooled estimate revealed an association between depression and tooth loss (OR 1.31; 95% CI 1.24–1.37) as displayed in Fig. 5. Individuals with depression presented 1.31 times higher odds of tooth loss. A prevalence of 13.4% of heterogeneity between studies was found, which is considered as low heterogeneity. All included studies statistically controlled their analyses for potential confounders, as described in Table 3. According to the sensitivity analyses, the omission of any study would not nullify the association between depression and tooth loss as indicated by Fig. 6. Meta-regression, publication bias analyses were not performed due to the low number of included studies.

Edentulism versus depression Seven studies [6, 10, 11, 17, 26, 28, 30] investigated the association between edentulism and depression, of which four tested depression as an exposure variable for full tooth loss. Three studies investigated the opposite direction of association, considering edentulism as an exposure variable for the development of depression. Five studies were conducted in high-income countries [6, 17, 26, 28, 30], one study in middle-income country [10], and other in low- and middle-income countries [11]. The studies were published between 2012 and 2017, with sample sizes ranging from 768 to 201,953 individuals with a high methodological quality, with the exception of Hybels' study [28], which was classified as moderate quality. Five studies assessed depression using validated scales, including the PHQ-8 [6], the Center for Epidemiological Studies-Depression Scale (CES-D) [10, 28], the Zung Self-Rating Depression Scale (ZSDS) [17], and the GDS [30]. One study used a self-reported measure [26], and the other study used both measures, the validated scale and the self-report [11]. Six studies assessed edentulism using self-reported measures [6, 10, 11, 26, 28, 30], and one assessed through clinical examination [17]. Five studies had cross-sectional design and two longitudinal design [28, 30].

Two meta-analyses were performed according to direction of association applied in studies' analyses. A positive association was found on the pooled estimate for depression as an exposure variable for edentulism. It was found that depressive individuals presented 1.17 times higher odds of edentulism (OR 1.17; 95% CI 1.02–1.34) (Fig. 7). All included studies statistically controlled their analyses for potential confounders,

Table 4 Main characteristics of the studies selected for the systematic review and meta-analysis with oral health as exposure (2018)

Author/year	Country/study design	Sample characteristics	Measure of depression (cutoff)	Measure of oral health (cutoff)	Statistical analysis (effect measure)	Adjustment variables	Results	Quality of the evidence
Edentulism								
Anttila et al. 2001 [17]	Finland/cross-sectional	768 subjects (according to Table 1) (55 years)	ZSDS (≥ 40 points)	Clinical examination: number of teeth missing (dentate and edentulous)	Logistic regression models were fitted separately for non-smoker and smoker men (odds ratio)	For this meta-analysis, crude association was calculated considering whole sample (odds ratio). In stratified analysis of the study, there were adjustments for self-perceived health, life satisfaction, work satisfaction, and occupational status.	An association in crude analysis was not observed (OR 1.39; 95% CI 0.98–1.97). Edentulism was independently associated with depressive symptoms among non-smoker men (OR 6.4; 95% CI 1.40–29.2).	High
Tyrovolas et al. 2016 [11]	40 low- and middle-income countries/cross--sectional	< 50-year group (122,633 subjects) and ≥ 50-year group (45,155 subjects). Total sample: 201,953 subjects (≥ 18 years)	It was defined as either or: DSM-IV and self-report of lifetime depression diagnosis	Self-report: having lost all of one's natural teeth. It was categorized as Yes/No.	Multivariable logistic regression (odds ratio)	Age, sex, country, education, wealth, alcohol consumption, smoking, disability	Positive association in < 50-year group (OR 1.57; 95% CI 1.23–2.00). In ≥ 50-year group, this association was not observed (OR 1.03; 95% CI 0.84–1.26)	High
Yamamoto et al. 2017 [30]	Japan/longitudinal	14,279 subjects (≥ 65 years)	Japanese short version of the GDS (≥ 5 points)	Self-report: number of teeth (20 or more teeth, 10–19 teeth, 1–9 teeth, or without teeth)	Multivariate logistic regression (odds ratio)	Age, sex, education, household income, marital status, present illness, exercise, frequency of going out, visits for dental treatment, GDS at baseline	Edentulism predicts an increase in the risk of depressive symptoms (OR 1.28; 95% CI 1.03–1.60)	High
Periodontal disease								
Hsu et al. 2015 [29]	Taiwan/longitudinal (follow-up period: 10 years)	Periodontitis group: 12,708 subjects. Non-periodontitis group: 50,832 subjects (> 20 years)	ICD (ICD-9-CM 523.4 × and 523.5 ×): records from a health insurance program	ICD (ICD-9-CM 296.2 ×, 296.3 ×, 300.4 ×, and 311. ×): records from a health insurance program	Multivariate Cox proportional hazards (hazard ratio)	Age, sex, diabetes, hyperlipidemia, alcohol abuse, hypertension, stroke, chronic obstructive pulmonary disease, cancer, ischemic heart disease, renal disease, anxiety, sleep disorder	Periodontitis increases the risk of subsequent depression (HR 1.73; 95% CI 1.58–1.89)	High

GDS Geriatric Depression Scale; *ICD*, International Classification of Diseases; *ZSDS*, Zung Self-Rating Depression Scale; *DSM-IV*, Diagnostic and Statistical Manual of Mental Disorders

as described in Table 3. A heterogeneity of 76.8% among studies in the final model was observed. Sensitivity analysis showed that omission of Okoro et al. [6], Ren et al. [10], and Saman et al. [8] would nullify the association found in meta-analysis as indicated in Fig. 8. Due to the low number of included studies, meta-regression, Funnel plot, and Egger test were not performed. As aforementioned, the study of Hybels et al. [28] was not included in the meta-analysis, since data for the estimate of effect measures, specifically confidence intervals, were missing.

A second meta-analyses was performed for those studies in which edentulism was tested as an exposure variable for the development of depression. The study of Tyrovolas et al. [11] was included twice in this meta-analysis because it presented the sample stratified by age. The pooled estimate revealed an association between edentulism and depression (OR 1.28; 95% CI 1.06–1.55) as displayed in Fig. 9. All included studies statistically controlled their analyses for potential confounders, as described in Table 3. A prevalence of 58.7% of heterogeneity among studies was found, which is considered as a low level of heterogeneity. Sensitivity analysis showed that omission of Yamamoto et al.'s study [30] would vanish the association between edentulism and depression as presented in Fig. 10. Due to the low number of included studies, meta-regression, Funnel plot, and Egger test were not performed.

Discussion

This systematic review and meta-analysis investigated the association between oral health and depression at a population level, exploring the direction of associations employed in the included studies. When depression was tested as an exposure variable for oral disease, dental caries, tooth loss, and edentulism were associated with depression. In this same direction, periodontal disease was not associated with depression. In opposite situation, when oral diseases were tested as independent variables, edentulism and periodontitis were associated with depression. No study that tested dental caries and tooth loss as exposure variables for the development of depression was found. This systematic review has some particularities, and thus, our results should be interpreted with caution.

Although a significant association between depression and poor oral health habits has been observed, the mechanism of this relationship is not well elucidated. Behavioral and biological components have been explored to explain association between depression and oral diseases. Throughout the years, a strong association between depression and harmful health behavior has been shown. Drinking alcohol frequently and smoking [61, 62], consuming of foods rich in fat and sugar [63], and a sedentary behavior [64] are some of the adverse habits observed in depressed people. Depression is capable to affect self-perceived oral health [27], oral health status [5–11, 65], dental attendance [6, 27], and acquisition and reinforcement of poor oral health behaviors, decreasing the frequency of tooth brushing and flossing habits [53]. In addition to the behavioral component, a biological component has also been used to explain this relationship. Studies have shown an association between depression and reduction on salivary flow, subjective oral dryness, and downregulation of immune system [18, 19, 66, 67]. Consequently, hyposalivation and induced changes in

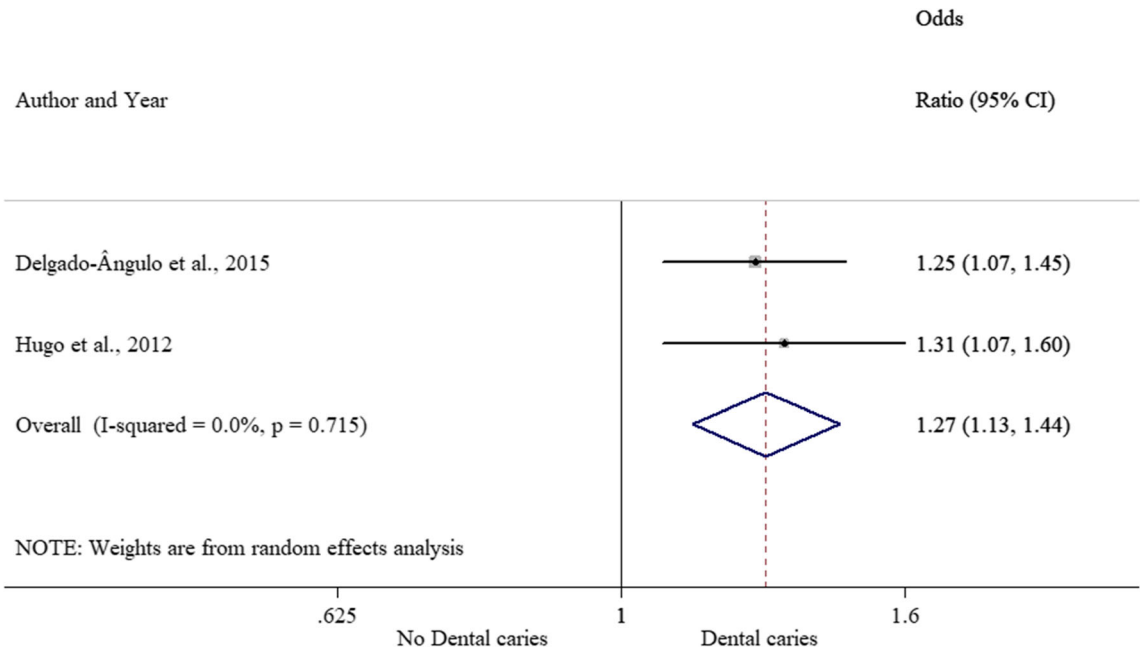

Fig. 2 Pooled effect of depression presence on dental caries status. CI confidence interval

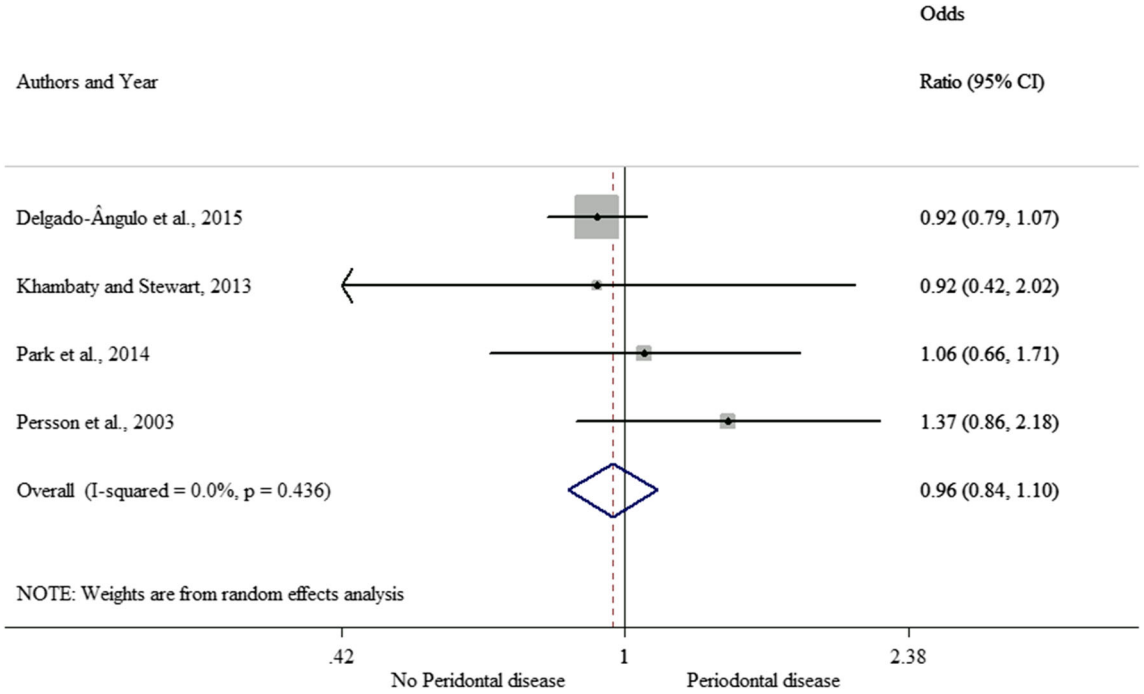

Fig. 3 Pooled effect of depression presence on periodontal status. CI confidence interval

the salivary immunity [19] increase the risk of developing oral diseases, especially periodontal disease and dental caries [67–69].

Only two studies were included that tested the association considering depression as exposure variable for dental caries. No study testing the association between dental caries as exposure variable for the development of depression was found. Our systematic review showed that depressed individuals presented more prevalence of dental caries when compared with non-depressed individuals. The selected studies presented a high methodological quality, used validated scales to measure depression and clinical examination for diagnostic of dental caries, and presented no heterogeneity among themselves. However, our result should be interpreted with caution, since only two studies were included, and more studies, preferably with longitudinal design, are necessary to strengthen this finding.

In relation to periodontal disease, when depression was considered as an exposure variable for periodontal disease, our study did not find an association between these disabilities. Our result corroborates with two previous systematic reviews. Facing the absence of association, Araújo and

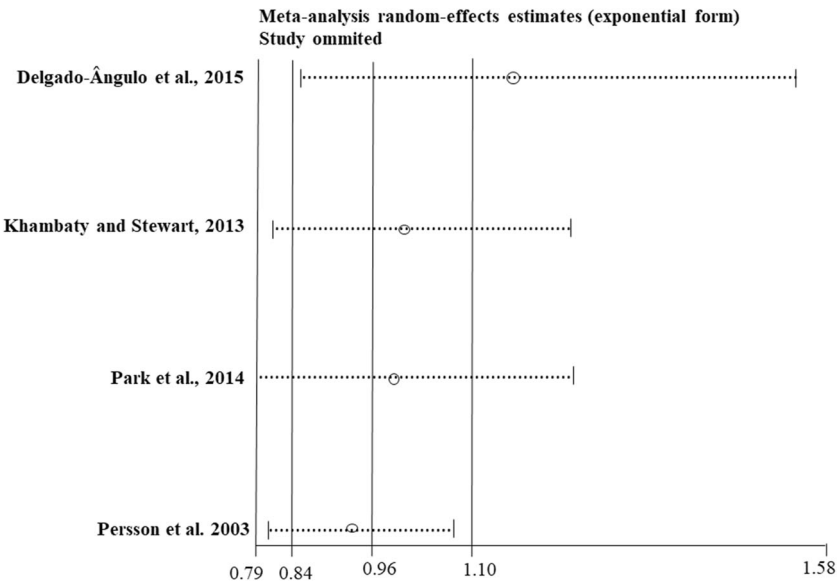

Fig. 4 Sensitivity analysis. The influence of omission of each study in the pooled effect of having depression on periodontal disease status

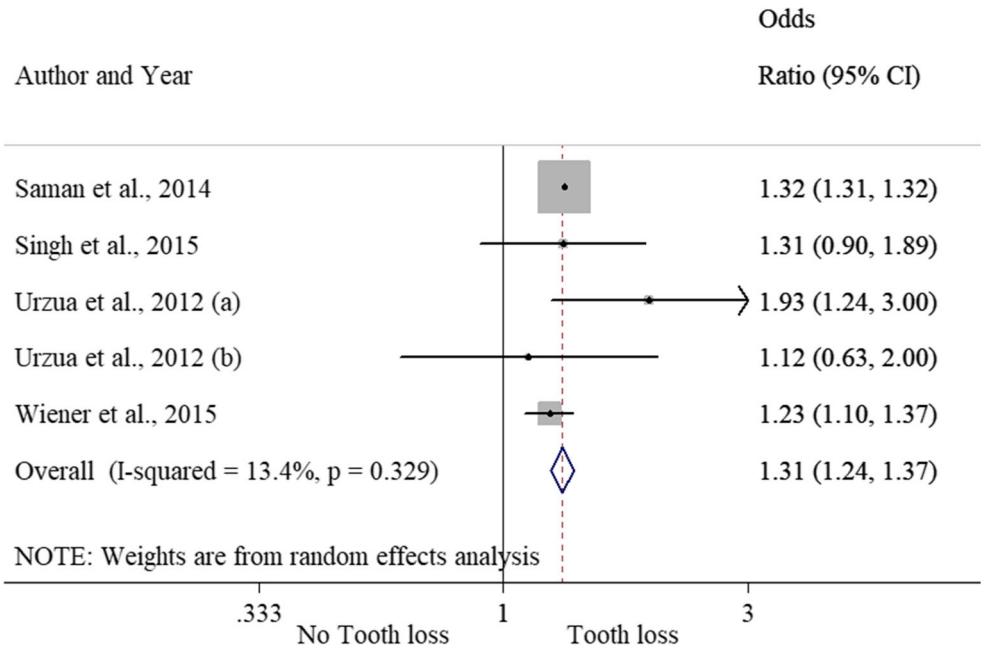

Fig. 5 Pooled effect of depression presence on tooth loss status. CI confidence interval

coworkers [70] discuss that although a low risk of publication bias was identified, there was a high heterogeneity among selected studies, including different cutoff points used to measure depression; different diagnosis criteria for periodontitis definition; and participants' age mixing younger adults and elders. Other issues pointed out by that study were related to sample. The vast majority of included studies had a convenience sample, compromising the representativeness of the findings. Other systematic review, performed by Kisely et al. [71], also found no association between depression and periodontitis. The authors had drawn attention to the methodological quality of the included studies, which was not optimal according to them, and to the high heterogeneity among selected studies including different definitions and cutoff points for measures of depression and periodontal disease. Besides that, this study included studies with convenience samples, case-control studies, and a wide range of common mental disorders, such as generalized anxiety disorder and panic disorder. Despite this, the authors report that the sensitivity analysis performed did not modify the result found. In our systematic review, only longitudinal or cross-sectional studies with population-based sample or with representative sample were included, ensuring the strength of our results. In relation to sensibility analysis, the omission of any study would not nullify the association found. Although our results corroborate the findings of previous systematic reviews, in

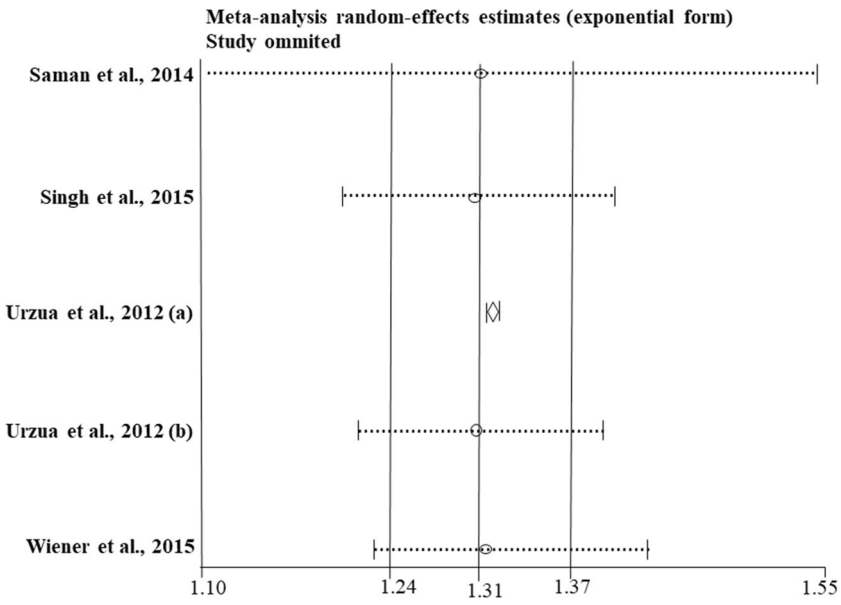

Fig. 6 Sensitivity analysis. The influence of omission of each study in the pooled effect of having depression on tooth loss status

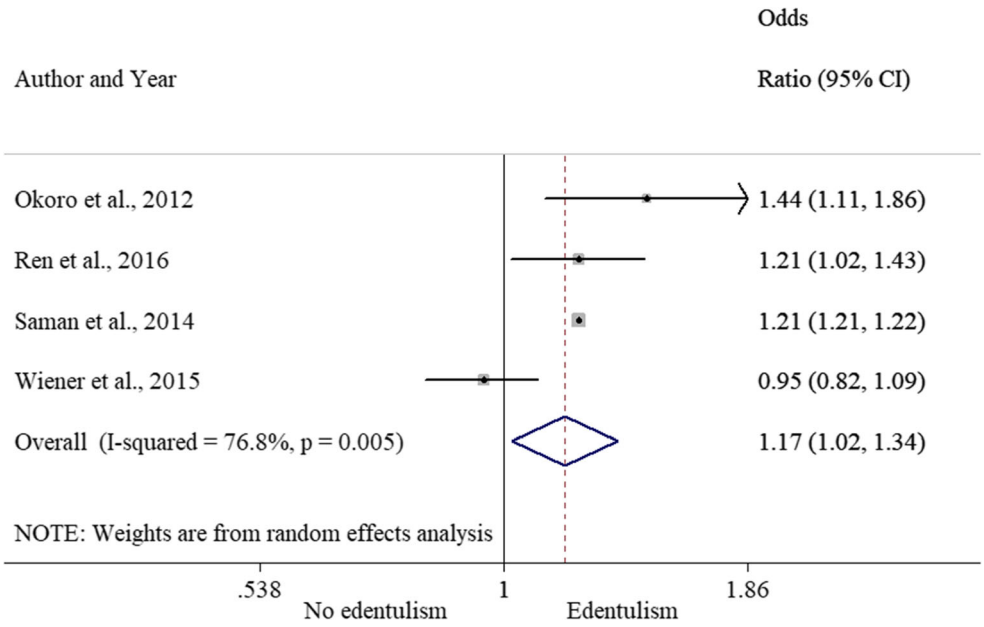

Fig. 7 Pooled effect of depression presence on edentulism status. CI confidence interval

which no association between depression and periodontitis was found, it should be emphasized that even though there was no heterogeneity between the included studies (according to the meta-analysis result), a lack of standardization between the measures in the assessment of the periodontal disease was observed. The included studies evaluated periodontal disease considering only depth of probing or clinical attachment loss. The American Academy of Periodontology recommends that periodontal disease be evaluated using measure of probing pocket depth associated with measure of clinical attachment loss [72]. The use of only one measure may lead to underestimation of disease' severity, which in combination to the cross-sectional design of the included studies possibly interfered in the results. This is particularly true when the longitudinal study performed by Hsu et al. [29] is observed. The study of Hsu et al. [29] was the only one that investigated the association of periodontal diseases as a risk factor to depression. This study has longitudinal design and high methodological quality and shows that periodontitis increases the risk of subsequent depression, regardless of demographic characteristics and presence of comorbidities, such as diabetes. More than 60,000 individuals over a 10-year follow-up period were enrolled, and the diagnostic for periodontal disease and depression was performed using the ICD and a full mouth examination. Facing the findings of our systematic review for the association between depression and periodontal

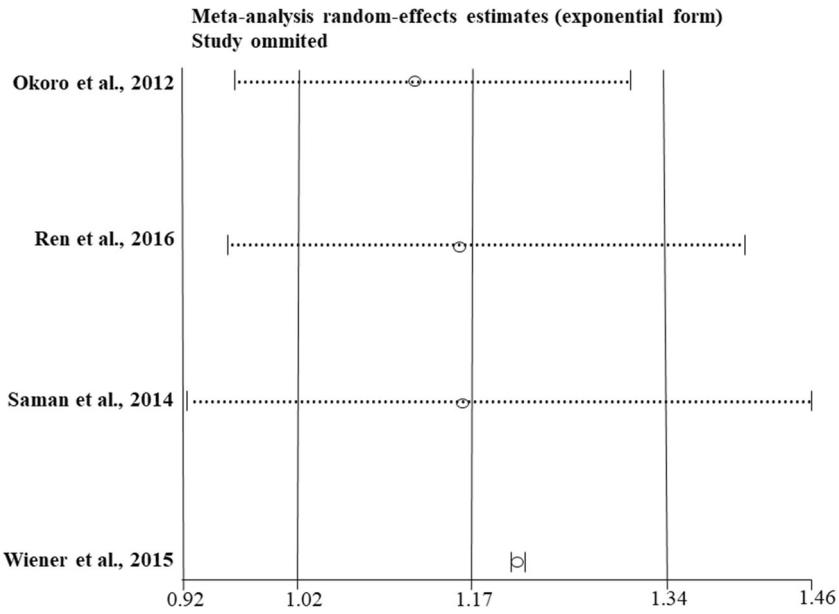

Fig. 8 Sensitivity analysis. The influence of omission of each study in the pooled effect of having depression on edentulism status

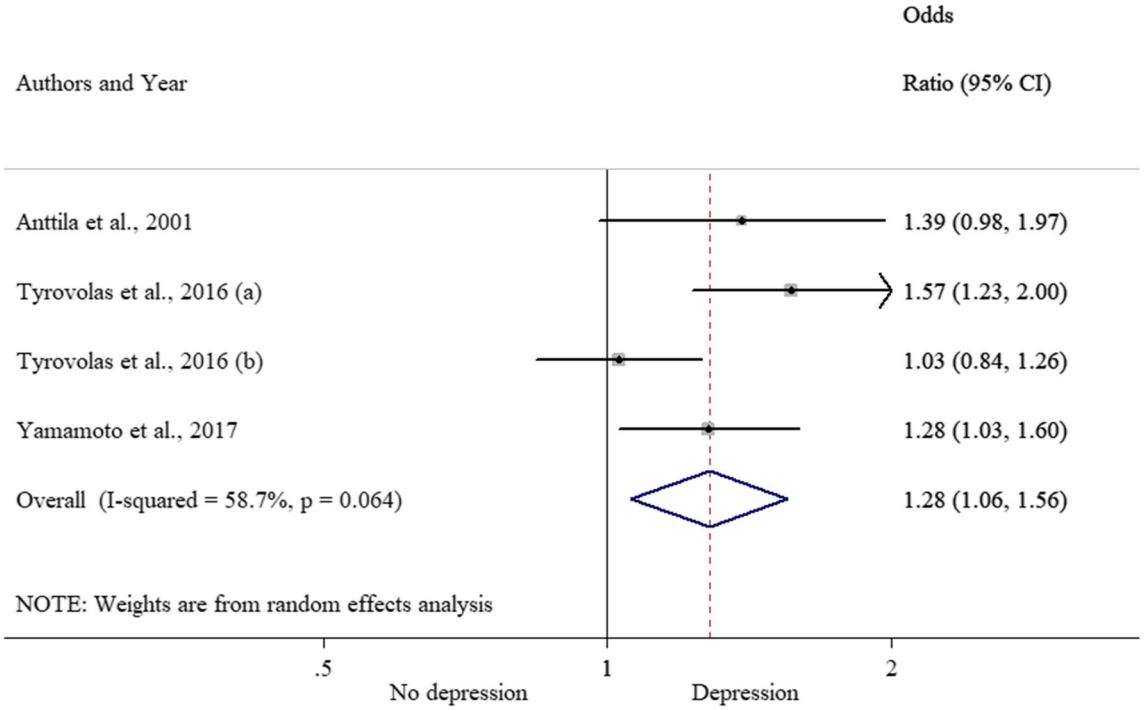

Fig. 9 Pooled effect of edentulism status on depression presence. CI confidence interval

disease, more studies with longitudinal design including samples with statistical power and measures of these two disabilities at baseline and during follow-up period should be performed, considering severity of the disease.

Untreated caries and periodontal diseases are the main causes of tooth loss [14, 16]. The present findings showed that depressive individuals are also more likely to have tooth loss than those who do not present signs and symptoms of depression. Given the results, some mechanisms linking depression with tooth loss could be addressed. First, depressive subjects are more likely to acquire or maintain unhealthy lifestyles. Harmful habits and stress, distress, and psychological resistance (*copping* and social support) are associated with periodontal disease [73], which cause destruction of periodontal ligament and loss of the adjacent supporting bone, leading to tooth loss. Second, adults with depression are less likely to have used the services of a dental health professional and to have healthy dental habits [6], which are risk factors to oral diseases. The fact is that the vast majority of studied samples were comprised of elderly people, which may explain why tooth loss was associated with depression. In 2017, Kassebaum and coworkers [16] found a global prevalence of severe tooth loss above 35% among seniors. An even higher percentage was found for people between 50 and 69 years of age [16]. In contrast, for periodontal disease, a prevalence of 18 and 15.1% was identified for people between 50 and 69 years of age and people with more than 70 years of age, respectively [16].

In the last years, a discussion about bi-directional association between depression and oral health has been drawn. However, most of the studies present a cross-sectional design, precluding temporal inferences between these two disabilities. In this systematic review and meta-analyses, only three studies presented longitudinal designs, of which two investigated the association between depression and edentulism. Each study tested one direction for this association. Researches have emphasized the possibility of oral health, along with other morbidities, to affect the subjects' mental health. A lot has been discussed about the negative predictive effect of oral health on health status and on quality of life of individuals [74], suggesting that both habits of oral and general health tend to be related to unhealthy lifestyle and, therefore, considered as potential factors associated to depression [27, 63]. In other words, it is likely that affective disorders and adverse oral health outcomes reinforce each other [71]. This hypothesis is proved in the Yamamoto et al.'s study [30], in which the authors performed a research with high methodological quality and with a longitudinal design, allowing inferring time and causality in the association tested. This study demonstrated that edentulism predicted an increase in risk of depressive symptoms among 7656 Japanese subjects over 65 years of age even after adjusting for demographic, economic, and social determinants of health. This population-based study also observed that oral health problems, such as problems with smiling, laughing, and showing teeth without embarrassment, were associated with an increase of depressive symptoms

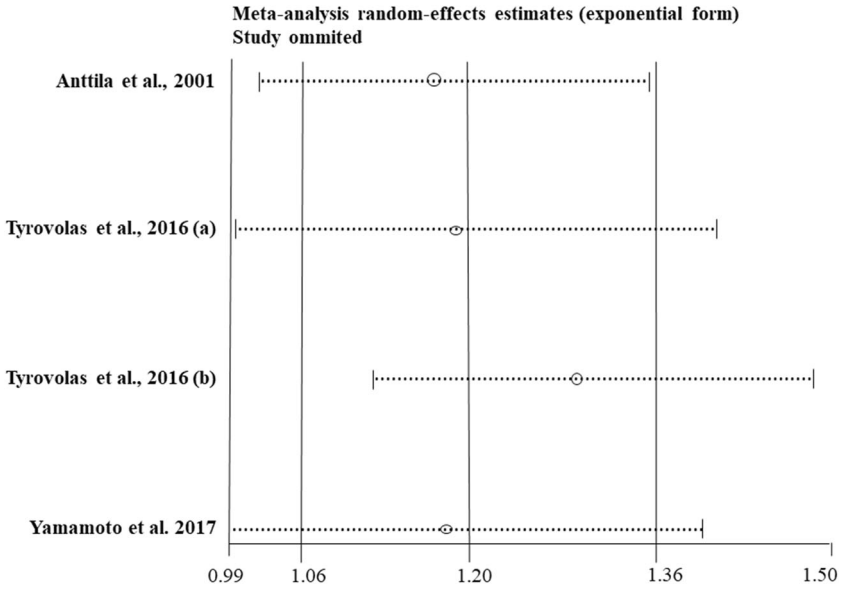

Fig. 10 Sensitivity analysis. The influence of omission of each study in the pooled effect of having edentulism on depression presence. Letter A refers to the group of participants under the age of 50 belonging to the study of Tyrovolas et al. 2016. Letter B refers to the group of participants aged 50 years or older belonging to the study of Tyrovolas et al. 2016

incidence. On the other hand, when Hybels and coworkers [28] investigated a 10-year trajectory of depressive symptoms predicting edentulism, no association was found having neither low nor moderate depressive symptoms with dentate status in a large representative sample of community-dwelling older adults in the USA. Although this longitudinal study did not find association, the authors discuss some limitations that may have interfered with the findings, including the fact that some problems with mouth conditions and tooth loss have preceded the collection of the depressive symptom information, and there are no information about oral health status at baseline. Yet according to the authors, neither information on antidepressant use nor other treatment performed or possible mediation of physical health and functioning variables were considered, underestimating the effect of depression group in these analyses. Unfortunately, the study of Hybels et al. [28] was not included on meta-analysis due to missing data about confidence intervals of effect measure.

This systematic review has some limitations. Studies conducted on pregnant women and studies based on high-risk populations, such as psychiatric patients or those with periodontal disease, were not included. Therefore, it is recommended that the findings of this study be extrapolated to these populations with caution; studies in high-risk populations may have possibly different risk factors. In addition, the vast majority of the included studies had a cross-sectional design, which limits causal and temporal inferences on the association between oral diseases and depression. However, the strength of association is one of the most well-known factors for inferring causality. Meta-analyses are capable to amplify the statistical power of analyses and are considered as robust sources of evidence. Another issue is that a tiny minority assessed the association between dental caries and depression, highlighting a gap on the literature.

Strengthening of this systematic review should be highlighted. Firstly, the vast majority of included studies presented high quality and had a larger representative sample, as well as a multivariate analysis adjusted for potential confounders. These characteristics gave a greater statistical power for included studies increasing the chance of detecting a true effect of exposure [75], reinforcing our findings. In order to identify the effect of omitting each study in the combined result, a sensitivity analysis was estimated for each oral disease. Unfortunately, due to the low number of included studies in each oral disease, publication bias among studies was not possible to investigate. In addition, meta-regression in order to identify sources of heterogeneity was also not performed for the same reason aforementioned. Lastly, our systematic review considered the direction of associations employed in each study, which led us to present our results in this way. Combining original datasets would be perfect to investigate the association between depression and oral diseases. However, the authors have not provided us these data. Therefore, we have kept the analysis in both directions, even with the limitations pointed out, such as the small number of studies considering oral disease as an exposure variable for depression. We consider that the results found in this systematic review and meta-analysis can stimulate the investigation of causal and temporal hypothesis in both ways.

The results of our systematic review and meta-analyses show a positive association between depression and oral diseases specifically dental caries, tooth loss, and edentulism in adults and elders. Although most included studies had a cross-sectional design, when only longitudinal studies were assessed, it was observed that periodontitis and edentulism increased the risk of subsequent depressive symptoms. For this reason, studies with longitudinal design should explore the association between oral and depression in both directions

in order to identify the cause and effect of this association. Besides that, it is recommended that studies should be performed not only in high-income, but in especially low- and middle-income countries, where the prevalence of depression and oral diseases is greater. This article helps to understand more about the relationship between both conditions, highlighting the importance for both clinicians and policy makers of considering individual's psychological status in management of oral health.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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