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Review article

Association between salivary characteristics and tooth wear: A systematic review and meta-analysis

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ABSTRACT

Objective: Literature was systematically reviewed to identify salivary characteristics and their association with tooth wear.
Data: A protocol was developed a priori (PROSPERO CRD42022338590). Established systematic review methods were used for screening, data extraction, and synthesis. Risk of bias and the certainty of evidence were assessed using the JBI tools and GRADE, respectively. Direct and indirect association between tooth wear and salivary components and characteristics were assessed.
Sources: MEDLINE, Embase, SCOPUS, Web of Science, CINAHL, and additional sources were searched.
Study selection: Studies reporting salivary characteristics in patients with tooth wear or models thereof were included. Animal and *in-vitro* studies and case reports were excluded.
Results: One-hundred eleven studies were included. Qualitative analyses showed a negative association between tooth wear and salivary pH and flow rate in many studies. The higher the study size the higher the chances that an association with pH and flow rate was found. Xerostomia, buffer capacity and salivary consistency/viscosity had also some degree of association with tooth wear in fewer studies. Associations with the 39 salivary components were scarcer. Random effects meta-analyses (7 studies) showed that pH levels in stimulated whole saliva were lower in patient with tooth wear compared to controls (−0.07 [−0.10 to −0.04]). However, there was not enough evidence to establish a quantitative association with flow rate. The general risk of bias was unclear and the certainty of evidence was low or very low. A large diversity of methodologies limited the inclusion of all studies in quantitative synthesis.
Conclusion: From all potential risk factors, stimulated whole saliva pH showed a negative association, both quantitatively and qualitatively with tooth wear, indicating potential usefulness of pH monitoring in these patients. Moreover, associations between flow rate and tooth wear were observed qualitatively. However, in both cases the risk of bias was mostly unclear, and the certainty of evidence was low. No causal associations could be observed.
Clinical significance: Tooth wear is a prevalent condition that may lead to functional or esthetic impairments and pain. Knowing the potential risk factors like salivary pH or flow rate and their dynamics could be relevant during tooth wear monitoring and to intervene accordingly, especially in conditions like gastroesophageal reflux disease.

1. Introduction

Tooth wear is the loss of dental structure due to mechanical and chemical factors, i.e., due to the interactions between teeth, acids, and foreign objects [1–3]. All individuals may present a certain degree of tooth wear over the course of life with a prevalence of around 29% for moderate levels and 3% for severe levels in Europe [1]. However, tooth wear is only considered pathological when the degree of dental wear does not correspond to the age of an individual—causing pain or impairments in function, aesthetics, or quality of life [3].

Among the etiological factors of tooth wear, the role of acids has been confirmed by several studies [1]. Teeth are exposed to extrinsic acids from the diet whilst on the other hand, they are vulnerable to internal gastric acids in combination (or not) with behaviours like sleep

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bruxism [4,5]. For example, a recent systematic review showed that in patients with gastroesophageal reflux disease (GERD) the odds of presenting tooth wear were 4.13 times higher than in healthy controls when GERD was objectively diagnosed (i.e., endoscopy or oesophageal pH measurements) [6]. Still, acids may not be the only one to blame; following the example above, another systematic review reported that characteristics of the saliva in these patients, such as buffering capacity and high flow rate, may help protect teeth from acidic exposure [7]. This is not surprising, since the buffering capacity of saliva (due to components like sodium bicarbonate) is known to help maintain physiological pH levels in the mouth [8].

Moreover, saliva is not only important for specific diseases like GERD; the circadian cycle of saliva creates pH fluctuations, which can reach values lower than 7 (acidic) even in systemically healthy persons during the night [9–11]. Saliva has a relatively neutral pH and when oral pH decreases it is known to promote demineralization [12]. This has been thoroughly studied in relation to caries and especially in combination with other salivary characteristics that mediate this effect [13–16]. The critical pH (5.5 on average) is not a constant value, and rather depends on other characteristics of the saliva like calcium or phosphate concentration as well [17]. Thus, while a high buffering capacity might protect teeth in people GERD, changes in flow rate and pH might facilitate tooth wear in healthy individuals.

However, despite our knowledge about pH and caries, the role of the characteristics of saliva on tooth wear is less clear. As mentioned, saliva has many factors potentially associated with protection against tooth wear, and research shows conflicting results regarding their unique contribution [18]. Therefore, the aim of this systematic review was to summarize and analyze all available evidence and identify the specific salivary characteristics that are associated with tooth wear, in both healthy and diseased individuals. A secondary aim of this review was to identify salivary characteristics that could be associated with the progression of tooth wear.

2. Materials and methods

2.1. Registration and protocol

This systematic review is reported following the PRISMA statement [19]. The protocol was written following the PRISMA-P guidelines [20] and registered (CRD42022338590) in the PROSPERO platform on the 9th of June 2022, before commencing the review process. Amendments were performed on the 06th of March 2023 since some articles were not captured by the first search string and adding additional terms improved the search strategy (the search strategy was updated previous to the publication of the amendment).

2.2. Eligibility criteria

The research question was formulated according to the following **PECOS** criteria: **Population** = Patients with (more severe/prevalent) tooth wear or *in-situ* human models thereof, **Exposure** = human saliva **Control** = for studies involving comparisons between groups, individuals with no tooth wear or less severe/prevalent tooth wear, and *in-situ or in-vitro* human models thereof were included as controls, **Outcome** = primary: degree of association between characteristics of the saliva (e.g., pH, buffering capacity, flow, etc.), and the presence or the characteristics of tooth wear; secondary: the presence of gastroesophageal reflux, consumption of acidic food or beverages, presence of bruxism, or other reported associations between salivary and oral characteristics that might be confounders of primary outcomes, **Study Designs** = primary studies in humans and *in-situ or in-vitro* studies (*in-situ* and *in-vitro* studies would only be considered if these described and analyzed characteristics of individual human saliva in an *in-vitro* experiment).

Based on the research question, studies in this systematic review were included according to the following inclusion criteria: articles reporting an association between salivary characteristics, including xerostomia, and the occurrence or characteristics of tooth wear in patients and *in-situ or in-vitro* models thereof; primary studies with individuals of any age, including children with any experimental design (e.g., observational, cross-sectional, randomized controlled trial), *in-situ* designs, and *in-vitro* designs (where characteristics of individual human saliva samples and tooth wear were studied). There was no limit for date of publication or language. Exclusion criteria were: narrative and systematic reviews; animal studies (tested on animals); case studies and case series.

2.3. Information sources and search strategy

The following databases (and search engines if different from the database itself) were used for retrieving records: MEDLINE (PubMed), CINAHL (EBSCOHost), Scopus, Embase (Ovid), and Web of Science Core Collection. Complementary to the gray literature obtained from databases, the electronic archives of the International Association of Dental Research (IADR) were also screened for conference abstracts. The first search took place on the 9th of June 2022 and was updated on the 19th of September 2022. Keywords used in different combinations for all searches were: “saliva”, “saliva characteristics”, “saliva buffering capacity”, “microbiota”, “microbiome”, “hyposalivation”, “xerostomia”, “salivary flow”, “pH”, “acidity”, “mineral”, “abrasion”, “attrition”, “erosion”, “tooth wear”, and “toothwear”. Specific search strings used per database can be found in the supplement (Table S1).

2.4. Selection and data collection process

After the searches were run, records from all databases (except for the IADR archives) were added to an online software (Rayyan; https://www.rayyan.ai/) for blind screening by two authors (VIM and TPC) [21]. Conference abstracts found in the IADR archives were manually added to a separate Microsoft Excel sheet (Microsoft Corporation, 2021. Microsoft Office Professional Plus 2021) by name, abstract, year of presentation and meeting, and authors.

The title and abstract stage of the selection process was performed as follows: first, records in Rayyan were screened for duplicates (using automatic duplicate detection), which were then manually removed by VIM when true. The screening criteria were established a priori (as outlined in our protocol) and calibrated amongst the team through a pilot test. After a discussion of the inclusion and exclusion criteria, the first 100 titles and their respective abstracts were screened by VIM and TPC, independently, in order to assess the level of agreement on interpreting the criteria, with a >85% agreement. Next, all abstracts were independently assessed by the same researchers. Conference abstracts in Microsoft excel (IADR archives' results) were independently screened for duplicates among the records in Rayyan, and the remaining conference abstracts (not duplicates) were screened for possible inclusion. Once all records were classified by both reviewers, the results were compared. Disagreements were solved through agreement.

After the title and abstract stage, full texts were retrieved when available and manually added to Rayyan. Authors were contacted in case relevant information from the full-text articles or the articles themselves could not be retrieved from either online databases, journal websites, or by analyzing the figures (using the online software webplotdigitizer version 4.6, Pacifica, United States; https://automeris.io/WebPlotDigitizer/). Once all relevant information was retrieved, the full texts were screened by both reviewers, independently. After the blind screening, the records categorized for inclusion were compared. Records classified for inclusion by both authors were immediately selected for the systematic review. Records that were classified for inclusion only by one author were discussed and selected upon consensus. The percentage of agreement regarding the full-text stage (not including abstracts or articles added at a later stage) was 80%.

Search updates were processed as follows: export files containing both the first and updated search were added to the reference manager software Mendeley Desktop version 1.19.8 (https://www.mendeley.com/search/). With the duplicate function, articles that were present in both searches were eliminated. New entries were screened for eligibility in the same way as for the first search.

References within selected full-texts were also screened using the online software Scholarcy (https://www.scholarcy.com/) to extract the reference titles from the available pdf files, which were then added to Mendeley. These references were screened and included using the same process, and inclusion and exclusion criteria described above.

Lastly, after all the relevant records were selected, these were added to an Excel sheet. Data from each individual record were extracted by VIM and a sample of these was cross-checked by TPC for consistency. No major differences in the extracted data were found. At this stage, some additional articles that were previously included were excluded from the data extraction due to relevant missing outcomes that made them not compatible with the inclusion criteria ($N = 21$).

If full-text articles were in a different language than English, Spanish, Dutch, or Portuguese, which were known by the authors, Google Translate was used to screen them for inclusion or extract their data (e.g., articles in Polish and German).

2.5. Data items

2.5.1. Outcomes

Primary outcome: association statistics, such as correlation coefficients and regression; comparison statistics; and descriptive statistics, that denote a relationship between salivary characteristics or xerostomia in patients with tooth wear or *in-situ* models thereof. These were obtained from comparison studies between groups (e.g., with and without tooth wear, with and without specific disease or disorder associated with tooth wear), prevalence studies, or correlation studies.

Secondary outcomes: any other reported association statistics, such as correlation coefficients and regression; comparison statistics; and descriptive statistics, that denote a relationship between salivary characteristics or xerostomia and other intraoral features, consumption of acidic drinks, and gastroesophageal reflux.

2.5.2. Other variables

Other variables extracted were: authors, year, location of the study, study design, age and sex of the participants, inclusion and exclusion criteria for study subjects, population type and sampling method, diagnostic criteria for tooth wear utilized (if any), the method used for saliva collection, protocols utilized previous to saliva collection (if any), times of the day at which saliva collection took place, methods utilized for measuring salivary characteristics, post-hoc analyses utilized (e.g., multiple comparisons), covariates selected for multiple regression, examiners, and blinding.

2.6. Risk of bias assessment

The risk of bias in the included studies was assessed using standard tools according to the respective study design. For observational studies (cross-sectional and cohort studies), the critical appraisal tools from the Joanna Briggs Institute (JBI) of the University of Adelaide (Australia) were utilized (https://jbi.global/).

The risk of bias was only assessed for articles in which the primary outcome matched the primary outcome of this review ($N = 49$). Other articles were assumed to have an unclear to high risk of bias with respect to the outcome of interest, since their designs were not tailored to address the research question of this study.

The risk of bias in the studies was evaluated by two reviewers, independently. The criteria and statements of each assessment tool were discussed by both reviewers before beginning the assessment. At the end of the complete independent assessment, results were compared and disagreements were solved upon discussion and consensus to achieve a final result.

2.7. Quantitative data synthesis

Articles were eligible for quantitative synthesis if a sufficient amount (at least five articles) of records were available in which the outcome measure was analyzed or was reported in a similar way (i.e. continuous data or same categories), results came from the same type of saliva (e.g., stimulated or unstimulated), tooth wear measurements were done in the same type of dentition (e.g., permanent, deciduous), and enough information was available (e.g., mean, standard deviation, sample size for comparisons). For comparison studies, additional criteria were applied: mean age differences between groups should not be larger than five years. Moreover, some information was derived or converted from other reported data, e.g., unit conversion or accepting median as mean and computing standard deviation from interquartile range. Pooled data were represented in a forest plot, and potential publication bias was explored using funnel plots.

2.8. Certainty assessment

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool was utilized for the assessment of confidence in the evidence using the GRADEpro GDT online tool (https://www.gradepro.org/). This was performed narratively, by subjectively classifying the evidence with respect to risk of bias, inconsistency, indirectness, imprecision, and publication bias, among other considerations, as previously described in the literature [22]. The analysis was done by VIM and was cross-checked by TPC.

2.9. Statistical analyses

Data were pooled using a random effects model, computing confidence and prediction intervals. Heterogeneity was calculated using I^2 and Tau^2 statistics. Statistical significance was set at $p< 0.05$.

Trim and fill approach was utilized to explore the influence of publication bias by simulating the effect of adding study results that partly counteract the funnel plot asymmetry. Sensitivity analysis was also performed by leave-one-out method to explore the effect of individual studies on the results. These approaches were only meant to partly explore the robustness of the data and not to discard the influence of bias.

Statistical analyses were performed using R version 4.2.3 (R Core Team, 2021, Boston, United States), RStudio (Rstudio Team, 2023, Vienna, Austria). Meta-analyses were performed mainly using the packages tidyverse, metafor, and meta [23]. Visualizations were obtained mainly using the packages ggplot2, meta, robvis, and cowplot.

3. Results

Ninety-eight articles and 13 conference abstracts were selected for inclusion in this systematic review and are presented in Table S1. A detailed description of the selection process is presented in Fig. 1. Articles excluded at the full-text stage and the corresponding reasons are presented in Table S2. No *in-situ* or *in-vitro* studies were eligible.As shown in Table S1, 101 studies were cross-sectional, 6 studies had a longitudinal design, 2 studies were experimental, and 2 studies were clinical trials. Twenty-six records focussed on children only, adolescents only, or a combination of both (mixed dentitions), 75 records included adults in combination with other ages or had adults only (focussed on permanent dentitions), and in the other 10 records the age group was unclear. Regarding salivary measurements, these were performed in the morning in 26 studies, the afternoon in 8 studies, and either morning or afternoon in 2 studies; in 68 records the time of the day was unclear and in 7 studies, salivary characteristics were not tested (only xerostomia

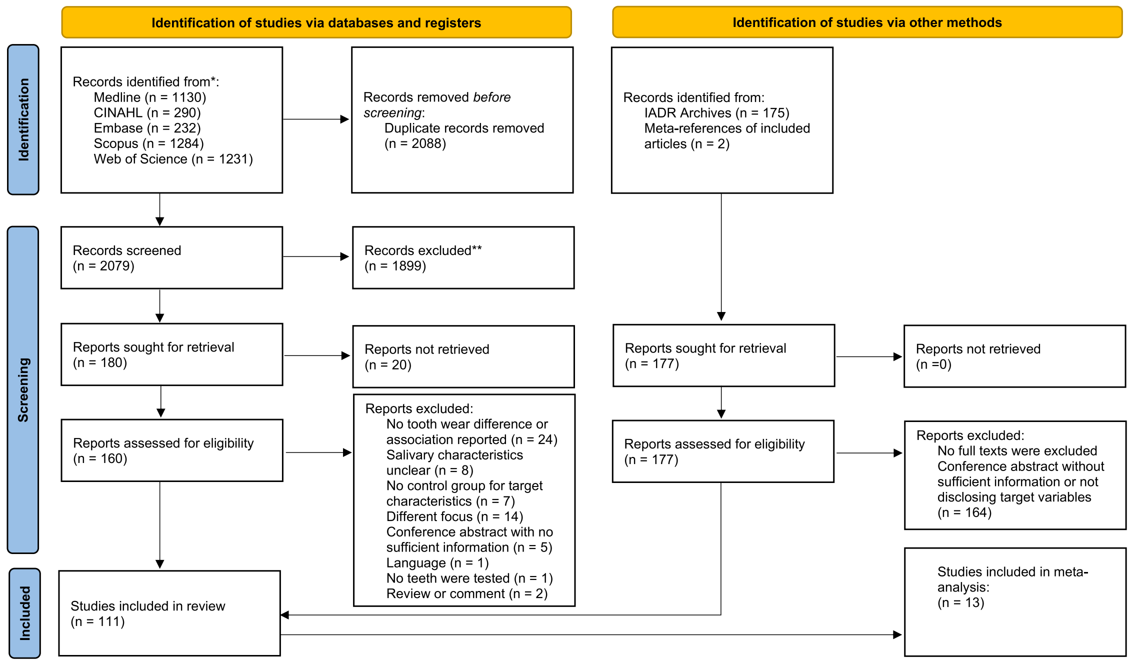

Fig. 1. PRISMA 2020 flowchart of systematic screening and selection of results. Adapted from Page et al., 2021 [19].

was assessed). Lastly, concerning location, study subjects in 11 studies were sampled from kindergartens or schools, 8 from the general population, and 21 from unclear sources; the rest of the studies had sampling performed at hospitals, clinics, and universities (including staff and students).

Regarding specific study groups, 1 study focussed on Prader-Willy syndrome, 1 study focussed on Sjögren's syndrome, 1 study focussed on chronic kidney disease, 1 study focussed on athletes, 1 study focussed on neurodevelopmental disorders, 1 study focussed on survivors of nasopharyngeal carcinoma, 1 study focused on diet, 2 studies focussed on specific occupations, 3 studies focussed on substances consumption, 5 studies focussed on asthma, 16 studies focussed on eating or psychiatric disorders, and 20 studies focussed on GERD or laryngopharyngeal reflux. Most studies ($N = 58$) reported results focussed on patients with tooth wear in general or in addition to caries (Table S3). From all these studies, 38 provided indirect data, by comparing groups from very different populations (e.g., patients with GERD and patients without GERD) in which one group had significantly higher degree or more frequent tooth wear.

Tooth wear measurements used varied greatly among studies; known systems reported were the basic erosive wear examination (BEWE), dental wear index (DWI), tooth wear index (TWI), Eccles and Jenkins system, visual erosion dental examination (VEDE), and Lussi index, together with modifications of these criteria and other specific criteria either obtained from the literature or self-implemented. Some studies did not mention the criteria utilized. Salivary assessments were also different among studies. Most studies focussed on stimulated or unstimulated whole saliva, but some studies included parotid saliva and minor salivary gland saliva as well. Furthermore, it was not always clear whether the saliva was stimulated or unstimulated, and the assessment protocols (e.g., methods and instruments used to evaluate specifics characteristics) were extremely variable (Table S3).

Fig. 2 shows a qualitative summary of the associations found in several studies between salivary content and tooth wear. Eighteen studies showed results regarding protein content and 25 studies showed results regarding non-protein content, both with varying degrees of agreement. Most studies reported no associations, and most of them focussed on electrolytes, salts, and/or proteins in general showing conflicting results. Other components were reported by very few studies, many of them by only one article. The level of directness was variable, but qualitatively high (i.e., the percentage of studies that assessed individuals of the same population in relation to tooth wear was higher compared to studies that assessed tooth wear in samples of different populations).

Regarding physicochemical characteristics and xerostomia, findings are qualitatively summarized in Fig. 3. Most studies showed no associations between physicochemical characteristics and tooth wear. However, a substantial amount of studies did find such a relationship, describing negative relationships between tooth wear and pH, flow rate, and buffer capacity, and a positive relationship between tooth wear and saliva consistency/viscosity. Regarding xerostomia, most articles showed a positive relationship with tooth wear. An interesting finding was that some studies showing these relationships were of considerable size compared to other studies showing no association or an opposite relationship between variables. Moreover, almost all groups had a share of direct and indirect data (i.e., studies looking at associations within the same population or between different populations with varying degrees or frequencies of tooth wear).

Figs. 4 and 5 show quantitative synthesis of results regarding the association between salivary characteristics and tooth wear. Eligible articles showed the comparison between patients with higher degree (or presence) of tooth wear compared to lower degree (or absence) of tooth wear, regarding flow rate and pH in either stimulated or unstimulated whole saliva. Only the pH from stimulated whole saliva showed a negative relationship with tooth wear, where the mean difference was significantly less in the groups with presence (or higher degree) of tooth wear. This pooled mean difference was 0.07. Funnel plots showed that, for stimulated whole saliva pH, all studies were situated to the left of the mean effect and close to statistical significance (Figure S1). However, after applying the trim and fill method, the result remained statistically significant (3 studies imputed, estimated confidence interval: -0.0938 -0.0398). Furthermore, leave-one-out sensitivity analysis showed that statistical significance of the estimated result did not depend on individual studies (estimated confidence intervals per permutation: -0.1131 -0.0337; -0.1012 -0.0251; -0.1162 -0.0633; -0.1023 -0.0394; -0.1044 -0.0350; -0.1009 -0.0372; -0.1040 -0.0363). Heterogeneity was high for unstimulated saliva and low for stimulated whole saliva. All funnel plots can be seen in Figure S1.

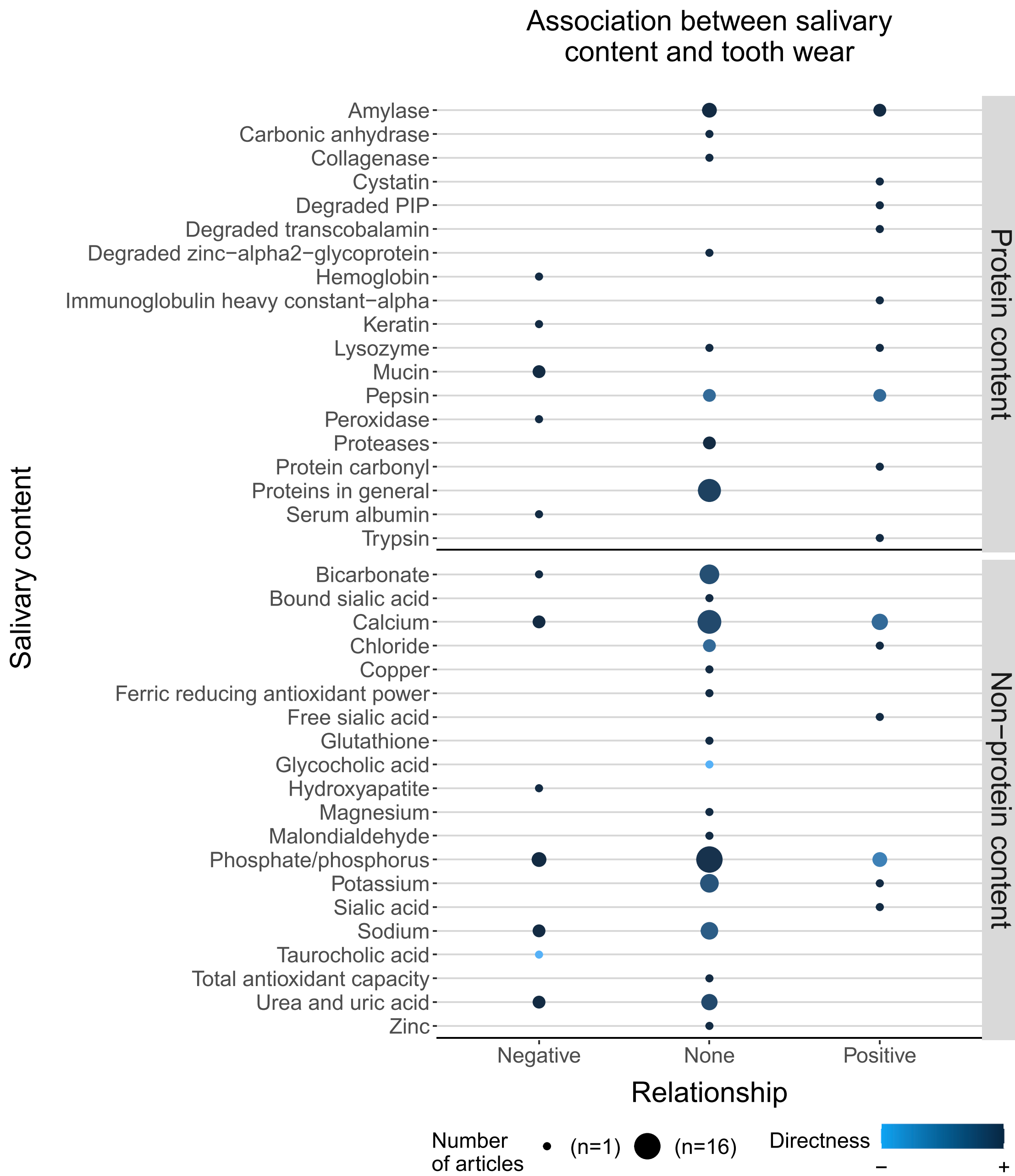

Fig. 2. Relationship between salivary content and tooth wear. Directness refers to the percentage of studies in which the studied populations had various degrees or frequencies of tooth wear in contrast to studies in which samples of different populations were compared (one sample had more or higher degree of tooth wear than the other). The more direct studies were the darker is the color (+). The total number of articles is represented by the size of the circle, which varied from one article to sixteen. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

From the longitudinal studies included [13,24–28], only one study showed that the flow rate in stimulated whole saliva was associated with progression of tooth wear, both when measured at baseline and during follow-up. This study focussed on tooth wear differences in a group of patients with eating disorders [25]. Further information about the characteristics of longitudinal studies can be found in Table S3.

A risk of bias assessment of the records evaluated (summarized in Figure S2) showed that risk of bias was unclear to low, with the lowest risk of bias in items regarding the clarity of inclusion criteria and the use of standard measurements for the condition for cross-sectional studies. For longitudinal studies, risk of bias was mainly low; the measurements of exposures and the integrity of the follow-up was less clear, raising some concerns.

Analysis of the certainty of evidence is shown in Table S4 for variables subjected to meta-analysis and Table S5 for all variables. Certainty of evidence was very low for the following parameters (number of articles included): amylase (5), collagenase (1), lysozyqme (2), pepsin (4), peroxidase (1), proteases (2), trypsin (1), degraded prolactin-induced protein (1), degraded zinc-α2-glycoprotein (1), degraded transcobalamin (1), protein carbonyl (1), calcium (18), sodium (7), potassium (7), phosphate and phosphorus (16), chloride (3), magnesium (1), zinc (1), copper (1), hydroxyapatite (1), bicarbonate (8), urea and uric acid (6), taurocholic acid (1), glycocholic acid (1), sialic acid (3), free sialic acid (2), ferric reducing antioxidant power (1), glutathione (1), total antioxidant capacity (1), malondialdehyde (1), and consistency or viscosity (8). Certainty of evidence was low for the following parameters (number of articles included): protein levels or amount of different proteins (10), hemoglobin (1), keratin (1), cystatin

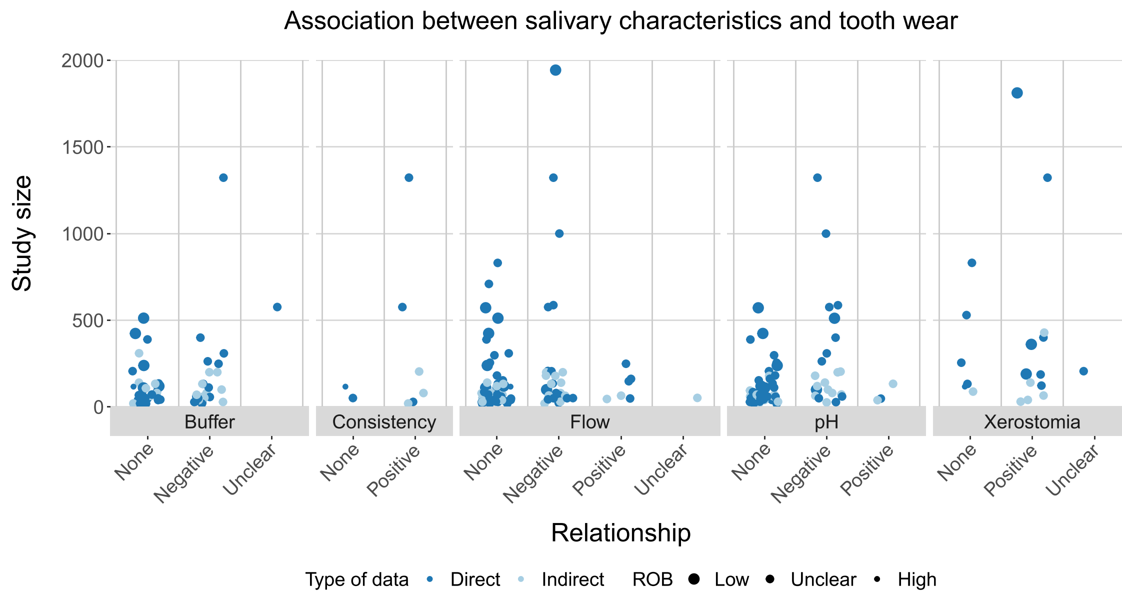

Fig. 3. Relationship between tooth wear and salivary flow rate, pH, buffer capacity, consistency or viscosity, and xerostomia. The figure shows whether in each included study no relationship was found (None), or whether the relationship found was negative or positive with respect to tooth wear, relative to the study size. In some studies, the presence of a relationship was unclear. Studies that investigated people with and without tooth wear in the same population were considered direct data. If studies investigated individuals coming from different populations (populations that differed in the degree or frequency of tooth wear) these were considered indirect data. Risk of bias (ROB) is represented by the size of the dots: bigger dots have the lower risk of bias.

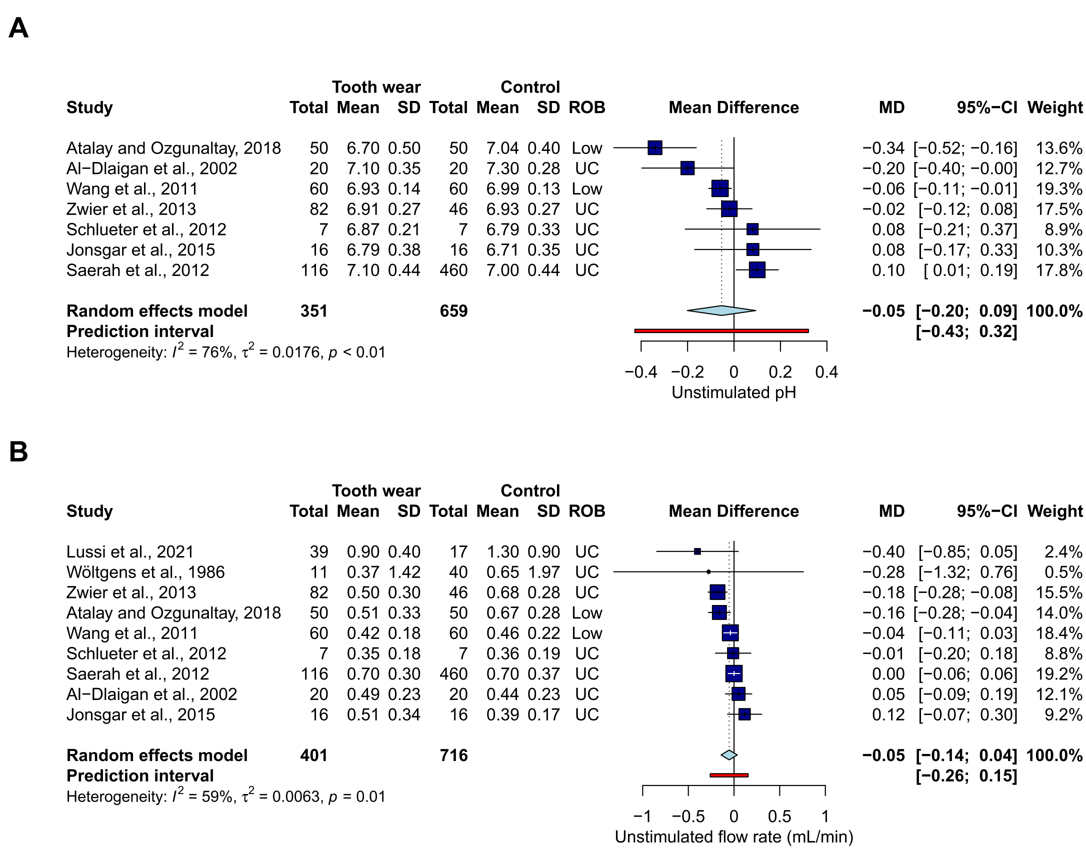

Fig. 4. Pooled mean differences in pH (A) and flow rate (B) of unstimulated whole saliva between patients with (more) tooth wear and controls. Studies are presented in order relative to their effect sizes. Pooled mean differences are shown together with confidence and prediction interval.

(1), mucin (2), immunoglobulin heavy constant α (1), serum albumin (1), carbonic anhydrase (1), bound sialic acid (2), flow rate (85), pH (65), buffer capacity (57), and xerostomia (19).

4. Discussion

Literature shows that tooth wear is an increasing problem worldwide while several factors have been studied as directly associated to the

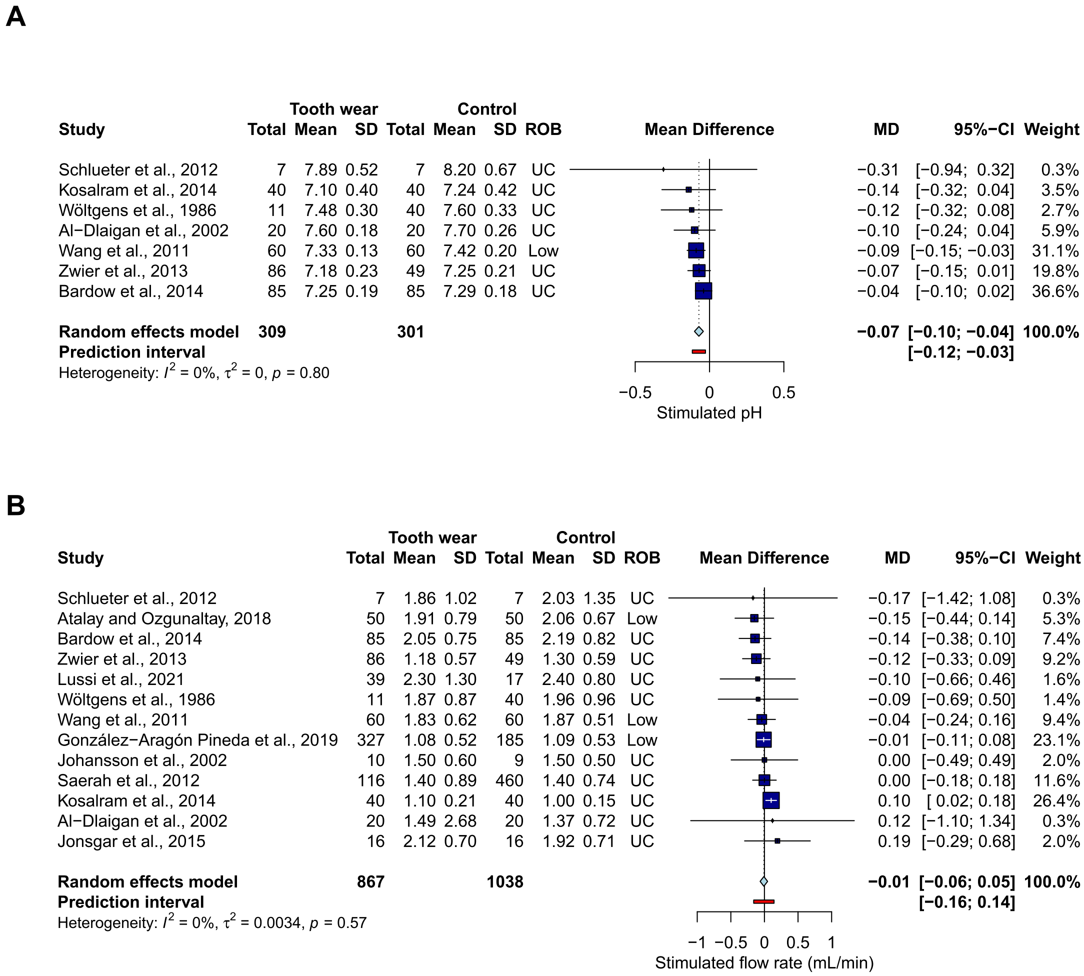

Fig. 5. Pooled mean differences in pH (A) and flow rate (B) of stimulated whole saliva between patients with (more) tooth wear and controls. Studies are presented in order relative to their effect sizes. Pooled mean differences are shown together with confidence and prediction interval.

onset, development and maintenance of tooth wear. GERD is accepted as a major risk factor for tooth wear and saliva is considered as one of the most important biological factors implicated; not only because of its buffering capacity, but also due to its rich-proteome [29]. Therefore, understanding the role of saliva and its components in tooth wear may help patients and clinicians to establish better monitoring modalities and treatment. Therefore, we systematically reviewed the literature including 111 studies about saliva and tooth wear, the majority with a cross-sectional design, and with high variety of methodologies and populations.

Although many studies did not report associations between salivary characteristics and tooth wear, several associations between salivary characteristics and tooth wear were found in this systematic review. Regarding physicochemical characteristics of saliva, the number of studies showing associations was higher in comparison to salivary content. Interestingly, and as expected, studies with larger sample size seemed to show associations more frequently, especially in relation to flow rate, pH, and xerostomia. Moreover, quantitative analyses support the evidence that pH is lower in patients with (more) tooth wear compared to controls. However, visual inspection of the funnel plots may be indicative of publication bias, which might be due to the selection of studies to pool the data as suggested by the large number of studies that could not be pooled. Only one longitudinal study supported the association between salivary flow rate and tooth wear, with no other associations reported. The risk of bias of the assessed studies was mostly unclear, and the certainty of the evidence was low to very low.

Regarding salivary content, the great majority of studies did not find associations between salivary content and tooth wear. However, when looking at variables that showed to be associated in at least more than one study, amylase and pepsin were positively associated with tooth wear and mucin, sodium, whilst urea or uric acid were negatively associated with it. Most of these associations have been not thoroughly studied, but in the particular case of mucin, an in-vitro study showed that this molecule was protective for tooth wear when embedded in neutral pH saline [30]; which goes in line with the findings of this systematic review. In the case of pepsin, this might be indicative of the presence of stomachal content in the oral cavity, such as acids that could contribute to dental erosion [6,31]. An interesting case is the one of hemoglobin, which was shown by the same study to be 22-fold lower in patients with tooth wear and to be protective in-vitro, probably related to its high affinity with hydroxyapatite and possibly forming part of the acquired pellicle [32,33].

The association between calcium or phosphate/phosphorus and tooth wear was more ambiguous, since studies showed both positive or negative relationships, although the evidence from a negative relationship tended to be more direct than for the positive one. It is difficult to determine with confidence what could be the cause of this ambiguity, however, calcium in the diet has been suggested to offer a protective effect against tooth wear, supporting the negative relationship when salivary levels are low [34,35].

Concerning salivary physicochemical characteristics, a large number of studies reported findings about the association between tooth wear and characteristics such as, flow rate (N = 85), pH (N = 65), buffer capacity (N = 57), and consistency of the saliva (N = 8). As expected, and although more than half of the studies did not find any associations, tooth wear was often negatively associated with pH and flow rate. The amount of studies showing the opposite (i.e., positive association) was substantially less. The relationship between pH (and buffer) and demineralization has been thoroughly studied especially regarding caries [17,36,37]. Saliva has also been shown to be important for the clearance of acids [38]. Therefore, it is not surprising that these relationships were found qualitatively. In fact, the larger the study size, the more likely an association was found.

A lower salivary pH can be due to extrinsic factors like diet [39] or intrinsic factors: in one of the included studies looking at bulimic patients, the tooth wear group had a slightly longer exposure to the disease [40]; in another study, the tooth wear group had significantly more patients with gastrointestinal problems (e.g., heartburn) [41]. A lower salivary flow can be the result of medication use [42], association also shown in one of the included studies [43].

However, quantitative analysis of the eligible studies only showed that there was a small difference between pH in stimulated whole saliva between individuals with (more) tooth wear compared to controls. This small difference could be due to several factors: first, the mean difference is dependent on the proportion of individuals in the target group showing a clear deviation from the "normal" pH. Second, groups were mainly categorized on the basis of the tooth wear level at a static moment without consideration of the progression of tooth wear at that specific time. It has been recognized that tooth wear is not a continuously active process and might fluctuate regarding the dynamic factors that enhance or diminish it over time [44]. Third, the categories of tooth wear were mainly based on presence and absence of tooth wear, using different criteria and not focussing on the severity of the problem. This could cause that the groups only slightly differed in the level of tooth wear present. Fourth, if a minor pH difference could be assumed, it might be that its relationship with tooth wear is due to a cumulative effect over time rather than a true difference in acidity. Fifth, most studies did salivary measurements during the waking hours, and the differences at night could be underestimated. It is known that both flow and salivary pH are at their lowest during sleeping hours—which in combination with sleep-related gastroesophageal reflux could produce a steeper pH decrease than during the day [45]. The visual assessment of the funnel plot suggested a bias. Nevertheless, given the number of articles that could not be pooled, this could be rather due to the selection of the articles for pooling rather than publication bias. The effect of either form of bias could not be estimated, but at least, the found effect was robust enough to not disappear after trim and fill and sensitivity analyses. The lack of effect shown by the quantitative analysis of flow rate could also be related to the fact that many studies could not be pooled. In fact, one of the longitudinal studies included in this review did find an association between flow rate and tooth wear progression.

Next, even though salivary pH showed some association with tooth wear, the relationship with buffer capacity was less clear. We hypothesize that this could be related to the difficulty in determining differences in buffer capacity given that most studies relied on colorimetric strips that provide a subjective estimation of this feature often reporting incomparable thresholds. If the differences are as small as those found for pH, then the use of strips could be unsuitable for the clinical analyses of saliva. In fact, in the quantitative analysis all studies but one used pH-meters instead of strips.

Concerning salivary consistency or viscosity the association with tooth wear was positive in most studies. Nevertheless, only a few studies reported these associations, and many of them compared groups coming from different populations.

Lastly, although the studies evaluated suggest an association between psychochemical characteristics and tooth wear that might be useful for risk assessment. Longitudinal analyses were not able to find significant associations over time apart from the previously described relationship with tooth wear. This could be related with three studies focussed on children and adolescents in which the cumulative effects of saliva might not be yet evident; three studies focussed on adults, however, these had small sample sizes [25,26,28].

The last aspect examined was xerostomia, defined as the subjective sensation of dry mouth, which does not necessarily correspond to hyposalivation (objective measurement) [46–48]. In this study, it could be observed that most studies showed a positive relationship with tooth wear. A reason behind this could be that patients with hyposalivation and tooth wear might have more often xerostomia as well, with a stronger relationship between diminished saliva production and the sensation thereof in this population. But this has to be proven empirically.

4.1. Certainty of evidence

The overall GRADE assessment showed that the certainty of the evidence was low to very low, which means that results must be interpreted carefully. Imprecision (small sample sizes) and inability to discard the influence of publication bias were the main factors contributing to the difference between low and very low confidence.

4.2. Strengths and limitations

The main strength of this systematic review is the comprehensive assessment of the many aspects of saliva that could be related to tooth wear given the multifactorial nature of the condition. Another strength of the study is the volume of data gathered for qualitative analysis, given the many reports published. Additionally, some aspects of the saliva were analysed both qualitatively and quantitatively. However, this study was not exempt from limitations: first, studies showed to be very different in terms of methodology, studied groups, and quality. This resulted in the impossibility of comparing results beyond the presence or absence of an association between features. The lack of significant findings in many studies may point towards insufficient evidence to establish associations between parameters in these investigations; it is therefore difficult to estimate the real impact of these studies is on our interpretations. Second, because of the heterogeneity, it was not possible to pool all the data during meta-analysis giving the impression of publication bias when analysing the funnel plot. This means that our conclusions regarding the quantitative synthesis are based on a small set of studies, and can only serve as support of the qualitative analysis in which a larger number of studies was analysed. Third, most of the studies were cross-sectional and the results from a small number of longitudinal studies were not conclusive. Hence, causal effects of the salivary variables on tooth wear could not be established. Fourth, the effective response rate of authors who were contacted for the raw data or information about the article was very low, which decreased the amount of studies that could be included. Lastly, since the certainty of the evidence in this study was low to very low, conclusions derived from the literature in this systematic review must be carefully formulated. Still, the evidence points towards an association between pH/flow rate and tooth wear, whilst better quality studies must be performed to confirm these results.

4.3. Clinical and research implications

This study has both clinical and research implications. First, there is some evidence that stimulated whole saliva pH may be risk factors for tooth wear, however, the small quantitative differences found in this study suggest that the clinical usefulness may be limited, especially when using strips. On the other hand, a low pH and tooth wear might be an indication of other problems, such as GERD as confirmed by other studies [6].

Second, qualitative analysis regarding consistency and viscosity or flow rate indicates that an intervention in these parameters could be useful for these patients, especially when the anamnesis reveals the use of specific drugs that may change affect these parameters. Xerostomia also seems to be an important symptom to consider in these patients since it is negatively associated with tooth wear; in this population, xerostomia could be more indicative of a lower flow rate than in other patients. However, these hypotheses have to be proven empirically and the findings in this study are not indicative of causality either.

From a research perspective, studies focussing on the progression and the severity of tooth wear and larger sample sizes must be performed to investigate if any of these factors indicate risk of progression, which is clinically more relevant in order to know how and when to intervene. Moreover, if acidity levels are lower during sleep, it makes sense to develop methods to monitor the impact of pH and flow at night (or when patients sleep), for example in patients with sleep-related gastroesophageal reflux disease.

5. Conclusion

It can be concluded that several factors in the saliva might be associated with tooth wear. Associations with salivary content have the least amount of evidence available; however, associations with molecules related to oral lubrication, acquired pellicle, and the digestive system might be plausible as seen in the literature. Regarding physicochemical characteristics of saliva, quantitative and qualitative evidence suggests that lower pH is associated with higher tooth wear, especially from stimulated whole saliva. This may indicate a potential usefulness in pH monitoring for risk assessment in tooth wear. Additionally, although the quantitative assessment showed no association between tooth wear and salivary flow rate, the qualitative assessment indicates that a treatment at this level might have some value. However, these conclusions must be carefully considered as the overall risk of bias was unclear and the certainty of evidence was low. Lastly, no causal effects could be derived from the analysis of the included records, since the number of longitudinal studies was very small, and had mostly inconclusive results.

Data availability statement

Data utilized for the analyses in this article are available in the supplements and the dataset is available at The Open Science Framework (https://osf.io/kcp5m).

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CRediT authorship contribution statement

Víctor I. Madariaga: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Tatiana Pereira-Cenci:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Supervision. **X. Frank Walboomers:** Writing – review & editing, Supervision. **Bas A.C. Loomans:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Supplementary materials

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