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REVIEW

The association of tooth loss with all-cause and circulatory mortality. Is there a benefit of replaced teeth? A systematic review and meta-analysis

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Abstract We systematically reviewed whether the number of teeth is related to all-cause or circulatory mortality and whether replaced teeth are protective against all-cause or circulatory mortality. The search was based on the PubMed database. All cohort studies published in peer-reviewed journals were selected. Studies on periodontal disease and mortality were excluded if they did not provide information on the number of teeth. Risk estimates from studies with appropriate exposure definition, confounder adjustment and sample size were included in a meta-analysis. Three high-quality studies found a relationship between the number of teeth and circulatory mortality, whereas a moderate study did not. Two out of four moderate- to high-quality studies reported a relationship between the number of teeth and all-cause mortality. No study has investigated whether replaced teeth are protective against mortality. Therefore, denture use was taken as proxy. The methodological quality of studies on denture use and mortality was generally low to moderate. The findings of two moderate studies indicated an effect of prosthodontic replacements on all-cause mortality, which was supported in bias analysis. It is open whether competing risks of cause-specific death other than circulatory mortality reduce an effect of the number of teeth on all-cause mortality. An effect of denture use on circulatory mortality remains to be established, as well as whether the number of replaced teeth affects mortality. Specifying the role of potential pathways by which tooth loss-related mortality is mediated will possibly increase the value of dental treatment for general health.

Keywords Mortality · Prospective studies · Dental prosthesis · Tooth loss · Meta-analysis

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Introduction

The number of teeth is discussed to predict all-cause and circulatory mortality. Two major pathways may mediate this relationship, including (1) the effects of masticatory dysfunction on dietary behaviour, nutrition and systemic diseases [1–4] and (2) the inflammatory effects of chronic periodontal infection on the circulatory system [5–7]. If tooth loss was a risk factor, its attributable fraction will be relevant because it is more common [8], from younger age onwards, than hypertension [9] as one of the primary predictors of circulatory mortality.

The role of the prosthodontic status has been rarely examined for the possible relationship between the number of teeth and mortality [10]. If the rehabilitation of missing teeth by wearing dental prostheses has the potential to change masticatory efficiency and diet [11–13], replacing missing teeth may hypothetically have an effect on mortality. The prosthodontic status is a time-dependent exposure, as further tooth loss may occur or missing teeth be replaced. If tooth loss is measured at baseline only, its risk on mortality is underestimated because some subjects

will improve their prosthodontic status (receive a prosthesis for missing teeth during the observation period) and some subjects will deteriorate (loose teeth during the observation period without replacement). Such non-differential misclassification following the baseline examination was described earlier for the risk of periodontal disease on cardiovascular disease [14]. Consequently, a long observation period is not only linked with a higher chance for changes in the dental status but it is also preferable to observe fatal events.

A highly relevant methodological factor for judging whether tooth loss or prosthodontic replacement plays a causal role for mortality is to consider the concept of confounding. A confounder is related both to the outcome and the exposure, and non-considering a confounder may overestimate the exposure effect. On the other hand, a confounder may also suppress the relationship of interest. To choose appropriate confounder sets, an innovative epidemiologic tool, namely, directed acyclic graphs (DAGs), has been suggested [15–17]. This combined analytical and graphical approach allows alternative confounder sets and may be particularly instructive for systematic reviews.

Based on these methodological aspects, we systematically reviewed (1) whether the number of teeth is related to all-cause or circulatory mortality and (2) whether replaced teeth are protective against all-cause or circulatory mortality.

Materials and methods

Search strategy

Literature searches were independently executed by three of the authors (I.P., C.S. and H.V.) using two strategies. Firstly, the PubMed database (1966 to May 2010) was screened to detect articles published in the English language on the association between the number of teeth and all-cause mortality/circulatory mortality or replaced teeth and all-cause mortality/circulatory mortality. The search was restricted to studies on human subjects by selecting the respective option provided by the PubMed search engine. For assessing a putative lifetime effect of the number of teeth, the Boolean search formulation was: (*tooth* OR *teeth* OR "*tooth loss*" OR "*tooth number*" OR "*number of teeth*" OR "*dental disease*" OR "*dental status*") AND (*survival* OR *mortality* OR *death* OR *fatal* OR *lethal*). To evaluate a putative beneficial effect of prosthodontic replacements, the Boolean search formulation was: ("*replaced teeth*" OR *denture* OR "*dental prosthesis*" OR "*dental prostheses*" OR *RPD* OR *FPD*) AND (*survival* OR *mortality* OR *death* OR *fatal* OR *lethal*). Secondly, after the electronic search, manual searches were made through reference lists from original research and review articles.

Study selection

All cohort studies published in peer-reviewed journals were considered for the present review. Studies on the association between the number of teeth and non-fatal circulatory events were excluded, as were studies on periodontal disease and mortality if they did not provide information on the number of teeth. Highly selected study populations were a further criterion for exclusion.

Quality assessment of selected studies

The selected studies were assessed for the exposure, the intermediates, the sample size and the confounders. With respect to confounding, we classified the studies into risk and prediction models [18]. In a risk model, a confounder is associated with both the outcome and the exposure, but must not be an effect of the exposure [19]. To assess a confounder, it would not be appropriate to use stepwise selection procedures because they ignore the relation between the risk factor and the exposure. Stepwise modelling makes more sense for prediction models [19]. The sample size was considered insufficient if less than ten outcome events per variable were available in prediction models or five events per variable in risk models [20]. If the number of events is less than the corresponding critical value, the results may be biased and should be cautiously interpreted [20].

Potential confounders

Many confounders (age [21, 22], sex [21, 22], social determinants such as socioeconomic status (SES) and marital status [22, 23], smoking [21–24], risky alcohol consumption [23, 24], physical activity [23, 25], metabolic factors such as diabetes and obesity [21–23], serum lipids such as triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol [26, 27], hypertension [22, 28], oral health behaviour [23, 25], periodontitis [29, 30] and caries [31]) have been considered for the relationship between the number of teeth and mortality. To reduce such a high number of potential confounders to minimal adjustment sets that are sufficient to control confounding, the DAG approach was used [16, 17]; for example, in Online Fig. 1 (Online Resource 1, p 9), the DAG for the teeth–mortality relation is drawn (generated by DAGitty v0.9b available at http://www.dagitty.net/dags.html). The confounder selection depends on the exposure of interest [19]. We investigated the effect of the number of teeth (I) or related oral exposures (number of contacts on natural teeth, II; presence of prostheses, III; number of unreplaced teeth, IV). The obtained minimally sufficient adjustment sets for different oral exposures (I–IV) used in selected studies and under different assumptions are presented in Online Table 1 (Online Resource 1, p 7).

The DAG approach clarifies that an exposure mixture of oral variables may be misleading. Moreover, the problem of residual confounding by smoking, which has been extensively discussed for the relationship between oral exposures and circulatory outcomes, may potentially be avoided by using DAGs.

Based on extensive DAG analysis, smoking and diabetes as the clinically most important (except periodontal disease) were considered for the quality assessment of studies with the exposure to the number of teeth. Age, sex, social determinants (SES) and the number of teeth were considered for the quality assessment of the studies on denture use or related exposures.

Additional methodological information on the selection of potential confounders based on DAGs is given in Online Resource 1 (pp 2 and 3).

Quality criteria

Exposure and intermediates (A–D)

(A) Empirical induction period. To investigate the length of the time period between the exposure and the outcome which should correspond to the proposed biological mechanism (0, not performed; 1, for exposed and not exposed subjects, an induction period was modelled; 2, solely for exposed subjects, an induction period was modelled).
(B) Age range. To facilitate a meaningful induction period analysis (0, ≥80 years; 1, 65–79 years; 2, <65 years).
(C) Change in exposure (0, not modelled; 1, modelled).
(D) Exposure (0, different exposures mixed; 1, exposure, but not the reference group, clearly defined; 2, exposure well defined, reference group adequately chosen).

Subtotal grades for exposure and intermediates (A–D; D for denture use or related exposures only)

High B=2; A, C≥1; D≥2;
Moderate B≥1; D≥1;
Low else.

Sample size

(E) Number of events per variable (0, insufficient; 1, sufficient).

Confounder assessment (F–L)

(F) Risk model chosen (0, no; 1, yes). In meta-analysis, bias analysis is possible for risk models only.

Variables considered as potential confounders for risk models or, for prediction models, included in the final model:

(G) Gender (0, no; 1, adjusted for; 2, stratified by).
(H) Age (0, no; 1, adjusted for; 2, stratified by).
(I) Smoking (0, not included; 1, less than three categories or three categories parameterised on an ordinal level for never, ex- and current smokers; 2, three categories: never, ex- and current smokers or a suitable age range to deal with never and current smokers only, but stratified analysis not reported; 3, three categories available or a suitable age range to deal with two categories and stratified analysis reported; 4, more than three categories for dose and duration used or different parameterisations of smoking regarding dose and duration performed).
(J) Diabetes (0, no; 1, body mass index or obesity as surrogates for diabetes included; 2, yes [diabetes, glucose, or haemoglobin A1c]).
(K) SES (including education, income, and occupation; for exposures other than number of teeth only) (0, no; 1, adjusted for; 2, stratified by).
(L) Number of teeth (for exposures other than number of teeth only) (0, no; 1, number of teeth mixed with exposure to denture use; 2, adjusted for or stratified by a surrogate for the number of teeth; 3, adjusted for or stratified by the number of teeth).

Subtotal grades for confounder assessment (F–J; I and J for number of teeth only, K and L for denture use or related exposures only)

High F=1; I≥3; G, H, J, K≥1; L≥2;
Moderate F=1; I≥2; G, H≥1;
Low else.

Total

High Exposure ≥ moderate and sample size=1 and confounding = high;
Moderate Exposure ≥ moderate and sample size=1 and confounding = moderate;
Low Exposure = low or sample size=0 or confounding = low.

According to the Oxford Centre for Evidence-Based Medicine [32], there are four levels of evidence: from level A, evidence from high-quality homogeneous randomised controlled trials (RCTs), to level D, weak evidence from inconsistent or inconclusive studies [32]. 'RCTs are unethical if the intervention is already known to be superior to the control in the population under investigation' [33]. Since the

relation between the number of natural or replaced teeth and mortality should not be examined within the scope of randomised clinical trials for ethical reasons, the highest possible level of recommendation is B, evidence based on cohort studies. Given evidence based on low- to moderate-quality cohort studies, the level of recommendation will be C.

Bias analysis

For the putative relationship between prosthodontic replacements and mortality, SES may be an important confounder, which is supported by DAGs (Online Resource 1, Online Table 1, p 7). If published results were not adjusted for SES, the effect of missing prosthodontic replacements on mortality is likely to be overestimated. The lack of confounder control can be diminished by bias analyses as recommended by experts for meta-analysis [34]. Here, we performed a probabilistic bias analysis [35] and chose study-specific bias assumptions as described in the supplementary material (Online Resource 1, pp 3 and 4). To decide for a relevant bias, we used the change-in-estimate criterion for risk models, which is usually fixed for a 10% change [19]. The simulation estimate and its interval, which are reflections of the combined data and bias analysis assumptions, were added to the conventional estimate and confidence interval in Table 2.

Results

General description of selected studies

Applying the inclusion and exclusion criteria, in total, 23 cohort studies [36–58] were selected for qualitative synthesis (Fig. 1).

As to the database search on tooth loss and mortality, six investigations [37, 38, 42, 54, 58, 59] were assigned to the denture use analysis. Other studies were not considered since they assessed tooth loss solely as an exposure category of periodontal disease [60–64], treated the number of teeth as a score variable [65, 66] or a confounding variable only [67] or no quantitative data have been given [68, 69]. One study was excluded for evaluating only incident tooth loss [70]. Between two studies [43, 44], an overlap of 94 subjects existed. Because the exposures were defined differently, both reports were included. Finally, three studies [25, 71, 72] were excluded for not assessing fatal events of disease separately from non-fatal outcomes.

There was no study on the relationship between the number of replaced teeth and mortality. Therefore, denture use was taken as proxy. As to the eligibility of denture-related studies, one investigation [59] was excluded, being based on data also used in another publication [37]. Two studies reported no quantitative data and were, therefore, not included [57, 60].

A descriptive summary of the selected studies is given in Tables 1 and 2; declared risk factors were not restricted to those in the final model. Most of the studies were conducted in Europe [37, 40, 43–46, 49, 50, 52, 55–57] or Japan [38, 41, 42, 48, 54, 58], four in the United States [39, 47, 51, 53] and one in China [36]. Study participants were recruited from the general population [36–46, 48–53, 57, 58], nursing facilities [54], registers [47, 55] and a university hospital [56]. Sample sizes ranged widely from 94 [43] to 41,000 subjects [39] in studies on all-cause mortality and from 1,462 [40] to 58,974 subjects [47] in studies on circulatory mortality (Table 1). In studies that considered denture use as exposure, the range was 697 [38] to 1,929 subjects [54] (Table 2). Denture-related studies did not analyse circulatory mortality as outcome. Similarly, the follow-up times differed and were at minimum 5 [43] or 6 years [47] and at maximum 57 years [56] in studies on all-cause or circulatory mortality (Table 1). In studies exploring the putative relation between denture use and mortality (Table 2), there were shorter observation periods of 4 [38] to 15 years [37].

Number of teeth and all-cause/circulatory mortality

There were 15 studies [36, 39–41, 43–46, 48–52, 55, 56] that investigated the relation between the number of teeth and *all-cause mortality* and 9 studies [36, 39, 40, 46, 47, 49, 52, 56, 57] that investigated the effect on *circulatory mortality* (Table 1). Irrespective of the assessed quality, 12 [36, 39–41, 43–46, 49–51, 55] out of 15 studies reported an increased risk of *unspecific death* among women or men with higher numbers of missing teeth, while 7 [36, 39, 40, 46, 47, 49, 56] out of 9 studies revealed increased *circulatory mortality*.

Study findings are limited by low number of events [20] in relation to the number of variables in the final model (for *all-cause mortality*: Table 3 [48, 51] and for *circulatory mortality*: Table 4 [57]). Notably, in one study [57], sample size considerations were not reported, although statistically non-significant findings were yielded for a low number of events. Findings are further limited by using prediction models [43, 44, 49–51, 55]. Moreover, the confounder sets of the studies were quite heterogeneous. Few risk models lacked adjustment for clinically relevant confounders such as smoking [39, 41] and diabetes [41, 46, 52] (Tables 3 and 4). Potential residual confounding by smoking was addressed in three studies by performing sensitivity analysis [36], using the number of cigarettes per day for current and former smokers [47], or stratifying by smoking status [56]. Tu et al. [56] reported separate analyses for smokers and non-smokers only for the association between tooth loss and circulatory mortality; for that relationship, the methodological quality scoring was, therefore, higher (Table 4) than for the all-cause mortality analyses (Table 3). Four studies [39, 45, 46, 52] discussed residual confounding qualitatively without trying

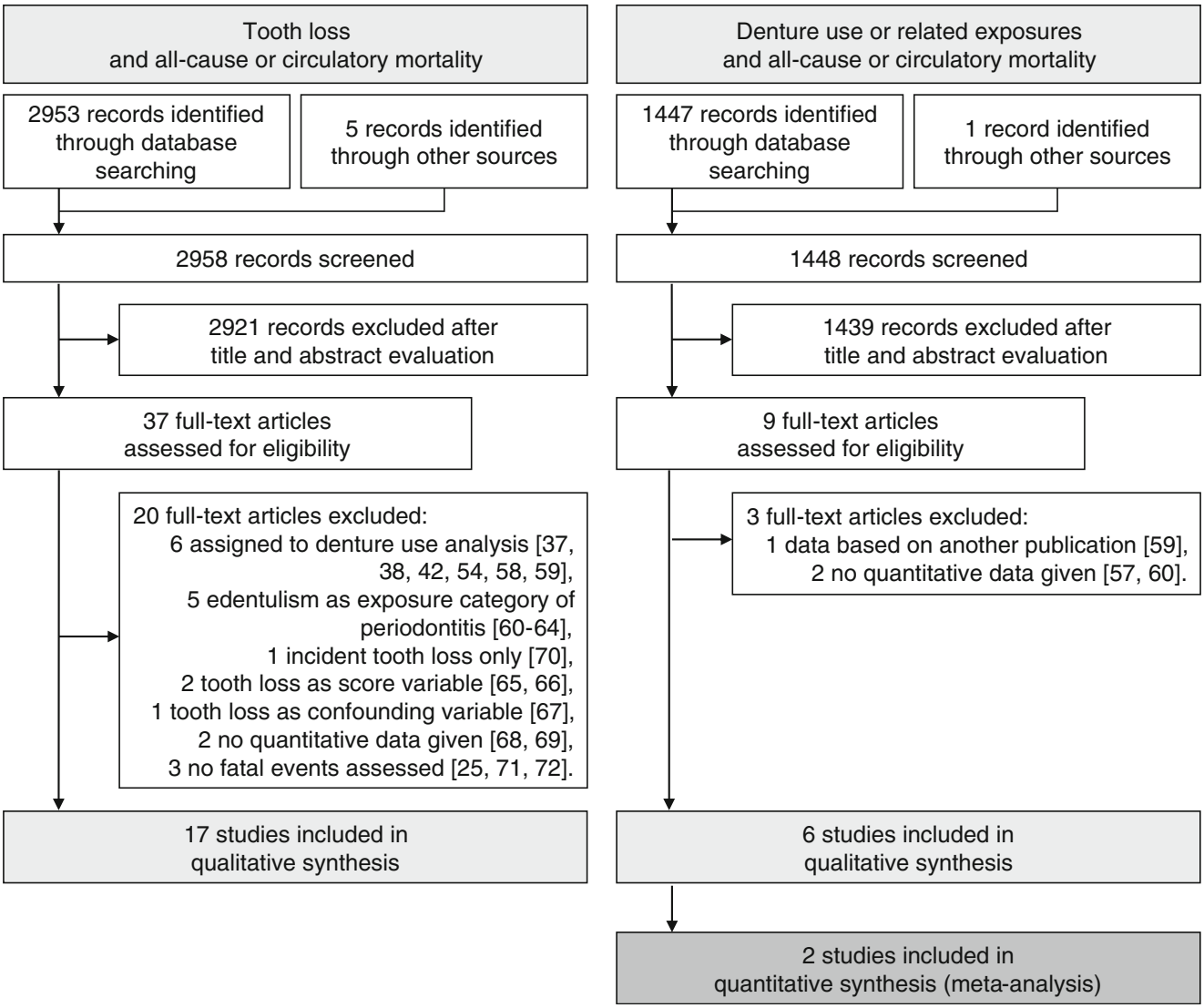

Fig. 1 Flow diagram of included studies

to quantify the effect, for instance, in a bias analysis. Quantification of the bias effect would have been advisable at least for Brown et al. [39]. In contrast, over-adjustment might be present for vitamin supplementation [47].

Different exposure definitions, namely, dichotomous (for example, >10 teeth), log-linear (continuous number of teeth) or potentially non-log-linear (categories, fractional polynomials), were used across studies (Table 1). Two studies [49, 56], having found a higher mortality risk, specified whether a linear exposure effect could be assumed. Whereas one study [49] revealed linearity, the other did not [56]. Notably, in two studies [36, 50], the number of teeth was not examined by dental professionals. In a study of health professionals, participants indicated their number of teeth (0, 1–10, 11–16, 17–24, 25–32 teeth) in a self-administered questionnaire [47]. Change in exposures or time-dependent variables were analysed by Hung et al. [47] only.

All studies had an observation period of at least 5 years. Four studies followed up the population for more than 15 years [40, 45, 49, 56]. The empirical induction period was not analysed. The age ranged from 16 [56] to at least 85 years [43] at baseline. Some studies specifically investigated mortality in elderly (65–79 years) [45, 49, 50] or very old populations (≥80 years) [43, 44, 48, 55]. Two studies observed selected samples for which high health awareness may be assumed [47, 56].

Quality of selected studies on the number of teeth and all-cause/circulatory mortality

Summary results of the quality assessment are presented for studies on *all-cause mortality* in Table 3 and for studies on *circulatory mortality* in Table 4. There was a higher methodological quality of analyses on the relation between

Table 1 Descriptive summary of studies that investigated the relation between *tooth loss* and *all-cause* or *circulatory mortality* or *survival* [36, 39–41, 43–52, 55–57]

Authors, publication year	Setting	Subjects	Response	Follow-up time (mean±SD)	Exposure, no. affected	Risk factors considered	Risk or prediction model/risk estimate	All-cause mortality (95% CI)	Circulatory mortality (95% CI)
Abnet et al., 2005 [36]	General population of Linxian, China	*n*=28,790 (55% females), aged 40–69 years, median age 52 years (IQR 44–59 years)	Baseline, n.sp.; follow-up, 99.15%	15 years (n.sp.), p-y n.sp.	Tooth loss greater than the loess-smoothed age-specific median number of teeth lost at baseline no. n.sp.	Age, gender, smoking, alcohol, height, weight, systolic blood pressure	Risk model; hazard ratio	1.13 (1.09;1.18)**, 9,362 cases	1.28 (1.17;1.40)** heart disease mortality, 1,932 cases; 1.11 (1.01;1.23)* stroke mortality, 2,866 cases
Brown, 2009 [39]	General population in the USA (National Health Interview Survey)	*n*=41,000 (47% females), aged ≥18 years	Baseline: >95%; follow-up: 70.6%	16 years (n.sp.), p-y n.sp.	Edentulism (*n*=5,043)	Age, gender, race, education, family income, living situation, health insurance, dental insurance, BMI, comorbidity[a]	Risk model; hazard ratio	5-year ratio: 18–64 years (801 cases), 1.5 (1.2;1.9)[b]; ≥65 years (no. of cases n.sp.), 1.3 (1.1;1.4)[b] 16-year ratio: 18–64 years (3,471 cases), 1.5 (1.3;1.7)[b]; ≥65 years (4,376 cases), 1.3 (1.2;1.4)[b]	5-year ratio: 18–64 years (259 cases), 1.4 (0.9;2.0)[b]; ≥65 years (no. of cases n.sp.), 1.3 (1.1;1.5)[b] 16-year ratio: 18–64 years (1,160 cases), 1.4 (1.1;1.7)[b]; ≥65 years (2,253 cases), 1.2 (1.1;1.3)[b]
Cabrera et al., 2005 [40]	General population of women from Gothenburg, Sweden	*n*=1,462 females, aged 38–60 years	Baseline, 90%; follow-up, 99%	24 years (n.sp.), p-y n.sp.	Number of missing teeth (>10 teeth) no. n.sp.	Age, waist–hip ratio, BMI, smoking, the husband's occupational category, plus parity *and* age at first birth for all-cause mortality ratio	Risk model; hazard ratio	1.27 (1.09;1.47)*, 177 cases	1.34 (1.05;1.71)*, 67 cases
Fukai et al., 2007 [41]	General population in three Japanese communities: Hirama City, Shimoji Town, Tarama Village (Okinawa Prefecture)	*n*=5,730 (61.6% females), aged >40 years	n.sp.	15 years (n.sp.), p-y n.ps.	Number of functional teeth (<10 teeth, *n*=3,031)	Age, presence of systemic diseases, bedridden state	Risk model; hazard ratio	Males, 1.33 (1.11;1.59)*, 499 cases; Females, 1.04 (0.83;1.30), 469 cases	n.sp.
Hämäläinen et al., 2003 [44]	General population of Jyväskylä, Finland	*n*=226 (71.2% females), aged 80 years	Baseline, 92.6% interview, 72.4% medical examination, 79.9% dental examination; follow-up, n.sp.	10 years (n.sp.), p-y n.sp.	Number of missing teeth (continuous) no. n.sp.	Gender, number of chronic diseases, self-rated health	Prediction model; hazard ratio	1.03 (1.00;1.05)*, 150 cases	n.sp.
Hämäläinen et al., 2005 [43]	General population of Jyväskylä, Finland	*n*=94 (no. of females n.sp.), aged 85 years	Baseline, 56.3% medical examination, 55.7% dental examination; follow-up, n.sp.	5 years (n.sp.), p-y n.sp.	Number of remaining teeth (continuous) no. n.sp.	Number of chronic diseases, urgent need of dental treatment, community periodontal index of treatment needs	Prediction model; hazard ratio	0.93 (0.87;0.99)*, 49 cases	n.sp.
Holm-Pedersen et al., 2008	General population of Copenhagen,	*n*=573 (51.7% females), aged	Baseline, 72%; 20-year follow-up,	21 years (n.sp.), p-y n.sp.	Edentulism (*n*=236)	Education, income, tiredness, comorbidity,	Risk model; hazard ratio	1.26 (1.03;1.55)*, 458 cases	n.sp.

Table 1 (continued)

Authors, publication year	Setting	Subjects	Response	Follow-up time (mean±SD)	Exposure, no. affected	Risk factors considered	Risk or prediction model/risk estimate	All-cause mortality (95% CI)	Circulatory mortality (95% CI)
[45]	Denmark	70 years	14%			arteriostenosis, smoking			
Holmlund et al., 2010 [46]	General population (*n*=886) and dental hospital patients (*n*=6,788) of Gävle, Sweden	*n*=7,674 (57.0% females), aged 20–89 years	n.sp.	29 years (12 years), 93,857 p-y	Number of remaining teeth (<10 teeth, 10–14 teeth, 15–19 teeth, 20–25 teeth, >25 teeth) no. n. sp.	Age, gender, smoking	Risk model; hazard ratio	>25 teeth, [reference] 20–25 teeth, 1.28 (1.02;1.60)* 15–19 teeth, 1.77 (1.37;2.27)** 10–14 teeth, 2.01 (1.52;2.66)** <10 teeth, 2.68 (1.96;3.67)**; 629 cases	CVD mortality >25 teeth [reference] 20–25 teeth, 1.79 (1.25;2.58)* 15–19 teeth, 2.75 (1.87;4.04)** 10–14 teeth, 3.29 (2.17;5.0)** <10 teeth, 4.63 (2.95;7.26)**; 299 cases
Hung et al., 2004 [47]	US-American male health professionals and female nurses	*n*=41,407 males, aged 40–75 years; *n*=58,974 females, aged 30–55 years	n.sp.	Males, 12 years (n.sp.); females, 6 years (n.sp.); p-y n.sp.	Self-reported number of teeth (0–10 teeth, *n*=1,183 males, *n*=6,134 females; 11–16 teeth, *n*=904 males, *n*=2,925 females; 17–24 teeth, *n*=4,532 males, *n*=11,883 females; 25–32 teeth, *n*=34,788 males, *n*=38,032 females)	Age, smoking, alcohol consumption, BMI, physical activity, family history of MI, multivitamin supplement use, vitamin E use, history of hypertension, diabetes, hypercholesterolemia, profession (for males only), menopausal status and hormonal use (for females only)	Risk model; relative risk	n.sp.	Males (562 cases) 25–32 teeth [reference] 17–24 teeth, 1.26 (1.01;1.57) 11–16 teeth, 1.19 (0.79;1.80) 0–10 teeth, 1.79 (1.34;2.40)[b] Females (158 cases) 25–32 teeth [reference] 17–24 teeth, 1.02 (0.66;1.55) 11–16 teeth, 1.07 (0.56;2.05) 0–10 teeth, 1.65 (1.11;2.46)[b]
Österberg et al., 2007 [50]	General population in three Scandinavian communities: Glostrup, Denmark; Jyväskylä, Finland; Göteborg, Sweden	*n*=1,004 (57.1% females) aged 75 years (7-year mortality: females, 21–29%; males, 31–39%)	Baseline: Jyväskylä 79%, Glostrup 69%, Göteborg 68%; follow-up: n.sp.	7 years (n.sp.), p-y n.sp.	Self-reported number of teeth (0 teeth [reference, 23–58%], 1–4 teeth, 5–9 teeth, 10–14 teeth, 15–19 teeth, 20–32 teeth [9–27%]) no. n.sp.	Education, economic situation, smoking, alcohol consumption, self-assessed health, physical activity, social activity, circulation disease, respiratory disease, no of other chronic diseases, activity of daily life, hospitalised last year, BMI, forced expiratory volume, walking speed, locality	Prediction model; hazard ratio	Males (no. of cases n.sp.), NS (n.sp.); Females (no. of cases n.sp.), 0.87 (0.78;0.97)*	n.sp.
Österberg et al., 2008 [49]	Four birth cohorts of the general population of Göteborg,	7 year follow-up: *n*=1,803 (52.6% females) aged 70 years	Baseline: 62–84% (earlier–later cohort); follow-up n.sp.	7–28 years (earlier–later cohort), 7-year follow-up:	Number of teeth (continuous and categorical, linearity tested: 0 teeth [reference,	Gender, marital status, smoking, physical activity, BMI, diabetes, ischemic heart disease,	Prediction model; hazard ratio	Continuous data[c]	Continuous data[c]

Table 1 (continued)

Authors, publication year	Setting	Subjects	Response	Follow-up time (mean±SD)	Exposure, no. affected	Risk factors considered	Risk or prediction model/risk estimate	All-cause mortality (95% CI)	Circulatory mortality (95% CI)
	Sweden	18 year follow-up: *n*=1,381 (51.2% females)		males, 5,213 p-y, females, 6,189 p-y; 18-year follow-up: males, 7,082 p-y, females, 9,706 p-y	51–16%], 1–9 teeth, 10–19 teeth, 20–32 teeth [14–38%])	claudicatio intermittens, chronic bronchitis, history of cancer, number of drugs, antihypertensive drug, feeling not healthy, serum triglycerides, blood haemoglobin, plasma glucose		7-year ratio: total (374 cases), 0.97 (0.95;0.98)**; males (239 cases), 0.96 (0.95;0.98)**; females (135 cases), 0.97 (0.95;0.99)*	7-year ratio: total (no. of cases n.sp.), 0.96**
								18-year ratio: total (1,003 cases), 0.99 (0.98;0.99)*; males (550 cases), 0.98 (0.97;0.99)*; females (453 cases), NS (n.sp.)	18-year ratio: n.sp.
Padilha et al., 2008 [51]	General population of Baltimore, Maryland, USA (BLSA)	*n*=500 (18.4% females) aged 57.5 (±17.4) years	n.sp.	185 (±90)months p-y n.sp.	Number of teeth (0 teeth, *n*=24; 1–19 teeth, *n*=78; ≥20 teeth, *n*=398)	Age, gender, education, smoking, self-rated health, serum lipids and glucose[d], white blood cell counts, physical activity, somatometric parameters[e], circulatory diseases[f], cancer, diabetes, no. of teeth with coronal and cervical caries, DMFT, periodontal parameters[g] oral health behaviour[h]	Prediction model hazard ratio	≥20 teeth [reference]; 1–19 teeth, 2.17 (1.50;3.13)**; 0 teeth, 1.76 (1.04;2.98)*; 198 cases	n.sp.
Ragnarsson et al., 2004 [52]	General population of Reykjavik, Iceland and the MONICA Project (WHO, 21 countries)	*n*=2,613 (52.7% females), aged 25–74 years	n.sp.	8–15 years (n. sp.), p-y n.sp.	Number of teeth (continuous, linearity tested), edentulism (*n*=909), number of years of edentulism (8.6±14.5 years)	Age, gender, cholesterol, systolic blood pressure, education, smoking	Risk model; hazard ratio	No. of teeth, 0.991 (0.979;1.003)	No. of teeth, 0.983 (0.958;1.009)
								Edentulism, 1.15 (0.94;1.50)	Edentulism, 1.46 (0.88;2.43)
								No. of years of edentulism, 1.007 (1.001;1.013)*; 353 cases	No. of years of edentulism, 1.004 (0.991;1.018); 82 cases
Tu et al., 2007 [56]	Students registered at the University of Glasgow, UK	*n*=12,223 (22% females), aged ≤30 years (median 19 years)	Baseline, 97%; follow-up, n.sp.	57 years (n.sp.), p-y n.sp.	Number of missing teeth (continuous; categorical, 0–4 missing teeth, *n*=7,403, 5–8 missing teeth, *n*=3,192, ≥9 missing teeth, *n*=953; fractional polynomial)	Age at examination, year of birth, gender, father's socioeconomic position, smoking, BMI, systolic blood pressure	Risk model; hazard ratio	Continuous, 1.01 (1.00;1.02); categorical, n.sp.; fractional polynomial, n.sp. 1,432 cases	Continuous, 1.01 (0.99;1.03); categorical, 0–4 missing teeth [reference], 5–8 missing teeth 1.14 (0.94;1.39), ≥9 missing teeth 1.35 (1.03;1.77)*; fractional polynomial, p value<0.05 509 cases
Tuominen et al., 2003 [57]	General population in Finland (Mini-Finland Health Survey)	*n*=6,527 (52,6% females), aged 30–69 years	Baseline, 90.2%; follow-up, n.sp.	12 years (±n.sp.), p-y n.sp.	Number of teeth (≥25 teeth, *n*=1,722; 11–24 teeth, *n*=1,921; ≤10 teeth, *n*=1,267)	Age, education, hypertension, hypercholesterolemia, smoking, diabetes,	Risk model; hazard ratio	n.sp.	Among dentate (2,303 males, 2,245 females): males (150 cases): ≥25 teeth [reference]; 11–24

Table 1 (continued)

Authors, publication year	Setting	Subjects	Response	Follow-up time (mean±SD)	Exposure, no. affected	Risk factors considered	Risk or prediction model/risk estimate	All-cause mortality (95% CI)	Circulatory mortality (95% CI)
						number of carious teeth number of filled teeth, number of retained roots, periodontal pockets, dental attendance			teeth, 0.8 (0.5;1.3); ≤10 teeth, 0.9 (0.5;1.6); females (36 cases): ≥25 teeth [reference]; 11–24 teeth, 0.5 (0.2;1.8); ≤10 teeth, 0.3 (0.1;1.0)
Morita et al., 2006 [48]	General population of Tokoname, Japan	Two matched groups of n=59 each (24 females), aged ≥80 years	Baseline, 64.6%; follow-up, ≥20 teeth group 33.9%, <20 teeth group 37.3%	10 years (n.sp.), p-y n.sp.	Number of teeth (≥20 teeth, n=59)	Smoking, alcohol consumption	Risk model; hazard ratio	No significant differences in the cumulative survival rates, 76 cases	n.sp.
Thorstensson and Johansson, 2009 [55]	Monozygotic or dizygotic like-gendered twins, living in housing or institutional settings in Sweden (OCTO-Twin)	n=357 (68.1% females), aged ≥80 years (median 86 years)	Baseline, 100% (register study); follow-up, n.sp.	8 years (n.sp.), p-y n.sp.	Being dentate (n=181)	Zygosity, household economy in childhood, financial status during work life, social class, education, marital status, current living conditions, smoking, psychosocial variables[i], periodontal disease experience, percent of carious or filled tooth surfaces	Prediction model; hazard ratio	≤85 years (males), 1.8 (1.0;3.0)* ≤85 years (females), NS (n.sp.) ≥86 years (males), NS (n.sp.) ≥86 years (females), NS (n.sp.) No. of cases, n.sp.	n.sp.

SD standard deviation, *no.* number, *CI* confidence interval, *n.sp.* not specified, *p-y* person-years at risk, *BMI* body mass index, *MI* myocardial infarction, *NS* non-significant, *DMFT* sum of the number of decayed, missing and filled teeth

*p<0.05, **p≤0.001

[a] Including activity limitation, arthritis, diabetes, ischemic heart disease, cerebrovascular disease, cancer (excluding lung), asthma, chronic bronchitis, emphysema, lung cancer

[b] Significance level not specified

[c] Risk estimates for the number of teeth categories are not markedly different from the continuous data and, therefore, not shown

[d] Including LDL cholesterol, HDL cholesterol, triglycerides, serum fasting glucose, 2-h post-challenge serum glucose

[e] Including BMI, lower waist circumference, abdominal skinfold thickness

[f] Including myocardial infarction, angina pectoris, stroke, transitory ischemic attack, congestive heart failure

[g] Including frequency of tooth brushing, frequency of visits to the dentist

[h] Defined as a sum of scores for the number of missing teeth, apical lesions, caries lesions and marginal bone loss

[i] Including self-evaluated healthy lifestyle, capacity to keep oneself neat and tidy, in need of help to keep neat and tidy, perceived loneliness, overall cognitive status

[j] Including average gingival index (grade of gingival inflammation), average periodontal index (grade of attachment loss)

Table 2 Descriptive summary of studies that considered *denture use or related exposures* in the investigation of the relation between dental status and *all-cause mortality* [37, 38, 42, 53, 54, 58]

Authors, publication year	Setting	Subjects	Response	Follow-up time (mean±SD)	Exposure (no. affected)	Risk factors considered	Risk estimate	All-cause mortality (95% CI)
Appollonio et al., 1997 [37]	General population of Brescia, Italy	*n*=1,124 (66.5% females), aged 70–75 years	Baseline, 91.3%; follow-up, 86.3%	10 years (n.sp.), p-y n.sp.	Naturally adequate dental status (ADS, *n*=281), denture wearers (DW, *n*=677), naturally inadequate dental status and subjects not using dentures (IDS, *n*=166); (type of prosthesis not considered)	Smoking, health service use, education, economic status	Hazard ratio	ADS [reference] DW 1.34 (1.06;1.704) IDS 1.51 (1.11;2.05)* 478 cases
Awano et al., 2008 [38]	General population of the Fukuoka Prefecture, Japan	*n*=697 (60.3% females), aged 80 years	Baseline, 54.4%; follow-up, 100%	4 years (n.sp.), p-y n.sp.	No denture[a] (*n*=298), using partial denture (*n*=150), using full denture (*n*=246); (fixed prostheses not considered)	Gender, history of stroke, serum albumin, serum total cholesterol, fasting serum glucose, BMI, smoking	Hazard ratio	No denture[a] [reference] Partial denture 1.2 (0.7;2.2) Full denture 1.5 (0.9;2.4) 108 cases
Fukai et al., 2008 [42]	General population of three Japanese communities: Hirama City, Shimoji Town, Tarama Village (Okinawa Prefecture)	*n*=5,688 (60.5% females), aged >40 years	n.sp.	15 years (n.sp.), p-y n.ps.	<10 functional teeth using dentures (*n*=2,247), <10 not using dentures (*n*=750); (type of prosthesis not considered)	Age, presence of systemic diseases, bedridden state, number of functional natural teeth (0–4, 5–9)	Hazard ratio	<10 teeth using denture [reference][b] Males, 0.99 (0.74;1.32)[b] Females, 1.39 (1.10;1.75)*,[b] 1,012 cases Relative risk after bias analysis (95% simulation interval) Males, 0.95 (0.70;1.29) Females, 1.36 (1.09;1.70)
Semba et al., 2006 [53]	General population of women from Baltimore, Maryland, USA(WHAS-I/II)	*n*=826 females, aged 70–79 years	Baseline: WHAS-I, 71.1%; WHAS-II, 49.5%; follow-up, n.sp.	5 years (±n.sp.), p-y n.sp.	Denture use and difficulty chewing or swallowing (*n*=61), denture use and no difficulty chewing or swallowing (*n*=464), no denture use[a] (*n*=301); (fixed prostheses not considered)	Age, race, education, BMI	Hazard ratio	No denture use[a] [reference] Denture use and difficulty chewing or swallowing 1.43 (1.05;1.97)[c] 135 cases
Shimazaki et al., 2001 [54]	Institutionalised elderly of Kitakyushu City, Japan	*n*=1,929 (72.2% females) aged 79.7±7.5 years	Baseline, 87%; follow-up, 37.5%	6 years (n.sp.), p-y n.sp.	≥20 teeth (*n*=129), 1–19 teeth using dentures (*n*=377), 1–19 teeth not using dentures (*n*=347), edentulous using dentures (*n*=575), edentulous not using dentures (*n*=334); (fixed prostheses not considered)	Age, gender, physical–mental health status, type of institution, cerebrovascular disorder, cardiovascular disease, musculoskeletal disease	Odds ratio	≥20 teeth [reference] 1–19 teeth using dentures, 1.3 (0.8;2.0) 1–19 teeth not using dentures, 1.5 (0.9;2.4) Edentulous using dentures, 1.3 (0.8;2.4) Edentulous not using dentures, 1.8 (1.1;2.8)* 856 cases
Yoshida et al., 2005 [58]	General population of Kure City, Hiroshima, Japan	*n*=1,030 (no. of females n.sp.), aged ≥65 years	Baseline, n.sp.; follow-up, 95.9%	8 years (n.sp.), p-y n.sp.	Occlusal contact in at least the bilateral premolar regions (A, *n*=239), insufficient occlusal contacts with unilateral molar and/or	Age, gender	Hazard ratio	A 0.78 (0.60;0.99)** B 1.08 (0.85;1.36) C [reference] 239 cases

Table 2 (continued)

Authors, publication year	Setting	Subjects	Response	Follow-up time (mean±SD)	Exposure (no. affected)	Risk factors considered	Risk estimate	All-cause mortality (95% CI)
					anterior teeth remaining (B, n=211), no occlusal contacts with or without remaining teeth (C, n=538 at follow-up), in group C: subdivision according denture use (n=60 non-user) (type of prosthesis not considered)		Among group C (161 cases) Denture user [reference] Denture non-user, 1.52 (1.25;1.83)** Relative risk after bias analysis (95% simulation interval), 1.46 (1.18;1.79)	

SD standard deviation, *no.* number, *CI* confidence interval, *n.sp.* not specified, *p-y* person-years at risk, *BMI* body mass index

*$p<0.05$, **$p\leq0.001$

[a] Including dentate subjects who do not need dentures and partially or fully edentulous subjects who do not wear dentures

[b] Different from the original data, the reference group was re-coded and reciprocal values of risk estimates are presented

[c] Significance level not specified

the number of teeth and circulatory mortality, which was moderate to high in half of all studies, compared with studies addressing all-cause mortality as outcome. Generally, lower quality scorings of the selected studies were partly attributable to a research question different from those of the present systematic review. Cabrera et al. [40], for example, assessed whether the SES can explain the relation between tooth loss and circulatory mortality; for that aim (SES as exposure), smoking would be an intermediary variable rather than a confounder.

Based on quality assessment, valid results for *all-cause mortality* can be assumed for Abnet et al. [36] and, to an essentially lower grade, for Holm-Pedersen et al. [45], Ragnarsson et al. [52] and Tu et al. [56]. Exposures differ across moderate- to high-quality studies [36, 45, 52, 56]. Therefore, a pooled estimation would be feasible only for two moderate studies [52, 56], both analysing the number of teeth as continuous variable. Quantitative synthesis ignoring high-quality data could be misleading and was, therefore, not performed. Two [36, 45] out of four moderate- to high-quality studies (Table 3), however, reported a relationship between the number of teeth and all-cause mortality (Table 1).

Valid results for *circulatory mortality* can be assumed for Abnet et al. [36], Hung et al. [47] and Tu et al. [56] (Table 4), who all have found a relationship between the exposure and the outcome (Table 1) and, to an essentially lower grade, for Ragnarsson et al. [52], who revealed no relationship between the number of teeth and circulatory mortality. A meta-analysis of the studies was not feasible for similar reasons as for well-designed studies on all-cause mortality; discrepancy in definitions of the exposures would demand exclusion of the two studies with the largest sample size [36, 47].

Denture use and all-cause mortality

No study particularly investigated whether the number of replaced or unreplaced teeth affects mortality. Six investigations [37, 38, 42, 53, 54, 58] explored the putative relation between denture use and all-cause mortality. The study of Semba et al. [53] was not further considered, since the exposure mixture to denture use and difficulty in chewing or swallowing was not suitable for the aim of our review. Four [37, 42, 54, 58] out of the remaining five studies yielded an increased risk of death among women or men not using dentures (Table 2). Interpretation of these findings is, however, limited by the methodological quality of the analyses (Table 5). One study [58] controlled only for age and gender for each exposure group (but additionally controlled tooth contacts for the exposure to denture use) and each study lacked adjustment for gender [37], age [37] or SES, including education and income [38, 42, 54, 58]. Only one study used risk modelling approaches [42]. None

Table 3 Quality scoring of the studies that investigated the relation between *tooth loss* and *all-cause mortality* [36, 39–41, 43–46, 48–52, 55, 56]

Authors, publication year	Exposure and intermediates				Sample size	Confounder assessment						Total
	A (0–2)	B (0–2)	C (0, 1)	A–C	E (0, 1)	F (0, 1)	G (0–2)	H (0–2)	I (0–4)	J (0–2)	F–J	A–J
Abnet et al., 2005 [36]	0	2	0	Moderate	1	1	1	1	4	1	High	High
Brown, 2009 [39]	0	2	0	Moderate	1	1	1	2	0	2	Low	Low
Cabrera et al., 2005 [40]	0	2	0	Moderate	1	1	–	1	≥1[a]	1	?[a]	?[a]
Fukai et al., 2007 [41]	0	2	0	Moderate	1	1	2	1	Females, 0 Males, 0	0	Low	Low
Hämäläinen et al., 2003 [44]	0	0	0	Low	1	0	1	–	0	0	Low	Low
Hämäläinen et al., 2005 [43]	0	0	0	Low	1	0	0	–	0	0	Low	Low
Holm-Pedersen et al., 2008 [45]	0	1	0	Moderate	1	1	1	–	2	2	Moderate	Moderate
Holmlund et al., 2010 [46]	0	2	0	Moderate	1	1	1	1	1	0	Low	Low
Österberg et al., 2007 [50]	0	1	0	Moderate	?	0	2	–	Females, 1[b] Males, 0	Females, 0 Males, 1	Low	Low
Österberg et al., 2008 [49]	0	1	0	Moderate	Females, 0 Males, 1	0	2	–	Females, 0 Males, 0	Females, 2 Males, 0	Low	Low
Padilha et al., 2008 [51]	0	2	0	Moderate	0[c]	0	0	1	1	2	Low	Low
Ragnarsson et al., 2004 [52]	0	2	0	Moderate	1	1	1	1	2	0	Moderate	Moderate
Tu et al., 2007 [56]	0	2	0	Moderate	1	1	1	1	2	–	Moderate	Moderate
Morita et al., 2006 [48]	0	0	0	Low	Females, 0 Males, 0[e]	1	2	1[d]	1	2[d]	Low	Low
Thorstensson and Johansson, 2009 [55]	0	0	0	Low	?	0	2	2	Females≤85 years, 0 Males≤85 years, 0 Females>85 years, 1 Males>85 years, 0	0	Low	Low

A empirical induction period, *B* age range, *C* change in exposure, *E* number of events per variable, *F* risk model chosen, *G* gender, *H* age, *I* smoking, *J* diabetes (for further details, see the "Quality criteria" section)

[a] Required supplementary information for ultimate quality assessment of the study was unfortunately not available

[b] Based on the "Materials and methods" section, two coefficients or hazard ratios were to be expected, but only one was presented. Similarly to parameterisation of other variables, it is to be assumed that, for smoking, an ordinal level was modelled (non-smoker < previous smoker < current smoker)

[c] Twenty-two variables with at least 22 coefficients were included in the initial multivariable model (198 events)

[d] Matched by age, sex, living environments (in parenthese) and health status including cardiovascular disease, diabetes and cancer

[e] Analyses were related to points in time (using a sequence of odds ratios) rather than to a time period (using one hazard ratio) and were not corrected for multiple testing; for analyses of points in time, fewer events than reported (females, 39 deaths; males, 37 deaths) were available before the end of the observation period

of the studies followed up the population longer than 15 years. The empirical induction period was not analysed by any of the studies. Most studies addressed mortality in old (65–79 years) [37, 54, 58] or very old adults (≥80 years) [38] and one of those specifically referred to institutionalised elderly [54].

Quality of selected studies on denture use and all-cause mortality

Quality estimates of the studies that considered denture use or related exposures in the relationship between dental status and all-cause mortality are presented in Table 5. Based on the proposed criteria, the quality scoring was low to moderate. This quality scoring was improved using bias analysis (Table 5). A valid statement on the effect of denture use on all-cause mortality can only be assumed for two Japanese studies [42, 58], which found that denture non-use is a risk factor for mortality. These exposure effects were changed less than 10% by SES in bias analyses (data are given in Online Resource 1, Online Table 2, p 8), which was expected mainly because wealth inequalities were relatively low in Japan [73]. Therefore, we used the original estimates in meta-analysis. The pooled estimate assuming

Table 4 Quality scoring of the studies that investigated the relation between *tooth loss* and *circulatory mortality* [36, 39, 40, 46, 47, 49, 52, 56, 57]

Authors, publication year	Exposure and intermediates				Sample size	Confounder assessment						Total
	A (0–2)	B (0–2)	C (0, 1)	A–C	E (0, 1)	F (0, 1)	G (0–2)	H (0–2)	I (0–4)	J (0–2)	F–J	A–J
Abnet et al., 2005 [36]	0	2	0	Moderate	1	1	1	1	4	1	High	High
Brown, 2009 [39]	0	2	0	Moderate	1	1	1	2	0	2	Low	Low
Cabrera et al., 2005 [40]	0	2	0	Moderate	1	1	–	1	≥1	1	?[a]	?[a]
Holmlund et al., 2010 [46]	0	2	0	Moderate	1	1	1	1	1	0	Low	Low
Hung et al., 2004 [47]	0	2	1	Moderate	1	1	2	1	4	2	High	High
Österberg et al., 2008 [49]	0	1	0	Moderate	?	0	2	–	?	?	Low	Low
Ragnarsson et al., 2004 [52]	0	2	0	Moderate	1	1	1	1	2	0	Moderate	Moderate
Tu et al., 2007 [56]	0	2	0	Moderate	1	1	1	1	3	–	High	High
Tuominen et al., 2003 [57]	0	2	0	Moderate	Females, 0 Males, 0[b]	1[b]	2	1	2	2	Moderate	Low

A empirical induction period, *B* age range, *C* change in exposure, *E* number of events per variable, *F* risk model chosen, *G* gender, *H* age, *I* smoking, *J* diabetes (for further details, see the "Quality criteria" section)

[a] Required supplementary information for ultimate quality assessment of the study was unfortunately not available

[b] In females, at least 18 coefficients were included in the final model (36 events). In males, at least 18 coefficients were included in the final model (150 events); here, the criterion of 5 events per variable is not appropriate for a risk model because the change of the 11 reported dental exposure coefficients would have been controlled for

random effects of the overall risk in Yoshida et al. [58] and the two gender-specific risks in Fukai et al. [42] yielded a hazard ratio of 1.31 for denture non-users compared with denture users (95% CI 1.03;1.65, using EPISHEET developed by Rothman [19] version of June 11, 2008) (Fig. 2), indicating an effect of prosthodontic replacements on mortality.

Discussion

In conducting a sound meta-analysis, we aimed for an average effect across studies by using well-established methods [34], which included state-of-the-art probabilistic bias analysis on study level [35]. The findings of this systematic review and meta-analysis, however, must be considered in the context of the following potential limitations. The small number of studies available for analysis limits not only the generalisability of the results but also the application of methods for detecting bias in meta-analysis (for example, publication bias and language bias) [74]. Moreover, possible sex differences could not be addressed in the relation between oral health and circulatory outcomes. The small number of studies included in this review did not permit to evaluate the quality of the assessment for circulatory mortality. Furthermore, we cannot exclude potential bias in the original studies, for example, because of measurement error or misclassification of confounders.

Number of teeth and all-cause/circulatory mortality

The three high-quality studies [36, 47, 56] (Table 4) revealed a relationship between the number of teeth and *circulatory mortality* (Table 1). Therefore, the recommendation regarding the number of teeth playing a causal role with respect to circulatory mortality is assessed as level B [32]. For the putative relationship between the number of teeth and *all-cause mortality*, only one high-quality study was found. Given the inconsistent results of moderate- and high-quality studies (Tables 1 and 3), a recommendation cannot be given [32].

At least three biological mechanisms are suggested for the link between the number of teeth and mortality: (1) inflammation, (2) infection and (3) diet and nutrition (for further information about the biological mechanisms, please refer to the supplementary material [Online Resource 1, p 5]).

Each aforementioned pathway relates to a specific confounder set and requires a corresponding induction period. If, for example, a nutritional pathway was taken, it would be unjustified to assume that having missing, unreplaced teeth instantly leads to death, but it would be reasonable to assume an induction period of at least 5 years, as suggested by two studies by Nakanishi and colleagues [75, 76]. They reported the effect of chewing disability on mortality for a 9-year observation period, but did not observe the outcome during the first 4.5 years of follow-up.

Table 5 Quality scoring of the studies on *denture use or related exposures* and *all-cause mortality* [37, 38, 42, 54, 58]

Authors, publication year	Exposure and intermediates					Sample size	Confounder assessment						Total
	A (0–2)	B (0–2)	C (0, 1)	D[a] (0–2)	A–D	E (0, 1)	F (0, 1)	G (0–2)	H (0–2)	K/K_{BA} (0–2)	L (0–3)	F–L/incl. K_{BA}	A–L/incl. K_{BA}
Appollonio et al., 1997 [37]	0	1	0	0[b]	Low	1	0	0	–/0	0/–	1	Low	Low
Awano et al., 2008 [38]	0	0	0	1[c]	Low	1	0	1	–	0/–	3	Low	Low
Fukai et al., 2008 [42]	0	2	0	2[d]	Moderate	1	1	2	1	0/1	3	Moderate/high	Moderate/high
Shimazaki et al., 2001 [54]	0	1	0	0[e]	Low	1	0	1	1	0/–	1	Low	Low
Yoshida et al., 2005 [58]	0	1	0	2[f]	Moderate	1	Across all exposure categories age and sex only	1	1	0/1	2 for exposure denture use within the group of no occlusal contacts	Moderate/high	Moderate/high

A empirical induction period, *B* age range, *C* change in exposure, *D* exposure, *E* number of events per variable, *F* risk model chosen, *G* gender, *H* age, *K* socioeconomic status, *BA* bias analysis, *L* number of teeth (for further details, see the "Quality criteria" section), *incl.* including

[a] Type of exposures:
I related to the number of natural teeth including edentulism
II related to the number of contacts on natural teeth only
III related to the presence of prostheses
IV related to the number of unreplaced teeth

[b] Three exposures were mixed (I, II and IV). Moreover, the exposure levels are referred to the Manson criteria [89], which do not clearly define adequate and inadequate natural dentition

[c] The exposure is related only to the type of prosthesis (III), but the reference group includes edentulous and fully dentate subjects

[d] The two exposures (I and III) were stratified for. Thus, the reference is adequate as well

[e] Two exposures were mixed (I and III)

[f] In the first analysis, exposure II was used; a second analysis was restricted to subjects based on exposure II and then exposure III was used

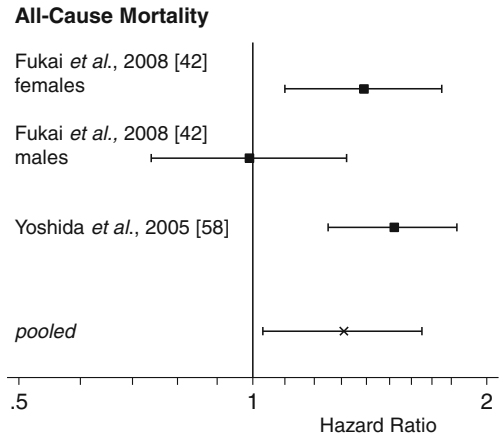

Fig. 2 All-cause mortality in subjects not using dentures compared with denture-wearing reference subjects

In addition, oral infection in the pathogenesis of coronary heart disease has been postulated to be involved at a very early stage of the disease [77]. As one cannot be sure about the true induction period, statistical methods may be used to estimate the most appropriate induction period [19]. This methodological issue, however, has not been applied yet in the reviewed research. Effects without appropriate allowance for the empirical induction period are underestimated [78]. Hence, it is not surprising that the reviewed studies have found, if at all, only small effects of tooth loss on mortality. The longer the supposed time sequence between the exposure and the occurrence of the outcome, the more crucial to analyse the empirical induction period. Under the assumption of an induction period of at least 5 years, a sample restricted to very old populations would decrease the statistical power because very old subjects are likely to die during the next 5 years [43, 44, 48, 55] before tooth loss may have an effect on mortality. Moreover, the accumulation of risk factors over a lengthy induction time complicates to explore whether and to what extent is death a consequence of oral risk factors and to identify the underlying pathway. To avoid a long induction period, intermediate stages are recommended to be observed [19]. Assessing intermediary variables, such as change in inflammatory markers or gastrointestinal symptoms, may elucidate how much of the putative effect of tooth loss on mortality is carried by each pathway.

The diversity of exposures is a further limitation to interpret and compare the studies. As has been discussed in an earlier review, misclassification of the exposure status can yield substantially biased parameter estimates [5]. The suppositious biological pathway should determine the exposure definition. If nutrition were assumed to be on the pathway, it would be more appropriate to use the number of unreplaced teeth as exposure of interest rather than the number of missing teeth. For nutrition as intermediate, it would be misleading to count the number of missing teeth, when subjects had the same number of missing teeth but different numbers of replaced teeth. In contrast, if the inflammatory pathway were taken, periodontal parameters or the number of missing teeth as a surrogate for past periodontal disease may be more suitable. Thereby periodontal disease should not be mixed with categories of tooth loss in the exposure status because the corresponding confounder sets may differ.

Confounding bias may further explain the inconsistent patterns of the associations between mortality and the number of teeth, albeit only few studies lacked adjustment for major confounders. Smoking has considerable influence on the development of clinically detectable periodontitis [79], which eventually over a period of time leads to tooth loss. As smoking is also an important risk factor for all-cause and circulatory mortality [80], its non-consideration or rough classification [81, 82] may have given rise to an overestimation of tooth number-related effects on mortality in some studies [39, 41, 43, 44, 50]. Residual confounding because of smoking has not always been discussed [41, 43, 44, 49, 50], although it was known that the relationship between periodontal and cardiovascular disease is prone to this major limitation [83]. Similarly, not controlling diabetes, body mass index or obesity as surrogates limits the validity of some findings [41, 43, 44, 46, 49, 50, 52, 55] because diabetes is an important risk factor of periodontal disease and strongly associated with increased mortality and thereby confounding the relationship between tooth loss and mortality [84].

Studies examining circulatory mortality (Table 1) might have lacked statistical power and were expected to have lower validity than studies of similar size that examined fatal events from all causes. Nevertheless, there was a higher evidence for circulatory mortality compared with all-cause mortality, which could, on the other hand, be expected because circulatory diseases are linked to both major pathways. Moreover, the number of competing risk factors for circulatory mortality is smaller compared with those for all-cause mortality. Thus, putative effects of the number of teeth on circulatory mortality may be less attenuated.

Denture use and all-cause mortality

In view of the amount of research on the relation between tooth loss and mortality, very few [37, 38, 42, 53, 54, 58] involved prosthodontic aspects and, to the best of our knowledge, the number of unreplaced teeth has not been addressed in this relationship yet. Therefore, denture (non-) use served as a proxy for the exposure to unreplaced teeth in this review (Table 2). Because of low- to moderate-quality studies (Table 5), especially regarding confounding

bias, the recommendation for a causal relationship between denture use and all-cause mortality is graded with level D. However, under the assumptions we chose for the bias analysis, an effect of denture use on *all-cause mortality* would be present.

Albeit relying on moderate level of evidence from two studies [42, 58], findings insinuate a protective effect of prostheses on survival in the elderly, which seems to increase with decreasing number of natural teeth and is at least present for subjects who have lost any occlusal contact on natural teeth [58] or edentulous individuals [54].

The same limitations as for studies on the number of teeth are present in studies on the exposure to denture use (Table 5). Particularly, lack of adjustment for SES is likely to bias the relationship between denture use and mortality, since higher income and higher educational levels may reduce mortality risk and privilege to get missing teeth replaced, at least in Western countries [29]. Additionally, the number of remaining natural teeth primarily determines the type of prosthesis and chewing ability and may, therefore, be a further variable that merits adjustment, as demonstrated by Fukai et al. [42] and supported by the DAG analysis (as stated above).

Misclassification of the unexposed reference category [85], as for example mixing dentate individuals who do not need dentures and individuals with missing or no teeth who do not use dentures [38], two extremely different dental status categories implying just as different chewing ability, could have made it difficult to detect a cause–effect relationship or distorted the relationship. Ill-fitting dentures may evoke denture stomatitis, allowing oral microorganisms to enter the bloodstream via mucosal lesions [60, 86], which may represent a further pathway besides nutrition in which the prosthodontic status acts. None of the studies [37, 38, 42, 54, 58, 87], however, enhanced the specificity of prosthodontic exposure definitions by quality (fixed or removable) of prostheses.

The majority of study participants were old (65–79 years) or very old (≥80 years), thereby limiting generalisability of the findings for younger populations. Older individuals may have been longer exposed to tooth loss and showing advanced alveolar bone resorption to the disadvantage of denture retention and stability and even more impaired chewing function [88]. For further details, please refer to the Supplementary discussion section of the Online Resource 1 on pp 5 and 6.

Conclusions and recommendations for further research

Given results demonstrated by well-designed studies for circulatory mortality and the limitations of the reviewed studies for all-cause mortality, it is open whether competing risks of cause-specific death other than circulatory mortality reduce an effect of the number of teeth on all-cause mortality. An effect of denture use on circulatory mortality remains to be established, as well as how the number of replaced teeth affects mortality.

Drawing on lessons learned, we offer some constructive recommendations for mortality research, which may address essential problems of the topic of this review and beyond [34].

1. Hypothesise different induction periods and reanalyse the data under each separate hypothesis. Define exposure variable dichotomously to allow combining the person-time of exposed subjects that is not related to the exposure (under the hypothesis of a specific induction time) with follow-up time of subjects who were never exposed.
2. Draw samples of adults not older than 65 years.
3. Assess change in exposure and use corresponding models with time-dependent variables.
4. Define the exposure according to the hypothesised pathway (periodontal disease or number of unreplaced teeth). Avoid mixing different types of exposure variables and choose a valid definition of the unexposed reference condition.
5. Assess confounders appropriately (including smoking, diabetes and income, with respect to prosthodontic replacements); avoid prediction models.
6. At least for the nutrition pathway, exclude subjects with history of cancer because they are likely to have changed dietary patterns and lost teeth.

Future research on the effect of tooth loss on mortality can essentially benefit from sophisticated methodological approaches. Acknowledging the aforementioned items may reduce bias in the design and analysis of epidemiological studies and substantiate the contribution of coexisting causal pathways to the exposure effect. Specifying the role of potential pathways by which tooth loss-related mortality is mediated will possibly increase the value of restorative and periodontal interventions for general health, with regard to cost-effectiveness of preventive strategies for healthy ageing as well.

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Conflict of interest This manuscript is free of any conflict of interest, which the authors are aware.

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