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ORIGINAL ARTICLE

Prevalence and severity of oral disease in adults with chronic kidney disease: a systematic review of observational studies

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ABSTRACT

Background. Oral disease may be increased in people with chronic kidney disease (CKD) and, due to associations with inflammation and malnutrition, represents a potential modifiable risk factor for cardiovascular disease and mortality. We summarized the prevalence of oral disease in adults with CKD and explored any association between oral disease and mortality.

Methods. We used systematic review of observational studies evaluating oral health in adults with CKD identified in MEDLINE (through September 2012) without language restriction. We summarized prevalence and associations with all-cause and cardiovascular mortality using random-effects

meta-analysis. We explored for sources of heterogeneity between studies using meta-regression.

Results. Eighty-eight studies in 125 populations comprising 11 340 adults were eligible. Edentulism affected one in five adults with CKD Stage 5D (dialysis) {20.6% [95% confidence interval (CI), 16.4–25.6]}. Periodontitis was more common in CKD Stage 5D [56.8% (CI, 39.3–72.8)] than less severe CKD [31.6% (CI, 19.0–47.6)], although data linking periodontitis with premature death were scant. One-quarter of patients with CKD Stage 5D reported never brushing their teeth [25.6% (CI, 10.2–51.1)] and a minority used dental floss [11.4% (CI, 6.2–19.8)]; oral pain was reported by one-sixth [18.7% (CI, 8.8–35.4)], while half of patients experienced a dry mouth [48.4% (CI, 37.5–59.5)]. Data for kidney transplant recipients and CKD Stages 1–5 were limited.

Conclusions. Oral disease is common in adults with CKD, potentially reflects low use of preventative dental services, and may be an important determinant of health in this clinical setting.

Keywords: chronic kidney disease, epidemiology, meta-analysis, oral health, periodontitis

INTRODUCTION

Chronic kidney disease (CKD) is present in disadvantaged populations disproportionately, exacerbating health disparities and creating a financial burden for health systems [1, 2]. People who have moderate–severe CKD experience rates of premature death at least two to three times that of the general population, due to excess cardiovascular and infectious disease [3–5]. Interventions that modify risk factors for mortality in people with CKD generally do not improve clinical outcomes, particularly those with CKD Stage 5D or transplantation [6–11]. Novel and modifiable determinants of adverse outcomes and disability in people with CKD warrant evaluation.

Oral disease represents a potential and preventable cause of poor health outcomes in people with CKD. It is highly prevalent globally and is the fourth most expensive disease to treat in most developed countries [12, 13]. In low-income countries, almost all tooth decay is untreated [14] and, despite effective prevention and treatment strategies, poor oral health affects disadvantaged groups disproportionately and impairs quality of life and social functioning [15]. As people with chronic disease generally have an increased unmet need for oral healthcare and use dental services less [16], the burden of low oral health may be increased in people with CKD. Dental visits in the public healthcare setting in the USA are low, particularly for those who have CKD [17]. The overlap between CKD and poverty increases the potential for neglected oral health in this large population [18]. In addition, poor oral health is associated with inflammation and malnutrition (including the protein-energy wasting syndrome) [19, 20], which affect CKD patients disproportionately and are risk factors for accelerated cardiovascular disease and mortality in this population [21]. Accordingly, oral health status is a potential modifiable risk factor for adverse patient-relevant outcomes in the setting of CKD that warrants further study.

The aims of our study were to evaluate oral health and oral hygiene habits in adults with CKD and to estimate the excess risk conferred by poor oral health on mortality in this population.

MATERIALS AND METHODS

We did a systematic review and meta-analysis of observational studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. We searched MEDLINE to Week 3, September 2012, without language restriction (Supplementary Table S1). We included in the systematic review observational studies in which oral health was evaluated in adults who had CKD [abnormal urine tests or renal imaging studies with or without reduced estimated glomerular filtration rate (below 60 mL/min/1.73 m^2)] [23]. Two authors independently evaluated retrieved citations by title and abstract and reviewed in full text all studies that appeared potentially eligible. They also independently extracted study characteristics, prevalence, severity and outcomes of oral health, and risk of bias according to previously published criteria [24]. The primary outcomes of interest were: (i) prevalence and severity of oral disease including dental, periodontal, mucosal and salivary conditions; (ii) oral hygiene habits; (iii) oral symptoms including dysgeusia (distorted sense of taste) and xerostomia and (iv) all-cause or cardiovascular mortality associated with any feature of oral health. Using keywords from the search strategy, we also searched for, and tabulated estimates of, the prevalence and characteristics of oral health in the general population that were available in published studies or reports (Supplementary Table S2).

Statistical analysis

We extracted the prevalence for oral health characteristics when the number or proportion of patients affected and the number at risk were both provided. When continuous scales were used [e.g. the decayed missing filled teeth (DMFT) index], we extracted the reported mean, standard deviation and sample size. Whenever available, we extracted the adjusted risk ratio and its 95% confidence interval (CI) for the risk of all-cause or cardiovascular mortality in adults with CKD who had oral disease compared with those without oral disease (reference category). Where a study reported data for more than one separate study population (e.g. several stages of CKD), we extracted data for each population separately.

We used random-effects meta-analysis to summarize data for the predefined outcomes and report prevalence and 95% CI for dichotomous variables and mean (95% CI) for continuous variables. We tested for between-study heterogeneity in summary estimates using the Cochran Q and I^2 statistics [25] and did prespecified random-effects subgroup and metaregression analyses to explore the effects of age, gender, time on dialysis or geographical region on estimates of prevalence or disease severity for edentulism, DMFT index, periodontitis, gingival index, plaque index, oral pain and candidiasis. Insufficient extractable data were available to conduct meta-regression analyses to control for the proportion of participants

with diabetes mellitus in individual studies. We did analyses using Comprehensive Meta-analysis (Biostat, Englewood, NJ, Version 2, 2005).

RESULTS

Description of studies

We retrieved 2230 citations from MEDLINE and identified five additional studies from reference lists (Supplementary Table S1). Eighty-eight studies in 125 populations (11 340 adults) met inclusion criteria (summarized in Table 1 and described in Supplementary Table S3) [26–113]. Most studies focused on adults with CKD Stage 5D (90 populations; n = 6171) [26–29, 31, 32, 34–38, 41–57, 59–64, 66, 67, 69, 71–75, 77, 78, 80, 82, 83, 85, 86–90, 94–98, 100–107, 110–113], with a smaller number evaluating oral health in those with CKD Stages 1–5 (14 populations; n = 3384) [33, 41, 64, 65, 68, 76, 98, 102, 103, 105, 106, 109, 110] or kidney transplant recipients (16 populations, n = 1345) [27, 30, 39, 40, 52, 60, 70, 79, 84, 89, 93, 94, 99, 108, 110, 112]. The remainder evaluated multiple stages of CKD or did not detail the stage of CKD (5 populations, n = 440) [58, 81, 91, 92]. Studies were generally small [median sample size, 44 (range 8–2303)]; all but three studies evaluated fewer than 500 participants [65, 76, 90]. The duration of dialysis varied between 0 and 125 months and time with a kidney transplant varied between 13 and 116 months. Most study populations were from Europe and the Americas, with the remainder from the Western Pacific and the Eastern Mediterranean and one from South-East Asia; none originated from Africa (Supplementary Figure S1). The risk of bias in available studies was generally high (Supplementary Figure S2).

Summary analyses

Data for summary estimates in adults with CKD Stage 5D are provided in Table 2.

Dental disease

Two studies reported edentulism in 42% of 617 adults and 6.4% of 2303 adults with CKD Stages 1–5 [65, 76]. In 10 studies of 1516 patients with CKD Stage 5D, edentulism affected 20.6% (CI, 16.4–25.6%) and was not modified by age, gender, time on dialysis or geographical region (Figure 1) [43, 45, 46, 50, 56, 72, 80, 88, 90, 113].

The DMFT index is the sum of decayed, missing or filled permanent teeth. The mean DMFT index in adults with CKD Stages 1–5 was moderate to high (range, 11.3 and 24.9) in three studies (n = 111, mean population age 45 years) [68, 98, 110] and was between 6.6 and 26 in adult patients with CKD Stage 5D [28 populations; n = 1345, mean population age 50 (CI 47–54) years] (Supplementary Figure S3) [29, 35, 38, 42, 44, 46, 49, 50, 53, 54, 59, 69, 78, 95, 98, 110, 113]. In one kidney transplant population (n = 9; mean population age 51 years), the mean DFMT index was 25.7 [110]. In summary analyses, DMFT indices were similarly high in adults with CKD Stages 1–5 [18.7 (CI, 10.5–27.0)] and those with CKD Stage 5D [14.5 (CI, 12.7–16.3)] (P for subgroup difference = 0.29). The mean DMFT index in adults with CKD Stage 5D increased with age (meta-regression P = 0.001), but was not associated with gender or dialysis duration. The DMFT index in adults with CKD Stage 5D also varied by geographical region, with studies in the Eastern Mediterranean reporting the lowest DMFT index [9.0 (CI 8.2–9.8)], with an increasing index in studies from Europe [14.2 (CI, 13.8–14.7)], the Western Pacific [16.5 (CI, 14.9–18.0)] and America [17.9 (CI 17.2–18.6)] (P < 0.001 for subgroup difference).

The mean number of decayed permanent teeth in 17 populations treated with CKD Stage 5D was 2.6 [CI, 2.0–3.2, n = 855, mean population age 50 (CI, 45–55) years] [29, 35, 38, 42, 44, 53, 59, 95, 98, 113] and was 2.9 (CI, 1.9–4.0) in four populations [n = 251, mean population age 50 (CI, 43–57)] with CKD Stages 1–5 [68, 98, 109]. The mean number of filled teeth in 16 populations with CKD Stage 5D [n = 839, mean population age 50 (CI, 45–55) years] was 3.8 (CI 2.8–4.9) [29, 35, 38, 42, 44, 53, 59, 95, 98, 113] and 2.6 and 4.0 in two populations with CKD Stages 1–5 (n = 102, mean population age 45 years) [68, 98].

Periodontal and gingival disease

Periodontal disease is a spectrum of disease involving inflammation of gingival tissues caused by plaque accumulation, ranging from gingivitis alone to substantial inflammatory destruction of supporting periodontal tissues (periodontitis). Definitions of periodontitis in the contributing studies varied widely (Supplementary Table S4). Periodontitis affected 31.6% (CI, 19.0–47.6) of adults with CKD Stages 1–5 (5 populations; n = 2961) [65, 76, 102, 109] and 56.8% (CI 39.3–72.8) of adults with CKD Stage 5D (Figure 1) [45–48, 51, 54–56, 66, 71, 82, 97, 102] (P = 0.04 for subgroup difference). The prevalence of periodontitis in CKD Stage 5D was unaffected by age, but increased as the proportion of women and duration of dialysis increased (meta-regression P < 0.001). In addition, prevalence varied by global region {America [27.1% (CI, 12.9–48.2)], South-East Asia [63.3% (CI, 45.1–78.4)], Europe [67.7% (CI 42.5–85.6)], Eastern Mediterranean [73.8% (CI, 58.6–84.9)] and Western Pacific [77.5% (67.5–85.1)]} (P < 0.001 for subgroup difference).

The mean periodontal probing depth (PPD) is also a measure of periodontal health and describes the deepening of the gingival sulcus along which dental plaque biofilm can migrate along the root surface. In CKD populations, the mean PPD was 2.3 mm (26 populations, CI, 2.0–2.6) in CKD Stage 5D (n = 726) [29, 37, 38, 46, 49, 50, 55, 67, 73, 77, 85, 95, 107, 112], 0.7 and 2.4 mm in two populations with CKD Stages 1–5 (n = 101) [68, 105] and 2.0 and 2.6 mm in two transplant populations (n = 74) [94, 112]. The clinical attachment loss (CAL) is the extent of periodontal support that has been destroyed around teeth. In data limited to populations treated with dialysis, the mean CAL was 3.5 mm (CI, 2.99–4.16) in 10 populations (n = 331) [41, 49, 50, 67, 69].

The gingival index assesses the severity of gingivitis. In adults with CKD Stage 5D (33 populations; n = 1399), gingival indices were of mild–moderate severity [mean 1.5 (CI, 1.3–1.6)] [29, 31, 37, 38, 45, 48–51, 55, 67, 68, 73, 75, 77, 85, 89, 94, 95, 102, 107, 112] and increased with age, proportion of men and duration on dialysis (meta-regression P <

Table 1. Summary characteristics of included studies according to stages of CKD

Stage of CKD[a]	Overall no. of populations (no. of participants)	Cohort description; number of populations (no. of participants)	No. of participants [median (range)]	WHO region; no. of populations (no. of participants)	Weighted mean age (range) (no. of populations with data)	Weighted proportion men (range) (no. of populations with data)	Weighted time treated with dialysis or with transplant, estimated glomerular filtration rate, mL/min/1.73 m^2 (range) (no. of populations with data)[b]	Weighted proportion with diabetes (range) (no. of populations with data)
CKD Stages 1–5	14 (3384)	CKD; 12 (3235) CKD; diabetic nephropathy; 1 (96) CKD; non-diabetic kidney disease; 1 (53)	44 (21–2303)	Africa; 0 (0) America; 2 (2920) Eastern Mediterranean; 0 (0) Europe; 11 (371) South-East Asia; 0 (0) Western Pacific; 1 (40)	48.7 years (44.5–51.0) (7)	53.6% (38.3–71.6%) (6)	— (20.2–80.4 mL/min/1.73 m^2) (3)	35.2% (0–100%) (5)
CKD Stage 5D	90 (6171)	Haemodialysis; 74 (4279) Peritoneal dialysis; 7 (364) Haemodialysis + peritoneal dialysis; 8 (812) Dialysis (type unspecified); 1 (716)	44 (8–716)	Africa; 0 (0) America; 17 (1720) Eastern Mediterranean; 13 (775) Europe; 50 (2424) South-East Asia; 1 (30) Western Pacific; 9 (1222)	49.5 years (31.6–66) (70)	52.7% (30–100%) (60)	44.9 months (0–125) (30)	30.2% (0–100%) (35)
Kidney transplant	16 (1345)	Kidney transplant recipients; 16 (1345)	42 (9–453)	Africa; 0 (0) America; 2 (53) Eastern Mediterranean; 2 (228) Europe; 12 (1064) South-East Asia; 0 (0) Western Pacific; 0 (0)	37.2 years (31.5–43.5) (8)	59.8% (39.4–88.9%) (10)	— (61.7–103) (2)	— (0–44%) (2)

[a]Summary data for studies with multiple stages of CKD that could not be disaggregated are not included.
[b]Weighted means calculated across all populations for which sufficient data were provided.
CKD, chronic kidney disease.

Table 2. Meta-analytical prevalence or severity of oral diseases in adults with CKD Stage 5D

Variable	No. of study populations (no. of participants)	Random effects prevalence or mean (95% CI)	Heterogeneity in summary estimate	
			I^2 (%)	P-value
Dental disease				
Edentulous (%)	10 (1516)	20.6 (16.4–25.6)	73	<0.001
Decayed missing filled teeth (DMFT)	28 (1345)	14.5 (12.7–16.3)	97	<0.001
Number of decayed permanent teeth (*n*)	17 (855)	2.6 (2.0–3.2)	95	<0.001
Number of filled permanent teeth (*n*)	16 (839)	3.8 (2.8–4.9)	97	<0.001
Periodontal disease				
Periodontitis (%)	13 (1117)	56.8 (39.3–72.8)	96	<0.001
Periodontal probing depth (PPD) (mm)	26 (726)	2.3 (2.0–2.6)	99	<0.001
Clinical attachment loss (CAL) (mm)	10 (331)	3.5 (2.99–4.16)	98	<0.001
Gingival index (mm)	33 (1399)	1.5 (1.3–1.6)	99	<0.001
Oral hygiene and symptoms				
Plaque index	41 (1826)	1.9 (1.7–2.0)	96	<0.001
Brushing (%)				
Never	4 (326)	25.6 (10.2–51.1)	94	<0.001
Once a day	4 (326)	26.8 (17.2–39.4)	78	0.003
Twice a day or more	4 (326)	24.0 (13.3–39.5)	85	<0.001
Floss (%)	9 (898)	11.4 (6.2–19.8)	88	<0.001
Mouth wash (%)	4 (522)	27.4 (9.0–59.0)	96	<0.001
Oral pain (%)	8 (582)	18.7 (8.8–35.4)	92	<0.001
Dysgeusia (%)	6 (424)	40.5 (20.1–64.7)	94	<0.001
Mucosal disease				
Ulceration (%)	11 (832)	8.6 (2.7–24.2)	92	<0.001
Oral candidiasis (%)	6 (404)	19.6 (12.1–30.1)	77	0.001
Oral cancer (%)	—	—	—	—
Salivary disease				
Xerostomia (%)	11 (898)	48.4 (37.5–59.5)	89	<0.001
Salivary flow rate pre-dialysis, stimulated (mL/min)	12 (579)	0.86 (0.73–0.99)	90	<0.001
Salivary flow rate pre-dialysis, unstimulated (mL/min)	12 (621)	0.22 (0.19–0.25)	85	<0.001

0.001 for all). The gingival index in patients with CKD Stage 5D also showed regional variation [increasing severity: America 0.90 (CI, 0.7–1.1), Europe 1.4 (CI, 1.1–1.7), Western Pacific 1.5 (CI, 1.3–1.6), Eastern Mediterranean 1.9 (CI, 1.3–2.5)] ($P < 0.001$ for subgroup differences). Gingival indices were 0.89 and 1.18 in two studies comprising 120 adults with CKD Stages 1–5 [68, 102].

Oral hygiene and symptoms

Oral hygiene practices were only reported in adults treated with CKD Stage 5D. In four studies reporting the brushing habits of 326 adults [31, 66, 72, 73], 25.6% (CI, 10.2–51.1) reported never brushing teeth, 26.8% (CI, 17.2–39.4) reported brushing once a day and 24.0% (CI, 13.3–39.5) reported brushing at least twice a day. In nine populations of 898 participants [31, 54, 61, 72, 73, 80, 95, 113], 11.4% (CI, 6.2–19.8) reported using dental floss and in four studies comprising 522 participants, 27.4% (CI, 9.0–59.0) reported using mouthwash [54, 61, 80, 113].

The plaque index is used to assess the thickness of plaque on tooth surfaces closest to the gum and is a measure of oral hygiene. The mean plaque indices were 1.14 and 1.62 in two populations with CKD Stages 1–5 ($n = 73$) [33, 102] and 2.19 in 54 kidney transplant recipients [94]. The mean plaque index in 41 populations with CKD Stage 5D ($n = 1826$) was 1.9 (CI 1.7–2.0) and increased with age but was not influenced by gender or time treated with dialysis [29, 31, 37, 38, 41, 47–51, 59, 67, 69, 73, 75, 77, 85, 89, 94, 102, 112]. The plaque index varied between regions [in increasing order of severity; America 1.4 (CI, 1.1–1.6), Western Pacific 1.7 (0.8–2.6); Eastern Mediterranean 1.8 (1.7–2.0); Europe 2.1 (1.9–2.2); South-East Asia 2.1 (1.8–2.5); P for subgroup difference < 0.001].

Oral pain or burning was reported in 18.7% (CI, 8.8–35.4) of eight populations with CKD Stage 5D ($n = 582$) [44, 50, 57, 60, 62, 73, 80] (Figure 1) and in 0% and 4.1% of kidney transplant recipients [60, 99]. The prevalence of oral pain increased with dialysis duration (meta-regression $P < 0.001$) but was unrelated to age, gender or region. In two populations with CKD Stage 5D, 4 of 126 (3.2%) and 30 of 47 (63.8%) reported trouble biting or chewing [44, 73]. Dysgeusia, an abnormal sense of taste, was reported by 40.5% (CI, 20.1–64.7) of six populations of adults with CKD Stage 5D ($n = 424$) (Figure 2) [44, 56, 57, 62, 73].

Mucosal disease

Mucosal ulceration affected 8.6% (CI, 2.7–24.2) of 11 populations treated with CKD Stage 5D ($n = 832$) [28, 44, 53, 57, 62, 69, 72, 74, 80] and 6 of 453 (1.3%) transplant recipients [84]. Oral candidiasis affected 2 of 9 (22.2%) adults with CKD Stages 1–5 [110], 19.6% of adults with CKD Stage 5D (CI 12.1–30.1; 6 populations; $n = 404$) [47, 52, 57, 60, 69, 104]

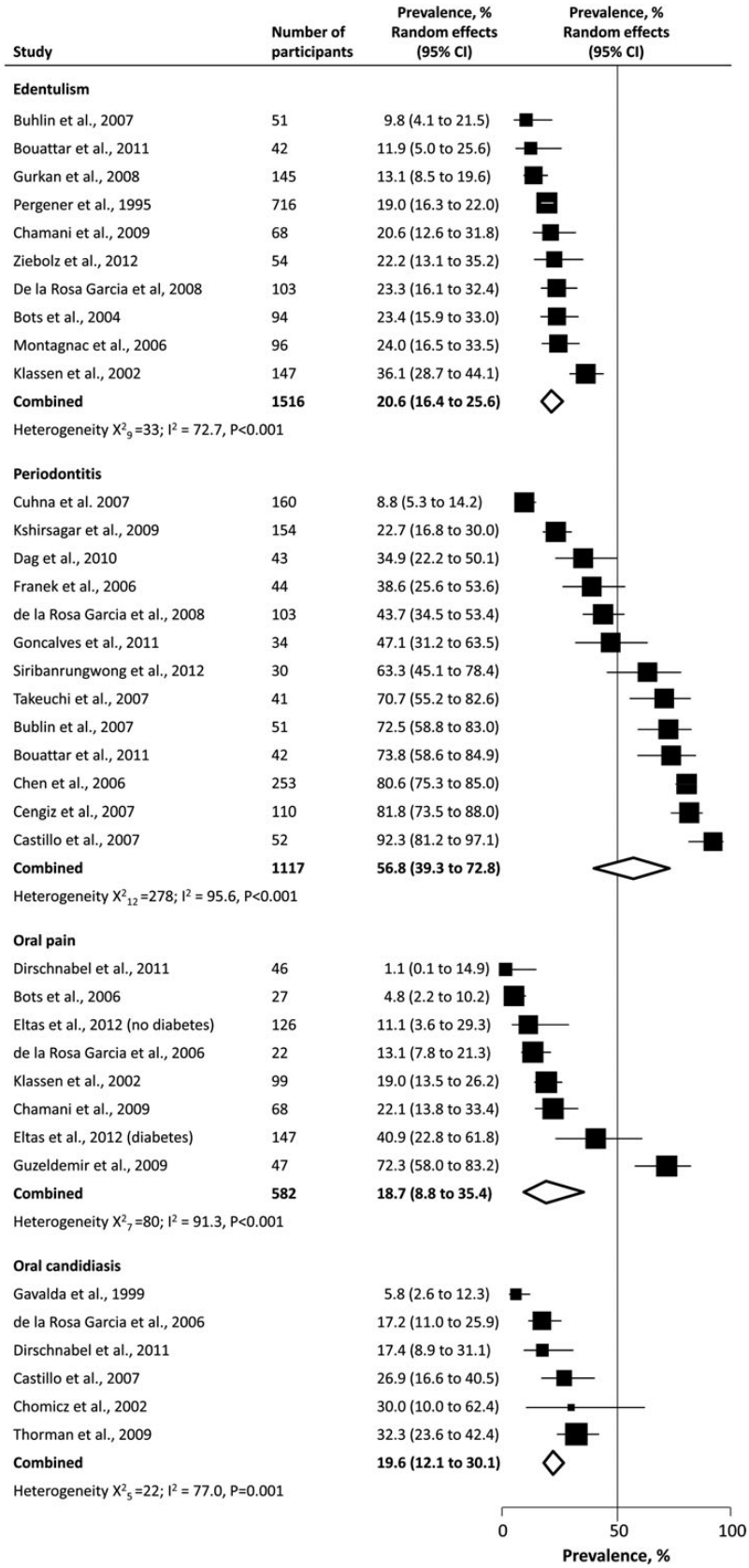

FIGURE 1: Prevalence of edentulism, periodontitis, oral pain and candidiasis in adults with CKD Stage 5D.

(Figure 1) and 13.3% (CI, 3.9–37.0) of four kidney transplant populations ($n = 230$) [52, 60, 79, 110]. The prevalence of oral candidiasis in patients with CKD Stage 5D increased with age (meta-regression $P < 0.01$), but not gender, time on dialysis or region. Oral herpetic lesions were reported in between 2.0 and 2.9% of adults with CKD Stage 5D ($n = 246$) [57, 60, 74]. The prevalence of oral cancer was not extractable from available studies.

Salivary abnormalities and thirst

Xerostomia is the subjective complaint of a dry mouth. In 11 populations with CKD Stage 5D ($n = 898$), xerostomia was reported by 48.4% (CI, 37.5–59.5) (Figure 2) [43, 45, 50, 54, 56, 57, 60, 62, 80, 100]. Sixty-five of 94 (69%) adults with CKD Stage 5D reported thirst [43] and 31.9 and 57.4% of adults with CKD Stage 5D in two populations ($n = 141$) reported difficulty swallowing [43, 73].

The major cause of xerostomia is salivary gland hypofunction, often as a side effect of medication [114]. On average, unstimulated flow rates are 0.3 mL/min and stimulated flow can reach a maximum of 7 mL/min [115]. The mean stimulated predialysis salivary flow rates reported in 12 populations with CKD Stage 5D ($n = 579$) was 0.86 mL/min (CI, 0.73–0.99) [34, 35, 38, 42, 43, 64, 86, 102, 103]. whereas the mean unstimulated salivary flow rates in the period before dialysis was 0.22 mL/min (CI, 0.19–0.25) in 12 populations, comprising 621 adults [26, 42, 43, 62, 64, 100, 101, 103, 106].

All-cause and cardiovascular mortality

Two studies focusing on long-term haemodialysis therapy reported risks of all-cause and cardiovascular mortality associated with moderate to severe periodontitis. These studies, which were at generally lower risk of bias, showed a consistently increased adjusted risk of mortality and cardiovascular mortality in participants with moderate to severe periodontitis compared with those with no or mild periodontitis (Figure 3), although reported risk estimates were generally imprecise and included the possibility of no association [51, 82]. Meta-analysis was not possible as three independent populations were not available. Risks of mortality associated with other features of oral health were not extractable.

DISCUSSION

This systematic review finds that poor oral health is highly prevalent and frequently severe for adults with CKD worldwide. In adults with CKD Stage 5D, approximately one in five are edentulous. The DMFT index in adults with CKD Stage 5D, which summarizes overall dental status, suggests dental health is poor as measured by WHO criteria for this population. The number of filled teeth is lower than the general US population, which may reflect lower use of dental services, while the number of permanent teeth is lower and the number of decayed teeth is higher [17]. Periodontitis affects over half of adults with CKD Stage 5D and PPDs, indicative of destructive periodontal disease, are increased, although estimates in those with earlier stages of kidney disease are less certain. One-quarter of adults with CKD Stage 5D never brush their teeth and a small minority use dental floss or mouth wash. Mucosal disease in all populations with CKD has been infrequently reported, especially oral cancerous lesions. Dry mouth is reported by approximately half of adults with CKD Stage 5D, although evidence for systematic salivary gland hypofunction is inconclusive. Periodontitis may increase risks of all-cause and cardiovascular mortality in adults with CKD, but associations are imprecise and additional data are required. Wide variation in estimates of oral disease are present with differences based in part on global region, patient age and duration of dialysis treatment, limiting confidence in the results. Data for oral health are particularly sparse for kidney transplant recipients.

Our finding that poor oral health is common and severe for adults who have CKD is relevant to new research prioritization in the field of kidney disease. Oral health, and particularly destructive periodontitis, is associated with poor prognostic factors in CKD patients including malnutrition, the protein-energy wasting syndrome and inflammation [51, 82, 116] and may predict progressive kidney disease [117]. It is biologically plausible that poor oral health causes adverse outcomes in CKD mediated via endothelial dysfunction [118], atherosclerosis [119], thrombosis [120], vascular injury and endotoxinaemia [121] and chronic inflammation [120, 122, 123].

Despite potential direct pathways explaining the link between oral health and clinical outcomes, it is also possible that oral health and cardiovascular disease share common causal pathways that explain their association. Such factors include age, health behaviours, nutrition, smoking and socioeconomic status pathways, although observational analyses controlling for some or all of these potentially explanatory variables still detect an association between oral health and mortality [122, 124]. Although periodontitis is associated with atherosclerotic disease in the general population, periodontal disease and cardiovascular disease share common risk factors such as tobacco use, diabetes and age, and the link with adverse outcomes is potentially confounded [125]. Randomized data are not available to show that treating periodontal inflammation reduces either systemic inflammation or cardiovascular events, although research indicates improved endothelial function following intensive periodontal treatment [126].

While extensive information about oral disease as a determinant of health is available in general populations, data exploring the link between oral health and mortality in CKD are based on few studies with imprecise but generally consistent risk estimates and are limited to periodontal disease. Additional prospective data in larger CKD populations would assist in greater understanding of the association between oral health and clinical outcomes in this population that may justify additional research targeted at treating dental disease and periodontitis. In addition, the prevalence and importance of quality-of-life indicators for oral disease (discomfort, self-assessment of oral health and appearance, avoidance of laughing or smiling, or being unable to chew) are largely uncertain in people with CKD and additional research would be valuable. Additional data suggesting a link between oral health and clinical outcomes in CKD would suggest the need to test

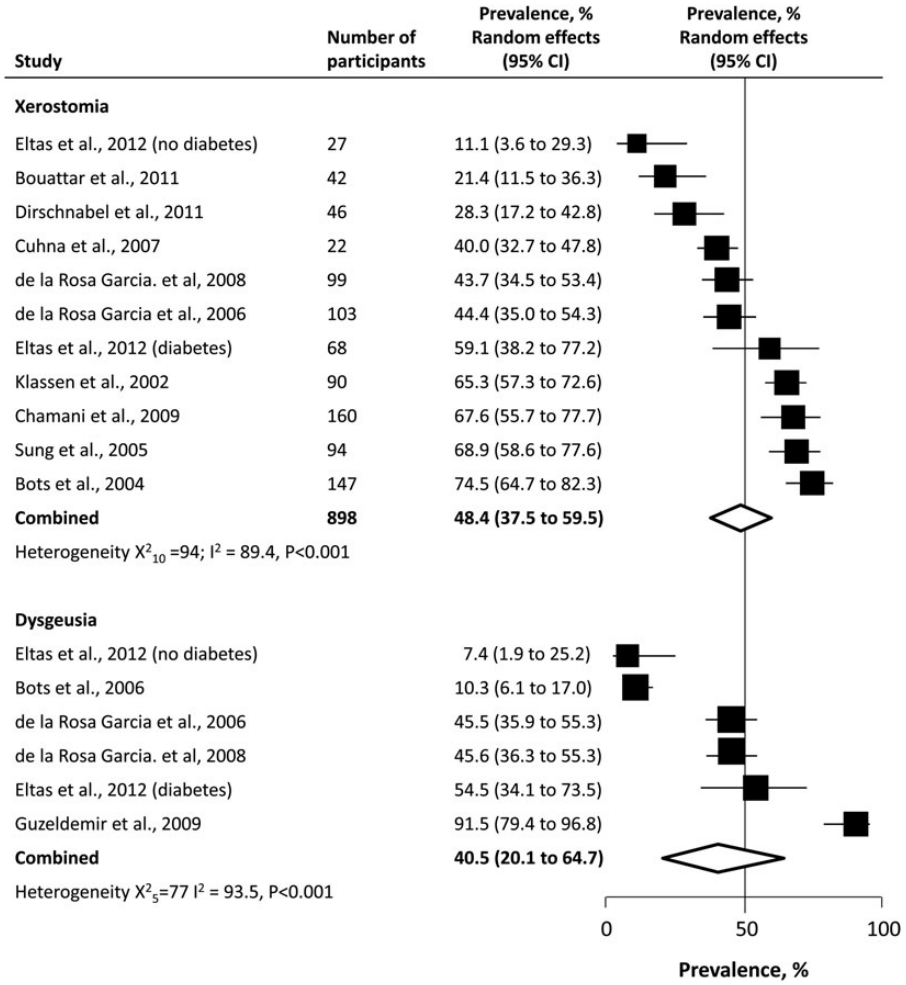

FIGURE 2: Prevalence or xerostomia and dysgeusia in adults with CKD Stage 5D.

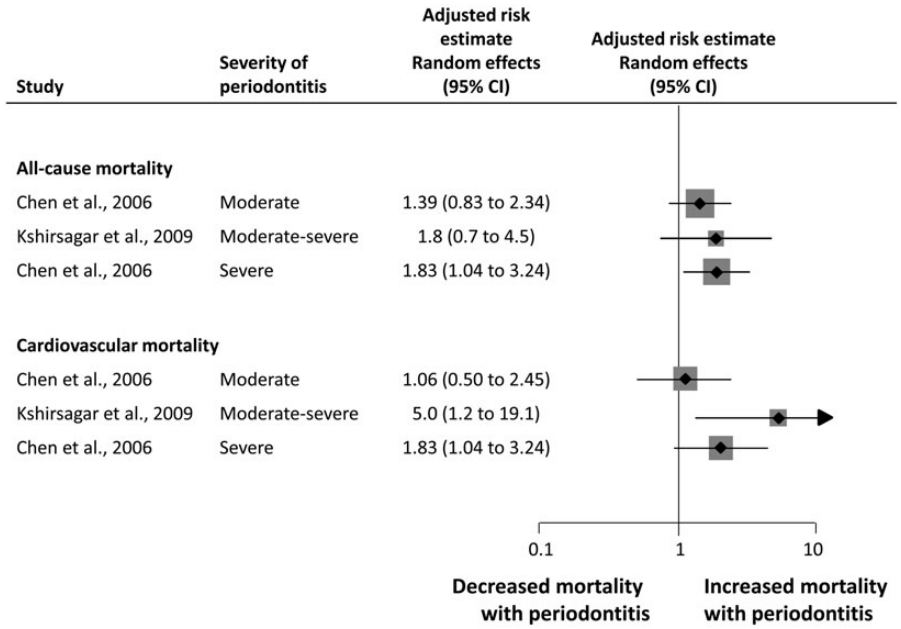

FIGURE 3: Risk of all-cause and cardiovascular mortality associated with moderate to severe periodontitis compared with no or mild periodontitis in adults with CKD Stage 5D. Summary estimates are not calculated as three or more separate study populations were not available for each outcome.

population-wide and individual-based strategies [127] to reduce dental and oral disease in populations with CKD. In addition, exploring CKD patient preferences and priorities for dental care could guide additional research and practice interventions. Regional variations in oral disease, as seen in the global population, indicate strategies for interventions should be locally developed and evaluated.

The global determinants of oral health are complex and include individual behaviour, such as oral hygiene and use of preventive and curative dental care services, as well as factors related to the health system and oral health services, including actual and perceived barriers to care, and broader political and environmental issues such as sanitation, nutrition and fluoridation [128]. International experience suggests that strong socioeconomic and ethnic gradients determine adult oral health even in the presence of childhood public oral health care programmes, and which are also likely to be relevant for people with CKD [128]. Across countries and oral health systems, better dental health controlled for socioeconomic factors is found in adults with preventive dental care habits and regular dental flossing [128]. These data, together with studies in this review, suggest that the risk factors for oral disease in people with coexisting CKD may be complex and likely to be contributed to by ethnic and socioeconomic factors that may require broad political and health system responses. Only about 1 in 10 adults who had CKD visited a dentist in 1 year in a US public healthcare system [17], which is consistent with our finding that people with CKD may have more decayed and missing teeth and fewer filled teeth, suggesting lower uptake of preventive and curative dental care.

We suggest some caution in the interpretation of our results. First, we have used a general population from the USA for comparisons with CKD populations, which may not be valid given the geographical variation in oral disease globally and between studies in our review. Secondly, our meta-analyses demonstrated high levels of between-study heterogeneity (differences in the estimates between studies that occurred beyond the level of chance) which were incompletely explained by meta-regression controlling for study-level variables and known determinants of oral health. Thirdly, while substantial data were available for adults with CKD in largely industrialized regions, we can shed little insight into the burden of oral disease in adults with earlier stages of CKD and in Asian and African regions, which represent a large proportion of the global population with chronic disease. Additional larger studies in these areas would be informative. Finally, data for the other aspects of oral diseases on clinical outcomes including quality of life are largely absent and we did not explore the link between periodontitis and risks of CKD progression, although studies suggest an association [65].

In conclusion, oral disease may be an important health burden in populations who have CKD. Additional research is needed to evaluate the patient-level impact of oral health in this population as well as patient perspectives and priorities for care and the cost-effectiveness of strategies to improve oral health. Periodontitis is a potential risk factor for mortality in CKD, but additional larger studies are required before intervention strategies can be tested.

AUTHOR CONTRIBUTIONS

M.R. assisted with designing the study methodology, located references, extracted data, assessed study quality and provided feedback on primary and subsequent drafts; S.C.P. designed the methodology, assisted with reference location, checked data extraction, assessed study quality, ran analyses and interpreted results, and drafted and submitted the primary report; J.C.C. helped to design the methodology, interpreted results and provided feedback on the primary and subsequent drafts; G.G. assisted with designing the study methodology, located references, extracted data, assessed study quality and provided feedback on primary and subsequent drafts; D.W.J. was consulted on methodology, helped interpret results and provided feedback on the primary and subsequent drafts; P.J.F. was consulted on methodology, helped interpret results and provided feedback on the primary and subsequent drafts; M.T. helped interpret results and provided feedback on primary and subsequent drafts; M.P. was consulted on methodology, helped interpret results and provided feedback on the primary and subsequent drafts; M.D.B. helped interpret results and provided feedback on primary and subsequent drafts; G.F.M.S. initiated the review, helped to design the methodology, assisted with drafting of the manuscript and helped interpret results. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors helped to interpret the findings and write the final report. G.F.M.S. is the guarantor.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

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