Association between Dental Factors and Mortality

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Introduction

Chronic oral infections and tooth loss are associated with an increased risk of cardiovascular diseases (CVD). Most research has studied the link between marginal periodontitis and systemic diseases, and periodontitis has been established as an independent risk factor for CVDs (Lockhart *et al.* 2012). Caries and gingival inflammation associate with CVD risk factors, starting already in childhood (Pussinen *et al.* 2019). Possible mechanisms linking oral infections to increased CVD risk are bacteremia, endotoxemia, and a systemic inflammatory burden (Pietiäinen *et al.* 2018, Schenkein *et al.* 2020). Since the inflammatory and microbial profiles of periodontitis and endodontic infections have similar features, endodontic infections may increase the risk of CVDs via comparable pathways (Segura-Egea *et al.* 2015, Cotti & Mercuro 2015, Pietiäinen *et al.* 2019). In recent years, studies have reported a possible link between endodontic infections and CVDs (Khalighinejad *et al.* 2016, Liljestrand *et al.* 2016, Berlin-Broner *et al.* 2016, Aminoshariae *et al.* 2018). However, the effect of endodontic treatment on systemic health remains controversial. Many epidemiological studies of endodontic infections and CVD do not consider root canal fillings at all (Khalighinejad *et al.* 2016), some use them as a proxy for endodontic infections (Joshipura *et al.* 2006, Caplan *et al.* 2009), and others suggest even protective features of root canal fillings, noting that they might be subject to bias (Meurman *et al.* 2017, Cowan *et al.* 2020). Thus, more research that clearly separates primary (e.g. radiographic lesion and no root canal filling), secondary (e.g. radiographic lesion appearing after root canal filling), and treated (e.g. radiographic lesion disappearing after root canal filling) endodontic lesions are warranted.

Prospective studies have independently associated tooth loss with the risk of incident CVD events and diabetes mellitus, as well as with CVD-related and all-cause mortality (Cabrera *et al.* 2005, Demmer *et al.* 2008, Watt *et al.* 2012, Hu *et al.* 2015, Liljestrand *et al.* 2015, Joshy *et al.* 2016). The two most common dental diseases, dental caries (endodontic infections) and periodontal disease, are also the two most common reasons for tooth loss (Phipps &

Stevens 1995, Richards *et al.* 2005). Missing teeth thus crudely reflect the accumulation of oral infections that an individual has experienced throughout their life, but one should bear in mind that teeth might also have been impacted, may be congenitally missing, or have been extracted due to, for example, orthodontic treatment, trauma, or malposition. Past oral infections and poor nutritional status due to impaired masticatory function are the two prevailing explanations for the persistently observed association between missing teeth and poor survival (Koka & Gupta 2018). A recent systematic review concluded that missing teeth are indeed associated with mortality, even though past research has found significant heterogeneity in experimental design and residual confounding cannot be ruled out (Koka & Gupta 2018). Masticatory function as well as nutritional status may be restored with prosthodontic rehabilitation among those who are financially able and motivated users of health care services. It has been suggested that wearing dentures might associate with lower mortality, but scientific evidence supporting this association is insufficient and to date, research on the effect of prosthodontic rehabilitation on life expectancy is scarce (Gupta *et al.* 2019).

Past research has largely focused on associations between pathologic oral conditions and survival, while the effect of professional intervention has attained less attention. The aim was to study if the number of teeth or the use of removable dentures was associated with mortality in an eight-year follow-up of the Parogene cohort. A further aim was to determine whether radiographically verified periapical lesions at baseline, with or without root canal fillings, were associated with cardiovascular mortality and all-cause mortality when missing teeth and use of dentures are accounted for. The oral status of the Parogene population was initially described and related to baseline coronary status by Buhlin *et al*. (2011). Endodontic pathosis have previously been investigated in two cross-sectional studies. Coronary status has been related to endodontic lesions (Liljestrand *et al*. 2016), which have been further investigated in respect of oral microbiota and serum and saliva immune responses (Liljestrand *et al.* 2016, Pietiäinen *et al.* 2019). This article emphasises the

endodontic/prosthodontic-treatment variables and is unique because of its follow-up of approximately eight years on mortality in the Parogene cohort: all previous studies have been based on cross-sectional data.

Materials and methods

Population

The Finnish Corogene study was designed to study coronary artery disease (CAD) and examined 5297 consecutive Finnish patients undergoing coronary angiography at the Helsinki University Hospital between June 2006 and March 2008 (Vaara *et al.* 2012). The Parogene population, a random gender-stratified subset of the Corogene cohort, consists of n=508 Finnish adults (mean age 63.3 years, SD 9.1) who were enrolled for extensive clinical and radiographic oral examinations 6 to 20 weeks after the angiography. The Parogene study complied with the principles of the Declaration of Helsinki and written informed consent was obtained from all study participants. The study design was approved by the Helsinki University Hospital ethics committee (Reg. no. 106/2007). The study complied with STROBE guidelines for observational studies (von Elm *et al.* 2008).

The initial coronary diagnosis was determined by the angiography results: no significant CAD (<50% stenosis of the coronary arteries, n=152), chronic CAD (≥50% stenosis in at least one coronary artery, n=184), or ACS (an episode of chest pain, typical ECG changes, elevated levels of cardiac biomarkers and ≥50% stenosis in at least one coronary artery; n=169). The number of occluded arteries was also determined on the basis of the angiography. Information on dyslipidaemia, hypertension, and diabetes was obtained from medical records, i.e. if patients had respective prescribed medications.

Oral examination

A detailed description of the data collection has been published earlier (Buhlin *et al.* 2011). The patients were asked to complete a questionnaire prior to the oral examinations, which included information on weight, height, medications, and smoking habits. Two calibrated periodontal specialists performed the oral examinations. The recorded parameters included probing pocket depth (PPD, registered from six sites of each tooth), bleeding on probing (BOP), suppuration, caries lesions, root remnants, dentures, and number of teeth and implants present. Data on removable dentures were dichotomized into 'no dentures' or 'any dentures', which included partial or full dentures in either jaw. The periodontal inflammatory burden index (PIBI) (Lindy *et al.* 2008) was calculated by adding the number of periodontal sites with PPD 4–5 mm to the number of periodontal sites with PPD ≥6 mm and multiplying it by two.

The recorded oral parameters were complemented by information from panoramic radiographs, namely: root canal fillings, endodontic lesions, and alveolar bone loss. All the radiographs were evaluated by one radiologist specialized in Oral and Maxillofacial Radiology. Endodontic lesions were diagnosed radiographically into widened periapical spaces (Periapical index=3) or larger apical rarefactions (Periapical index 4-5), according to the Periapical index (Ørstavik *et al.* 1986). As one of the aims was to make a clear distinction between previously treated and untreated endodontic lesions, an 'endodontic treatment score' was calculated for each dentate patient with available radiographs, as previously described by Pietiäinen *et al.* (2019): I, no endodontic lesions (n=361, 76.6%); II, teeth with apical rarefactions, all with root canal fillings (n=57, 12.1%); and III, apical rarefactions in tooth/teeth without root canal fillings (n=53, 11.3%)

Statistical analysis

Data on mortality and cause of death were assessed via record linkage with the Finnish Causes of Death register (mean follow-up time 7.81 years, SD 1.45 years). Cardiovascular mortality was defined on the basis of the ICD-10 codes for the cause of death (codes I00-I99, Diseases of the circulatory system, regarded as cardiovascular reasons for death).

Edentulous patients (n=32) and those without radiographs available (n=3) were excluded from further analyses, resulting in n=471 patients. The differences between the baseline characteristics of patients who survived and of those who died for any cause or due to cardiovascular issues during the follow-up were compared using the chi-squared test for categorical variables and the Mann-Whitney U-test for continuous variables. The association between the number of widened periapical spaces, apical rarefactions, and root canal fillings, and all-cause and cardiovascular mortality was analysed using Cox regression with Firth's penalized maximum likelihood method. Age at angiography was used as the entry point and age at death or age the end of the follow-up was used as the exit point in the model. The Cox regression model was adjusted for gender, smoking (never/ever), number of occluded arteries in the angiography, PIBI index, number of teeth, and use of removable dentures. A similar model was calculated for the association between the endodontic treatment score and all-cause and cardiovascular mortality. All statistical analyses were performed using R software (www.r-project.com).

Results

A total of n=69 deaths were recorded during the follow-up, most of which, n=41 (59.4%) were due to CVDs. Although more patients died among those with CAD at baseline (15.9 vs 11.8%), the difference was not statistically significant (p=0.24) (Figure 1). Other causes of death were neoplasms (n=15), diseases of the digestive system (n=4), diseases of the musculoskeletal system and connective tissue (n=1), diseases of the nervous system (n=2), diabetes mellitus (n=1) and unknown reasons (n=5).

The baseline characteristics of the population are displayed in Table 1 and Table 2, along with a comparison of those who died during follow-up and the whole population. Patients who died of any cause were more often male (77% vs. 64%, p=0.03), current or ex-smokers (67% vs. 44%, p=0.03) and had more occluded arteries in coronary angiography than those

who survived. They were generally older at baseline (mean 67 years vs 62 years, $p<0.001$) and had significantly fewer teeth (median 20 vs 24, $p<0.001$). Those who died due to CVD had largely similar characteristics to the all-cause mortality group at baseline.

Multi-adjusted Cox regression was performed to test the association between oral parameters and the risk of death (mean follow-up time 7.81 years, Table 3). The number of teeth had a strong inverse association with both all-cause ($p=0.001$, Figure 2) and cardiovascular mortality ($p=0.003$). In addition, the use of removable dentures had a negative association with mortality ($p=0.003$ for all-cause mortality and $p=0.01$ for cardiovascular mortality). This association was independent of the number of teeth.

The number of widened periapical spaces or apical rarefactions was not associated with the risk of all-cause or cardiovascular death. However, the number of root canal fillings was associated with a reduced risk of all-cause and cardiovascular death, disregarding the periapical status. Endodontic treatment score II (teeth with apical periodontitis, all with root canal fillings) was also inversely associated with all-cause and cardiovascular mortality. Endodontic treatment score III (apical periodontitis in tooth/teeth without root canal fillings) was not associated with the risk of death.

The relationship between the number of teeth and cardiovascular risk factors (Table 4) was investigated further. Patients with 26 or more teeth were most often never-smokers, whereas those with fewer teeth were more often ex-smokers. The number of occluded arteries detected in coronary angiography was higher in the groups of patients with fewer teeth. In addition, diabetes was less common among patients with more than 26 teeth.

Discussion

Oral health, defined as a state free from pain, tooth loss, infections, and other diseases, should be considered a prerequisite for healthy eating habits and psychosocial wellbeing. In this well-characterized prospective cohort of patients with cardiac symptoms, those who died

due to CVD or any cause during the follow-up had fewer natural teeth. They also had a lower number of treated apical lesions than the survivors, possibly reflecting a logical consequence of tooth extractions. When the number of teeth was taken into account, patients with root fillings had better survival rates regardless of the radiologically determined success of root canal treatment. Both the survivors and the deceased displayed a similar prevalence of untreated apical periodontitis. Among all dental parameters, missing teeth was the strongest predictor of poor survival, and advanced tooth loss was associated with smoking, severity of CAD, and diabetes. The two most common reasons for tooth extractions are periodontitis and caries, with associated endodontic complications (Phipps & Stevens 1995, Richards *et al.* 2005). This complies with the findings of a previous study, which concluded that the number of missing teeth is an easily detectable risk-indicator of incident CVD, diabetes and death (Liljestrand *et al.* 2015). Interestingly, in the present study, patients with denture-rehabilitated dentition had superior survival rates.

The role of apical periodontitis in systemic health, especially in CVD, is often investigated (Aminoshariae *et al.* 2018). However, only a few studies are prospective. Among young men (aged ≤40), the cumulative burden of chronic endodontic inflammation associated inversely with the time to CAD diagnosis (Caplan *et al.* 2006), and participants with CAD were more likely to have greater self-reported history of endodontic lesions (Caplan *et al.* 2009) and high endodontic burden associated with incident cardiovascular events (Gomes *et al.* 2016). In one study, patients with at least one RCT were at a relative risk of 1.2 (1.14-1.67) for incident myocardial infarction or CAD death (Joshipura *et al.* 2006), whereas another study reported that at least one root filled tooth associated with a lower risk of CVD mortality (Meurman *et al.* 2017). These two studies did not consider endodontic lesions with treatment needs, although the study by Joshipura *et al.* (2006) took into account the extent of caries. A recent report by Cowan *et al.* (2020), based on 15.8 years of follow-up of n=6638 subjects, found that self-reported endodontic treatment associated with a lower risk of coronary events in unadjusted models only. Interestingly, the model's statistical significance was further

diluted by ‘access to care’ and ‘dental care use’ data, confounders that are rarely controlled for in this context (Cowan *et al.* 2020). In the present study, the continuous parameters of ‘number of teeth with root canal fillings’ and ‘endodontic lesions in only root canal treated teeth’ were associated with a lower risk of all cause and CVD death, whereas neither widened periapical spaces nor apical rarefactions associated significantly with mortality. These results suggest that conservative dentistry, i.e. saving the tooth by endodontic procedures, partly negates the adverse effects of advanced tooth loss on CVD survival (Liljestrand *et al.* 2015). This also highlights the diagnostic problematics of periapical regeneration/repair following root canal treatment. A radiolucent periapical lesion in root canal treated teeth might indicate persisting intraradicular infection, but also more benign processes such as irritation from foreign bodies or accumulated cholesterol crystals, periradicular cysts, scar tissue formation, or a granuloma in the healing phase (Nair 2006). Periapical radiolucencies might therefore not be as systematically detrimental in treated teeth as in untreated teeth; a subject that requires further research. Lastly, endodontically treated teeth function as an epidemiological indicator of high patient motivation and utilization of dental services, much like the possession of dentures.

Even a slightly reduced dentition has been linked with poorer intake of nutrient-rich foods and dietary fibres (Nowjack-Raymer & Sheiham 2007). The present results are in line with a systematic review by Gupta *et al*.(2019), which concluded that wearing dentures might reduce patient mortality. A removable denture can be regarded as a non-essential optional device, which nevertheless increases experienced quality of life (Hultin *et al.* 2012) and restores masticatory function (Ali *et al.* 2018). Having dentures might also reflect patient motivation to lead a healthy lifestyle in general (Gupta *et al.* 2019) and to use health care services (Wanyonyi *et al.* 2017). The possession of removable dentures constitutes an interesting protective factor, independently of the number of teeth.

Insufficient masticatory function has been associated with hazards of 1.96 (1.68-2.29) for all-cause mortality (Adolph *et al.* 2017). On the one hand, the Paris Prospective study has

recently reported that adults with a preserved chewing capacity present higher odds of better behavioural cardiovascular health, which is mainly associated with a healthy diet (Range *et al.* 2019). On the other hand, in another study, restoration to complete dental arches or to 10 occluding pairs improved the mastication performance of old people compared to baseline, but the nutrition biomarkers did not differ between the groups, suggesting that mastication performance may only have minor effects on nutritional status (Wallace *et al.* 2018). A similar observation was made in a national FINDIET97 study (n=2452) with 24-hour dietary recall, in which intake of energy, carbohydrates, fat, or protein did not differ significantly across categories of missing teeth (Liljestrand *et al.* 2015). However, loose-fitting partial dentures may impair chewing and consumption of hard foods (Liedberg *et al.* 2004). Hence, it could be postulated that impaired masticatory function tends to debilitate nutritional intake, but the mere rehabilitation of the masticatory function beyond the necessary number of occluding units is not a sufficient intervention for restoring dietary habits (Tada & Miura 2014).

In this context, it is noteworthy that prosthetic care in public dental services in Finland is only partly subsidized and excludes laboratory work. The National Health Insurance system in Finland, developed to reimburse some of the expenses of private health care, has never included dental prosthetics or laboratory costs (Suominen *et al.* 2017). Moreover, private health insurance in Finland does not usually cover the costs of dental treatment, unless it is due to an accident. Therefore, accessibility to prosthodontic rehabilitation is related to socioeconomic status, an important confounding factor that could not be controlled for in this cohort.

The present study setup was limited by its small sample size, and consequently a small number of endpoints, which diluted the statistical power of the analyses. The effect of a small sample size was visible in the rather wide 95% confidence interval of the results (Table 3), Therefore the direction of statistically significant results have been emphasized rather than actual risk estimates. Information on the activity of endodontic lesions was not

available, as the status was only radiographically determined at one timepoint. In addition, the follow-up data were limited to information available from the Finnish Causes of Death register, i.e. time and cause of eventual death. The lack of dietary parameters was one of the limitations of the study, and thus these were not accounted for.

Conclusions

In this study, the most evident predictor of fatal outcomes was the number of missing teeth, while endodontic infections per se did not impose additional risk. However, signs of professional intervention in these complications, i.e. root canal treatment of infected teeth and removable dentures for rehabilitation of reduced dentition, associated with superior survival rates. These findings might partly be explained by utilization of health care services, which in turn reflects the status of patients' knowledge and motivation. Due to the limitations of a rather small sample size, these results should be interpreted as indicative and encourage further investigation within larger populations.

References

Adolph M, Darnaud C, Thomas F *et al.* (2017) Oral health in relation to all-cause mortality: The IPC cohort study. *Scientific Reports* **7,** 44604.

Ali Z, Baker SR, Shahrbaf S, Martin N, Vettore MV. (2018) Oral health-related quality of life after prosthodontic treatment for patients with partial edentulism: A systematic review and meta-analysis. *The Journal of Prosthetic Dentistry* **121**, 59-68.

Aminoshariae A, Kulild JC, Fouad AF. (2018) The impact of endodontic infections on the pathogenesis of cardiovascular disease(s): A systematic review with meta-analysis using GRADE. *Journal of Endodontics* **44,** 1361-1366.

Berlin-Broner Y, Febbraio M, Levin L. (2016) Association between apical periodontitis and cardiovascular diseases: A systematic review of the literature. *International Endodontic Journal* **50**, 847-859.

Buhlin K, Mäntyla P, Paju S *et al.* (2011) Periodontitis is associated with angiographically verified coronary artery disease. *Journal of Clinical Periodontology* **38,** 1007-1014.

Cabrera C, Hakeberg M, Ahlqwist M *et al.* (2005) Can the relation between tooth loss and chronic disease be explained by socio-economic status? A 24-year follow-up from the population study of women in Gothenburg, Sweden. *European Journal of Epidemiology* **20,** 229-236.

Caplan DJ, Chasen JB, Krall EA *et al.* (2006) Lesions of endodontic origin and risk of coronary heart disease. *Journal of Dental Research* **85,** 996-1000.

Caplan DJ, Pankow JS, Cai J, Offenbacher S, Beck JD. (2009) The relationship between self-reported history of endodontic therapy and coronary heart disease in the Atherosclerosis Risk in Communities Study. *Journal of the American Dental Association* **140,** 1004-1012.

Cotti E & Mercuro G. (2015) Apical periodontitis and cardiovascular diseases: Previous findings and ongoing research. *International Endodontic Journal* **48**, 926-32.

Cowan LT, Lakshminarayan K, Lutsey PL, Beck J, Offenbacher S, Pankow JS. (2020) Endodontic therapy and incident cardiovascular disease: The Atherosclerosis Risk in Communities (ARIC) study. *Journal of Public Health Dentistry* **80,** 79-91.

Demmer RT, Jacobs DR,Jr, Desvarieux M. (2008) Periodontal disease and incident type 2 diabetes: Results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. *Diabetes Care* **31,** 1373-1379.

Gomes MS, Hugo FN, Hilgert JB *et al.* (2016) Apical periodontitis and incident cardiovascular events in the Baltimore Longitudinal Study of Ageing. *International Endodontic Journal* **49,** 334-342.

Gupta A, Felton DA, Jemt T, Koka S. (2019) Rehabilitation of edentulism and mortality: A systematic review. *Journal of Prosthodontics* **28,** 526-535.

Hu HY, Lee YL, Lin SY *et al.* (2015) Association between tooth loss, body mass index, and all-cause mortality among elderly patients in Taiwan. *Medicine* **94,** e1543.

Hultin M, Davidson T, Gynther G *et al.* (2012) Oral rehabilitation of tooth loss: A systematic review of quantitative studies of OHRQoL. *The International Journal of Prosthodontics* **25,** 543-552.

Joshipura KJ, Pitiphat W, Hung HC, Willett WC, Colditz GA, Douglass CW. (2006) Pulpal inflammation and incidence of coronary heart disease. *Journal of Endodontics* **32,** 99-103.

Joshy G, Arora M, Korda RJ, Chalmers J, Banks E. (2016) Is poor oral health a risk marker for incident cardiovascular disease hospitalisation and all-cause mortality? Findings from 172 630 participants from the prospective 45 and Up Study. *BMJ Open* **6,** e012386.

Khalighinejad N, Aminoshariae MR, Aminoshariae A, Kulild JC, Mickel A, Fouad AF. (2016) Association between systemic diseases and apical periodontitis. *Journal of Endodontics* **42**, 1427-34.

Koka S, Gupta A. (2018) Association between missing tooth count and mortality: a systematic review. *Journal of Prosthodontic Research* **62**, 134-151.

Liedberg B, Norlen P, Owall B, Stoltze K. (2004) Masticatory and nutritional aspects on fixed and removable partial dentures. *Clinical Oral Investigations* **8,** 11-17.

Liljestrand JM, Havulinna AS, Paju S, Männistö S, Salomaa V, Pussinen PJ. (2015) Missing teeth predict incident cardiovascular events, diabetes, and death. *Journal of Dental Research* **94,** 1055-1062.

Liljestrand JM, Mäntyla P, Paju S *et al.* (2016) Association of endodontic lesions with coronary artery disease. *Journal of Dental Research* **95**, 1358-1365.

Lindy O, Suomalainen K, Mäkelä M, Lindy S. (2008) Statin use is associated with fewer periodontal lesions: A retrospective study. *BMC Oral Health* **8,** 16.

Lockhart PB, Bolger AF, Papapanou PN *et al.* (2012) Periodontal disease and atherosclerotic vascular disease: Does the evidence support an independent association?: A scientific statement from the American Heart Association. *Circulation* **125,** 2520-2544.

Meurman JH, Janket SJ, Surakka M *et al.* (2017) Lower risk for cardiovascular mortality for patients with root filled teeth in a Finnish population. *International Endodontic Journal* **50**, 1158-1168.

Nair PN. (2006) On the causes of persistent apical periodontitis: A review. *International Endodontic Journal* **39,** 249-281.

Nowjack-Raymer RE & Sheiham A. (2007) Numbers of natural teeth, diet, and nutritional status in US adults. *Journal of Dental Research* **86,** 1171-1175.

Phipps KR, Stevens VJ. (1995) Relative contribution of caries and periodontal disease in adult tooth loss for an HMO dental population. *Journal of Public Health Dentistry* **55**, 250–252.

Pietiäinen M, Kopra KA, Vuorenkoski J *et al.* (2018) *Aggregatibacter actinomycetemcomitans* serotypes associate with periodontal and coronary artery disease status. *Journal of Clinical Periodontology* **45**, 413-421.

Pietiäinen M, Liljestrand JM, Kopra E, Pussinen PJ. (2018) Mediators between oral dysbiosis and cardiovascular diseases. *European Journal of Oral Sciences* **126** (Suppl. 1), 26-36.

Pietiäinen M, Liljestrand JM, Akhi R *et al.* (2019) Saliva and serum immune responses in apical periodontitis. *Journal of Clinical Medicine* **8,** 889.

Pussinen PJ, Paju S, Koponen J *et al.* (2019) Association of childhood oral infections with cardiovascular risk factors and subclinical atherosclerosis in adulthood. *JAMA Network Open* **2,** e192523.

Range H, Perier MC, Boillot A *et al.* (2019) Chewing capacity and ideal cardiovascular health in adulthood: A cross-sectional analysis of a population-based cohort study. *Clinical Nutrition* **39**, 1440-1446.

Richards W, Ameen J, Coll AM, Higgs G. (2005) Reasons for tooth extraction in four general dental practices in South Wales. *British Dental Journal* **198**, 275–278.

Schenkein HA, Papapanou PN, Genco R, Sanz M. (2020) Mechanisms underlying the association between periodontitis and atherosclerotic disease. *Periodontology 2000* **83**, 90-106.

Segura-Egea JJ, Martin-Gonzalez J, Castellanos-Cosano L. (2015) Endodontic medicine: Connections between apical periodontitis and systemic diseases. *International Endodontic Journal* **48,** 933-951.

Suominen AL, Helminen S, Lahti S *et al.* (2017) Use of oral health care services in Finnish adults - results from the cross-sectional Health 2000 and 2011 Surveys. *BMC Oral Health* **17,** 78.

Tada A & Miura H. (2014) Systematic review of the association of mastication with food and nutrient intake in the independent elderly. *Archives of Gerontology and Geriatrics* **59,** 497-505.

Vaara S, Nieminen MS, Lokki ML *et al.* (2012) Cohort Profile: the Corogene study. *International Journal of Epidemiology* **41***,* 1265–1271*.*

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Journal of Clinical Epidemiology* **61**, 344-9.

Wallace S, Samietz S, Abbas M, McKenna G, Woodside JV, Schimmel M. (2018) Impact of prosthodontic rehabilitation on the masticatory performance of partially dentate older patients: Can it predict nutritional state? Results from a RCT. *Journal of Dentistry* **68,** 66-71.

Wanyonyi KL, Radford DR, Gallagher JE. (2017) Dental treatment in a state-funded primary dental care facility: Contextual and individual predictors of treatment need? *PloS One* **12,** e0169004.

Watt RG, Tsakos G, de Oliveira C, Hamer M. (2012) Tooth loss and cardiovascular disease mortality risk--results from the Scottish Health Survey. *PloS One* **7,** e30797.

Ørstavik D, Kerekes K, Eriksen HM. (1986) The periapical index: A scoring system for radiographic assessment of apical periodontitis. *Endodontics & Dental Traumatology* **2,** 20-34.

Figure legends

Figure 1: Flowchart of study population.

Figure 2: Unadjusted survival curve according to number of teeth at baseline.

Table 1. Characteristics of study population by categorical variables.

		Survivors (n=402)	Death by any cause, (n=69)	p[1]	Death by CVD, (n=41)	p[1]
		n (%)			n (%)	
Gender (male)	Male	256 (64)	53 (77)	**0.03**	32 (78)	0.08
	Female	146 (36)	16 (23)		9 (22)	
Diabetes		88 (22)	19 (28)	0.27	13 (32)	0.17
Dyslipidaemia		321 (81)	53 (79)	0.80	33 (81)	0.97
Hypertension		252 (63)	43 (64)	0.85	26 (63)	0.97
Smoking	No	202 (50)	23 (33)		13 (32)	
	Ex	154 (33)	35 (51)	**0.03**	21 (51)	0.09
	Current	46 (11)	11 (16)		7 (17)	
Number of occluded arteries	0	12 (31)	15 (22)		11 (27)	
	1	116 (29)	6 (9)		2 (5.0)	
	2	75 (19)	18 (26)	**<0.001**	9 (22)	**0.001**
	3	84 (21)	28 (41)		19 (46)	
Alveolar bone loss (moderate-total)		121 (30)	25 (36)	0.32	19 (46)	**0.027**
≥1 Widened periapical spaces		223 (56)	30 (44)	0.07	18 (44)	0.19
≥1 Apical rarefactions		101 (25)	10 (15)	0.06	5 (12)	0.07
≥1 Root canal filling		294 (73)	44 (64)	0.11	24 (59)	**0.049**
≥1 Rarefaction and root canal filling		63 (16)	5 (7)	0.07	2 (5)	0.07
≥1 Rarefactions without root canal filling		46 (11)	6 (9)	0.50	4 (10)	0.78
Removable dentures		93 (23)	21 (30)	0.19	13 (32)	0.24

Endodontic treatment score	I	301 (75)	59 (87)		36 (90)	
	II	55 (14)	3 (4)	0.06	0 (0)	**0.039**
	III	46 (11)	6 (9)		4 (10)	

Median follow up time was 3013 days (8.3 years, SD 1.5 years)

[1] Pearson’s chi-squared test

CVD, cardiovascular disease

Table 2. Characteristics of study population by continuous variables.

	Survivors (n=402)	Death by any cause, (n=69)		Death by CVD, (n=41)	
	Mean (SD)		**p[1]**	**Mean (SD)**	**p[1]**
Age	62.4 (9.32)	67.0 (7.37)	**<0.001**	67.5 (7.94)	**0.001**
BMI	27.9 (5.06)	27.8 (5.46)	0.69	28.0 (5.20)	0.96
Bleeding on probing (4 surfaces)	37.2 (18.9)	39.5 (19.5)	0.34	41.7 (18.9)	0.10
Number of 4–5 mm pockets[2]	14.0 (13.2)	10.1 (11.9)	**0.01**	9.54 (9.25)	0.08
Number of over 5 mm pockets[2]	3.64 (8.72)	2.16 (5.81)	0.06	2.02 (5.14)	0.17
Widened periapical spaces	0.82 (0.93)	0.64 (0.91)	0.07	0.73 (1.05)	0.33
Apical rarefactions	0.39 (0.96)	0.25 (0.76)	0.06	0.20 (0.68)	0.07
Root canal fillings	2.30 (2.34)	1.57 (1.64)	**0.03**	1.44 (1.63)	**0.03**
Number of teeth with root canal filling and rarefaction	0.19 (0.48)	0.09 (0.33)	0.07	0.05 (0.22)	0.07
	Median (IQR)		**p[1]**	**Median (IQR)**	**p[1]**
Number of teeth	24 (8)	20 (15)	**<0.001**	18 (14)	**0.002**

Median follow up time was 3013 days (8.3 years, SD 1.5 years)

1 Mann-Whitney U test

2 Measured from 6 surfaces on each tooth

CVD, cardiovascular disease; BMI, body mass index

Table 3. Cox regression models for association between oral parameters and risk of death.

		All-cause death		Cardiovascular death	
		HR (95% CI)	**p**	**HR (95% CI)**	**p**
Model 1					
Number of teeth		0.91 (0.86 - 0.96)	**0.001**	0.89 (0.83 - 0.96)	**0.003**
Use of removable denture		0.24 (0.09 - 0.62)	**0.003**	0.20 (0.06 - 0.72)	**0.01**
Model 2					
Widened periapical spaces		0.78 (0.55 - 1.05)	0.10	0.93 (0.62 - 1.33)	0.69
Model 3					
Apical rarefactions		0.80 (0.49 - 1.14)	0.25	0.74 (0.35 - 1.21)	0.29
Model 4					
Root canal fillings		0.82 (0.70 - 0.94)	**0.005**	0.79 (0.63 - 0.96)	**0.01**
Model 5					
Endodontic treatment score[1]	I	1		1	
	II	0.27 (0.06 - 0.79)	**0.01**	0.09 (0.01 - 0.63)	**0.008**
	III	0.81 (0.32 - 1.74)	0.61	0.92 (0.29 - 2.28)	0.86

Model 1. Cox regression fitted by penalized maximum likelihood method using age as timescale, adjusted for gender, smoking, number of occluded arteries, and PIBI index. Model 2. Number of widened periapical spaces as an additional covariate in Model 1. Model 3. Number of apical rarefactions as an additional covariate in Model 1. Model 4. Number of root canal fillings as an additional covariate in Model 1. Model 5. Endodontic treatment score as an additional covariate in Model 1.

[1] I, no endodontic lesions; II, teeth with apical rarefactions, all with root canal fillings; III, apical rarefactions in tooth/teeth without root canal fillings.

Table 4. Cardiovascular risk factors in subgroups of patients divided according to number of teeth.

		Number of teeth				p[1]
		1–10	**11–20**	**21–25**	**26–**	
		n = 68	**n = 83**	**n = 140**	**n = 180**	
Dyslipidaemia	no	13 (19%)	9 (11%)	33 (24%)	37 (21%)	0.127
	yes	55 (81%)	74 (89%)	106 (76%)	141 (79%)	
Hypertension	no	21 (31%)	23 (28%)	50 (36%)	78 (44%)	0.056
	yes	47 (69%)	60 (72%)	89 (64%)	101 (56%)	
Smoking	never	20 (29%)	33 (40%)	62 (44%)	109 (61%)	**<0.001**
	ex	38 (56%)	36 (43%)	64 (46%)	52 (27%)	
	current	10 (15%)	14 (17%)	14 (10%)	19 (11%)	
Number of occluded arteries	0	14 (21%)	9 (11%)	51 (36%)	69 (38%)	**<0.001**
	1	12 (18%)	23 (28%)	38 (27%)	50 (28%)	
	2	19 (28%)	21 (25%)	18 (13%)	35 (19%)	
	3	23 (34%)	30 (36%)	33 (24%)	26 (14%)	
Diabetes	no	48 (71%)	59 (72%)	99 (72%)	153 (86%)	**0.005**
	yes	20 (29%)	23 (28%)	39 (28%)	25 (14%)	

[1] Pearson’s chi-squared test