Lower risk for cardiovascular mortality for patients with root filled teeth in a Finnish population

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Abstract

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Aim To investigate the relationship of radiographic evidence of root filled teeth to cardiovascular outcomes.

Methodology Baseline data for 506 subjects including 256 angiographically verified heart disease patients and 250 matched cardiologically healthy controls participating in the Kuopio Oral Health and Heart study were collected in 1995–1996. Cardiovascular disease (CVD) mortalities were accrued until 31 May 2015 and appended to the baseline data. Mortality status data were obtained from the Finnish National Death Register where all mortality cases and the causes of death are compiled for all Finnish citizens. Of the 506 participants, 473 subjects who had no missing values in the predictor, outcome or confounding factors were included in the analyses to assess the relationship of radiographic evidence of root filled teeth with prevalent coronary artery disease (CAD) cross sectionally and also with CVD mortality longitudinally. Multivariable logistic regression was used for the cross-sectional part and proportional hazard regression analyses for the longitudinal part of the study were used adjusting for age, sex, smoking, edentulism, diabetes, hypertension, total/HDL cholesterol ratio and income. Additionally, whether this association was independent of periodontitis, and a systemic marker of inflammation, serum C-reactive protein (CRP) was examined.

Results Having ≥1 root filled teeth was associated with 84% lower odds of prevalent CAD with Odds Ratio (OR) = 0.16, 95% confidence interval (CI) 0.09–0.28, $P < 0.0001$. The OR for edentulism was 1.32 (CI: 0.73–2.38), $P = 0.36$, suggesting a nonsignificant increase in risk. Prospectively, having at least one root filled teeth was associated with a 49% lower risk of CVD mortality (hazard ratio [HR] = 0.51, CI = 0.27–0.97, $P = 0.04$) whilst edentulism was associated with nonsignificantly increased risk for CVD mortality: HR = 1.25 (CI: 0.65–2.42), $P = 0.36$. Adjustment for periodontitis or serum CRP levels changed the OR or HR slightly but the associations remained significant.

Conclusions Having ≥1 root filled teeth was associated with significantly lower odds for prevalent CAD cross sectionally and lower risk of cardiovascular mortality prospectively. These reduced associations with CVD were independent of periodontitis or serum CRP levels.

Keywords: cardiovascular mortality, coronary artery disease, C-reactive protein, endodontic treatment, pulpitis.

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Introduction

Chronic oral infections including periodontitis (Beck *et al.* 1996) have been associated with increased risk of CVD and a healthy dentition as a marker for reduced past oral infections has been associated with a significantly lower risk of CVD mortality (Janket *et al.* 2014). Acute infections (Corrales-Medina *et al.* 2013) including upper and lower respiratory tract infections are established risk factors for acute coronary syndrome (Hao *et al.* 2013). In acute infections, bacterial toxins may activate the innate immune system (Hotchkiss & Karl 2003) and initiate intravascular inflammation and thrombosis and consequently may contribute to cardiac events (Cotti *et al.* 2011).

The microorganisms in advanced dental caries cause pulpitis that can lead to irreversible pulpitis and pulp necrosis with apical periodontitis that elicits systemic inflammatory responses (Gomes *et al.* 2013). Such inflammatory responses are risk factors for the development of atherosclerosis and CVD outcomes (Pasqualini *et al.* 2012, Petersen *et al.* 2014, Gomes *et al.* 2016). Early root canal infection is dominated by Gram-positive microbiota comprising approximately 69% followed by Gram-negative bacteria (27%) and fungi (Kouchi *et al.* 1980, Love & Jenkinson 2002). In addition to the Gram-negative anaerobes native to the infected root canal system (Bae *et al.* 1997), necrotic pulp tissue can become co-infected with periodontal pathogens (Liljestrand *et al.* 2016) through lateral canals and denuded dentine surfaces with nonvital pulp (Jansson 2015). Avoiding discomfort from advanced dental caries is the most important priority for many patients (Stoller *et al.* 2004), and extraction of the offending tooth is often chosen by the patients as a preferred treatment option. But this decision is based on nondental factors such as patient/family requests or finances (Johnson 1993). However, extraction can affect subsequent nutritional intake (Nowjack-Raymer & Sheiham 2003, Janket *et al.* 2008, Savoca *et al.* 2010) and the adverse effects of edentulism on health have been well substantiated (Brown 2009). However, no previous studies have compared adverse outcomes of edentulism to saving teeth by root canal treatment. The adverse effects of edentulism on CVD were estimated by separating the edentulous group. In this cohort, 60% of extractions were reported to be due to advanced dental caries and 40% were due to periodontitis, aesthetic reasons or trauma. Inflamed pulpal tissue or periradicular tissue expresses interleukin-6 (IL-6) (Euler *et al.* 1998). Additionally, interleukin-1α and IL-1β are expressed by polymorphonuclear leukocytes in the periradicular tissue (Miller *et al.* 1996). Because these cytokines play major roles in the pathogenesis of CVD (Volpato *et al.* 2001, Bujak & Frangogiannis 2009, Gomes *et al.* 2013, 2016), it was postulated that root fillings will reduce IL-6 or IL-1β leading to decreased risk of future cardiovascular events. Therefore, the aims of this study were to investigate whether:

1. The radiographic evidence of root fillings at baseline would be associated with decreased risk of prevalent coronary artery disease (CAD) cross sectionally and with reduced CVD mortality longitudinally;

2. Concurrent periodontitis will affect the association between root fillings and CVD. Periodontitis has been reported as a contributing factor to CVD and some study participants had both periodontitis and root fillings. Thus, periodontitis is another source of inflammation that may contribute to atherosclerosis. Therefore, the inflammatory burden from periodontitis was controlled to establish the independent contribution of inflammation reduction from root fillings on CVD mortality.

3. Systemic inflammation measured by CRP would affect the association of root fillings and CVD outcomes. CRP has been an independent predictor for CVD (Ridker *et al.* 1998), and the contribution of oral infection to CVD was mediated in part via CRP (Janket *et al.* 2014). Therefore, oral inflammation and CRP are in a confounding relationship. Whether the contribution of reduced inflammation from root fillings to CVD outcomes is independent of CRP was examined.

Materials and methods

Ethical consideration and human subjects' protection

This study was approved by the Joint Ethical Committee of the Kuopio University Hospital and the University of Kuopio. Written informed consent was obtained from all participants. The longitudinal portion of the study was approved by the Boston University Institutional Review Board. This project adhered to the guidelines set forth by the Declaration of Helsinki and the Belmont Accord to assure the safety of human research subjects.

Study population

Kuopio Oral Health and Heart (KOHH) study was initiated as a case–control study in 1995–1996, to investigate the association between oral health and CAD in Kuopio, Finland. For the current study, mortality data (median follow-up of 18.8-years) was appended to the baseline data to create a prospective follow-up study assessing CVD mortality. At baseline 256 consecutive patients attending Kuopio University Hospital coronary angiography unit and with a confirmed diagnosis of CAD were invited to participate in the KOHH study. The CAD diagnosis was made by the presence of at least 50% stenosis in one of the epicardial arteries. Also, 250 age- and gender-matched controls were recruited from the general surgery or otorhinolaryngology departments at the same hospital for elective surgery. They were considered as not having heart disease based on their medical history and electrocardiogram taken during the pre-admission tests. The controls were representative of the population of the same catchment area where the cases arose. The same exclusion and inclusion criteria were applied to the control subjects. Potential subjects who had taken antibiotics during the previous 30 days or had chronic infection other than dental disease were excluded. Additional exclusion criteria for the CAD group were (i) those who needed emergency coronary by-pass surgery or valvular replacement surgery; (ii) those whose disease status was so grave that a dental examination or dental X-ray could not be performed safely; and (iii) those who were deemed to require antibiotic prophylaxis prior to periodontal probing at the time of baseline data collection. Further details regarding this cohort have been published elsewhere (Janket *et al.* 2010, 2014).

Ascertainment of the endpoints

The outcome, CVD mortality, was assessed using the mortality records obtained from the Finnish Death Registry in 2009, 2010, 2011, 2014 and 2015. The World Health Organization International Classification of Diseases (ICD)-10 codes I00 through I99 were considered deaths due to cardiac causes, and the most prevalent one was I25 (chronic ischaemic heart disease). Each resident of Finland has a unique identifier number and the Office of Statistics Finland collects all health data including mortality. The reliability of mortality data was determined to be 99% after comparing 2009 and 2011 records in a random sample

of 100 records. The validity of the mortality records was tested by comparing them to the physician's diagnosis of death from the subjects' medical records. Three disagreements in ICD-10 codes were found in 100 randomly examined records, but upon further detailed investigation, all turned out to be in agreement. For example, one case the Finnish Death Registry listed as 'I21.4: Acute subendocardial myocardial infarction' whilst the physician's diagnosis of death was 'I25.1 Atherosclerotic heart disease'. Although ICD-10 codes were different, they described the similar pathology. Thus, validity was judged to be excellent. These facts were published previously (Janket *et al.* 2014).

Exposure assessment

At the initiation of this study (1995–1996), a single examiner (MS) performed all clinical dental examinations and pantomographic readings according to the World Health Organization format. Pantomographic evidence of root fillings was enumerated by the images of the radiopaque root filling for each patient. The two pantomogram readings by this examiner (MS) exhibited an excellent agreement ($\kappa = 0.9$). Edentulous subjects who could not have root fillings were separately categorized from the root filling assessment. There was one person who was edentulous but had root fillings. This was presumed to be a case of an overdenture where root fillings were provided to improve denture retention. The details of clinical oral examination including number of teeth, amount of vertical bone loss (measured from cemento-enamel junction in mm), calculus deposits and restorations with overhangs as well as salivary immunoglobulins were measured and the results were reported previously (Janket *et al.* 2004, Qvarnstrom *et al.* 2008).

Assessment of covariates

Baseline behavioural and demographic factors were assessed, and the results were published elsewhere (Janket *et al.* 2010, Qvarnstrom *et al.* 2010). Briefly, age in years and smoking in three categories (never-smokers, current smokers and past smokers) were assessed. Body mass index (BMI) was calculated by weight in kg divided by squared height in metres. Total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL) were measured by the automated enzymatic technique. Low-density

lipoprotein (LDL) cholesterol levels were estimated by the Friedewald formula. Hypertension and diabetes were ascertained by medical record review by one of the authors (MS). Subjects were categorized as hypertensive or diabetic if their medical records documented these diagnoses or they received treatments. Periodontitis was categorized using the updated periodontitis definition by which more than one site with probing depth ≥5 mm indicates periodontitis (Eke *et al.* 2012). CRP was measured by immunoturbidimetry utilizing the HITACHI 717 analyzer (Boehringer Mannheim, Mannheim, Germany).

Statistical analyses

Of the original cohort of 506 subjects, 33 were excluded from the analyses because of missing values in the outcomes, the predictors or the covariates. Thus, using SAS version 9.3, basic characteristics such as age, gender, smoking status, BMI, number of teeth and cholesterol levels were compared in 473 subjects without any missing values stratified by root filling status. There were 117 edentulous subjects, and amongst the 356 dentate subjects, 160 had radiographic evidence of root fillings whilst 196 did not. In the bivariate analyses, Fisher's exact or nonparametric tests were used. In multivariate analyses, logistic regression was used in the cross-sectional portion of the study to examine the association of prevalent CAD as the outcome with baseline root filling status as the exposure. In the longitudinal portion of the study, Cox proportional hazard modelling was performed after testing the proportional hazard assumption. The outcome in longitudinal analyses was mortality due to cardiovascular causes. The established confounding factors such as age at the entry to the study, gender, smoking (never, past, current), diabetes, hypertension, total cholesterol-to-HDL ratio (TC/HDL ratio) and personal income were controlled in both cross-sectional and longitudinal portions of the study. Whether concurrent periodontitis or systemic inflammation assessed by serum CRP levels would alter the association of root fillings with CVD mortality was also tested. Additionally, to test whether baseline CAD affects the relationship of root fillings and CVD mortality differentially (effect modification by baseline CAD), the interaction term between baseline CAD and root fillings was analysed. To assess whether affluence alters the relationship of root fillings and CVD mortality, income was controlled. Also the impact of confounding by a generally healthy lifestyle that may be concurrent

with root fillings was tested utilizing sensitivity analyses in non-CVD mortality where inflammation may have lesser influence than CVD.

Results

A total of 148 deaths in the cohort were accrued of which 90 were due to CVD. The leading non-CVD causes were cancer, followed by respiratory diseases and neurologic disorders such as Alzheimer's disease. The sample size was too small to analyse the data on non-CVD mortality.

The baseline characteristics stratified by CAD status are presented in Table 1. As expected, most established CVD risk factors were significantly more prevalent in the CAD group. Of the dental variables, number of remaining teeth and prevalence of periodontitis were higher and the proportion of edentulism was lower in controls. Moreover, 53.6% of the control group had radiographic evidence of root fillings whilst only 14.5% had evidence of root fillings in the CAD group. In general, poor oral health was evident in CAD cases.

In multivariate analyses where age, gender, smoking, hypertension, diabetes, income and TC/HDL cholesterol ratio were adjusted, the edentate subjects were at increased odds of prevalent CAD, albeit nonsignificantly (OR = 1.32, 95% CI: [0.73–2.38], $P = 0.36$) compared with those who did not have evidence of root fillings. By contrast, those who had evidence of root fillings were at 84% lower odds of having prevalent CAD compared to those with no evidence of root fillings (OR = 0.16, 95% CI: 0.09–0.28, $P < 0.0001$). Controlling for periodontitis, which is a different source of oral inflammation, changed the OR slightly to 0.17 but the *P*-value remained highly significant ($P < 0.0001$). In this cohort, the prevalence of periodontitis was 22.6%. Adjusting for either periodontitis or serum CRP levels did not materially alter the results (OR = 0.18, $P < 0.0001$). The majority of the confounding variables were significantly associated with CAD. Nevertheless, root fillings remained significantly and inversely associated with prevalent CAD even after adjusting for these confounders. These results are presented in Table 2.

In the longitudinal portion of the analyses, having at least one root filled tooth was associated with a 49% reduction in the risk of CVD mortality (HR = 0.51, 95% CI: 0.27–0.97, $P = 0.04$) in multivariate analyses. The edentulous group was again at a nonsignificantly elevated risk of CVD mortality

Table 1 Baseline characteristics of the cohort

	No CAD (n = 242)	CAD (n = 231)	P-value
Age, Mean (SD)	59.3 (9.8)	59.9 (9.1)	0.5
Sex (n, %)			
Men	155 (64)	145 (63)	0.77
Women	87 (36)	86 (37)	
Body mass index (BMI)	25.6 (3.7)	23.6 (3.3)	<.0001
Mean (SD)			
Number of teeth	15.7 (10.5)	7.7 (10.5)	<.0001
Mean (SD)			
Proportion with edentulism, n (%)	36 (14.9)	81 (35.1)	<.0001
Periodontitis	54 (22.3)	28 (12.1)	<.0001
Proportion with at least 1 endoTx, n (%)	134 (53.6)	37 (14.5)	<.0001
CVD mortality, n (%)	21 (8.7)	69 (29.9)	<.0001
Education (years)	11.8 (3.5)	10.5 (2.6)	<.0001
Mean (SD)			
Annual income in Euro (SD)	34 058 (11 525)	31 319 (9723)	0.005
Smoking, n (%)			
Never	197 (81.4)	121 (52.4)	0.001
Current	24 (9.9)	25 (10.8)	0.74
Past	21 (8.7)	85 (36.8)	0.0001
Hypertension, n (%)	50 (20.7)	115 (49.8)	0.001
Diabetes, n (%)	14 (5.8)	36 (15.6)	0.0004
LDL cholesterol[a] (mmol L^{-1}) Median[b] (IQR)	3.7 (3.1–4.3)	3.4 (2.9–4.2)	0.003
Triglyceride (mmol L^{-1})[c] Median (IQR)	1.5 (1.2–2.0)	2.0 (1.4–2.6)	<.0001
HDL cholesterol (mmol L^{-1})[d] Median (IQR)	1.3 (1.1–1.5)	1.1 (0.9–1.3)	<.0001
Total/HDL cholesterol ratio, Median (IQR)	4.7 (3.8–5.4)	5.2 (4.2–6.2)	<.0001
CRP (mg L^{-1}) Median (IQR)	4.0 (2–5)	10 (8–26)	<.0001
Fibrinogen (g L^{-1}) Median (IQR)	2.9 (2.6–3.2)	3.1 (2.8–3.7)	<.0001

[a]LDL was estimated by Friedewald formula.
[b]IQR, inter-quartile range.
[c]To convert mmol L^{-1} of triglyceride to mg dL^{-1}, multiply by 88.57.
[d]To convert mmol L^{-1} of cholesterol to mg dL^{-1}, multiply by 38.67.

(HR = 1.27, 95% CI: [0.77–2.11], P = 0.38). Similar to the results in the cross-sectional analyses, the adjustment of periodontitis or serum CRP levels did not materially alter the inverse association of root fillings and CVD mortality (HR = 0.51, 95% CI: 0.27–0.98, P = 0.04). Unlike the results from cross-sectional analyses, the only risk factors significantly predictive of CVD mortality in addition to the radiographic evidence of root fillings were age, smoking and hypertension. These results are presented in Table 3 and illustrated in Fig. 1.

In the testing of effect modification by baseline CAD, the interaction was not a significant predictor for CVD mortality (HR = 1.15, CI: 0.55–2.43, P = 0.71) adjusting for age, smoking and hypertension. To confirm this, the cohort was stratified by baseline CAD status and separate analyses were conducted. The results showed a similar inverse relationship in both cases and controls albeit not significant due to sample size reduction (HR = 0.81 in controls

and HR = 0.82 in cases) confirming no interaction between baseline CAD and root fillings.

Although root fillings are considered an affluence-dependent intervention, adjusting for income did not materially alter the relationship of root fillings and CVD mortality. In a multivariable adjusted model, being in the top 25% of income was inversely associated with CVD mortality (HR = 0.71, 95% CI = 0.39–1.30) but this was not statistically significant (P = 0.21).

Discussion

Within the limitations of this study, radiographic evidence of root fillings was associated with a significantly lower risk of cardiovascular mortality after adjusting for established confounding factors. Moreover, this association was independent of baseline periodontitis or systemic inflammation measured by serum CRP levels. Additionally, baseline CAD did not

Table 2 Multivariate-adjusted odds ratios for the prevalent coronary artery disease

	Exposure groups	Odds ratio (95% confidence interval)	P-value
Model 1	Edentate	1.32 (0.73–2.38)	0.36
	No EndoTx[a]	1 (reference)	–
	EndoTx	0.16 (0.09–0.28)	**0.0001**
Confounding adjusted for Model 1	Sex	2.35 (1.33- 4.14)	**0.003**
	Age	0.98 (0.95–1.00)	0.05
	Smoking	3.10 (2.21–4.30)	**<.0001**
	Total/HDL cholesterol ratio	1.37 (1.15–1.64)	**<.0001**
	Hypertension	3.57 (2.14–5.98)	**<.0001**
	Diabetes	1.67 (0.74–3.78)	0.22
	Income >75 percentile	1.18 (0.66–2.13)	0.57
Model 2	Edentate	1.21 (0.66–2.23)	0.54
	No EndoTx	1 (reference)	–
	EndoTx	0.17 (0.10–0.29)	**0.0001**
Confounding adjusted for Model 2	Sex	2.35 (1.33–4.15)	**0.003**
	Age	0.98 (0.95–1.00)	0.06
	Smoking	3.10 (2.21–4.35)	**<.0001**
	Total/HDL cholesterol ratio	1.37 (1.15–1.64)	**0.0006**
	Hypertension	3.60 (2.15–6.04)	**<.0001**
	Diabetes	1.69 (0.74–3.83)	0.21
	Income >75 percentile	1.18 (0.66–2.13)	0.57
	Periodontitis	0.82 (0.42–1.61)	0.56
Model 3	Edentate	1.25 (0.65–2.42)	0.50
	No EndoTx[a]	1 (reference)	–
	EndoTx	0.18 (0.10–0.32)	**0.0001**
Confounding adjusted for Model 3	Sex	2.63 (1.45–4.77)	**0.002**
	Age	0.96 (0.94–0.99)	**0.01**
	Smoking	3.03 (2.11–4.35)	**0.0001**
	Total/HDL cholesterol ratio	1.28 (1.06–1.54)	**0.01**
	Hypertension	3.43 (1.97–5.98)	**0.0001**
	Diabetes	1.40 (0.60–3.31)	0.44
	Income >75 percentile	1.46 (0.77–2.77)	0.25
	Serum CRP >3 mg L^{-1}	22.1 (7.37–66.6)	**0.0001**

All models were controlled for age, sex, smoking, hypertension, diabetes, T/H cholesterol ratio and income.
Model 2 adjusted for the covariates controlled in the model 1 plus periodontitis.
Model 3 adjusted for the covariates controlled in the model 1 plus C-reactive protein >3 mg L^{-1}.
Bold *P*-values denote significance.
[a]EndoTx: Pantomographic evidence of endodontic treatment amongst dentate subjects.

influence the association of root fillings to CVD mortality.

In the cross-sectional analyses (Table 2), an association between poor oral health and CAD was evident

but this association cannot be considered as a causal relationship. Rather, baseline characteristics may describe the state of oral health due to CAD. Age and gender in relation to CAD were the opposite of generally accepted knowledge that those who are younger or female are less prone to CAD in the general population. However, these young and female subjects in the cohort already had CAD at baseline and their increased risks are described in Table 2.

On the contrary, the prospective results in Table 3 showed that individuals who were older or male were at increased risk for CVD mortality in agreement with generally accepted pattern of risk in CVD. This fact suggests that baseline CAD-related factors are not necessarily risk factors for CVD mortality prospectively. For example, the CRP levels which had strong association with prevalent CAD (OR = 22) or the Total to HDL cholesterol ratio was not a significant predictor for CVD mortality.

Of the total CVD mortality (*n* = 90), 69 CVD deaths (77%) occurred in the CAD group. Because nearly 80% of CVD mortality occurred in the baseline CAD group, it is reasonable to assume that baseline CAD is on the causal pathway to CVD mortality, and adjusting for an intermediate variable on the causal pathway to the endpoint of disease is not appropriate in epidemiology (Hennekens & Buring 1987). Such adjustment would actually bias the results and could even reverse the direction of the association (Cook 2011).

The postulated mechanism is that root fillings may reduce cytokine production such as IL-6 and/or IL-1β which increase atherosclerotic inflammation. However, it is possible that confounding by healthy lifestyle could be the reason for the apparent beneficial effects of root fillings. Therefore, a sensitivity analysis was performed to allay this concern for Hawthorn Effects by testing the relationship between root fillings and non-CVD mortality where inflammation may play a lesser role. Indeed, the results were not significant suggesting that a healthy lifestyle may not be the reason for the decreased CVD mortality. If the observed results were due to healthy lifestyle, the same beneficial effects would have been observed in non-CVD mortality.

Although previous studies suggested that a self-reported history of endodontic therapy increased the risk of incident CVD (Caplan *et al.* 2009), the precise estimation of inflammation from endodontic origin was difficult to measure (Caplan *et al.* 2006). To overcome this difficulty, the radiographic evidence of removal of inflammation from endodontic origin was assessed in

Table 3 Multivariate-adjusted hazard ratios for the cardiovascular mortality

	Exposures	Hazard ratio (95% confidence interval)	P-value
Model 1	Edentate	1.27 (0.77–2.11)	0.34
	No EndoTx[a]	1 (reference)	–
	EndoTx	0.51 (0.27–0.97)	**0.041**
Confounding adjusted for Model 1	Sex	0.73 (0.41–1.29)	0.28
	Age	1.11 (1.07–1.14)	**<.0001**
	Smoking	1.54 (1.18–2.02)	**0.001**
	Total/HDL cholesterol ratio	1.05 (0.89–1.24)	0.59
	Hypertension	1.64 (1.07–2.52)	**0.02**
	Diabetes	1.03 (0.57–1.84)	0.93
	Income >75 percentile	0.71 (0.39–1.30)	0.26
Model 2	Edentate	1.27 (0.74–2.16)	0.38
	No EndoTx	1 (reference)	–
	EndoTx	0.52 (0.27–0.97)	**0.042**
Confounding adjusted for Model 2	Sex	0.73 (0.41–1.29)	0.33
	Age	1.11 (1.07–1.14)	**<.0001**
	Smoking	1.54 (1.18–2.02)	**0.002**
	Total/HDL cholesterol ratio	1.05 (0.89–1.24)	0.50
	Hypertension	1.64 (1.07–2.52)	**0.03**
	Diabetes	1.03 (0.57–1.86)	0.91
	Income >75 percentile	0.71 (0.39–1.30)	0.29
	Periodontitis	0.99 (0.51–1.93)	0.88
Model 3	Edentate	1.19 (0.70–2.04)	0.52
	No EndoTx[a]	1 (reference)	–
	EndoTx	0.51 (0.27–0.98)	**0.043**
Confounding adjusted for Model 3	Sex	0.75 (0.42–1.34)	0.33
	Age	1.11 (1.08–1.15)	**<.0001**
	Smoking	1.55 (1.18–2.04)	**0.002**
	Total/HDL cholesterol ratio	1.06 (0.90–1.25)	0.50
	Hypertension	1.60 (1.04–2.46)	**0.03**
	Diabetes	1.03 (0.58–1.86)	0.91
	Income >75 percentile	0.72 (0.40–1.32)	0.29
	Serum CRP >3 mg L^{-1}	1.06 (0.49–2.29)	0.88

All models were controlled for age, sex, smoking, hypertension, diabetes, T/H cholesterol ratio and income.
Model 2 adjusted for the covariates controlled in the model 1 plus periodontitis.
Model 3 adjusted for the covariates controlled in the model 1 plus C-reactive protein >3 mg L^{-1}.
Bold P-values denote significance.
[a]EndoTx: Pantomographic evidence of endodontic treatment amongst dentate subjects.

the current study. Whilst the exact data on the cause for the root fillings is not available, the highly significant correlation between the number of teeth with root fillings and the number of periapical lesions (apical periodontitis) appears to suggest that root fillings were typically rendered to treat apical periodontitis (Spearman's correlation coefficient = 0.43, P = 0.0001).

This assumption appears to contradict the recent report by Huumonen and colleagues that apical periodontitis was more prevalent in root filled than nonroot filled teeth (Huumonen et al. 2017). However, not all apical radiolucencies (typically assumed apical periodontitis) resolve post-treatment. In fact approximately 36% of post-treatment periapical

radiolucencies remained unchanged in size or even increased after 12 months (Zhang et al. 2015). The reason for this is because not all periapical radiolucencies are pathologic apical periodontitis: some are scar tissues and others can be cysts or tumours (Garcia et al. 2007). Thus, the prevalence of apical periodontitis does not translate well to CVD outcomes (Berlin-Broner et al. 2017) and some radiolucencies may not need root filling (Nair 2006). Moreover, if there were residual apical radiolucencies after root filling, the total inflammatory burden and subsequent risk of CVD would be much less in root filled teeth than in nonroot filled teeth as reported by Liljestrand et al. (2016). These facts are corroborated by a report
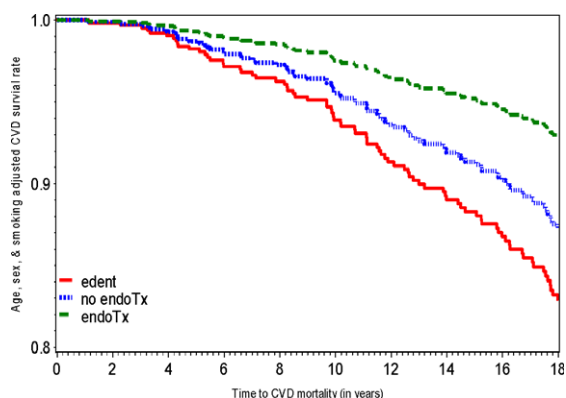
Figure 1 Age, gender and smoking adjusted CVD survival estimates stratified by edentulism and endodontic treatment status.

that apical periodontitis increased oxidative stress (Inchingolo *et al.* 2014) which is a risk factor for atherosclerosis (Sugamura & Keaney 2011, Kornfeld *et al.* 2015) and endodontic treatment reduced reactive oxygen species and increased anti-oxidant potential (Inchingolo *et al.* 2014). These are highly supportive of the hypothesis that root canal treatment will decrease the harmful effects generated by apical periodontitis and will therefore reduce the risk for CVD outcomes. In longitudinal analyses, age, smoking, and hypertension were the independent and significant risk factors to CVD mortality. The close relationship of endodontic inflammation and hypertension was reported in a previous longitudinal study where the risk of incident hypertension was significantly increased (RR = 2.0, 95% CI = 1.16–3.46) with the presence of apical periodontitis (Gomes *et al.* 2016).

The present cohort has been extended from a case–control study to a longitudinal form. As such, concerns for potential risk amplification due to the high prevalence of baseline CAD were raised (Sommerfelt *et al.* 2012). However, the simulated data have proven that the 'time to event analyses' such as Cox proportional hazard regressions which use semi-nonparametric method were unaffected by the high CAD proportion at baseline (Janket *et al.* 2014). Therefore, the results from the present study can be generalized to other populations.

Serum CRP can originate from two different sources: infection- or obesity-related inflammation. Metabolic inflammation is sterile, low grade inflammation observed in obesity, diabetes or atherosclerosis (Janket *et al.* 2015). Obesity and diabetes can increase

intestinal permeability and cause spontaneous endo-toxemia (Cani *et al.* 2007) reflected as an increased serum level of lipopolysaccharide (LPS) (Amar *et al.* 2008). LPS is a component of the Gram-negative bacterial cell wall. This is important because Gram-negative bacteria are the predominant pathogens in periodontitis, and periodontitis is associated with obesity and diabetes. Thus, metabolic inflammation and periodontitis are in a confounding relationship, and the impact of obesity-related metabolic inflammation has to be controlled to establish the independent contribution of periodontitis to CVD risk increase. As CRP which is largely a marker for metabolic inflammation (Gupta *et al.* 2012) has been controlled in the present study, the results are, therefore, independent of metabolic inflammation.

Others reported that CRP levels were inversely associated with socio-economic status (SES)(Kohler *et al.* 2013). The present data also show significant association between low income and increased CRP levels in a *t*-test but this did not translate to CVD mortality in the multivariable adjusted models. The current results from a Finnish cohort with uniformly high living standard are in agreement with other studies from Scandinavia reporting nonsignificant impact of SES on oral health and chronic diseases association (Cabrera *et al.* 2005).

Strengths

Previous research considered self-reported history of endodontic therapy as a marker for inflammation (Caplan *et al.* 2006, Joshipura *et al.* 2006). However, assessing inflammation from self-report may not be reliable as the authors stated (Caplan *et al.* 2006). This difficulty was avoided by assessing the radiological proof of root fillings which is one of the strengths. A long follow-up (median = 18.8 years) and precise dental examination given at baseline are additional strengths of the present study because precise dental measurements increase the fidelity of the results.

Limitations

As shown in Table 1, those who did not opt for root fillings have fewer remaining teeth. This indirectly suggests that these individuals might have chosen extraction rather than root canal treatment. Unfortunately, information regarding the cause for the fewer remaining teeth is not available. It has been presumed

that edentulism results from severe cases of dental infection/inflammation leading to significant adverse outcomes (Lee *et al.* 2006). In the present study where dentate groups were divided by root filling status as well as edentulism, edentulism was not a significant risk factor for CVD outcomes ($P = 0.34$) due to small sample sizes resulting from stratification. However, when the edentulous group was compared to the dentate group without stratifying by root filling status, a significant association of edentulism to CVD mortality (HR = 1.63 [CI: 1.02–2.60]; $P = 0.04$) was observed. This is consistent with the previous reports showing detrimental consequences of edentulism (Osterberg *et al.* 2007, Brown 2009).

Conclusion

Within the limitations of this study, radiographic evidence of root fillings was significantly associated with lower odds for prevalent CAD at baseline and reduced risk of CVD mortality longitudinally controlling for established confounders. These results suggest that root fillings may be associated with reduced CVD risk. However, the residual confounding from the baseline CAD cannot be completely ruled out.

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

References

Amar J, Burcelin R, Ruidavets JB *et al.* (2008) Energy intake is associated with endotoxemia in apparently healthy men. *American Journal of Clinical Nutrition* **87**, 1219–23.

Bae KS, Baumgartner JC, Shearer TR, David LL (1997) Occurrence of *Prevotella nigrescens* and *Prevotella intermedia* in infections of endodontic origin. *Journal of Endodontics* **23**, 620–3.

Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S (1996) Periodontal disease and cardiovascular disease. *Journal of Periodontology* **67**, 1123–37.

Berlin-Broner Y, Febbraio M, Levin L (2017) Association between apical periodontitis and cardiovascular diseases: a systematic review of the literature. *International Endodontic Journal* **50**, 847–59.

Brown DW (2009) Complete edentulism prior to the age of 65 years is associated with all-cause mortality. *Journal of Public Health Dentistry* **69**, 260–6.

Bujak M, Frangogiannis NG (2009) The role of IL-1 in the pathogenesis of heart disease. *Archivum Immunologiae et Therapiae Experimentalis* **57**, 165–76.

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**, 229–36.

Cani PD, Amar J, Iglesias MA *et al.* (2007) Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **56**, 1761–72.

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**, 1004–12.

Cook NR (2011) Urinary sodium excretion and cardiovascular disease mortality. *JAMA* **306**, 1085; author reply 6-7.

Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA (2013) Acute pneumonia and the cardiovascular system. *Lancet* **381**, 496–505.

Cotti E, Dessi C, Piras A *et al.* (2011) Association of endodontic infection with detection of an initial lesion to the cardiovascular system. *Journal of Endodontics* **37**, 1624–9.

Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ (2012) Update of the case definitions for population-based surveillance of periodontitis. *Journal of Periodontology* **83**, 1449–54.

Euler GJ, Miller GA, Hutter JW, D'Alesandro MM (1998) Interleukin-6 in neutrophils from peripheral blood and inflammatory periradicular tissues. *Journal of Endodontics* **24**, 480–4.

Garcia CC, Sempere FV, Diago MP, Bowen EM (2007) The post-endodontic periapical lesion: histologic and etiopathogenic aspects. *Medicina Oral, Patología Oral y Cirugía Bucal* **12**, E585–90.

Gomes MS, Blattner TC, Sant'Ana Filho M *et al.* (2013) Can apical periodontitis modify systemic levels of inflammatory markers? A systematic review and meta-analysis. *Journal of Endodontics* **39**, 1205–17.

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**, 334–42.

Gupta NK, de Lemos JA, Ayers CR, Abdullah SM, McGuire DK, Khera A (2012) The relationship between C-reactive protein and atherosclerosis differs on the basis of body mass index: the Dallas Heart Study. *Journal of the American College of Cardiology* **60**, 1148–55.

Hao WR, Lin HW, Chao PZ *et al.* (2013) Risk of myocardial infarction in patients with rhinosinusitis. *Atherosclerosis* **226**, 263–8.

Hennekens CH, Buring JE (1987) *Epidemiology in Medicine.* Hagerstown, MD: Lippincott Williams & Wilkins.

Hotchkiss RS, Karl IE (2003) The pathophysiology and treatment of sepsis. *New England Journal of Medicine* **348**, 138–50.

Huumonen S, Suominen AL, Vehkalahti MM (2017) Prevalence of apical periodontitis in root filled teeth: findings from a nationwide survey in Finland. *International Endodontic Journal* **50**, 229–36.

Inchingolo F, Marrelli M, Annibali S *et al.* (2014) Influence of endodontic treatment on systemic oxidative stress. *International Journal of Medical Sciences* **11**, 1–6.

Janket SJ, Qvarnstrom M, Meurman JH, Baird AE, Nuutinen P, Jones JA (2004) Asymptotic dental score and prevalent coronary heart disease. *Circulation* **109**, 1095–100.

Janket SJ, Jones JA, Meurman JH, Baird AE, Van Dyke TE (2008) Oral infection, hyperglycemia, and endothelial dysfunction. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **105**, 173–9.

Janket S, Meurman JH, Baird AE *et al.* (2010) Salivary immunoglobulins and prevalent coronary artery disease. *Journal of Dental Research* **89**, 389–94.

Janket SJ, Baird AE, Jones JA *et al.* (2014) Number of teeth, C-reactive protein, fibrinogen and cardiovascular mortality: a 15-year follow-up study in a Finnish cohort. *Journal of Clinical Periodontology* **41**, 131–40.

Janket SJ, Javaheri H, Ackerson LK, Ayilavarapu S, Meurman JH (2015) Oral infections, metabolic inflammation, genetics, and cardiometabolic diseases. *Journal of Dental Research* **94**, 119s–27s.

Jansson L (2015) Relationship between apical periodontitis and marginal bone loss at individual level from a general population. *International Dental Journal* **65**, 71–6.

Johnson TE (1993) Factors contributing to dentists' extraction decisions in older adults. *Special Care in Dentistry* **13**, 195–9.

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

Kohler IV, Soldo BJ, Anglewicz P, Chilima B, Kohler HP (2013) Association of blood lipids, creatinine, albumin, and CRP with socioeconomic status in Malawi. *Population Health Metrics* **11**, 4.

Kornfeld OS, Hwang S, Disatnik MH, Chen CH, Qvit N, Mochly-Rosen D (2015) Mitochondrial reactive oxygen species at the heart of the matter: new therapeutic approaches for cardiovascular diseases. *Circulation Research* **116**, 1783–99.

Kouchi Y, Ninomiya J, Yasuda H, Fukui K, Moriyama T, Okamoto H (1980) Location of Streptococcus mutans in the dentinal tubules of open infected root canals. *Journal of Dental Research* **59**, 2038–46.

Lee HJ, Garcia RI, Janket SJ *et al.* (2006) The association between cumulative periodontal disease and stroke history in older adults. *Journal of Periodontology* **77**, 1744–54.

Liljestrand JM, Mantyla P, Paju S *et al.* (2016) Association of endodontic lesions with coronary artery disease. *Journal of Dental Research* **95**, 1358–65.

Love RM, Jenkinson HF (2002) Invasion of dentinal tubules by oral bacteria. *Critical Reviews in Oral Biology and Medicine* **13**, 171–83.

Miller GA, DeMayo T, Hutter JW (1996) Production of interleukin-1 by polymorphonuclear leucocytes resident in periradicular tissue. *Journal of Endodontics* **22**, 346–51.

Nair PN (2006) On the causes of persistent apical periodontitis: a review. *International Endodontic Journal* **39**, 249–81.

Nowjack-Raymer RE, Sheiham A (2003) Association of edentulism and diet and nutrition in US adults. *Journal of Dental Research* **82**, 123–6.

Osterberg T, Carlsson GE, Sundh V, Steen B (2007) Number of teeth–a predictor of mortality in the elderly? A population study in three Nordic localities. *Acta Odontologica Scandinavica* **65**, 335–40.

Pasqualini D, Bergandi L, Palumbo L *et al.* (2012) Association among oral health, apical periodontitis, CD14 polymorphisms, and coronary heart disease in middle-aged adults. *Journal of Endodontics* **38**, 1570–7.

Petersen J, Glassl EM, Nasseri P *et al.* (2014) The association of chronic apical periodontitis and endodontic therapy with atherosclerosis. *Clinical Oral Investigations* **18**, 1813–23.

Qvarnstrom M, Janket S, Jones JA *et al.* (2008) Salivary lysozyme and prevalent hypertension. *Journal of Dental Research* **87**, 480–4.

Qvarnstrom M, Janket SJ, Jones JA *et al.* (2010) Association of salivary lysozyme and C-reactive protein with metabolic syndrome. *Journal of Clinical Periodontology* **37**, 805–11.

Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH (1998) Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* **98**, 731–3.

Savoca MR, Arcury TA, Leng X *et al.* (2010) Severe tooth loss in older adults as a key indicator of compromised dietary quality. *Public Health Nutrition* **13**, 466–74.

Sommerfelt H, Steinsland H, van der Merwe L *et al.* (2012) Case/control studies with follow-up: constructing the

source population to estimate effects of risk factors on development, disease, and survival. *Clinical Infectious Diseases* **55**(Suppl. 4), S262–70.

Stoller EP, Pyle MA, Perzynski AT (2004) Priorities for oral health goals in a sample of older adults. *Special Care in Dentistry* **24**, 220–8.

Sugamura K, Keaney JF Jr (2011) Reactive oxygen species in cardiovascular disease. *Free Radical Biology and Medicine* **51**, 978–92.

Volpato S, Guralnik JM, Ferrucci L *et al.* (2001) Cardiovascular disease, interleukin-6, and risk of mortality in older women: the women's health and aging study. *Circulation* **103**, 947–53.

Zhang MM, Liang YH, Gao XJ, Jiang L, van der Sluis L, Wu MK (2015) Management of apical periodontitis: healing of post-treatment periapical lesions present 1 year after endodontic treatment. *Journal of Endodontics* **41**, 1020–5.