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Number of teeth, C-reactive protein, fibrinogen and cardiovascular mortality: a 15-year follow-up study in a Finnish cohort

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Abstract

Aim: To test whether the number of teeth, an inverse proxy for composite oral infection scores is associated with better survival.

Materials and Methods: The Kuopio Oral Health and Heart study initiated a case–control study in 1995–1996 consisting of 256 consecutive coronary artery disease patients and 250 age and gender-matched controls. We appended the mortality data and formulated a longitudinal study. By May 31st, 2011, 124 mortalities had occurred and 80 of which were of cardiovascular origin. Using Cox proportional hazards models, we assessed the association of the teeth group (Teethgrp) – consisting of 10 teeth – with cardiovascular and all-cause mortality after 15.8 years of median follow-up.

Results: In multivariate models, with the edentulous state as reference, one level increase in Teethgrp was associated with significantly increased survival from cardiovascular disease (CVD) mortality with a Hazard Ratio (HR) 0.73, *p*-value = 0.02 but not with all-cause mortality (HR = 0.87, $p = 0.13$). The findings were not mediated by C-reactive protein (CRP) levels ≥3 mg/L or by median fibrinogen levels, but were mediated by CRP levels >5 mg/L.

Conclusion: Each increment of 10 teeth from the edentulous state was associated with a 27% improved CVD survival, independent of low-grade systemic inflammation.

Key words: C-reactive protein; CVD mortality; fibrinogen; mediation analyses; number of teeth

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Conflict of interest and source of funding statement

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Infections (Minick et al. 1979), including oral infections (Beck et al. 1996, Janket et al. 2004) may contribute to atherosclerosis and subsequent cardiovascular disease (CVD), the most important cause of death worldwide (AHA 2009). Oral health has been shown to be predictive of all-cause mortality (Garcia et al. 1998, Morita et al. 2006) and tooth loss has been associated with cardiovascular mortality (Tu et al. 2007, Watt et al. 2010). Inflammation may be the causative biological process in mortality (Reuben et al. 2002, Hamalainen et al. 2003). However, the ageing process itself is also associated with inflammation (Schrager et al. 2007, Cartier et al. 2009) and in the inflammatory states, cholesterol is depressed (Salanitro et al. 2012). This inverse association of cholesterol and inflammation was supported by several reports where low cholesterol levels and high C-reactive protein (CRP) levels predicted mortality(Reuben et al. 1999) (Van Hemelrijck et al. 2012).

The number of teeth has been presumed to impact systemic health via nutrition (Ritchie et al. 2000) and inflammation (Beck & Offenbacher 2005). The number of remaining teeth was inversely associated with previous oral infections which may contribute to the pathogenesis of cardiovascular diseases (Burt et al. 1990, Joshipura et al. 2003). The number of remaining teeth may be the results of past oral infections and in this cohort, it demonstrated a significant inverse association with composite oral infection score ($r = -0.8$, $p < 0.0001$). Given the close correlation of oral health with several systemic inflammatory diseases, (Qvarnstrom et al. 2008, 2010) we postulated that remaining teeth may serve as a simple and practical predictor for mortality without any laboratory tests or venipuncture. Although some oral infections such as pericoronitis or root remnants generated powerful inflammation in our previous study (Janket et al. 2004), not everyone has these specific infections. Meanwhile, the ubiquitous presence of teeth will assess the population risk better than the composite oral infection score in public health perspectives. Thus, we chose the number of teeth, an inverse proxy for oral inflammation burden, as our predictor. The primary aim of this study was to investigate whether the number of remaining teeth at baseline, as an inverse proxy for oral inflammation, would predict CVD and all-cause mortality in 15 years and longer follow-up. The secondary aim was to evaluate whether the relationship of remaining teeth to mortality was independent of systemic inflammation assessed by CRP or fibrinogen by mediation analyses.

Materials and methods

Ethical and human subjects' protection

This study was approved by the Joint Ethical Committee of the Kuopio University Hospital and the University of Kuopio, and 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 ensure the safety of human research subjects.

Study population

Kuopio Oral Health and Heart (KOHH) study was initiated as a cross-sectional study in 1995–1996 to investigate the association between oral health and coronary artery disease (CAD) in Kuopio, Finland. For this study, we merged mortality outcome to the baseline data consisting of 256 CAD patients and 250 age- and sex-matched controls with a mean age of 60 and created a prospective follow-up study.

At baseline, 256 consecutive cardiac patients at Kuopio University Hospital who were referred for coronary angiography and confirmed as having CAD were invited to participate in the KOHH study. The CAD diagnosis was determined by the presence of at least 50% stenosis in one of the epicardial arteries. Potential subjects were excluded if they took antibiotics during the previous 30 days or had chronic infection other than dental disease. Also recruited were 250 age- and gender-matched controls who were admitted to the general surgery or otorhinolaryngology (ORL) departments at the same hospital for elective surgery. They were considered as not having heart disease based on their medical history and pre-admission electrocardiogram (ECG). The controls were recruited from the population of the same catchment area where the cases arose and would have come to the same hospital if they had developed heart disease. The same exclusion and inclusion criteria were applied to non-cardiac patients. Additional exclusion criteria were as follows: (1) those who needed emergency coronary by-pass surgery or valvular replacement surgery; (2) those whose disease status was so grave that a dental examination or dental x-ray could not be performed safely and (3) those who required antibiotic prophylaxis prior to periodontal probing. Further details regarding this cohort have been published elsewhere (Janket et al. 2004, 2006, Qvarnstrom et al. 2008, 2010) (http://www.ncbi.nlm.nih.gov/pubmed/14967717; http://www.ncbi.nlm.nih.gov/pubmed/20666873; http://www.ncbi.nlm.nih.gov/pubmed/20177131).

Exposure assessment

At the beginning of the study (1995–1996), a single examiner (MS) performed all clinical dental examinations and pantomographic radiology examinations following the World Health Organization format (Ainamo et al. 1982). The number of teeth as a predictor in this study included sound or repaired teeth excluding non-restorable root tips. Dental infections such as periapical lesions that generally signify long standing dental caries, pericoronitis defined as infection/inflammation surrounding 3rd molars, (radiolucent follicle around the retained or erupting third molars with diameter >3 mm in the pantomogram), or numbers of root remnants with soft tissue inflammation (dental hard tissues are usually destroyed by advanced dental caries leaving only tips of the root), amount of vertical bone loss (measured from cemento-enamel junction in mm), calculus deposits and restorations with overhangs were recorded. The details of dental examinations have been published elsewhere (Janket et al. 2004). The two pantomogram readings by

this examiner (MS) exhibited an excellent agreement (kappa = 0.9).

Ascertainment of the endpoints

The outcome, CVD mortality, has been assessed using the mortality records obtained from the Finnish Death Registry in 2008, 2009, 2010 and 2011. ICD-10 codes I00 and 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 mortality records was tested by comparing them to the physician's diagnosis of death from the medical records. In 100 records we examined, we observed three disagreements in ICD-10 codes, but upon further detailed investigation, all turned out to be in agreement. For example, the Finnish death registry listed one case as "I21.4: Acute subendocardial myocardial infarction", whereas physician's diagnosis of death was "I25.1: Atherosclerotic heart disease". In the second case, mortality record showed as "I21.9: Acute myocardial infarction, unspecified" whereas physician's diagnosis for death was "I70.9: Generalized and unspecified atherosclerosis". Thus, although ICD-10 codes were different in these cases, they described the same pathology with different codes. Thus, validity was judged to be 100%.

Confounding factor

Age in years and smoking in three categories (never-smokers, current smokers and past smokers) were assessed. Weights were measured without shoes and in light clothing. Heights were measured without shoes using a stadiometer with Frankfort plane in a horizontal position. 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 cholesterol levels were estimated by the Friedewald formula (Warnick et al. 1990). Hypertension (HTN) 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 their treatments.

Assessment of the mediators

Fibrinogen was measured by the Clauss method and CRP was measured by immuno-turbidimetry utilizing the HITACHI 717 analyzer (Boehringer Mannheim, Mannheim, Germany). This method was not the hs-CRP assay and the lowest sensitivity level was 1.0 mg/L. In the clinical context, this method has been proven to be comparable to hs-CRP assay (Rifai et al. 2006). The reported Coefficient of Variation (CV) for CRP assay was between 8.1 and 11.4% (Sung et al. 2002, Aziz et al. 2003). All blood samples were collected after fasting if required and analysed immediately in the hospital laboratory. The analyses were performed in batches including both cases and controls to evenly distribute any potential environmental changes and measurement variability.

Statistical analysis

Using Statistical Analysis System (SAS Institute Inc., Cary, NC, USA) version 9.1, the basic characteristics such as mean age, sex, smoking status, body mass index, number of teeth and cholesterol subgroup levels were compared between those who died during the follow-up and who survived. In the bivariate analyses, chi square tests or non-parametric Kruskal–Wallis tests were used to make three group comparisons. In multivariate analyses, we used Cox proportional hazard modelling after testing the proportional hazard assumption. Because the log-hazard ratio for CVD survival and the number of teeth appeared to be non-linear, we categorized the number of teeth in four groups: the number of teeth (N_{teeth}) = 0; $0 < N_{\text{teeth}} \leq 10$; $10 < N_{\text{teeth}} \leq 20$; $N_{\text{teeth}} > 20$ and evaluated the relationship of the N_{teeth} groups to mortality. To prevent model saturation in ancillary models with CRP and fibrinogen, we omitted the two most uninformative variables, sex (HR = 1.03, $p = 0.93$) and education (HR = 1.00, $p = 0.98$). This is justified judging from model 2 (in Table 4) without these two variables did not materially alter the parameter estimates in the fully adjusted model 3 (in Table 4) that included these variables. In the cardiovascular mortality modelling, non-CVD deaths were censored. The established confounding factors such as age, sex, smoking, total cholesterol to HDL ratio (T/H ratio), HTN, diabetes and education were controlled. Although 82.6% of CVD mortality occurred in individuals who had diagnosis of CAD at baseline, to formally test whether baseline CAD status is confounder or collinear factor, we adjusted baseline CAD in the modelling. Although our primary interest was CVD mortality, we also conducted analyses for the prediction of all-cause mortality.

We further tested whether the relationship of mortality and the N_{teeth} groups were mediated by systemic inflammation or systemic thrombosis by conducting formal mediation analyses according to the methods described by Fritz and MacKinnon (2007) and Jasti et al. (2008). The requirement(s) for the presence of mediation by CRP or fibrinogen are the following:

- The total effect of X, (Number of teeth) on Y (CVD mortality (τ) must be significant.
- The effect of X (Number of teeth) on M, (CRP or Fibrinogen) (α) must be significant.
- The effect of CRP or Fibrinogen on Y (CVD mortality) controlled for Number of teeth (β) must be significant.
- The direct effect of "Number of teeth" on "CVD mortality" adjusted for "CRP or fibrinogen" (τ') must be non-significant.

$$Y = \varphi_1 + \tau X \qquad \text{eqn1}$$

$$M = \varphi_2 + \alpha X \qquad \text{eqn2}$$

$$Y = \varphi_3 +' \tau' X + \beta M \qquad \text{eqn3, 4}$$

Therefore, if the mediation effect is significant, τ' must be non-significant while β must be significant in equation (3), (4). where τ is the estimate of the total effect of X on Y, τ' is the estimate of the direct effect of X

on Y adjusted for M, β is the estimate of the effect of M on Y adjusted for X and α is the estimate of the effect of X on M. ϕ_1, ϕ_2 and ϕ_3 are the intercepts. In our study Y = CVD mortality, X = number of teeth and M = CRP or fibrinogen.

If all four criteria are satisfied, we then tested the mediation by the Sobel test. We also tested whether daily tooth brushing, flossing and regular dental check-ups would be associated with CVD mortality by stochastically combining these variables and created an Oral Care Index (OCI). OCI was the sum of weighted score from a logistic model predicting survival from CVD. Tooth Brushing was not informative (everyone was doing it) and dropped from the model. We weighted daily flossing by 7, dental appointment within the past year by 1.2 and going to a private dentist in Finland by 1.6.

Sommerfelt et al. (2012) raised concerns that studies started as case–control format and extended to longitudinal studies such as ours may over-estimate the true risk. Therefore, we estimated the population risk by increasing the controls by computer simulation to be similar to the age-specific population in Finland with CHD prevalence of 20% which was reported (Kattainen et al. 2006).

Results

By May 31st, 2011, of 505 KOHH study participants (one subject was lost during the follow-up), 124 mortalities were documented. Of these mortalities, 80 were cardiovascular deaths with documented ICD-10 codes I00–I99. Given a 50% of the baseline prevalence of CAD, high CVD mortality was expected. When we restricted our analyses to those without missing values, the final sample size decreased to 473, the number of CVD mortalities to 69 and all-cause mortalities to 110. Non-CVD deaths, censored in the CVD mortality analyses, were mostly from cancer followed by respiratory disease, Alzheimer's disease, depression and suicide.

Table 1 displays non-parametric Spearman correlations between several important biomarkers. The number of teeth was inversely correlated with various inflammatory markers. Specifically, both CRP and fibrinogen were significantly associated with number of teeth ($r = -0.29$, $p < 0.0001$; $r = -0.28$, $p < 0.001$ respectively). The baseline characteristics for the three groups are presented in Table 2. Most cardiac risk factors such as age, smoking, HTN, diabetes, CRP and education were significantly different between the survivors and non-survivors of the CVD. However, unlike in younger cohorts, BMI was lower among the non-survivors.

In age-, sex- and smoking-adjusted Kaplan–Meier curves demonstrated that the association of the increased number of teeth with better CVD survival in males (Fig. 1) and females (figure not presented). In Table 3, number of event, total person-years and incidence rates stratified by the number of teeth groups are presented. A trend for improved survival in both CVD and all-cause mortality was evident, but the gradient of all-cause mortality was less steep and was not significant ($p = 0.08$). In fully adjusted multivariate models controlling for age, sex, smoking (never, past and current smokers), HTN, total/HDL cholesterol ratio, diabetes and education (in years), each 10 tooth increment from the edentulous state was associated with an approximately 27% increased survival rate from CVD death (Table 4, model 3). Besides the number of teeth, age, total/HDL cholesterol ratio and smoking were the significant predictors of CVD mortality. Controlling for education in three categories (low, medium, high) did not substantially alter the results. When we tested whether the baseline CAD status is a collinear factor or a confounding by adjusting baseline CAD status in the modelling, the number of teeth lost its significance, HR = 0.72 (0.49–1.05), $p = 0.09$. These results suggested that the baseline CAD is on the causal pathway to CVD mortality.

In fully adjusted model, all-cause mortality was not statistically significant (HR = 0.82, $p = 0.13$). Unlike CVD mortality, diabetes in addition to age and smoking were significantly associated with all-cause mortality. These results are presented in Table 5.

Table 1. Non-parametric Spearman Correlation Matrix of inflammatory markers

	Score Rho* (*p*-value)	CRP Rho (*p*-value)	LDL Rho (*p*-value)	HDL Rho (*p*-value)	Trigly Rho (*p*-value)	Fibrino Rho (*p*-value)	BMI Rho (*p*-value)
Number of teeth*	**−0.79** **(< 0.0001)**	**−0.29** **(< 0.0001)**	0.04 (0.37)	**0.12** **(0.006)**	**−0.11** **(0.01)**	**−0.28** **(< 0.0001)**	0.02 (0.66)
Asymptotic dental infection Score (Score)	1	**0.25** **(< 0.0001)**	−0.08 (0.09)	**−0.14** **(0.002)**	**0.10** **(0.02)**	**0.24** **(< 0.0001)**	0.018 (0.69)
C-reactive protein (CRP) (mg/L)		1	**−0.11** **(0.01)**	**−0.26** **(< 0.0001)**	**0.25** **(< 0.0001)**	**0.22** **(< 0.0001)**	**−0.16** **(0.0003)**
LDL cholesterol (LDL) (mmol/L)			1	**0.21** **(< 0.0001)**	0.02 (0.65)	**0.13** **(0.004)**	0.002 (0.97)
HDL cholesterol (HDL) (mmol/L)				1	**−0.48** **(< 0.0001)**	**−0.10** **(0.02)**	**−0.15** **(0.001)**
Triglyceride (Trigly) (mmol/L)					1	0.06 (0.2)	**0.25** **(< 0.0001)**
Fibrinogen (Fibrino) (g/L)						1	−0.0002 (0.99)

*Rho: Spearman's non-parametric correlation coefficient
Significant correlations are in bold.
Juxtaposing correlations are in blank. The correlation of HDL to CRP is the same as CRP to HDL.

Table 2. Baseline characteristics of the cohort

	Alive $n = 363$	Died of non-CVD $n = 41$	Died of CVD $n = 69$	*p*-value
Age, Median (inter-quartile range)	59.0 (51–65)	64 (59–70)	67 (62–70)	<0.0001*
Sex (*n*, %)				
Men	224 (61.7%)	28 (68.3%)	47 (68.1%)	0.42
Women	139 (38.3%)	13 (31.7%)	22 (31.9%)	
Body Mass Index (BMI) Median (inter-quartile range)	24.7 (22.9–27.0)	24.7 (23.2–26.2)	23.8 (22.1– 26.0)	0.10
Smoking, *n* (%)				
Never	259 (71.3%)	29 (70.7%)	30 (43.5%)	<0.0001
Current	36 (10%)	5 (12.2%)	7 (10.1%)	0.86
Past	68 (18.7%)	7 (17.1%)	32 (46.4%)	<0.0001
% with Baseline CAD diagnosis	172 (42.6%)	12 (29.3%)	57 (82.6%)	0.0001*
Hypertension, (%)	116 (32%)	10 (24.4%)	32 (52.9%)	0.0009*
Diabetes, (%)	28 (7.7%)	6 (14.6%)	16 (22.9%)	0.0005*
Education (years) Median (inter-quartile range)	11 (10–14)	11 (9–14)	11 (9–12)	0.03*
LDL cholesterol (mmol/L) Median (inter-quartile range)	3.6 (3.1–4.3)	3.77 (3.1–4.5)	3.4 (3.1–4.2)	0.61
Triglyceride (mmol/L) Median (inter-quartile range)	1.7 (1.23–2.3)	1.5 (1.2–1.9)	1.9 (1.2–2.5)	0.09
HDL cholesterol (mmol/L) Median (inter-quartile range)	1.2 (0.98–1.4)	1.2 (1.0–1.4)	1.1 (0.9–1.3)	0.05*
Total/HDL cholesterol ratio Median (inter-quartile range)	4.8 (4.0–5.7)	4.6 (3.9–5.3)	5.4 (4.3–6.2)	0.06
CRP (mg/L) Median (inter-quartile range)	5.0 (4.0–10.0)	5.0 (4–8)	9.0 (6–15)	0.001*
Fibrinogen (g/L) Median (inter-quartile range)	2.9 (2.6–3.3)	3.0 (2.7–3.5)	3.3 (2.9–3.9)	0.001*

*Significant at the α-level of 0.05.

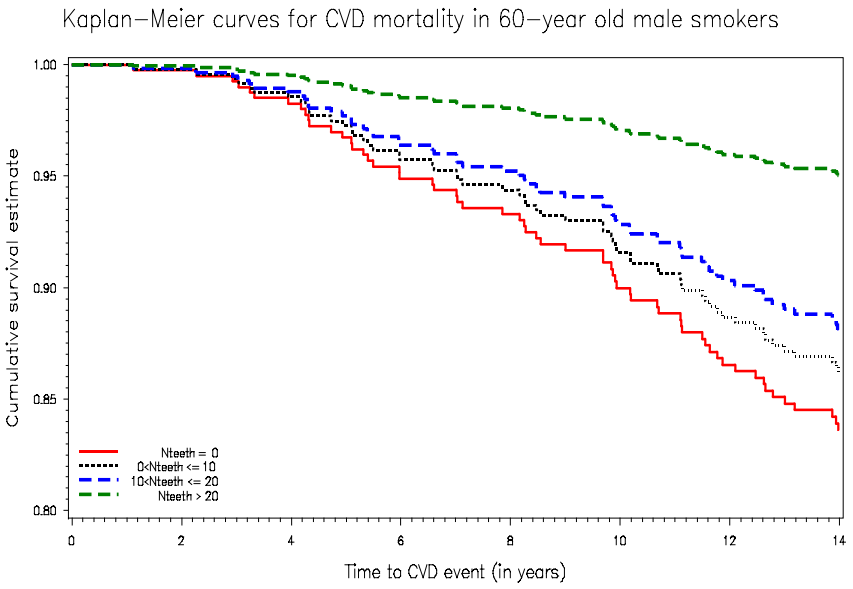

Fig. 1. Survival prediction from CVD mortality by the teeth groups among 60-year-old smoking males.

The results of mediation analyses indicated that CRP ≥3 mg/L or fibrinogen 3 g/L did not mediate the relationship of the number of teeth to the CVD mortality because the number of teeth retained its significance even when these mediators were controlled (Mediation test criteria 3 and 4 were not satisfied). Meanwhile, at the CRP level >5 mg/L, we observed a significant (0.013) mediation effect of CRP on the relationship of the number of teeth to CVD mortality (Table 6). Approximately, 25.7% of total effects of the tooth count on CVD mortality were mediated by CRP levels >5 mg/L. Adjusting good oral care (top 25% of oral care index) further improved CVD survival to HR = 0.68, $p = 0.03$. Similar to the previous report (Paganini-Hill et al. 2011), top 25% of OCI was significantly associated with improved CVD survival (HR = 0.41, $p = 0.04$), but when the number of teeth entered the model, it lost its significance suggesting OCI was mediated by the number of teeth. The population risk estimates in the simulated data did not change materially from the original results with HR = 0.73 (0.61–0.88), *p*-value = 0.001.

Discussion

In this study of 473 persons, with median follow-up of over 15.8 years, each 10 tooth increment from the edentulous state was associated with a significantly improved survival rate from cardiovascular death by approximately 27% controlling for age, smoking, total/HDL cholesterol ratio, HTN, diabetes and education.

Although several previous studies investigated oral health and mortality, most of them adjusted confounding factors inadequately. Only recently, results of longitudi-

Table 3. Number of mortalities and the incidence rates stratified by the teeth groups

	Number of teeth(0) $n = 117$	Number of teeth(1–10) $n = 117$	Number of teeth(11–20) $n = 72$	Number of teeth(>20) $n = 167$
Number of cardiac deaths	35	24	10	11
Number of all-cause deaths	46	33	15	30
Total person-years (p/y)*	1752.74	1846.28	1147.93	2656.04
CVD mortality Incidence rate (per 1000 p/y)	20	13	9	4
All-cause mortality Incidence rate (per 1000 p/y)	26	18	13	11

*p/y: person-years.

Table 4. Multivariate proportional hazard models predicting cardiovascular mortality by the teeth groups

	Exposure	Hazard ratio (95% confidence interval)	*p*-value
Model 1	Group 1 ($N_{teeth} = 0$)*	1.0 (reference)	–
	Group 2 ($0 < N_{teeth} \leq 10$)	0.90 (0.50–1.61)	0.71
	Group 3 ($10 < N_{teeth} \leq 20$)	0.62 (0.28–1.39)	0.24
	Group 4 ($N_{teeth} > 20$)	0.31 (0.10–0.70)	0.005
	As a trend across the groups	**0.70 (0.56–0.89)**	**0.003**†
Model 2	Group 1	1.0 (reference)	–
	Group 2	1.05 (0.58–1.90)	0.89
	Group 3	0.62 (0.28–1.38)	0.24
	Group 4	0.37 (0.17–0.84)	0.02
	As a trend across the groups	0.73 (0.57–0.94)	**0.02**†
Model 3	Group 1	1.0 (reference)	–
	Group 2	1.06 (0.62–1.93)	0.85
	Group 3	0.62 (0.27–1.41)	0.24
	Group 4	0.37 (0.17–0.85)	0.02
	As a trend across the groups	0.73 (0.58–0.93)	**0.02**†
Model 4	Group 1	1.0 (reference)	–
(Additional CRP>3 mg/L adjusted)	Group 2	1.12 (0.59–2.03)	0.83
	Group 3	0.65 (0.29–1.45)	0.29
	Group 4	0.40 (0.17–0.89)	0.02
	As a trend across the groups	0.75 (0.57–0.97)	**0.03**†
Model 5	Group 1	1.0 (reference)	–
(Additional CRP>5 mg/L adjusted)	Group 2	1.18 (0.65–2.15)	0.58
	Group 3	0.74 (0.33–1.65)	0.46
	Group 4	0.47 (0.21–1.07)	0.07
	As a trend across the groups	0.80 (0.57–0.94)	**0.09**†
Model 6	Group 1	1.0 (reference)	–
(Additional Fibrinogen > 3 g/L adjusted)	Group 2	1.06 (0.59–1.92)	0.83
	Group 3	0.64 (0.29–1.44)	0.28
	Group 4	0.40 (0.18–0.90)	0.03
	As a trend across the groups	0.75 (0.58–0.96)	**0.02**†

*N_{teeth} = number of teeth
†Denotes significant at the α-level of 0.05.
Model 1 adjusted for age, sex and smoking.
Model 2 adjusted for age, smoking (never, past and current smokers), hypertension, diabetes and Total/HDL cholesterol ratio.
Model 3 adjusted for age, sex, smoking (never, past and current), hypertension, diabetes, Total/HDL cholesterol ratio and education (in years).
Model 4 adjusted for all the covariates adjusted in model 2 and CRP ≥ 3 mg/L.
Model 5 adjusted for all the covariates adjusted in model 2 and CRP > 5 mg/L.
Model 6 adjusted for all the covariates adjusted in model 2 and fibrinogen > median (3.0 gm/L).

nal studies with reasonable confounding adjustment have been published (Schwahn et al. 2012, Janket et al. 2013). As far as we know, our study is the first study that formally tested whether the relationship of the number of teeth to CVD mortality was mediated by systemic inflammation as assessed by fibrinogen and CRP levels. The mediation effects by low levels of systemic inflammation (CRP ≥ 3 mg/L) or systemic thrombosis were not statistically significant. However, at much higher levels of CRP (>5 mg/L), there appeared to be mediation effects.

Alternatively, good oral health may improve cardiac outcomes by dietary benefits. (Nowjack-Raymer & Sheiham 2003) As discussed in a

Table 5. Multivariate proportional hazard models predicting all-cause mortality by the teeth groups

	Exposure	Hazard ratio (95% confidence interval)	*p*-value
Model 1	Group 1 ($N_{teeth} = 0$)	1.0 (reference)	–
	Group 2 (($0 < N_{teeth} \leq 10$)	0.99 (0.61–1.16)	0.95
	Group 3 ($10 < N_{teeth} \leq 20$)	0.69 (0.36–1.30)	0.25
	Group 4 ($N_{teeth} > 20$)	0.67 (0.40–1.21)	0.13
	As a trend across the groups	0.86 (0.72–1.00)	0.08
Model 2	Group 1	1.0 (reference)	–
	Group 2	1.04 (0.64–1.71)	0.86
	Group 3	0.68 (0.36–1.29)	0.24
	Group 4	0.74 (0.44–1.25)	0.26
	As a trend across the groups	0.87 (0.73–1.04)	**0.13**
Model 3	Group 1	1.0 (reference)	–
(Additional CRP>3 mg/L adjusted)	Group 2	1.09 (0.66–1.78)	0.75
	Group 3	0.70 (0.37–1.34)	0.28
	Group 4	0.76 (0.45–1.30)	0.32
	As a trend across the groups	0.88 (0.733–1.06)	0.18
Model 4	Group 1	1.0 (reference)	–
(Additional Fibrinogen >3 g/L adjusted)	Group 2	1.05 (0.64–1.72)	0.85
	Group 3	0.70 (0.37–1.33)	0.28
	Group 4	0.79 (0.47–1.35)	0.39
	As a trend across the groups	0.89 (0.74–1.07)	0.22

Model 1 simultaneously adjusted for age, sex and smoking (never, past and current).
Model 2 simultaneously adjusted for age, sex, smoking (never, past and current), hypertension, Total/HDL cholesterol ratio, diabetes and education (in years).
Model 3 simultaneously adjusted all covariates in model 2 plus CRP >3 mg/L.
Model 4 simultaneously adjusted all covariates in model 2 plus fibrinogen > median (3.0 g/L).

Table 6. Mediation analyses of CRP on the relationship of number of teeth and CVD mortality

		Parameter	Estimate	SE	*p*-value
Model 1.	Equation 1	Number of	−0.30	0.15	0.04
At the cut-off CRP level 3 mg/L	(τ)	teeth			
	Equation 2	Number of	−0.17	0.12	0.16
	(α)	teeth			

No need to proceed because equation 2 is not significant. Suggests that mediation by CRP 3 mg/L is not present.

		Parameter	Estimate	SE	*p*-value
Model 2.	Equation 1	Number of	−0.30	0.15	0.04
At the cut-off CRP level 5 mg/L	(τ)	teeth			
	Equation 2	Number of	−0.39	0.10	<0.0001
	(α)	teeth			
	Equation 3	CRP ≥ 5	1.10	0.34	0.001
	(β)	mg/L			
	Equation 4	Number of	−0.19	0.15	0.19
	(τ′)	teeth			

All 4 criteria for mediation analyses are satisfied. Proceed to Sobel mediation test.

	Test statistic	SE	*p*-value
Sobel's test	−2.5	0.17	**0.013**

All mediation equations were controlled for age, sex, smoking, hypertension, Total/HDL cholesterol ratio, diabetes and education.
Bold significant at the α-level of 0.05 after 0.013.

previous study (Schwahn et al. 2012), without a healthy dentition, individuals cannot ingest healthy foods that are low in glycemic index (Janket et al. 2008) and high in fruits and vegetables (Liu et al. 2004) which may lead to obesity, diabetes and subsequent CVD. (Janket et al. 2008) Thus, it appears that a good dentition is a prerequisite for good nutrition that may lead to overall good health. However, adjusting dietary benefits are inappropriate because diet is an intermediate outcome on the causal pathway (Tu et al. 2007).

Sommerfelt et al. (2012) raised an interesting issue of potential risk

amplification in the case–control studies that subsequently have been extended to longitudinal studies. However, our simulated results did not appear to support his theory. We disagree with Sommerfelt et al. (2012) on the following basis.

- Relative risk amplification is not uniform in all studies and may vary depending on the specific outcomes and the explanatory variables.
- The exposure in our study is not clearly divided between cases and controls. Unlike the binary variable such as "pregnant" and "not pregnant", the controls in our study are also exposed in some degree because they have some teeth. Thus, the exposure contrast is not as drastic in our study.
- The outcome, cardiac deaths, is also prevalent in non-cases. Approximately, 50% of cardiac events occur in non-cases without traditional risk factors (Braunwald 1997). This proportion was 42% in our study.
- In the "time to event analyses" such as Cox regression, the risk is calculated by the time to the event, not by the proportion of exposed in the population. Thus, risk amplification described by Sommerfelt et al. (2012) may not be applicable when Cox regression analyses are employed.

The recent American Heart Association (AHA) scientific statement stipulated that there was no evidence that periodontal treatment improved cardiac outcomes citing inadequately adjusted confounding factors such as smoking and diabetes (Lockhart et al. 2012). However, our results appear to suggest that oral infection may be an important contributor to CRP levels. This observation is consistent with the consensus statement of The European Federation of Periodontology and American Academy of Periodontology on Periodontitis and atherosclerotic cardiovascular disease (Tonetti et al. 2013).

The fact that CRP levels ≥3 mg/L were inversely associated with CVD mortality suggests that in this elderly cohort, 3 mg/L of CRP might illustrate physiological ageing or its anti-inflammatory function. CRP is non-specific inflammatory marker and it can be pro-inflammatory or anti-inflammatory, (Marnell et al. 2005, Kushner & Agrawal 2007) depending on the circumstances. Noting the median CRP levels of 4.0 mg/L among asymptomatic controls in this cohort (Qvarnstrom et al. 2010) and 4.2 mg/L in the asymptomatic JUPITER cohort (Ridker et al. 2009), the mortality discrimination beyond this median level appears to be plausible. Moreover, CRP level defining CVD mortality could be higher than the levels defining incident CVD. It is also plausible that when pro-inflammatory component of CRP was explained by oral infections, the remaining CRP might describe its anti-inflammatory functions. Some of CRP's anti-inflammatory functions include its inhibitory actions against neutrophil leucocytes' (PMNs) activities: suppressing the chemotaxis of PMNs to both IL-8 and bacterial chemotactic peptide (Zhong et al. 1998); and the production of reactive oxygen species and degranulation (Dobrinich & Spagnuolo 1991); inhibition of neutrophil movement by decreasing mitogen-activated protein kinases (MAP kinase) (Yates-Siilata et al. 2004).

To explore the level where the pro- and anti-inflammatory actions of CRP intersect, we assessed the HRs for CVD mortality associated with a small increment of CRP level keeping CRP ≤ 2 mg as a reference (the same as the JUPITER trial). At CRP level 3–4 mg/L, the HR was 0.24; at 5 mg/L, 0.56; at 6–8 mg/L, 1.06 and at above 8 mg/L, the HR was 1.54 controlling for age, sex, smoking and the number of teeth. These results suggested that the relationship of CRP to CVD mortality had changed its direction from inverse to positive with CRP levels at 6 mg/L and above. This can be interpreted that CRP was associated with better CVD survival (inverse) at the lower levels and with the increased risk for CVD deaths (positive) at CRP levels higher than 5 mg/L. It should be noted that the median baseline CRP level for those who survived after 15.8 years of follow-up was 5 mg/L (Table 1) and this level might indicate the CRP level associated with physiological ageing in this cohort (Kushner & Sehgal 2002, Schrager et al. 2007, Cartier et al. 2009).

One point to note is that many previous studies reporting CRP as a CVD risk marker did not control for oral infections. The statin administration at this low level of CRP ≥ 2 or 3 mg/L has been criticized by others (Ray 2010, Ray et al. 2010, Mascitelli & Goldstein 2012, 2013), because statin administration accompanies some serious adverse effects including the risk of increased diabetes incidence (Ridker et al. 2008, Sattar et al. 2010).

Good oral hygiene practice was associated with longevity in a population-based cohort (Paganini-Hill et al. 2011). Our results are consistent with this report showing that good oral self-care was also associated with significantly improved CVD survival (HR = 0.41, $p = 0.04$) which was mediated by the number of teeth. Regarding access to dental care in our cohort, 95% of our study participants had public or private dental care coverage. Thus, access to dental care does not appear to be a problem in Finland.

Socioeconomic status has been implicated as a confounding factor for the relationship of oral health and cardiovascular health (Sabbah et al. 2008). However, in our analyses, adjusting for education did not materially alter the relationship of number of teeth and CVD mortality. Our results are consistent with other studies from Scandinavia where the living standard is high and access to healthcare is adequate (Cabrera et al. 2005, Heitmann & Gamborg 2008).

Strengths

Firstly, small sample size can be both a limitation and strength. In large studies, any nebulous risk factors will appear as significant, because the *p*-value is a function of sample size (Gardner & Altman 1986). However, our small sample size enabled us to distinguish subtle differences such as changes in the direction of CRP relative to mortality. The second strength is the homogeneous Finnish ethnicity and uniformly high living standard that minimized confounding by the SES factors.

Limitations

The first limitation is that baseline data were collected only once and we have no information on the changes in some time-varying variables. The

second limitation is that we do not have information on non-fatal cardiac events and the difference between fatal and non-fatal cardiac events could not be assessed. The third limitation is the small sample size that did not allow testing the interaction terms and conducting stratified analyses if effect modification was evident. However, we were able to adjust most important risk factors albeit in simpler linear forms to avoid model overfitting. The final limitation is that because this is not a population-based study, our results may not be applicable to general populations. However, our population risk estimates in simulated data appear to support the generalizability of our results.

Conclusion

Based on the results of this longitudinal study, a higher baseline tooth count was associated with increased CVD survival. This improved survival was independent of CRP level ≥3 mg/L or fibrinogen ≥3 g/L. However, the association between the number of teeth and CVD mortality appeared to be mediated by high CRP levels (>5 mg/L). Future larger studies are warranted.

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Clinical Relevance

Scientific rationale for the study: Does the number of teeth, as an inverse proxy of oral inflammation predict longevity and was this relationship mediated through systemic inflammation?

Principal findings: Each increment of 10 teeth from the edentulous state was associated with a 27% improvement in CVD survival. The inverse association of tooth count on CVD mortality was independent of systemic inflammation assessed by C-reactive protein ≥3 mg/L or fibrinogen. However, there appeared to be mediation effects of CRP levels >5 mg/L.

Practical implications: Maintaining many healthy teeth may be associated with longer CVD survival. When the number of remaining teeth (oral infection proxy) is controlled, CRP level ≥3 mg/L was inversely associated with CVD mortality. Approximately, 26% of the association between the number of teeth and CVD survival might be mediated by CRP levels >5 mg/L in this cohort.