EPIDEMIOLOGY

Associations between tooth loss and mortality patterns in the Glasgow Alumni Cohort

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Objective: To use data from the Glasgow Alumni Cohort to investigate whether oral health in young adulthood is independently associated with later life cardiovascular disease (CVD) and cancer mortality.
Methods and results: Of the original cohort (n = 15 322), 12 631 subjects were traced through the National Health Service Central Register. Of these, 9569 men and 2654 women were 30 years or younger at baseline. During up to 57 years of follow-up, 1432 deaths occurred among subjects with complete data, including 509 deaths from CVD and 549 from cancer. After adjusting for potential confounders, no substantial association was found between the number of missing teeth (as a continuous variable) and all-cause mortality (hazard ratio (HR) for each extra missing tooth = 1.01; 95% confidence interval (CI) 1.00 to 1.02), CVD mortality (HR = 1.01; 95% CI 0.99 to 1.03) or cancer mortality (HR = 1.00; 95% CI 0.98 to 1.02). When the number of missing teeth was treated as a categorical variable, there was evidence that students with nine or more missing teeth at baseline had an increased risk of CVD (HR = 1.35; 95% CI 1.03 to 1.77) compared with those with fewer than five missing teeth. When the number of missing teeth was transformed using fractional polynomials, there seemed to be a non-linear relation between missing teeth and CVD mortality.
Conclusions: Although some evidence was found to support the relation between tooth loss and CVD mortality, causal mechanisms underlying this association remain uncertain.

Over the past decade, evidence has emerged that there may be associations between oral infection and systemic chronic diseases. Many studies have found that poor oral health, mainly caused by periodontal disease, is associated with an increased risk of both cardiovascular disease (CVD)[1–6] and, possibly, cancer.[7 8] The increasing recognition of the role of chronic infection in the pathogenesis of these chronic diseases[9 10] indicates that the potential adverse association between chronic oral infection and general health should also be considered. Although there is increasing epidemiological evidence to suggest this association may be causal, it has been argued that these associations might be due to unmeasured confounders, such as poor nutrition, or imprecise measurement of important risk factors of adult chronic diseases, such as socioeconomic background and cigarette smoking.[7 11–13] For instance, smoking is a major risk factor for poor oral health (especially periodontal disease), CVD and some cancers. Thus, residual confounding due to the imprecision of self-reported smoking history or inadequate control for life course smoking history might lead to an observed spurious relation between oral health and systemic health.[7 11 13]

This study aimed at using data from the Glasgow Alumni Cohort[14] to investigate whether oral health in young adulthood (ie, subjects aged $\leqslant$30 years) is independently associated with cause-specific mortality after accounting for childhood socioeconomic background and other risk factors in young adulthood. One advantage of studying this cohort is that as baseline data were collected at young ages, even among smokers, direct exposure to tobacco—if at all—would have been for a relatively short period, and smoking would not therefore have had substantial impact on their oral health.

MATERIALS AND METHODS

Students registered at the University of Glasgow (1948–68) were invited to annual medical examinations at the Student Health Service. Medical examinations were performed by doctors with at least 3 years' post-registration experience. Dental data, including details of the numbers of missing, filled and decayed teeth at baseline, were available. The number of missing teeth was chosen as the index of oral health status in this study because it is less prone to measurement error than the other two items, and has been used in other epidemiological studies.[4 8 15–17] Participants were traced through the National Health Service Central Register to obtain mortality data up to 14 January 2005.

Primary outcomes for this study are all-cause mortality, cancer (International Classification of Diseases (ICD)–9: 140–208; or ICD–10: C00–C97), CVD (ICD–9: 390–459; or ICD–10: I00–I09 and G45), coronary heart disease (CHD) (ICD–9: 410–414 and 429.2; or ICD–10: I20–I25 and I51.6) and stroke (ICD–9: 430–438; or ICD–10: I60–69 and G45) mortality. To explore whether or not residual confounding effects might give rise to spurious associations between tooth loss and cause-specific mortality, we tested the association between tooth loss and external causes of death, such as accidents, suicide and violence (ICD9: 800–999, E800–E999; or ICD10: S00–T98, V01–Y89) and lung cancer (ICD–9: 162; or ICD–10: C34); two outcomes which we did not expect to be associated with dental infection. An association with lung cancer would also suggest residual confounding due to smoking.

Statistical analysis

Cox proportional hazards models were used to estimate the association between the number of missing teeth in young adults and mortality, by taking into consideration the age of each subject. The proportional hazards assumption was evaluated using a χ^2 test based on Schoenfeld residuals. All models were adjusted for age at examination, sex, father's socioeconomic position (derived from father's occupation),

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; ICD, International Classification of Diseases

Table 1 Baseline characteristics of 12 223 students from the Glasgow Alumni cohort, according to numbers of teeth lost at examination (median age 19 years)

	Number of teeth lost				
	0–4	5–8	9+	Not available*	p Value§
Number of students	7403	3192	953	675	
Male students (%)	6066 (81.9)	2213 (69.3)	708 (74.3)	582 (86.2)	<0.001
Father's social class (%)					
I	22.1	18.0	17.7	19.6	<0.001
II	36.0	37.2	34.8	35.9	
III	35.8	37.6	38.6	32.9	
IV/V	6.1	7.2	8.9	11.7	
Cigarette smoking (yes) %	29.4	30.3	35.8	34.4	<0.001
Age (years)†	20.1 (2.5)	20.2 (2.8)	21.3 (3.6)	21.3(3.6)	<0.001
BMI (kg/m^2)†	21.6 (2.2)	21.5 (2.3)	21.3 (2.4)	21.5(2.4)	0.011
Systolic blood pressure (mm Hg)†	130.0 (13.0)	129.6 (13.5)	129.9 (13.8)	127.7(13.4)	0.031
Years of follow-up‡	45 (13)	46 (12)	47 (11)	43 (11)	<0.001
Total deaths	943	417	179	96	
Deaths from:					
CVD	319	165	73	39	
Cancer	371	158	60	35	
CHD	222	118	44	21	
Stroke	64	25	20	4	

BMI, body mass index.
*Baseline oral health status is not available in these students.
†Values are mean (standard deviation).
‡Median and interquartile range.
§p Values are from χ^2 test; one-way analysis of variance or Kruskal–Wallis test to compare the differences between three categories of tooth loss.

smoking status, body mass index (BMI), computed as weight divided by height squared, and systolic blood pressure, all measured in early adulthood. As this cohort was recruited over a period of 20 years, and the students' year of birth ranged from 1918 to 1951, year of birth was included in the models to explore whether or not there was a period effect on the association between number of missing teeth and mortality. As only 22% of this cohort was female, we did not perform analyses stratified by sex. Age at examination, BMI and systolic blood pressure were treated as continuous variables, and sex (male students as the reference group), socioeconomic position (social class I as the reference group) and smoking status (non-smokers as the reference group) were treated as categorical variables. The number of missing teeth was treated either as a continuous variable or as a categorical variable—four or fewer (the reference group), five to eight, and nine or more. These cut-off values were chosen owing to the young ages in this cohort at baseline, as most students had lost fewer than nine teeth.

Further statistical analyses were performed by transforming the number of missing teeth using fractional polynomials as described by Royston *et al*[18] to explore a non-linear relationship between missing teeth and disease mortality. In short, this technique allows statistical software to use a stepwise procedure to select two polynomial terms which optimally explore the non-linear relation between the outcome (log hazard ratio) and the number of missing teeth.

As oral infection in the pathogenesis of systemic diseases has been postulated to be at a very early stage of the disease processes,[19] we investigated an interaction between the age at examination and the number of missing teeth for each of the mortality outcomes by performing subgroup analyses by category of age at examination: 16–19, 20–23 and 24–30 years. All statistical analyses were performed using Stata version 9.1 (StataCorp, Texas, USA).

RESULTS

The original cohort comprised 15 322 students. Of these, 12 631 had been successfully traced and 97% (12 223, including 9569 men and 2654 women) were aged ⩽30 years at the time of their baseline examination (median age 19 years; interquartile range 3 years). Of these 12 223 subjects, 1631 (13.3%) had missing data on one or more of the potential confounding factors (675 had no baseline data on missing teeth). All Cox proportional hazard models were based only on those subjects who had complete baseline information of the number of missing teeth and the confounders for which we adjusted.

The distribution of the number of missing teeth was positively skewed, as these students were young at the time of examination and the majority had lost few teeth (table 1). Smokers had, on average, lost more teeth at baseline (4.2 teeth) than non-smokers (3.9 teeth), but this might be partly because smokers, in general, were older than non-smokers. Smokers, on average, had lost 0.18 more teeth (95% confidence interval (CI) 0.03 to 0.34) than non-smokers after adjusting for father's social class, year of birth, and age at baseline examination. Older students had lost more teeth at baseline measurement and, on average, had a greater BMI, and systolic blood pressure, and included a higher percentage of smokers (table 2). The majority of students (>90%) came from families with fathers in social classes I to III.

During follow-up to 14 January 2005, 1635 deaths occurred in the total cohort, including 596 deaths from CVD and 624 deaths from cancer, and 1432 deaths occurred in the restricted cohort with complete data, including 509 deaths from CVD, 549 deaths from cancers. After adjusting for potential confounders, there was no evidence for an association between the number of missing teeth (as a continuous variable) and all-cause mortality (hazard ratio (HR) = 1.01 for each extra missing tooth; 95% confidence interval (CI): 1.00 to 1.02), CVD mortality (HR = 1.01; 95% CI 0.99 to 1.03) or cancer mortality (HR = 1.00; 95% CI 0.98 to 1.02).

When the number of missing teeth was treated as a categorical variable, students with nine or more missing teeth at baseline had a moderately increased risk of CVD (HR = 1.35, 95% CI 1.03 to 1.77) compared with those with fewer than five missing teeth. Both CHD and stroke showed increased

Table 2 Baseline characteristics of 12 223 students from the Glasgow Alumni according to age group at baseline examination

	Age groups (years)				
	⩽30	16–19	20–23	24–30	p Value‡
Number of students	12 223	6376	4315	1532	
Male students (%)	9569 (78)	4607 (72)	3511 (81)	1451 (95)	<0.001
Father's social class (%)					
I	20.5	21.0	20.7	18.2	0.002
II	36.2	35.9	36.9	35.3	
III	36.3	36.0	36.4	37.4	
IV/V	6.9	7.1	6.0	9.1	
Cigarette smoking (yes) (%)	30.4	22.3	35.4	51.2	<0.001
Number of missing teeth (%)					
0–4	64.1	65.3	66.0	53.9	<0.001
5–8	27.6	28.0	26.5	29.4	
⩾9	8.3	6.7	7.5	16.7	
BMI (kg/m^2)*	21.5 (2.3)	21.4 (2.2)	21.6 (2.3)	22.0 (2.5)	<0.001
Systolic blood pressure (mm Hg)*	129.1 (13.1)	128.7 (13.4)	129.2 (13.1)	131.0 (12.6)	<0.001
Number of missing teeth*	4.0 (3.7)	3.8 (3.3)	3.9 (3.6)	5.2 (4.9)	<0.001
Years of follow-up†	46 (12)	44 (11)	46 (13)	49 (13)	<0.001
Deaths					
Total	1635	567	603	465	
From CVD	596	172	226	198	
From cancer	624	227	233	164	
From CHD	405	127	157	121	
From stroke	123	31	42	50	

BMI, body mass index.
*Values are mean (standard deviation).
†Median and interquartile range.
‡p Values are from χ^2 test; one-way analysis of variance or Kruskal–Wallis test to compare the differences between three age groups.

mortality risks of 19% and 64%, respectively, but with wide confidence intervals (table 3). When the number of missing teeth was transformed using fractional polynomials with two power terms selected using the likelihood ratio test, this non-linear model fitted the data better than the linear model in the association between CVD mortality and the number of teeth lost (table 3; fig 1).

The interaction between the age at examination and the number of missing teeth (as a continuous variable) for CVD mortality was not significant (p = 0.10). However, a small positive association between the number of missing teeth and CVD mortality was noted in students aged between 16 and 19 years (HR = 1.05 for each extra missing tooth; 95% CI 1.01 to 1.10), whereas this association was not present between the ages of 20 and 23 years (HR = 1.00, 95% CI 0.97 to 1.04) or between the ages of 24 and 30 years (HR = 1.00, 95% CI 0.97 to 1.03). In contrast, there was no evidence that the number of missing teeth was associated with cancer mortality for any age stratum. Similar results were found when the number of missing teeth was categorised or transformed using fractional polynomials (table 3).

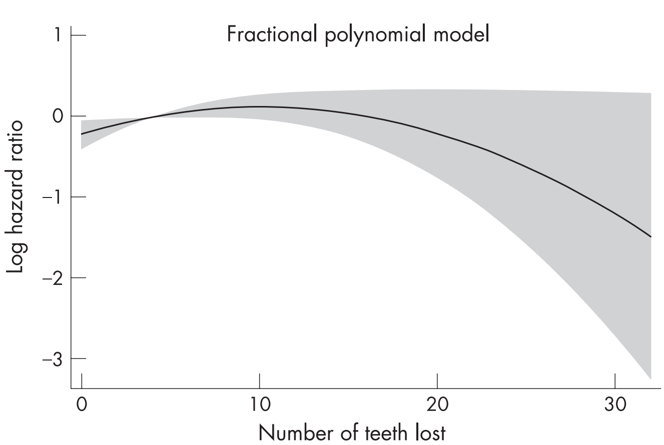

Figure 1 Fractional polynomial model for the relationship between CVD mortality and the number of missing teeth with adjustment for age at examination, year of birth, gender, smoking status, BMI, systolic blood pressure, father's socioeconomic status. The grey area is the width of the confidence interval.

For the associations between tooth loss and the two subcategories of CVD, an increased hazard ratio between the number of missing teeth (as a categorical variable) and CHD mortality (table 3) was seen in former students aged between 16 and 19 years at the time of examination, whereas no such association was seen among those aged 20–23 or 24–30 years at baseline examination, but the interaction with the continuous measure was not significant (p = 0.12). In contrast, although an interaction with the continuous measure was not significant (p = 0.61), an increased HR between the number of missing teeth (as a categorical variable) and stroke mortality (table 3) was observed in former students who were examined when aged 24–30 years, whereas such an association was not present among those examined at 16–19 or 20–23 years old.

There was no association between external causes of death and tooth loss as a continuous (HR = 0.97; 95% CI 0.92 to 1.03) or categorical variable (missing teeth 5–8: HR = 0.74; 95% CI 0.45 to 1.21; missing teeth ⩾9: HR = 0.89; 95% CI 0.42 to 1.88), nor was there evidence of an association between lung cancer and tooth loss as a continuous variable with (HR = 1.01; 95% CI 0.97 to 1.06) or without (HR = 1.02; 95% CI 0.98 to 1.07) adjustment for baseline smoking status, or as a categorical variable with (5–8 missing teeth: HR = 1.29; 95% CI 0.81 to 2.06; ⩾9 missing teeth: HR = 1.36; 95% CI 0.71 to 2.61) or without (5–8 missing teeth: HR = 1.39; 95% CI 0.88 to 2.21; ⩾9 missing teeth: HR = 1.40; 95% CI 0.73 to 2.69) adjustment for baseline smoking status.

To test whether the associations between tooth loss and cause-specific mortality might be mediated by residual confounding of smoking, the statistical analyses were also performed separately in non-smokers and smokers. For CVD,

Table 3 Hazard ratio (HR) and 95% confidence interval (CI) for the number of missing teeth as either continuous, categorical covariate or fractional polynomials (fp) for cardiovascular disease and cancer mortality, adjusting for potential confounders

	HR* (95% CI)	p Value	Missing teeth	HR* (95% CI)	p Value	Fractional polynomial†	HR* (95% CI)	p Value
CVD (n = 509)								
All students ⩽30 years								
For each additional missing tooth	1.01 (0.99 to 1.03)	0.372	0–4	1	0.024‡			
			5–9	1.14 (0.94 to 1.39)	0.186	fp1(x−0.51)	2.08 (1.19 to 3.62)	0.010
			9+	1.35 (1.03 to 1.77)	0.030	fp2(x̂2−0.26)	0.72 (0.54 to 0.96)	0.023
Interaction§		0.097						
Students 16–19 years								
For each additional missing tooth	1.05 (1.01 to 1.10)	0.023	0–4	1.00	0.003‡			
			5–9	1.26 (0.87 to 1.82)	0.222	fp1(x̂3–0.12)	2.12 (1.34 to 3.36)	0.001
			9+	2.24 (1.36 to 3.70)	0.002	fp2(x̂3*ln(x)+0.08)	0.33 (0.13 to 0.87)	0.024
Students 20–23 years								
For each additional missing tooth	1.00 (0.97 to 1.04)	0.915	0–4		0.600‡			
			5–9	1.05 (0.78 to 1.46)	0.684	fp1(x̂−2–4.10)	1.00 (0.99 to 1.00)	0.129
			9+	1.10 (0.68 to 1.82)	0.680	fp2(x̂3–0.12)	0.95 (0.85 to 1.06)	0.326
Students 24–30 years								
For each additional missing tooth	1.00 (0.97 to 1.03)	0.979	0–4	1.00	0.325‡			
			5–9	1.17 (0.82 to 1.67)	0.390	fp1(x̂−2–2.57)	0.94 (0.87 to 1.02)	0.134
			9+	1.20 (0.79 to 1.85)	0.394	fp2(x̂2*ln(x)+1.21)	0.97 (0.94 to 1.01)	0.131
CHD (n = 349)								
All students ⩽30 years								
For each additional missing tooth	1.01 (0.98 to 1.03)	0.661	0–4	1.00	0.160‡			
			5–9	1.18 (0.94 to 1.50)	0.159	fp1(x̂2–0.26)	1.65 (0.98 to 2.77)	0.060
			9+	1.19 (0.84 to 1.69)	0.319	fp2(x̂3–0.13)	0.78 (0.60 to 1.01)	0.064
Interaction§		0.122						
Students 16–19 years								
For each additional missing tooth	1.04 (0.99 to 1.10)	0.100	0–4	1.00	0.019‡			
			5–9	1.31 (0.86 to 2.00)	0.215	fp1(x̂3–0.12)	1.94 (1.14 to 3.31)	0.015
			9+	2.04 (1.11 to 3.72)	0.020	fp2(x̂3*ln(x)+0.08)	0.38 (0.13 to 1.11)	0.076
Students 20–23 years								
For each additional missing tooth	1.00 (0.96 to 1.05)	0.963	0–4	1.00	0.538‡			
			5–9	1.14 (0.80 to 1.67)	0.439	fp1(x̂3–0.12)	1.17 (0.80 to 1.73)	0.415
			9+	1.08 (0.59 to 1.98)	0.808	fp2(x̂3*ln(x)+0.08)	0.82 (0.53 to 1.25)	0.349
Students 24–30 years								
For each additional missing tooth	0.99 (0.95 to 1.03)	0.628	0–4	1.00	0.796‡	fp1(x̂−2–2.57)	0.95 (0.86 to 1.06)	0.363
			5–9	1.09 (0.70 to 1.70)	0.712	fp2(x̂2*ln(x)+1.21)	0.98 (0.94 to 1.02)	0.338
			9+	0.87 (0.48 to 1.56)	0.642			
Stroke (n = 102)								
All students ⩽30 years								
For each additional missing tooth	1.02 (0.98 to 1.06)	0.409	0–4	1.00	0.222‡			
			5–9	0.88 (0.55 to 1.41)	0.599	fp1(x̂–2–3.88)	1.00 (0.99 to 1.00)	0.236
			9+	1.64 (0.96 to 2.80)	0.072	fp2(x̂3–0.13)	1.01 (0.94 to 1.08)	0.763
Interaction§		0.606						
Students 16–19 years								
For each additional missing tooth	1.04 (0.93 to 1.17)	0.485	0–4	1.00	0.478‡			
			5–9	0.95 (0.37 to 2.47)	0.917	fp1(x̂3–0.12)	1.83 (0.64 to 5.19)	0.258
			9+	1.96 (0.56 to 6.84)	0.292	fp2(x̂3*ln(x)+0.08)	0.49 (0.09 to 2.64)	0.410
Students 20–23 years								
For each additional missing tooth	0.96 (0.87 to 1.06)	0.431	0–4	1.00	0.166‡			
			5–9	0.56 (0.25 to 1.33)	0.201	fp1(x̂–2–4.10)	0.98 (0.96 to 1.00)	0.036
			9+	0.53 (0.13 to 2.23)	0.387	fp2(x–0.49)	0.2 (0.04 to 1.05)	0.058
Students 24–30 years								
For each additional missing tooth	1.04 (0.98 to 1.09)	0.168	0–4	1.00	0.010‡			
			5–9	1.43 (0.66 to 3.11)	0.369	fp1(x−0.51)	0.84 (0.70 to 1.01)	0.067
			9+	2.79 (1.30 to 5.97)	0.008	fp2(x̂2–0.26)	0.93 (0.86 to 1.01)	0.074
Cancer (n = 549)								
All students ⩽30 years								
For each additional missing tooth	1.00 (0.98 to 1.02)	0.858	0–4	1.00	0.763‡			
			5–9	0.93 (0.76 to 1.12)	0.442	fp1(x̂–2–3.88)	0.98 (0.94 to 1.02)	0.374
			9+	1.01 (0.76 to 1.35)	0.919	fp2(x̂2*ln(x)+2.63)	0.99 (0.97 to 1.01)	0.381
Interaction§		0.455						
Students 16–19 years								
For each additional missing tooth	1.02 (0.99 to 1.07)	0.227	0–4	1.00	0.656‡			
			5–9	0.96 (0.70 to 1.30)	0.776	fp1(x̂–2–4.16)	0.94 (0.87 to 1.02)	0.163
			9+	1.23 (0.76 to 2.00)	0.400	fp2(x̂2*ln(x)+2.97)	0.97 (0.94 to 1.01)	0.167
Students 20–23 years								
For each additional missing tooth	0.99 (0.95 to 1.03)	0.702	0–4	1.00	0.515‡			
			5–9	0.98 (0.71 to 1.34)	0.885	fp1(x̂2–0.24)	0.8 (0.45 to 1.44)	0.461
			9+	0.80 (0.45 to 1.41)	0.438	fp2(x̂3–0.12)	1.08 (0.88 to 1.32)	0.462
Students 24–30 years								
For each additional missing tooth	0.99 (0.95 to 1.02)	0.502	0–4	1.00	0.497‡			
			5–9	0.77 (0.52 to 1.15)	0.197	fp1(x̂3–0.24)	0.86 (0.66 to 1.11)	0.253
			9+	0.93 (0.59 to 1.48)	0.752	fp2(x̂3*ln(x)+0.11)	1.14 (0.89 to 1.46)	0.288

*Adjusted for age at examination, year of birth, gender, smoking status, body mass index, systolic blood pressure, father's socioeconomic status
†x, (the number of missing teeth+1)/10; fp1, the first fractional polynomial term; fp2, the second fractional polynomial term.
‡Test for trend.
§Likelihood ratio test for the interaction between examined ages and number of missing teeth.

the HR for missing teeth as a continuous variable was 1.03 (95% CI 1.00 to 1.06) in non-smokers and 0.99 (95% CI 0.96 to 1.02) in smokers, and the HR of missing teeth ⩾9 was 1.43 (95% CI 0.98 to 2.09) in non-smokers and 1.27 (95% CI 0.86 to 1.87) in smokers. For CHD, the HR for missing teeth as a continuous variable was 1.03 (95% CI 0.99 to 1.06) in non-smokers and 0.99

(95% CI 0.95 to 1.02) in smokers, and the HR for ⩾9 missing teeth was 1.38 (95% CI 0.86 to 2.20) in non-smokers and 1.00 (95% CI 0.60 to 1.69) in smokers. For stroke, the HR of missing teeth as a continuous variable was 1.04 (95% CI 0.98 to 1.10) in non-smokers and 1.00 (95% CI 0.94 to 1.07) in smokers, and the HR for ⩾9 missing teeth was 1.52 (95% CI 0.71 to 3.25) in non-smokers and 1.76 (95% CI 0.81 to 3.84) in smokers. In general, there was no substantial difference between smokers and non-smokers, indicating that residual confounding by level of smoking is unlikely to explain the observed associations in the main analyses.

DISCUSSION

In this study of the association between early adult oral health and cause-specific mortality, we found no association between the number of missing teeth (as a continuous variable) measured at baseline examination and CVD or cancer mortality, but when examined as a categorical variable we found that former students with nine or more missing teeth at baseline had a 35% greater risk of CVD mortality than those with four or fewer missing teeth. Results from the transformation of the number of missing teeth using fractional polynomials also indicated that this association might not be linear (fig 1). Some of the age groups also had higher risks of CHD and stroke in subjects with nine or more missing teeth at baseline. Our findings may have greater implications for the cardiovascular health of the general public, and, in view of the continuing decline in the number of dentists offering non-private care in the UK, may give even greater cause for concern.

The strength of this study, in comparison with the published reports on this topic, is that tooth loss was measured before smoking could have had a substantial adverse effect on oral health. It has been argued that residual confounding due to smoking might give rise to a spurious association between oral health and chronic disease outcomes.[13] Our results suggest that neither tooth loss nor later disease are likely to be caused by smoking. Analysis of the relation between tooth loss and lung cancer further supports this conclusion. There is no evidence for an association between tooth loss and lung cancer, even without adjustment for baseline smoking status, which, itself, is strongly associated with an increased risk of smoking-related cancers in this cohort.[20] The separate analyses for smokers and non-smokers also showed that the relation between tooth loss and mortality did not seem to be stronger in smokers. Therefore, we consider that residual confounding due to smoking is not a major concern in this study.

Among the confounders adjusted for in our analysis, age at examination had the strongest impact on the relation between missing teeth and mortality, as older students had fewer teeth at baseline. Most students (over 90%) in this cohort came from families of social classes I, II or III. We have previously reported a strong association between paternal social class and CVD mortality.[21] However, in the current analysis, adjusting for father's socioeconomic position had a negligible effect on the results. We also found no association between tooth loss and external causes of death. Recent epidemiological studies have suggested an association between periodontal diseases and obesity,[22 23] which is also linked to many systemic diseases. However, BMI and other confounders had little effect on the association between missing teeth and mortality. All these findings indicate that residual or unmeasured confounders are unlikely to explain our results, although significant relationships were mostly found in the subgroup analyses of different age groups.

Tooth loss might have an impact on diet change, which has therefore been considered a ''confounder'' in the association between oral and systemic health.[12 24] However, if diet change is the consequence of tooth loss, diet change is on the causal path from tooth loss to the risk of CVD. Thus, diet change might not be a genuine confounder and should therefore not be adjusted for as a confounder in the usual way.[25]

Different indices of oral health have been used in previous studies, and a few studies (including the current study) use the number of missing teeth as an index of oral health. An increased risk of ischaemic stroke[4] and prevalence of carotid artery plaque[15] have been found to be associated with greater tooth loss, but no association has been found for CHD mortality.[16] One recent study also found that tooth loss was associated with increased risk of both upper gastrointestinal cancer and stroke mortality.[8] Another study found increased risk of all-cause and CVD mortality with greater tooth loss in a cohort of women, but no such association was found with cancer mortality.[17] These differing patterns of associations, which we also found in the current study, suggest there are different pathways linking oral health/infection with different diseases, although it is possible that these associations may have emerged simply by chance.

Measuring the number of missing teeth is straightforward, unlike other oral health indices that need to be measured by dentists or dental hygienists. Nevertheless, interpretation of the relation between the number of missing teeth and systemic health outcomes is not simple.[26] The number of missing teeth can be viewed as an index of lifetime accumulation of poor oral health, caused mainly by dental caries and periodontal disease. Although current evidence suggests that chronic infection due to periodontal disease is a potential cause of systemic diseases,[3–7] people with fewer remaining teeth might have less exposure/risk of periodontal infection in later life; indeed, edentulous people have no subsequent exposure to periodontal infection.[27] In fig 1, the non-linear relationship between number of teeth lost (transformed using fractional polynomials) and CVD mortality showed that students who lost most of their teeth at young ages had a smaller risk than those who retained most teeth. Although intriguing and biologically plausible, more epidemiological research is required to validate this observation.

Because we restricted our analyses to students who were ⩽30 years at baseline examination, a group in which severe periodontal disease is not common, dental caries is likely to be the main cause of tooth loss. Periodontal disease is generally a mix of infections; more than 20 species of bacteria have been identified as potential pathogens,[28] and some of these pathogens have been linked with cardiovascular diseases.[29 30] As a result, any association between tooth loss and chronic disease mortality in this study, if due to periodontal disease, will be attenuated by the influence of tooth loss due to caries.

In this study, we found no overall associations between tooth loss as a continuous variable and mortality. However, we observed an increased risk of CVD mortality for students with nine or more missing teeth at baseline, and this non-linear relation was supported by transforming the number of missing teeth using fractional polynomials. This might indicate that the association between increased risk of CVD mortality and the number of teeth lost is not on a multiplicative scale. As the pathological pathways between oral infection and various systemic diseases are still unclear, and most evidence remains circumstantial, prospective clinical and epidemiological studies with more informative measures of oral health are needed before causal relationships can be established.

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