Poor oral health and inflammatory, haemostatic and cardiac biomarkers in older age: Results from two studies in the UK and USA

Eftychia Kotronia MSc[1], S. Goya Wannamethee PhD[2], A. Olia Papacosta MSc[2], Peter H. Whincup PhD[3], Lucy T. Lennon MSc[2], Marjolein Visser PhD[4], Yvonne L. Kapila DDS, PhD[5], Robert J. Weyant DMD, DrPh[6], Sheena E. Ramsay PhD[1]

[1]Population Health Sciences Institute, Newcastle University, Newcastle Upon Tyne, United Kingdom

[2]Department of Primary Care & Population Health, Institute of Epidemiology and Health Care, University College London, London, United Kingdom

[3]Population Health Research Institute, St George's University of London, London, United Kingdom

[4]Department of Health Sciences, Amsterdam Public Health Research Institute, Vrije Universiteit, Amsterdam, Netherlands

[5]Department of Orofacial Sciences, School of Dentistry, University of California, San Francisco, California, United States of America

[6]Department of Dental Public Health, School of Dental Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

Corresponding author:

Eftychia Kotronia, Population Health Sciences Institute, Newcastle University, The Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne NE2 4AX, United Kingdom

Email: e.kotronia2@newcastle.ac.uk

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Abstract

Background: We examined the association of objective and subjective oral health markers with inflammatory, haemostatic and cardiac biomarkers in older age.

Methods: Cross-sectional analyses were based on the British Regional Heart Study (BRHS) comprising British men aged 71-92 years (n=2147), and the Health, Aging and Body Composition (HABC) Study comprising American men and women aged 71-80 years (n=3075). Oral health markers included periodontal disease, tooth count, dry mouth. Inflammatory biomarkers included C-reactive protein (CRP), interleukin-6 (IL-6) in both studies, and tissue plasminogen activator (t-PA), von Willebrand Factor (vWF), fibrin D-dimer, high sensitivity Troponin T (hsTnT) and N-terminal pro-brain natriuretic peptide (NTproBNP) only in the BRHS.

Results: In both studies, tooth loss, was associated with the top tertile of CRP – odds ratios (95%CI) are 1.31 (1.02-1.68) in BRHS; and 1.40 (1.13-1.75) in the HABC Study, after adjusting for confounders. In the HABC Study, cumulative (≥3) oral health problems were associated with higher levels of CRP (OR (95%CI) =1.42 (1.01-1.99)). In the BRHS, complete and partial tooth loss were associated with haemostatic factors, in particular with the top tertile of fibrin D-dimer (OR (95%CI) = 1.64 (1.16-2.30) and 1.37 (1.05-1.77) respectively). Tooth loss and periodontal disease were associated with increased levels of hsTnT.

Conclusions: Poor oral health in older age, particularly tooth loss, was consistently associated with some inflammatory, haemostatic and cardiac biomarkers. Prospective studies and intervention trials could help understand better if poor oral health is causally linked to inflammatory, haemostatic and cardiac biomarkers.

Keywords: tooth loss, C-reactive protein, fibrin D-dimer, Troponin T, cardiovascular disease

Introduction

Poor oral health including tooth loss, periodontal disease, and dryness of mouth, are common conditions in aging populations (1). Poor oral health is associated with adverse age-related health outcomes, such as disability, cardiovascular disease, type 2 diabetes and mortality (2-5). Aging is also characterised by an increase in markers of general inflammation such as C-reactive protein (CRP), and interleukin-6 (IL-6) (6). Likewise, haemostatic factors including fibrin D-dimer, von Willebrand factor (vWF) and tissue plasminogen activator (t-PA) and cardiac biomarkers such as high sensitivity Troponin T (hsTnT) and N-terminal pro-brain natriuretic peptide (NTproBNP) increase with age (7-9). Increased inflammation is associated with chronic diseases and in particular haemostatic and cardiac biomarkers are strongly associated with cardiovascular disease (CVD) (10-13).

Poor oral health, particularly periodontal disease (chronic gum disease), is associated with a number of inflammatory markers in adults. Studies in middle-aged adults demonstrated that participants with periodontal disease had increased levels of CRP compared to those with no periodontal disease, whereas no differences were observed in IL-6 levels (14-16). Furthermore, improvement in periodontal disease status resulted in a decline in CRP and IL-6 levels (17). Additionally, tooth loss and poor tooth brushing were associated with higher levels of CRP and IL-6 in studies including both middle-aged and older individuals (18-20). Also, individuals with dry mouth (xerostomia), which may be a consequence of chronic diseases and medications, were at risk of inflammation of the oral mucosa as well as oral infections and potentially increased levels of systemic inflammation (21). Periodontal disease was also associated with high levels of vWF (22). Furthermore, having less than 24 teeth was associated with high levels of t-PA (23). Again, these studies included both middle-aged and older individuals. In the only study focusing on older people, periodontal disease was not associated with high levels of CRP and IL-6 (24). Additionally, tooth loss was associated

with an increase in levels of NTproBNP in older individuals diagnosed with stable coronary heart disease (CHD) (25). Also, periodontal disease correlated significantly with high levels of NTproBNP (26). However, no studies have examined the associations of poor oral health with cardiac biomarkers in a large population of community-dwelling older individuals.

Previous research on the associations between oral health and inflammation has mainly been conducted in middle-aged populations, with limited evidence in older individuals. Moreover, the majority of studies have looked at periodontal disease and tooth loss, with few details on other markers of oral health, such as dry mouth, and self-rated oral health. Little is also known about the associations of poor oral health with haemostatic and cardiac biomarkers. Therefore, in this study we examined the associations of a range of oral health measures with markers of inflammation/haemostasis, and cardiac biomarkers in two studies of older people in the UK and USA.

Methods

The British Regional Heart Study

The British Regional Heart Study (BRHS) is a prospective cohort study that included 7735 men aged 40-59 years, who were recruited in 1978-80 from 24 towns across the UK (27). Surviving participants were invited to a 30-year re-assessment in 2010-2012 when they were aged 71-92 years (27). A total of 2147 participants (68% response rate) completed the postal questionnaire, and 1722 participated in the physical examination (55% response rate) and had blood samples taken. Ethical approval was provided by the relevant ethical committees. Written informed consent was obtained from individuals for their participation in the investigations, which were conducted in accordance with the Declaration of Helsinki.

The Health, Aging, and Body Composition Study (Health ABC Study)

The Health ABC (HABC) Study is a prospective cohort study aiming to study the decline in physical function of older individuals and the role of changes in body composition with age. In 1997-1998, 3075 white and African-American men and women were recruited, aged 70-79 years. White participants were randomly selected through Medicare, whereas African-American from neighbourhoods with a ZIP code around Memphis and Pittsburgh (28). Only individuals who were able to walk 0.25 miles or climb 10 steps without any difficulty were included in the study at baseline. In Year 2 (1998-1999) surviving participants aged 71-80 years underwent an oral health (n=1975) and physical assessment, gave blood samples and completed questionnaires. All participants provided written informed consent. Ethical approval was provided by several institutional review boards (28).

Oral health markers

In both studies, an oral examination comprised objective measures including a count of natural teeth, and periodontal disease measures (loss of attachment and pocket depth). In the BRHS, brief periodontal assessments were conducted in six index teeth, one per sextant of the mouth (1). In the HABC Study, periodontal measures were conducted in all teeth (full mouth) (29). Further details of these measurements can be found elsewhere (1, 29). Subjective oral health markers were assessed through questionnaires and consisted of self-rated oral health, dry mouth, difficulty eating due to mouth, teeth or dentures problems, sensitivity to hot/cold/sweets, and limitation of food due to gum problems. In the BRHS, dry mouth was measured based on the Xerostomia Inventory Scale (30); in the HABC Study, participants were asked if they had dry mouth symptoms when eating. Number of natural teeth was categorised as: five-level category (0, 1-7, 8-14, 15-20, ≥21 teeth); edentulism (no

natural teeth and ≥1 teeth); and having ≥21 and <21 remaining teeth (31). For the categorisation of periodontal disease, in both studies, we used the Extent and Severity Index, where groups are created on the basis of the percentage of sites being affected (32). Periodontal pocket depth was grouped as follows, for BRHS: >20% sites affected >3.5 mm, and for HABC Study: >20% sites affected ≥3 mm. Loss of attachment was grouped as, for BRHS: >20% sites affected >5.5 mm, and HABC Study >20% sites affected with ≥3mm (1, 24). Self-rated oral health was categorised as excellent/good and fair/poor in both studies. In the BRHS, dry mouth was categorised into 0, 1-2 or ≥3 dry mouth symptoms, whereas in the HABC Study dry mouth was binary, either yes or no. A cumulative measure of oral problems was created – in the BRHS, it was based on having: ≥3 dry mouth symptoms, <21 natural teeth, any difficulty eating and sensitivity to hot/cold/sweets ; in the HABC Study, it comprised of the following: dry mouth when eating, <21 natural teeth, any difficulty eating and limitation of food due to gum problems. The cumulative oral health problem variable was then grouped as 0, 1, 2, and ≥3 problems.

Inflammatory, haemostatic and cardiac biomarkers

In the BRHS, plasma levels of IL-6 (pg·mL−1), CRP (mg·L−1), t-PA (ng·mL−1), vWF (IU·dL−1), fibrin D-Dimer (ng·mL−1), NTproBNP (ng/L) and hsTnT (ng/L) were assessed. CRP was assayed by ultra-sensitive nephelometry (Dade Behring, Milton Keynes, UK). IL-6 was assayed using a high-sensitivity ELISA (R&D Systems, Oxford, UK) (33). T-PA and fibrin D-dimer (Asserachrom assays; Stago, Theale, UK), and vWF antigen (Technozym assay; Pathway Diagnostics, Dorking, UK) were measured using high-sensitivity enzyme-linked immunosorbent assays (34). NTproBNP and hsTnT were measured using the Elecsys 2010 electrochemiluminescence method (Roche Diagnostics, Burgess Hill, UK) (33).

In the HABC Study, CRP was measured in anticoagulated EDTA-plasma by an automated chemiluminescent immunoassay system (IMMULITE, Diagnostic Products Corporation, Los Angeles) (35). IL-6 levels were assessed in duplicate EDTA plasma by a high-sensitivity Quantikine colorimetric immunoassay kit from R&D Systems (Minneapolis, MN) (35). Measurements were performed by the Wake Forest University laboratory.

Covariates

In both studies, information on socioeconomic position, smoking, and history of doctor-diagnosed CVD and diabetes were obtained from questionnaires (27, 29). In the BRHS, socioeconomic position was based on occupational social class which was derived from longest-held occupation when participants entered the study (1). Smoking history was based on combined set of questions from previous questionnaires. In the HABC Study, socioeconomic position was based on the highest level of education accomplished (29). Body weight and height measured at the physical examinations were used to create body mass index (BMI) (34, 36). For both studies, regular use of prescribed medications causing dry mouth (xerostomia) were identified (37).

Statistical Analysis

Separate logistic regression analyses were performed for the two studies. Markers of inflammation were divided into tertiles (as low, medium and high levels) and the top tertile of each marker was used as the outcome of the regression model. Odds ratios and 95% confidence intervals (CI) were obtained. In the BRHS, we adjusted for age, social class, smoking, history of CVD and diabetes and BMI. In the HABC Study, age, gender, race, education, smoking, history of CVD and diabetes and BMI were entered as potential confounders in the model. In both studies, dry mouth analyses were further adjusted for use of medications.

In a sensitivity analysis, CRP was added in the fully adjusted regression models to examine whether associations of oral health with IL-6, haemostatic and cardiac biomarkers were attenuated on adjustment for CRP. All analyses were performed using SAS, version 9.4 software (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics and prevalence of oral health markers in the BRHS and HABC Study populations are presented in Table 1. The mean age of BRHS participants, with data on inflammatory, haemostatic and cardiac biomarkers, was 78.8 years, and 46% were in the manual social class, 20% were edentulous, 34% reported poor self-rated oral health, 62% had at least 1 dry mouth symptom, and 33% had at least 2 oral health problems. In the HABC Study, the mean age of participants with data on inflammation was 74.7 years, 49% were male and 51% females, and 60% were White whereas 40% were African-American. Additionally, 44% completed post-secondary education, 11% had no natural teeth, and 30% reported poor self-rated oral health, 4% had dry mouth and 23% had at least 2 oral health problems.

Oral health and inflammatory markers in the BRHS and HABC Study

The odds ratios (OR) and 95% CI for the association between poor oral health and the top tertiles of CRP and IL-6 in the BRHS can be found in Table 2. Having no teeth was associated with the top tertile of CRP when compared to having ≥21 teeth (OR=1.52, 95% CI: 1.09-2.13) after adjusting for age, social class, smoking, history of CVD and diabetes, and BMI (fully adjusted model). Likewise, partial tooth loss (<21 teeth) was associated with increased risk of being in the top tertile of CRP (OR=1.31, 95% CI: 1.02-1.68). Furthermore, complete (0 vs ≥ 21 teeth), and partial (<21 vs. ≥ 21 teeth) tooth loss and loss of attachment

were associated with the top tertile of IL-6 in age-adjusted models (OR=1.47, 95% CI: 1.09-1.99; OR= 1.35, 95% CI: 1.08-1.70; OR=1.39, 95% CI: 1.04-1.85, respectively). However, these associations were attenuated after full adjustment and were no longer statistically significant. No significant associations were observed for dry mouth and self-rated oral health with CRP or IL6.

Table 3 presents the odds ratios for the associations of objective and subjective oral health markers with CRP and IL-6 in the HABC Study. Complete and partial tooth loss were both associated with being in the top tertile of CRP in the fully adjusted models (OR=1.57, 95%CI: 1.10-2.25; OR=1.40, 95%CI: 1.13-1.75, respectively). Having ≥3 oral health problems, compared to those with none, was associated with the top tertiles of both CRP and IL-6 (OR=1.42, 95%CI: 1.01-1.99; OR=1.65 95%CI: 1.19-2.31, respectively) after full adjustment. Mean attachment loss and mean pocket depth were associated with being in the top tertile of IL-6, but were attenuated and did not remain significant after adjustment for age, gender, race, education, smoking, history of CVD and diabetes, and BMI. Dry mouth was not significantly associated with high levels of CRP or IL6.

Oral health and haemostatic biomarkers in the BRHS

Odds ratios and 95% CI for poor oral health and haemostatic biomarkers in the BRHS are presented in Table 4. Having 1-7 teeth and 0 teeth were associated with the top tertile of fibrin D-dimer when compared to having ≥21 teeth in the fully adjusted models (OR=1.93, 95%CI: 1.22-3.05; OR=1.64, 95%CI: 1.16-2.30, respectively). Similarly, having <21 teeth was associated with being in the top tertile of fibrin D-dimer in both age and fully adjusted models (OR=1.45, 95%CI: 1.15-1.84; OR=1.37, 95%CI: 1.05-1.77, respectively). For vWF, associations with fair/poor self-rated oral health were observed only in the age-adjusted models, which were attenuated on full adjustment. Having 2 oral health problems compared

to those with none, was associated with the top tertile of vWF (OR=1.49, 95%CI: 1.05-2.09) after full adjustment, but not with fibrin D-dimer or t-PA. Most associations did not change materially after further adjustment for CRP (results in Supplemental Material eTable 3).

Oral health and cardiac biomarkers in the BRHS

Table 5 presents associations between poor oral health and cardiac biomarkers. In the BRHS, partial tooth loss and loss of attachment (periodontal disease marker) were associated with higher levels of hsTnT in the age and fully adjusted models (fully adjusted model, OR=1.32, 95% CI: 1.01-1.74 for partial tooth loss; OR=1.49, 95%CI: 1.08-2.07 for loss of attachment). The association with loss of attachment remained significant even after adjustment for CRP (see Supplemental Material eTable 4). Fewer associations were observed with NTproBNP. Having ≥3 dry mouth symptoms was associated with the top tertile of NTproBNP in the age adjusted model (OR=1.37, 95%CI: 1.04-1.81), but the association was not statistically significant after full adjustment. Moreover, having 15-20 teeth was associated with the top tertile of NTproBNP when compared to having ≥21 teeth, in the fully adjusted model (OR=1.40, 95%CI: 1.01-1.94).

Discussion

In this cross-sectional study of older individuals in the UK and USA, poor oral health, particularly tooth loss, was associated with increased levels of CRP, fibrin D-dimer, and hsTnT after adjustment for age and other confounding factors. Haemostatic factors, including vWF and t-Pa, and cardiac marker, NTproBNP, also showed associations with some measures of poor oral health in the BRHS. This is one of the first studies demonstrating relationships between poor oral health and a range of inflammatory, haemostatic and cardiac biomarkers in older people.

Poor oral health and general inflammation (CRP and IL-6)

In accordance with previous studies in middle-aged populations (18-20), tooth loss and edentulism were associated with high levels of CRP in both studies. Partial and complete tooth loss (edentulism), can lead to masticatory problems (38) which in turn influence nutritional intake, which results in a diet poor in antioxidants and vitamins (18). This may affect levels of systemic inflammation (18). Additionally, edentulism may be an indicator of persistent oral inflammation throughout the lifespan; it could also possibly be a marker of systemic health and therefore associated with inflammation and higher rate of chronic diseases (3). Similar to a previous study in an older population (24), periodontal disease was not associated with high levels of CRP. Our study population consisted of older individuals, where it is possible that teeth with severe periodontal disease may have already been lost and only the healthiest teeth remained and were assessed for loss of attachment and pocket depth. Furthermore, in the HABC Study, we found that having more than one oral health problem was associated with high levels of CRP and IL-6. This finding highlights the potential burden of oral health on inflammation in older individuals. Moreover, the observed associations for CRP remained significant even after adjustment for smoking, chronic diseases and BMI, indicating that there may be an independent association between markers of poor oral health and CRP in older people. The majority of associations between oral health and high levels of IL-6 did not remain significant after adjusting for confounders.

Poor oral health and haemostatic biomarkers

Self-rated oral health was associated with increased levels of vWF (age-adjusted) and t-PA (age and borderline significant in the fully adjusted) in the BRHS. Although previous studies have been unable to establish which oral health factors influence an individual's grading of their oral health, self-rated oral health is known to be associated with oral diseases and declines with age (39). Therefore, we hypothesize that the observed associations, may be a result of accumulation of oral health problems, which may also be associated with worsening

health and increase of inflammation levels. In the BRHS, we also found associations between tooth loss (complete and partial) and high fibrin D-dimer. Tooth loss, which can be a result of chronic periodontal disease and root carries (40), could be linked with oral infections and inflammation (3). Oral bacteria entering the circulatory system could indirectly influence thrombosis and the formation of atherosclerotic plaques and in turn contribute to inflammation associated with cardiovascular disease (41). Furthermore, it has been shown that ageing is characterised by an elevation in levels of fibrin D-dimer, which is implicated in fibrinolysis and general inflammation (42). Previous studies observed that fibrin D-dimer is closely linked to chronic conditions such as atherosclerosis, functional disability and frailty and mortality (7, 42, 43). We can hypothesize that in older people, poor oral health may add to the inflammatory burden and contribute to increased fibrinolysis and levels of fibrin D-dimer. It is possible that fibrin D-dimer may be one of the pathways linking poor oral health with disability and impaired physical function in older people.

Poor oral health and cardiac biomarkers

Poor oral health, periodontal disease and partial tooth loss, were associated with hsTnT. These associations of periodontal disease with hsTnT remained significant even after adjustment for CRP. There are few studies on the association of poor oral health with levels of hsTnT in older people. Troponin T is a marker of myocardial injury and has been associated with hypertension, atherosclerosis, CHD and heart failure (44-46). Periodontal disease contributes to chronic inflammation, through its contribution to atherosclerosis and thrombus formation (47). Therefore, the observed association of periodontal disease with high levels of hsTnT, may offer a potential link between periodontal disease and CHD. This is supported by previous research demonstrating an association between periodontal disease and the incidence of CHD (48). Similarly, tooth loss, whether as a result of periodontal disease or life stressors/behaviours, may also be associated with CHD. However, for

NTproBNP, a marker of left ventricular stress, fewer associations were observed, and only partial tooth loss was associated with high levels of NTproBNP after full adjustment.

Our study has a number of strengths. We investigated the associations of a range of objective and subjective oral health markers with a variety of inflammatory, haemostatic and cardiac biomarkers in community-dwelling older people. Furthermore, we examined these associations in diverse populations of older people, in contrast to previous studies, which have mainly focused on young and middle-aged individuals. The two studies are reasonably sized with detailed and comparable oral health data. Our study has some limitations. The study was cross-sectional and therefore cannot establish causal relationships or the direction of associations between poor oral health and inflammation. Furthermore, while the study populations of the BRHS and HABC Study were comparable in terms of comprising older people, differences in some other characteristics were present. The HABC Study comprised of White and African-American men and women, whilst the BRHS included only White men. Moreover, the assessment of some oral health measures (i.e. periodontal disease, dry mouth) and availability of inflammation markers (only CRP and IL-6 in the HABC Study) differed between the two studies, and therefore it was not possible to compare the findings of all the biomarkers between the two studies. However, similar associations were observed for poor oral health and CRP in both study populations. Additionally, both cohorts may not be representative of the general populations of the UK and USA. It is also possible that healthier individuals attended the physical examinations in both studies and survivor bias may be present. Moreover, since we tested a number of associations with oral health markers and performed multiple comparisons, there is the potential for reporting false-positive results. Although we were able to adjust for a number of covariates, the possibility of residual confounding also remains.

In conclusion, poor oral health in community-dwelling older people – in particular tooth loss and accumulation of oral health problems, were associated with a number of biomarkers, such as increased levels of CRP, fibrin D-dimer and hsTnT. Our findings indicate that poor oral health is associated with high levels of inflammatory markers. Moreover, they provide valuable evidence on the possible associations of poor oral health (predominantly tooth loss) with haemostatic and cardiac biomarkers and highlight a potential link between poor oral health and CHD in older people. Further investigations on longitudinal associations of oral health with these biomarkers and intervention trials are potentially important to understand whether oral health problems are causally associated with inflammation and chronic diseases in older age.

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Study concept and design: Kotronia E, Ramsay SE, Wannamethee SG, Papacosta AO, Whincup PH.

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Table 1. Population characteristics and prevalence of oral health problems in the British Regional Heart Study (BRHS) and the Health ABC (HABC) Study

BRHS (n=1557)		**HABC Study (n=2780)**	
Age (years), mean ± standard deviation	78.4 ± 4.7	**Age (years), mean ± standard deviation**	74.7 ± 2.9
Social class, n (%)		**Gender, n (%)**	
Nonmanual	812 (54%)	Male	1355 (49%)
Manual	699 (46%)	Female	1425 (51%)
Smoking, n (%)		**Race, n (%)**	
Never	593 (38%)	White	1679 (60%)
Long-term exsmoker (gave up before 1983)	836 (54%)	African-American	1101 (40%)
Recent exsmoker	65 (4%)	**Education, n (%)**	
Current smoker	53 (4%)	Less than high school	668 (24%)
History of cardiovascular disease, n (%)	343 (23%)	High school graduate	894 (32%)
History of diabetes, n (%)	230 (16%)	Postsecondary	1211 (44%)
Body Mass Index, n (%)		**Smoking[a], n (%)**	

BRHS (n=1557)		**HABC Study (n=2780)**	
Normal	458 (30%)	Never	1226 (44%)
Overweight	789 (51%)	Current smoker	270 (10%)
Obese	294 (19%)	Former	1280 (46%)
		History of cardiovascular disease, n (%)	104 (4%)
		History of diabetes, n (%)	140 (5%)
		Body Mass Index, n (%)	
		Normal	941 (34%)
		Overweight	1170 (42%)
		Obese	667 (24%)
Oral health measures		**Oral health measures**	
Edentulism (no natural teeth)	298 (20%)	Edentulism (no natural teeth)	199 (11%)
<21 teeth	952 (63%)	<21 teeth	1012 (52%)
>20 % sites with loss of attachment >3.5mm	267 (23%)	>20 % sites with loss of attachment ≥3mm	708 (63%)

BRHS (n=1557)		**HABC Study (n=2780)**	
>20% sites with pocket depth >5.5mm	334 (29%)	>20% sites with pocket depth ≥3mm	617 (55%)
Fair/poor self–rated oral health	503 (34%)	Fair/poor self–rated oral health	818 (30%)
Difficulty eating	134 (12%)	Difficulty Eating	528 (20%)
Sensitivity to hot or cold or sweets	339 (23%)	Limit of food due to gum problems	385 (14%)
≥ 1 dry mouth symptoms	919 (62%)	Dry mouth	106 (4%)
≥ 2 oral health problems	512 (33%)	≥2 oral health problems	612 (23%)

[a] Baseline data (Year 1)

Table 2. Odds ratios (95%CI) for the associations of oral health markers with top tertiles of CRP, and IL6 in British men aged 71-92 years in the BRHS

	Top tertile of CRP[a]		**Top tertile of IL-6**[a]	
Oral Health Markers				
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
Objective	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tooth Loss				
≥21teeth	1.00	1.00	1.00	1.00
15-20 teeth	1.38 (1.02, 1.86)	1.35 (0.99, 1.85)	1.27 (0.94, 1.72)	1.29 (0.94, 1.77)
8-14 teeth	1.31 (0.95, 1.92)	1.13 (0.80, 1.61)	1.35 (0.98, 1.86)	1.20 (0.85, 1.70)
1-7 teeth	1.24 (0.80, 1.92)	1.11 (0.70, 1.77)	1.31 (0.85, 2.02)	1.18 (0.75, 1.88)
0 teeth	1.90 (1.41, 2.56)	1.52 (1.09, 2.13)	1.47 (1.09, 1.99)	1.22 (0.87, 1.71)
Edentulism				
≥1 teeth	1.00	1.00	1.00	1.00
0 teeth	1.61 (1.24, 2.09)	1.35 (1.01, 1.80)	1.26 (0.97, 1.64)	1.06 (0.79, 1.43)

	Top tertile of CRP[a]		Top tertile of IL-6[a]	
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tooth Loss				
≥21teeth	1.00	1.00	1.00	1.00
<21 teeth	1.49 (1.18, 1.87)	1.31 (1.02, 1.68)	1.35 (1.08, 1.70)	1.23 (0.96, 1.59)
Periodontal disease (% of sites with loss of attachment >5.5 mm)				
≤20%	1.00	1.00	1.00	1.00
>20%	1.33 (1.00, 1.78)	1.34 (0.99, 1.81)	1.39 (1.04, 1.85)	1.32 (0.97, 1.78)
Subjective				
Self-rated oral health				
Good or excellent	1.00	1.00	1.00	1.00
Fair or poor	1.18 (0.94, 1.48)	1.13 (0.89, 1.43)	1.23 (0.98, 1.54)	1.24 (0.98, 1.58)

	Top tertile of CRP[a]		Top tertile of IL-6[a]	
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Dry mouth symptoms				
0	1.00	1.00	1.00	1.00
1-2	1.04 (0.81, 1.34)	1.01 (0.77, 1.33)	0.92 (0.71, 1.19)	0.84 (0.65, 1.11)
≥3	1.19 (0.92, 1.55)	1.20 (0.91, 1.59)	0.99 (0.76, 1.29)	0.96 (0.73, 1.27)
Number of oral health problems[c]				
0	1.00	1.00	1.00	1.00
1	1.28 (0.96, 1.71)	1.11 (0.81, 1.51)	1.31 (0.98, 1.75)	1.23 (0.90, 1.68)
2	1.33 (0.96, 1.84)	1.17 (0.82, 1.66)	1.36 (0.98, 1.89)	1.21 (0.85, 1.72)
≥3	1.54 (1.03, 2.31)	1.37 (0.89, 2.12)	1.07 (0.70, 1.63)	1.07 (0.68, 1.68)

[a] values for top tertile of CRP: 2.24-239.8 ug/ml; for IL-6: 3.90-30 pg/ml

[b] adjusted for age, social class, smoking, history of CVD and diabetes, BMI

[c] ≥3 dry mouth symptoms, <21 remaining natural teeth, difficulty eating due to gum/mouth/dentures problems, sensitivity to hot/cold/sweets

Table 3. Odds ratios (95%CI) for the associations of oral health markers with top tertiles of CRP, and IL6 in American men and women aged 71-80 years in the HABC Study

	Top tertile of CRP[a]		**Top tertile of IL-6**[a]	
Oral Health Markers				
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
Objective	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tooth Loss				
≥21teeth	1.00	1.00	1.00	1.00
15-20 teeth	1.65 (1.27, 2.15)	1.39 (1.05, 1.84)	1.30 (1.00, 1.70)	1.05 (0.79, 1.39)
8-14 teeth	1.67 (1.25, 2.22)	1.26 (0.92, 1.72)	1.88 (1.42, 2.48)	1.45 (1.07, 1.96)
1-7 teeth	2.02 (1.45, 2.82)	1.52 (1.07, 2.18)	1.74 (1.25, 2.43)	1.27 (0.89, 1.82)
0 teeth	1.89 (1.37, 2.60)	1.57 (1.10, 2.25)	1.56 (1.13, 2.15)	1.24 (0.87, 1.78)
Edentulism				
≥1 teeth	1.00	1.00	1.00	1.00
0 teeth	1.42 (1.05, 1.92)	1.28 (0.92, 1.78)	1.26 (0.93, 1.71)	1.10 (0.79, 1.53)

	Top tertile of CRP[a]		Top tertile of IL-6[a]	
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tooth Loss				
≥21teeth	1.00	1.00	1.00	1.00
<21 teeth	1.76 (1.45, 2.15)	1.40 (1.13, 1.75)	1.58 (1.30, 1.91)	1.22 (0.98, 1.51)
Periodontal disease (% of sites with loss of attachment ≥3 mm)				
≤20%	1.00	1.00	1.00	1.00
>20%	1.18 (0.90, 1.55)	1.08 (0.80, 1.44)	1.30 (0.99, 1.71)	1.11 (0.83, 1.48)
Subjective				
Self-rated oral health				
Good or excellent	1.00	1.00	1.00	1.00
Fair or poor	1.23 (1.04, 1.47)	1.03 (0.85, 1.24)	1.34 (1.13, 1.59)	1.17 (0.97, 1.41)

	Top tertile of CRP[a]		Top tertile of IL-6[a]	
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Dry mouth symptoms				
No	1.00	1.00	1.00	1.00
Yes	1.28 (0.86, 1.91)	1.10 (0.72, 1.66)	1.39 (0.93, 2.07)	1.29 (0.85, 1.95)
Number of oral health problems[c]				
0	1.00	1.00	1.00	1.00
1	1.50 (1.24, 1.83)	1.25 (1.01, 1.55)	1.43 (1.18, 1.74)	1.18 (0.96, 1.46)
2	1.76 (1.35, 2.28)	1.43 (1.09, 1.89)	1.24 (0.95, 1.62)	1.05 (0.79, 1.39)
≥3	1.97 (1.44, 2.70)	1.42 (1.01, 1.99)	2.12 (1.55, 2.89)	1.65 (1.19, 2.31)

[a] values for top tertile of CRP: 4.96-141 ug/ml; for IL-6: 3.29-32.87 pg/ml

[b] adjusted for age, gender, race, education, smoking, history of CVD and diabetes, BMI

[c] dry mouth when eating, <21 remaining teeth, any difficulty eating or chewing, limitation of food due to gum problems

Table 4. Odds ratios (95%CI) for the associations of oral health markers with top tertiles of fibrin D-dimer, vWF and t-PA in British men aged 71-92 years in the BRHS

	Top tertile of fibrin D-dimer[a]		**Top tertile of vWF**[a]		**Top tertile of t-PA**[a]	
Oral Health Markers						
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
Objective	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tooth Loss						
≥21teeth	1.00	1.00	1.00	1.00	1.00	1.00
15-20 teeth	1.17 (0.85, 1.60)	1.17 (0.84, 1.62)	0.92 (0.68, 1.25)	0.88 (0.64, 1.21)	0.90 (0.67, 1.22)	0.93 (0.67, 1.28)
8-14 teeth	1.24 (0.88, 1.74)	1.19 (0.83, 1.72)	1.11 (0.80, 1.52)	1.02 (0.72, 1.44)	1.16 (0.84, 1.59)	1.13 (0.80, 1.60)
1-7 teeth	1.93 (1.26, 2.97)	1.93 (1.22, 3.05)	1.48 (0.98, 2.25)	1.44 (0.93, 2.23)	1.18 (0.77, 1.81)	1.08 (0.68, 1.71)
0 teeth	1.83 (1.35, 2.49)	1.64 (1.16, 2.30)	1.08 (0.80, 1.46)	0.91 (0.65, 1.28)	1.22 (0.90, 1.64)	1.08 (0.76, 1.52)
Edentulism						
≥1 teeth	1.00	1.00	1.00	1.00	1.00	1.00
0 teeth	1.57 (1.20, 2.05)	1.38 (1.03, 1.85)	1.04 (0.79, 1.35)	0.89 (0.66, 1.19)	1.19 (0.91, 1.55)	1.06 (0.78, 1.43)

	Top tertile of fibrin D-dimer[a]		Top tertile of vWF[a]		Top tertile of t-PA[a]	
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tooth Loss						
≥21teeth	1.00	1.00	1.00	1.00	1.00	1.00
<21 teeth	1.45 (1.15, 1.84)	1.37 (1.05, 1.77)	1.07 (0.86, 1.34)	0.98 (0.77, 1.25)	1.09 (0.87, 1.36)	1.03 (0.80, 1.33)
Periodontal disease (% of sites with loss of attachment >5.5 mm)						
≤20%	1.00	1.00	1.00	1.00	1.00	1.00
>20%	1.05 (0.77, 1.42)	0.98 (0.71, 1.36)	1.32 (0.99, 1.75)	1.17 (0.87, 1.58)	1.17 (0.87, 1.56)	1.12 (0.82, 1.52)
Subjective						
Self-rated oral health						
Good or excellent	1.00	1.00	1.00	1.00	1.00	1.00
Fair or poor	1.08 (0.86, 1.36)	1.06 (0.83, 1.36)	1.31 (1.05, 1.64)	1.24 (0.98, 1.57)	1.31 (1.05, 1.63)	1.27 (1.00, 1.61)

	Top tertile of fibrin D-dimer[a]		Top tertile of vWF[a]		Top tertile of t-PA[a]	
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Dry mouth symptoms						
0	1.00	1.00	1.00	1.00	1.00	1.00
1-2	1.07 (0.82, 1.40)	1.11 (0.84, 1.46)	0.90 (0.69, 1.16)	0.90 (0.69, 1.18)	1.08 (0.84, 1.39)	1.06 (0.81, 1.39)
≥3	1.24 (0.94, 1.64)	1.24 (0.93, 1.66)	1.20 (0.92, 1.56)	1.27 (0.97, 1.67)	1.04 (0.80, 1.36)	0.95 (0.71, 1.27)
Number of oral health problems[c]						
0	1.00	1.00	1.00	1.00	1.00	1.00
1	1.14 (0.84, 1.54)	1.09 (0.79, 1.50)	1.19 (0.89, 1.58)	1.16 (0.85, 1.58)	0.98 (0.74, 1.30)	0.97 (0.71, 1.32)
2	1.48 (1.06, 2.07)	1.38 (0.97, 1.98)	1.51 (1.09, 2.08)	1.49 (1.05, 2.09)	1.28 (0.93, 1.75)	1.11 (0.78, 1.56)
3	1.35 (0.89, 2.06)	1.23 (0.78, 1.94)	1.49 (1.00, 2.24)	1.49 (0.97, 2.30)	1.18 (0.79, 1.76)	1.16 (0.74, 1.80)

[a] values for top tertile of fibrin D-dimer: 277.27-2000 ng/ml; for vWF: 132.69-433.17 IU/dl; for t-PA: 10.63-50 ng/ml

[b] adjusted for age, social class, smoking, history of CVD and diabetes, BMI

[c] ≥3 dry mouth symptoms, <21 remaining teeth, difficulty eating due to gum/mouth/dentures problems, sensitivity to hot/cold/sweets

Table 5. Odds ratios (95%CI) for the associations of oral health markers with top tertiles of hsTnT and NTproBNP in British men aged 71-92 years in the BRHS

	Top tertile of hsTnT[a]		**Top tertile of NTproBNP**[a]	
Oral Health Markers				
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
Objective	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tooth Loss				
≥21teeth	1.00	1.00	1.00	1.00
15-20 teeth	1.24 (0.90, 1.72)	1.33 (0.94, 1.87)	1.30 (0.96, 1.77)	1.40 (1.01, 1.94)
8-14 teeth	1.27 (0.90, 1.80)	1.24 (0.85, 1.81)	1.00 (0.71, 1.40)	1.08 (0.75, 1.56)
1-7 teeth	1.44 (0.92, 2.25)	1.31 (0.81, 2.12)	0.95 (0.61, 1.48)	0.95 (0.59, 1.53)
0 teeth	1.42 (1.03, 1.96)	1.40 (0.98, 2.02)	1.15 (0.84, 1.57)	1.09 (0.76, 1.55)
Edentulism				
≥1 teeth	1.00	1.00	1.00	1.00
0 teeth	1.23 (0.93, 1.63)	1.19 (0.87, 1.63)	1.08 (0.82, 1.42)	0.99 (0.73, 1.34)

	Top tertile of hsTnT[a]		Top tertile of NTproBNP[a]	
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tooth Loss				
≥21teeth	1.00	1.00	1.00	1.00
<21 teeth	1.33 (1.04, 1.70)	1.32 (1.01, 1.74)	1.13 (0.90, 1.43)	1.17 (0.91, 1.52)
Periodontal disease (% of sites with loss of attachment >5.5 mm)				
≤20%	1.00	1.00	1.00	1.00
>20%	1.64 (1.21, 2.23)	1.49 (1.08, 2.07)	1.16 (0.86, 1.56)	1.12 (0.81, 1.54)
Subjective				
Self-rated oral health				
Good or excellent	1.00	1.00	1.00	1.00
Fair or poor	1.23 (0.97, 1.57)	1.20 (0.93, 1.56)	1.04 (0.82, 1.32)	1.07 (0.83, 1.38)

	Top tertile of hsTnT[a]		Top tertile of NTproBNP[a]	
	Age-adjusted	Fully-adjusted[b]	Age-adjusted	Fully-adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Dry mouth symptoms				
0	1.00	1.00	1.00	1.00
1-2	0.96 (0.73, 1.27)	0.87 (0.65, 1.16)	1.29 (0.99, 1.69)	1.20 (0.90, 1.59)
≥3	1.12 (0.84, 1.48)	1.00 (0.74, 1.35)	1.37 (1.04, 1.81)	1.25 (0.93, 1.68)
Number of oral health problems[c]				
0	1.00	1.00	1.00	1.00
1	1.18 (0.86, 1.60)	1.17 (0.84, 1.63)	0.84 (0.63, 1.13)	0.81 (0.59, 1.12)
2	1.41 (1.00, 2.00)	1.33 (0.91, 1.93)	1.26 (0.91, 1.75)	1.16 (0.81, 1.66)
≥3	1.31 (0.85, 2.03)	1.31 (0.82, 2.10)	1.01 (0.66, 1.53)	1.03 (0.65, 1.62)

[a] values for top tertile of hsTnT: 14.34-407.10 ng/l; for NTproBNP: 226-15899 ng/l

[b] adjusted for age, social class, smoking, history of CVD and diabetes, BMI

[c] ≥3 dry mouth symptoms, <21 remaining teeth, difficulty eating due to gum/mouth/dentures problems, sensitivity to hot/cold/sweets