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Periodontal disease in patients with chronic coronary heart disease: Prevalence and association with cardiovascular risk factors

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Abstract

Aim: There are reported links between periodontal disease (PD) and cardiovascular (CV) risk but data are lacking, especially from populations with established coronary heart disease (CHD). This study describes self-reported indicators of PD and associations with CV risk factors in a global stable CHD population.

Methods and results: A total of 15,828 participants in the global STABILITY trial underwent a physical examination, blood sampling, and completed a lifestyle questionnaire. They reported remaining number of teeth (none, 1–14, 15–20, 21–25 or 26–32 (all)) and frequency of gum bleeding (never/rarely, sometimes, often or always). Adjusted linear and logistic regression models assessed associations between tooth loss, gum bleeding, and socioeconomic and CV risk factors.

A total of 40.9% of participants had <15 remaining teeth; 16.4% had no teeth; and 25.6% reported gum bleeding with large differences in prevalence among countries, regions and ethnic groups. Less tooth loss was associated with lower levels of glucose, low-density lipoprotein (LDL) cholesterol, systolic blood pressure, waist circumference and hs-CRP; higher estimated glomerular filtration rate; decreased odds for diabetes and smoking, and increased odds for higher education, alcohol consumption and work stress. Gum bleeding was associated with higher LDL cholesterol and systolic blood pressure; decreased odds for smoking, but increased odds for higher education, alcohol consumption and stress.

Conclusion: Self-reported indicators of PD were common in this chronic CHD population and were associated with an increasing socioeconomic and CV risk factor burden. However, causality between self-reported PD and CV risk and outcome needs further investigation.

Keywords

Tooth loss, gum bleeding, periodontal disease, coronary heart disease, risk factors

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Introduction

Over the last decades, oral health has emerged as a focus of interest in the search for new coronary heart disease (CHD) prevention targets and risk markers.[1–3] Dental disease comprises a wide variety of conditions, of which periodontal disease (PD) is the most important in the context of its proposed link to CHD.[3] PD affects the tissues that surround and support the teeth and ranges from gingivitis, an early and reversible form, manifested as gum bleeding, to the final and

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chronic stage of tooth loss.[4] PD and CHD share certain risk factors, most importantly age and smoking, but whether the two conditions are causally related remains unclear.[1,5,6]

PD has been suggested to be associated with a wide variety of cardiovascular (CV) risk factors and biomarkers but there is considerable heterogeneity in methodology, demographics and results among these reports. Moreover, no previous study has performed comprehensive analyses of these relationships in large contemporary stable CHD populations. Thus, in further evaluating the relationship between dental health and CV risk, more information about prevalence of PD and its relation to risk factors in patients with CHD is needed.

The purpose of this report was to explore the prevalence of self-reported indicators of periodontal disease in a global high-risk population with stable CHD and to study associations between these indicators and a wide range of CV risk factors.

Methods and materials

Study population

This study population consists of participants from the global STABILITY trial, a clinical trial comparing darapladib, a selective oral inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2), with placebo. It includes 15,828 participants from 39 countries globally. All patients had chronic CHD (prior myocardial infarction (MI), prior coronary revascularization or multivessel CHD without revascularization), and at least one additional risk factor: age $\geq$60 years; diabetes mellitus requiring pharmacotherapy; high-density lipoprotein (HDL) cholesterol $<$1.03 mmol/l; current or previous smoker defined as $\geq$5 cigarettes per day on average; significant renal dysfunction (estimated glomerular filtration rate (eGFR) $\geq$30 and $<$60 ml/min/1.73 m^2 or urine albumin:creatinine ratio $\geq$30 mg albumin/g creatinine); or polyvascular disease. Patients with eGFR $<$30 ml/min/1.73 m^2 were excluded. A more detailed description of the study design and population has been published elsewhere.[7,8] The relevant ethics committees of each participating country has approved the study. The trial is registered under ClinicalTrials.gov identifier NCT00799903. The authors had full access to, and take full responsibility for, the integrity of the data. All authors have read and agree to the manuscript as written.

Data collection

At baseline, a medical history and fasting blood samples were obtained and participants underwent a physical examination and completed an extensive lifestyle questionnaire.

Dental health

Participants were asked 'How many teeth do you have in your mouth?' and possible responses were: no teeth; 1–14; 15–20; 20–25, or 26–32 (all). Patients were also asked 'Do your gums bleed when brushing your teeth or at other times?' with the following possible responses: 'never/rarely', 'sometimes', 'often', or 'always'.

Physical status and blood samples

Waist circumference was recorded and blood pressure was calculated as the mean of three measurements in the same arm in a sitting position with an automatic digital sphygmomanometer. Fasting blood samples were obtained for analysis of plasma low-density lipoprotein (LDL) cholesterol, glucose, high sensitivity C-reactive protein (hs-CRP), white blood cell count (WBCC) and eGFR based on the modification of diet in renal disease (MDRD) formula. Blood sample analyses were performed at a central laboratory.

Ethnicity, education, stress, alcohol consumption and physical activity

Participants were classified into one of the following ethnic groups based on self-report: White, Asian, or other. Education level was categorized as follows: none, 1–8 years, 9–12 years, trade school and college/university. Participants were asked: 'How often do you experience financial stress, stress at home, and stress at work?' and possible responses were: 'never/rarely', 'sometimes', 'often' or 'always'. The question on work-related stress also included the possible response: 'do not work'. Alcohol consumption was categorized by weekly intake to one of the following groups: 0 drinks/week, 1–4 drinks/week, 5–14 drinks/week and $\geq$15 drinks/week. To evaluate physical activity, participants were asked: 'How active are you during leisure time?' and possible responses were: 'mainly sedentary', 'mild exercise', 'moderate exercise' or 'strenuous physical exercise'.

Statistics

All data included in this report were collected prior to randomization. Descriptive statistics are presented as median and interquartile range for continuous variables and as frequency and percentages for categorical variables. The prevalence of each PD marker is reported by country and by region.

Regression models adjusted for age, smoking, diabetes and education assessed each CV risk factor as a function of number of teeth and gum bleeding,

separately. Gum bleeding was dichotomized into two categories: 'never/rarely' and 'sometimes, often or always'.

For every move from a higher to a lower tooth loss level and for any gum bleeding versus no gum bleeding, linear regression was used to estimate the average unit change of the following variables: fasting glucose, eGFR, LDL cholesterol, systolic blood pressure (SBP), WBCC, waist circumference, and hs-CRP. To satisfy the regression normality assumption LDL outliers (>99th %-ile or <1st %-ile) and glucose = 1 mmol/l were removed and glucose, LDL cholesterol, WBCC, and hs-CRP were log-base2 transformed prior to analysis. Regression estimates for these variables are shown on the log2 scale.

For every move from a higher to a lower tooth loss level and for any gum bleeding versus no gum bleeding, cumulative logit regression was used to assess odds ratios (ORs) of higher vs lower values for the following risk factors: education level; alcohol consumption per week; work, home and financial stress and leisure physical activity. Pairwise logistic regression was used to assess ORs for ethnicity and smoking. Logistic regression was used to assess ORs for diabetes.

To adjust for potential Type I error rate inflation due to multiple testing, Bonferroni adjusted confidence intervals and *p*-values are presented for the regression analyses for each PD marker. Results were deemed significant at the 0.05 level. Analyses were performed at the Duke Clinical Research Institute in Durham, North Carolina, USA and were performed using SAS 9.2 (SAS Institute Inc. Cary, North Carolina, USA).

Results

Prevalence of tooth loss and gum bleeding

Questions on tooth loss and gum bleeding were completed by 15,533 (98.1%) and 15,512 (98.0%) participants, respectively. Baseline characteristics for the study population are given in Table 1, showing a high overall prevalence of tooth loss; 16.4% reported having no teeth, and a total of 40.9% reported having less than 15 remaining teeth. Approximately one-quarter of the patients reported any gum bleeding. Figure 1 and Table 2 show marked differences in prevalence for both PD variables among geographic regions, but also among countries within the same region.

Tooth loss, risk factors and biomarkers

Table 3 reports the adjusted association between tooth loss and CV risk factors, listing the estimated average change in the level of each risk factor and biomarker for every move from a higher to a lower tooth loss level; for instance when moving from 'no teeth' to '1–14

Table 1. Baseline characteristics

Age (years)	65.0 (59, 71)
Gender	*n* = 15,828
Female	2967 (18.7%)
Male	12,861 (81.3%)
Number of remaining teeth	*n* = 15,533
No teeth	2551 (16.4%)
1–14	3803 (24.5%)
15–20	2174 (14.0%)
21–25	3689 (23.2%)
26–32 (All)	3316 (21.3%)
Gum bleeding	*n* = 15,512
Never/rarely	11,548 (74.4%)
Sometimes/often/always	3964 (25.6%)
Smoking status	*n* = 15,826
Never	4892 (30.9%)
Former	8079 (51.0%)
Current	2855 (18.0%)
Education	*n* = 15,511
None/1–8 years	3566 (23.0%)
9–12 years	4750 (30.6%)
Trade school	2831 (18.3%)
College/university	4364 (28.1%)
Ethnicity	*n* = 15,828
White	2,412 (78.4%)
Asian	2717 (17.2%)
Other	699 (4.4%)
Diabetes[1]	*n* = 15,828
No	9762 (61.7%)
Yes	6066 (38.3%)
Alcohol consumption (drinks/week)	*n* = 15,412
0	7243 (47.0%)
1–4	3747 (24.3%)
5–14	3370 (21.9%)
≥15	1052 (6.8%)
Work stress	*n* = 15,455
Do not work/rarely/never	10,737 (69.5%)
Sometimes	3026 (19.6%)
Often/always	1692 (10.9%)
Home stress	*n* = 15,146
Never/rarely	6378 (42.1%)
Sometimes	6964 (46.0%)
Often/always	1804 (11.9%)
Financial stress	*n* = 15,117
Never/rarely	7683 (50.8%)
Sometimes	4935 (32.6%)
Often/always	2499 (16.5%)
Leisure time physical activity	*n* = 15,170
Mainly sedentary	4929 (32.5%)
Mild exercise	6701 (44.2%)

(continued)

Table 1. Continued

Age (years)	65.0 (59, 71)
Moderate/strenuous exercise	3540 (23.3%)
Low-density lipoprotein cholesterol (mmol/l)	2.1 (2, 3)
Systolic blood pressure (mm Hg)	131.0 (120, 142)
Waist circumference (cm)	100.5 (93, 109)
Fasting p-glucose (mmol/l)	5.9 (5, 7)
Estimated glomerular filtration rate (ml/min/1.73 m^2)	77.8 (65.9, 89.8)
White blood cell count (10^9/l)	6.6 (6, 8)
High sensitivity C-reactive protein (mg/l)	1.3 (1, 3)

Data are median (25^{th}, 75^{th}) for continuous variables and *n* (%) for categorical variables; [I] Type 1 or type 2 diabetes with or without treatment.

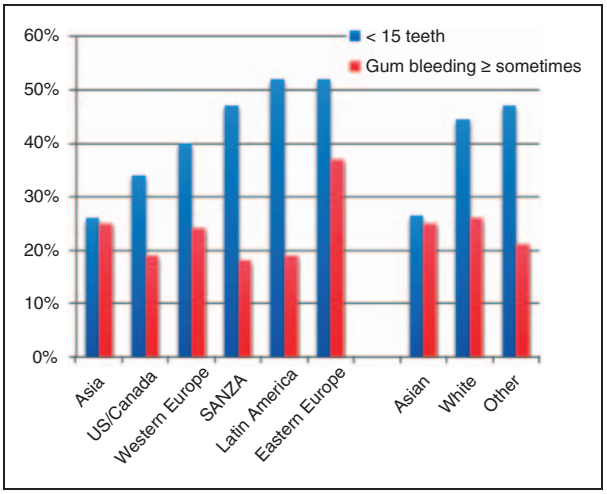

Figure 1. Prevalence of tooth loss (<15 remaining teeth) and gum bleeding (sometimes/often/always) by geographic region and ethnicity.
SANZA: South Africa/New Zealand/Australia.

teeth', or from '15–20 teeth' to '21–25 teeth'. Figure 2 shows associations between tooth loss and categorical risk factors.

Gum bleeding, risk factors and biomarkers

Table 3 also reports the adjusted association between gum bleeding and continuous CV risk factors, listing the estimated average change of each risk factor and biomarker between participants with and without gum bleeding. Figure 3 shows associations between gum bleeding and categorical risk factors.

Discussion

Approximately 40% of participants in this large, global stable CHD cohort reported missing more than half of their teeth, with substantial differences in prevalence among geographic regions, countries and ethnic groups. Associations between tooth loss and gum bleeding and an increased burden of CV risk factors and biomarkers were demonstrated. Not only do these observations suggest common risk factors for dental disease and CHD but also raise the question whether self-reported dental health can be useful in assessing future CV risk in patients with CHD.

Previous studies validating indicators of dental health support the use of self-reported number of remaining teeth, especially if categorized, and the use of self-reported gum bleeding.[9,10] Comparing these indicators to those of other populations would be desirable but hazardous and perhaps not even feasible due to the lack of valid studies using comparable methodology and populations.[11]

To our knowledge, there are no other studies of this size and geographic scope reporting prevalence of self-reported PD indicators and associations to CV risk in CHD patients. The seemingly high prevalence in this population, for tooth loss in particular, illustrates a major oral health issue that may in part be due to the influence of risk factors common to both PD and CHD, such as age and smoking. It supports previous findings showing a high prevalence of PD among patients with stable CHD compared with healthy individuals even after adjusting for major confounders.[12] The regional variation in PD prevalence can partly be explained by regional differences in CV risk factor prevalence; for instance smoking.[8] However, the considerable differences also seen among countries within the same region and between ethnic groups indicate a complex relationship in which demographic, genetic and socioeconomic disparities are likely contributing factors.[11,13]

Tooth loss was associated with a wide range of socioeconomic and CV risk factors, with a heavier CV risk factor burden in patients with a higher degree of tooth loss. Compared with tooth loss, there were fewer associations for gum bleeding, possibly reflecting the fact that tooth loss, as opposed to gum bleeding, is a result of long-term chronic exposure to etiological factors that are at least partly common to both CHD and PD and could therefore result in stronger associations to CV risk. Moreover, and unlike gum bleeding, tooth loss can also have other causes than PD, including caries, trauma and deliberate extractions and may therefore not be treated strictly as an indicator of PD, but rather a marker of overall dental health and possibly even a marker of general health, socioeconomic factors and psychosocial status, which could also contribute to its stronger association with CV risk.

The degree of association differed among risk factors, with stronger relationships for some, e.g. smoking and education. However, as a whole they were

Table 2. Proportion of patients with evidence of periodontal disease by country

Country	Region	*n* participants (% of total)	% with <15 teeth	% with gum bleeding sometimes/often/always
All countries		15,533 (100%)	40.9%	25.6%
Slovakia	Eastern Europe	118 (0.8%)	68.6%	17.8%
Poland	Eastern Europe	490 (3.2%)	66.7%	28.5%
South Africa	SANZA	383 (2.5%)	62.7%	12.8%
Hungary	Eastern Europe	396 (2.5%)	62.4%	36.8%
Czech Republic	Eastern Europe	767 (4.9%)	60.4%	35.3%
Brazil	Latin America	376 (2.4%)	60.1%	13.6%
Netherlands	Western Europe	444 (2.9%)	59.2%	16.2%
Chile	Latin America	194 (1.2%)	54.1%	26.8%
Argentina	Latin America	537 (3.5%)	53.8%	16.2%
Estonia	Eastern Europe	77 (0.5%)	51.9%	44.2%
Romania	Eastern Europe	408 (2.6%)	49.8%	47.9%
Italy	Western Europe	196 (1.3%)	48.0%	25.0%
Belgium	Western Europe	202 (1.3%)	46.5%	19.9%
Germany	Western Europe	1,063 (6.8%)	46.4%	22.8%
Bulgaria	Eastern Europe	219 (1.4%)	46.1%	38.1%
Philippines	Asia	214 (1.4%)	45.3%	21.3%
Canada	USA/Canada	777 (5.0%)	45.0%	19.6%
New Zealand	SANZA	201 (1.3%)	43.3%	19.8%
Japan	Asia	316 (2.0%)	41.8%	30.2%
Hong Kong	Asia	116 (0.7%)	40.5%	36.8%
Spain	Western Europe	435 (2.8%)	40.5%	35.3%
United Kingdom	Western Europe	183 (1.2%)	39.9%	21.3%
Greece	Western Europe	187 (1.2%)	38.5%	22.5%
Peru	Latin America	78 (0.5%)	37.2%	25.6%
Russian Federation	Eastern Europe	652 (4.2%)	37.1%	42.5%
Ukraine	Eastern Europe	352 (2.3%)	34.7%	46.9%
Taiwan	Asia	197 (1.3%)	32.5%	38.7%
Mexico	Latin America	137 (0.9%)	31.4%	31.9%
United States	USA/Canada	3067 (19.7%)	31.4%	18.7%
Australia	SANZA	301 (1.9%)	30.6%	24.4%
France	Western Europe	236 (1.5%)	29.2%	34.4%
Thailand	Asia	206 (1.3%)	28.2%	24.8%
Denmark	Western Europe	100 (0.6%)	28.0%	23.2%
Korea, Republic of	Asia	502 (3.2%)	24.5%	19.0%
Sweden	Western Europe	296 (1.9%)	19.3%	28.0%
Pakistan	Asia	230 (1.5%)	18.3%	21.9%
China	Asia	369 (2.4%)	16.3%	31.3%
Norway	Western Europe	113 (0.7%)	14.2%	34.5%
India	Asia	398 (2.6%)	11.3%	15.6%

SANZA: South Africa/New Zealand/Australia.

indicative of an evident and consistent relationship between self-reported dental status and CV risk in this population, which could point towards PD being a risk factor for incident CHD. A few observations were unexpected, such as the slightly elevated odds of higher alcohol consumption and increased work stress in patients with more teeth. Although these associations were weak and are difficult to explain without further analysis, socioeconomic factors likely play a role. For instance, it is possible that work stress is a marker of

Table 3. Association between tooth loss, gum bleeding and continuous cardiovascular risk factors

	Tooth loss		Gum bleeding	
	Estimate (99.76% CI)[1]	Bonferroni *p*-value	Estimate (99.76% CI)[1]	Bonferroni *p*-value
Fasting p-glucose (mmol/l)[2,3,4]	–0.03 (–0.04– –0.02)	<0.0001	0.01 (–0.01–0.03)	1.000
eGFR (ml/min/1.73 m^2)	0.48 (0.18–0.79)	<0.0001	0.28 (–0.67–1.2)	1.000
LDL cholesterol (mmol/l)[3,4]	–0.03 (–0.04– –0.02)	<0.0001	0.04 (0.01–0.07)	0.0003
Systolic blood pressure (mm Hg)	–0.41 (–0.71– –0.1)	0.0010	1.28 (0.36–2.2)	0.0005
WBCC (10^9/l)[3]	–0.02 (–0.02– –0.01)	<0.0001	–0.01 (–0.03–0.01)	1.000
Waist circumference (cm)	–0.51 (–0.75– –0.27)	<0.0001	0.14 (–0.59–0.88)	1.000
hs-CRP (mg/l)[3]	–0.14 (–0.17– –0.1)	<0.0001	0.01 (–0.09–0.11)	1.000

CI: confidence interval; eGFR: estimated Glomerular Filtration Rate; hs-CRP: high sensitivity C-reactive protein; LDL: low-density lipoprotein; WBCC: white blood cell count; Results in tooth loss column show change in level of risk factor when moving from a higher to a lower tooth loss level, e.g. from 'No teeth' to '1–14 teeth'. Results in gum bleeding column show change in level of risk factors for any gum bleeding vs no gum bleeding; [1]Adjusted for age, smoking, diabetes and education level; [2]Adjusted for age, smoking and education level; [3]Log (base 2) transformed; [4]LDL values >99th %-ile or ≤1 %-ile were removed. Fasting P-glucose ≤1 was removed.

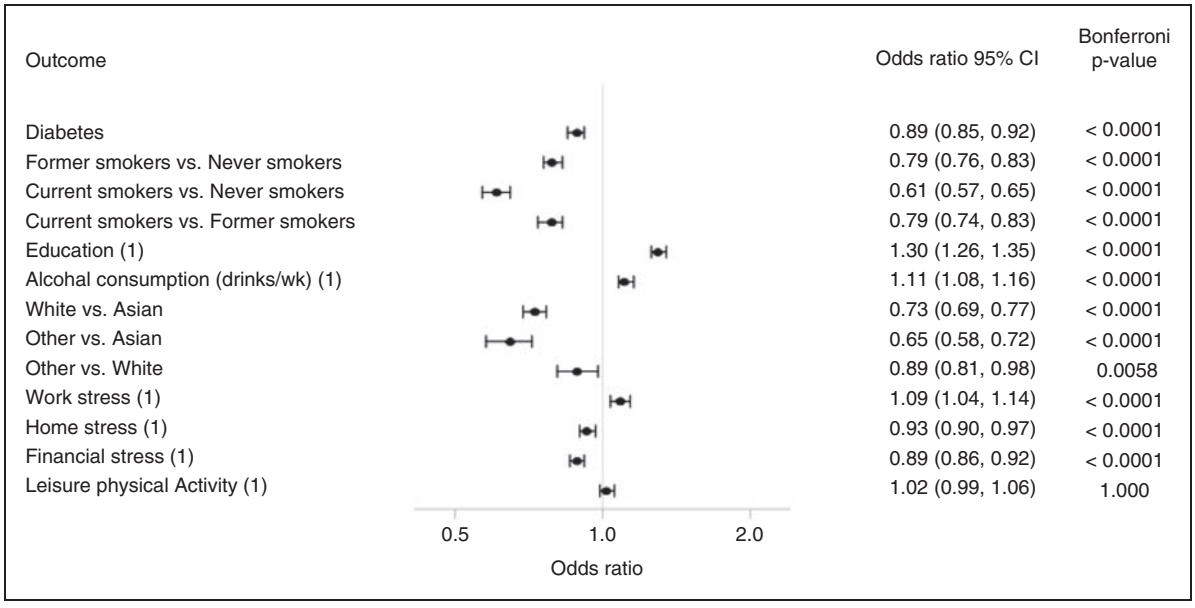

Figure 2. Association between tooth loss and categorical cardiovascular risk factors. Odds ratio (OR) for risk factors when moving from a higher to a lower tooth loss level, e.g. from 'no teeth' to '1-14 teeth'. All ORs adjusted for age, smoking status, educational level and diabetes, except for the following: diabetes: adjusted for age, smoking, and education level; smoking: adjusted for age, diabetes, and education level; education: adjusted for age, smoking, and diabetes. To satisfy proportional odds assumption, education levels of 'none' and '1–8 years' of education were collapsed. Work stress categories of 'do not work' and 'never/rarely work' were also collapsed prior to analysis. [1] Cumulative logit displays odds of higher value of variable vs lower value of variable. CI: confidence interval.

higher socioeconomic status whereas home stress and financial stress are indicative of the opposite. It has previously been shown that smoking exerts a dose-dependent suppressive effect on gum bleeding,[14] a finding also supported by our results where participants with gum bleeding were less likely to be smokers.

Positive associations between dental disease and CV risk factors,[1,15–19] have often been met by contradictory reports[18,20–23] with substantial variation in methodology, population size and demographics among studies.[13] Importantly, very few associations have been studied or confirmed in large CHD populations, in whom the risk of recurrent cardiovascular events is high and optimized prevention crucial. The findings from this study add new information on dental disease in stable CHD patients, consolidating the concept that these chronic conditions share common ground. Although these descriptive analyses cannot confirm a causal relationship between dental health and CV risk, causality is widely accepted for certain associations,

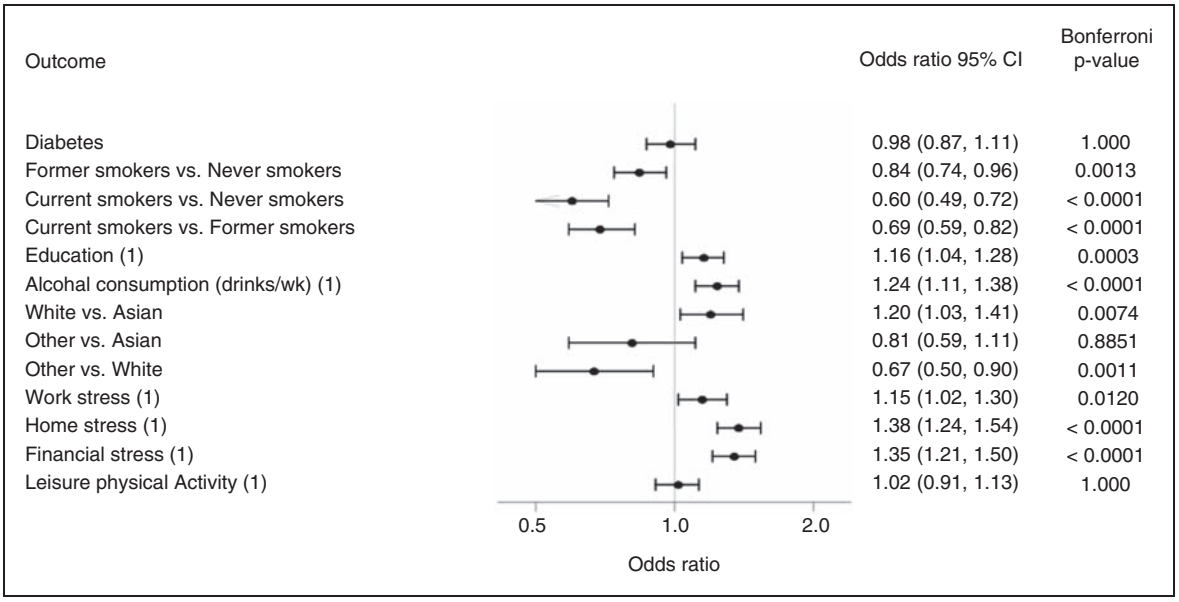

Figure 3. Association between gum bleeding and categorical cardiovascular risk factors. Odds ration (OR) for risk factors for any gum bleeding vs no gum bleeding. All ORs adjusted for age, smoking status, educational level and diabetes, except for the following: diabetes: model adjusted for age, smoking status, and education level; smoking: model adjusted for age, diabetes, and education; education: model adjusted for age, smoking, and diabetes. To satisfy proportional odds assumption, education levels of 'none' and '1–8 years' of education were collapsed. Work stress categories of 'do not work' and 'never/rarely work' were also collapsed prior to analysis. [1] Cumulative logit displays odds of higher value of variable vs lower value of variable. CI: confidence interval.

particularly smoking. For certain other relationships, including diabetes and obesity, causality and causal direction are debated and sometimes even a bidirectional association has been proposed.[13]

Mechanistic explanations for a direct association between PD and CHD include PD-generated systemic inflammation, which is supported by elevated levels of inflammatory markers and cytokines.[16] Several roles of oral pathogens are also debated, either as triggers of a systemic serological response linked to CHD; through local effects on the vascular endothelium; or by mediation of platelet aggregation.[4] However, none of these theories have been sufficiently substantiated by evidence to prove causality. While some studies have shown that oral health promoting measures result in improved levels of inflammatory markers and certain CV risk factors,[24] little is known about the impact of such measures on CV outcome. One study has failed to prove such a positive relationship[25] and there is a need for large prospective intervention studies to determine whether PD treatment actually reduces CV events.

Limitations

Despite previous validation, there is no self-reported, or even clinical measure, alone reflecting manifest periodontal disease. Factors including education level, socioeconomic status and dental care utilization may influence unadjusted prevalence estimates[10] and may contribute to selection bias, particularly in countries with relatively few participants. Further, adjusted results may still be influenced by residual confounding.[26]

Changes in CV risk factor units between adjacent tooth loss levels should be considered trends rather than exact changes, as this analysis cannot determine whether a change between any two adjacent tooth loss levels is greater or smaller than that between two others.

The dichotomization of gum bleeding categories could lead to an underestimation of possible associations with more frequent gum bleeding. Recall bias and underreporting of gum bleeding is possible, especially in individuals with irregular dental hygiene habits. Almost all participants (96%) were on anti-platelet medication,[8] however instances of dual anti-platelet or anti-coagulation treatment have not been adjusted for, which could affect gum bleeding results. The differences in prevalence by country, less pronounced associations with CV risk factors, and lack of apparent association with tooth loss, could support the notion that gum bleeding is a weaker measure of PD than tooth loss.

Conclusion

Poor dental health, characterized by self-reported tooth loss and gum bleeding, was common in this global population with stable CHD and was associated with

an increased burden of CV and socioeconomic risk factors. Whether these findings translate into an increased risk of recurring myocardial infarction, CV death and stroke needs to be established.

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Conflict of interest

Vedin, Hagström, Stewart, Sritara, Koenig, Budaj, White, Wallentin, and Held are STABILITY study investigators. Gallup and Neely declare they have no conflicts of interest.

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