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Cardiovascular risks associated with incident and prevalent periodontal disease

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Abstract

Aim: While prevalent periodontal disease associates with cardiovascular risk, little is known about how incident periodontal disease influences future vascular risk. We compared effects of incident versus prevalent periodontal disease in developing major cardiovascular diseases (CVD), myocardial infarction (MI), ischaemic stroke and total CVD.

Material and Methods: In a prospective cohort of 39,863 predominantly white women, age ≥45 years and free of cardiovascular disease at baseline were followed for an average of 15.7 years. Cox proportional hazard models with time-varying periodontal status [prevalent (18%), incident (7.3%) *versus* never (74.7%)] were used to assess future cardiovascular risks.

Results: Incidence rates of all CVD outcomes were higher in women with prevalent or incident periodontal disease. For women with incident periodontal disease, risk factor adjusted hazard ratios (HRs) were 1.42 (95% CI, 1.14–1.77) for major CVD, 1.72 (1.25–2.38) for MI, 1.41 (1.02–1.95) for ischaemic stroke and 1.27 (1.06–1.52) for total CVD. For women with prevalent periodontal disease, adjusted HRs were 1.14 (1.00–1.31) for major CVD, 1.27 (1.04–1.56) for MI, 1.12 (0.91–1.37) for ischaemic stroke and 1.15 (1.03–1.28) for total CVD.

Conclusion: New cases of periodontal disease, not just those that are pre-existing, place women at significantly elevated risks for future cardiovascular events.

Key words: cardiovascular disease; C-reactive protein; diabetes; family history of MI; periodontal disease; smoking; survival analysis

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Evidence accumulating over the past decade demonstrates a significant association between prevalent periodontal disease and future cardiovascular events (Heidenreich et al. 2011, Eke et al. 2012, Lockhart et al. 2012, Tonetti & Van Dyke 2013). Prevalence studies, however, are limited as they typically include wide variation in terms of disease duration prior to study enrolment, a source of variation that can lead to considerable uncertainty with regard to the true magnitude of association between an exposure of interest and a future clinical outcome (Joshipura et al. 1996b, 2003, Hujoel et al. 2000, Wu et al. 2000, Howell et al. 2001, Tuominen et al. 2003, Hung et al. 2004, Tu et al. 2007, Dorn et al. 2010, Holmlund et al. 2010, de Oliveira et al. 2010). In contrast, analysis of incident events that accrue during the course of a prospective observational study often provides a better measure of exposure duration and hence a more accurate estimate of risk. Research efforts examining effects of periodontal therapy on subclinical cardiovascular disease (CVD) surrogates such as endothelial function and carotid artery intima–media thickness (Tonetti et al. 2007, Jung

Conflict of interest and source of funding statement

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et al. 2014), or reducing inflammatory markers were abundant (Bokhari et al. 2012, Caula et al. 2014); however, evidence is still limited to support the relief of CVD burden after periodontal treatment (D'Aiuto et al. 2013). To date, analyses of incident periodontal disease as a determinant of future vascular risk have been sparse (Dietrich et al. 2008, Jimenez et al. 2009).

Common risk factors such as diabetes and smoking are shared between cardiovascular and periodontal diseases (Lockhart et al. 2012, Dietrich et al. 2013, Tonetti & Van Dyke 2013). Therefore, efforts have been made in prior investigations to examine the association between periodontal disease and cardiovascular outcomes in non-smokers (Dorn et al. 2010) and in non-diabetic patients (Kodovazenitis et al. 2013). However, it remains an open question as to how the inter-relationships between these risk factors and periodontal disease may modify the process of developing cardiovascular disease. Furthermore, genetic studies (Mucci et al. 2009, Schaefer et al. 2009, Ernst et al. 2010) have suggested shared links between periodontal disease and coronary heart disease. Thus, it is of additional interest to evaluate the interaction between family history of myocardial infarction (MI), periodontal disease and future vascular risks.

To address these issues, we examined the relationships of both prevalent and incident periodontal disease to the occurrence of first ever cardiovascular events in a prospective cohort of 39,863 American women followed for an average period of 15.7 years. We further sought evidence of effect modification between periodontal disease, cardiovascular disease and common exposures such as obesity, smoking, diabetes and family history of MI.

Material and Methods

Study population

The Women's Health Study (WHS) is an NIH-funded prospective cohort that was initiated as a randomized, placebo-controlled trial examining low-dose aspirin and vitamin E in a 2×2 factorial design for the primary prevention of cardiovascular disease and cancer in initially healthy middle-aged women. Details of the study design have been described previously (Ridker et al. 2005a). Between September 1992 and May 1995, 39,876 female healthcare professionals in the US, aged 45 years or older, free of cardiovascular disease and cancer were enrolled and have been followed prospectively since that time for incident cardiovascular events. Approximately 72% of WHS participants provided a blood sample at baseline that was stored in liquid nitrogen for subsequent measurement of blood-based biomarkers. The study was approved by the institutional review board of Brigham and Women's Hospital, Boston, Massachusetts.

Self-reported periodontal disease

At study entry, participants in the WHS were asked about whether they had prevalent periodontal disease. New incident periodontal disease cases were then assessed at 36, 48, 60, 72, 84, 96, 108, 120 months during the randomized trial, and then subsequently at the first follow-up (about 1 year after trial completion) that occurred during the observational extension study. The month and year of the periodontal diagnosis as well as the number of teeth loss during the study interval were requested for the participants reporting incident periodontal disease.

Cardiovascular events

Participants were followed for cardiovascular endpoints of by annual follow-up questionnaires, letters or telephone calls. Medical records were obtained and reviewed in a blinded fashion for reported endpoints. Cardiovascular deaths were confirmed by family members, postal authorities, autopsy reports, medical records and the National Death Index. Myocardial infarction was assessed by physician review of medical records according to WHO criteria as well as associated abnormal levels of cardiac enzymes or diagnostic electrocardiograms. Stroke was confirmed if the participant had a new focal neurological deficit of sudden onset that persisted for more than 24 h. Clinical information, computed tomographical scan and magnetic resonance images were used to distinguish haemorrhagic from ischaemic events. Reports of coronary revascularization procedures (bypass surgery or percutaneous coronary angioplasty) were confirmed by record reviews. Composite cardiovascular outcomes were used in the analysis. Major cardiovascular disease (CVD) events included non-fatal myocardial infarction, ischaemic stroke or death from cardiovascular causes. Total CVD events were defined as major CVD as well as bypass surgery, or percutaneous coronary angioplasty.

Assessment of covariates

Details of the study protocol have been described in the primary endpoint report of the randomized control trial (Ridker et al. 2005a). Covariates of interests were collected at the baseline by validated questionnaires and used in the analysis – age, body mass index, race/ethnicity, education, diabetes, hypertension, hypercholesterolaemia, smoking, family history of myocardial infarction and physical activities. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg or self-reported physician-diagnosed hypertension; hyperlipidaemia was defined as a total cholesterol level of at least 240 mg/dl (6.2 mmol/l) or self-reported physician-diagnosed high cholesterol levels; other covariates were self-reported diagnosis of diabetes or estimation of physical activities. In the subset of WHS participants who provided a blood sample at baseline, plasma lipid fractions and high-sensitivity C-reactive protein (hsCRP) were measured as described (Ridker et al. 2005b).

Statistical analyses

We used time-varying survival analysis to investigate the effects of prevalent as well as incident periodontal disease as determinants of future vascular events. Prevalent periodontal disease (PD) was defined as PD reported as having occurred at or before baseline; while incident periodontal disease, defined as PD having occurred during the follow-up and before incident CVD if any, was encoded as time-varying independent

Table 1. Baseline characteristics of study participants according to the periodontal disease status

Characteristics*	No periodontal disease	Baseline prevalent periodontal disease	Incident periodontal disease	*p* Value†
No. (%) of patients	*n* = 29,787 (74.7)	*n* = 7185 (18.0)	*n* = 2891 (7.3)	
Age	52.5 (48.7–58.4)	54.5 (50.0–60.3)	53.3 (49.1–59.2)	<0.001
Body mass index (kg/m^2)				
<25	14,907 (51.1)	3569 (50.7)	1367 (48.1)	0.012
25 ~ <30	9020 (30.9)	2159 (30.7)	900 (31.7)	
≥30	5240 (18.0)	1308 (18.6)	574 (20.2)	
Race/ethnicity				
White	28,061 (95.0)	6746 (94.8)	2662 (92.8)	<0.001
Other	1481 (5.0)	368 (5.2)	205 (7.2)	
Highest education level				
<Bachelor's degree	16,879 (57.7)	3978 (56.3)	1586 (55.6)	<0.001
Bachelor's degree	6800 (23.2)	1572 (22.2)	671 (23.5)	
Master's degree or doctorate	5593 (19.1)	1520 (21.5)	593 (20.8)	
Smoking				
Current	3254 (11.0)	1501 (20.9)	474 (16.4)	<0.001
Past	10,191 (34.2)	3067 (42.7)	1005 (34.8)	
Never	16,313 (54.8)	2612 (36.4)	1410 (48.8)	
Hypertension				
Yes	7574 (25.4)	1983 (27.6)	756 (26.2)	<0.001
No	22,206 (74.6)	5201 (72.4)	2134 (73.8)	
Hypercholesterolaemia				
Yes	8470 (28.4)	2402 (33.4)	868 (30.0)	<0.001
No	21,306 (71.6)	4780 (66.6)	2021 (70.0)	
Family Hx MI				
Yes	3375 (12.6)	891 (13.9)	366 (14.1)	0.003
No	23,449 (87.4)	5523 (86.1)	2228 (85.9)	
Hx of diabetes				
Yes	780 (2.6)	274 (3.8)	88 (3.0)	<0.001
No	29,007 (97.4)	6911 (96.2)	2803 (97.0)	
Physical activities				
Rarely/Never	11,218 (37.7)	2879 (40.1)	1179 (40.8)	<0.001
<1 time per week	5899 (19.8)	1454 (20.3)	571 (19.8)	
1–3 times per week	9406 (31.6)	2135 (29.7)	864 (29.9)	
4+ times per week	3250 (10.9)	712 (9.9)	276 (9.6)	
Total cholesterol (mg/l)‡	207 (183–235)	212 (187–238)	209 (183–238)	<0.01
HDL (mg/l)‡	52.0 (43.2–62.5)	51.5 (42.7–62.0)	51.4 (42.5–61.2)	0.021
LDL (mg/l)‡	120.7 (100.1–143.5)	124.0 (102.4–147.1)	123.0 (100.2–146.2)	<0.001
Triglyceride (mg/l)‡	118 (83–175.0)	124 (87–178)	117 (82–174)	<0.001
hsCRP (mg/l)‡	2.0 (0.8–4.3)	2.1 (0.9–4.7)	2.0 (0.8–4.3)	<0.001

BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*Data are expressed as median (inter-quartile range) for continuous variables and as number (percentage) of participants unless otherwise indicated. Number across categories may not sum to the given total because of the missing data.
†*p* values are based on Kruskal–Wallis test for continuous variables and of the chi-square tests for categorical variables.
‡Number of women having blood samples collected at the baseline and tested were 27,939.

variable in the data structure for the survival analysis with Cox proportional hazard model. Similarly, ever-having had PD status was combined from the baseline prevalent PD as well as the time-varying incident PD. Other covariates used in the analysis were based on the baseline characteristics (Therneau & Crowson 2014). All analyses were performed using the "survival" package of R software. Analyses were adjusted on an a priori basis for age alone as well as for age, race/ethnicity, body mass index, education, smoking, diabetes, hypertension, hypercholesterolaemia, family history of myocardial infarction and physical activity (model 1). Given that smoking is a strong risk indicator in both periodontal and cardiovascular disease, we adjusted for never- vs. current/past-smokers as has been shown to be more robust in recent reports (Dorn et al. 2010, Jung et al. 2014). Estimates were also obtained after further adjustment for C-reactive protein, a biomarker of inflammation (model 2). To assess effect modification by relevant risk factors, analyses were stratified by the presence or absence of obesity, smoking, hypertension, hypercholesterolaemia, a family history of myocardial infarction and diabetes. Survival curves were generated separately for the component endpoints of myocardial infarction and ischaemic stroke, as well as for the joint endpoints of major CVD and total CVD.

Results

Baseline characteristics

Women having either prevalent or incident periodontal diseases were older compared to those without periodontal disease (mean age: 54.5 and 53.3 *versus* 52.5; Table 1), more likely to be over-weight or obese, more likely to be current or former smokers (63.6% and 51.2% *versus* 45.2%), and exercised less frequently.

Table 2. Risk of cardiovascular events among women with periodontal disease

Outcome	*N* (Events)	No periodontal disease	Prevalent periodontal disease at baseline		Incident periodontal disease during follow-up*	
Major CVD						
Incidence rate (95% CI)†	39,863 (1549)	2.25 (2.11–2.38)	3.24 (2.90–3.57)		2.98 (2.49–3.48)	
			HR (95% CIs)	*p*	HR (95% CIs)	*p*
Age-adjusted‡	39,863 (1549)	[Reference]	1.27 (1.12–1.43)	***<0.001***	1.40 (1.15–1.72)	***0.001***
Multivariate model 1§	34,228 (1274)	[Reference]	1.14 (1.00–1.31)	***0.05***	1.42 (1.14–1.77)	***0.002***
Multivariate model 2¶	24,033 (883)	[Reference]	1.17 (0.99–1.37)	0.06	1.31 (1.01–1.71)	***0.045***
Myocardial Infarction (MI)						
Incidence rate (95% CI)†	39,863 (642)	0.91 (0.82–0.99)	1.36 (1.15–1.58)		1.33 (1.00–1.66)	
			HR (95% CIs)	*p*	HR (95% CIs)	*p*
Age-adjusted‡	39,863 (642)	[Reference]	1.34 (1.12–1.62)	***0.002***	1.56 (1.15–2.12)	***0.005***
Multivariate model 1§	34,228 (525)	[Reference]	1.27 (1.04–1.56)	***0.02***	1.72 (1.25–2.38)	***<0.001***
Multivariate model 2¶	24,033 (353)	[Reference]	1.35 (1.05–1.73)	***0.02***	1.65 (1.11–2.45)	***0.01***
Ischaemic stroke						
Incidence rate (95% CI)†	39,863 (677)	0.96 (0.87–1.05)	1.43 (1.21–1.65)		1.41 (1.07–1.76)	
			HR (95% CIs)	*p*	HR (95% CIs)	*p*
Age-adjusted‡	39,863 (677)	[Reference]	1.28 (1.07–1.54)	***0.006***	1.40 (1.04–1.90)	***0.03***
Multivariate model 1§	34,228 (558)	[Reference]	1.12 (0.91–1.37)	0.3	1.41 (1.02–1.95)	***0.04***
Multivariate model 2¶	24,033 (394)	[Reference]	1.05 (0.82–1.35)	0.7	1.28 (0.87–1.88)	0.2
Total CVD						
Incidence rate (95% CI)†	39,863 (2387)	3.52 (3.35–3.69)	5.03 (4.61–5.45)		4.39 (3.78–5.00)	
			HR (95% CIs)	*p*	HR (95% CIs)	*p*
Age-adjusted‡	39,863 (2387)	[Reference]	1.27 (1.15–1.4)	***<0.001***	1.25 (1.06–1.48)	***0.009***
Multivariate model 1§	34,228 (1968)	[Reference]	1.15 (1.03–1.28)	***0.01***	1.27 (1.06–1.52)	***0.01***
Multivariate model 2¶	24,033 (1388)	[Reference]	1.12 (1.05–1.36)	***0.007***	1.2 (0.97–1.49)	0.1

HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; p, p-value, with significance level set at 0.05, highlighted bold and italic.
*Follow up time of incident periodontal disease ended on 31 March 2006 and follow-up of cardiovascular outcomes ended on 14 March 2012.
†Per 1000 person-years of follow-up.
‡Models were adjusted for the age at randomization. These models were based on 1549, 642, 677, 2387 events of major CVD, MI, ischaemic stroke and total CVD, respectively, among 39, 863 women.
§Additionally adjusted for race/ethnicity, body mass index, education, smoking, diabetes, hypertension, hypercholesterolaemia, family history of myocardial infarction and physical activities. These multivariable models were based on 1274, 525, 588, 1968 events of major CVD, MI, ischaemic stroke and total CVD, respectively, among 34,228 women, due to missing data.
¶Additionally adjusted for natural-log-transformed serum levels of C-reactive protein. These multivariable models were based on 883, 353, 394, 1388 events of major CVD, MI, ischaemic stroke and total CVD, respectively, among 24,033 women, due to missing data.

Serum levels of total cholesterol, LDL cholesterol, triglyceride and hsCRP were higher in women with prevalent periodontal disease at the baseline, and a higher prevalence of hypertension, diabetes and hypercholesterolaemia were also noted in participants with periodontal disease. We also provide demographical information for women corresponding to the different statistical analyses in Table S2. Women having blood samples tended to have more education and fewer cardiovascular events.

Periodontal disease and future cardiovascular events

Overall in the full cohort, compared to women without periodontal disease, age-adjusted hazard ratios for the major CVD events were higher in women with prevalent [hazard ratio (HR), 1.27 (95% CI, 1.12–1.43); $p < 0.001$] or incident [HR, 1.40 (95% CI, 1.15–1.72); $p < 0.001$] periodontal disease. These effects remained comparable after adjustment for traditional vascular risk factors (multivariate model 1, Table 2). For women with incident periodontal disease, hazard ratios (HRs) were 1.42 (95% CI, 1.14–1.77; $p = 0.002$) for major CVD, 1.72 (95% CI, 1.25–2.38; $p < 0.001$) for MI, 1.41(95% CI, 1.02–1.95; $p = 0.04$) for ischaemic stroke and 1.27(95% CI, 1.06–1.52; $p = 0.01$) for total CVD after adjusting for established risk factors and physical activity. After further accounting for inflammation indices such as serum level of hsCRP, effects were attenuated but still significant for major CVD [HR, 1.31 (95% CI, 1.01–1.71); $p = 0.045$] and MI [HR, 1.65 (1.11–2.45); $p = 0.01$]. Likewise, for women with prevalent periodontal disease at baseline, adjusted hazard ratios were 1.14 (95% CI, 1.00–1.31; $p = 0.05$) for major CVD, 1.27 (95% CI, 1.04–1.56; $p = 0.02$) for MI, 1.12 (95% CI, 0.91–1.37; $p = 0.3$) for ischaemic stroke and 1.15 (95% CI, 1.03–1.28; $p = 0.01$) for total CVD (Multivariate model 1, Table 2). Similarly, effects were attenuated after further adjusting for hsCRP, but remained statistically significant for MI [HR, 1.35 (95% CI, 1.05–1.73); $p = 0.02$] and total CVD [HR, 1.12 (95% CI, 1.05–1.36); $p = 0.007$]. Further including aspirin vs. placebo allocation in the multivariate analysis had negligible effects on the hazard ratios (data not shown). The cumulative incidences of these events are presented graphically in Fig. 1

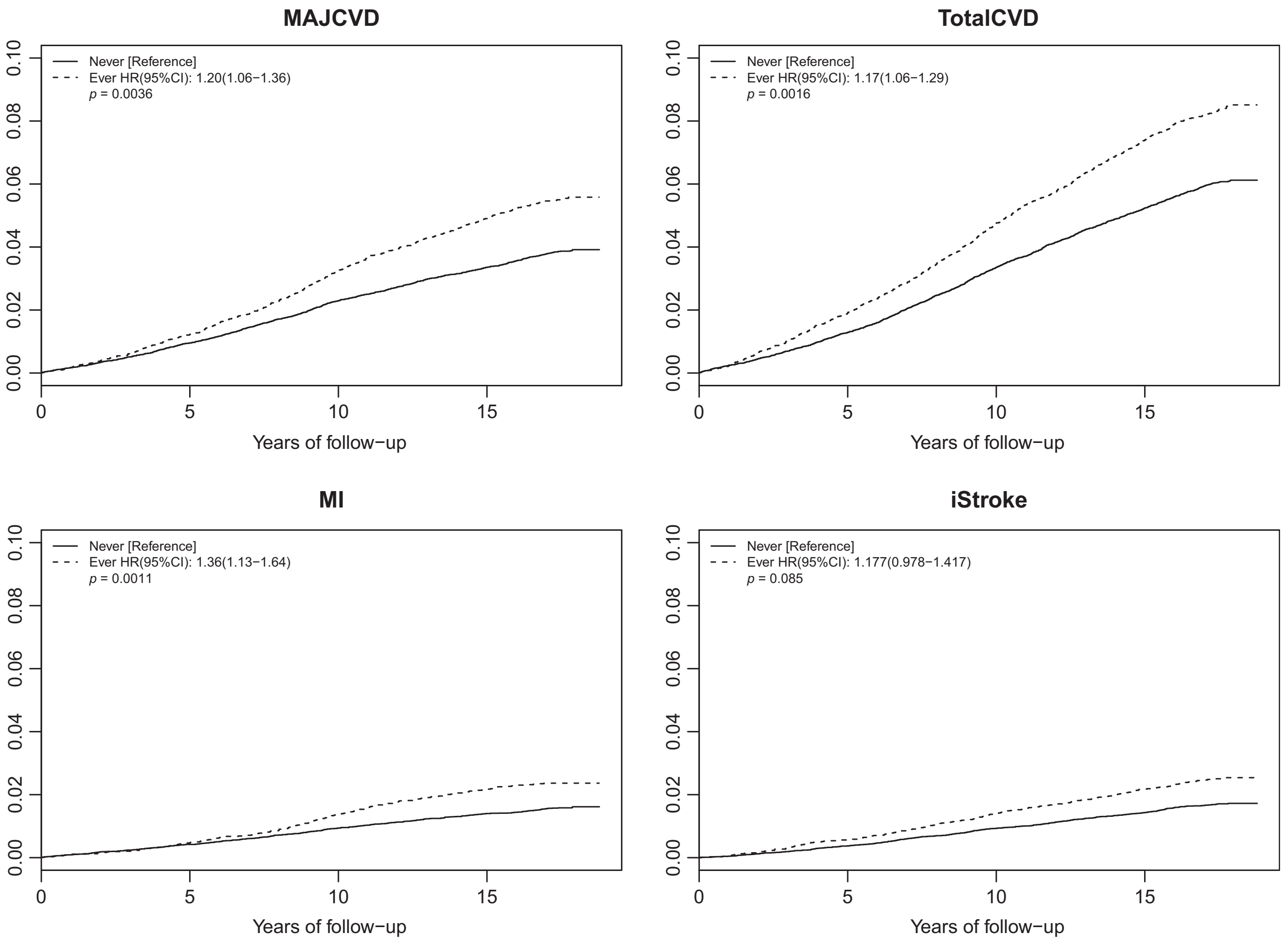

Fig. 1. Cumulative incidence rates of major cardiovascular disease (CVD), total CVD, myocardial infarction (MI) and ischaemic stroke (iStroke) between women having either prevalent or incident periodontal disease *versus* never. Hazard ratios and *p*-values were calculated after accounting for established cardiovascular risk factors, and physical activities (Multivariate model 1 in Table S1).

for those with any evident (i.e. either prevalent or incident) periodontal disease. Supplementary analyses examining risks of cardiovascular events in women having either prevalent or incident periodontal disease *versus* never are provided in Table S1. As a sensitivity analysis, we also repeated the analyses restricted to women having blood samples (the reduced set). Results were similar that effects were slightly attenuated after further adjusting for hsCRP and that higher CVD risks were found in women having incident vs. prevalent periodontal disease.

As shown in Table 3, the magnitude of association between any evident periodontal disease and future vascular events was less prominent in women who were obese, diabetic or did not smoke. However, none of these differential effects were statistically significant in analyses assessing for a multiplicative interaction ($\boldsymbol{P} > 0.05$), except smoking vs. total CVD ($p = 0.02$); obesity *versus* major CVD ($p = 0.03$) and total CVD ($\boldsymbol{p} = 0.02$). Of note, confidence intervals still overlap between these stratified subsets of women as well as that care should be taken into the consideration of multiple testing given the stratifications ($p < 0.05/6 = 0.008$).

Discussion

In this large, prospective cohort of middle-aged women, incident as well as prevalent periodontal disease (PD) was associated with statistically significant increased risks of developing future cardiovascular events. Moreover, in these data, the magnitude of vascular risk associated with incident periodontal disease was at least as large as that for prevalent periodontal disease. Thus, these data not only confirm prior work for prevalent periodontal disease, but importantly provide new evidence that incident periodontal disease is also associated with high vascular event rates. We believe these data likely to have relevance for the practice of periodontal medicine as they demonstrate that new cases of periodontal disease, not just those that have been present for long periods of time, put women at significantly elevated risks for vascular disease. It is possible that the lower hazard ratios shown in women having prevalent PD compared to women with incident PD may be due to treatment history or greater awareness of the oral hygiene care. However, this issue is complex and will require additional research. Lastly, our estimated cardiovascular risks among

Table 3. Age-adjusted risk of cardiovascular events among subgroups of women ever having had periodontal diseases

Outcomes			Major CVD		MI		Ischaemic stroke		Total CVD	
Stratification[a]		*N*	*E*	HR (95% CIs)[a]	*E*	HR (95% CIs)[a]	*E*	HR (95% CIs)[a]	*E*	HR (95% CIs)[a]
Obese	+	7123	*356*	1.04 (0.82–1.32)	*149*	1.22 (0.85–1.75)	148	1.02 (0.7–1.47)	*587*	1.05 (0.87–1.27)
	−	31,923	*1147*	**1.38 (1.22–1.56)*****	*470*	**1.46 (1.2–1.78)*****	*515*	**1.39 (1.15–1.67)****	*1727*	**1.34 (1.21–1.49)*****
Smoking	+	19,493	*897*	**1.33 (1.16–1.53)*****	*401*	**1.39 (1.13–1.7)****	*368*	**1.34 (1.09–1.66)****	*1348*	**1.33 (1.19–1.49)*****
	−	20,336	*648*	1.05 (0.87–1.27)	*239*	1.08 (0.79–1.48)	*307*	1.16 (0.88–1.51)	*1035*	1.02 (0.88–1.19)
Hypertension	+	10,314	*737*	**1.21 (1.03–1.42)****	*298*	**1.34 (1.05–1.72)***	*333*	1.26 (1–1.59)	*1127*	**1.18 (1.04–1.34)***
	−	29,542	*811*	**1.37 (1.18–1.59)*****	*344*	**1.41 (1.13–1.78)****	*343*	**1.35 (1.07–1.7)***	*1259*	**1.33 (1.18–1.5)*****
Hypercholesterolaemia	+	11,741	*632*	**1.43 (1.21–1.69)*****	*275*	**1.54 (1.2–1.97)****	*286*	1.23 (0.96–1.58)	*1063*	**1.35 (1.19–1.53)*****
	−	28,108	*917*	**1.18 (1.02–1.37)***	*367*	1.25 (1–1.57)	*391*	**1.35 (1.09–1.68)****	*1324*	**1.17 (1.04–1.32)***
Family Hx MI	+	4633	*204*	1.28 (0.95–1.73)	*103*	**1.64 (1.1–2.45)***	*75*	1.03 (0.62–1.71)	*355*	1.14 (0.91–1.44)
	−	31,201	*1148*	**1.28 (1.13–1.45)*****	*460*	**1.38 (1.13–1.69)****	*514*	**1.3 (1.08–1.58)****	*1727*	**1.25 (1.13–1.39)*****
Hx of diabetes	+	1142	*175*	1.21 (0.88–1.67)	*81*	1.13 (0.71–1.82)	*68*	1.44 (0.88–2.36)	*293*	1.14 (0.89–1.46)
	−	38,721	*1374*	**1.27 (1.13–1.43)*****	*561*	**1.39 (1.16–1.66)*****	*609*	**1.27 (1.06–1.51)****	*2094*	**1.25 (1.14–1.37)*****

N, number of women in the stratified subset; *E*, number of events; HR, hazard ratio; CVD, cardiovascular disease; MI, myocardial infarction; CHD, coronary heart disease.
[a]***$p < 0.001$; **$p < 0.01$; *$p < 0.05$ as highlighted in bold.

women having prevalent periodontal disease were similar to previous published population studies examining effects of existing periodontal disease on CVD risks (Helfand et al. 2009).

In addition to providing incidence data, the current analysis also provides a comprehensive analysis of effect modification by established risk factors. In these data, risks of vascular events associated with periodontal disease were generally similar in most clinical subgroups, but tended to be preferentially elevated among women who smoked and who were not obese.

In contrast, the magnitude of association between periodontal disease and cardiovascular disease risk generally did not vary in our data according to family history of myocardial infarction, except for a slightly higher risk of MI among women ever having had periodontal disease as well as a family history of MI (Table 3 and Table S4) although this enhanced effect did not meet statistical significance. While this observation is somewhat discordant with prior work (Mucci et al. 2009, Schaefer et al. 2009, Ernst et al. 2010), questionnaire data on family history are qualitative only and not equivalent to or representative of shared genetic risks. In this regard, recent genome-wide association studies have suggested that some loci might have effects on periodontal risk, albeit most of the signals were below genome-wide significance level (Schaefer et al. 2010, Divaris et al. 2012, Teumer et al. 2013). Further research of periodontal disease *versus* cardiovascular risks in genomic medicine could lead to more insight of the underlying biology.

Strength and limitation

Our study has several strengths including its prospective design, large sample size and confirmation of all incident vascular events. Our approach using time-varying periodontal disease status in the survival analysis is an additional strength as it provides a more accurate assessment of future CVD risk associated with periodontal disease than available from retrospective case–control designs or studies that employ only prevalent periodontal disease. Nonetheless, the generalizability of our findings may be limited due to the study population of middle-aged female healthcare professionals. Previous reports from male healthcare professionals in the Physician Health Study (Howell et al. 2001) and the Healthy Professional Follow-Up Study (Joshipura et al. 1996b) did not identify self-reported periodontal disease status as a significant risk factor for cardiovascular disease. Second, while self-reported periodontal status has been widely used and previously validated for its discriminatory power among healthcare professionals (Joshipura et al. 1996a) as well as for a high correlation with PD defined by clinical examination among the general population in the National Health and Nutrition Examination Survey (Eke et al. 2013), it is a far less useful method than direct examination which can address disease severity. Given the design of the questionnaire, we unfortunately did not have information regarding tooth loss for the majority of women. Furthermore, history of periodontal treatment, unavailable in our data set, could be a potential confounder in the association. Third, censored or misclassified periodontal disease status might have led to an underestimation of the magnitude of true effects. Such misclassification, however, would not have resulted in a false-positive finding.

Conclusion

Incident periodontal disease confers at least as high a risk of future cardiovascular events as prevalent periodontal disease in middle-aged women.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Risk of cardiovascular events among women never vs. ever having had periodontal disease.
Table S2. Baseline characteristics of women used in different statistical analyses.
Table S3. Risk of cardiovascular events among women in the reduced set as in the multivariate model 2 analysis.
Table S4. Risk of cardiovascular events among subgroups of women in the reduced set by periodontal disease status and family history of MI.

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Clinical Relevance

Scientific rationale for the study: Does incident periodontal disease, recorded during a prospective observational study, support previously known associations between cardiovascular events and prevalent periodontal disease?

Principle findings: Among middle-aged women, having either incident or baseline prevalent periodontal disease imposed greater chances of developing future myocardial infarction, ischaemic stroke and vascular procedures when compared with women free of periodontal disease. Hazard ratios of women with incident periodontal disease were at least as high as those with baseline prevalent periodontal disease.

Practical implications: Women with either incident or prevalent periodontal disease are at elevated lifetime risk for life-threatening cardiovascular events.