2014

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Citation: Clinical and Translational Gastroenterology (2014) 5, e49; doi:10.1038/ctg.2013.14

www.nature.com/ctg

A Prospective Study of Periodontal Disease and Risk of Gastric and Duodenal Ulcer in Male Health Professionals

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OBJECTIVES: Periodontal disease has been associated with higher circulating levels of inflammatory markers and conditions associated with chronic inflammation, including vascular disease, diabetes mellitus, and cancer. Limited data exist on the relationship between periodontal disease and gastric and duodenal ulcer.

METHODS: We conducted a prospective cohort study of 49,120 men in the Health Professionals Follow-up Study, aged 40–75 years at enrollment in 1986. Biennially, we assessed periodontal disease, tooth loss, and other risk factors for gastric and duodenal ulcer. We validated diagnoses of gastric and duodenal ulcer through medical record review. We used Cox proportional hazards modeling, adjusting for potential confounders, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS: We documented 138 cases of gastric ulcer and 124 cases of duodenal ulcer with available information on *Helicobacter pylori* status over 24 years of follow-up. After adjustment for risk factors, including smoking and regular use of aspirin and non-steroidal anti-inflammatory drugs, men with periodontal disease with bone loss had a multivariate HR of ulcer of 1.62 (95% CI, 1.24–2.12). Periodontal disease appeared to be associated with a similar risk of developing ulcers that were *H. pylori* negative (HR 1.75; 95% CI, 1.26–2.43) than *H. pylori* positive (HR 1.40; 95% CI, 0.87-2.24), as well as ulcers in the stomach (HR 1.75; 95% CI, 1.21–2.53) than ulcers in the duodenum (HR 1.47; 95% CI, 0.98–2.19).

CONCLUSIONS: Periodontal disease is associated with an increased risk of incident gastric and duodenal ulcer. This relationship may be mediated by alterations in the oral and gastrointestinal microbiome and/or systemic inflammatory factors.

Clinical and Translational Gastroenterology (2014) **5,** e49; doi:10.1038/ctg.2013.14; published online 13 February 2014
Subject Category: Stomach

INTRODUCTION

Periodontal disease is characterized by microbial shifts within the oral cavity and chronic inflammation of the gingival tissue, and can lead to tooth loss. Several studies support an association between periodontal disease and risk of chronic systemic conditions, including vascular disease, chronic obstructive pulmonary disease, diabetes mellitus, and cancer, including gastric adenocarcinoma.[1–15] These associations may be mediated by systemic inflammation, the immune response to periodontal infection, or direct invasion by pathogens. Previous studies of periodontal disease and risk of peptic ulcer have been limited by cross-sectional design, diagnoses that were not confirmed by medical record review, and a lack of information on key confounders, including smoking, aspirin and non-steroidal anti-inflammatory drug (NSAID) use, socioeconomic status, and *Helicobacter pylori* infection status.[16–19]

To address these limitations, we investigated the relationship between periodontal disease and the risk of gastric and duodenal ulcer among men enrolled in the Health Professionals Follow-up Study (HPFS), a large cohort of US male health professionals who provided updated data on oral health and other risk factors, including smoking and aspirin and NSAID use, over 24 total years of follow-up. This population is relatively homogenous in terms of socioeconomic and educational status, which minimizes the potential influence of confounding lifestyle factors.

METHODS

Study population. The HPFS is a prospective cohort of 51,529 US male dentists (58%), veterinarians (20%), pharmacists (8%), optometrists (7%), osteopathic physicians (4%), and podiatrists (3%), aged 40–75 years at enrollment, who returned a mailed health questionnaire in 1986. Subsequently, biennial questionnaires were returned by participants with a follow-up rate exceeding 90%. Data on newly diagnosed medical conditions, including periodontal disease and peptic ulcer, as well as lifestyle factors, including smoking and alcohol use, were obtained from follow-up

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Received 15 May 2013; revised 13 July 2013; accepted 9 September 2013

questionnaires. The National Death Index was searched for questionnaire non-respondents with a sensitivity of 98%.[20]

Assessment of periodontal disease. In the 1986 questionnaire and every 2 years thereafter, participants were asked if they had been diagnosed with ''periodontal disease with bone loss.'' Participant responses to this question have been previously validated against dental X-rays of 140 dentists and 212 non-dentists with and without a self-reported diagnosis of periodontal disease.[21,22] Bone loss was assessed from the radiographs by blinded examiners and was used as the standard measure of cumulative periodontal disease. Among dentists, the positive predictive value was 0.76 and the negative predictive value was 0.74. In non-dentists, the positive predictive value was 0.80 and the negative predictive value was 0.68.

In the 1986 questionnaire, participants were asked to classify their number of natural teeth into one of the following categories: 0, 1–10, 11–16, 17–24, or 25–32 teeth. Starting in 1988 and every 2 years thereafter, participants also reported any incident tooth loss over each follow-up period. Self-reported tooth count has been highly correlated with actual number of teeth on clinical examination in a general population cohort (correlation coefficient: 0.97).[23]

Assessment of smoking history and other risk factors. In the 1986 questionnaire and every 2 years thereafter, participants were asked to report information on their smoking status, regular use of aspirin and NSAIDs, and if they had been diagnosed with diabetes. Every 4 years, intake of alcohol was reported as part of a dietary questionnaire.[24] Body mass index (kg/m^2) was calculated from self-reported body weight (updated biennially) and height (reported at baseline in 1986). The accuracy of body measures has been previously validated within this cohort.[25]

Ascertainment of outcome. At baseline in 1986, participants were asked to report any previous history of peptic ulcer, including the type of ulcer (gastric or duodenal) and an approximate time of occurrence. Every two years thereafter, participants were asked to report new diagnoses of gastric or duodenal ulcer and the year of their diagnosis. Over the 24-year follow-up period, 2,006 total participants reported an ulcer diagnosis and were subsequently sent a detailed supplemental questionnaire and a request for permission to obtain relevant medical records. On the basis of a more detailed definition of ulcer on this supplemental questionnaire, 406 (20%) men subsequently denied an ulcer diagnosis and 280 men (14%) denied permission to review their medical records. Thus, we requested medical records for 1,320 men, obtaining records with adequate information for review for 1,214 men. Two study team members, blinded to exposure information, independently reviewed and extracted data from hospital notes, discharge summaries, endoscopy reports, and pathology reports. Based on diagnosis by upper endoscopy (84%), barium study (13%), and/or surgery (3%), we confirmed 934 ulcer cases. For the 46 cases with both a gastric and duodenal ulcer, we categorized each case according to the location of the primary ulcer as assessed by ulcer size, number, and/or stigmata. We further classified ulcers as *H. pylori* positive or negative based on available information in the medical record or if a participant reported a history of previous *H. pylori* infection on the 2004 questionnaire. Among 934 confirmed ulcer cases, we excluded 257 prevalent cases (diagnosed previous to 1986), 71 cases with ulcers identified by methods other than endoscopy or surgery or with a primary location outside the stomach or duodenum, 30 cases with a history of cancer at baseline, and 34 cases with unknown periodontal disease status. In addition, we excluded 14 cases with recurrent history of ulcer disease diagnosed during the follow-up period. Because of the causal association between *H. pylori* infection and ulcer disease, we restricted our population to participants with available *H. pylori* data and therefore excluded an additional 265 cases.

Statistical analysis. After exclusions, there were 49,120 men and 262 incident ulcer cases for our analyses. Person-time for each participant was calculated from the date of return of the baseline questionnaire to the date of the first gastric or duodenal ulcer event, death from any cause, or 1 January 2010, whichever came first. Individuals who reported an ulcer but for whom we had insufficient records to confirm the diagnosis or assign *H. pylori* infection status at the time of the ulcer event were censored at the time period in which they reported their ulcer. We used Cox proportional hazards modeling, using time-varying variables with the most updated information for periodontal disease and other covariates before each 2-year interval, to compute hazard ratios (HRs) and 95% confidence intervals (CIs). We also tested for statistical heterogeneity within our analyses by calculating stratum-specific HRs and likelihood-ratios for other potential ulcer risk factors. All analyses in this study were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). All *P*-values were two-sided, and $P<0.05$ was considered statistically significant.

RESULTS

Among the 49,120 eligible men, we documented 138 incident cases of gastric ulcer and 124 cases of duodenal ulcer with available information on *H. pylori* infection status over 936,931 person-years and 24 calendar years of follow-up. At baseline, compared with participants who reported no history of periodontal disease with bone loss, men reporting this diagnosis were more likely to be older, dentists, diabetic, self-report as non-white, smoke currently or in the past, have fewer natural teeth, have a higher body mass index, consume more alcohol, and regularly use aspirin (Table 1).

Hospitalization was required for 50% of the cases, with 61% of those hospitalized requiring transfusion and 26% requiring admission to the intensive care unit. Among the 568 ulcers diagnosed endoscopically and/or surgically, 72% were clean-based, 7% had a visible vessel, 7% had an adherent clot, 6% had active arterial bleeding, 5% had a pigmented or flat spot, 3% were oozing without a clot or visible vessel, and 2% were perforated. Among the gastric ulcers, 56% were in the antrum, 24% were in the body, 13% were in the pylorus, 4% were in the fundus, and 3% were in the cardia.

Table 1 Age-adjusted baseline characteristics of participants in the Health Professionals Follow-up Study according to diagnosis of periodontal disease with bone loss

	Periodontal disease with bone loss	
	No (*N* = 41,316)	**Yes (*N* = 7,804)**
Mean (s.d.) age, years	53.8 (97)	58.3 (9.2)
Non-white race, %	5	7
Dentist, %	56	67
Diabetic, %	3	5
Number of natural teeth, %		
0–24	15	29
25–32	85	71
Body mass index (kg/m^2), %		
<25	46	43
25.0–29.9	46	48
≥30.0	8	9
Smoking, %		
Never	50	30
Past	42	53
Current	9	17
Alcohol intake (g/day), %		
0.0	23	21
0.1–4.9	24	23
5.0–14.9	29	29
≥15.0	24	27
Regular user of aspirin[a], %	29	30
Regular user of NSAID[a], %	5	5

Abbreviation: NSAID, non-steroidal anti-inflammatory drug.
[a]Defined as intake ≥2 times/week.

Table 2 Risk of gastric or duodenal ulcer according to the diagnosis of periodontal disease with bone loss

	Periodontal disease with bone loss	
	No	**Yes**
Gastric and duodenal ulcer		
Number of cases/person-years	176/746,133	86/190,798
Age-adjusted (95% CI)	1.00	1.66 (1.27–2.16)
Multivariate-adjusted[a] (95% CI)	1.00	1.62 (1.24–2.12)
Gastric ulcer		
Number of cases/person-years	90/744,014	48/190,196
Age-adjusted (95% CI)	1.00	1.85 (1.29–2.65)
Multivariate-adjusted[a] (95% CI)	1.00	1.75 (1.21–2.53)
Duodenal ulcer		
Number of cases/person-years	86/744,029	38/190,053
Age-adjusted (95% CI)	1.00	1.47 (0.99–2.18)
Multivariate-adjusted[a] (95% CI)	1.00	1.47 (0.98–2.19)
H. pylori-*negative ulcer*		
Number of cases/person-years	114/746.054	59/190,742
Age-adjusted (95% CI)	1.00	1.75 (1.26–2.41)
Multivariate-adjusted[a] (95% CI)	1.00	1.75 (1.26–2.43)
H. pylori-*positive ulcer*		
Number of cases/person-years	62/745,946	27/190,720
Age-adjusted (95% CI)	1.00	1.50 (0.94–2.39)
Multivariate-adjusted[a] (95% CI)	1.00	1.40 (0.87–2.24)
All ulcers[b]		
Number of cases/person-years	401/743,711	149/190,337
Age-adjusted (95% CI)	1.00	1.27 (1.05–1.55)
Multivariate-adjusted[a] (95% CI)	1.00	1.24 (1.02–1.51)

Abbreviation: CI, confidence interval.
[a]Models adjusted for age (months), race (white, non-white), profession (non-dental profession, dentist), diabetes (yes, no), body mass index (<25, 25–29.9, ≥30 kg/m^2), smoking (never, past, current), alcohol intake (0–4.9, 5–14.9, ≥15 g/day), regular aspirin use (<2, ≥2 times/week), and regular non-steroidal anti-inflammatory drug use (<2, ≥2 times/week).
[b]Sensitivity analysis of all ulcer cases, including those with missing *H. pylori* data.

The absolute risk of gastric or duodenal ulcer among participants with periodontal disease with bone loss was 0.24 events per 1,000 person-years compared with 0.45 events per 1,000 person-years among participants with no history of periodontal disease. Men with periodontal disease had an age-adjusted HR of gastric or duodenal ulcer of 1.66 (95% CI,1.27–2.16). This association remained significant even after adjusting for other risk factors, including race, profession, diabetes, smoking, body mass index, alcohol intake, and regular use of aspirin and NSAIDs (multivariate-adjusted HR, 1.62; 95% CI, 1.24–2.12) (Table 2).

Periodontal disease appeared to be associated with risk of both gastric ulcer (multivariate HR, 1.75; 95% CI, 1.21–2.53) and duodenal ulcer (multivariate HR, 1.47; 95% CI, 0.98–2.19), as well as *H. pylori* negative (multivariate HR, 1.75; 95% CI, 1.26–2.41) and *H. pylori* positive (multivariate HR, 1.40; 95% CI, 0.87–2.24) ulcers (Table 2). Periodontal disease had a multivariate HR of 1.72 (95% CI, 1.16–2.53) for ulcer requiring hospitalization, 2.11 (95% CI, 1.28–3.46) for ulcer requiring transfusion, and 2.06 (95% CI, 0.96–4.41) for ulcer requiring intensive care unit admission.

We also examined the association between baseline number of teeth and risk of gastric or duodenal ulcer. Compared with men who reported 25–32 natural teeth, men reporting 24 or fewer teeth had an age-adjusted HR of gastric or duodenal ulcer of 1.44 (95% CI, 1.06–1.96). However, this association was somewhat attenuated after adjustment for other risk factors (multivariate-adjusted HR, 1.35; 95% CI, 0.99–1.85). Baseline number of teeth had similar associations with risk of gastric ulcer (multivariate-adjusted HR, 1.34; 95% CI, 0.86–2.08) and duodenal ulcer (multivariate-adjusted HR, 1.37; 95% CI, 0.88–2.13) (Table 3).

We also evaluated the association between incident tooth loss during follow-up and subsequent risk of ulcer. Compared with men with no tooth loss, men reporting tooth loss during follow-up had an age-adjusted HR of gastric or duodenal ulcer of 1.25 (95% CI, 0.95–1.65), which was further attenuated after adjustment for other risk factors (multivariate-adjusted HR, 1.07; 95% CI, 0.81–1.42). Tooth loss during follow-up was not strongly associated with either risk of gastric ulcer (multivariate-adjusted HR, 1.04; 95% CI, 0.70–1.53) or duodenal ulcer (multivariate-adjusted HR, 1.11; 95% CI, 0.74–1.67) (Table 3).

We examined the possibility that our observed relationships were modified by other known or potential risk factors for ulcer. We did not observe any significant heterogeneity in the association of periodontal disease with ulcer by subgroups defined according to body mass index, smoking, alcohol intake, regular use of aspirin or NSAIDs, and profession. Most notably, the effect of periodontal disease persisted among never

Table 3 Risk of gastric or duodenal ulcer according to tooth loss

	Number of natural teeth[a]	
	25–32	0–24
Gastric and duodenal ulcer		
Number of cases/person-years[b]	203/787,375	58/141,770
Age-adjusted (95% CI)	1.00	1.44 (1.06–1.96)
Multivariate-adjusted[c] (95% CI)	1.00	1.35 (0.99–1.85)
Gastric ulcer		
Number of cases/person-years	108/785,156	29/141,296
Age-adjusted (95% CI)	1.00	1.46 (0.95–2.25)
Multivariate-adjusted[c] (95% CI)	1.00	1.34 (0.86–2.08)
Duodenal ulcer		
Number of cases/person-years	95/141,183	29/785,122
Age-adjusted (95% CI)	1.00	1.43 (0.93–2.21)
Multivariate-adjusted[c] (95% CI)	1.00	1.37 (0.88–2.13)
	Tooth loss during follow-up[d]	
	No	**Yes**
Gastric and duodenal ulcer		
Number of cases/person-years[b]	179/662,667	82/194,809
Age-adjusted (95% CI)	1.00	1.25 (0.95–1.65)
Multivariate-adjusted[c] (95% CI)	1.00	1.07 (0.81–1.42)
Gastric ulcer		
Number of cases/person-years	96/660,949	42/194,319
Age-adjusted (95% CI)	1.00	1.25 (0.85–1.83)
Multivariate-adjusted[c] (95% CI)	1.00	1.04 (0.70–1.53)
Duodenal ulcer		
Number of cases/person-years	83/660,793	40/194,278
Age-adjusted (95% CI)	1.00	1.25 (0.84–1.86)
Multivariate-adjusted[c] (95% CI)	1.00	1.11 (0.74–1.67)

Abbreviation: CI, confidence interval.
[a]Reported by participants on baseline questionnaire in 1986.
[b]One case was excluded from both analyses due to missing data on tooth loss at baseline.
[c]Models adjusted for age (months), race (white, non-white), profession (non-dental profession, dentist), diabetes (no, yes), body mass index (<25, 25-29.9, ≥30 kg/m^2), smoking (never, past, current), alcohol intake (0–4.9, 5–14.9, ≥15 g/day), regular aspirin use (<2, ≥2 times/week) and regular non-steroidal anti-inflammatory drug use (<2, ≥2 times/week).
[d]Updated biennially beginning in 1988.

smokers ($P_{heterogeneity} = 0.13$) and individuals who did not regularly use aspirin or NSAIDs ($P_{heterogeneity} = 0.10$) (Table 4).

In sensitivity analyses, we conducted a cross-sectional study evaluating the association between periodontal disease and prevalent ulcer cases and observed similar association between periodontal disease and ulcer risk. Compared with participants without periodontal disease, participants with periodontal disease had a multivariate-adjusted OR of 1.89 (95% CI, 1.46–2.46) for gastric and duodenal ulcer, 2.06 (95% CI, 1.45–2.94) for gastric ulcer, and 1.73 (95% CI, 1.18–2.53) for duodenal ulcer.

DISCUSSION

In this prospective cohort of men, we found that periodontal disease with bone loss was associated with an increased risk of gastric and duodenal ulcer. The association appeared largely consistent for gastric and duodenal ulcers as well as *H. pylori* positive and *H. pylori* negative ulcers. These

Table 4 Risk of gastric or duodenal ulcer according to diagnosis of periodontal disease with bone loss, stratified by other risk factors for ulcer

	Periodontal disease with bone loss	
	No	**Yes**
Age <65 years		
Number of cases/person-years	85/458,291	20/82,983
Age-adjusted (95% CI)	1.00	1.21 (0.74–1.99)
Multivariate-adjusted[a] (95% CI)	1.00	1.14 (0.69–1.89)
Age ≥65 years		
Number of cases/person-years	91/287,843	66/107,815
Age-adjusted (95% CI)	1.00	1.93 (1.40–2.65)
Multivariate-adjusted[a] (95% CI)	1.00	1.92 (1.38–2.67)
		$P_{heterogeneity} = 0.11$
Body mass index <25 kg/m^2		
Number of cases/person-years	63/313,633	37/79,011
Age-adjusted (95% CI)	1.00	1.99 (1.30–3.03)
Multivariate-adjusted[a] (95% CI)	1.00	2.00 (1.29–3.09)
Body mass index ≥25 kg/m^2		
Number of cases/person-years	113/432,500	49/111,787
Age-adjusted (95% CI)	1.,00	1.51 (1.07–2.14)
Multivariate-adjusted[a] (95% CI)	1.00	1.43 (1.00–2.03)
		$P_{heterogeneity} = 0.33$
Never smoker		
Number of cases/person-years	71/301,651	26/48,477
Age-adjusted (95% CI)	1.00	2.11 (1.31–3.38)
Multivariate-adjusted[a] (95% CI)	1.00	2.14 (1.32–3.47)
Past/current smoker		
Number of cases/person-years	85/277,104	46/96,582
Age-adjusted (95% CI)	1.00	1.36 (0.94–1.97)
Multivariate-adjusted[a] (95% CI)	1.00	1.34 (0.92–1.95)
		$P_{heterogeneity} = 0.13$
Alcohol <5 g/day		
Number of cases/person-years	78/358,995	33/87,310
Age-adjusted (95% CI)	1.00	1.41 (0.93–2.15)
Multivariate-adjusted[a] (95% CI)	1.00	1.47 (0.95–2.25)
Alcohol ≥5 g/day		
Number of cases/person-years	98/387,138	53/103,488
Age-adjusted (95% CI)	1.00	1.84 (1.30–2.60)
Multivariate-adjusted[a] (95% CI)	1.00	1.76 (1.23–2.51)
		$P_{heterogeneity} = 0.53$
Non-regular aspirin or NSAID user[b]		
Number of cases/person-years	47/363,369	30/84,842
Age-adjusted (95% CI)	1.00	2.11 (1.31–3.42)
Multivariate-adjusted[a] (95% CI)	1.00	2.08 (1.26–3.43)
Regular aspirin or NSAID user[b]		
Number of cases/person-years	129/382,765	56/105,956
Age-adjusted (95% CI)	1.00	1.47 (1.06–2.03)
Multivariate-adjusted[a] (95% CI)	1.00	1.42 (1.02–1.97)
		$P_{heterogeneity} = 0.10$
Non-dental profession		
Number of cases/person-years	86/325,252	38/70,615
Age-adjusted (95% CI)	1.00	1.73 (1.16–2.58)
Multivariate-adjusted[a] (95% CI)	1.00	1.69 (1.12–2.54)
Dental profession		
Number of cases/person-years	90/420,881	48/120,183
Age-adjusted (95% CI)	1.00	1.72 (1.20–2.48)
Multivariate-adjusted[a] (95% CI)	1.00	1.66 (1.14–2.41)
		$P_{heterogeneity} = 0.74$

Abbreviations: CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.
[a]Models adjusted for age (months), race (white, non-white), profession (non-dental profession, dentist), diabetes (no, yes), body mass index (<25, 25–29.9, ≥30 kg/m^2), smoking (never, past, current), alcohol intake (0–4.9, 5–14.9, ≥15 g/day), regular aspirin use (<2, ≥2 times/week), and regular NSAID use (<2, ≥2 times/week). For each stratified analysis, the variable for the strata of interest was omitted.
[b]Non-regular aspirin or NSAID user was defined as intake of aspirin or NSAIDs <2 times/week. Regular aspirin or NSAID user was defined as intake of aspirin or NSAIDs ≥2 times/week.

observed associations persisted even after adjusting for putative risk factors, including smoking, alcohol intake, and regular use of aspirin and NSAIDs.

Our results are largely consistent with previous studies. In a recent cross-sectional analysis of 28,765 Japanese insurance workers, self-reported peptic ulcer was associated with a history of periodontitis, loss of five or more teeth, and a 1-point increase in a periodontal risk score.[16] Similarly, severe alveolar bone loss was associated with self-reported "stomach ulcers" in 2,006 patients undergoing dental radiograph and chart review.[17] In a Polish case-control study of 186 *H. pylori*-infected subjects in which NSAID-associated ulcers were excluded, various measures of oral health and tooth decay, but not tooth loss, were associated with ulcer.[18] A cross-sectional study of 603 subjects who underwent oral examination found that increased clinical attachment loss, but not missing teeth, gingival recession, or probing depth, was associated with peptic ulcers.[19] Our study significantly extends these results by using prospective assessments of periodontal disease before the diagnosis of ulcer, minimizing the likelihood of recall bias that may have influenced these previous cross-sectional analyses.[16–19] Moreover, these previous studies relied on self-reported periodontal health measures[16] and ulcer outcomes[16,17,19] and were unable to account for key confounding factors, including NSAID use,[16,17,19] socioeconomic status,[16–19] and smoking.[18]

Periodontal disease has been associated with chronic systemic inflammation. Previous studies have shown significantly higher levels of plasma C-reactive protein among subjects with periodontal disease,[10,26,27] including men in this cohort.[1] In addition, within this cohort, periodontal disease has been associated with risks of conditions associated with chronic inflammation, including cardiovascular disease, ischemic stroke, and cancers of the lung, kidney, and pancreas.[1–5] Thus, it is possible that periodontal disease may be associated with a systemic inflammatory response that predisposes to ulcer risk.

Periodontal disease is also known to be associated with shifts in oral microbiota, and this may affect the integrity of gastrointestinal mucosa. In previous studies, individuals with periodontal disease and tooth loss have exhibited increased oral and gastric populations of *H. pylori*, a well-established cause of peptic ulcer.[28–33] Adding periodontal treatment to standard triple antibiotic therapy also increased the effectiveness of gastric *H. pylori* eradication in studies of a general population cohort and of patients with chronic gastric illness.[34–35] However, periodontal disease's association with gastric and duodenal ulcer may be related to mechanisms other than *H. pylori* colonization, as our data showed similar associations between periodontal disease and risk of *H. pylori*-positive and *H. pylori*-negative ulcers. One hypothesis is that oral microbiota, which have been associated with the impaired healing of periodontal lesions,[36–39] may also be a source of chronic inflammation and impaired wound healing of gastrointestinal tract mucosa.

Our analyses of both natural teeth at baseline and tooth loss during follow-up and risk of gastric and duodenal ulcer were generally in agreement with our findings for periodontal disease. However, these associations were weaker and also attenuated with multivariate adjustment. Tooth loss reflects both periodontal disease and other factors, including caries, trauma, cosmetic procedures, use of bisphosphonates, and access to dental care. Hence, tooth loss, especially at later ages, could be used as a marker of periodontal disease but needs to be interpreted more cautiously.

The strengths of our study include a relatively large number of incident cases of gastric and duodenal ulcer, detailed and updated information on periodontal disease and ulcer diagnoses for >20 years of follow-up, and extensive and detailed information on potential confounders, particularly smoking, alcohol intake, and use of aspirin and NSAIDs. Because our cohort is comprised of health professionals, confounding by education, socioeconomic status, and inaccurate reporting of periodontal disease and incident ulcer was minimized.

There are several limitations of our study that deserve mention. First, data on periodontal disease was self-reported, which may affect the reliability of our results. However, previous examination of periodontal disease within the HPFS has shown self-reporting within this cohort to have high positive and negative predictive value among both non-dentists and dentists.[21,22] In addition, the risk of ulcer associated with periodontal disease was not modified according to dental vs. non-dental profession in our stratified analysis. Second, our study population consists of predominantly white, US, male health professionals, which may limit the generalizability of our findings to other populations. Furthermore, although our cohort is occupationally homogenous, we acknowledge the possibility that residual difference in the socioeconomic status of participants (such as in early childhood) may have influenced our results. Third, we could not confirm all cases of self-reported ulcer and our data on *H. pylori* infection status was incomplete. However, to minimize bias, we censored such men from our analyses and used self-reported *H. pylori* infection data to classify a portion of the unknown data. Furthermore, sensitivity analyses that included all confirmed ulcer cases, irrespective of the availability of data on *H. pylori* status, showed similar risk estimates to our main analyses, which included only cases with available *H. pylori* data (see Table 2, All ulcers). Fourth, our findings might not be generalizable to less severe forms of ulcer cases that do not require hospitalization, endoscopy, or imaging. Finally, our study is observational, and we cannot rule out the possibility of residual confounding. However, residual confounding by some of the strongest risk factors for ulcer disease, such as smoking or aspirin/NSAID use is unlikely, as we observed consistent results within strata of never smokers and non-users of aspirin/NSAIDs.

In conclusion, our study showed that periodontal disease and tooth loss were associated with an increased risk of gastric and duodenal ulcer. These findings provide additional support for a potential association between chronic inflammation, oral microbiota dissemination, and gastrointestinal ulceration. Further study is needed to determine whether practices that promote periodontal health may help reduce risk of peptic ulcer disease.

CONFLICT OF INTEREST

Guarantor of the article: Andrew T. Chan, MD, MPH.
Specific author contributions: A.T.C., M.R.B., H.K., and

E.S.H. conceived and designed the study. M.R.B., H.K., A.T.C., E.S.H., D.S.M., K.J., and J.I. analyzed the data. A.T.C. supervised the study. M.R.B., A.T.C., H.K., E.S.H., K.J., and J.I. wrote the paper.

Financial Support: Funded by UM1 CA167552 (Willett) and R21 CA139193 (J.I.) from NCI/NIH and K24 DK098311 (A.T.C.) from the NIDDK/NIH. A.T.C. is a Damon Runyon Cancer Research Foundation Clinical Investigator. H.K. is supported by a career development award from the Crohn's and Colitis Foundation of America (CCFA).

Potential Competing interests: A.T. Chan has served as a consultant for Bayer HealthCare, Millennium Pharmaceuticals, Inc., Pfizer, Inc., and Pozen, Inc. The other authors declare no conflict of interest.

Acknowledgments. We thank the continued dedication of the participants in the HPFS as well as the research assistants at the Harvard School of Public Health for their assistance in medical record collection.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Periodontal disease has been associated with several chronic inflammatory conditions, including gastric cancer.
- Limited previous research has suggested a possible association with peptic ulcer disease.

WHAT IS NEW HERE

- This is the first prospective study of the association between periodontal disease and peptic ulcer.
- Periodontal disease was associated with incident peptic ulcer even after accounting for other risk factors for ulcers, including smoking and use of NSAIDs.
- Further studies are needed to elucidate possible mechanisms that underlie this association.

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