The relationship between inflammatory dietary pattern and incidence of periodontitis

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Abstract

The long-term inflammatory impact of diet could potentially elevate the risk of periodontal disease through modification of systemic inflammation. The aim of the present study was to prospectively investigate the associations between a food-based, reduced rank regression (RRR)-derived, empirical dietary inflammatory pattern (EDIP) and incidence of periodontitis. The study population was composed of 34 940 men from the Health Professionals Follow-Up Study, who were free of periodontal disease and major illnesses at baseline (1986). Participants provided medical and dental history through mailed questionnaires every 2 years and dietary data through validated semi-quantitative FFQ every 4 years. We used Cox proportional hazard models to examine the associations between EDIP scores and validated self-reported incidence of periodontal disease over a 24-year follow-up period. No overall association between EDIP and the risk of periodontitis was observed; the hazard ratio comparing the highest EDIP quintile (most proinflammatory diet) with the lowest quintile was 0·99 (95 % CI 0·89, 1·10, *P*-value for trend = 0·97). A secondary analysis showed that among obese non-smokers (i.e. never and former smokers at baseline), the hazard ratio for periodontitis comparing the highest EDIP quintile with the lowest was 1·39 (95 % CI 0·98, 1·96, *P*-value for trend = 0·03). In conclusion, no overall association was detected between EDIP and incidence of self-reported periodontitis in the study population. From the subgroups evaluated, EDIP was significantly associated with increased risk of periodontitis only among non-smokers who were obese. Hence, this association must be interpreted with caution.

Key words: **Periodontitis: Periodontal disease: Dietary patterns: Inflammatory diets**

Gingivitis and periodontitis are among the most common inflammatory conditions in human adults[1]. The inflammatory process in gingivitis is restricted to the superficial periodontal tissue and does not lead to periodontal attachment loss, making gingivitis lesions reversible in nature once the cause(s) is/are removed. Periodontitis, on the other hand, is characterised by more profound inflammation that leads to breakdown of the tooth-supporting apparatus and may lead to tooth loss eventually. The pathogenesis of periodontal disease is not yet fully understood, but there is substantial evidence that most of the periodontal tissue destruction is caused by the host immune response to the bacterial challenge of periodontal pathogens[2]. Pro-inflammatory mediators, such as TNF-α, IL-1, IL-6, IL-8 and PGE$_2$, are key players in this process[2]. To date, only a few of the established periodontal disease predictors can be modified through improvement of lifestyle factors. Prevention of periodontal disease at the population level requires better understanding of modifiable risk factors for periodontal disease[3].

The relationship between periodontitis and systemic inflammation is complex, and current evidence proposes that the

relationship is bidirectional. In fact, systemic inflammation seems to pathophysiologically elucidate several of the reported associations between periodontal disease and multiple cardio-metabolic conditions[3]. Much of the published work in the last three decades has focused on the potential effect of periodontitis on elevated systemic inflammatory biomarkers[4–9]. The reverse was only reported in humans recently, that is, baseline systemic inflammation measures were positively correlated with perio-dontal disease progression[10]. The impact of diet on modifying the risk of periodontitis is strongly biologically plausible through modulation of systemic inflammation[11]. However, the literature relating diet and periodontal disease in humans is relatively scarce[3].

An empirical dietary inflammatory pattern (EDIP) was recently developed by Tabung *et al.* using reduced rank regression (RRR)[12]. Dietary pattern analyses are practical platforms to study the overall impact of diet on disease outcomes beyond the specific effects of certain foods or nutrients. Dietary patterns can be generally classified into either *a priori* or *a posteriori* indices. While *a priori* index is hypothesis-oriented and is based on the current scientific evidence regarding the relationship between diet and diseases (e.g. Alternate Healthy Eating Index), *a posteriori* method on the other hand is data-driven and is based on statistical exploratory methods (e.g. principal component analysis-driven dietary pattern). RRR is an innovative approach in nutrition epidemiology in that it is *a posteriori* in nature, but it incorporates prior knowledge about diseases and their pathways[13]. When applied, information about food or nutrients intake is used by RRR to maximally explain the variability in response variables, which can be disease mediators (e.g. inflammatory biomarkers). An advantage of RRR over other methods of dietary patterns is that it is based on biological principles and mechanisms of disease development, which could bolster evidence of causality between diet and an outcome of interest[14].

The aim of the current study was to test the hypothesis that the inflammatory potential of diet could modify the risk of periodontitis, by prospectively evaluating the association between EDIP and incidence of periodontal disease in the Health Professionals Follow-up Study (HPFS).

Methods

Study population

The HPFS is an ongoing cohort study that enrolled 51 529 male health professionals (dentists, pharmacists, optometrists, osteopathic physicians, podiatrists and veterinarians) who answered and returned the baseline mailed questionnaire in 1986 when they were 40–75 years old. Study participants provided thorough medical and dental history in addition to lifestyle behaviour and body measurements (e.g. height and weight) through biennial questionnaires. Data about participants' diet were collected through semi-quantitative FFQ every 4 years, starting at baseline. The adequacy, reproducibility and validity of the FFQ in assessing diet have been previously reported[14,15].

We excluded participants who only responded to the baseline questionnaire (*n* 3309) and those who had missing periodontal data (*n* 1117). Participants who reported periodontitis

at baseline (*n* 8333) and those who were edentulous (*n* 485) were excluded because they were not at risk for incident periodontal disease. In addition, we excluded participants who reported myocardial infarction (*n* 1486), coronary artery surgery (*n* 671), diabetes (*n* 809) or cancer (*n* 1317) at baseline because those events could strongly modify dietary habits. We also excluded participants with missing data on BMI (*n* 902), physical activity (*n* 128) or age (*n* 36) at baseline. Participants with energetic intake outside the plausible range (3347–17 573 kJ/d (800–4200 kcal/d)) and those who left 70 or more out of the 131 FFQ items blank were also excluded (*n* 1033). Our analysis consists of 34 940 men at baseline. The study was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Outcome assessment

The endpoint in our study was self-reported incidence of periodontal disease, defined as answering 'yes' to the question 'have you been professionally diagnosed with periodontal disease with bone loss?', which was asked biennially in the mailed questionnaire. The self-reported data for assessing periodontal disease were shown to be valid in a subsample of the HPFS when compared with bitewing radiographs[16,17]. There were no secondary endpoints in our study.

Main exposures assessment

The main exposure in the current study is RRR-derived EDIP, which was developed in the Nurses' Health Study and was validated in the Nurses' Health Study II and the HPFS[12]. In summary, the index was derived in a subsample of Nurses' Health Study (*n* 5239) for whom dietary data and plasma concentrations of IL-6, C-reactive protein, TNF-α receptor 2 were available. Blood was collected in 1989 and 1990. Diet was measured by averaging the two FFQ that were close to the blood collection, that is, 1986 and 1990 cycles. The 131 FFQ items were grouped into thirty-nine pre-defined food groups based on nutrient composition and on culinary use. Those groups were used in the RRR to explain as much variability in IL-6, C-reactive protein and TNF-α receptor 2 as possible. The first factor explained most of the variation, and it was retained. Then, stepwise linear regression models were fitted to identify food groups most predictive of that factor. The analysis resulted in eighteen food groups and beverages. EDIP scores are a weighted average of those food groups. Negative scores indicated anti-inflammatory diets, while positive scores indicated proinflammatory diets. Fish (other than dark-meat fish), tomatoes, processed meats, high-energy beverages, other vegetables (i.e. vegetables other than leafy green vegetables and dark yellow vegetables), red meats, low-energy beverages, refined grains and organ meats were associated with higher concentrations of the inflammatory biomarkers, whereas pizza, wine, leafy green vegetables, dark yellow vegetables (comprising carrots, yellow squash and yams), beer, coffee, fruit juice, snacks and tea were inversely associated with the biomarkers. The construct validity of EDIP was evaluated in independent subsamples from Nurses' Health Study II and HPFS[12], and in other cohorts[18,19]. For our analysis, we calculated EDIP scores for each FFQ cycle (i.e. every 4 years) until the start of each 2-year

follow-up interval. The cumulative average of the EDIP scores was calculated, to better represent the long-term dietary intake and to minimise within-person variability and measurement error. EDIP scores were divided into quintiles.

Covariates assessment

We controlled for confounding by adjusting the analysis for important risk factors of periodontal disease, that may also modify the exposure, that is, age, smoking, BMI, physical activity and alcohol consumption[3,20–25]. We controlled for smoking by using the Comprehensive Smoking Index, which is an algorithm that takes into account the updated information on each questionnaire cycle regarding: duration of smoking in years, smoking intensity (calculated as number of cigarettes smoked per d), time since smoking cessation in years and a specific biological half-life of smoking effect on the disease, estimated to be 1·5 years for periodontal disease[26,27]. BMI was updated biennially, and values were categorised as follows (<18·5, 18·5–24·9, 25–29·9 and ≥30 kg/m^2). We used updated BMI, as a positive association between updated BMI and periodontal disease was reported previously in this cohort[25]. Self-reported physical activity data were quantified using the metabolic equivalent of task to calculate metabolic equivalent of task hours on each cycle. Metabolic equivalent of task-h for each participant was added, and data were categorised into quintiles. We controlled for physical activity using the updated measures for each follow-up. We used the cumulative average of alcohol intake estimated from the FFQ and classified the data into: 0, 0·1–4·9, 5–14·9, 15–29 and ≥30 g/d. Cumulative average energetic intake was estimated from the FFQ, and EDIP scores were adjusted for total energy intake using the residual method. Information about self-reported diagnosis of diabetes during the follow-up was updated at each questionnaire cycle. Self-reported diabetes in this cohort showed good validity[28].

Statistical analysis

Baseline descriptive statistics for the study cohort by quintiles of EDIP were calculated, using means for continuous data and percentages for categorical data. The hazard ratio of periodontal disease was calculated by comparing each of the higher quintiles of EDIP to the lowest, by fitting Cox proportional hazard models with age in months as the underlying timescale. Person-time was calculated from the return of the baseline questionnaire until incidence of periodontal disease, mortality, last available response or end of follow-up (which was 31 January 2010), whichever came first. The models were adjusted for the confounding variables. We conducted the test for linear trend by assigning each individual the median value of their EDIP quintile. All missing exposure or covariate data during follow-up were handled by carrying forward values from the last cycle.

We compared the results with and without including BMI in the models, to evaluate any potential mediation by adiposity. We also stratified the models by updated BMI categories (18·5–29·9 and ≥30 kg/m^2). Underweight men (BMI < 18·5 kg/m^2) were excluded from the stratified analysis as they only contributed <0·5 % of the total person-time. To investigate the association within other covariates besides BMI, we also stratified the

analysis by occupation (dentist *v.* non-dentist), age (≥65 *v.* <65 years), physical activity (above the median *v.* below), smoking at baseline (never, former, current), alcohol consumption (0, 0·1–4·9 and ≥5 g/d) and diabetes over the follow-up. The stratified analysis models were fully adjusted except for the stratification variable. To test for the statistical significance of interactions, we created indicator variables for the following: being a dentist, updated obesity status (BMI ≥ 30 kg/m^2), updated binary physical activity level, updated binary age and updated diabetes. We fitted adjusted models that included interaction terms between the dietary patterns (using the median values of quintiles) and the indicator variables for stratifying factors. For smoking, we used continuous Comprehensive Smoking Index value, instead of an indicator variable. We did the same for alcohol consumption, where we used the continuous intake of alcohol (g/d), instead of an indicator variable. The P–value for each interaction was calculated using a Wald test (one df test). All the analysis was performed using SAS for UNIX statistical software (version 9.4; SAS Institute).

Results

The number of reported new cases of periodontitis was 3738 over the 24 years of the study follow-up (747 517 person-years). Table 1 shows the distribution of age-adjusted baseline characteristics by quintiles of EDIP. Participants with higher scores of EDIP tended to be less physically active, were more likely to be never smokers and consumed less alcohol than those with lower scores of EDIP. Number of teeth was similar across EDIP quintiles. The mean intake of proinflammatory food groups increased with higher EDIP, while the mean intake of anti-inflammatory food groups decreased.

EDIP scores showed no overall association with the risk of periodontal disease in our analysis; the hazard ratio (HR) in the highest quintile of EDIP was 1·01 compared with the lowest quintile (95 % CI 0·90, 1·12, P-value for trend = 0·80) (Table 2). Adjusting for BMI in the models did not significantly change the association (HR 0·99, 95 % CI 0·89, 1·10, P-value for trend = 0·97). The results were similar among subgroups defined by age, physical activity level, diabetes and profession (Table 3). We detected a marginally significant effect modification by obesity (defined as BMI ≥ 30 kg/m^2 *v.* non-obese) (P-value for interaction = 0·06) (Table 3). There was a modest elevated risk of periodontal disease for obese individuals comparing the highest quintile of EDIP with the lowest quintile (HR 1·27, 95 % CI 0·94, 1·73, P-value for trend = 0·07). We performed a secondary analysis evaluating the association among non-smokers by excluding current smokers at baseline. Participants who reported being 'current smokers' at baseline on average contributed more than 50 % of their person-time being current smokers during the follow-up, while those who reported being 'former' or 'never' smokers only contributed <2 % of the person-time being current smokers. Also, there is evidence that the periodontal status and response to treatment for former smoker are closer to never smokers than to current smokers and seem to get similar to never smokers several years after quitting[29]. Smoking is a very strong risk factor of periodontitis in this cohort

Table 1. Age-standardised characteristics of the Health Professionals Follow-up Study (HPFS) study population in1986 (baseline) by quintile of the empirical dietary inflammatory pattern (EDIP)*
(Mean values and standard deviations; numbers and percentages)

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
n	7231		7049		6969		6844		6847	
%	20·7		20·2		19·9		19·6		19·6	
Age (years)	51·4	8·8	52·6	9·4	52·8	9·5	52·8	9·6	52·05	9·6
White (%)	97		97		96		94		93	
BMI (kg/m²)	25·2	3·1	25·3	3·1	25·3	3·1	25·5	3·3	26·1	3·8
Smoking (%)										
Former	48		43		39		35		33	
Current	11		8		8		7		9	
Alcohol (g/d)	21·5	20·6	11·9	13·4	8·7	11·8	6·9	10·3	6·0	10·0
Total activity (MET/week)	24·1	29·7	22·7	30·9	21·5	30·8	20·6	30·3	19·3	28·9
Dentist (%)	56		58		58		58		55	
Number of teeth										
25–32	88		89		89		88		87	
17–24	9		9		9		9		10	
11–16	1		1		1		1		2	
1–10	1		1		1		1		1	
Intake of EDIP foods groups (servings/d)										
Pro-inflammatory										
Fish (non-dark meat)	0·29	0·22	0·30	0·23	0·30	0·24	0·32	0·25	0·36	0·37
Tomatoes	0·55	0·45	0·54	0·43	0·55	0·41	0·57	0·43	0·73	0·71
Processed meat	0·30	0·32	0·31	0·33	0·32	0·34	0·36	0·37	0·55	0·64
High-energy beverages	0·20	0·34	0·24	0·38	0·30	0·46	0·37	0·52	0·75	1·03
Other vegetables	0·82	0·67	0·78	0·60	0·78	0·60	0·79	0·63	0·95	0·85
Red meat	0·55	0·40	0·56	0·41	0·57	0·42	0·62	0·44	0·81	0·59
Low-energy beverages	0·33	0·63	0·37	0·69	0·40	0·70	0·49	0·85	0·89	1·54
Refined grains	0·96	0·79	1·02	0·85	1·09	0·94	1·22	1·01	1·80	1·52
Organ meats	0·02	0·03	0·02	0·03	0·02	0·04	0·02	0·04	0·02	0·04
Anti-inflammatory										
Pizza	0·13	0·16	0·09	0·09	0·08	0·08	0·07	0·07	0·06	0·06
Wine	0·65	0·96	0·27	0·35	0·17	0·25	0·12	0·20	0·08	0·17
Leafy green vegetables	0·95	0·85	0·79	0·58	0·69	0·50	0·62	0·47	0·61	0·51
Dark yellow vegetables	0·39	0·51	0·33	0·34	0·31	0·30	0·29	0·28	0·28	0·29
Beer	0·67	1·13	0·30	0·53	0·20	0·38	0·15	0·30	0·11	0·26
Coffee	3·40	2·14	2·36	1·76	1·68	1·56	1·16	1·31	0·94	1·24
Fruit juice	0·93	1·15	0·85	0·84	0·77	0·74	0·71	0·68	0·67	0·70
Snacks	0·71	0·98	0·58	0·73	0·53	0·63	0·49	0·58	0·53	0·63
Tea	0·48	0·99	0·45	0·89	0·44	0·84	0·41	0·79	0·39	0·79

MET, metabolic equivalent of task.
* Values are standardised to the age distribution of the study population.

Table 2. Relating quintiles of empirical dietary inflammatory pattern (EDIP) scores and incidence of periodontitis
(Hazard ratios (HR) and 95 % confidence intervals)

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5		
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	P_{trend}
Cases	767		726		746		743		756		
Person-years	142 239		141 736		141 281		141 006		140 909		
Model 1*	1		0·94	0·85, 1·04	0·96	0·87, 1·06	0·95	0·86, 1·05	0·96	0·87, 1·07	0·53
Model 2†	1		0·96	0·87, 1·07	1·00	0·90, 1·11	0·99	0·89, 1·10	1·01	0·90, 1·12	0·80
Model 3‡	1		0·96	0·87, 1·07	0·99	0·89, 1·10	0·99	0·89, 1·10	0·99	0·89, 1·10	0·97

* Model 1: age adjusted.
† Model 2: adjusted for age, smoking (Comprehensive Smoking Index), physical activity (metabolic equivalent of task (MET) quintiles), alcohol (g/d: 0, 0·1–4·9, 5–14·9, 15–29, 30+), occupation (dentist v. non-dentist) and race (White/Black/Asian/Other).
‡ Model 3: model 2 and adjusted for BMI (<18·5, 18·5–24·9, 25–29·9, 30+ kg/m²).

(online Supplementary Table S1). After exclusion of current smokers at baseline, the number of new cases of periodontitis was 3199, over 655 151 person-years. We stratified this secondary analysis among non-smokers by the other periodontitis risk factors (Table 4). Obese men in the highest quintile of EDIP had 39 % more risk of periodontitis than those in the lowest quintile of EDIP (HR 1·39, 95 % CI 0·98, 1·96, P-value for trend = 0·03) (P-value for interaction by obesity = 0·07). The association was similar among all the other risk factors subgroups. We also examined the joint associations between EDIP and BMI on

Table 3. Multi-variate association between quintiles of empirical dietary inflammatory pattern (EDIP) and periodontal disease within subgroups*
(Hazard ratios (HR) and 95 % confidence intervals)

Subgroup		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}†	$P_{interaction}$‡
BMI (kg/m²)								
18·5–29·9	Cases	698	647	661	631	608	0·55	0·06 (obese v. non-obese)
	Person-years	128,989	127,565	126,388	123,562	117,264		
	HR and 95 % CI	1	0·95 0·85, 1·06	0·98 0·88, 1·10	0·96 0·85, 1·07	0·96 0·86, 1·08		
≥30	Cases	69	78	82	108	146	0·07	
	Person-years	12,852	13,699	14,301	16,900	23,067		
	HR and 95 % CI	1	1·07 0·77, 1·50	1·08 0·78, 1·51	1·26 0·92, 1·73	1·27 0·94, 1·73		
Age (years)								
<65	Cases	495	415	416	402	472	0·88	0·63
	Person-years	93,984	85,026	82,418	84,099	93,006		
	HR and 95 % CI	1	0·97 0·84, 1·10	1·00 0·88, 1·15	0·95 0·83, 1·09	0·99 0·87, 1·14		
≥65	Cases	272	311	330	341	284	0·87	
	Person-years	48,255	56,710	58,863	56,907	47,903		
	HR and 95 % CI	1	0·97 0·82, 1·14	0·99 0·84, 1·17	1·04 0·88, 1·23	0·98 0·82, 1·18		
Physical activity								
<Median	Cases	373	353	388	403	448	0·66	0·37
	Person-years	62,871	65,369	69,152	71,493	75,309		
	HR and 95 % CI	1	0·94 0·81, 1·09	0·99 0·86, 1·15	0·99 0·85, 1·15	1·02 0·88, 1·18		
≥Median	Cases	394	373	358	340	308	0·58	
	Person-years	79,367	76,368	72,129	69,513	65,600		
	HR and 95 % CI	1	0·98 0·85, 1·14	1·00 0·86, 1·16	0·98 0·84, 1·15	0·95 0·81, 1·12		
Diabetes (follow-up)								
No	Cases	749	692	715	706	716	0·97	0·32
	Person-years	139,112	137,298	135,818	134,835	133,304		
	HR and 95 % CI	1	0·95 0·85, 1·05	0·99 0·89, 1·10	0·98 0·88, 1·09	0·99 0·89, 1·11		
Yes	Cases	18	34	31	37	40	0·72	
	Person-years	31,27	4438	5463	6171	7605		
	HR and 95 % CI	1	1·62 0·89, 2·95	1·12 0·60, 2·10	1·41 0·76, 2·61	1·05 0·57, 1·94		
Dentist								
No	Cases	324	310	304	306	324	0·94	0·34
	Person-years	61,127	59,240	58,550	59,749	64,893		
	HR and 95 % CI	1	1·03 0·88, 1·21	1·05 0·89, 1·23	1·03 0·88, 1·22	1·00 0·85, 1·19		
Yes	Cases	443	416	442	437	432	0·95	
	Person-years	81,112	82,496	82,730	81,257	76,016		
	HR and 95 % CI	1	0·92 0·81, 1·06	0·96 0·84, 1·11	0·96 0·83, 1·10	0·98 0·85, 1·14		
Smoking at baseline								
Current	Cases	146	105	98	86	104	0·06	0·11
	Person-years	12,493	10,006	9193	9572	10,757		
	HR and 95 % CI	1	0·90 0·69, 1·16	0·90 0·69, 1·18	0·74 0·56, 0·98	0·82 0·63, 1·06		

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Table 3. (*Continued*)

Subgroup		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}†	$P_{interaction}$‡
Former	Cases	340	335	299	295	269	0.07	0.35
	Person-years	66,693	57,929	52,274	46,356	42,730		
	HR and 95 % CI	1	1.12 0.96, 1.30	1.09 0.93, 1.28	1.17 0.99, 1.38	1.15 0.97, 1.37		
Never	Cases	281	286	349	362	383	0.99	
	Person-years	63,053	73,801	79,815	85,078	87,422		
	HR and 95 % CI	1	0.85 0.72, 1.01	0.95 0.81, 1.12	0.94 0.79, 1.11	0.96 0.81, 1.13		
Alcohol consumption								
0 g/d	Cases	38	68	103	164	218	0.30	
	Person-years	8454	15,952	23,956	34,608	46,554		
	HR and 95 % CI	1	0.98 0.66, 1.47	0.98 0.67, 1.44	1.08 0.76, 1.55	1.10 0.78, 1.57		
0·1, 4·9 g/d	Cases	133	165	245	269	272	0.31	
	Person-years	18,459	34,639	44,934	48,683	48,770		
	HR and 95 % CI	1	0.68 0.54, 0.85	0.80 0.65, 0.99	0.81 0.65, 0.99	0.78 0.63, 0.96		
≥5 g/d	Cases	596	493	398	310	266	0.90	
	Person-years	115,325	91,145	72,390	57,715	45,585		
	HR and 95 % CI	1	1.05 0.93, 1.18	1.04 0.91, 1.18	0.97 0.84, 1.11	1.01 0.87, 1.17		

* Models adjusted for age, smoking (Comprehensive Smoking Index), physical activity (metabolic equivalent of task (MET) quintiles), alcohol (g/d: 0, 0.1–4.9, 5–14.9, 15–29, 30+), occupation (dentist v. non-dentist), race (White/Black/Asian/Other) and BMI (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m²), except for the stratified variable.
† P-value when each quintile was assigned the median value and treated as a continuous variable.
‡ P-value for the interaction term between an indicator variable for stratifying term and the continuous variable for dietary pattern (that was used for test of trend).

periodontitis, overall and among non-smokers (Figs. 1 and 2). Obese individuals with the highest EDIP scores had significantly higher risk of periodontal disease.

Results among obese non-smokers remained similar through multiple sensitivity analyses (online Supplementary Table S2). First, we re-did the BMI-stratified analysis adjusting for continuous BMI (model B), and the results remained similar (HR 1·39, 95 % CI 0·99, 1·97, P-value for trend = 0·03). Then, we evaluated if diabetes could mediate the relationship between inflammatory diet and periodontitis incidence. The relationship between diabetes and periodontal disease is complex and often described as 'bidirectional'[30,31]. In addition, proinflammatory diet is reported to be associated with increased risk of diabetes[32]; hence, diabetes could be a mediator. We re-did the analysis adjusting for incident diabetes during follow-up (model C), and the association was slightly attenuated (HR 1·35, 95 % CI 0·96, 1·91, P-value for trend = 0·05). In addition, we conducted a separate analysis where we censored individuals when they reported diabetes diagnosis during follow-up (model D), and the results remained significant (HR 1·38, 95 % CI 0·96, 1·99, P-value for trend = 0·03). We also did the analysis excluding those who had less than seventeen teeth at baseline (model E), and the association was similar (HR 1·41, 95 % CI 0·99, 2·01, P-value for trend = 0·03). In addition, we evaluated potential confounding by nutritional supplements, including multi-vitamins, vitamin D, fish oil, cod liver and dehydroepiandrosterone (model F), and the results were similar. We also adjusted for medications that could downgrade systemic inflammation, including aspirin, acetaminophen, non-steroidal anti-inflammatory drugs and lipid lowering drugs[33], and the results remained similar. Furthermore, we included medications and nutritional supplements in the models (model H), and that did not significantly change the results. Also, we conducted the analysis excluding participants who reported signs of cognitive impairment during follow-up (model I)[34]. Cognitive impairment was defined by answering 'yes' to any of the following questions: 'do you have trouble remembering things from one second to the next?', 'do you have any difficulty in understanding or following spoken instructions?', 'do you have more trouble than usual following a group conversation or a plot in a TV programme due to your memory?' or 'do you have trouble finding you way around familiar streets?'. The association remained similar (HR 1·42, 95 % CI 0·97, 2·07, P-value for trend <0·05). We also did the analysis excluding those with BMI ≥ 35 kg/m² (model J), and that attenuated the results (HR 1·28, 95 % CI 0·88, 1·86, P-value for trend = 0·11). We also evaluated the association after censoring individuals who had major health condition, MI, stroke, cancer or coronary artery surgery during the follow-up, as those events may independently modify the exposure and/or the risk of the outcome (model K), and the results were attenuated (HR 1·33, 95 % CI 0·93, 1·91, P-value for trend = 0·10). We evaluated the association among former smokers at baseline only (model L, HR 1·51, 95 % CI 0·95, 2·39, P-value for trend = 0·05), and among never smokers at baseline only (model M, HR 1·26, 95 % CI 0·73, 2·19, P-value for trend = 0·31), and the association was attenuated but remained in the same direction.

Table 4. Multi-variate association among non-smokers (excluding current smokers at baseline) between quintiles of empirical dietary inflammatory pattern (EDIP) and periodontal disease within subgroups* (Hazard ratios (HR) and 95 % confidence intervals)

Subgroup		Quintile 1	Quintile 2		Quintile 3		Quintile 4		Quintile 5		P_{trend}†	$P_{interaction}$‡
BMI (kg/m²)												
18·5–29·9	Cases/person-years	568/117,918	552/118,667		582/118,546		555/115,463		524/108,331		0·83	0·07 (obese v. non-obese)
	HR and 95 % CI	1	0·96	0·85, 1·08	1·01	0·89, 1·14	0·99	0·87, 1·12	1·01	0·88, 1·14		
≥30	Cases/person-years	53/11,465	68/12,625		64/12,993		98/15,517		127/21,343		0·03	
	HR and 95 % CI	1	1·19	0·82, 1·72	1·07	0·73, 1·57	1·45	1·02, 2·07	1·39	0·98, 1·96		
Age (years)												
<65	Cases/person-years	380/84,956	338/78,426		354/76,571		346/77,922		397/85,600		0·41	0·55
	HR and 95 % CI	1	0·99	0·85, 1·14	1·06	0·91, 1·23	1·02	0·87, 1·19	1·06	0·91, 1·24		
≥65	Cases/person-years	241/44790	283/53304		294/55518		311/53512		255/44552		0·80	
	HR and 95 % CI	1	0·98	0·82, 1·16	0·97	0·81, 1·16	1·05	0·87, 1·25	1·00	0·83, 1·20		
Physical activity												
<Median	Cases/person-years	283/55,618	290/59,700		327/63,734		354/65,808		386/68,594		0·11	0·15
	HR and 95 % CI	1	0·97	0·82, 1·15	1·03	0·87, 1·21	1·07	0·91, 1·27	1·11	0·94, 1·31		
≥Median	Cases/person-years	338/74,129	331/72,031		321/68,354		303/65,626		266/61,559		0·57	
	HR and 95 % CI	1	0·99	0·85, 1·16	1·00	0·85, 1·17	0·99	0·84, 1·17	0·94	0·79, 1·12		
Diabetes												
No	Cases/person-years	608/127,003	589/127,693		622/127,195		627/125,801		616/123,172		0·38	0·68
	HR and 95 % CI	1	0·96	0·85, 1·08	1·01	0·90, 1·13	1·03	0·91, 1·15	1·03	0·92, 1·17		
Yes	Cases/person-years	13/2743	32/4037		26/4893		30/5633		36/6980		0·56	
	HR and 95 % CI	1	1·72	0·87, 3·38	1·04	0·50, 2·13	1·25	0·61, 2·55	1·07	0·53, 2·14		
Dentist												
No	Cases/person-years	266/55,442	264/54,662		264/54,521		270/55,741		283/59,986		0·60	0·25
	HR and 95 % CI	1	1·03	0·86, 1·22	1·05	0·88, 1·26	1·05	0·88, 1·26	1·04	0·87, 1·25		
Yes	Cases/person-years	355/74,304	357/77,068		384/77,567		387/75,692		369/70,166		0·52	
	HR and 95 % CI	1	0·96	0·83, 1·11	0·99	0·85, 1·16	1·02	0·88, 1·19	1·03	0·88, 1·21		
Dentist												
0 g/d	Cases/person-years	33/7615	61/14,996		97/22,875		154/33,291		196/44,585		0·48	0·26
	HR and 95 % CI	1	0·93	0·60, 1·42	0·96	0·64, 1·43	1·05	0·72, 1·54	1·04	0·71, 1·51		
0·1–4·9 g/d	Cases/person-years	103/16,784	140/32,380		218/42,734		247/46,156		239/45,662		0·98	
	HR and 95 % CI	1	0·71	0·55, 0·91	0·84	0·66, 1·06	0·89	0·71, 1·13	0·85	0·68, 1·08		
≥5 g/d	Cases/person-years	485/10,5348	420/84,354		333/66,480		256/51,987		217/39,905		0·59	
	HR and 95 % CI	1	1·07	0·94, 1·22	1·05	0·91, 1·21	0·99	0·85, 1·16	1·07	0·91, 1·26		

* Models adjusted for age, smoking (Comprehensive Smoking Index), physical activity (metabolic equivalent of task (MET) quintiles), alcohol (g/d: 0, 0.1–4.9, 5–14.9, 15–29, 30+), occupation (dentist v. non-dentist), race (White/Black/Asian/Other) and BMI (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m²), except for the stratified variable.
† P-value when each quintile was assigned the median value and treated as a continuous variable.
‡ P-value for the interaction term between an indicator variable for the stratifying term and the continuous variable for dietary pattern (that was used for test of trend).
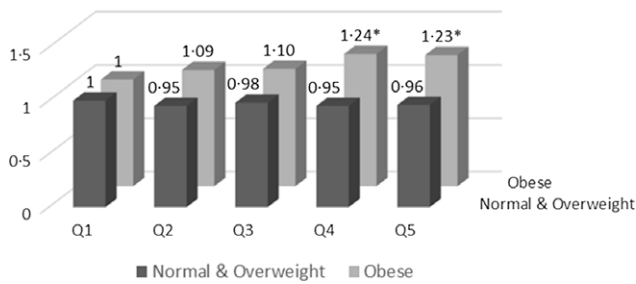
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Fig. 1. Multi-variable hazard ratio (HR) for periodontal disease by joint classification of empirical dietary inflammatory pattern (EDIP) and BMI categories.
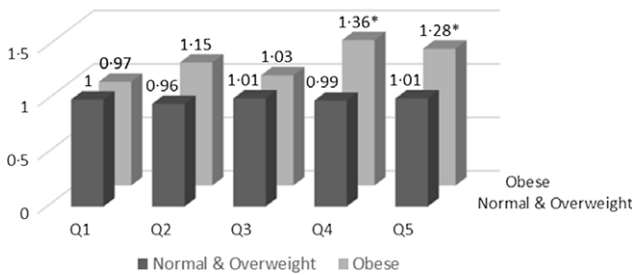

Fig. 2. Multi-variable hazard ratio (HR) for periodontal disease by joint classification of empirical dietary inflammatory pattern (EDIP) and BMI categories, excluding current smokers at baseline. Adjusted for age, smoking (Comprehensive Smoking Index), physical activity (metabolic equivalent of task (MET) quintiles), alcohol (g/d: 0, 0·1–4·9, 5–14·9, 15–29, 30+), occupation (dentist v. non-dentist) and race (White/Black/Asian/Other). *P-value < 0·05.

Discussion

We used EDIP as an RRR-derived dietary index in a large cohort of men with 24 years of follow-up to examine the empirical cumulative inflammatory impact of diet on incidence of periodontal disease. The results showed no overall association between EDIP scores and periodontitis. Subgroup analyses suggested a small non-significant elevated risk of periodontitis among obese men with higher EDIP scores. We performed a secondary analysis among non-smokers during the follow-up and observed a statistically significant association between EDIP and incidence of periodontitis among obese non-smokers.

EDIP scores were weighted averages of the pro- and anti-inflammatory food groups that maximally explained the variability in IL-6, C-reactive protein and TNF-α receptor 2 inflammatory mediators. To our knowledge, this is the first study that primarily investigated the association between the systemic inflammatory impact of diet and incidence of periodontitis. Although a few studies have prospectively investigated the relationship between some of the food groups that composed of EDIP and periodontitis as an outcome[20,35–38], comparing our RRR pattern approach with the 'single food/nutrient' approach may not be appropriate, due to the distinct methodological differences between the two methods. For instance, alcohol is an anti-inflammatory component of EDIP and hence could be viewed as being protective against periodontal disease. However, consumption of alcohol has been associated with increased risk of periodontitis, most likely through other mechanisms other than systemic

inflammation[20,36], and we addressed this issue by controlling for the cumulative alcohol intake in the adjusted models. A finding that is more analogous to the current study is the positive association we observed in another analysis between the principal component analysis-derived Western dietary pattern, which was high in processed meat, red meat, butter, high-fat dairy products, eggs and refined grains, and periodontal disease that was limited to obese[39]. Although the Western pattern was not derived using inflammatory mediators, it has repeatedly been associated with systemic inflammation[40–42]; hence, we previously hypothesised that the apparent impact in obese could be due to modification of systemic inflammation.

Our current results show no indication of an overall association between EDIP and periodontitis, suggesting that the inflammatory aspects of diet may not have a significant impact on periodontitis risk. Nevertheless, this null association between EDIP and periodontitis in the current study could alternatively be attributable to methodological factors. First, inherent to dietary pattern analysis is the potential dilution of some components' effects, as foods and nutrients that compose the pattern do have the biological potential to either embellish or abolish each other's impact[43]. For example, Ng et al. recently reported that higher consumption of coffee was associated with a lower risk of periodontal bone loss over the follow-up period of their study[35]. The influence of coffee as an anti-inflammatory component of EDIP could have been weakened by other components of the index either through systemic inflammation or through other mechanisms. Second, the incidence of periodontitis in our study was defined by answering 'yes' to the question 'have you been professionally diagnosed with periodontal disease with bone loss?' in the biennial questionnaire. Self-reported periodontal disease was evaluated in a subsample of the HPFS and showed appropriate validity. The positive predictive value among the dentists in HPFS was 0·76, and the negative predictive value was 0·74. For non-dentists, the positive predictive value was 0·83 and the negative predictive value was 0·69, making the method a suitable proxy and a valid 'endpoint' in this cohort[16,17]. Clinically, periodontal tissue breakdown is assessed based on a continuum of measures in addition to many signs and symptoms that determine periodontitis case diagnosis at an individual-patient level; the extent, rate and risk of future disease are evaluated to diagnose periodontitis stage and grade[44]. However, there is a lack of consensus of what determines a periodontitis case at the population level[45,46]. Although several associations with periodontal disease have been documented in this cohort[25,38,47,48], it is possible that the case ascertainment method in the present study may not have been sensitive to detect a potential impact of inflammatory diet on periodontal tissue.

Our results suggest that BMI, mainly obesity, may act as an effect modifier, rather than a mediator or a confounder. Obese individuals in the highest quintile of EDIP had a higher risk of periodontitis compared with the lowest quintile, but the association was only statistically significant after exclusions of current smokers at baseline. Smoking is the most important environmental risk factor of periodontitis[49], with the population attributable risk of periodontitis due to smoking estimated to be up to and even more than 50 %, depending on the periodontitis case

definition and participants' age[50–52], our secondary analysis among non-smokers suggests that the prominent deleterious effect of smoking on periodontal health could mask other risk factors, and hence the observed relationship in our study in obese individuals was definite only among non-smokers. Recently, Jauhiainen *et al.* prospectively investigated the association between diet quality, using the Baltic Sea Diet Score and the Recommended Finnish Diet Score, and periodontal disease over 11 years of follow-up[53]. They found a stronger impact of poor diet among the non-smokers.

The longitudinal prospective association between systemic inflammation and periodontal disease progression has been reported recently by Pink *et al.*[10]. They found a positive association between baseline measures of fibrinogen and leucocytes as markers of systemic inflammation and periodontal tissue loss over the 11-year follow-up period of the study[10]. As obesity is associated with 'metainflammation', a state of low-grade chronic systemic inflammation orchestrated by host cells in response to excessive energy and nutrients intake[54], it is plausible that the harmful inflammatory impact of diet on the periodontium is mainly through exacerbation of this 'baseline' metainflammation state; hence, the observed association in our study was limited to obese individuals and was not observed in other subgroups. Another potential mechanism by which proinflammatory diet may attribute to the pathogenesis of periodontal disease is mediated by diabetes. An RRR-derived inflammatory dietary pattern has been previously associated with increased risk of diabetes[32]. Also, the association between EDIP and periodontitis among obese non-smokers was attenuated when we adjusted for incidence diabetes in the model, which suggests that among those who reported diabetes during follow-up, diabetes could have acted as a mediator in the relationship between EDIP and periodontitis. However, in a separate analysis where we censored men if they reported diabetes diagnosis during follow-up, the observed association between EDIP and periodontitis remained significant, which insinuates that the relationship could be related to other inflammatory mechanisms other than diabetes. On the other hand, as obese are at higher risk of diabetes[55], we cannot eliminate the possibility that undiagnosed pre-diabetes insulin resistance and glucose intolerance may have mediated the association between EDIP and periodontitis in the obese–non-smokers subgroup. There is a strong evidence that insulin resistance does exaggerate the adverse metabolic effects of diet[56–59]. In addition, pre-diabetes and insulin resistance have been associated with increased periodontal disease[30,60–63].

Our study has several strengths. The study population is a large cohort of highly educated and motivated participants, which minimises information bias. The prospective panel design of the study with the long follow-up time, and updated measures, does support better understanding of temporality and may aid in establishing causality. Our study however has several limitations. First, the study is observational in nature; hence, confounding cannot be ruled out. Another limitation is the self-reported data. However, the validity of self-administered FFQ and the self-reported periodontal disease have been evaluated. FFQ data showed reasonable correlations with diet records, and self-reported periodontal disease had acceptable positive and negative predictive values compared with intraoral radiographs[14–17]. It is expected however that some degree of misclassification occurred, which we assumed would be non-differential, and could have attenuated the results towards the null[64]. In addition, we used the cumulative average of EDIP scores, which in addition to the energy adjustment, mitigate the issue of measurement error. Furthermore, the study population is composed of health professional men, mainly of Caucasian descent; hence, the generalisability of the results may be limited. However, the homogeneity of the cohort improves the internal validity of the study as confounding by socio-economic and educational factors was inherently minimised. Furthermore, some EDIP components may appear contrary to the prevailing knowledge, for example, the positive association of tomatoes and the inverse association of pizza with concentrations of inflammatory markers. EDIP scores were developed using an empirical approach in which the combination of foods that maximally predicted concentrations of inflammatory biomarkers (IL-6, C-reactive protein and TNF-α receptor 2) were selected in an unbiased and unsupervised manner. Fresh tomatoes have a low content of bioavailable lycopene which is a major anti-inflammatory nutrient, whereas cooked tomato paste (e.g. in pizza) contains 2–5 times higher concentrations of bioavailable lycopene[65,66]. Also, if fresh tomatoes are incorporated in salads that include sources of fats like olive oil or avocado, this would make the lycopene more bioavailable. However, a limitation of FFQ is that they do not generally assess the way foods are prepared, combined or eaten. Also, not all EDIP components are universally confirmed as pro- or anti-inflammatory. For instance, tomatoes are positively associated with inflammation in EDIP. Yet, studies have found either no association[67,68] or inverse association between tomatoes and inflammatory markers[69,70].

In conclusion, we observed no overall association between EDIP scores and the risk of self-reported periodontal disease assessed using questionnaires in this population over the study period. However, only among obese non-smokers, those with higher EDIP scores had a significantly higher risk of periodontal disease compared with those with lower scores. Findings of the current study suggest a potential role of diet in modifying the risk of periodontitis, through systemic inflammation, in obese non-smokers. Future research could focus on using clinical periodontal measures (such as probing depth and periodontal attachment loss) to explore if inflammatory dietary pattern could influence the risk in other subgroups and to explore the specific components of diets that are more germane to periodontal health.

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Supplementary material

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References

1. Eke PI, Dye BA, Wei L, *et al.* (2015) Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *J Periodontol* **86**, 611–622.
2. (1999) The pathogenesis of periodontal diseases. *J Periodontol* **70**, 457–470.
3. Joshipura KJ & Andriankaja OM (2016) Modifiable systemic factors for periodontal disease prevention and management. In *Periodontal Disease: Diagnosis, Management Options and Clinical Features*, pp. 47–85 [E Wallace, editor] New York: Nova Science Publishers.
4. Loos BG & Van Dyke TE (2020) The role of inflammation and genetics in periodontal disease. *Periodontol 2000* **83**, 26–39.
5. Loos BG, Craandijk J, Hoek FJ, *et al.* (2000) Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontol* **71**, 1528–1534.
6. Schwahn C, Volzke H, Robinson DM, *et al.* (2004) Periodontal disease, but not edentulism, is independently associated with increased plasma fibrinogen levels. Results from a population-based study. *Thromb Haemost* **92**, 244–252.
7. Tonetti MS, D'Aiuto F, Nibali L, *et al.* (2007) Treatment of periodontitis and endothelial function. *N Engl J Med* **356**, 911–920.
8. Correa FO, Goncalves D, Figueredo CM, *et al.* (2010) Effect of periodontal treatment on metabolic control, systemic inflammation and cytokines in patients with type 2 diabetes. *J Clin Periodontol* **37**, 53–58.
9. Gocke C, Holtfreter B, Meisel P, *et al.* (2014) Abdominal obesity modifies long-term associations between periodontitis and markers of systemic inflammation. *Atherosclerosis* **235**, 351–357.
10. Pink C, Kocher T, Meisel P, *et al.* (2015) Longitudinal effects of systemic inflammation markers on periodontitis. *J Clin Periodontol* **42**, 988–997.
11. Chapple IL (2009) Potential mechanisms underpinning the nutritional modulation of periodontal inflammation. *J Am Dent Assoc* **140**, 178–184.
12. Tabung FK, Smith-Warner SA, Chavarro JE, *et al.* (2016) Development and validation of an empirical dietary inflammatory index. *J Nutr* **146**, 1560–1570.
13. Hoffmann K, Schulze MB, Schienkiewitz A, *et al.* (2004) Application of a new statistical method to derive dietary patterns in nutritional epidemiology. *Am J Epidemiol* **159**, 935–944.
14. Willett W (2012) *Nutritional Epidemiology*, 3rd ed., *Monographs in Epidemiology and Biostatistics*. Oxford; New York: Oxford University Press.
15. Rimm EB, Giovannucci EL, Stampfer MJ, *et al.* (1992) Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* **135**, 1114–1126; discussion 1127–1136.
16. Joshipura KJ, Pitiphat W & Douglass CW (2002) Validation of self-reported periodontal measures among health professionals. *J Public Health Dent* **62**, 115–121.
17. Joshipura KJ, Douglass CW, Garcia RI, *et al.* (1996) Validity of a self-reported periodontal disease measure. *J Public Health Dent* **56**, 205–212.
18. Aroke D, Folefac E, Shi N, *et al.* (2020) Inflammatory and Insulinemic dietary patterns: influence on circulating biomarkers and prostate cancer risk. *Cancer Prev Res (Phila)* **13**, 841–852.
19. Tabung FK, Giovannucci EL, Giulianini F, *et al.* (2018) An empirical dietary inflammatory pattern score is associated with circulating inflammatory biomarkers in a multi-ethnic population of postmenopausal women in the United States. *J Nut* **148**, 771–780.
20. Pitiphat W, Merchant AT, Rimm EB, *et al.* (2003) Alcohol consumption increases periodontitis risk. *J Dent Res* **82**, 509–513.
21. Albandar JM (2005) Epidemiology and risk factors of periodontal diseases. *Dent Clin North Am* **49**, 517–532, v–vi.
22. Al-Zahrani MS, Borawski EA & Bissada NF (2005) Increased physical activity reduces prevalence of periodontitis. *J Dent* **33**, 703–710.
23. Al-Zahrani MS, Bissada NF & Borawskit EA (2003) Obesity and periodontal disease in young, middle-aged, and older adults. *J Periodontol* **74**, 610–615.
24. Al-Zahrani MS, Borawski EA & Bissada NF (2005) Periodontitis and three health-enhancing behaviors: maintaining normal weight, engaging in recommended level of exercise, and consuming a high-quality diet. *J Periodontol* **76**, 1362–1366.
25. Jimenez M, Hu FB, Marino M, *et al.* (2012) Prospective associations between measures of adiposity and periodontal disease. *Obesity (Silver Spring)* **20**, 1718–1725.
26. Dietrich T & Hoffmann K (2004) A comprehensive index for the modeling of smoking history in periodontal research. *J Dent Res* **83**, 859–863.
27. Leffondre K, Abrahamowicz M, Siemiatycki J, *et al.* (2002) Modeling smoking history: a comparison of different approaches. *Am J Epidemiol* **156**, 813–823.
28. Hu FB, Leitzmann MF, Stampfer MJ, *et al.* (2001) Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med* **161**, 1542–1548.
29. Warnakulasuriya S, Dietrich T, Bornstein MM, *et al.* (2010) Oral health risks of tobacco use and effects of cessation. *Int Dent J* **60**, 7–30.
30. D'Aiuto F, Gable D, Syed Z, *et al.* (2017) Evidence summary: the relationship between oral diseases and diabetes. *Br Dent J* **222**, 944–948.
31. Taylor GW (2001) Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. *Ann Periodontol* **6**, 99–112.
32. Schulze MB, Hoffmann K, Manson JE, *et al.* (2005) Dietary pattern, inflammation, and incidence of type 2 diabetes in women. *Am J Clin Nutr* **82**, 675–684; quiz 714–675.

33. Andriankaja OM, Jimenez JJ, Munoz-Torres FJ, *et al.* (2015) Lipid-Lowering agents use and systemic and oral inflammation in overweight or obese adult Puerto Ricans: the San Juan Overweight Adults Longitudinal Study (SOALS). *J Clin Periodontol* **42**, 1090–1096.

34. Fondell E, Townsend MK, Unger LD, *et al.* (2018) Physical activity across adulthood and subjective cognitive function in older men. *Eur J Epidemiol* **33**, 79–87.

35. Ng N, Kaye EK & Garcia RI (2014) Coffee consumption and periodontal disease in males. *J Periodontol* **85**, 1042–1049.

36. Wagner MC, Haas AN, Oppermann RV, *et al.* (2017) Effect of alcohol consumption on clinical attachment loss progression in an Urban population from South Brazil: a 5-year longitudinal study. *J Periodontol* **88**, 1271–1280.

37. Iwasaki M, Yoshihara A, Moynihan P, *et al.* (2010) Longitudinal relationship between dietary ω-3 fatty acids and periodontal disease. *Nutrition* **26**, 1105–1109.

38. Merchant AT, Pitiphat W, Franz M, *et al.* (2006) Whole-Grain and fiber intakes and periodontitis risk in men. *Am J Clin Nutr* **83**, 1395–1400.

39. Alhassani AA, Hu FB, Li Y, *et al.* (2021) The associations between major dietary patterns and risk of periodontitis. *J Clin Periodontol* **48**, 2–14.

40. Barbaresko J, Koch M, Schulze MB, *et al.* (2013) Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review. *Nutr Rev* **71**, 511–527.

41. Esmaillzadeh A, Kimiagar M, Mehrabi Y, *et al.* (2007) Dietary patterns and markers of systemic inflammation among Iranian women. *J Nutr* **137**, 992–998.

42. Lopez-Garcia E, Schulze MB, Fung TT, *et al.* (2004) Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr* **80**, 1029–1035.

43. Hu FB (2002) Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol* **13**, 3–9.

44. Caton JG, Armitage G, Berglundh T, *et al.* (2018) A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification. *J Clin Periodontol* **45**, Suppl. 20, S1–S8.

45. Kingman A, Susin C & Albandar JM (2008) Effect of partial recording protocols on severity estimates of periodontal disease. *J Clin Periodontol* **35**, 659–667.

46. Holtfreter B, Albandar JM, Dietrich T, *et al.* (2015) Standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies: proposed standards from the Joint EU/USA Periodontal Epidemiology Working Group. *J Clin Periodontol* **42**, 407–412.

47. Jimenez M, Giovannucci E, Krall Kaye E, *et al.* (2014) Predicted vitamin D status and incidence of tooth loss and periodontitis. *Public Health Nutr* **17**, 844–852.

48. Jimenez M, Hu FB, Marino M, *et al.* (2012) Type 2 diabetes mellitus and 20 year incidence of periodontitis and tooth loss. *Diabetes Res Clin Pract* **98**, 494–500.

49. Johannsen A, Susin C & Gustafsson A (2014) Smoking and inflammation: evidence for a synergistic role in chronic disease. *Periodontology* **64**, 111–126.

50. Hyman JJ & Reid BC (2003) Epidemiologic risk factors for periodontal attachment loss among adults in the United States. *J Clin Periodontol* **30**, 230–237.

51. Haber J, Wattles J, Crowley M, *et al.* (1993) Evidence for cigarette smoking as a major risk factor for periodontitis. *J Periodontol* **64**, 16–23.

52. Tomar SL & Asma S (2000) Smoking-attributable periodontitis in the United States: findings From NHANES III. *J Periodontol* **71**, 743–751.

53. Jauhiainen LM, Ylostalo PV, Knuuttila M, *et al.* (2020) Poor diet predicts periodontal disease development in 11-year follow-up study. *Community Dent Oral Epidemiol* **48**, 143–151.

54. Gregor MF & Hotamisligil GS (2011) Inflammatory mechanisms in obesity. *Annu Rev Immunol* **29**, 415–445.

55. Koh-Banerjee P, Wang Y, Hu FB, *et al.* (2004) Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. *Am J Epidemiol* **159**, 1150–1159.

56. Liu S, Willett WC, Stampfer MJ, *et al.* (2000) A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* **71**, 1455–1461.

57. Miller JC (1994) Importance of glycemic index in diabetes. *Am J Clin Nutr* **59**, 747s–752s.

58. Jeppesen J, Schaaf P, Jones C, *et al.* (1997) Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. *Am J Clin Nutr* **65**, 1027–1033.

59. Tabung FK, Wang W, Fung TT, *et al.* (2016) Development and validation of empirical indices to assess the insulinaemic potential of diet and lifestyle. *Br J Nutr* **116**, 1787–1798.

60. Timonen P, Saxlin T, Knuuttila M, *et al.* (2013) Role of insulin sensitivity and beta cell function in the development of periodontal disease in adults without diabetes. *J Clin Periodontol* **40**, 1079–1086.

61. Andriankaja OM & Joshipura K (2014) Potential association between prediabetic conditions and gingival and/or periodontal inflammation. *J Diabetes Invest* **5**, 108–114.

62. Benguigui C, Bongard V, Ruidavets JB, *et al.* (2010) Metabolic syndrome, insulin resistance, and periodontitis: a cross-sectional study in a middle-aged French population. *J Clin Periodontol* **37**, 601–608.

63. Islam SK, Seo M, Lee YS, *et al.* (2015) Association of periodontitis with insulin resistance, beta-cell function, and impaired fasting glucose before onset of diabetes. *Endocr J* **62**, 981–989.

64. Rothman KJ, Greenland S & Lash TL (2008) Validity in epidemiologic studies. *In Modern Epidemiology*, 3rd ed., pp. 128–147 [KJ Rothman, S Greenland and TL Lash, editors]. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.

65. Gartner C, Stahl W & Sies H (1997) Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *Am J Clin Nutr* **66**, 116–122.

66. Marcotorchino J, Romier B, Gouranton E, *et al.* (2012) Lycopene attenuates LPS-induced TNF-alpha secretion in macrophages and inflammatory markers in adipocytes exposed to macrophage-conditioned media. *Mol Nutr Food Res* **56**, 725–732.

67. Blum A, Monir M, Khazim K, *et al.* (2007) Tomato-rich (Mediterranean) diet does not modify inflammatory markers. *Clin Invest Med* **30**, E70–E74.

68. Markovits N, Ben Amotz A & Levy Y (2009) The effect of tomato-derived lycopene on low carotenoids and enhanced systemic inflammation and oxidation in severe obesity. *Isr Med Assoc J* **11**, 598–601.

69. Li YF, Chang YY, Huang HC, *et al.* (2015) Tomato juice supplementation in young women reduces inflammatory adipokine levels independently of body fat reduction. *Nutrition* **31**, 691–696.

70. Mohri S, Takahashi H, Sakai M, *et al.* (2018) Wide-range screening of anti-inflammatory compounds in tomato using LC-MS and elucidating the mechanism of their functions. *PLOS ONE* **13**, e0191203.