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Dietary inflammatory index in relation to salivary cytokine concentrations and periodontitis: A cross-sectional analysis

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Abstract

Aim: To examine the associations of dietary inflammatory index (DII) with salivary cytokine concentrations and periodontitis after controlling for body mass index (BMI), socio-demographic factors and lifestyle.

Materials and Methods: Subgroups from two Finnish surveys, DILGOM 2007 and Health 2000, were included (total $n = 727$). The DII scores were calculated based on a food frequency questionnaire. Periodontal status was assessed with a cumulative risk score in DILGOM 2007 and by pocket depth measurement in Health 2000. From saliva, interleukin (IL)-1β, IL-1 receptor antagonist, IL-6, IL-8, IL-10 and tumour necrosis factor (TNF)-α concentrations were measured.

Results: The DII scores did not differ between non-periodontitis and periodontitis participants in pairwise comparison. After adjusting for energy intake, periodontal status, BMI, age, education level, smoking habit and physical activity, DII was not associated with salivary cytokine concentrations. After adjusting for salivary cytokine levels and other confounding factors, DII was associated with periodontitis in the Health 2000 subgroup but not in the DILGOM 2007 subgroup.

Conclusions: The current data support the evidence that diet is not associated with salivary cytokine levels but may be associated with periodontitis. The association observed between diet and periodontitis is related to factors other than diet-dependent inflammatory tendency in the oral cavity.

KEYWORDS
cytokines, diet, inflammation, obesity, periodontitis

Clinical Relevance

Scientific rationale for study: Diet is a common modulator of systemic inflammation. There is a link between periodontitis and proinflammatory diet, suggesting that the inflammatory potential of diet could be a risk factor for periodontitis.

Principal findings: Periodontitis, but not salivary cytokines, is associated with diet.

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Practical implications: Inflammatory potential of diet may have independent influence on periodontal inflammation, suggesting that the evaluation of dietary habits would be of benefit as part of patient examination.

1 | INTRODUCTION

Periodontitis is a multifactorial inflammatory disease of tooth-supporting tissues, initiated by the interplay between dysbiotic biofilm and host response (Könönen et al., 2019). Periodontal tissue destruction is driven by chronic inflammatory reactions of the host accompanied by excessive production of cytokines such as interleukin (IL)-1β, tumour necrosis factor-α (TNF-α) and IL-6, which can be detected in the saliva (Jaedicke et al., 2016). On the other hand, systemic inflammatory conditions, such as obesity or inflammatory diet, may increase the risk of periodontitis (Ganesan et al., 2021; Woelber et al., 2019).

Diet modulates systemic inflammation via its anti- and pro-inflammatory components that include macro and micronutrients as well as food components (Minihane et al., 2015). To quantify the inflammatory property of diet—distinguishing its anti- and pro-inflammatory components—a literature-derived scoring system, namely the dietary inflammatory index (DII), was developed (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014). The association between DII and the inflammatory markers in serum has already been demonstrated (Millar et al., 2022; Phillips et al., 2018). Moreover, the National Health and Nutrition Examination Survey (NHANES) 2011–2012 and 2013–2014 ($n = 7081$) found an association between DII scores and periodontal health (Li et al., 2021). There are a few other studies describing the impact of diet on periodontal status or diseases (Costa et al., 2022; Woelber et al., 2019). Diet and other lifestyle factors, such as physical activity, of the obese individuals differ from those of healthy weight individuals, with the obese having more pro-inflammatory diet and less physical activity (Shi et al., 2023). A recent meta-analysis containing 37 observational studies also confirmed a positive association between obesity and periodontitis (Kim et al., 2022). Interestingly, there are also studies showing strong associations between Western-type diet and periodontitis only in obese men (Alhassani et al., 2021), indicating that obesity can be one explanatory factor in the association between diet and periodontitis. In obesity, adipose tissue dysfunction causes changes in the number and function of a variety of immune cells and leads to the secretion of pro-inflammatory cytokines (Trim et al., 2018). This induces low-grade systemic inflammation, which may expose individuals to systemic diseases and periodontitis (Pamuk & Kantarci, 2022).

There is growing evidence on the effect of diet on inflammatory markers in serum (Minihane et al., 2015). To date, however, the potential link between diet and salivary inflammatory markers has been investigated only in one cross-sectional study, which included 90 young female adults (Attlee et al., 2019). In line with the current evidence, it is expected that systemic low-grade inflammation caused by a pro-inflammatory diet affects salivary inflammatory status, creating a risk for developing periodontitis. We hypothesized that elevated DII scores due to pro-inflammatory diet components are associated with increased salivary cytokine concentrations and periodontitis. Our objective was therefore to examine the independent associations of DII with salivary cytokine concentrations and periodontitis after controlling for body mass index (BMI) and other possible confounding factors.

2 | MATERIALS AND METHODS

2.1 | Study population

The population of this cross-sectional study consisted of participants from two Finnish surveys conducted and coordinated by the Finnish Institute for Health and Welfare (THL): the DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome 2007 (DILGOM 2007) study, and the Health 2000 (H2000) survey. Both studies were approved by the Ethical Committee of the Hospital District of Helsinki and Uusimaa, and written informed consent from each participant was obtained.

DILGOM 2007 was an extension of the population-based National FINRISK 2007 study conducted between January and March 2007 (Borodulin et al., 2018; Konttinen et al., 2018). All those who participated in FINRISK 2007 ($n = 6258$) were invited to DILGOM 2007, conducted 3 months later, and 5024 (84%) participated. In DILGOM 2007, paraffin-stimulated whole saliva samples were collected. For salivary cytokine analyses, subsamples of 287 participants with severe obesity (BMI ≥ 35 kg/m^2) were selected as cases and 293 participants with healthy weight (BMI 18.5–25 kg/m^2) as controls, resulting in a total of 580 participants. The cases and controls were matched for sex, age, and smoking status (current smoker vs. non-smoker). Exclusion criteria were diabetes, cardiovascular disease, cancer or medication for hypercholesterolemia.

H2000 was conducted in 2000–2001 (Heistaro, 2008). The main sample comprised 8028 participants aged 30 years or over from five geographical districts around university hospitals in Finland, from which 80 health centres (out of 249) were selected. Individual persons were then sampled from those districts. Clinical oral examination was accomplished for 6335 participants (Suominen-Taipale et al., 2008). Paraffin-stimulated whole saliva samples were collected in the southern district from 1294 participants (Könönen et al., 2007). For the present study, saliva samples of 165 participants were selected based on their periodontal status: 84 had probing pocket depth (PPD) ≥4 mm at 14 or more teeth (advanced periodontitis group), while 81 had all teeth with PPD <4 mm (non-periodontitis group) (Gursoy et al., 2010). From the 165 participants, those with no food frequency questionnaire (FFQ) data were excluded (7 non-periodontitis and 11 periodontitis participants), resulting finally in 147 participants.

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The socio-economic factors, age, smoking status, physical activity and general health status were recorded in DILGOM 2007 by a questionnaire and in H2000 by an interview. The education information was combined into a variable describing three levels of education: basic education, vocational education or higher education. For BMI calculations, height and weight were measured in a health examination. If data from the health examination were missing, self-reported height and weight were used. Physical activity was categorized according to leisure time activity into four groups: no physical activity, light activity (such as walking or cycling) of at least 4 h, physical exercise of at least 3 h or hard physical exercise (such as competitive sport activity) weekly.

2.2 | Assessment of dietary data

The habitual diet over the last 12 months was measured by the validated semi-quantitative FFQ (Kaartinen et al., 2012; Männistö et al., 1996). The FFQ covered the consumption of 131 food items recorded by nine frequency categories ranging from 'never or seldom' to 'at least six times a day'. The portion size was fixed for each food item or mixed dish (e.g., slice and glass). The FFQ was filled in DILGOM 2007 during the health examination and in H2000 by participants at home. The dietary data were converted into average daily food consumption and nutrient intake using the National Food Composition Database, Fineli, and the Finessi software of THL (Reinivuo et al., 2010).

2.3 | Dietary inflammatory index

The development and construct validation of DII have been described elsewhere (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014; Shivappa, Steck, Hurley, Hussey, Ma, et al., 2014; Tabung et al., 2015). In the calculation of DII, the intake of each food component was standardized against the world intake database, including 11 datasets representing a wide range of diets across diverse populations (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014). An *z*-score was created for each food component by subtracting the world standard mean from the actual food intake and dividing the difference by world reference standard deviation. To minimize the effect of right skewing, the *z*-score was converted to percentile scores. The percentile score was doubled and then '1' was subtracted to achieve a symmetric distribution with values centred on 0 (null) and bounded between −1 and +1. These centred percentiles were multiplied by the representative 'food parameter-specific inflammatory effect score' provided by Shivappa, Steck, Hurley, Hussey, and Hébert (2014). Thereafter, the food parameter-specific overall inflammatory effect scores were summed to create the overall DII scores for each individual. The theoretical range for DII scores, when all food components are included, is −8.87 to 7.98, representing maximally anti-inflammatory to maximally pro-inflammatory diet, respectively.

Recently, DII was used in a large cohort study, using the datasets from The European Investigation into Cancer and Nutrition (EPIC) study, with a few modifications (Agudo et al., 2018), which we used in our study as well. First, to avoid overestimation of the effect of total fat on inflammation, total fat intake was excluded from DII. Second, as the anti-inflammatory effect of alcohol has been shown only among moderate consumers (Avellone et al., 2006; Sierksma et al., 2002), the inflammatory weight for alcohol was set to zero for the participants consuming alcohol >40 g/day. Food components included and not included in DII calculations in the current study are presented in Table 1.

TABLE 1 Dietary components included and not included into dietary inflammatory index (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014) calculation.

Food components included	Food components not included
Alcohol, β-carotene, carbohydrate, cholesterol, energy, fibre, folic acid, green/black tea, iron, isoflavones, magnesium, monounsaturated fatty acids, niacin, n-3 fatty acids, n-6 fatty acids, protein, poly-unsaturated fatty acids, riboflavin, saturated fatty acids, selenium, thiamin, trans fats, vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, zinc	Anthocyanidins, caffeine, eugenol, flavan-3-ol, flavones, flavonols, flavonones, garlic, ginger, onion, pepper, rosemary, saffron, thyme/oregano, total fat, turmeric, thyme/oregano

2.4 | Periodontal status assessment

In DILGOM 2007, periodontal status was defined according to the cumulative risk score (CRS), which is a mathematical model to define the individual risk of having periodontitis (Gursoy et al., 2011). In CRS, the salivary concentrations of *Porphyromonas gingivalis* (a biomarker of infection), IL-1β (a biomarker of inflammation) and matrix metalloproteinase (MMP)-8 (a biomarker of enzymatic degradation) were divided into tertiles according to their concentrations. The individual's cumulative score was calculated by multiplying the three biomarkers' tertile values. According to this calculation, the individual's cumulative risk score can be 1, 2, 3, 4, 8, 9, 12, 18 or 27. Individuals were then divided into groups as follows: CRS I (the lowest risk of having periodontitis; cumulative score 1, 2, 3), CRS II (medium risk; cumulative scores 4, 8, 9) and CRS III (the highest risk; cumulative scores 12, 18, 27). The validity of CRS in the detection of moderate to severe periodontitis has been described previously (Gursoy et al., 2018; Salminen et al., 2014). In the present study, participants of DILGOM 2007 with CRS I are classified as not having periodontitis and those with CRS II or III are classified as having periodontitis.

In H2000, periodontal status was determined during the field stage of the study by five field teams, each including one dentist who made the clinical examinations (Suominen-Taipale et al., 2008). The periodontal pocket depth was measured from all teeth except the third molars and residual roots. The measurements were made

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at four points around each tooth: the distal angle, the midpoint of the buccal side, the midpoint of the oral side and the mesial angle. The deepest measurement from each tooth was registered and used to diagnose periodontitis as follows: 'no teeth with deepened periodontal pocket' indicating no periodontitis, and 'teeth with periodontal pocket of 4 mm or more' indicating periodontitis. The quality assurance of oral health examinations was evaluated by a reference dentist, who took parallel measurements of pocket depths at several visits to each field team. The agreement for pocket depth measurements between the reference dentist and the field dentist was 77% (κ-value .41). Also, repeated measurements for randomly selected participants were carried out by each field dentist, and the κ-value was .83.

2.5 | Cytokine and *P. gingivalis* measurements from salivary samples

Paraffin-stimulated saliva samples were stored at −70°C until laboratory analyses. Melted samples were centrifuged at

TABLE 2 Characteristic of two study populations according to their periodontal status.

	DILGOM 2007			H2000		
	Periodontitis	Non-periodontitis		Periodontitis	Non-periodontitis	
	n = 442	*n* = 138	*p*-Value	*n* = 73	*n* = 74	*p*-Value
Age, years, median (IQ)	58.0 (18)	57.0 (17)	.20[a]	49.4 (8)	48.2 (9)	.08[c]
Men, *n* (%)	154 [34.8]	42 [30.4]	.34[b]	43 [58.9]	26 [35.1]	**.01**[b]
Basic education, *n* (%)	136 [31.1]	43 [31.2]	.55[b]	25 [34.2]	9 [12.2]	**<.001**
BMI, median (IQ)	35.1 (14.6)	24.5 (13.8)	**.02**[a]	28.0 (6.1)	24.9 (5.5)	**<.001**[c]
Current smokers, *n* (%)	57 [12.9]	33 [23.9]	**.02**[b]	43 [58.9]	16 [21.6]	**<.001**[b]
Salivary cytokines (pg/mL), median (IQ)						
IL-1Ra	9870 (9040)	4020 (3370)	**<.001**[a]	NA	NA	
IL-6	3.3 (4.6)	3.9 (4.7)	.54[a]	2.0 (3.9)	2.4 (4.5)	.67[c]
TNF-α	10.3 (13.8)	22.4 (26.2)	**<.001**[a]	1.3 (2.4)	1.6 (2.6)	1.0[c]
IL-8	452 (450)	168 (122)	**<.001**[a]	NA	NA	
IL-10	1.5 (2.3)	4.8 (7.8)	**<.001**[a]	NA	NA	
IL-1β	103 (155)	13.3 (14.3)	**<.001**[a]	676 (439)	466 (353)	**<.001**[c]

Note: Basic education refers to participants without vocational or higher education. In DILGOM 2007: non-periodontitis includes participants with CRS I and periodontitis include participants with CRS II and CRS III. In H2000: non-periodontitis includes participants without deepened periodontal pockets and periodontitis include participants with periodontal pockets ≥4 mm. Significant association ($p < .05$) are bolded.
Abbreviations: BMI, body mass index; IL, interleukin; IQ, interquartile range; NA, not available; TNF, tumour necrosis factor.
[a]Mann–Whitney *U* test.
[b]Chi-square test.
[c]Wilcoxon signed-rank test.

TABLE 3 Dietary inflammatory index (DII) scores according to periodontitis in different DII tertiles.

	DILGOM 2007		H2000	
	Periodontitis *n* = 442	Non-periodontitis *n* = 138	Periodontitis *n* = 73	Non-periodontitis *n* = 74
Energy (kcal)[a]	2510 (955)	2450 (854)	2050 (1170)	1890 (842)
DII scores[a]	−3.6 (2.7)	−3.6 (2.6)	−2.1 (4.6)	−2.1 (3.7)
DII tertiles				
Tertile 1	−6.5 to −4.7	−6.2 to −4.7	−5.7 to −4.1	−6.1 to −4.0
Tertile 2	−4.7 to −3.1	−4.7 to −3.2	−3.7 to −1.9	−3.7 to −1.9
Tertile 3	−3.1 to 2.5	−3.1 to 2.5	−1.3 to 2.9	−1.7 to 3.2

[a]Values are mean (interquartile range). In DILGOM 2007: non-periodontitis includes participants with CRS I and periodontitis include participants with CRS II and CRS III. In H2000: non-periodontitis includes participants without deepened periodontal pockets and periodontitis include participants with periodontal pockets ≥4 mm.

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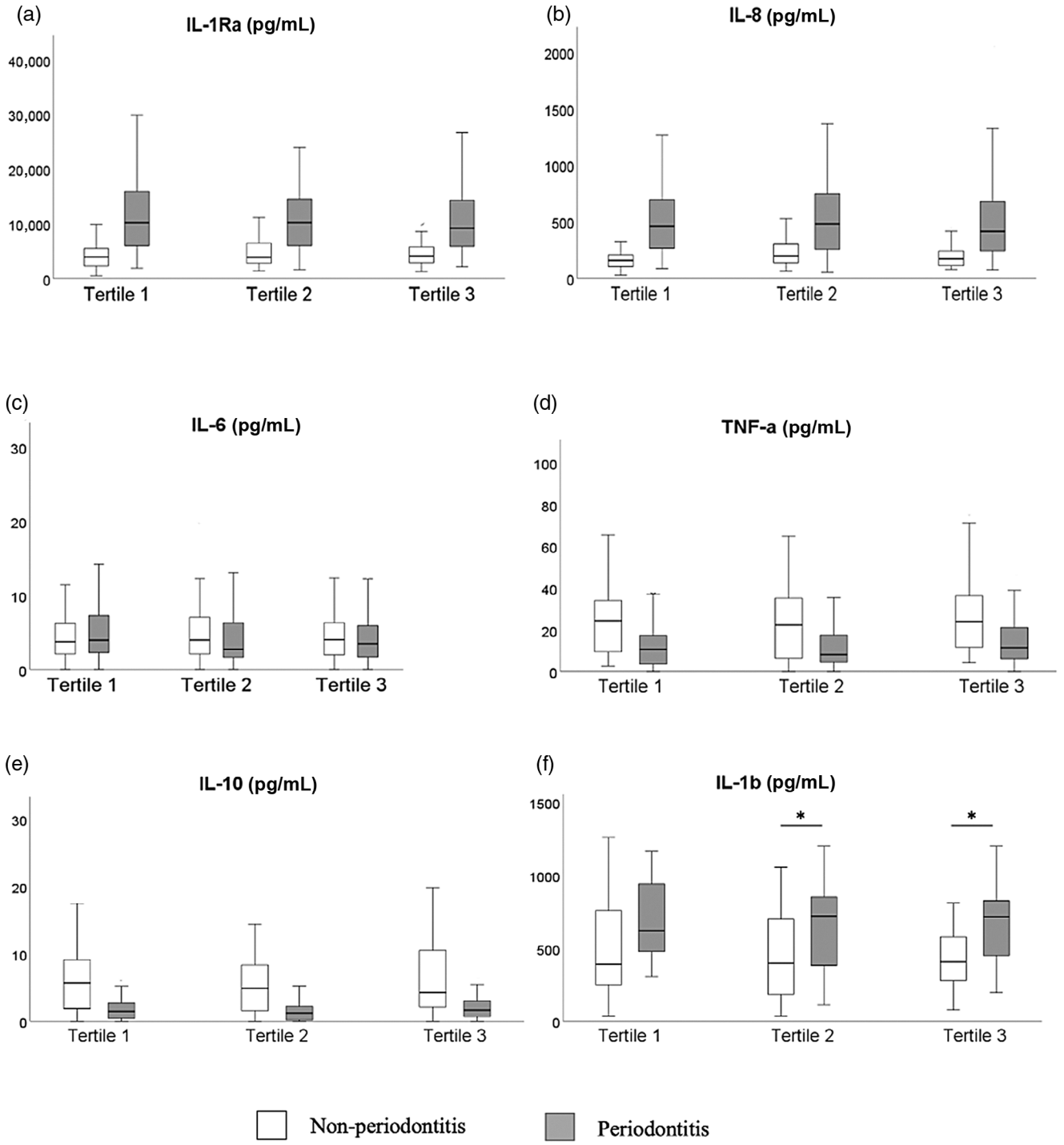

FIGURE 1 Salivary cytokine concentrations in dietary inflammatory index tertiles. (a–e) are from DILGOM 2007 and (f) from H2000. *p-value <.05, Wilcoxon signed-rank test. In DILGOM: non-periodontitis includes participants with CRS I ($n = 138$) and periodontitis include participants with CRS II and CRS III ($n = 442$). In H2000: non-periodontitis includes participants without deepened periodontal pockets ($n = 74$) and periodontitis includes participants with periodontal pockets ≥4 mm ($n = 73$). IL, interleukin; TNF, tumour necrosis factor.

10,000*g* for 5 min in DILGOM 2007 and for 3 min in H2000. In DILGOM 2007, salivary concentrations of IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-6, IL-8, IL-10, TNF-α and MMP-8 were analysed with the flow cytometric Luminex xMAP technique with commercially available kits (Bio-PlexTM 200, Bio-Rad Laboratories Inc., USA). The limit of detections (LOD) for IL-1β was 0.8 pg/mL; for IL-1Ra, 5.5 pg/mL; for IL-8, 1 pg/mL; for IL-6, 2.8 pg/mL; for IL-10, 0.3 pg/mL; and for TNF-α, 6 pg/mL. In H2000, salivary IL-1β, IL-6 and TNF-α were determined using commercial ELISA kits (GE Healthcare, Buckinghamshire, UK). LOD for IL-1β and IL-6 was <1 pg/mL and for TNF-α <5 pg/mL. In DILGOM 2007, salivary *P. gingivalis* was determined with

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TABLE 4 Associations (odd ratios [95% intervals]) of dietary inflammatory index with salivary cytokine concentrations expressed in tertiles in multinomial logistic regression model.

	Range (pg/mL)	Model 1	Model 2	Model 3
DILGOM				
Il-1Ra				
First tertile	483–5460	1	1	1
Second tertile	5470–11,400	1.18 (0.73–1.91)	1.11 (0.67–1.86)	1.20 (0.69–2.07)
Third tertile	11,400–111,000	0.88 (0.55–1.41)	0.78 (0.46–1.38)	0.93 (0.51–1.68)
IL-6				
First tertile	0–2.42	1	1	1
Second tertile	2.44–5.27	0.66 (0.41–1.07)	0.67 (0.41–1.08)	0.63 (0.38–1.06)
Third tertile	5.28–153	0.86 (0.53–1.39)	0.86 (0.53–1.39)	0.73 (0.44–1.22)
TNF-α				
First tertile	0–7.11	1	1	1
Second tertile	7.43–18.2	1.26 (0.78–2.04)	1.27 (0.78–2.07)	1.23 (0.74–2.07)
Third tertile	18.3–208	1.22 (0.76–1.96)	1.27 (0.78–2.08)	1.07 (0.64–1.81)
IL-8				
First tertile	26.7–232	1	1	1
Second tertile	233–498	1.03 (0.64–1.66)	1.01 (0.61–1.69)	0.99 (0.58–1.71)
Third tertile	499–6160	1.11 (0.69–1.79)	1.08 (0.61–1.91)	1.18 (0.64–2.18)
IL-10				
First tertile	0–0.93	1	1	1
Second tertile	0.95–2.84	0.86 (0.53–1.38)	0.87 (0.54–1.40)	0.84 (0.51–1.40)
Third tertile	2.86–68.2	1.18 (0.73–1.90)	1.27 (0.76–2.13)	1.04 (0.60–1.80)
HEALTH 2000				
IL-1β				
First tertile	35.1–412	1	1	1
Second tertile	420–685	1.68 (0.23–12.39)	1.19 (0.15–9.50)	1.36 (0.13–14.6)
Third tertile	717–1260	2.91 (0.41–20.64)	1.98 (0.25–16.05)	2.70 (0.23–32.5)

Note: Model 1: adjusted with energy intake. Model 2: adjusted with energy intake and periodontitis. Model 3: adjusted with energy intake, periodontitis, body mass index, age, education, smoking habits and physical activity.
Abbreviations: IL, interleukin; TNF, tumour necrosis factor.

quantitative real-time PCR (qPCR) assay (Hyvärinen et al., 2009) with a few modifications as described in our previous study (Syrjäläinen et al., 2019).

2.6 | Statistical analyses

Normal distributions of continuous variables were checked by the Kolmogorov–Smirnov test or visually. To achieve normality, a log transformation was made to DII, energy intake and cytokine concentrations. Cytokine concentrations did not reach complete normality after the log transformation and therefore were analysed with non-parametric tests, or cytokine concentrations were divided into tertiles to generate categorical variables. When adjusting regression models with cytokine concentrations, log-transformed concentrations were used, as their distribution was visually normal and the sample size was large. Continuous variables were compared between periodontitis and non-periodontitis groups in DILGOM 2007 with the Mann–Whitney *U* test and in H2000 with the Wilcoxon signed-rank test. Distributions between categorical variables were analysed using the chi-square test. For H2000, the salivary IL-6 and TNF-α concentrations are given in Table 2. These cytokines were not included in further analyses because of the high percentage of data left below the limit of detection.

Associations between DII and categorized salivary cytokines or periodontitis were analysed with multinomial logistic regression. Both subgroups (i.e., DILGOM 2007 and H2000) were analysed separately. Model 1 included DII as an independent factor and either salivary cytokines or periodontitis as the dependent factor. Model 2 was adjusted with periodontitis or salivary cytokine concentrations, respectively. Model 3 was further adjusted with BMI, age, education level, smoking status and physical activity. In all models including DII, energy intake was included in the analyses to control DII with energy intake. The main effects were analysed for each factor. A *p*-value of <.05 was considered statistically significant. Statistical analyses were

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TABLE 5 Associations [odd ratios (95% intervals)] of dietary inflammatory index with periodontitis in multinomial logistic regression model.

	Model 1	Model 2	Model 3
DILGOM			
Non-periodontitis	1	1	1
Periodontitis	1.07 (0.68–1.68)	1.04 (0.58–1.87)	0.96 (0.51–1.83)
HEALTH 2000			
Non-periodontitis	1	1	1
Periodontitis	3.00 (0.58–5.47)	3.15 (0.56–17.68)	**10.63 (1.09–103.60)**

Note: Model 1: adjusted with energy intake. Model 2: adjusted with energy intake and salivary IL-1Ra, IL-6, TNF-α, IL-8 and IL-10 concentrations in DILGOM and with energy intake and salivary IL-1β concentrations in Health 2000. Model 3: adjusted with energy intake, salivary cytokine concentrations (IL-1Ra, IL-6, TNF-α, IL-8 and IL-10 concentrations in DILGOM and IL-1β in Health 2000), body mass index, age, education, smoking habits and physical activity. Significant associations ($p < .05$) are bolded. Abbreviations: IL, interleukin; TNF, tumour necrosis factor.

performed with IBM SPSS Statistic 28.0 (https://www.ibm.com/products/spss-statistics, RRID:SCR_019096).

3 | RESULTS

The present study comprised a total of 727 individuals from two separate surveys, divided into periodontitis and non-periodontitis groups (Table 2). In DILGOM 2007, 76% of participants had periodontitis, whereas in H2000 the proportion was 50%. In both surveys, participants with periodontitis had higher BMI than those without periodontitis ($p < .05$). In DILGOM 2007, salivary IL-1Ra, IL-8 and IL-1β concentrations were higher, and IL-10 and TNF-α concentrations were lower in participants with periodontitis than without ($p < .001$), whereas no difference was detected in IL-6 ($p = .54$). Likewise, in H2000, salivary IL-1β concentrations were significantly increased in participants with periodontitis ($p < .001$).

There was no difference in the mean DII scores between the periodontitis and non-periodontitis groups (DILGOM: $p = .865$; H2000: $p = .623$) (Table 3). The DII scores ranged from −6.51 to 2.54 in DILGOM 2007 and from −6.13 to 3.17 in H2000.

Salivary cytokine concentrations across the DII tertiles did not differ in DILGOM 2007 nor in H2000 (p-value >.05, Wilcoxon signed rank test) (Figure 1). Salivary IL-1β concentrations were higher in participants with periodontitis in three DII tertiles, especially in the second and third tertiles (p-values, first tertile 0.068, second tertile 0.03, and third tertile 0.004, Wilcoxon signed rank test). In DILGOM 2007, statistically significant difference in IL-1Ra, TNF-α, IL-8 and IL-10 concentrations between periodontitis and non-periodontitis participants was lost when these groups were compared in DII tertiles.

In the multinomial logistic regression model, there were no associations between DII and salivary cytokine concentrations (Table 4). DII was not associated with periodontitis in the DILGOM population either (Table 5). In H2000, DII was not associated with periodontitis in models adjusted only with energy or with salivary IL-1β. When the model was further adjusted with BMI, age, education level, smoking habit and physical activity (model 3, Table 5), there was a statistically significant association between DII and periodontitis (odds ratio [OR] 10.63; 95% confidence interval [CI]: 1.09–103.60).

4 | DISCUSSION

In this study, we examined whether the inflammatory potential of diet is associated with salivary cytokine concentrations, which could mediate the risk between diet and periodontal inflammation. According to our findings, DII was not independently associated with salivary cytokine concentrations. A strong positive association between DII and periodontitis was observed in the H2000 subgroup, suggesting an independent association between pro-inflammatory diet and periodontitis, which is not related to the salivary inflammatory milieu.

There is substantial evidence that regular consumption of nutrients (e.g., vitamins C and E, saturated fat) and foods (e.g., vegetables, fruits, processed meat) can modulate systemic inflammation (Calder et al., 2011). DII is a validated dietary scoring system containing 45 food parameters attempting to measure the inflammatory potential of diet (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014). Higher DII scores are associated with higher C-reactive protein (CRP), IL-6 and TNF-α concentrations in serum, reflecting systemic inflammation (Phillips et al., 2018). DII was developed in 2009 and revised in 2014, and since then it has been widely used when examining large study populations (Hébert et al., 2019). DII scores have been associated with multiple systemic diseases such as cardiovascular diseases (Choi et al., 2023), different types of cancers (Abulimiti et al., 2020; Gholamalizadeh et al., 2022) and diabetes mellitus (Denova-Gutiérrez et al., 2018). Moreover, there are studies utilizing the data from NHANES 2009–2014 evaluating the association between DII and periodontitis (Feng et al., 2022; Li et al., 2021; Machado et al., 2021), consistently reporting that higher DII increases the risk of periodontitis and tooth loss. There is also evidence that anti-inflammatory diets reduce the periodontal inflammatory burden (Woelber et al., 2019; Wu et al., 2023).

In the present study, the association between DII and periodontitis was limited to the H2000 subgroup, while no association was observed in the DILGOM 2007 subgroup. The underlying reasons behind this observation can be several. First, the higher DII scores indicate a pro-inflammatory tendency for the H2000 subgroup. High DII scores are also associated with other systemic conditions (Abulimiti et al., 2020; Choi et al., 2023; Denova-Gutiérrez et al., 2018; Gholamalizadeh

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et al., 2022), which may all reduce the association between DII and periodontitis. Second, differences in diagnosing periodontitis might have had an impact on the results; while a saliva-based molecular diagnostic method, namely CRS, was used in DILGOM 2007 (Gursoy et al., 2011), diagnosis in H2000 study was based on periodontal pocket depth measurements. Third, inclusion criteria of the DILGOM 2007 subgroup were either being obese or having normal weight, which created distinct BMI levels between the groups. As obesity was presented as a strong confounding factor on the association between diet and periodontitis (Alhassani et al., 2021), the reduced association between diet and periodontitis that is observed in the present study can be related to the participant recruitment protocols. Finally, in contrast to the H2000 subgroup, in the DILGOM 2007 subgroup extension of periodontal disease to advanced periodontitis was not included in the statistical analysis, which may have affected the outcomes of the study.

In the current study, we examined whether DII was associated with salivary cytokine concentrations, reflecting the local inflammation in the oral cavity. Attlee and co-workers (2019) investigated the relationship between diet and three salivary inflammatory markers (adiponectin, TNF-α, IL-10) in female adults with a median age of 21 years, divided into normal weight, overweight and obese groups (30 women in each group). The diet quality was assessed with the MEDFICTS Dietary Assessment questionnaire, which is a rapid instrument for identifying high-fat diets, consisting of eight food categories (meats, eggs, dairy, fried foods, fats in baked goods, convenience foods, fats added at the table and snacks). In that cross-sectional study, selected salivary cytokines were not shown to associate with diet (Attlee et al., 2019). Our results are in line with their results, as no association was found between diet and salivary cytokine concentrations. In a Spanish study of 129 children aged 8–12 years, however, energy, fat and protein intake correlated with salivary IL-1β, IL-6 and TNF-α concentrations (Tvarijonaviciute et al., 2020).

It is known that diet is a modulator of systemic inflammation (Minihane et al., 2015). So, why is diet not associated with salivary cytokine concentrations? One explanation could be that cytokine concentrations in the saliva may not be sensitive enough to indicate diet-related changes in low-grade inflammation (Attlee et al., 2019). Most salivary proteins are secreted into saliva from acinar cells in salivary glands, and only a small amount of material enters the saliva from extra-glandular sources, for example, serum (Baum et al., 2011). Hence, saliva may not be an optimal source of inflammatory biomarkers in nutrition studies (Calder et al., 2013). Moreover, the effect of resident cells in the oral cavity on salivary cytokine concentrations may be more than systemic effects. This is supported by the current study, where the inflammatory milieu of the oral cavity was not associated with diet.

It is also reasonable to consider how sensitive DII is to assess dietary diversities in subgroups. In the present study, the DII scores varied between −6.13 and 3.17, being in the highest tertile between −3.1 and 2.5 in DILGOM 2007, and between −1.7 and 3.2 in H2000, indicating that some individuals even in the highest tertile had an anti-inflammatory diet (the DII scores below zero). The DII utilized by us was modified from the original version; thus it is not fully comparable to that used in other studies. The same calculation method was used in the EPIC study, which examined the association between the inflammatory potential of diet and gastric carcinoma (Agudo et al., 2018). In the nutrition intake standardization, the authors used their own European-based database instead of the original database. Nevertheless, their DII-based scores ranged from −6.44 to 5.67, the highest scores being above ours. This indicates that the number of participants consuming a heavily pro-inflammatory diet in our study was too small. This may explain why the associations between a pro-inflammatory diet and cytokines were not observed.

Some comments on DII should also be pointed out. First, our dietary data included only 29 of the original 45 dietary components of DII. This is, however, a common practice in studies utilizing DII, as rarely are all food components available (Millar et al., 2022; Shivappa, Steck, Hurley, Hussey, Ma, et al., 2014). Missing dietary components are mainly spices (e.g., saffron and turmeric), which are not consumed in large quantities in the Finnish food culture and would have little or no impact on DII scores. Second, energy, a common confounding factor in nutritional studies (Willett et al., 1997), is included in the DII calculation. Energy intake is associated with the intake of dietary components as well as with body size, and its presence in the index is problematic from that aspect. However, we controlled the effect of energy by adding energy intake into the analyses together with DII.

Obesity is a known risk factor for periodontitis (Ganesan et al., 2021). The mechanism linking obesity and periodontitis risk is being actively investigated, and the chronic low-grade systemic inflammation related to obesity is one proposed mechanism to explain the association. As diet and other lifestyle factors of obese individuals may differ from those of healthy weight individuals, in the DILGOM 2007 subgroup we chose participants with very high BMI (≥35 kg/m^2) and their healthy weight counterparts as controls. This categorization enabled us to pursue extreme differences in dietary habits but decreased the sample size to 580. In our previous study with the same DILGOM 2007 subgroup, we found that severe obesity was not associated with salivary IL-1Ra, IL-6, IL-8, IL-10 or TNF-α after adjusting with periodontal status (Syrjäläinen et al., 2019). In the current study, DII was not associated with salivary cytokine levels, even though BMI was considered as a confounding factor.

There are some strengths in our research. As studies examining periodontitis and salivary cytokines are usually conducted with smaller populations (about 100 participants or less) (Jentsch et al., 2017; Johnston et al., 2021; Kibune et al., 2022), the strength of our study is the larger sample size. In both studies, DILGOM 2007 and H2000, dietary information was gathered with the same validated FFQ (Männistö et al., 1996). The estimation of periodontal status in both surveys and the random sampling used are among the strengths of the present study. Moreover, large background information and health examinations gathered in both surveys allowed us to combine three inflammatory states, namely periodontitis, obesity and diet, into the same statistical model controlled for other confounding factors.

The limitations of our study include the fact that the dietary intake in both surveys was collected with FFQ, which may have resulted in recall bias leading to over-reporting of healthy foods and underreporting of unhealthy foods (Männistö et al., 1996). Furthermore, as an epidemiological study, the cross-sectional design

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in both surveys does not allow us to make any conclusions about causality between variables, which is also a common limitation of similar studies (Wu et al., 2023). When comparing with the original DILGOM 2007 and H2000 surveys, the dataset in the present study is quite small and selective, which limits the generalizability of the study findings. Finally, saliva-based diagnostic method, that is, CRS, was applied to diagnose periodontitis in the DILGOM 2007 study. CRS is a cumulative analysis method of bacteria- and host-derived biomarkers, which are composed of the salivary levels of *P. gingivalis*, IL-1β and MMP-8 (Gursoy et al., 2011). Recent systematic reviews have indicated that salivary biomarkers have acceptable performance characteristics such as high sensitivity, specificity and predictive values (Arias-Bujanda et al., 2020; Blanco-Pintos et al., 2023; Sánchez-Medrano et al., 2023). Indeed, our group has successfully demonstrated that the cumulative use of biomarkers with an adaptive design has significant superiority over single biomarkers with respect to accuracy and has also validated the diagnostic accuracy of CRS in studies with unrelated populations (Gursoy et al., 2018; Salminen et al., 2014). Nevertheless, as CRS includes salivary IL-1β, it can be expected to display a causal association between CRS and other salivary cytokines. Although this type of bias is a common drawback of molecular biomarkers, to eliminate the risk we did not analyse the direct association between CRS and salivary cytokine levels. In addition, to replicate the results we included a subgroup of H2000 participants in our analysis, as well to examine whether the results are different when periodontitis is diagnosed by clinical oral examination including pocket depths measurements. To confirm a history of robust disease, we only included participants with advanced periodontitis (deepened pockets at least in 14 teeth) and compared them with those with a healthy periodontium, which limited the sample size to 165 (Gursoy et al., 2010). Future studies should include larger study populations including participants also with localized periodontitis and different stages of overweight and obesity. Moreover, different pro-inflammatory dietary components, such as diets high in meat or high in saturated fats, and their association with local inflammation in the oral cavity should be investigated as well.

5 | CONCLUSIONS

DII was associated with periodontitis but not with salivary cytokine concentrations. This could indicate that the association between diet and periodontitis is to be explained by other lifestyle factors and not by diet-dependent inflammatory tendency in the oral cavity.

Future studies on diet and periodontitis should include larger populations, more specific dietary components and biomarkers of systemic inflammation.

AUTHOR CONTRIBUTIONS

Conceptualization: Sanna Syrjäläinen, Satu Männistö, Eija Könönen and Ulvi Kahraman Gürsoy. *Data curation*: Eija Könönen, Mervi Gürsoy, Anna Liisa Suominen and Pekka Jousilahti. *Formal analysis*: Sanna Syrjäläinen. *Project administration*: Satu Männistö, Eija Könönen and Ulvi Kahraman Gürsoy. *Visualization*: Sanna Syrjäläinen. *Writing—original draft*: Sanna Syrjäläinen. *Writing—review and editing*: Sanna Syrjäläinen, Satu Männistö, Eija Könönen, Eija Könönen, Anna Liisa Suominen, Pekka Jousilahti and Ulvi Kahraman Gürsoy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Finnish Institute for Health and Welfare. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://thl.fi/en/web/thlfi-en/statistics-and-data/data-and-services with the permission of Finnish Institute for Health and Welfare.

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