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UNIVERSITY OF TURKU

Linking diet, obesity, and periodontitis via inflammatory biomarkers in serum and saliva

Results from cross-sectional and longitudinal analyses using Finnish population-based datasets

Sanna Syrjäläinen

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To my family

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ABSTRACT

Low-grade systemic inflammation is linked with chronic diseases. Periodontitis, diet quality, and obesity are associated with systemic inflammation, yet their simultaneous association with salivary or serum markers of inflammation remains unexplored. This thesis aimed to evaluate their association with inflammation in the oral cavity and with serum C-reactive protein (CRP) concentration.

This study was based on the subsamples from three population-based surveys conducted by the National Institute for Health and Welfare: the DILGOM study (n = 584), the Health 2000 survey (n = 165), and participants attending Health 2000 and Health 2011 surveys (n = 3434). The periodontal status was assessed by a salivary-based Cumulative Risk Score (DILGOM study) and by clinical examination (Health 2000 study). Dietary habits were collected with a food frequency questionnaire. The Dietary Inflammatory Index (DII) was used to analyze the diet's inflammatory potential and the Baltic Sea Diet Score to assess the adherence to the Baltic Sea diet. Key outcome variables included salivary cytokines (e.g. interleukin [IL]-1β, IL-6, IL-10) and serum CRP concentration.

Periodontal status was associated with the concentrations of most salivary cytokines, whereas obesity was associated with higher IL-6 levels in participants with worse periodontal status and lower TNF-α and IL-10 levels in participants with non-periodontitis. Association between DII and salivary cytokines was not found. Serum CRP was higher in participants with advanced periodontitis, also when combined with the index of diet quality. In addition, advanced periodontitis combined with non-adherence to the Baltic Sea diet increased the odds of having serum CRP $\geq$ 2mg/l after 11 years, but this disappeared after adjusting for confounding factors.

In conclusion, salivary cytokines were mainly associated with periodontal status but less with obesity and not at all with diet. An association also existed between periodontitis and serum CRP, and this association was stronger than with diet and serum CRP. A slight synergistic association of diet and periodontitis existed with serum CRP, which remained significant even after 11 years.

KEYWORDS: Obesity, diet, inflammation, periodontitis, cytokines

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TIIVISTELMÄ

Matala-asteinen tulehdus liittyy moniin kroonisiin sairauksiin. Parodontiitti, ruokavalio ja lihavuus ovat systeemisen tulehduksen riskitekijöitä, mutta niiden samanaikaisen esiintymisen yhteyttä syljen tai seerumin tulehdusmarkkereihin on tutkittu vähän. Tavoitteena oli selvittää näiden riskitekijöiden yhteyttä paikalliseen tulehdukseen suussa ja seerumin C-reaktiivisen proteiinin (CRP) pitoisuuteen.

Tutkimus perustui Terveyden ja hyvinvoinnin laitoksen kolmeen väestötutkimuksen osa-aineistoon: DILGOM-tutkimus (n = 584), Terveys 2000 -tutkimus (n = 165) sekä aineisto osallistujista, jotka olivat mukana sekä Terveys 2000 että Terveys 2011 -tutkimuksissa (n = 3434). Parodontiitti määritettiin sylkeen perustuvalla, kumulatiivisella riskipisteellä (DILGOM), ja kliinisellä tutkimuksella (Terveys 2000). Ruoankäyttöä mitattiin frekvenssityyppisellä ruoankäyttökyselyllä. Ruokavaliota arvioitiin tulehduspotentiaali-indeksillä (DII, engl. Dietary Inflammatory Index) ja Itämeren ruokavalioindeksillä. Syljen sytokiinit (mm. interleukiini [IL]-1β, IL-6 ja IL-10) sekä seerumin CRP pitoisuus olivat keskeiset vastemuuttujat

Parodontiitti oli yhteydessä useimpiin syljen sytokiineihin, kun taas lihavuus liittyi vain korkeampaan IL-6 pitoisuuteen niillä, joilla oli parodontiitti sekä matalampaan IL-10 ja TNF-α pitoisuuteen niillä, joilla ei ollut parodontiittia. DII ei ollut yhteydessä syljen sytokiineihin. Seerumin CRP oli korkeampi vaikea-asteisin parodontiitin ja epäterveellisen ruokavalion yhteydessä. Lisäksi vaikea-asteinen parodontiitti yhdessä epäterveellisen ruokavalion kanssa lisäsi kohonneen CRP:n riskiä (CRP $\geq$ 2 mg/l) 11 vuoden jälkeen, mutta tilastollinen merkitsevyys katosi kun sekoittavat tekijät lisättiin malliin.

Johtopäätöksenä syljen sytokiinit liittyivät pääasiassa parodontiittiin, sillä lihavuus oli yhteydessä vain osaan sytokiineista, eikä ruokavalio ollut yhteydessä yhteenkään sytokiiniin. Parodontiitilla oli vahvempi yhteys seerumin CRP:hen kuin ruokavaliolla. Ruokavaliolla ja parodontiitilla havaittiin myös synergistinen yhteys seerumin CRP pitoisuuteen, joka säilyi 11 vuoden seurannan aikana.

AVAINSANAT: Lihavuus, ruokavalio, tulehdus, parodontiitti, sytokiinit

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Abbreviations

AHEI	Alternative Healthy Eating Index
AP	Advanced periodontitis
AUC	Area under curve
BMI	Body mass index
BSDS	Baltic Sea Diet Score
CI	Confidence interval
CRP	C-reactive protein
CRS	Cumulative risk score
DAMP	Damage-associated molecular pattern
DASH	The Dietary Approaches to Stop Hypertension
DII	Dietary Inflammatory Index
DILGOM	DIetary, Lifestyle and Genetic Determinant of Obesity and Metabolic Syndrome Study
ELISA	Enzyme-linked immunosorbent assay
FFQ	Food frequency questionnaire
GCF	Gingival crevicular fluid
H2000	Health 2000 survey
H2011	Health 2011 survey
HbA1c	Glycated hemoglobin
HEI	Healthy Eating Index
Hs	High sensitivity
IL	Interleukin
INF-γ	Interferon-gamma
LOD	Limit of detection
MMP	Matrix metalloproteinase
MP	Moderate periodontitis
NHANES	National Health and Nutrition Examination Survey
NKT cells	Natural killer T cells
NP	Non-periodontitis
OR	Odds ratio
PAMP	Pathogen-associated molecular pattern

PPD	Probing pocket depth
PRR	Pattern recognition receptor
Ra	Receptor antagonist
RANK	Nuclear factor-κB receptor
RANKL	Nuclear factor-κB receptor ligand
RR	Relative risk
THL	National Institute for Health and Welfare
TNF-α	Tumour necrosis factor alpha
WBC	White blood cell count
WHO	The World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Syrjäläinen, S., Gürsoy, U. K., Gürsoy, M., Pussinen, P., Pietiäinen, M., Jula, A., Salomaa, V., Jousilahti, P., & Könönen, E. Salivary cytokine biomarker concentrations in relation to obesity and periodontitis. *Journal of Clinical Medicine*, 2019; 8(12):2152.

II Syrjäläinen, S., Männistö, S., Könönen, E., Pussinen, P., Gürsoy, M., Suominen, A. L., Jousilahti, P., & Gürsoy, U. K. Dietary inflammatory index in relation to salivary cytokine concentrations and periodontitis: A cross-sectional analysis. *Journal of Clinical Periodontology*, 2024; *51*(4), 406–416.

III Syrjäläinen, S., Männistö, S., Könönen, E., Suominen, A. L., & Gürsoy, U. K. Diet quality and advanced periodontitis in relation to serum CRP levels: An 11-year follow-up study (manuscript).

1 Introduction

Periodontitis is a multifactorial inflammatory disease of tooth-supporting tissues (Könönen et al., 2019). It is initiated by a complex interplay between dysbiotic biofilm and host immune response, leading to gingival pocket formation, attachment loss, and alveolar bone loss. A severe form of the disease affects approximately 796 million people globally, representing 9.8% of the global population, while its milder forms are even more widespread (Bernabe et al., 2020; Wu et al., 2022). During the last 30 years, the prevalence of periodontitis has increased worldwide. In Finland, periodontitis affects two-thirds of the adult population and is more common in men (Suominen etl al., 2025).

Periodontitis is associated with obesity and several chronic diseases, such as type 2 diabetes, cardiovascular diseases, and certain cancers (Ganesan et al., 2021; Hajishengallis, 2022). It has been suggested that low-grade systemic inflammation related to periodontitis could explain the association between periodontitis and comorbidities (Hajishengallis & Chavakis, 2021). Recent studies have also highlighted the association between healthy dietary patterns and periodontal health (Shi et al., 2024). Periodontitis, obesity, and diet are all known risk factors for low-grade systemic inflammation, which affects overall health (Calder et al., 2009; Machado, Botelho, Escalda, et al., 2021a; Soták et al., 2025).

So far, no studies have investigated how concurrent exposure to diet quality, obesity, and periodontitis is related to inflammatory markers in the oral cavity or bloodstream. This study aimed to evaluate periodontitis and its two risk factors—obesity and diet—and to analyse how these factors combined are associated with local inflammation in the oral cavity and serum C-reactive protein (CRP) concentration. As periodontitis is an inflammatory disease, the Dietary Inflammatory Index (DII) was used to measure the inflammatory potential of diet. Additionally, to assess the quality of a local diet in Finland, the Baltic Sea Diet Score (BSDS) was used to measure adherence to the Baltic Sea diet.

2 Review of the Literature

2.1 From acute inflammation to chronic systemic inflammation

Inflammatory response is an essential part of human health. It protects the host from foreign pathogens, limits tissue damage during injuries, and initiates the repair of lost tissues. Dysregulation of this process, whether due to prolonged proinflammatory stimuli or an overreaction to otherwise harmless triggers, can lead to various health disorders. Immune cells in response to recognizing microbe-associated molecular patterns (MAMPs) or damage-associated molecular patterns (DAMPs) activate acute inflammation (Rossi et al., 2021; Stiel et al., 2024). MAMPs are structures of pathogens, including lipopolysaccharides from cell wall lipids or mannan carbohydrates from fungi or bacteria. DAMPs are a variety of intra- and extracellular proteins released when cells are damaged, inducing the so-called "sterile inflammation". Pattern recognition receptors (PRRs) are expressed by various mammalian cells, including epithelial cells at body barriers, endothelial cells, or tissue-resident immune cells such as macrophages or dendritic cells.

Activation of PRRs by MAMPs or DAMPs triggers the expression and excretion of inflammation effectors such as cytokines, prostaglandins, platelet activation factors, and CRP (Ravaut et al., 2021). Neutrophils are recruited to the site of infection or damage by effectors and arrive there within a few minutes (Rossi et al., 2021). They are the first cells present after infection or injury and protect the host by phagocytosis of microbial and tissue damage patterns (Stiel et al., 2024). The second group of phagocytes that migrate to the infection site are macrophages. In addition to their role in phagocytosis, they participate in host defense by initiating the adaptive immune system through antigen presentation, helping remove damaged tissues, and initiating wound repair. After eliminating the injurious agents, the synthesis of proinflammatory mediators is suspended, leading to the end of further leukocyte recruitment (Fullerton & Gilroy, 2016). Normally, the inflammatory response is temporary and is resolved when the threat has been eliminated.

When local inflammation is unresolved, it leads to chronic systemic inflammation, which persists over time and may cause collateral damage to tissues and organs (Furman et al., 2019; Ravaut et al., 2021). Chronic inflammation is more often triggered by DAMPs and increases by age, sedentary lifestyle, and other lifestyle factors. It also increases the risk of many non-communicable diseases, including the risk of type 2 diabetes, non-alcoholic fatty liver, and cardiovascular diseases (Minihane et al., 2015).

2.1.1 Serum biomarkers of chronic systemic inflammation

CRP is an acute phase protein produced by hepatocytes in the liver in response to elevated levels of inflammatory cytokines, particularly interleukin (IL)-6, and, to a lesser extent, IL-1 and tumour necrosis factor alpha (TNF-α) (Bhattacharya & Munshi, 2023). CRP's main role during inflammation seemingly relates to complement activation, but different isoforms have different actions. It also participates in apoptosis, phagocytosis, monocyte recruitment, and vascular cell activation. The average concentration of serum CRP in healthy adults is around 0.8 mg/l. During bacterial infections, CRP levels may increase to 1000-fold (Sproston & Ashworth, 2018). It has been demonstrated that high-sensitivity (hs) CRP level greater than 2 mg/l is prevalent in a wide variety of morbidities and is associated especially with infectious- and cardiovascular deaths (Drozd et al., 2022). In addition, the values greater than 10 mg/l may indicate acute infection (Ridker, 2016). Higher serum CRP concentrations have been commonly linked with unhealthy lifestyle factors, including diet quality, smoking, alcohol consumption, and physical activity (Guo et al., 2024).

Cytokines are soluble proteins produced primarily by macrophages, T lymphocytes, and a wide variety of cells (Brenner et al., 2014). They orchestrate the inflammatory response by exhibiting negative and positive regulatory effects on various target cells. Cytokine release leads to the activation of immune cells and the release of further cytokines, i.e., a positive feedback loop (Kany et al., 2019). Different cell populations can produce the same cytokines, but their effect depends on the target cell. Cytokines may also have synergistic effects, and the anti- and proinflammatory forms are released simultaneously during the immune response. IL-6—produced by T-cells, monocytes, endothelial cells, and fibroblasts—is one of the most central cytokines in activating and maintaining the inflammatory response (Kany et al., 2019). One main effect of IL-6 is the triggering of acute phase proteins in the liver, the regulation of the macrophages, T-cell differentiation, and the stimulation of T-cells to produce cytokines (Grebenciucova & VanHaerents, 2023). The serum concentration of IL-6 among healthy individuals is close to 1 pg/ml, but the concentration increases up to 150 ng/ml in patients with autoimmune diseases (Schaper & Rose-John, 2015). TNF-α originates mainly from macrophages and T-cells and exhibits a wide range of functions, including initiating the immune process, inducing cell death and regulating the inflammatory process (Kany et al., 2019).

2.1.2 Salivary biomarkers of systemic inflammation

Saliva—an easy-to-collect, non-invasive, and cost-effective sample—has been used as a diagnostic fluid to identify pathologies with oral or systemic origin. Proteins may enter saliva from acinar cells in salivary glands and by passive diffuse or active transport from blood to gingival crevicular fluid (GCF) (Baum et al., 2011; Dongiovanni et al., 2023). Various host markers—including proteins, gene transcripts, or metabolites—are presented as markers of systemic diseases and conditions. Indeed, salivary concentrations of inflammatory markers have shown good reliability in repeated measurements, improving saliva's diagnostic applicability (Nam et al., 2019). However, inconsistent study outcomes in the literature also exist due to the heterogeneities in sample collection techniques, applied laboratory methods, statistical analysis, and data interpretations (Gürsoy & Kantarci, 2022).

Whether salivary cytokines accurately reflect systemic inflammation remains uncertain. For example, when the correlations between salivary and serum cytokine concentrations were evaluated in a cross-sectional study of 37 healthy young men (mean age 26.7), IL-6 was the only inflammatory marker whose concentration correlated between saliva and blood (Nam et al., 2019). No other inflammatory markers, including CRP, IL-1β, or TNF-α, showed a similar relationship. In a similar investigation with the elderly (mean age 70.3), correlations were observed between saliva and blood in interferon-gamma (IFN-γ), IL-6, and TNF-α concentrations, but not with that of IL-10 or IL-8 (Parkin et al., 2023). They also observed a strong intercorrelation between salivary cytokines, with the strongest association between TNF-α and other salivary cytokines. Furthermore, an examination of 129 children (median age 11, ages 8–12) showed a positive relationship in CRP concentration between saliva and blood but no significant link with IL-1β, IL-6, IL-8, or TNF-α (Tvarijonaviciute et al., 2020). In light of these studies, salivary cytokines seemingly also reflect local production in the oral cavity.

However, salivary inflammatory markers in relation to systemic diseases have been actively studied. Recent studies have indicated that certain salivary cytokines are associated with stroke (Maciejczyk et al., 2021), type 2 diabetes (Agho et al., 2021), and cardiovascular diseases (Bahbah et al., 2021). Moreover, salivary cytokine concentrations seemingly are affected by age (Yakar et al., 2024), gender (Parkin et al., 2023), and smoking habits (e-cigarette smoking or conventional smoking) (Verma et al., 2021).

2.2 Periodontitis as an inflammatory disease

2.2.1 From homeostasis to dysbiosis

Even in a healthy periodontium, microbes constantly interact with immune cells (Könönen et al., 2019). From early infancy to adulthood, microbial diversity in the oral cavity increases until it starts decreasing in older adults (Corrêa et al., 2025). The predominant species include *Streptococcus*, *Prevotella*, *Haemophilus*, *Fusobacteritum*, and *Veillonella* (Cui et al., 2025) —the first colonizers of periodontal tissue that do not trigger an inflammatory response but live in symbiosis with the host. The resident microbiota causes neutrophil recruitment from the bloodstream to connective tissue (Uriarte et al., 2016). Some of these neutrophils migrate through junctional epithelium to eliminate symbiotic micro-organisms, reducing the overall microbial load and contributing to a steady state between the microbes and host.

During periodontitis development, biofilm accumulates around the gingival margin. In addition to the increasing number of microbial populations, the diversity also rises (Costalonga & Herzberg, 2014). *Porphyromonas gingivalis* is one of the keystone pathogens that initiate microbial dysbiosis. It impairs the host defense, facilitating the development of the disease-related microbial community. The subgingival bacterial species have been recognized to exist in complexes where certain microbes tend to appear together (Socransky et al., 1998; Socransky & Haffajee, 2005). These complexes have been color-coded to describe their relationship with the clinical parameters of periodontitis. The microbes in green, purple, and yellow complexes are early colonizers found predominantly in healthy periodontium. They act as a bridge for the bacteria in orange and, eventually, red complexes, which are abundant in chronic periodontitis. Along with *P.gingivalis*, *Tannerella forsythia*, and *Treponema denticola* are pathogens of red complex, which are associated with the most severe form of periodontitis. In addition to bacteria, various herpes viruses have been detected in periodontal lesions, contributing to pathogenic bacteria growth (Contreras & Slots, 2000). However, specific bacteria colonizing does not cause the dysbiosis leading to periodontal tissue destruction (Roberts & Darveau, 2015). Instead, dysbiosis results from the overgrowth of specific or nonspecific micro-organisms and changes in the host response.

Oral plaque is the primary etiological factor in gingival inflammation; in gingivitis, the inflammation is limited to the soft tissue, epithelium, and connective tissue (Kurgan & Kantarci, 2018). Neutrophils are essential in controlling microbial accumulation and maintaining homeostasis in healthy gingival tissue (Uriarte et al., 2016). They migrate into the gingival sulcus by following the chemoattractant gradient of IL-8. If the microbial accumulation continues, the other immune cells—

including macrophages, lymphocytes, plasma cells, and mast cells—start appearing (Kurgan & Kantarci, 2018). Individual variation in the inflammatory response to microbial accumulation is identified as high, low, and slow responders (Bamashmous et al., 2021). In the slow responders, the measures of gingival inflammation—including bleeding on probing and gingival index and the concentration of IL-1β in GCF—have been recognized as lower than the high responders. In addition, the rate of plaque growth and microbial composition differed between these groups. Furthermore, the microbial load was similar between the high and low responders, but the gingival inflammation did not reach the same degree in low responders as with the high responders, indicating there is also variation in the host response. Moreover, a recent cross-sectional study demonstrated sex-dependent variation in periodontal inflammation, indicating that smoking was a determinant of lower bleeding on probing in men, whereas aging was associated with increased bleeding on probing in women (Farina et al., 2025).

If the gingival inflammation cannot be resolved, the inflammatory reaction becomes uncontrolled, leading to irreversible tissue destruction: loss of connective tissue attachment and alveolar bone (Kurgan & Kantarci, 2018). The causal components involved in periodontitis development are multifaceted and co-occur. The enhanced inflammatory reaction to accumulated microbiota in the gingival sulcus leads to alterations in the sulcular environment (Bartold & Van Dyke, 2019). This, with some lifestyle-related factors (e.g., smoking, or unfavorable nutrition), promotes the development of a dysbiotic biofilm (Bartold & Van Dyke, 2019; Uriarte et al., 2016). Conversely, one's susceptibility to accumulated microbiota varies because the disease has been recognized as a result of a complex interaction between genetics and the environment (Loos & Van Dyke, 2020). For example, some health-related conditions, including type 2 diabetes, may modulate the inflammatory reaction, predisposing one to periodontitis (Sanz et al., 2018). In addition, sex-based difference in immune response is proposed to contribute to the increased prevalence of periodontitis in men (Shiau & Reynolds, 2010). However, dysbiotic biofilm and/or dysregulation of the host immune reaction can disturb the balance between immune reaction and microbial invasion, leading to periodontal inflammation and periodontitis (Figure 1).

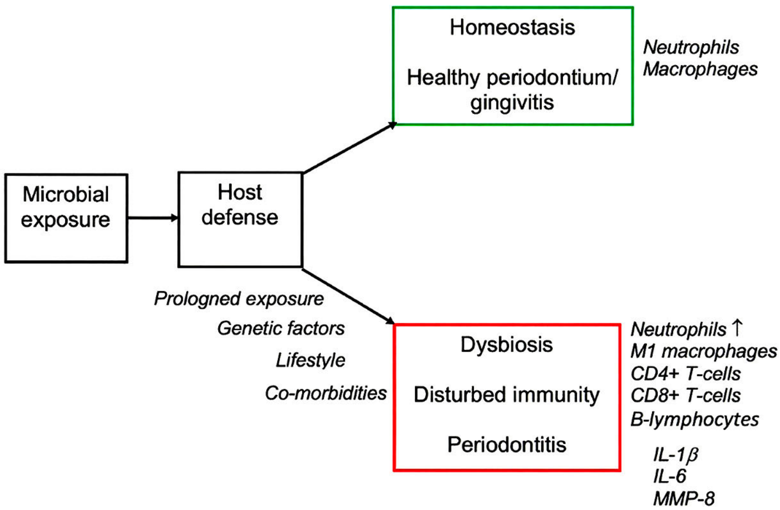

Figure 1. Development of periodontitis in response to microbial exposure and dysregulation of host response. IL = interleukin, MMP = matrix metalloproteinase.

2.2.2 Inflammatory-immune response in periodontitis

Neutrophils represent the first line of defense against microbes, starting the tissue damage and the release of enzymes and metabolites (Cafiero et al., 2021; Könönen et al., 2019). If pathogens cannot be effectively eliminated and the immune-inflammatory response activation is extended, a neutrophil's protective function is impaired and tends to be destructive. Neutrophils participate in tissue breakdown by secreting matrix metalloproteinase-8 (MMP-8), which degrades type I, II, and III collagens. They also have regulatory effects on other cell types by producing chemokines and cytokines that, for example, attract macrophages to the site of inflammation and modulate their polarization to the M1 phenotype (Zhang et al., 2024).

Macrophages, an important source of inflammatory mediators, achieve the second line of defense (Cafiero et al., 2021; Könönen et al., 2019). Macrophages can be polarized to the M1 phenotype, which supports the neutrophilic antimicrobial response but produces high levels of proinflammatory cytokines and exacerbates tissue damage and inflammation, or to the M2 phenotype, which produces anti-inflammatory molecules and participates in tissue repair, regeneration, and inflammation resolution (Zhang et al., 2024). Alongside macrophages, dendritic cells capture and present antigens and induce antigen-specific immune systems.

The innate immune cells of periodontium present intra- and extracellular antigens to lymphocytes—the main regulator of bone resorption in periodontitis (Cafiero et al., 2021; Könönen et al., 2019). Adaptive immune cells in periodontitis include CD4+ T-cells, CD8+T-cells, and B lymphocytes (Zhang et al., 2024). CD4+ T-cells further differentiate into a variety of T helper cell subsets, which produce anti- and proinflammatory cytokines. For example, Th17 cells produce IL-17, which induces bone resorption by activating nuclear factor-κB receptor ligand (RANKL) secretion from osteoblast-lineage cells. When chronic gingivitis progresses to periodontitis, the number of B-cells increases, further enhancing bone loss by increasing RANKL production (Könönen et al., 2019; Zhang et al., 2024). RANKL activates osteoclasts by binding to nuclear factor-κB receptor (RANK) expressed on the membrane of osteoclast precursors (Becerra-Ruiz et al., 2022).

2.2.3 Periodontitis in relation to systemic or salivary inflammatory markers

Cytokines produced by resident and immune cells during periodontitis development can be detected in saliva and serum (Jaedicke et al., 2016; Machado, Botelho, Escalda, et al., 2021b; Medara et al., 2021). Periodontitis-driven systemic inflammation may result from the dissemination of bacterial pathogens or salivary inflammatory markers to the bloodstream, where they may stimulate the secretion of cytokines or acute phase proteins (Hajishengallis & Chavakis, 2021). It may also be due to the aspiration or digestion of periodontal pathogens. One plausible mechanism is that periodontal pathogens trigger gut inflammation after swallowing, but this requires that the host's gut microbiota is somehow disturbed in advance (Kitamoto et al., 2020). Yet, the exact mechanism linking periodontal and systemic inflammation remains unresolved (Luthra et al., 2023).

A review of 77 studies performed in Asia, Europe, America, and Oceania analyzed the relationship between serum CRP concentration and periodontitis, finding a strong association between them (Machado, Botelho, Escalda, et al., 2021b). They also observed that the more aggressive the periodontitis, the greater the increase in serum CRP concentrations. Another meta-analysis of 26 studies conducted in Asia, Europe, and the Americas reported a decrease in serum CRP and serum IL-6 after non-surgical periodontal treatment but inconsistent results regarding serum IL-8, IL-10, and TNF-α concentrations after treatment (Luthra et al., 2023). Evidence shows that periodontitis increases the risk of high CRP concentration, even in the long term. A follow-up study of 3621 U.S. participants aged 45 to 64 at baseline showed periodontitis was associated with elevated CRP concentrations after 13 years of follow-up (Molinsky et al., 2022).

IL-1β, and especially its concentration in saliva, is the most extensively studied biomarker for periodontal disease (Jaedicke et al., 2016; Medara et al., 2021). It is produced by various cells during periodontitis progression, including lymphocytes, neutrophils, macrophages, fibroblasts, and keratinocytes. It participates in neutrophil recruitment, osteoclast activation, and T- and B-cell activation. TNF-α, another cytokine produced during periodontitis, is expressed mainly by macrophages, T-cells, and resident cells in tissue. It mediates bone resorption by osteoclast activation but also has anti-inflammatory properties by limiting the extent and duration of the inflammatory process. IL-6 is secreted by macrophages, dendritic cells, certain CD4+ T-cells, and resident cells of tissues. In periodontitis, IL-6 activates Th17 cells and promotes B-cells' maturation.

Salivary and serum cytokines related to periodontitis have been comprehensively reviewed lately (Medara et al., 2021). In that review, authors reviewed 178 cross-sectional and longitudinal studies and found IL-1β, IL-6, and TNF-α to be the most extensively studied cytokines showing positive associations with periodontitis. However, they state that the results are inconclusive, as some studies show no association. Table 1 presents the studies regarding salivary cytokines in relation to periodontitis in otherwise healthy participants, which were published during the last five years. During the same period, only one study evaluated serum cytokines related to periodontitis in otherwise healthy participants (Eldzharov et al., 2021). A comparative study of Russian adults aged 30 to 65 included 40 generalized periodontitis patients and 40 healthy controls. The results showed that higher serum IL-1β, IL-6, and TNF-α and lower IL-10 concentrations were associated with periodontitis, aligning with Medara et al.'s review (2021).

Recent studies have confirmed higher salivary IL-1β and IL-6 concentrations in periodontitis patients compared to healthy controls (Kawamoto et al., 2020; Reddahi et al., 2022; Relvas et al., 2024; Tang et al., 2023; F. R. F. Teles et al., 2024), although some controversial results also exist (Majeed et al., 2022; Roy et al., 2022). Instead, the results for salivary IL-10 and TNF-α were inconclusive. Differences between results may be due to varying study designs and sampling methods. While some studies compared healthy individuals to those with different stages of periodontitis, others only categorized participants into healthy and periodontitis patients. Also, the sample size was quite low in some of the studies.

A follow-up study of 113 healthy individuals and 302 patients with stage II or III periodontitis aged 25 or older who were recruited as a part of a multicenter study at four clinical centers in the United States evaluated how inflammatory biomarkers in saliva were associated with periodontitis progression (F. R. F. Teles et al., 2024). The study's results showed that salivary cytokines (IL-1β, IL-6, IL-8, and IL-10) were higher at baseline in those periodontitis patients whose disease progressed in at least three sites during the following 12 months compared to those periodontitis patients whose disease did not progress. The authors speculated this to relate to the nature of IL-6 and IL-8 as a chemoattractant of neutrophils and macrophages and their ability to promote TH1-cells and increase osteoclast activity. The same study found that higher serum CRP levels were associated with disease progression in healthy participants but not with periodontitis patients.

Increased knowledge about periodontitis development and its associated microbiological and host-related components has increased interest in defining biomarkers for disease detection (Belibasakis et al., 2023). Two meta-analyses have concluded that salivary IL-1β and IL-6 are suitable biomarkers for periodontitis alone (Arias-Bujanda et al., 2020) or in combination with MMP-8 (Blanco-Pintos et al., 2023). The cytokines as biomarkers represent only the inflammatory reaction in periodontitis progression. At a specific time point, this reaction may be downregulated due to the decreased bacterial burden, even though the same reaction just started the tissue destruction. Therefore, a diagnostic test to consider the episodic nature of periodontitis has been developed (Gürsoy et al., 2011). Cumulative risk score (CRS) is a salivary-based diagnostic tool that combines the concentrations of three salivary biomarkers: *P. gingivalis* (a biomarker of infection), IL-1β (a biomarker of inflammation), and MMP-8 (a biomarker of enzymatic degradation). These biomarkers were chosen for CRS due to their high prevalence and significantly different levels between periodontitis and healthy patients.

Table 1. Studies on salivary cytokine concentrations related to periodontitis were published within the past five years. All salivary cytokines analyses were done using a cross-sectional design.

Study	Country	Sample size	Classification of study participants	Age range	Main finding
Relvas et al., (2024)	Portugal	N = 68	Healthy (n = 22) Mild to moderate periodontitis (stage I/II) (n = 17) Severe periodontitis (stage III/IV) (n = 29)	18–70	IL-6 ↑ in severe periodontitis vs healthy or moderate periodontitis IL-1β ↑ in severe periodontitis vs healthy IL-1Ra ↑ in healthy vs severe periodontitis IL-10 ↑ in severe periodontitis vs moderate periodontitis TNF-α no difference between groups
Uçan Yarkaç et al., (2024)	Turkey	N = 120	Healthy (n = 40) Gingivitis (n = 40) Periodontitis (n = 40) All were divided into young and old participants	18–80	TNF-α ↑ in periodontitis vs healthy
f.r.f. Teles et al., (2024)	USA	N = 415	Healthy (n = 113) Stage II periodontitis (n = 34) Stage III periodontitis (n = 268)	≥ 25	IL-1β ↑ in periodontitis vs healthy IL-6 ↑ in periodontitis vs healthy IL-10 ↑ in periodontitis vs healthy IL-8 ↑ in periodontitis vs healthy
Tang et al., (2023)	USA	N = 67	All stage III or IV periodontitis	≥ 45	Periodontal Inflamed Surface Area correlated with IL-1β, IL-6, IL-8, TNF-α but not with IL-10
Majeed et al., (2022)	Pakistan	N = 60	Healthy (n = 20) Periodontitis (n = 40)	18–65	IL-6 no difference between groups IL-8 no difference between groups
Reddahi et al., (2022)	Morocco	N = 40	Healthy (n = 10) Periodontitis (n = 30)	≥ 18	IL-6 ↑ in periodontitis vs healthy patients IL-1β ↑ in periodontitis vs healthy IL-10 no difference between groups

Study	Country	Sample size	Classification of study participants	Age range	Main finding
Roy et al., (2022)	Canada	N = 23	Healthy (n = 12) Severe generalized periodontitis (n = 11)	≥ 18	IL-6 no difference between groups IL-1β no difference between groups IL-8 ↑ in periodontitis vs healthy patients TNF-α no difference between groups
Kawamoto et al., (2022)	Brazil	N = 32	Periodontitis stage III Grade B (generalized chronic periodontitis) (n = 9) Healthy controls (n = 9) Periodontitis stage III Grade C/Incisor-molar pattern (localized aggressive periodontitis) (n = 7) Healthy controls (n = 7)	18–24 35–55	IL-1β ↑ in generalized chronic periodontitis than their healthy controls IL-6 ↑ in generalized chronic periodontitis than their healthy controls. IL-10 no difference between groups TNF-α no difference between groups

IL = interleukin, TNF = tumor necrosis factor.

2.3 Obesity is an inflammatory disease

Obesity, characterized by excessive fat accumulation, is a chronic disease that develops due to excess energy intake and low energy expenditure, which a complex interplay of environmental, genetic, and biological mechanisms regulate (Gordon-Larsen & Heymsfield, 2018). The World Health Organization (WHO) defines overweight as a body mass index (BMI) ≥ 25 kg/m^2 and obesity as a BMI ≥ 30 kg/m^2 (World Health Organization, 2025). The prevalence of obesity has increased worldwide since 1990, with women being slightly more affected than men, and the onset of obesity shifting to younger ages (Koliaki et al., 2023; Phelps et al., 2024). In Finland, 27% of men and 30% of women were living with obesity 2023 (Lehtoranta et al., 2023). Obesity's prevalence is estimated to continue increasing, reaching 40% by 2040 (Kestilä & Karvonen, 2025).

2.3.1 Adipose tissue-derived inflammation

Obesity contributes to two inflammatory processes: the systemic low-grade inflammation that damages the vascular endothelium and causes organ dysfunction, and adipose tissue inflammation, which is responsible for peripheral insulin resistance and systemic inflammation through the release of cytokines and adipokines (Soták et al., 2025). During weight gain, white adipose tissue goes through phenotypic modification, resulting in dysfunctional adipocytes accompanied by infiltrated immune cells (Figure 2) (Kawai et al., 2021). This leads to the local and systematic secretion of proinflammatory cytokines, disturbing normal function in adipose tissue and other organs.

Like normal inflammatory reactions, neutrophils are the first immune cells to infiltrate the adipose tissue after a high-fat diet (Elgazar-Carmon et al., 2008). With an increased amount of free fatty acids, cholesterol, and lipopolysaccharides, neutrophils recruit macrophages to the site (Kawai et al., 2021). Macrophages of adipose tissue have traditionally been classified into M1 and M2 type macrophages; currently, however, it is known that there is a wider range of macrophage subtypes involved in adipose tissue-related inflammation (Jacks & Lumeng, 2024). In obesity, the dominant macrophage type in body fat is lipid-associated macrophages, which contribute to the crown-like structure formation around dead and dying adipocytes. The several functions of these macrophages include cytokine production (TNF-α, IL-6, IL-18), T-cell activation, and angiogenesis, among others (Jacks & Lumeng, 2024; Kawai et al., 2021).

T cells are the second-largest immune cell population in adipose tissue (Jacks & Lumeng, 2024). Adipose tissue in lean mice contains mainly Treg and CD4+ Th2 cells, which function to maintain an anti-inflammatory environment. In obese states, CD4+ Th1 cells, CD4+Th17 cells, CD8+ T cells, and natural killer T cells (NKT cells) are prominent. These, with macrophages, are responsible for producing IL-1β, IL-6, IFN-γ, and leptin, which may locally affect adipose tissue or through systemic circulation (Kawai et al., 2021).

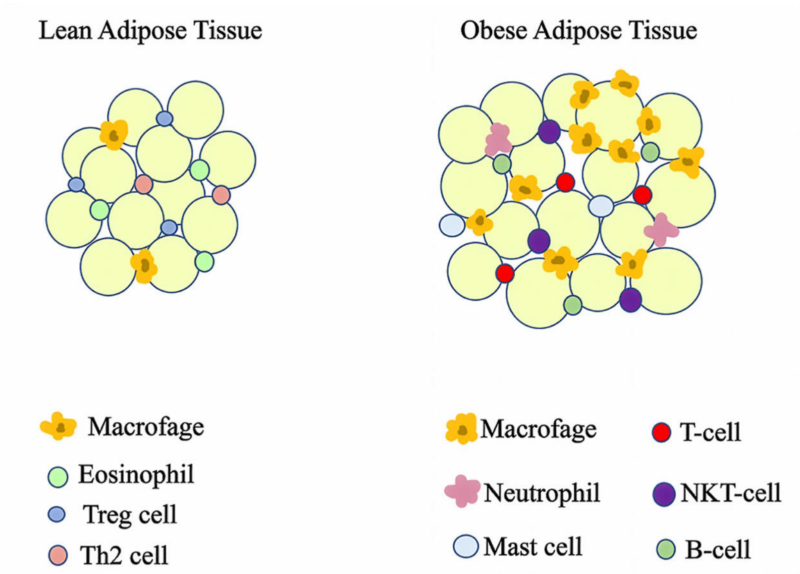

Figure 2. The inflammatory phenotype of lean and obese adipose tissue, modified from Kawai et al. (2021). NKT = natural killer T cells.

2.3.2 Obesity and inflammatory markers in serum and saliva

Convincing evidence shows that inflammatory markers are elevated in the serum of persons living with obesity compared to persons with normal-weight. In a cross-sectional study on 10,745 Israeli adults, participants living with obesity presented higher white blood cell counts (WBC) and CRP concentrations than those of normal weight (Cohen et al., 2021). Among 600 Koreans aged 19 to 65, an elevated WBC and hs-CRP concentration was associated with visceral but not subcutaneous adipose tissue (Yu et al., 2019). A recent study using the data from the National Health and Nutrition Examination Survey (NHANES), comprising 9443 individuals, revealed that generalized obesity (BMI ≥ 30 kg/m^2) and abdominal obesity (waist circumference ≥ 120 cm in men or ≥ 88 cm in women) are linked with serum inflammatory markers, including the neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, and especially CRP concentration and CRP to albumin ratio (He et al., 2024). Additionally, serum proinflammatory cytokines—such as IL-1-receptor antagonist (Ra), IL-6, and TNF-α—have been associated with BMI and body fat percentage in a Finnish population-based study of 3369 adults (Tuomisto et al., 2019).

In contrast, only a few studies evaluated salivary inflammatory markers in relation to obesity, the majority dealing with children or adolescents (Zyśk et al., 2021). In adults, higher salivary concentrations of IL-1β, IL-6, IL-8, and TNF-α have been reported in participants living with obesity when compared to those of normal weight (Lehmann-Kalata et al., 2018; Ostrowska et al., 2023; Safabakhsh et al., 2022). A recent systematic review demonstrated that saliva contains several biomarkers with differing concentrations in metabolically unhealthy individuals living with obesity compared to normal-weight controls (Habobe et al., 2025). However, challenges regarding inconsistency in saliva collection methods, lack of validation against blood-based standards, and limited longitudinal data complicate the interpretation and diagnostic utility of these findings.

2.3.3 Obesity and periodontitis

To date, eight systematic reviews and meta-analysis concerning the association between periodontitis and overweight, obesity, or weight gain have been published (Table 2) (Chaffee & Weston, 2010; da Silva et al., 2021; Keller et al., 2015; Kim et al., 2022; Martinez-Herrera et al., 2017; Moura-Grec et al., 2014; Nascimento et al., 2015; Suvan et al., 2011). These reports have consistently shown a positive association between periodontitis and obesity. One of the meta-analyses also observed the association between weight gain and incidence of periodontitis, giving a longitudinal perspective as well (Nascimento et al., 2015). In the most recent meta-analysis, it was recognized that the odds of having periodontitis were greater in younger participants living with obesity, aged 18–34 (odds ratio [OR] 2.21, 95% confidence interval [CI] 1.26–3.89) compared to older ones (OR 1.53, 95% CI 1.17–2.00 for those aged 35–54 and OR 1.82, 95% CI 1.16–2.83 for those aged 55 or older) (Kim et al., 2022). This was explained by the presence of fewer risk factors in young people, making obesity a more significant contributor to periodontitis development.

Recent studies have further confirmed the association between obesity and periodontitis. An analysis using data from NHANES 2011–2014 (n = 6662) identified a statistically significant association between periodontitis and obesity (OR 1.18, 95% CI 1.04–1.33) (Liu et al., 2024). Additionally, a subgroup examination revealed that this connection remained significant only in participants aged 30–44 but not in older age groups, aligning with the findings of one of the meta-analyses (Kim et al., 2022). Similarly, an investigation of 60 participants (n = 20 normal weight, BMI 18.5–24.9 kg/m^2; n = 20 participants with overweight, BMI 25–29.9 kg/m^2, and n = 20 participants with obesity, BMI ≥ 30 kg/m^2) conducted in India demonstrated higher periodontal pocket depths and clinical attachment loss in participants living with obesity and overweight compared to those of normal weight (Harris & Rajasekar, 2024). Moreover, a small-scale study of 34 individuals of normal weight and 11 with obesity indicated higher Periodontal Inflamed Surface Area among participants with obesity than among those with normal weight (Lê et al., 2023). This evidence reinforces the link between obesity and periodontitis, highlighting increased attachment loss in individuals with higher body weight.

While the underlying mechanism explaining the association between obesity and periodontitis remains unclear, some potential explanations have been proposed. Obesity-related low-grade inflammation and altered pro- and anti-inflammatory cytokine networks are suggested as one plausible link (Pamuk & Kantarci, 2022). Additionally, a recent study, utilizing the NHANES 2009-2014 dataset, found systemic inflammation to mediate the link between Body Roundness Index and periodontitis (Zhang et al., 2025). A second hypothesis is that the cytokines from adipose tissue and periodontal tissue, combined with unresolved inflammation, contribute to an increased inflammatory burden in individuals with obesity (Pamuks & Kantarci, 2022). This heightened inflammation may, in turn, lead to persistent low-level periodontal inflammation triggered by periodontal bacteria and their virulence factors.

A recent meta-analysis investigated inflammatory markers in serum, GCF, and saliva, comparing individuals with obesity and periodontitis to those of either normal weight and periodontitis or obesity but no periodontitis (Kandaswamy et al., 2024). The analyses showed higher serum concentrations of TNF-α, IL-6, and CRP in those with obesity and periodontitis than in those with only periodontitis. However, no difference was observed when individuals with obesity and periodontitis were compared to those with obesity but without periodontitis, indicating that obesity may play a more crucial role in defining serum inflammatory markers than periodontitis. Additionally, TNF-α and resistin concentrations in GCF were elevated in individuals with obesity and periodontitis compared to those with only periodontitis. Yet, no difference was found when compared to individuals with obesity but without periodontitis.

A meta-analysis regarding salivary concentrations of proinflammatory markers in relation to obesity and periodontitis could not be conducted due to the limited number of studies (Kandaswamy et al., 2024). Salivary IL-1β concentrations in relation to obesity and periodontitis were assessed in two cross-sectional surveys. In the first study of 60 participants, higher salivary IL-1β levels were observed in periodontitis patients of normal weight compared to periodontally healthy individuals of normal weight, yet no connection was noted with obesity (Jentsch et al., 2017). On the contrary, another examination of 96 individuals (47 normal weight, BMI $< 25kg/m^2$, and 49 living with overweight or obesity, BMI $\geq 25kg/m^2$)

identified higher salivary IL-1β in relation to obesity and periodontitis (Kemer Doğan & Duran, 2022). One cross-sectional analysis of 88 subjects evaluated the TNF-α and IL-6 concentrations in relation to obesity and periodontitis. Higher salivary TNF-α and IL-6 were detected in participants with periodontitis, obesity, or both when compared to those without obesity and periodontitis (Kose et al., 2015). IL-6 was also higher in participants with periodontitis and obesity compared to only obesity or only periodontitis, showing some synergistic association between periodontitis and obesity.

Mechanisms other than adipose tissue-related inflammation could also explain the association between obesity and periodontitis. In a recent study of 55 participants (24 in a control group [BMI < 23 kg/m^2] and 31 participants living with obesity [BMI ≥ 30 kg/m^2]), different oral microbiota were observed between groups in samples obtained from saliva, buccal swabs, and subgingival plaque (Kim et al., 2025). The samples form obesity group were more enriched with periodontopathogens than control group. Another study of 45 participants proposed different microbiota in periodontal pockets in participants with obesity when compared to normal-weight subjects, revealing a higher amount of Gram-positive bacteria and reduced microbial diversity in relation to obesity (Lê et al., 2023). Altered subgingival microbiota among participants living with obesity and periodontitis was also observed in an earlier study (Maciel et al., 2016). Moreover, periodontitis and obesity share some comorbidities, such as type 2 diabetes and glucose intolerance, which may act as a link between obesity and periodontitis (Marruganti et al., 2023). Obesity and periodontitis also have common risk factors, including unhealthy eating, low physical activity, and low socioeconomic status (Blüher, 2019; Iwasaki et al., 2018; Khajavi et al., 2022).

Table 2. Meta-analysis and systematic reviews regarding the association between periodontitis and overweight, obesity, or weight gain in adults

Study	Study design and number of studies included	Study design in included studies	Study question	Main finding
Kim et al., (2022)	Systematic review and meta-analysis, n = 37	Observational studies	To update the earlier meta-analysis of Moura-Grec et al. (2014) and analyze the association between obesity and periodontitis with subgroup analyses.	OR = 1.35 (95% CI 1.05–1.75), increased odds for periodontal disease in participants with obesity compared to those of normal weight. When ORs were stratified by age, there was OR = 2.21 (95% CI 1.26–3.89) in ages 18–34, OR = 1.53 (95% CI 1.17–2.00) in ages 35–54, and OR = 1.82 (95% CI 1.16–2.83) in ages 55+.
da Silva et al., (2021)	Systematic review and meta-analysis, n = 90	Observational studies	Do individuals with obesity or overweight present higher clinical measures of gingival inflammation compared to those of normal weight?	In gingivitis or periodontitis patients: Individuals with obesity had higher measures of gingival inflammation (bleeding on probing, gingival index, or marginal gingival bleeding) than those of normal weight.
Martinez-Herrera et al., (2017)	Systematic review, n = 28	Clinical trials and observational studies	Do obese subjects have more periodontal disease? Is periodontal disease more aggressive in the obese? What biological mechanism is involved in that association?	17 out of 19 observational studies found an association between periodontitis and obesity.
Keller et al., (2015)	Systematic review, n = 13	Clinical trials and observational studies	To examine the time-dependent association between obesity and periodontitis.	Overweight, obesity, weight gain, and increased waist circumference may be a risk factor for developing periodontitis.
Nascimento et al., (2015)	Systematic review and meta-analysis, n = 5	Observational studies	Association of weight gain with incidence of periodontitis.	Subjects who became overweight (RR = 1.13, 95% CI 1.06–1.20) or obese (RR = 1.33, 95% CI 1.21–1.47) had a greater risk of developing periodontitis than those who stayed at a normal weight for the same period.

Study	Study design and number of studies included	Study design in included studies	Study question	Main finding
Moura-Grec et al., (2014)	Systematic review and meta-analysis, n = 31	Observational studies	To analyze the association between overweight or obesity and periodontitis.	OR = 1.30 (95% CI 1.25–1.35), increased odds of overweight or obese participants having periodontitis compared to normal-weight participants.
Suvan et al., (2011)	Systematic review, n = 33	Observational studies	To analyze the association between overweight or obesity and periodontitis.	OR = 2.13 (CI 1.40–3.26), increased odds of overweight or obese participants having periodontitis compared to normal-weight participants.
Chaffee & Weston, (2010)	Systematic review and meta-analysis, n = 28	Observational studies	To analyze the association between obesity and periodontitis.	OR = 1.35 (95% CI 1.23–1.47) for an association between prevalent periodontal disease and obesity.

OR = odds ratio, RR = relative risk.

2.4 The role of diet in systemic and oral health

2.4.1 Diet quality predicting overall health

The habitual diet comprises foods and beverages consumed daily (Hu, 2002). The components of the habitual diet act synergistically to affect health; therefore, diet quality may predict overall health or disease risk better than single nutrients or foods. Several indices or scoring systems attempt to measure the quality of a diet. The Healthy Eating Index (HEI) assesses adherence to the Dietary Guidelines for Americans (Shams-White et al., 2023). These guidelines are updated every five years, so HEI is regularly updated to correspond to the latest guidelines. The Alternative Healthy Eating Index (AHEI) was created in 2002 and updated in 2012. As an alternative to HEI, AHEI is more predictive of chronic disease risk (Chiuve et al., 2012). The Dietary Approaches to Stop Hypertension (DASH) is a diet rich in fruits, vegetables, low-fat dairy products, and reduced saturated and total fat, which lowers systolic blood pressure (Appel et al., 1997). Over time, DASH has been widely studied and was associated with reduced all-cause mortality (Soltani et al., 2020) and other health outcomes (Morze et al., 2020).

Each country or region has its own characteristic food culture, including local food preferences, taste preferences, cooking methods, and eating habits (Sproesser et al., 2022). Therefore, when investigating the association between dietary patterns and health, a culturally specific dietary index can provide more accurate information on the diet of the investigated population. Perhaps the most popular culture-specific dietary index is the Mediterranean diet, which reflects the traditional diet of the Mediterranean region (Trichopoulou et al., 1995). In the Nordic countries, adherence to a healthy Nordic diet may be evaluated with the Baltic Sea Diet Score (BSDS) (Kanerva, Kaartinen, et al., 2014) or the Healthy Nordic Food Index (Olsen et al., 2011). BSDS was developed in 2012 and was based on the Baltic Sea Diet Pyramid, which was created by the University of Eastern Finland, the Finnish Heart Association, and the Finnish Diabetes Association, as a template (Kanerva, Kaartinen, et al., 2014). Higher BSDS scores represent adherence to the Baltic Sea diet and associate well with health-promoting nutrients—including fiber, vitamins A, C, and D, and folate—in a Finnish population-based cohort of 4,710 participants. Afterwards, higher BSDS scores have been inversely associated with lower serum CRP concentration in three separate Finnish cohorts (Kanerva, Loo, et al., 2014; Tertsunen et al., 2022). Moreover, higher BSDS has been related to a lower incidence of type 2 diabetes (Tertsunen et al., 2021) and a lower risk of all-cause mortality (Tertsunen et al., 2020) among middle-aged Finnish men.

The DII is a literature-derived scoring system that quantifies the inflammatory properties of diet and distinguishes dietary patterns from anti-inflammatory to proinflammatory (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014). The index was developed in response to the finding that the diet influences low-grade inflammation—a risk factor for several diseases. DII is based on 1943 peer-reviewed research articles examining the diet's effect on inflammation. The reviewed studies examined the relationship between foodstuffs or nutrients and specific inflammatory markers in serum (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP). Studies were weighted according to study characteristics (human experimental, prospective cohort, case-control or cross-sectional study, experimental animal study, cell culture study); using these weighted values, the overall inflammatory effect scores were calculated for each food component. Final DII includes 45 foodstuffs or nutrients associated with decreasing or increasing inflammatory markers. The dietary components that decreased the serum inflammatory markers in literature received anti-inflammatory effect scores (e.g., polyunsaturated fatty acids, inflammatory effect score -0.337 or Vitamin D, inflammatory effect score -0.446); those components that increased the inflammatory markers received proinflammatory effects scores (e.g., saturated fat, inflammatory effect score 0.373 or iron intake, inflammatory effect score 0.032).

Several studies have shown an association between DII and inflammatory markers in serum, such as CRP, IL-6, and TNF-α (Millar et al., 2022; Shivappa et al., 2017; Shivappa, Steck, Hurley, Hussey, Ma, et al., 2014; Tabung et al., 2015). Higher DII scores have also been associated with multiple systemic diseases such as cardiovascular diseases (M. K. Choi et al., 2023), different types of cancers (Abulimiti et al., 2020; Gholamalizadeh et al., 2022), and diabetes mellitus (Denova-Gutiérrez et al., 2018).

2.4.2 Dietary patterns and periodontitis

The association of four dietary patterns (HEI, AHEI, DASH, and alternate Mediterranean diet) with the severity and progression of periodontitis was analyzed in an OsteoPerio cohort study of 1,197 post-menopausal women aged 51–83 (Yue et al., 2024). All study participants were recruited from the Women's Health Initiative Observational Study in Buffalo, New York. Better adherence to healthy dietary patterns was associated with better clinical periodontal measures, including reduced clinical attachment loss and fewer teeth lost due to periodontitis. However, after five years of follow-up, those adherent to a healthy diet have greater progression in alveolar bone loss. This may be explained by the tendency to extract teeth with the poorest diagnosis, which has improved the periodontal health in those with the most severe condition. The sensitive analyses conducted in the study supported this possibility. A Finnish study using the data from the population-based Health 2000 survey analyzed the association between the BSDS and periodontal condition in participants aged 30–49 and 50–79 (L. Jauhiainen et al., 2016). They found the BSDS to be inversely associated with gingival bleeding, especially in younger age groups and among those with poor oral hygiene. A low-quality diet, as assessed by the BSDS, was associated with an increased risk of periodontal pocket formation over an 11-year follow-up (L. M. Jauhiainen et al., 2020).

As periodontitis is an inflammatory disease, there has been interest in evaluating the inflammatory potential of diet in relation to gingivitis and periodontitis. A randomized controlled trial of 30 participants with gingivitis evaluated the effect of an anti-inflammatory diet –defined by the exclusion of processed carbohydrates and industrial animal proteins, and increased intake of omega-3 fatty acids, vitamins C and D, antioxidants, fiber, and nitrate-rich vegetables –on periodontal parameters (Woelber et al., 2019). After 4 weeks, participants in the experimental group showed reduced gingival inflammation, despite unchanged plaque levels, when compared to controls. A positive association of the DII with periodontitis was first recognized in the study using the data from NHANES 2011–2014 (Li et al., 2021). The study population of 7,081 participants (aged ≥ 30) showed a non-linear, positive relationship between moderate and severe periodontitis, with increasing risk, especially after DII scores reached the value of 2. Since then, the higher DII scores have been linked to an increased risk of periodontitis in other studies (S. W. Choi et al., 2023; Feng et al., 2022; Ghaemmaghami et al., 2023; Machado, Botelho, Viana, et al., 2021). However, a recent study, also utilizing the dataset from NHANES 2009-2014, found an inverse association between DII and periodontitis (Zhang et al., 2025). Another perspective for the diet's inflammatory potential was evaluated in a cohort study of older Hamburg citizens (n = 6209, age 45–75), in which they constructed their own anti-inflammatory dietary score (Lieske et al., 2023). They also found higher anti-inflammatory dietary scores to be associated with lower odds of periodontitis.

Systemic inflammation may mediate the association between diet and periodontitis. Diet can modulate systemic inflammation in several ways, including adipose tissue remodeling, increased free fatty acids/saturated fatty acids concentration in the bloodstream, bioactive compounds in a plant-based diet, or through modifying gut microbiota, among others (Minihane et al., 2015). The other mechanisms explaining the link between diet and periodontitis may include the antioxidant capacities of different vitamins or the glycemic index induced by dietary carbohydrates (Martinon et al., 2021). Moreover, dietary habits potentially affect subgingival microbiota, even though the significance of this in periodontitis development has not been established (Khocht et al., 2021; Molinsky et al., 2025).

2.5 Summary of the literature and gaps in previous knowledge

Convincing evidence shows that periodontitis is associated with systemic inflammation as well as with local inflammation in the oral cavity. This is supported by numerous studies reporting increased levels of inflammatory markers in serum and saliva among individuals with periodontitis when compared to healthy controls. Obesity is also well-established as a strong contributor to low-grade systemic inflammation. However, only a limited number of studies have evaluated the association between obesity and inflammatory markers in saliva, and their results have been inconclusive. Moreover, saliva has not been routinely used to assess obesity-related inflammation, partly due to the unavailability of established reference values. As periodontitis and obesity are inflammatory diseases, it is commonly speculated that inflammation could provide a link between these two conditions. In addition, diet quality may be associated with the inflammatory markers in circulation. Some evidence also shows the link between diet quality and periodontitis. Yet, the association between diet quality and salivary cytokine levels remains unexplored, with only one study currently available.

So far, no studies have investigated how concurrent exposure to non-adherence to the Baltic Sea diet or adherence to the proinflammatory diet, obesity, and periodontitis, is related to inflammatory markers in the oral cavity or bloodstream. This study aimed to fill this gap in knowledge by analyzing how these three variables together are associated with local inflammation in the oral cavity and long-term serum CRP concentration. Additionally, it explored whether inflammatory markers could explain the relationship between diet quality, obesity, and periodontitis. Saliva and serum contain valuable biomarkers for diagnostic tools, but their interpretation requires an understanding of the local and systemic factors that influence them. Moreover, this research supports a comprehensive approach to human health, where diet and oral health are recognized as integral components of overall systemic well-being.

3 Aims

This PhD study generally aims to investigate the relationship between periodontitis, diet quality, and obesity and explore their associations with systemic and salivary inflammatory markers. More precisely, the study focuses on Finnish adults aged 30 years and over who were examined in three population-based surveys conducted between 2000 and 2011. The hypotheses and specific research questions are:

1. Is severe obesity associated with increased inflammatory biomarkers in saliva? (**Study I**)

   Hypothesis: Obesity, which is associated with systemic low-grade inflammation, is also associated with increased inflammatory cytokine concentrations in saliva.

2. Is the inflammatory potential of diet associated with cytokine concentrations in saliva? (**Study II**)

   Hypothesis: The inflammatory potential of diet is associated with salivary cytokine concentrations, especially in participants with periodontitis.

3. Are non-adherence to the Baltic Sea diet or adherence to the proinflammatory diet and advanced periodontitis associated with serum CRP concentration at baseline and after an 11-year follow-up? (**Study III**)

   Hypothesis: The simultaneous presence of non-adherence to the Baltic Sea diet or adherence to the proinflammatory diet and periodontitis compounds the risk for increased CRP concentrations in serum.

4 Materials and Methods

4.1 Study population

4.1.1 The DILGOM study

The DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) study was an extension of the population-based National FINRISK 2007 study (FINRISK, 2007) conducted between January and March 2007 by the Finnish Institute for Health and Welfare (THL) (Borodulin et al., 2018; Konttinen et al., 2018). FINRISK 2007 is a part of the long-term study series that assesses cardiovascular and other non-communicable disease risk in the Finnish population every five years. In the FINRISK 2007 study, a random sample of 11,953 adults (aged 25–74, stratified by area, sex, and 10-year age group) from five geographical study areas aged 25–74 was drawn from the National Population Information System and invited to a health examination. All those who participated in the health examination (n = 6,258, 53%) were also invited to participate in the DILGOM study, which was conducted three months later—from April to June 2007 (Figure 3). Of those, 5,024 (84%) got involved (2325 men and 2699 women)(Table 3).

In **Studies I** and **II**, all DILGOM participants living with severe obesity (BMI ≥ 35 kg/m^2, n = 287) were selected to study more precisely the association with obesity and selected biomarkers. For those participants with obesity, 293 of their age- and smoking status-matched controls with normal weight (BMI 18.5–25 kg/m^2) were included. Exclusion criteria for both groups were diabetes, cardiovascular diseases, cancers, or medication for hypercholesterolemia.

4.1.2 The Health 2000 Survey

The Health 2000 survey (H2000) was a nationally representative study that the THL conducted from 2000 to 2001 to acquire information on Finland's public health problems, their causes and treatments, and the population's functional capacity (Heistaro, 2008). The main sample comprised 8,028 participants (3637 men and 4391 women) aged 30 year or older from 80 health centers (Figure 3). Of those invited, 6,986 (87%) were interviewed in their home or an institution, and 6,770 (84%) participated in a proper health examination or an at-home examination. A clinical oral examination was accomplished as part of a proper health examination for 6,335 participants (Suominen-Taipale et al., 2008), and paraffin-stimulated whole saliva samples were collected in the southern district from 1,294 participants (Könönen et al., 2007).

Study II includes participants of H2000 whose salivary samples were available and whose periodontal status was generalized periodontitis (probing pocket depth [PPD] ≥ 4 mm at 14 or more teeth, n = 84) and their non-periodontitis controls (all teeth with PPD < 4 mm, n = 81), resulting in 165 participants. **Study III** includes all participants who had hs-CRP concentrations measured in H2000 and Health 2011 (H2011) studies (n = 3434) (Figure 3). Exclusion criteria were CRP concentration above 10 mg/l, representing acute inflammation (n = 75 at baseline and n = 127 at follow-up), and missing data from clinical oral examination at baseline, resulting in 3,058 participants for baseline analysis and 3,007 for follow-up analysis.

4.1.3 The Health 2011 Survey

The H2011 survey was a follow-up study of H2000 (Lundqvist & Mäki-Opas, 2016). All participants of the H2000 study who were alive and steadily living in Finland, had available contact details, and had not refused further participation were invited to participate in H2011 during 2011 and 2012. Furthermore, participants of the young adult sample of the H2000 were invited but not included in the current study. Altogether, 8,135 individuals were invited, and 5,903 (74%) participated.

Table 3. Gender and age distribution in original DILGOM, Health 2000, and Health 2011 surveys and among selected participants in the current study.

	N	Men	%	Women	%	Mean age (years)	Age range (Years)
DILGOM	5024	2325	46	2699	54	53	25–74
Participants in **Study I**	580	196	34	384	66	55	25–74
HEALTH 2000	8028	3637	45	4391	55	54	30–99
Participants in **Study II**	147	69	47	78	53	49	40–60
Participants in **Study III**	3434	1542	45	1892	55	49	30–86

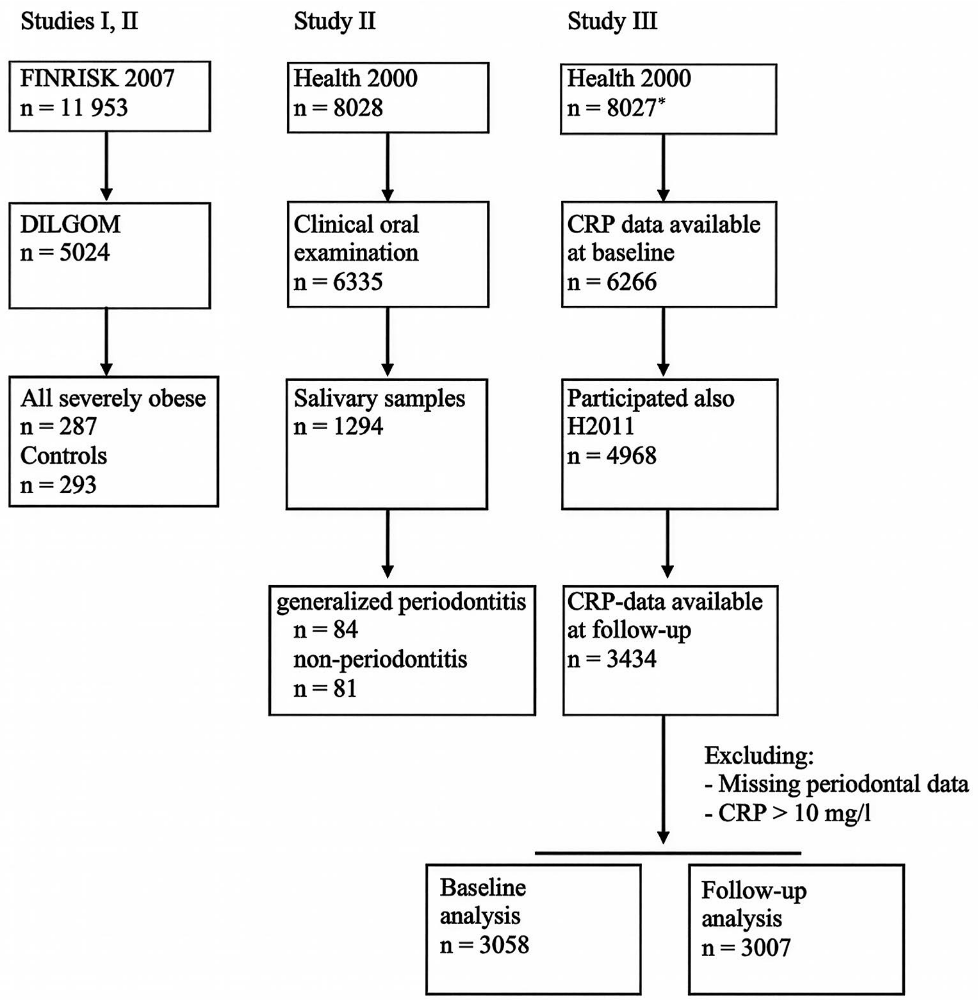

Figure 3. Flowchart for selection of study participants. * One participant asked to be removed from the H2000 -study between the publication of Studies II and III.

4.2 Exposure variables

Table 4 summarizes the variables examined in this study.

Table 4. Summary of variables used in the present study.

	Research method	**Data source**	**Sub-study**
Exposure variables			
Periodontal status	CRS	Saliva	Study I
	PPD	Clinical oral examination	Studies I, II
Diet quality	DII	FFQ	Studies II, III
	BSDS	FFQ	Study III
Obesity	BMI	Measurement of height and weight, questionnaire	Studies I, II, III
Outcome variables			
Salivary inflammatory markers	Luminex and ELISA	Saliva	Studies I, II
Serum CRP	ELISA	Serum	Study III
Covariates			
Age	Questionnaire/ interview	Self-reported	Studies I, II, III
Smoking status	Questionnaire/ interview	Self-reported	Studies I, II, III
Physical activity	Questionnaire/ interview	Self-reported	Studies II, III
Education level	Questionnaire/ interview	Self-reported	Studies I, II, III
HbA1C	Immunoturbidometric	Serum	Studies II, III
Use of lipid-modifying agents	Interview	Self-reported	Study III
Body mass index	BMI	Measurement of height and weight, questionnaire	Studies II, III

CRS = cumulative risk score, PPD = probing pocket depth, DII = Dietary Inflammatory Index, BSDS = Baltic Sea Diet score, BMI = body mass index, FFQ = food frequency questionnaire, ELISA = enzyme-linked immunosorbent assay, HbA1C = glycated haemoglobin.

4.2.1 Periodontal status

Cumulative Risk Scores

DILGOM defined periodontal status according to CRS—a mathematical model to determine one's risk of periodontitis (Gürsoy et al., 2011). It includes the salivary concentrations of *P.gingivalis*, IL-1β, and MMP-8. Salivary IL-1β and MMP-8 were analyzed with the flow-cytometric Luminex xMAP technique (Bio-PlexTM 200, Bio-Rad Laboratories Incorporation, USA), and the salivary *P.gingivalis* levels were analyzed with quantitative real-time PCR using Mx3005P Real-Time QPCR System (Stratagene). Details of *P.gingivalis* analyses are published earlier (Hyvärinen et al., 2009). The concentration of each biomarker in saliva was divided into tertiles and converted to the numerical values 1, 2, or 3. One's cumulative scores were calculated by multiplying three biomarkers' tertile values. Individuals were then divided into groups: CRS I, the lowest risk (cumulative scores 1, 2, 3); CRS II, medium risk (cumulative scores 4, 8, 9); and CRS III, the highest risk of having periodontitis (cumulative scores 12, 18, 27). In **Study I**, participants were categorized into three CRS groups. In **Study II**, participants with CRS I were classified as non-periodontitis if they were in CRS I, and those with CRS II or III were classified as having periodontitis.

Clinical assessment

Five field teams, each including one dentist who conducted the examination, performed clinical oral examinations during the H2000 field stage (Suominen-Taipale et al., 2008). The periodontal pocket depths were measured at four points around each tooth (excluding third molars and residuals): the distal and mesial angles, as well as the midpoint of the oral and buccal sides. The deepest measurement from each tooth was registered. Periodontal status was categorized in **Study II** as non-periodontitis (NP) if there were no teeth with PPD ≥ 4 mm and generalized periodontitis if there were at least 14 teeth with PPD ≥ 4 mm. In **Study III**, periodontal status was categorized as NP (PPD < 4 mm), moderate periodontitis (MP, PPD = 4–5 mm), or advanced periodontitis (AP, PPD ≥ 6 mm).

A reference dentist, who took repeat and parallel measurements of pocket depths during several visits to each field team, ensured the quality assurance of an oral health examination. Altogether, parallel measurements were conducted in 269 participants and repeat measurements for 111. The agreement on pocket depth measurements between the reference dentist and field dentist was 77% (κappa value 0.41). Furthermore, the repeated measurements for randomly selected participants showed a κappa value of 0.83.

4.2.2 Dietary assessment

Food Frequency Questionnaire

Food frequency questionnaire (FFQ) is a retrospective method to assess diet over long periods (Sierra-Ruelas et al., 2021). FFQ is considered cost-effective and easy to implement. Unlike food records—prospective methods usually encompassing several consecutive days—FFQs are less burdensome for participants and are suitable for extensive epidemiological studies (Kowalkowska et al., 2013). While food records provide accurate data on food or nutrient intake during a few days, FFQ is more suitable for ranking participants based on their food intake. The benefit of FFQ is its ability to cover long-term dietary habits, making it ideal for studying the habitual diet. Therefore, FFQ is commonly used to analyze the associations between diet and chronic diseases, which tend to develop over time.

In the DILGOM and H2000 studies, the diet quality of study participants was assessed by a validated semi-quantitative FFQ, including a list of approximately 130 food items and dishes (Kaartinen et al., 2012; Montonen et al., 2008). It measured the diet over the preceding 12 months. In DILGOM, participants completed the FFQ during the health examination at the study site, and a trained nurse reviewed the questionnaire. In contrast, participants of H2000 received the FFQ during the health examination, completed it at home, and returned it to THL, where nutrition researchers reviewed the questionnaires. Participants were advised to record the frequency of consumption for each food item or dish, 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., a slice and a glass). Additionally, participants could report other frequently consumed foods that were not listed. The dietary data were converted into average daily food and nutrient intake using the National Food Composition Database, Fineli, and the Finessi software of THL (Reinivuo et al., 2010). The dietary information was missing for 13 DILGOM (**Study I**) and 18 H2000 participants (**Study II**). All H2000 participants in **Study III** adequately completed the FFQ

Dietary Inflammatory Index

The diet's inflammatory potential was analyzed with the DII. The DII was calculated using the creators' instructions (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014). First, the intake of each available food component was standardized against the world intake database. A z-score was created for each food component by subtracting the world standard mean from actual food intake and dividing the difference by the world reference standard deviation. Second, to minimize the effect of right skewing, the z-score was converted to percentile scores. The percentile score was then doubled, and '1' was subtracted to achieve a symmetric distribution with values centered on 0 (null) and bounded between -1 and +1, allowing the comparison of the DII scores between studies. Third, these centered percentiles were multiplied by their representative 'food parameter specific inflammatory effect score' provided by the authors. Finally, the 'food parameter-specific overall inflammatory effect scores' were summed to create the overall DII scores for each participant. The theoretical range for DII scores, when all food components are included, is from -8.87 to 7.98, representing a maximally anti-inflammatory (scores have a minus sign) to a maximally proinflammatory diet, respectively.

As the original DII includes total fat and all separate fatty acids, there is a risk of overestimating the impact of fat. Furthermore, alcohol is classified as an anti-inflammatory food component (the food parameter-specific inflammatory effect score has a minus sign); therefore, increased alcohol consumption increases the diet's anti-inflammatory properties. However, only moderate consumers have recognized alcohol's anti-inflammatory properties (Avellone et al., 2006; Sierksma et al., 2002). These issues were addressed by excluding the total fat intake from the index and by setting the inflammatory weight for alcohol at zero for those consuming alcohol more than 40 g/d, following the approach used in The European Investigation into Cancer and Nutrition Study (Agudo et al., 2018). The DII used in the present investigation included 29 of 45 original dietary components (Table 5). The missing dietary components were mainly spices, as FFQ could not accurately measure their amounts.

Baltic Sea Diet Score

Adherence to the Baltic Sea diet was assessed with BSDS. The original BSDS included nine dietary components common in Nordic food culture (Kanerva, Kaartinen, et al., 2014). This study used a modified BSDS excluding total fat, thus including only eight dietary components (Männistö et al., 2021) (Table 6). The intake of each component, except alcohol, was scored according to sex-specific consumption quartiles receiving the numerical values 0, 1, 2, or 3. For meat products, the scoring was reversed. For alcohol, the cut-off for moderate consumption was assigned according to Finnish nutrition recommendations published in 2014 (National Nutrition Council, 2014). Men consuming ≤ 20 g and women consuming ≤ 10 g of ethanol per day received 1 point, while others received 0. The total BSDS scores ranged from 0 to 22, with higher scores representing greater adherence to the Baltic Sea diet.

Table 5. Dietary components of the original Dietary Inflammatory Index which are included and not included in the present study (Shivappa, Steck, Hurley, Hussey, & Hébrt, 2014).

Dietary components included	Dietary components not included
alcohol, carbohydrates, cholesterol, energy, fiber, monounsaturated fatty acids, n-3 fatty acids, n-6 fatty acids, protein, polyunsaturated fatty acids, saturated fatty acids, trans fats, β-carotene, folic acid, iron, isoflavones, magnesium, niacin, riboflavin, selenium, thiamin, vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, zinc, green/black tea	total fat, anthocyanidins, flavan-3-ol, flavones, flavonols, flavanones, garlic, ginger, onion, pepper, rosemary, saffron, thyme/oregano, turmeric, thyme/oregano, caffeine, eugenol

Table 6. Dietary components of Baltic Sea Diet Score (Kanerva, Kaartinen, et al., 2014)*.

Dietary component	Content
Fruits and berries	Apples, berries, pears
Vegetables	Cabbage, cucumber, lettuce, peas, roots, tomato
Whole-grain products	Barley, oats, rye
Low-fat milk	Fat-free milk and milk < 2%
Fish	Freshwater fish, salmon
Meat products	Beef, pork, processed meat products, sausages
Fatratio	A ratio of polyunsaturated fatty acids to saturated fatty acids and trans-fatty acids
Alcohol	Ethanol

* Updated from the original version by excluding total fat from the score.

4.2.3 Body Mass Index

Height and weight were measured as part of the health examination during the field stage of DILGOM and H2000. If these measurements were unavailable, self-reported height and weight were used from the questionnaire. BMI (kg/m^2) was calculated from height and weight. **Study I** participants were normal weight (BMI 18.5–25 kg/m2) or living with severe obesity (BMI ≥ 35 kg/m2). In **Studies II** and **III**, BMI was used as a continuous variable.

4.2.4 Categorization of study participants

Study III categorized participants into four groups according to their risk factors for elevated serum CRP (non-adherence to the Baltic Sea diet/adherence to the proinflammatory diet and advanced periodontitis). Before categorization, the participants were divided into tertiles according to their BSDS or DII scores, where BSDS tertile 1 represents those with the least adherence to the Baltic Sea diet. In contrast, DII tertile 3 represents those with the most proinflammatory diet. In the analyses evaluating the non-adherence to the Baltic Sea diet in combination with advanced periodontitis, the participants were grouped as follows:

Reference (R1): participants who adhered to the Baltic Sea diet (BSDS tertiles 2 or 3) and not diagnosed with advanced periodontitis (non-periodontitis or moderate periodontitis)

Non-adherence to the Baltic Sea diet (BSDS1): participants who were at BSDS tertile 1 and not diagnosed with advanced periodontitis

Advanced periodontitis (AP1): participants who were diagnosed with advanced periodontitis and adhered to the Baltic Sea diet (BSDS tertile 2 or 3)

Non-adherence to the Baltic Sea diet and advanced periodontitis (BSDS1 and AP1): participants who were at BSDS tertile 1 and diagnosed with advanced periodontitis

In the analyses evaluating the association of proinflammatory diet combined with advanced periodontitis, the participants were grouped as follows:

Reference (R2): participants who adhered to anti-inflammatory diet (DII tertiles 1 or 2) and not diagnosed with advanced periodontitis (non-periodontitis or moderate periodontitis)

Proinflammatory diet (DII3): participants who adhered to proinflammatory diet (DII tertile 3) and not diagnosed with advanced periodontitis

Advanced periodontitis (AP2): participants who were diagnosed with advanced periodontitis and adhered to an anti-inflammatory diet (DII tertile 1 or 2)

Proinflammatory diet and advanced periodontitis (DII3 and AP2): participants who adhered to a proinflammatory diet (DII tertile 3) and had advanced periodontitis

4.3 Outcome variables

4.3.1 Salivary cytokines

Paraffin-stimulated saliva samples were collected into calibrated medical cups and divided into two Eppendorf tubes (Könönen et al., 2007). Samples were frozen immediately in carbonic acid ice for one to three days before and during transportation to THL. At THL, samples were stored at -70 °C until laboratory analyses. Melted samples were centrifuged at 10,000 g for 5 min in DILGOM and 3 min in H2000. In DILGOM, salivary concentrations (pg/ml) of IL-1β, IL-1Ra, IL-6, IL-8, IL-10, TNF–α, and MMP-8 were analyzed with the flow-cytometric Luminex xMAP technique with commercially available kits (Bio-PlexTM 200, Bio-Rad Laboratories Incorporation, USA). In H2000, salivary concentrations (pg/ml) of IL-1β, IL-6, and TNF-α were determined using commercial Enzyme-Linked Immuno-Sorbent Assay (ELISA) kits (GE Healthcare, Buckinghamshire, UK). Table 7 presents the lowest limit of detection (LLOD) for biomarkers. At H2000, salivary IL-6 and TNF-a concentrations were not included in further analyses due to the high percentage of data left under the LLOD.

Table 7. The lowest limit of detection (LLOD) for biomarkers used in the study.

Biomarker	LLODs (pg/ml) in DILGOM[1] study	LLODs (pg/ml) in Health 2000[2] study
IL-1β	0.8	< 1.0
IL-1RA	5.5	N/A
IL-6	2.8	< 1.0
IL-8	1.0	N/A
IL-10	0.3	N/A
TNF-A	6.0	< 5.0

1 = cytokines were analyzed with the flow-cytometric Luminex xMAP technique with commercially available kits (Bio-PlexTM 200, Bio-Rad Laboratories Incorporation, USA), 2 = cytokines were analyzed with commercial ELISA kits (GE Healthcare, Buckinghamshire, UK). IL = interleukin, Ra = receptor antagonist, TNF = tumour necrosis factor, N/A = unavailable, ELISA = enzyme-linked immunosorbent assay.

4.3.2 Serum C-reactive protein

In H2000 and H2011, venous blood samples were collected after four hours of fasting. Samples were centrifuged at examination sites and stored at -20 °C within 45–60 minutes. Samples were transferred in dry ice to THL and stored at -70 °C until analyses. In H2000, serum hs-CRP was determined using an ultrasensitive immunoturbidometric test (Orion Diagnostica, Espoo, Finland) with Optima analyzer (Thermo Electron Corporation, Vantaa, Finland) and in H2011 with an immunoturbidometric test (CRP Vario) with Abbott c8000 analyzer (Abbott Laboratories, Abbott Park, IL, USA). The LOD was 0.2 mg/l. All values below the LOD were coded as 0.1 mg/l.

4.4 Covariates

Age, smoking, physical activity, and education were self-reported in DILGOM through a questionnaire and in H2000 during interviews. Smoking was categorized as current or non-smokers in **Study II** and as current, former, and non-smokers in **Study III**. Leisure-time physical activity was categorized into two groups: those who participated in physical activity or light activity (e.g., walking or cycling) for at least four hours per week and those who participated in moderate physical activity for at least three hours per week or vigorous exercise (e.g., competitive sport). Education was categorized into two groups based on the education level: basic education and vocational or higher education. Height and weight were measured during the survey or recorded as self-reported data. Glycated hemoglobin (HbA1c) concentration was determined with an immunoturbidimetric method (Hemoglobin A1c assay; Abbott Laboratories). Medication use for lipid-modifying agents was self-reported. The covariates were chosen based on their known association with systemic inflammation or periodontal health (Chen et al., 2025; Genco & Borgnakke., 2013).

4.5 Statistical analyses

All statistical analyses were conducted with IBM SPSS Statistics 28.0. Before analysis, normal distributions of continuous variables were checked with the Kolmogorov–Smirnov test or visually with bar charts. Due to their skewed distributions, a log transformation was made to DII, energy intake, salivary cytokine concentrations, and serum CRP concentrations. Cytokine and CRP concentrations did not reach complete normality after log transformation; therefore, non-parametric analyses were used to compare the differences between groups. In a multinomial logistic regression using salivary cytokine as an outcome, cytokines were divided into tertiles.

The basic characteristics of the study population between non-periodontitis and periodontitis patients were analyzed with the Mann–Whitney U test (continuous variables) and chi-square test (categorical variables) (Table 8).

Differences in salivary cytokines between study groups were examined with the Mann–Whitney U (**Study I**), Wilcoxon signed-rank test (**Study II**), or the Kruskal–Wallis test (**Study II**). When analyzing the association of diet and periodontitis with systemic inflammation, the serum CRP concentration between the four study groups was analyzed with the Kruskal–Wallis test (**Study III**).

Associations between DII and categorized salivary cytokines were analyzed using multinomial logistic regression analysis. Both subgroups—DILGOM and H2000—were analyzed separately. Model 1 included DII as an independent variable and salivary cytokine tertiles as a dependent variable, using tertile 1 as the reference, and was adjusted for energy intake. Model 2 was adjusted for periodontitis and energy intake. Model 3 was further adjusted for age, education, smoking, BMI, and physical activity. The main effects for each variable were analyzed. A p-value of <0.05 was considered statistically significant.

The chi-square test was used to analyze if the periodontitis was associated with the change in serum CRP concentration during 11 years of follow-up. Binary logistic regression analysis was used to determine the association between the diet perceptions of periodontitis patients and elevated (≥ 2 mg/l) serum CRP concentrations during the follow-up period. Model 1 included four groups as an independent factor and serum CRP $\geq$ 2mg/l as an outcome variable and was adjusted for energy intake at baseline. Model 2 was further adjusted with baseline age, BMI, smoking status, physical activity, education level, CRP, HbA1c, medication of lipid-modifying agents, and energy intake.

Table 8. Summary of statistical methods used in this study.

The study question examined	Statistical method	Study
Is there a difference in variables describing the basic characteristics of study participants divided into periodontitis and non-periodontitis groups?	Mann–Whitney U test Chi–square	Study II
Is there a difference in the DII or BSDS scores between periodontitis and non-periodontitis?	Mann–Whitney U test Kruskal–Wallis test	Study II
Is there a difference in salivary cytokine concentrations between periodontitis and non-periodontitis?	Wilcoxon signed-rank test	Study II
Is there a difference in salivary cytokine concentrations between CRS groups? A pairwise analyses of each group.	Mann–Whitney U test	Study I
Is there a difference in salivary cytokine concentrations between normal weight and obese?	Mann–Whitney U test	Study I
Is there a difference in salivary cytokine concentrations between DII tertiles?	Kruskal–Wallis test	Study II
Is DII associated with salivary cytokine concentration tertiles?	Multinomial logistic regression	Study II
Is there a difference in serum CRP concentration between participants grouped according to dietary preferences and periodontal status?	Kruskal–Wallis test	Study III
Is periodontal status associated with the change of serum CRP concentration during 11 years of follow-up?	Chi–square	Study III
Is a combination of diet and periodontal status associated with increased serum CRP (>2mg/l) concentrations after 11 years of follow-up?	Binary logistic regression	Study III

CRP = C-reactive protein, DII = Dietary Inflammatory Index, BSDS = Baltic Sea Diet Score.

4.6 Ethical considerations

The Ethical Committee of the Hospital District of Helsinki and Uusimaa (Health 2000, 15.7.2004 reference 407/E3/2000; Finriski 27.2.2007, reference 229/E0/06; and Health 2011, 22.3.2011 reference 45/13/03/00/11) approved all studies, and written informed consent was obtained from each participant. Before attending, participants received detailed information about the study. Participation was voluntary, and participants could withdraw from the study at any time. Examination codes were used throughout the study to secure the personal data of participants. The data was stored and processed according to the General Data Protection Regulation (GDPR) of the European Union, the instructions of the University of Turku and THL, and the Data Protection Act of Finnish legislation.

Artificial intelligence (Grammarly, Microsoft Copilot) was used for language editing in this dissertation, specifically for revisions made after the review process and the initial professional language check.

5 Results

5.1 Baseline characteristics

As Table 9 presented, some demographic differences exist between DILGOM and H2000 study populations categorized by the presence of periodontitis. The subpopulations drawn from DILGOM and H2000 in the present study differ in the sampling approach. Specifically, DILGOM participants were categorized into groups of those living with severe obesity and those with normal weight. This difference was especially evident in BMI; while both studies showed higher BMI measures in participants with periodontitis than non-periodontitis, the difference was more pronounced in DILGOM participants.

Table 9. Basic characteristics of DILGOM and H2000 study populations according to their periodontal status.

	DILGOM			H2000		
	Non-periodontitis[a]	Periodontitis	P-value	Non-periodontitis[b]	Periodontitis	P-value
N (%)	138 (23.8)	442 (76.2)		1,184 (38.7)	1,874 (61.3)	
Age, years, median (IQ)	57.0 (17)	58.0 (18)	0.20[d]	43.5 (17)	49.0 (16)	<0.001[d]
Men, n (%)	42 (30.4)	154 (34.8)	0.34[e]	430 (36.3)	958 (51.1)	<0.001[e]
Basic education[c], n (%)	43 (31.2)	136 (31.1)	0.55[e]	282 (24.0)	502 (27.0)	0.07[e]
BMI, median (IQ)[f]	24.5 (13.8)	35.1 (14.6)	**0.02[d]**	25.4 (5.4)	26.1 (5.7)	<0.001[d]
Current smokers, n (%)	33 (23.9)	57 (12.9)	**0.02[e]**	247 (20.9)	520 (25.2)	<0.001[e]

a: In DILGOM, non-periodontitis patients include participants with CRS I and periodontitis patients include participants with CRS II and III. b: In H2000, non-periodontitis includes participants without deepened periodontal pockets, and periodontitis includes participants with periodontal pockets ≥4 mm. c: Basic education refers to participants without vocational or higher education. d: Mann–Whitney U test. e: Chi–square test. f: The subsample drawn from DILGOM was selected based on their weight status (subjects with severe obesity and their matched controls with normal weight). CRS = cumulative risk score, IQ = interquartile range, BMI = body mass index.

Dietary parameters (unpublished data)

The intake of selected dietary components (i.e., carbohydrates, proteins, vitamins A, C, D, and E) of the DII was at the same level in both studies (Table 10). The DII scores did not differ among non-periodontitis and periodontitis participants (p-value 0.865 in DILGOM and 0.359 in H2000) (Table 11). The DII scores of H2000 subjects are presented across three periodontitis groups, as this categorization was used in **Study III**. However, the results were similar when study participants were categorized into non-periodontitis and periodontitis groups (chi-square > 0.05). The maximum DII score in the highest tertile (tertile III) was slightly higher in H2000 than in DILGOM. In both studies, non-periodontitis and periodontitis participants were evenly distributed across DII tertiles (chi-square > 0.05). The BSDS scores did not differ between periodontitis and non-periodontitis participants (p-value 0.529) (**Study III**). Non-periodontitis and periodontitis participants were evenly distributed into the BSDS tertiles (chi-square > 0.05).

Table 10. Mean (standard deviation) daily intake of selected dietary components of DII.

	DILGOM		H2000		
	Non-periodontitis	Periodontitis	Non-periodontitis	Moderate periodontitis	Periodontitis
N	136	431	1184	1329	545
Carbohydrates (g)	295 (92)	294 (113)	250 (87)	243 (82)	244 (92)
Protein (g)	106 (33)	111 (45)	96 (33)	94 (31)	96 (34)
SFA (g)	30 (14)	31 (15)	36 (15)	36 (14)	36 (15)
PUFA (g)	14 (5.4)	15 (6.9)	14 (5.3)	14 (5.8)	14 (5.9)
MUFA (g)	28 (12)	30 (14)	30 (11)	30 (11)	30 (12)
Alcohol (g)	5.6 (10)	6.4 (12)	5.2 (8.0)	6.1 (10)	5.9 (8.8)
Vitamin A (mg)	1.3 (0.7)	1.3 (0.9)	1.7 (1.0)	1.7 (1.0)	1.7 (1.1)
Vitamin C (mg)	211 (114)	208 (147)	146 (79)	138 (76)	138 (83)
Vitamin D (μg)	8.8 (4.1)	11 (7.3)	6.6 (3.8)	6.6 (3.7)	6.8 (3.8)
Vitamin E (mg)	12 (3.8)	12 (5.4)	14 (5.0)	14 (5.4)	14 (5.5)
Fe (mg)	17 (4.9)	17 (7.1)	16 (5.4)	15 (5.1)	16 (5.7)
Zn (mg)	16 (4.8)	17 (6.7)	15 (5.1)	15 (4.7)	15 (5.4)

In DILGOM, periodontal status is diagnosed with Cumulative Risk Score (CRS): non-periodontitis (CRS I) and periodontitis (CRS II and III). In H2000, periodontal status is diagnosed with porbing pocket depth (PPD) non-periodontitis (PPD < 4 mm), moderate periodontitis (PPD = 4–5 mm), and advanced periodontitis (PPD ≥ 6 mm). DII = Dietary inflammatory index, SFA = saturated fatty acids, PUFA= Polyunsaturated fatty acids, MUFA= Monounsaturated fatty acids.

Table 11. DII and BSDS scores in the DILGOM and H2000 studies.

	DILGOM		H2000		
	Non-periodontitis	Periodontitis	Non-periodontitis	Moderate periodontitis	Advanced periodontitis
N	136	431	1184	1329	545
Energy (kcal)[A]	2,270 (849)	2,310 (1050)	2,290 (850)	2,250 (926)	2,274 (921)
DII scores[a,b]	-3.8 (2.6)	-4.0 (2.7)	-2.9 (3.0)	-2.9 (3.0)	-2.9 (3.4)
DII tertiles					
Tertile 1	-6.2–-4.7	-6.5–-4.7	-6.3–-3.8	-6.4–-3.8	-6.30–-3.8
Tertile 2	-4.7–-3.2	-4.7–-3.1	-3.8–-1.7	-3.8–-1.7	-3.8–-1-8
Tertile 3	-3.1–2.5	-3.1–2.5	-1.7–3.7	-1.7–4.4	-1.7–3.7
BSDS[c]			11 (5)	12 (5)	11 (5)
BSDS tertiles					
Tertile 1			1–10	2–10	2–10
Tertile 2			11–13	11–13	11–13
Tertile 3			14–22	14–21	14–22

In DILGOM, periodontal status is diagnosed with Cumulative Risk Score (CRS): non-periodontitis (CRS I) and periodontitis (CRS II and III). In H2000, periodontal status is diagnosed with porbing pocket depth (PPD) non-periodontitis (PPD < 4 mm), moderate periodontitis (PPD = 4–5 mm), and advanced periodontitis (PPD ≥ 6 mm). A: values are means and interquartile ranges, B: P-values 0.865 in DILGOM (Mann–Whitney U test) and 0.359 in H2000 (Kruskal–Wallis test). C: P-value 0.526 (Kruskal–Wallis test). DII= Dieatary Inflammatory Index, BSDS = Baltic Sea Diet Score.

5.2 Salivary cytokine concentrations in relation to periodontitis, diet, and obesity

The concentrations of IL-1Ra, IL-8, and IL-1β were statistically significantly higher, and concentrations of TNF-α and IL-10 were lower among those with periodontitis than non-periodontitis (Figure 4) (**Study II**). IL-6 concentrations did not differ between the groups.

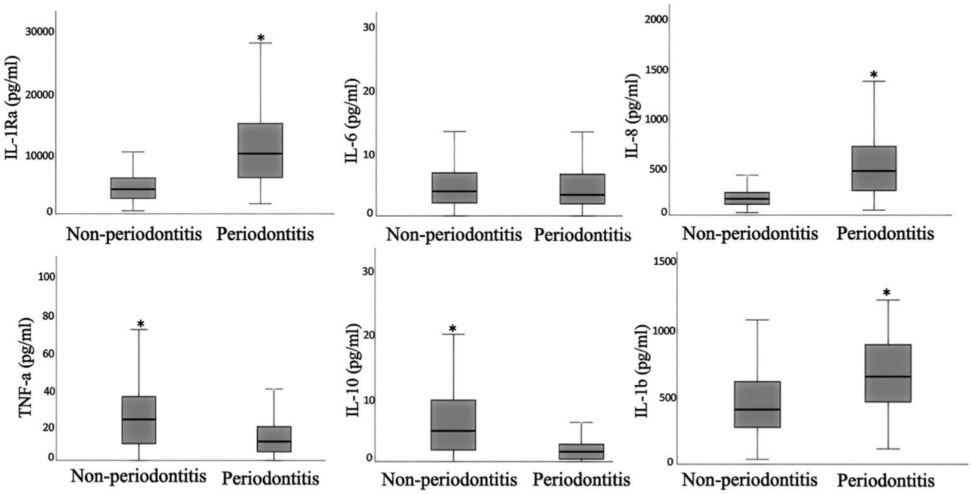

Figure 4. Salivary cytokine concentrations (pg/ml) in participants according to their periodontal status (**Study II**). The results regarding IL-1Ra, IL-6, IL-8, TNF-α, and IL-10 are from DILGOM study participants (non-periodontitis n = 442, periodontitis n = 138). The results regarding IL-1β are from Health 2000 study participants (non-periodontitis n = 74, periodontitis n = 73). In DILGOM, non-periodontitis patients include participants with CRS I and periodontitis patients include participants with CRS II and III. In Health 2000, non-periodontitis includes participants without deepened periodontal pockets, and periodontitis includes participants with periodontal pockets ≥4 mm.* Indicate statistically significantly higher concentration analyzed in the Wilcoxon signed-rank test. IL = interleukin, Ra = receptor antagonist, TNF = tumour necrosis factor, CRS = Cumulative Risk Score.

When participants were grouped according to the presence of periodontitis and divided to DII tertiles (**Study II**), the significant difference between periodontitis and non-periodontitis participants persisted in all cytokines, except for IL-1β in the DII tertile 2 (Figure 5). No difference in salivary cytokine concentration existed between DII tertiles.

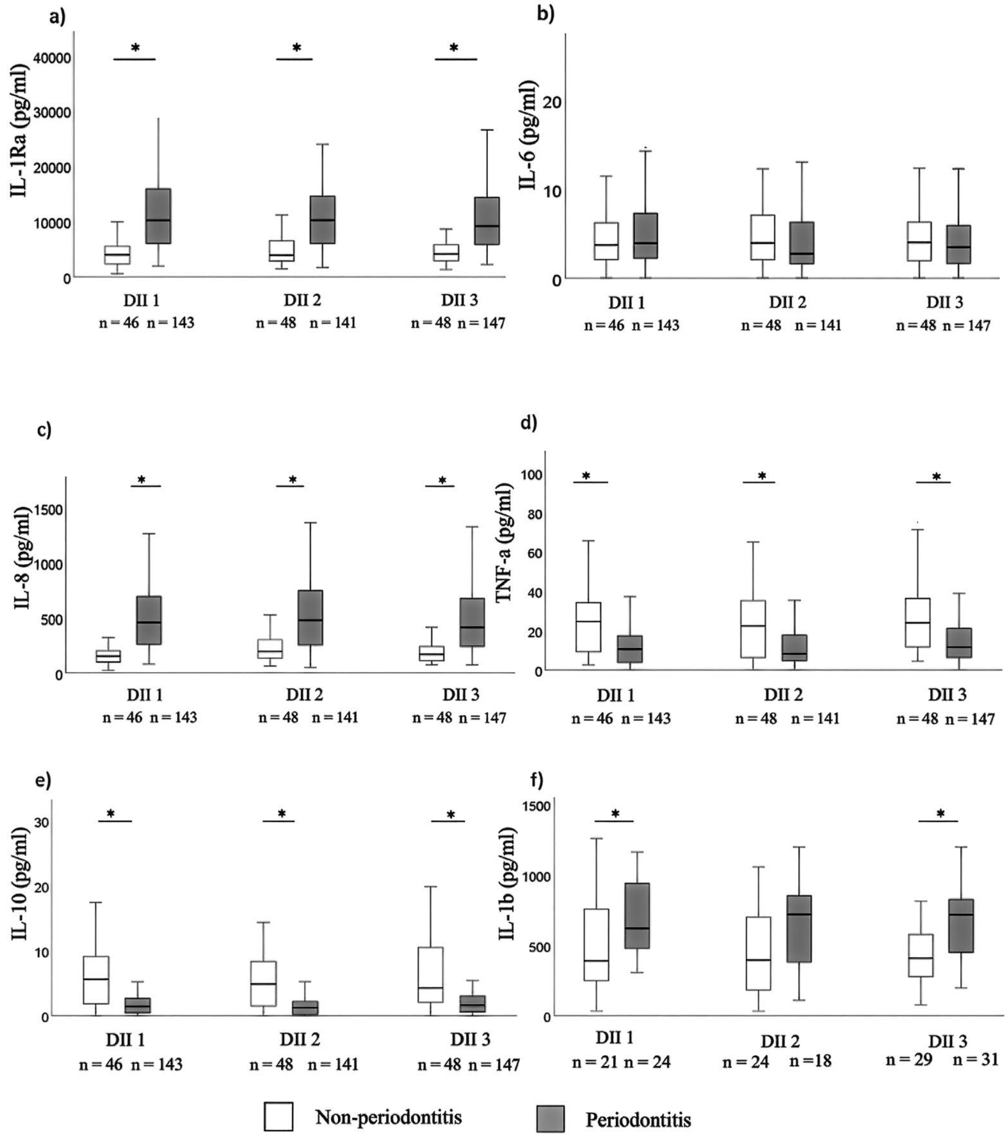

Figure 5. Salivary cytokine concentrations in DII tertiles **(Study II)**. a-e: DILGOM study participants with (CRS II and III) or without (CRS I) periodontitis; f: Health 2000 participants with or without deepened periodontal pockets (PPD ≥ 4 mm). Asterisk (*) indicates a statistically significant difference in the Kruskall–Wallis test. DII = Dietary Inflammatory Index, IL = interleukin, Ra = receptor antagonist TNF = tumour necrosis factor. The Figure 5 has been modified after publication of **Study II,** due to the verification analyses.

When study participants were further grouped into participants having normal weight or living with obesity (**Study I**), obesity was associated with lower concentrations of TNF-α and IL-10 in the CRS I group and higher IL-6 concentrations in the CRS III group (Figure 6). Moreover, higher IL-1Ra and IL-8 concentrations and lower TNF-α and IL-10 concentrations were observed in participants with periodontitis compared to those without periodontitis ($p < 0.05$).

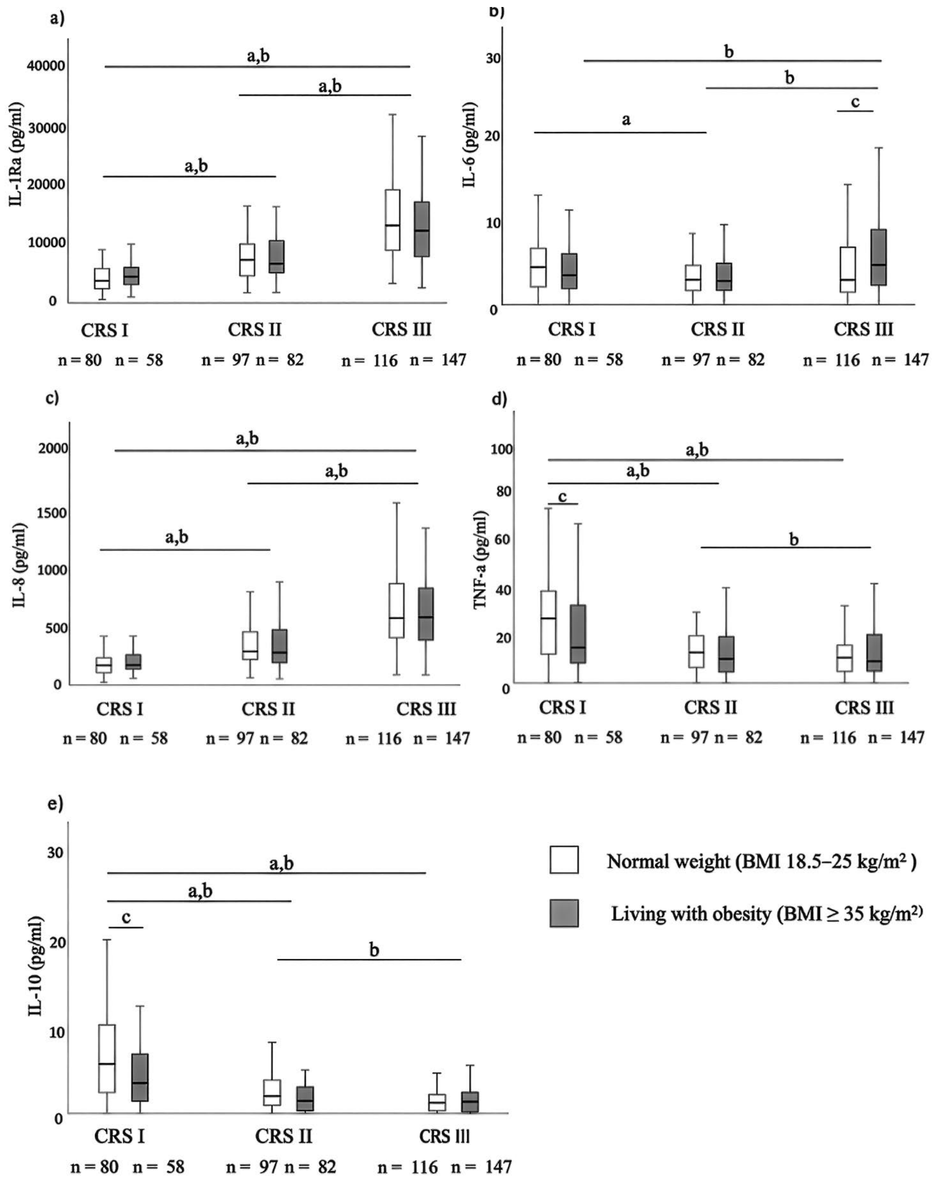

Figure 6. Salivary cytokine concentrations (pg/ml) according to CRS and body weight (**Study I**). Statistical significances (Mann–Whitney U test) are marked with the letters “a, b, and c” as follows: a = significant difference between normal weights, b = significant difference between participants living with obesity, c = significant difference between participants living with obesity and normal weight. CRS = cumulative risk score, IL = interleukin, Ra = receptor antagonist, TNF = tumour necrosis factor.

In multinomial logistic regression, the DII was not associated with salivary cytokine tertiles (Table 12). The results remained similar when the regression model was adjusted for only periodontitis, or for periodontitis, BMI, age, education, smoking habits, and physical activity. In the models including periodontitis, periodontitis was statistically significantly associated with all salivary cytokines ($p < 0.05$).

Table 12. Associations (odd ratios [95% confidence intervals]) between DII (independent variable) and salivary cytokine concentrations expressed in tertiles (dependent variable) in the multinomial logistic regression model.

	Range (pg/ml)	Model 1	Model 2	Model 3
DILGOM (N=584)				
Il-1Ra				
1st tertile	483–5460	1	1	1
2nd tertile	5470–11400	1.18 (0.73–1.91)	1.11 (0.67–1.86)	1.20 (0.69–2.07)
3rd tertile	11400–111000	0.88 (0.55–1.41)	0.78 (0.46–1.38)	0.93 (0.51–1.68)
IL-6				
1st tertile	0–2.42	1	1	1
2nd tertile	2.44–5.27	0.66 (0.41–1.07)	0.67 (0.41–1.08)	0.63 (0.38–1.06)
3rd tertile	5.28–153	0.86 (0.53–1.39)	0.86 (0.53–1.39)	0.73 (0.44–1.22)
TNF-α				
1st tertile	0–7.11	1	1	1
2nd tertile	7.43–18.2	1.26 (0.78–2.04)	1.27 (0.78–2.07)	1.23 (0.74–2.07)
3rd tertile	18.3–208	1.22 (0.76–1.96)	1.27 (0.78–2.08)	1.07 (0.64–1.81)
IL-8				
1st tertile	26.7–232	1	1	1
2nd tertile	233–498	1.03 (0.64–1.66)	1.01 (0.61–1.69)	0.99 (0.58–1.71)
3rd tertile	499–6160	1.11 (0.69–1.79)	1.08 (0.61–1.91)	1.18 (0.64–2.18)
IL-10				
1st tertile	0–0.93	1	1	1
2nd tertile	0.95–2.84	0.86 (0.53–1.38)	0.87 (0.54–1.40)	0.84 (0.51–1.40)
3rd 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 (n=165)				
IL-1β				
1st tertile	35.1–412	1	1	1
2nd tertile	420–685	1.68 (0.23–12.39)	1.19 (0.15–9.50)	1.36 (0.13–14.6)
3rd tertile	717–1260	2.91 (0.41–20.64)	1.98 (0.25–16.05)	2.70 (0.23–32.5)

Model 1: adjusted for energy intake. Model 2: adjusted for energy intake and periodontitis. Model 3: adjusted for energy intake, periodontitis, BMI, age, education, smoking habits, and physical activity. Significant associations ($p < 0.05$) are bolded. DII = Dietary Inflammatory Index, BMI = Body Mass Index, IL = interleukin, Ra = receptor antagonist, TNF = tumour necrosis factor.

5.3 Association of periodontitis and diet with serum CRP (unpublished data)

Of the **Study III** participants, 1,184 (38%) were non-periodontitis (PPD ≤ 3mm), 1,329 (44%) had moderate periodontitis (PPD 4–5 mm), and 545 (18%) had advanced periodontitis (PPD ≥ 6 mm) at baseline. Serum CRP concentrations were studied in **Study III**, where participants were categorized into four groups according to their dietary and periodontal status. Participants in AP1 or AP2 groups had statistically significantly higher serum CRP concentrations than reference in both dietary analyses (p = 0.002 and p = 0.001, Figures 7 and 8). They also had higher CRP than those in BSDS1 (p = 0.002) or DII3 (p = 0.014) groups. When participants had AP1/AP2 combined with BSDS1 or DII3, the CRP concentration was statistically significantly higher than in reference (p = 0.035 and p = 0.025), but it did not differ from those being only in a BSDS1, DII2, or AP1/AP2 groups.

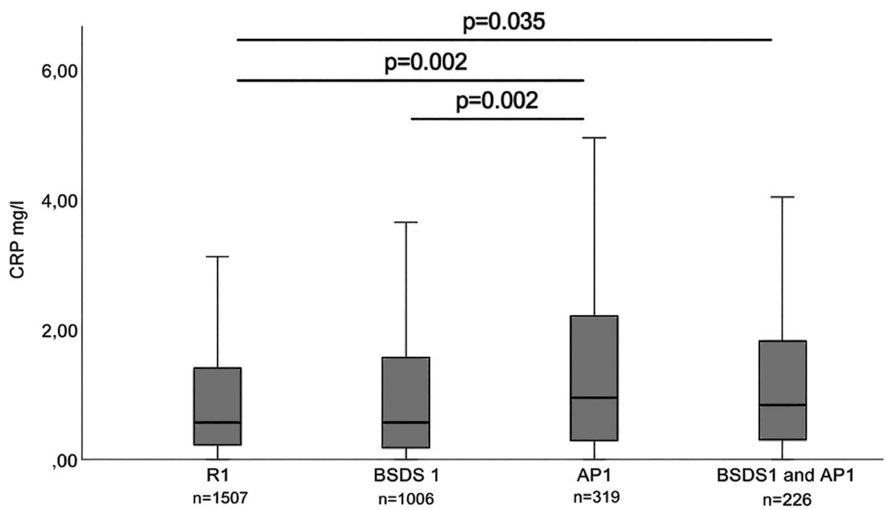

Figure 7. Serum CRP concentrations (mg/l) at baseline in H2000 participants categorized into R1, BSDS1, AP1, or BSDS 1 and AP1. R1 = reference group (BSDS tertiles 2 or 3 and not diagnosed with advanced periodontitis, BSDS1 = non adherence to the Baltic Sea diet (BSDS tertile 1), AP1 = advanced periodontitis group (at least one pocket depth ≥ 6 mm). BSDS = Baltic Sea Diet Scores. P-values from Kruskal–Wallis test. Unadjusted models. P-values other than those in the figure were non-significant (p > 0.05).

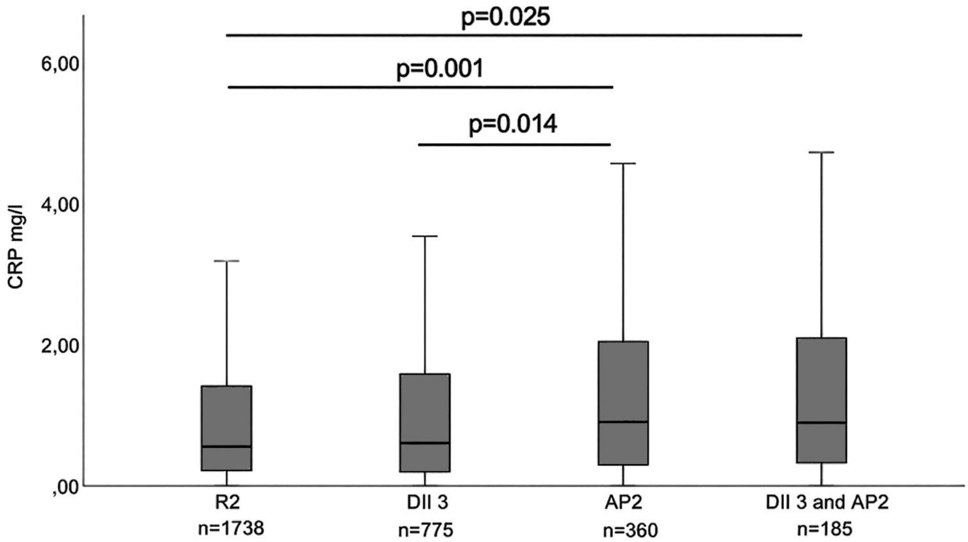

Figure 8. Serum CRP concentrations (mg/l) at baseline in participants categorized into R1, DII3, AP2, or DII3 and AP2 groups. R2 = reference group (DII tertiles 1 or 2 and not diagnosed with advanced periodontitis), DII3 = proinflammatory diet group (DII tertile 3), AP2 = advanced periodontitis group (at least one pocket depth ≥ 6 mm). DII = Dietary Inflammatory Index. P-values from Kruskal–Wallis test. Unadjusted models. P-values other than those in the figure were non-significant ($p > 0.05$).

5.4 Association of periodontitis and diet with serum CRP after 11 years of follow-up (unpublished data)

After excluding those with CRP > 10 mg/l at follow-up, 3,307 participants were left in the final analyses. Of those, periodontal status at baseline was available from 3,007 (NP = 1165, MP = 1312, and AP = 530). The mean change in serum CRP concentration during the follow-up was 0.1 mg/l (SD 4.09); the concentration increased in 71% of participants (mean increase of 1.2 mg/l, SD 1.5) and decreased in 29% of participants (mean decrease of -2.8 mg/l, SD 8.2) (Table 13). Baseline periodontitis was not associated with the change in CRP concentrations during the follow-up ($p = 0.758$, chi-square).

Table 13. Mean (standard deviation) serum CRP (mg/l) during H2000 baseline and after the 11-year follow-up according to periodontal status in.

	Non-periodontitis	Moderate periodontitis	Advanced periodontitis
n	1,165	1,312	530
Baseline	1.5 (3.5)	1.5 (3.5)	1.7 (3.5)
Follow-up	1.6 (1.7)	1.7 (1.7)	2.0 (1.9)
Change	0.2 (3.7)	0.2 (3.5)	0.3 (2.8)

In H2000, periodontal status is diagnosed with porbing pocket depth (PPD): non-periodontitis (PPD < 4 mm), moderate periodontitis (PPD = 4–5 mm), and advanced periodontitis (PPD ≥ 6 mm). CRP = C-reactive protein.

After 11 years of follow-up, serum CRP levels were over 2 mg/l in 926 participants, and the percentage of individuals with ≥ 2 mg/l CRP was higher in the AP group than the NP ($p < 0.001$, chi-square). In a binary logistic regression model, AP1 or AP1 combined with BSDS1 but not BSDS1 alone were statistically significantly associated with elevated serum CRP (≥ 2 mg/l) (OR 1.07, 95% CI 0.89–1.29 for BSDS1; OR 1.46 95% CI 1.13–1.90 for AP1; OR 1.41, 95% CI 1.04–1.91 for combination of BSDS1 and AP1) (Table 14, Model 1). However, only AP2 but not AP2 combined with DII3, or DII3 alone were associated with elevated serum CRP (OR 1.08, 95% CI 0.86–1.34 for DII3; OR 1.44, 95% CI 1.14–1.86 for AP2; OR 1.39, 95% CI 0.98–1.96 for combination of DII3 and AP2) (Table 15, Model 1). All statistically significant associations disappeared in fully adjusted models (Model 2, adjusted for baseline age, BMI, smoking status, physical activity, education level, CRP, HbA1c, medication of lipid-modifying agents, and energy intake). In Model 2, the main determinants of elevated serum CRP concentrations after 11 years were baseline BMI, CRP concentration, and smoking status (data not shown).

Table 14. Odds ratios (95% confidence intervals) of serum CRP ≥ 2 mg/l in H2011 participants after 11 years of follow-up (n=3007), grouped according to the status of non-adherence to the Baltic Sea diet and advanced periodontitis.

	Model 1	p-value	Model 2	p-value
Reference	ref		ref	
BSDS 1	1.07 (0.89–1.29)	0.460	1.12 (0.91–1.38)	0.298
AP1	1.46 (1.13–1.90)	0.004	1.15 (0.86–1.55)	0.341
BSDS1 and AP1	1.41 (1.04–1.91)	0.029	1.22 (0.87–1.73)	0.251

Reference = BSDS tertiles 2 or 3 and not diagnosed with advanced periodontitis. BSDS 1 = BSDS tertile 1, indicating non-adherence to the Baltic Sea diet. AP1 = Advanced periodontitis (at least one pocket depth ≥ 6 mm). Model 1: adjusted for energy intake. Model 2: adjusted for baseline age, body mass index, smoking status, physical activity, education level, C-reactive protein, HbA1c, medication of lipid-modifying agents, and energy intake. BSDS = Balti Sea Diet Score, HbA1c = glycated hemoglobin.

Table 15. Odds ratios (95% confidence intervals) of serum CRP ≥ 2 mg/l in H2011 participants after 11 years of follow-up (n=3007), grouped according to the status of the proinflammatory diet and advanced periodontitis.

	Model 1	p-value	Model 2	p-value
Reference	ref		ref	
DII3	1.07 (0.86–1.34)	0.520	1.05 (0.82–1.35)	0.678
AP2	1.44 (1.14–1.86)	0.003	1.19 (0.91–1.57)	0.207
DII3 and AP2	1.39 (0.98–1.96)	0.064	1.07 (0.72–1.59)	0.737

Reference = DII tertiles 1 or 2 and not diagnosed with advanced periodontitis. DII3 = DII tertile 3, adherence to proinflammatory diet. AP2 = Advanced periodontitis (at least one pocket depth ≥ 6 mm). Model 1: adjusted for energy intake. Model 2: adjusted for baseline age, body mass index, smoking status, physical activity, education level, C-reactive protein, HbA1c, medication of lipid-modifying agents, and energy intake. DII = Dietary Inflammatory Index, HbA1c = glycated hemoglobin.

5.5 Sensitivity analyses (unpublished data)

Separately analyses for men and women revealed certain discrepancies in the results. In subgroup analyses, some of the previously observed association in salivary cytokine concentration related to obesity and periodontitis were no longer evident. For example, the concentration of IL-8 did not differ between CRS 1 and CRS 2 groups in men. Similarly, the difference in TNF-α concentrations between periodontitis and non-periodontitis patients were no longer statistically significant in DII 2 and DII 3 tertiles when only men were analyzed. In addition, no difference in IL-1β levels were observed between periodontitis and non-periodontitis among women in DII tertile 1. In contrast, in the DII tertile 2, women with periodontitis showed higher salivary IL-1β levels compared to non-periodontitis. The results from multinomial logistic regression, however, were similar when men and women were analyzed separately.

When the association between BSDS1 combined with AP and serum CRP was analyzed in men, the ORs remained statistically significant after adjusting for covariates (Model 2, OR 1.79, 95% CI 1.12–2.86, p-value = 0.015). The BSDS1 or AP1 alone did not reach statistically significant results (OR 1.24, 95% CI 0.88–1.73, p-value 0.223 for BSDS1 and OR 1.19, 95%CI 0.79–1.80, p-value 0.415 for AP1). No comparable difference was noted when DII was combined with AP, as the results remained statistically non-significant. Also, in analyses conducted with women, the results were non-significant.

6 Discussion

The present study observed that salivary cytokine concentrations were consistently associated with periodontitis, being less influenced by obesity or diet. There was also a relationship between periodontitis and serum CRP, and this association was stronger than that between diet and serum CRP. A slight synergistic association was noted between diet and periodontitis, together with serum CRP, after 11 years of follow-up. However, the strength of the association was diminished after adjusting the statistical model for confounding factors, especially for baseline BMI and serum CRP concentration –except in men.

6.1 Local inflammation

6.1.1 Obesity, periodontitis, and salivary cytokines

Obesity and adipose tissue are well acknowledged as being related to inflammatory reactions affecting systemic health (Soták et al., 2025). Different measures of adipose tissue (i.e., high BMI, adipose tissue distribution in the body, and fat percentage) have shown a positive association with inflammatory markers in serum (Cohen et al., 2021; He et al., 2024; Tuomisto et al., 2019; Yu et al., 2019). Due to this strong relationship between obesity and systemic inflammation, this study hypothesized that severe obesity and periodontitis are also associated with increased saliva cytokine concentrations. However, severe obesity was only related to lower salivary TNF-α and IL-10 concentrations among non-periodontitis participants and higher IL-6 concentrations in participants with severe periodontitis compared to normal-weight participants. The double burden of having periodontitis and obesity in relation to salivary cytokines was not observed, except in the case of IL-6 concentration.

A previous examination compared salivary IL-6 and TNF-α concentrations in participants of normal weight or with obesity and with or without periodontitis (n = 88), finding higher IL-6 concentrations in participants living with obesity and periodontitis compared to participants living only with obesity or only with periodontitis, indicating some synergistic effect with these factors (Kose et al., 2015). The results of the present study were similar, as there were the highest IL-6 concentrations among those with severe periodontitis and obesity compared to the other groups. Two earlier investigations have evaluated the salivary IL-1β in connection with the combination of obesity and periodontitis, with conflicting results (Jentsch et al., 2017; Kemer Doğan & Duran, 2022). However, the analysis of IL-1β related to obesity was not examined in this study as the association of obesity and cytokines was examined in **Study I**, in which the periodontitis was determined based on the CRS, and IL-1β is a component of CRS.

The results regarding salivary TNF-α were unexpected as the present study observed lower concentrations of this cytokine among non-periodontitis participants living with severe obesity than those of normal weight; this result did not align with earlier research. A small-scale study involving only 44 participants indicated higher salivary TNF-α levels in participants with obesity than those of normal weight (Lehmann-Kalata et al., 2018). However, they did not include participants with periodontitis, although some parameters related to periodontal status (plaque index, sulcus bleeding index, gingival index) were enhanced in participants with obesity. The meta-analysis of GCF and cytokines showed higher TNF-α concentrations in subjects with obesity and periodontitis compared to those of normal weight and with periodontitis, but no difference in subjects living with obesity and without periodontitis, indicating that obesity had a more significant role in determining GCFs TNF-α concentration than periodontitis (Kandaswamy et al., 2024).

6.1.2 Diet, periodontitis, and salivary cytokines

Substantial evidence shows that regular consumption of specific nutrients (e.g., vitamins C and E, saturated fat) and foods (e.g., vegetables, fruits, or processed meat) can modulate systemic inflammation (Calder et al., 2011). Moreover, DII has been associated with the biomarkers of systemic inflammation in large observational studies (Millar et al., 2022; Shivappa et al., 2017; Shivappa, Steck, Hurley, Hussey, Ma, et al., 2014; Tabung et al., 2015). Therefore, this study hypothesized that DII is also associated with inflammatory markers in saliva. However, the results did not support the hypothesis. When salivary cytokine concentrations were analyzed across DII tertiles in **Study II**, the concentration of each cytokine remained relatively consistent across all tertiles, and the observed differences were mainly attributed to the presence of periodontitis.

Only one earlier piece of research examined the association between diet quality and salivary cytokine concentrations in adults (Attlee et al., 2019). A cross-sectional study conducted in the United Arab Emirates analyzed the association of diet and physical activity with three salivary inflammatory markers (adiponectin, TNF-α, and IL-10) in young females of healthy weight and with obesity. The study included 90 subjects (30 normal weight, 30 participants with overweight, and 30 participants with obesity) aged 18–35. The diet quality was assessed with the MEDFICTS Dietary Assessment questionnaire—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). Although salivary TNF-α was higher in those with obesity than other study participants, diet quality was not associated with salivary cytokines. These results correlate with the results of this thesis, as there was no association between DII and salivary cytokine concentrations.

When the association between diet, periodontitis, and salivary inflammatory markers was evaluated using regression models, a statistically significant association was found between periodontitis and salivary cytokine concentrations. This aligned with comparative analyses made in participants according to periodontitis and obesity or periodontitis and dietary tertiles, showing constantly higher concentrations of IL-1Ra, IL-8, and IL-1β and lower IL-10 and TNF-α among periodontitis patients compared to non-periodontitis. Earlier studies have consistently demonstrated that salivary cytokines are associated with periodontitis and have recognized their potential as biomarkers for the disease (Arias-Bujanda et al., 2020; Blanco-Pintos et al., 2023), although some controversial results have also been presented (R. P. Teles et al., 2009). The added value of the present study is that obesity and diet are unrelated to salivary cytokine concentrations, even though they were expected to be because of their strong association with systemic inflammation. This, in turn, increases the confidence to use these cytokines specifically for diagnosing periodontitis.

6.1.3 Interpretation of salivary cytokine findings

Possible explanations exist for the lack of elevated salivary cytokine levels in participants living with severe obesity compared to those of normal weight. First, although obesity increases the inflammatory markers in circulation, it is uncertain that these proteins can effectively invade from the bloodstream into the saliva. While such molecules have been detected in oral fluids, the results regarding their correlation with serum have been inconclusive (Nam et al., 2019; Parkin et al., 2023; Tvarijonaviciute et al., 2020). IL-6 seems to correlate between blood and saliva, whereas findings related to TNF-α have shown less consistency (Nam et al., 2019; Parkin et al., 2023). In the present study, IL-6 was also the only salivary cytokine found to be elevated in obese individuals with periodontitis when compared to the other groups. This could suggest that IL-6 plays a central role in the link between systemic and oral inflammation. Second, although there would have been an influx from blood to saliva, there is also local production of cytokines in the oral cavity, the effect of which may be superior to those invaded from the systemic fluids. An examination of 39 US and Canadian participants who were periodontally healthy supports this notion (Khocht et al., 2023). That study observed that obesity was associated with GCF CRP concentration when a periodontitis-related increase in cytokine was not masking the results. In addition, obesity was associated with decreased GCF cytokines, which was speculated to result from a disturbance in the cytokine response caused by obesity.

Similarly, DII was unrelated to salivary cytokines, although diet is a known modulator of systemic inflammation (Minihane et al., 2015). One explanation could be that cytokine concentrations in saliva may not be sensitive enough to indicate diet-related changes in low-grade inflammation (Attlee et al., 2019). Moreover, saliva may not be an optimal source of inflammatory biomarkers in nutrition studies if it represents disease-specific markers for periodontitis instead of the subject's dietary status (Calder et al., 2013). Considering how sensitive DII is to assess dietary diversity in subgroups is also reasonable. In the present study, the DII scores varied from -6.13 to 3.17, being in the tertile III between -3.1 and 2.5 in DILGOM and between -1.7 and 3.2 in H2000, indicating that some individuals in this study with the most proinflammatory diet had the scores that factual represent the anti-inflammatory diet (the DII scores below zero).

In the cohort study of 71 older adults, certain salivary cytokines, including IL-β, IL-8, and TNF-α, were higher in men than in women (Parkin et al., 2023). In the present study, salivary cytokines were not compared between sexes. Nevertheless, some differences in salivary cytokine concentrations, observed when study participants were grouped according to obesity and periodontal status, lost statistical significance when men and women were analyzed separately. This was likely due to the reduced sample sizes resulting from further stratification by sex. Therefore, a larger cohort would be needed to investigate whether the associations between diet, obesity, periodontitis, and salivary cytokines differ between men and women.

Smoking was used as a matching criterion in **Study I** and as a covariate in **Study II.** It is one of the most significant risk factors for periodontitis, influencing the prevalence, development, and severity of the disease (Selva Süme Keşir & Ebru Olgun, 2018). However, according to the literature, smoking has only limited impact directly to the salivary cytokine concentrations (Jaedicke et al., 2015). A cross-sectional study of 60 non-periodontitis participants found lower levels of salivary CRP and TNF-α in non-smokers compared to conventional or e-cigarette users, but no difference in IL-1Ra, IL-6, or IL-8 concentrations (Verma et al., 2021). On the other hand, in the original publication of **Study I,** the observed differences in IL-8 and IL-10 concentrations between participants living with obesity and those of normal weigh disappeared when only non-smokers were analyzed (Syrjäläinen et al., 2019). The results regarding DII and salivary cytokine concentrations might also have appeared differently if smoking had been more thoroughly accounted for.

Contrary to prior evidence showing periodontitis to be associated with proinflammatory cytokines in saliva, it was surprising that individuals with periodontitis and obesity had lower salivary TNF-α than their non-periodontitis counterparts either living with obesity or normal weight. One explanation could be that as TNF-α is produced mainly by macrophages, which are already present early at gingival inflammation, the concentration of TNF-α has decreased, while the concentrations of other immune cells, i.e., T- and B-lymphocytes, have increased due to the progression of the disease. Another explanation could relate to the knowledge that cytokines regulate the secretion of each other, and anti-inflammatory cytokines are released in response to proinflammatory cytokines to limit the inflammatory cascade (Kany et al., 2019). So, while periodontitis has developed from mild to severe periodontitis, there may have been some regulatory feedback from anti-inflammatory cytokines that have attenuated the secretion of TNF-α. Parkin et al.'s (2023) study showed a positive correlation between proinflammatory TNF-α and anti-inflammatory IL-10. Finally, cytokines are prone to enzymatic degradation. An increase in proteolytic enzymes in periodontitis decreases the detectability of various cytokines in saliva and gingival crevicular fluid.

Saliva-based diagnostic methods of systemic diseases have gained a considerable interest due to their cost-effectiveness, ease of collection, and non-invasive nature (Kumari et al., 2023). In light of the present study, however, these applications should be interpreted with caution. Periodontitis appears to play a primary role in shaping the inflammatory profile of saliva. Therefore, when systemic inflammation is analyzed by saliva-based tests, the periodontal status should be considered. Furthermore, the findings of this study challenge the assumption that the association between periodontitis and diet or obesity is mediated by inflammatory markers, as this may not be the case.

6.2 Serum CRP

6.2.1 Periodontitis, diet, and serum CRP

Robust evidence shows that periodontitis is implicated in elevated serum CRP concentration (Machado, Botelho, Escalda, et al., 2021a). In addition, nutrition is one of the key modulators of systemic inflammation (Calder et al., 2009). Therefore, **Study III** hypothesized that the simultaneous load of these risk factors of systemic inflammation would be associated with increased serum CRP concentration in the long term. This hypothesis proved incorrect as the higher serum CRP concentrations at baseline were related to advanced periodontitis and were not further increased when advanced periodontitis was combined with non-adherence to the Baltic Sea diet or adherence to the proinflammatory diet. In addition, the observed association between non-adherence to the Baltic Sea diet and periodontitis with serum CRP after 11 years of follow-up was lost when the model was adjusted for confounding factors –except in men.

No previous research has investigated the simultaneous associations of periodontitis and diet with serum CRP. However, one earlier cross-sectional study evaluated the mediating role of DII in the link between CRP and periodontitis in 3,238 adults using the NHANES 2009–2010 datasets and observed that DII mediates the association between periodontal status and systemic inflammation (Machado, Botelho, Viana, et al., 2021). Additionally, another examination of 1,014 patients with coronary artery disease showed that the presence of at least two modifiable risk factors (smoking, low physical activity, overweight, or poor adherence to the Mediterranean diet) contributed to higher serum CRP concentrations compared to the presence of a single risk factor (Blaum et al., 2021). The results of these earlier investigations do not align with the present study's findings, as there was no higher serum CRP in those with two risk factors—non-adherence to the Baltic Sea diet or adherence to the proinflammatory diet and advanced periodontitis—compared to those with only one.

A slight synergistic association of the diet and periodontitis with long-term serum CRP was identified in current analyses, as participants with advanced periodontitis and non-adherent to the Baltic Sea diet were at risk for increased CRP concentrations (≥ 2 mg/l) after 11 years of follow-up. This observation aligned with earlier research of 3,979 adults, indicating baseline periodontitis is associated with higher CRP levels and a lesser decrease in CRP concentration after 13 years of follow-up (Molinsky et al., 2022). However, in the present study, the association was attenuated when baseline BMI or CRP concentration was added to the model. This could have been expected as BMI strongly contributes to systemic inflammation (Soták et al., 2025). An interesting observation emerged when the results were stratified by sex: the association between advanced periodontitis, BSDS 1, and serum CRP concentrations remained statistically significant only in the subgroup analyses that included men.

6.2.2 Possible explanations for the results regarding serum CRP

According to the results, periodontitis seemingly had a stronger association with CRP than diet. This can be concluded from the baseline and follow-up analyses showing no difference between the groups of those who were non-adherent to the Baltic Sea diet or adherent to the proinflammatory diet and reference, whereas participants with advanced periodontitis had a higher serum CRP concentration and increased ORs for having serum CRP ≥ 2mg/l. This could be attributed to the greater role that periodontitis has over diet in stimulating CRP secretion.

The results showing no association between the BSDS or DII and serum CRP were unexpected. One explanation could relate to the nature of CRP as an unspecific marker of inflammation. CRP is not a specific marker of a single disease or diet-related systemic inflammation; instead, its concentration is increased in many chronic conditions, including autoimmune diseases, cardiovascular diseases, and infections (Rizo-Téllez et al., 2023). Moreover, psychosocial conditions other than diseases, including prolonged stress or frailty, affect serum CRP concentration (Johnson et al., 2013; Luo et al., 2024). Yet, CRP is widely used as an inflammatory biomarker in nutrition studies and is associated with unhealthy dietary patterns (Hart et al., 2021). However, including multiple inflammatory markers could have provided deeper insight into the association between diet and systemic inflammation.

Another explanation may relate to the dietary indices used. The BSDS evaluates the adherence to the Baltic Sea diet, while the DII aims to determine the inflammatory potential of the consumed food. The development of the DII was based on the literature by evaluating each food component and its association with serum IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP concentrations (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014). Transcription of the CRP gene in hepatocytes occurs in response to inflammatory cytokines (Sproston & Ashworth, 2018); therefore, it was expected that, as DII associates with cytokines, it would also be associated with CRP. Similarly, evidence exists on the Baltic Sea Diet's relationship to serum CRP; a cross-sectional study using two independent cohorts of Finnish adults (n = 4,579 and n = 1911) demonstrated an inverse association between the BSDS and hs-CRP concentrations (Kanerva, Loo, et al., 2014). One possible explanation for the lack of association between dietary indices and serum CRP concentration could be the use of dietary tertiles. The first tertile of BSDS was used to indicate non-adherence to the Baltic Sea diet, while the third tertile of DII indicated a proinflammatory diet. The BSDS scores in the first tertile ranged from 1 to 10 (out of 22); therefore, those participants may not be homogenous enough to accurately represent those with the unhealthiest diet. In addition, the DII scores in the third DII tertile ranged from -1.7 to 4.4, meaning participants with the anti-inflammatory diet (DII scores below zero) were also included in the third tertile.

To date, no studies have evaluated the combined association of diet and periodontitis with serum CRP separately in men and women. However, some explanations for the observed association –namely, that advanced periodontitis combined with BSDS1 was linked to elevated serum CRP in men but not in women –can be inferred from previous research. A German population-based study involving 3265 participants found that indicators of periodontitis (PPD, bleeding on probing, plaque) were associated with serum CRP concentration only in men (Meisel et al., 2019). In addition, obesity was associated with serum CRP in both sexes, but with higher impact in women. These findings align with the present study, suggesting that periodontitis may be more strongly linked to CRP levels in men, whereas in women, adiposity could be a more dominant contributor to systemic inflammation, potentially explaining why the statistically significant associations disappeared after adjusting for BMI. Furthermore, a study analyzing NHANES 2003–2018 datasets (n=39 567) demonstrated that women benefit more from healthy eating than men, particularly in terms of all-cause mortality and cardiovascular outcomes (Yao et al., 2024). Differences in CRP responses to various lifestyle factors may explain why, in the present study, the association between periodontitis and diet with serum CRP was observed only in men.

6.3 Methodological aspects

6.3.1 Study design and participants

The study populations examined in this thesis were drawn from three Finnish cohorts: DILGOM, H2000, and H2011—all observational studies where the exposures and outcomes are gathered from participants without influencing them. In general, the results apply to the Finnish population aged 30 or older, with some restrictions described later in this section. Some common biases in epidemiological studies should be considered here. Three major biases are selection bias, measurement bias, and confounding bias (Brown et al., 2024).

The selection bias occurs when the sampling of study participants results in a study population that would systematically differ from the population of interest (Brown et al., 2024). DILGOM and H2000 were based on random samples drawn from the National Population Information System and the Social Insurance Institution of Finland, respectively—databases of the Finnish population (Borodulin et al., 2018; Heistaro, 2008). These samples are seen as representing the target population well (Borodulin et al., 2018; Aromaa & Koskinen, 2004). In addition, the participation rates in all studies were sufficiently high. However, it cannot be ruled out that the participants of these surveys may have included more of those who were interested in health and healthy lifestyles, which could have modified the results. For example, the subjects who consumed the unhealthiest or most anti-inflammatory diet may have been missing in this study. Thus, this study may have underestimated the association between obesity or diet and inflammatory markers due to the lack of unhealthy lifestyles.

In addition, the original sample size of H2000 (n=8028) was reduced to 3007 in the follow-up analyses due to the exclusion criteria used. The gender distribution was similar between included and excluded participants. However, those who remained in the study were younger (mean age 49 years compared to 58 years, $p<0.001$), and more likely to have higher education ($p<0.001$). This inevitably limits the generalizability of the findings in **Study III**, particularly given that ageing and lower education are associated with increased morbidity (Fonseca et al., 2020; Straka et al., 2024). Therefore, this study may underestimate the association between diet, periodontitis, and serum CRP, as those who are more likely to suffer chronic diseases or are at the highest risk to develop one, are missing.

Measurement errors in variables cause measurement bias (a.k.a. information bias) (Brown et al., 2024). In this study, such bias may have arisen from self-reported health behaviour (e.g., smoking status, alcohol consumption, or dietary habits) if participants misreported their habits. It may also occur due to measurement errors during health examinations. **Study III** acknowledges this type of bias regarding periodontitis determination, where classifying advanced periodontitis was based solely on one tooth with a periodontal pocket ≥ 6mm.

Confounding bias arises when some unmeasured external factor explains the observed association between exposure and outcome (Brown et al., 2024). While adding confounding factors into the analyses commonly solves this kind of bias, there is a risk of sparse data bias after including multiple variables in the models (Greenland et al., 2016). In sparse data bias, the estimates (e.g., ORs) from statistical models may be overestimated as the data lack adequate case numbers in some combinations of dependent and independent variables. These biases are controlled by avoiding unnecessary adjustments. However, there is a possibility of some unknown residual confounding factors that could not be controlled.

As the regression models controlled for multiple covariates, the possibility of overadjustment cannot be excluded (Schisterman et al., 2009). Overadjustment occurs when the association between an exposure and an outcome is controlled for a variable that lies on the causal pathway between them. In such cases, the true association may be attenuated, as controlling for an intermediate variable can block part of the causal effect, potentially leading to biased –or even null– estimate of the total effect. In **Study III**, this bias was plausible, as the observed association between diet quality, periodontitis, and serum CRP disappeared after adjustment for covariates, including BMI. It is likely that BMI is related to diet and may act as one component in the causal pathway between diet and CRP. However, to examine this possibility more closely, the analyses were conducted also without adjusting with baseline BMI and serum CRP concentrations, but the results remained non-significant.

This thesis involved three study designs: cross-sectional, case-control, and longitudinal. Although the observational designs do not allow conclusions about causality, the 11 years of follow-up in H2011 gave a longitudinal perspective to CRP concentrations—a strength of this study. The case-control design in **Studies I** and **II** enabled the examination of the risk factors (obesity and periodontitis) more precisely, as the cases represented extreme conditions. Case-control design is considered cost-effective, as fewer participants are needed to detect differences between groups. Conversely, the generalizability of the results in **Studies I** and **II** decreased due to the case-control design, as results may only be extrapolated to the groups examined.

The large data sets acquired from those surveys are one strength of this study. Also, the wide variety of background information and health examinations gathered made it possible to adjust the study variables with appropriate confounding factors. Furthermore, for participants drawn from DILGOM, the exclusion criteria for cases and controls were diabetes, cardiovascular diseases, cancers, or medication for hypercholesterolemia—common comorbidities related to obesity (Lin & Li, 2021). This exclusion allowed a more precise study of the association between obesity and salivary inflammatory markers without the effect of comorbidities. Finally, it was observed that participants from DILGOM were older than those drawn from H2000, which may have somewhat impacted the results regarding inflammatory markers, as aging is a known modulator of the immune system (Santoro et al., 2021).

6.3.2 Variables

Periodontal assessment

The periodontal status was recorded by clinical examination in participants drawn from H2000 and by CRS in participants drawn from DILGOM. Both methods have some advantages. However, the variability in the definition of periodontitis across studies compromises the generalizability of the results as well as the comparability of the three studies. Periodontitis is traditionally diagnosed by clinical and radiographic assessment; however, CRS is a suitable method, especially in large population-based studies, where conducting the whole mouth oral examination is impossible. Furthermore, as a clinical examination of connective tissue and bone resorption describes the cumulative effect of historical tissue destruction, salivary-based biomarkers have been proposed to detect periodontal disease early on and to identify disease progression (Jaedicke et al., 2016). By combining three biomarkers, CRS considers distinct biological phases related to periodontitis (e.g., when the bacterial burden is decreased due to the strong host response, the concentration of the other two biomarkers is still at the level indicating the disease) (Gürsoy et al., 2011).

The diagnostic accuracy of CRS in detecting moderate to severe periodontitis has been validated previously (Gürsoy et al., 2018; Liukkonen et al., 2020; Salminen et al., 2014). A Finnish cohort of 493 subjects showed CRS to be more strongly associated with moderate to severe periodontitis than *P.gingivalis*, IL-1β, or MMP-8 alone (OR 6.13, 95% CI 3.11–12.09 for CRS) (Salminen et al., 2014). In another study with the same population, CRS distinguished the subjects from healthy to periodontitis patients and provided the area under curve (AUC) in a receiver operating characteristic curve of 0.725, which was higher than AUC for dichotomous variables of *P.gingivalis*, IL-1β, or MMP-8 (AUC between 0.539 and 0.663) (Gürsoy et al., 2018). In addition, CRS was associated with salivary IgA and IgG burden as well as with subgingival Gram-negative bacteria species with the same population (Liukkonen et al., 2020).

Repeated measurements by field dentists and parallel measurements by a reference dentist conducted the validity of oral examination in H2000 (κappa value 0.83 for repeated measurements and 0.41 for parallel measurements) (Suominen-Taipale et al., 2008). The κappa value for repeated measurements is at a good level, indicating good repeatability among field dentists. The κappa value for parallel measures was moderate, indicating some variability between field dentists and the reference dentist. There was also skewness in pocket depth measurement, so field dentists reported fewer teeth with deepened periodontal pockets than the reference dentist, which may have caused some bias in the results. As the periodontitis diagnosis of participants in **Study III** was based on only a single deepened pocket, some persons with deepened pockets may have been classified as having moderate periodontitis instead of advanced periodontitis, and vice versa.

The most crucial source of bias regarding the use of CRS in the current thesis is the intercorrelation between salivary cytokines observed in an earlier study (Parkin et al., 2023). Cytokines are produced in a cascade and regulate each other's secretion. Therefore, the association between salivary cytokines and CRS may be attributed to the presence of IL-1β in CRS instead of the actual periodontal status, as IL-1β acts in the same network as other cytokines.

Another limitation concerning periodontal assessment in the present study relates to the clinical examination of the H2000, which did not include measurements of clinical attachment loss. Therefore, in **Study II** and **Study III**, periodontal diagnosis was based solely on probing pocket depths. This approach may lead to overestimation due to inflammation-induced swelling, or underestimation in cases with gingival recession, where attachment loss is present despite shallow pockets. In addition, the diagnostic criteria used in H2000 do not permit direct comparison with studies that have adopted the current classification of periodontitis (Papapanou et al., 2018).

Dietary assessment

A validated semi-quantitative FFQ measured the habitual diet of study participants (Kaartinen et al., 2012; Montonen et al., 2008). FFQ is easy to complete and a cost-effective method to estimate the long-term diet of study participants in epidemiological studies. Unlike food records, which are more accurate methods to measure the intake of nutrients or food groups, the FFQ is suitable for ranking participants according to their intake of foods or nutrients (Kowalkowska et al., 2013). This approach is adequate when studying the association between diet and the risk of chronic diseases. As a retrospective method, it is based on the respondent's memory, which may be a limitation of FFQ. However, compared to food records, which measure the diet over a short period (usually three to seven days), FFQ estimates the diet composition over a longer period. The longer timeframe is more appropriate for studying chronic diseases, which may take years to develop.

THL developed the FFQ used in DILGOM and H2000, which is updated regularly. Its primary purpose is to rank participants according to their average food consumption and nutrient intake. The FFQ used in both surveys is validated against dietary records (Kaartinen et al., 2012; Männistö et al., 1996; Paalanen et al., 2006). The intake of nutrients measured by the FFQ was observed to be within 20% of the values measured by the diet records, except for alcohol and vitamins A and D (Männistö et al., 1996). The FFQ appeared to underestimate the intake of alcohol and overestimate the intake of vitamins A and D. In both methods, the proportion of subjects classified into the same or adjacent quintiles of intake went from 55% to 96%, and less than 10% of subjects were classified to the lowest quintile in food records but the highest quintile in FFQ. The correlation between the same FFQ filled in three-month intervals was between 0.6 and 0.7 for most nutrients. Other studies showed that the FFQ overestimates the intake of nutrients, except alcohol and some foods compared to food records, especially in women (Kaartinen et al., 2012; Paalanen et al., 2006). A correlation also existed from 0.34 to 0.68 between the FFQ and dietary record in women and 0.16 to 0.67 in men, while in nine out of 11 energy-adjusted dietary factors, the correlation coefficient exceeded 0.4 in both sexes (Kaartinen et al., 2012). Because a tendency exists to underreport food consumption in food records, part of the overestimation observed may be due to the underreporting in food records (Paalanen et al., 2006). Healthy foods may also be overestimated due to the desire to achieve social acceptance. This bias in reporting practice may have led some participants' classification to a tertile of a healthier or more anti-inflammatory diet than their true diet would have required, which may have caused a weaker association observed between diet and inflammatory markers.

The DII, a scoring system that classifies a diet from proinflammatory to anti-inflammatory, was used to estimate a diet's inflammatory potential. The DII was developed in 2009 and revised in 2014; since then, it has been widely used when examining large study populations (Hébert et al., 2019). Some remarks regarding DII should be discussed here. First, our dietary data included only 29 of the original 45 dietary components of DII. However, this practice is common 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. We also excluded the total fat intake from the index to avoid overestimating the impact of total fat, as DII already includes the intake of separate fatty acids (e.g., saturated fatty acids, n-3 fatty acids). Second, the DII calculation includes energy intake as one component of the diet. Energy is a common confounding factor in nutritional studies, as increased energy intake is associated with body size and the intake of other nutrients (Willett et al., 1997). This was controlled in this study using energy as a confounding factor in analyses. Third, as calculating the index is quite complex, miscalculation is possible when constructing the index. However, the range of DII scores among participants is within the range given by the developers (Shivappa, Steck, Hurley, Hussey, & Hébert, 2014).

The BSDS was developed in 2012 to indicate the adherence to the healthy Nordic diet, also referred to as the Baltic Sea diet (Kanerva et al., 2012). Since its development, dietary recommendation regarding alcohol consumption have changed (National Nutrition Council & Finnish Institute for Health and Welfare, 2024). The current guidelines do not define a safe threshold for alcohol intake. Instead, the consumption of alcohol is not recommended. In the BSDS, individuals receive one point if their daily alcohol intake is less than 20 grams for men and less than 10 grams for women. Although this scoring no longer aligns with the latest recommendations, awarding one point for moderate alcohol consumption is unlikely to substantially affect the overall inflammatory potential of the participant's diet, and its impact on the results is considered minimal. Other limitation related to the BSDS is that it does not account for total energy intake or portion sizes, therefore the high scores may be achieved even if energy intake is excessively high.

Body Mass Index

The adipose tissue-related inflammation was one key fundamental of the current study, as it was hypothesized to be associated with oral inflammation related to periodontitis. In this study, obesity was defined by BMI. A source of bias relates to this as BMI does not measure body fat directly (Rubino et al., 2025). BMI cannot separate the fat or nonfat (bone or muscle) mass in the body, so there may be lean persons with increased body fat who have low BMI or lean persons with high muscle mass who have high BMI. This bias was controlled in **Studies I** and **II** by selecting only participants living with severe obesity (BMI ≥ 35 kg/m^2), increasing the likelihood of increased adipose tissue. A large cohort study of the UK Biobank (n = 337,078) found that the waist-to-hip ratio, compared to BMI, was more consistently associated with mortality (Khan et al., 2023). The waist-to-hip ratio is a better indicator of fat distribution and does not require expensive equipment, which future studies should consider. However, in a recent study involving 2,225 U.S. adults aged 20-59 years, 98% of those classified as suffering from obesity based on BMI were found to have excess adiposity when measured using dual-energy x-ray absorptiometry (Aryee et al., 2025).

Salivary markers

Paraffin-stimulated whole saliva samples were used in this study. A golden standard for saliva collection is "passive drool," where saliva is allowed to accumulate in the mouth and collected after a prespecified time with straws (Dongiovanni et al., 2023). However, this may cause problems if the flow rate of saliva is minimal; therefore, it is not the optimal method in large cross-sectional studies involving patients with different health conditions. A study of ten healthy participants (mean age 23) compared different saliva collection methods and demonstrated the higher flow rate and lower intra- and inter-subject variation in paraffin-stimulated saliva compared to unstimulated whole saliva (Jasim et al., 2016).

The cytokine concentrations in saliva samples were analyzed using ELISA kits (H2000) and the Luminex xMAP technique (DILGOM). ELISA and LUMINEX are immunoassay techniques, but when H2000 and DILGOM studies were conducted, the LUMINEX multiplex bead array assays were the only ones that measured multiple targets simultaneously, while in ELISA kits, each cytokine required separate assays (Mountjoy, 2021). Therefore, working with ELISA kits increased the sample volume needed, whereas LUMINEX was considered cost- and time-effective. Currently, analyzing a panel of biomarkers simultaneously with ELISA is also possible (Dongiovanni et al., 2023).

Serum CRP

In **Study III**, the outcome was serum CRP concentration, which was measured in H2000 and H2011. In both surveys, the analyses were made with immunoturbidometric tests but from different manufacturers. To evaluate the differences between these laboratory methods, the samples of 70 participants who attended both studies were chosen during H2011 for repeated analyses (Lundqvist & Mäki-Opas, 2016). The Pearson correlation (r = 0.9948) was produced from the samples from the same individuals collected in H2000 and analyzed during H2000 and again during H2011. In this study, the CRP at baseline and after 11 years of follow-up was used independently when analyzing the association of diet and periodontitis with serum CRP. In addition, the change in serum CRP concentrations was analyzed in relation to periodontitis, and at this point these two measurements (H2000 and H2011) were compared. The high correlation coefficient between methods does not raise any doubts regarding these results.

6.4 Practical implications and future perspectives

This study showed periodontitis as the main determinant of salivary cytokines when diet and obesity were also considered. According to these results, if salivary cytokines are used in diagnostics to monitor systemic health, the periodontal status should be evaluated to rule out the impact of periodontal inflammation. Additionally, this study supports using saliva as a marker of periodontal inflammation, as systemic factors, obesity, and diet do not reflect in salivary concentrations at the same level.

The results of this thesis support the view that periodontitis should be considered a systemic risk factor for many chronic diseases, highlighting the importance of its early diagnosis and treatment. Elevated serum CRP concentration (≥ 2 mg/l) is associated with a wide range of morbidities and mortality (Drozd et al., 2022). Here, it was observed that the odds of having CRP above this threshold were higher in those combining advanced periodontitis and non-adherence to the Baltic Sea diet, especially in men. This indicates that the dietary counseling would have some favorable effect on the systemic health of periodontitis patients.

In future studies relating the associations of obesity and periodontitis, sex should be considered more carefully due to the differences in body fat percentage and fat distribution between men and women. Studies regarding periodontitis and diet should also more specifically examine the main components of the diet related to periodontitis and try to explore the mechanisms explaining the association. One study area could be diet-related changes in oral microbiota, which could have some explanatory value in elucidating the link between diet and periodontitis. Another future perspective could be examining other components of the diet, such as a high intake of saturated fatty acids or low intake of fiber—in combination with periodontitis—and analyze their combined risk with some specific diseases. As periodontitis is a chronic disease that takes years to develop, intervention studies regarding the disease onset and diet are unrealistic. Therefore, intervention studies about dietary patterns and periodontitis should concentrate on periodontal healing after periodontal therapy. When the association between diet and periodontitis is more specifically described, the optimal dietary guidelines for periodontitis patients could be developed

7 Conclusions

These results may indicate that even though obesity and diet are well-established modulators of systemic inflammation, they were not directly associated with salivary inflammatory markers. This finding offers a new perspective on the complex interplay between diet, obesity, and periodontitis –suggesting that inflammation may not be the only explanatory pathway. Moreover, these results highlight periodontal status as the primary determinant of salivary cytokine concentrations. If salivary cytokines are to be used as indicators of systemic health, their interpretation should be approached with caution. Notably, the combination of obesity and periodontitis was associated with elevated levels of salivary IL-6, suggesting a compounding effect of these conditions. The potential role of IL-6 as a link between oral and systemic inflammation warrants further investigation.

In addition, the findings regarding diet and periodontitis revealed a modest synergistic relationship with serum CRP levels after an 11-year follow-up, despite the lack of statistical significance following adjustment for covariates. However, the association between periodontitis and serum CRP was stronger than that between diet and CRP, emphasizing the role of periodontitis as a significant systemic risk factor. The disappearance of the association after controlling for covariates may reflect the influence of multiple systemic factors on CRP levels, with periodontitis representing only one of several contributors.

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