Prevalence of periodontitis and its association to non-communicable diseases in a Norwegian population

by
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Thesis submitted for the degree of

Philosophiae Doctor

Faculty of Dentistry, University of Oslo

Institute of Clinical Dentistry

Department of Periodontology

November 2023

Series of dissertations submitted to the
Faculty of Dentistry, University of Oslo

ISBN 978-82-8327-083-9

Cover: UiO.
Print production: Graphic center, University of Oslo.

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Acknowledgements

The work presented in this thesis was carried out at the Department of Periodontology at the University of Oslo in collaboration with Center for Oral Health Services and Research, Mid-Norway (TkMN), Trondheim. The project was funded by The Faculty of Dentistry, University of Oslo, Norway and Center for Oral Health Services and Research, Mid-Norway (TkMidt), Trondheim, Norway.

I appreciate the opportunity to give my sincere gratitude to the Department of Periodontology with its present and former staff, not only for giving me the opportunity to carry out this work, but also for teaching me everything I know about periodontology, and for opening my eyes to research. And to all of the talented postgraduate students in periodontology and PhD-candidates I am fortunate enough to spend some time with.

Many have contributed to this work, to whom I wish to express my gratitude.
First and foremost, to my main supervisor, associate professor Odd Carsten Koldsland. Impossible to catch in a bad mood, always supportive and with a kind touch to everyone who crosses his path. Thank you for your guidance throughout this project. I am grateful for your encouragement and that you are always willing to help.
Just as much, to my supervisor, associate professor Anders Verket, never asleep, always ready with constructive criticism. Your will and effort to lift the department is impressive.
To both of you, I am grateful to have had the opportunity to work with you!

A big thanks to my co-authors Hedda Høvik and Abijit Sen, who have had to put up with my endless questions about statistics and what not, and who have contributed significantly to the work of this thesis. Also, to the rest of the helpful and ever-welcoming colleagues and staff at TkMN, thank you.

I would also like to thank my co-authors at NTNU and St.Olav's Hospital, Eivind Ness-Jensen, Polina Lukina, Ina L. Andersen, Patricia Mjønes and Elin Rønne for insightful and knowledgeable contributions.

I would like to thank professor emeritus Anne Merete Aass, who has always reached out when needed, and who has told me repeatedly to look at the bright side and to remember that it will all look better in a few days- I think of this often. I feel privileged to have been a part of the department while led by a female, confident leader.

A special thank you to professor Janne Reseland for help in the final parts of the work with thesis writing.

Becoming a specialist in periodontology came with many new friends. Thank you for professional discussions, sharing of clinical cases and experience, but most importantly, for your friendships.

I have come to know many kind people working at the Faculty of Dentistry, who have formed an important part of my everyday life over several years, among the administrative staff, in IT-services, the ladies at the dental clinics and last but not least, Elisabeth Kjenstad, who is always helpful and understanding.

To my friends from outside periodontology, you mean a lot to me!
To my parents, my four siblings and two sisters in law, I know I can count on you, thank you! To my dearest Are, and our two children, Erle and Eskil Syver, you are the most important people in my life.

Abbreviations

AC – alveolar crest

AGE – advanced glycation end product

BoP – bleeding on probing

CAL – clinical attachment loss

CEJ – cementoenamel junction

CI – confidence interval

COPD – chronic obstructive pulmonary disease

CRP – C-reactive protein

CVD – cardiovascular disease

HLA – human leukocyte antigen

HUNT – The Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag)

ICC – intraclass correlation coefficient

IL – interleukin

M-CSF – macrophages colony stimulating factor

MIP1a – macrophage inflammatory protein 1-alpha

iNOS – inducible nitric oxide synthases

NCD – non-communicable disease

OR – odds ratio

PDL – periodontal ligament

PPD – periodontal probing depth

PR – prevalence ratio

PR-receptors, pattern recognition receptors

PRA – periodontal risk assessment

RA – rheumatoid arthritis

RANKL – receptor activator of nuclear factor kappa B ligand

TLR – toll-like receptor

TNF-alpha – tumor necrosis factor-alpha

T2DM – type 2 diabetes mellitus

VEGF-a – vascular endothelial growth factor-a

Summary

Periodontitis affects a large part of the world's population, and is shown to be associated with other common inflammatory diseases. This imposes a significant social and economic impact. In the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions new criteria and case definitions of periodontitis were introduced, and offered a universal approach to determine prevalence of periodontitis. The overall aim of the thesis was to identify potential associations between periodontitis and common non-communicable diseases (NCDs), related to periodontitis severity, in a large Norwegian population, by using the 2017 Classification of Periodontal and Peri-implant Diseases and Conditions.

Three cross-sectional studies were conducted to address the overall aim of the project. As part of a large population health study (The HUNT Study) in Norway, 7347 adult participants were invited to the HUNT4 Oral Health Study. The first study included clinical and radiographic examination of 4933 adult participants to assess the prevalence of periodontitis. Periodontitis according to the 2017 Classification was frequently observed. Stage I and Stage II combined, were observed in 55% of the population, while periodontitis Stage III and Stage IV were observed in approximately 17%.

In the second study, according to the distribution of periodontitis stages determined in the first study, the effect of periodontitis on cardiovascular disease (CVD), rheumatoid disorders, poorly controlled diabetes and chronic obstructive pulmonary disease (COPD)/emphysema, were explored using adjusted logistic regression models. Associations were observed between periodontitis Stage II and Stage III/IV, and CVD, poorly controlled diabetes and COPD/emphysema, relative to no periodontitis/Stage I. The strengths of the associations increased with periodontitis severity.

In the third study, participants with newly diagnosed coeliac disease were examined radiographically to determine bone loss, which was compared to bone loss in non-coeliacs. The outcome radiographic bone loss was evaluated using adjusted Poisson regression. Alveolar bone loss ≥15% was less likely in individuals with newly diagnosed coeliac disease compared to individuals without coeliac disease. In conclusion, this thesis demonstrates significant associations between periodontitis and NCDs and therefore periodontitis should be addressed for patients with concomitant diseases.

List of papers

Paper 1

Stødle, I. H., Verket, A., Høvik, H., Sen, A., & Koldsland, O. C. (2021). Prevalence of periodontitis based on the 2017 classification in a Norwegian population: The HUNT study. *Journal of Clinical Periodontology*, *48*(9), 1189-1199.

Paper 2

Stødle, I. H., Sen, A., Høvik, H., Verket, A., Koldsland, O. C.

Association between Periodontitis Stages and Self-reported Diseases in a Norwegian population: the HUNT Study.

(Submitted, in review)

Paper 3

Stødle, I. H., Koldsland, O. C., Lukina, P., Andersen, I. L., Mjønes, P., Rønne, E., Høvik, H., Ness-Jensen, E., Verket, A. Undiagnosed Coeliac Disease and Periodontal Bone Loss: A Cross-sectional Radiological Assessment from The HUNT Study.

(Submitted, in review)

Introduction

What is periodontitis?

Some of the earliest descriptions of periodontitis and alveolar bone loss originate from China, India, Assyria and Egypt 2700–260 BC (Carranza & Shklar, 2003; Guerini, 1909). In Ancient India, Sushruta (approximately 6th century BC) described periodontal conditions in *Sushruta Samhita*, a comprehensive medical work in Sanskrit (Carranza & Shklar, 2003). Periodontitis was explained with religious elements, but was described as inflammatory in nature, such as in Sushruta describing periodontitis as a disease where "teeth become loose in the gums, with discharge of blood and pus".

The emergence of a bacterial etiology in periodontitis appeared in the late 19th century (Miller, 1890). Although periodontitis has been associated with inflammation since the very first descriptions, there has been concurrent perceptions of periodontitis as a non-inflammatory condition. Degeneration of the periodontium seen in non-inflammatory conditions are still recognized, although as an expression or manifestation of systemic diseases or conditions, which are considered different disease entities (Albandar et al., 2018; Jepsen et al., 2018). Today, periodontitis is considered a microbially initiated odontogenic infection characterized by inflammation of the periodontal tissues (Haffajee & Socransky, 1994). In susceptible individuals, the initial inflammatory reaction proceeds through immune processes, entailing destruction of the periodontal ligament (PDL) and alveolar bone (Figure 1), potentially causing tooth loss. Further, with inflammation and destruction of the tooth supporting tissues, inflammatory mediators and bacteria or bacterial deposits may enter the circulation, hence is essential for the link between periodontitis and systemic disease (Ebersole & Taubman, 1994; G. Salvi et al., 1998). Porphyromonas gingivalis is an example of a species considered a driver or a so-called key-stone pathogen (Hajishengallis et al., 2012) of the periodontal inflammation, however, periodontitis is a characterized by dysbiosis, rather than a specific infection (Diaz et al., 2016), mediated by a shift in the microbiome favoring anaerobic or facultatively anaerobic species.

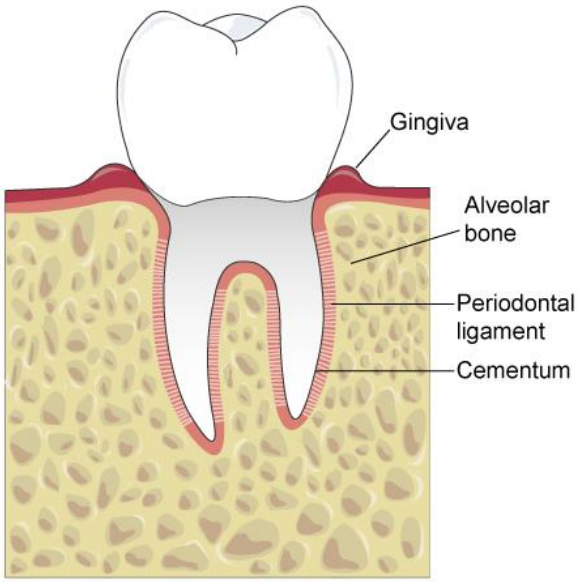

Figure 1. Tooth supporting tissues

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While the role of the genetic component in periodontal disease has been established, the identification of specific genes involved has proven cumbersome (Corey et al., 1993; Michalowicz et al., 2000; Schaefer et al., 2013). A number of factors affecting the pathogenesis of periodontitis have over the years been suggested or demonstrated, including smoking (Albandar et al., 2000; Axelsson et al., 1998), diabetes (Emrich et al., 1991), obesity (Linden et al., 2007) and nutrition (Chapple et al., 2007).

Diagnosis and classifications

The Merriam Webster dictionary defines “diagnosis” as the art or act of identifying a disease from its signs and symptoms. Diagnostic criteria are generally broad and should reflect the different features and heterogeneity of a disease, to accurately identify affected individuals. Classifications are subgroups of diagnoses, to capture the individuals with key shared features (Aggarwal et al., 2015). As diagnosis may be different from classification, it has been said that both represent two ends of a continuum and that a diagnosis applies classification criteria to an individual patient (Yazici, 2009). Classification of disease is necessary to segregate clinical phenotypes for accurate diagnosis and appropriate treatment, as it is in research of disease etiology, pathogenesis and treatment (Dentino et al., 2013).

Methods for assessment of periodontal parameters and classifications of periodontitis have evolved in line with increasing understanding of etiology and pathogenesis. With the development of indices, thorough and reproducible investigation of periodontal parameters is possible, and diagnostic criteria and segregation of

disease into different entities have emerged. In the 1966 World Workshop in Periodontics (Periodontology, 1966), the only term recognized, was “chronic marginal periodontitis” and the workshop did not consent on a definite system of classification for periodontitis (Highfield, 2009). In 1977, the American Academy of Periodontology (AAP) decided to include juvenile periodontitis as a separate disease entity. Threshold values for assessment of periodontal disease were introduced with the Extent and Severity Index (ESI), developed by Carlos and co-workers (Carlos et al., 1986), who proposed an attachment loss threshold of >1mm to qualify as affected by periodontitis. Further revisions of periodontitis definitions occurred through the classifications of 1986,1989, 1993 and 1999 (Armitage, 1999; Attstrom, 1993; Periodontology, 1989). The 1999 classification (Armitage, 1999) included gingival diseases, which had not previously been emphasized. A wide range of conditions were included in non-plaque associated disease, such as hereditary conditions, viral or bacterial infections and manifestation of systemic conditions. Adult periodontitis and early onset-periodontitis were replaced by chronic and aggressive periodontitis, diminishing age as a descriptor. Periodontitis as a manifestation of systemic disease was introduced, and additional categories were included; abscesses of the periodontium, periodontitis associated with endodontic lesions and developmental and acquired deformities and conditions. The 1999 classification was widely used until the most recent classification was published in 2018.

In addition to the evolution of the periodontitis classifications, case definitions particularly suitable for epidemiological purposes have been developed over the years. Case definitions have been based on combinations of periodontal probing depth (PPD), clinical attachment loss (CAL), radiographic bone loss and bleeding on probing (BoP), and have traditionally divided periodontitis into mild, moderate and severe forms based on thresholds and extent of attachment loss (Eke et al., 2012; Hugoson & Jordan, 1982; Page & Eke, 2007; Tonetti & Claffey, 2005).

The 2017 EFP/AAP World Workshop classification

The 2017-classification, compared to previous classifications and definitions, focuses to a larger extent on patient related risk factors, such as smoking and systemic diseases, and on clinical characteristics used to identify severe periodontitis, e.g., furcation involvement and teeth lost due to periodontitis. The workshop in 2017 addressed unresolved issues from the 1999 classification. Periodontal health and health in a reduced periodontium was incorporated in a classification for the first time. Specific definitions of gingival health and inflammation was agreed on. It was agreed that three forms of periodontitis could be identified: necrotizing periodontitis, periodontitis as a manifestation of systemic disease, and the forms of the disease previously recognized as “chronic” or “aggressive”, now denoted “periodontitis” (Caton et al., 2018). This was a result of the current perception that although forms of periodontitis may be phenotypically different, there is not sufficient evidence to claim pathophysiological differences between the two entities (Fine et al., 2018). A multidimensional staging and grading system constitute the base of the latest classification. Staging reflects the severity and complexity of periodontitis and is determined after consideration of clinical and radiological features. The grading allows assessment of individual patient related characteristics, in terms of longitudinal data of clinical or radiographic

bone loss, attachment loss as a function of age or biofilm deposits in relation to destruction. Additionally, the risk factors diabetes and smoking habits are considered. Assessment of grades aims to predict individual risk and anticipated disease development (Tonetti et al., 2018). The staging and grading system of the 2017-classification represents the first combination of disease classification and case definition, thereby providing a holistic approach to periodontal diagnostics.

Prevalence of periodontitis

Uniform criteria and accurate definitions are fundamental to assess comparable and valid data on disease prevalence and incidence across time and populations. Comparison of previous reports of periodontitis prevalence are hampered by lack of consensus on case definitions. Both PPD, CAL and radiographic bone loss have been applied as parameters of periodontitis case-definitions. Different indices and number of teeth and surfaces used to assess disease, together with different threshold values further complicate a uniform understanding of the prevalence of periodontitis. In the 1940s and the 1950s, studies were performed on American, Indian and African populations, reporting periodontitis prevalence ranging from 42% to 97% (Belting et al., 1953; Dawson, 1948; Day & Shourie, 1949; Miller & Seidler, 1940). The authors of an investigation of periodontitis in Boston in 1955 (Marshall-Day et al., 1955) described that gingival inflammation without bone loss decreased with increasing age, and conversely that detectable periodontal destruction was observed in all study participants older than 40 years. Destructive periodontal disease was defined as radiographic "evidence of destruction of the alveolar bone surrounding one or more teeth". Periodontitis was reported in approximately 70% of the total population, which included individuals from 13 years of age. Bone resorption was graded from 0 to 10, based on "interdental bony crests" in radiographs. A distance between the alveolar crest (AC) and the cementoenamel junction (CEJ) up to 2mm was considered within normality. The perspective of periodontitis as a progression of gingivitis into destructive tissue loss, seen more frequently with older age and with poor oral hygiene as predisposing factor, dominated the literature through the seventies (Loe et al., 1978). Research from the same era substantiated periodontitis as a major global health problem in adults (Scherp, 1964). Differences between individuals within a population and between populations, became more prominent based on observations in the eighties (Baelum et al., 1986; Baelum et al., 1988). Expressions like severity, extent and susceptibility were devoted more attention. Löe and coworkers (1986) reported variability in prevalence and rates of disease progression between groups of male Sri Lankans, based on longitudinal studies.

Rapid periodontitis progression was observed in 8%, while no disease progression was observed in 11% of the examined individuals, leading to increased awareness of individual susceptibility and fluctuations in prevalence across and within populations. In the Jönköping-studies, using the classification of Hugoson & Jordan (1982), research of periodontal health and disease in individuals 20-80 years over several decades, revealed that the mean number of teeth increased and number of edentulous individuals decreased. Further, since the 1970s, the number of individuals with no or minimal periodontitis increased, from 43% in 1983 to 60% in 2013. Moderate periodontitis decreased in the same time period from 41% to 29%, however, severe forms demonstrated less

change. The prevalence of the two most severe forms of periodontitis was 13% and 11% in 1993 and 2003, respectively, which remained in the same range through 2013 (Hugoson et al., 2008; Wahlin et al., 2018). Extensive reviews of worldwide prevalence of periodontitis have been published in 2014, 2017 and again in 2020 (Bernabe et al., 2020; Kassebaum et al., 2014; Kassebaum et al., 2017). The global burden of age-standardized severe periodontitis was reported to be 9.8% in 2017 (Bernabe et al., 2020), which was an increase from 7.4% in 2015 (Kassebaum et al., 2017). The prevalence was highest in individuals aged 60-64 years, but it was observed considerable variation in prevalence between regions and countries (Bernabe et al., 2020). Between 1990 and 2010, the age-standardized prevalence of severe periodontitis was reported to be static at 11.2% (Kassebaum et al., 2014). A large epidemiological survey with a population of 10683 individuals (Eke et al., 2018) reported periodontitis in 42.2% of an adult American population, where 7.8% had severe periodontitis and 34.4% had moderate or mild periodontitis (termed non-severe by the authors), according to the CDC/AAP case definition (Eke et al., 2012). Recent Norwegian studies (Bongo et al., 2020; Sødal et al., 2022) and a reclassification of the work by Holde and co-workers (Holde, 2019; 2017), have reported periodontitis prevalence using the 2017 classification. In these studies, where age, geographical location, clinical protocol and number of participants vary, total prevalence of periodontitis was reported in approximately 50% of participants. For Stage III and IV combined, the reported prevalence ranged from 20% to more than 36%.

The aforementioned studies of periodontitis constitute a span of variety in reporting of prevalence, caused by different case definitions, criteria and thresholds. Taken together, the reported prevalence of severe periodontitis based on former case definitions, is roughly in the order of 10%, while moderate and mild periodontitis vary to a greater extent, from 30% to more than 50%, throughout decades of epidemiological studies. The definitions and criteria of the classification from 2017 seem to include more individuals in Stage III and Stage IV combined, as compared to what has been defined as ‘severe’ periodontitis in previous classifications.

When considering prevalence of periodontitis, it should be noted that previous tooth loss may result in underestimation of extent and severity. Approximately 30-35% of overall tooth loss is attributed to periodontitis (McCaul et al., 2001; Reich & Hiller, 1993). Prevalence of periodontitis is reported in association with age and genetic predisposition (Michalowicz et al., 1991; Schaefer et al., 2010). Age-related occurrence of periodontitis may in reality be expression of physiological alterations seen with increasing age, for instance in immunity (Hajishengallis, 2010) or a reflection of the cumulative nature of periodontal attachment loss. Ethnical susceptibility may be a result of cultural or social elements in relation to availability of resources, socio-economic status and cultural habits, rather than biological inherent differences (Borrell, 2017).

Links between periodontitis and inflammatory related systemic diseases

The hypotheses behind the suggested interconnections of periodontitis and non-communicable diseases are based on shared pathophysiological features (Hajishengallis, 2022). Even if the diseases occur in different tissues and with different clinical expressions, they are mediated by the same or similar inflammatory and immunological pathways.

Early theories and investigations

Frank Billings postulated that "chronic focal infections" led to systemic diseases (Billings, 1912). Billings claimed that "abscesses of the gums and alveolar sockets, pyorrhea alveolaris and septic types of gingivitis" were some of several infected foci that potentially caused systemic disease, and listed arthritis, nephritis, cardiovascular degenerations, neuritis and myalgia. The relationship between systemic diseases and infectious sites was controversial, and the methods of bacterial identification at the time was poor. Those who were in favor of such relationships suggested that the mechanisms included lymphatic or hematogenous pathways, direct effect on local tissue from bacterial pathogens and from swallowing or aspirating infectious material (Appleton, 1944; Miller, 1950). In a study of 1299 hospitalized male veterans, diabetes, cardiovascular disease and malignant neoplasms were found to be associated with alveolar bone resorption (Sandler & Stahl, 1954). Type 2 Diabetes Mellitus (T2DM) was prevalent among Pima Indians in Arizona in the eighties. The global prevalence of diabetes is presently approximately 10% (Saeedi et al., 2019). Among Pima Indians older than 45 years, as many as 60-70% had T2DM (Shlossman et al., 1990), making them a suitable population for investigation of factors associated with diabetes. In this study of Pima Indians, prevalence and severity of periodontitis were assessed clinically and radiographically, and found to be associated with diabetes, age and presence of calculus in adjusted analyses (Emrich et al., 1991).

Present theories

More recent research suggests that periodontitis is associated with systemic diseases, such as CVD, diabetes, rheumatoid arthritis (RA), pregnancy complications, respiratory tract diseases and Alzheimer's disease (Beydoun et al., 2020; Monsarrat et al., 2016; Sanz et al., 2020) (Figure 2). It has been debated whether the observed associations are simply correlations caused by coinciding inflammatory reactions, or if the associations are independent. Experimental and animal studies indicate that systemic inflammation of periodontal origin and periodontal microorganisms found in extraoral tissue, represent independent factors linking periodontal disease and systemic conditions (Hajishengallis, 2015; Reyes et al., 2013). The plausible mechanisms of such associations derive from observations of increased systemic inflammatory markers caused by periodontitis that are similar and coincide with inflammatory reactions of other diseases. Inflammatory mediators induced by periodontitis and disseminated oral pathogens transported from the oral environment to respiratory tissue, the gastrointestinal

tract or to other sites through hematogenous pathways is a potential link between periodontitis and comorbid conditions. Immune cells may be activated at distant sites by these disseminated species and inflammatory mediators, leading to a cascade of reactions that bridge periodontitis to other non-communicable diseases and promote development of disease in susceptible hosts. These reactions include induction of oxidative stress and tissue damage (Hajishengallis & Chavakis, 2021; Schenkein et al., 2020), bacterial invasion in phagocytic and dendritic cells (Hajishengallis et al., 2006) and endothelial cell change (Kitamoto et al., 2020).

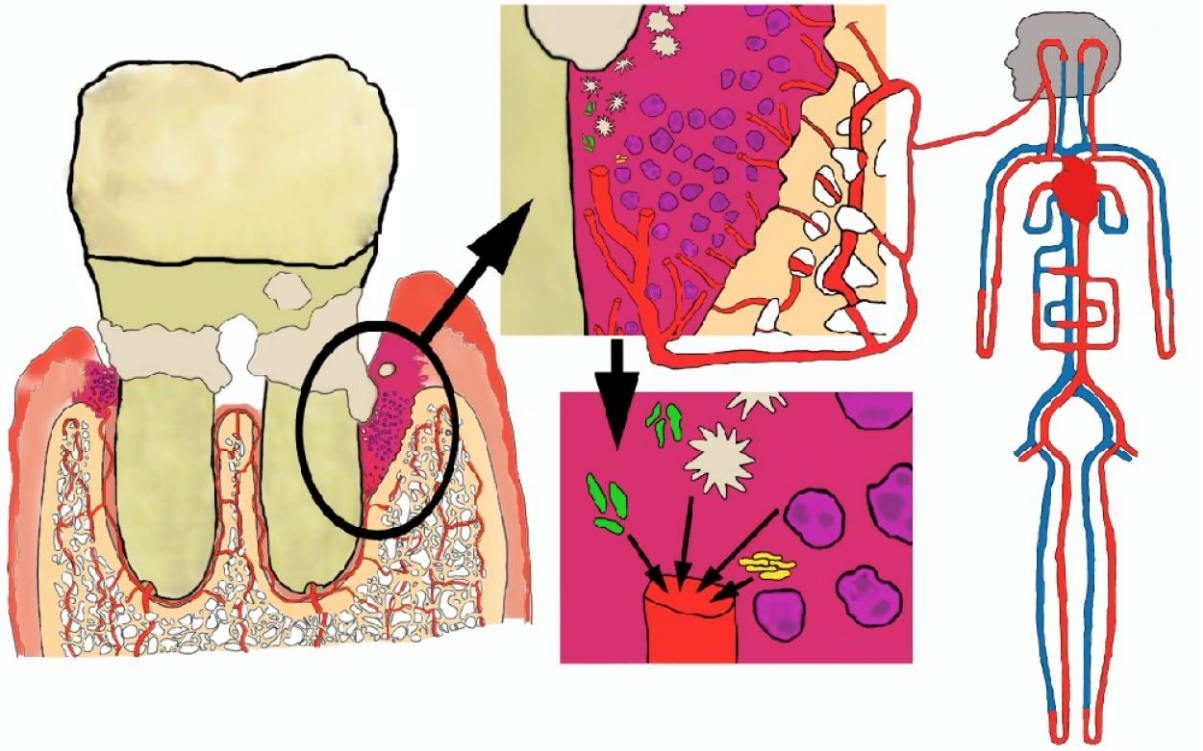

Figure 2. Associations between periodontitis and systemic conditions are mediated through periodontal pathogens, products from periodontal pathogens or periodontal inflammatory mediators

Cardiovascular disease

Periodontitis as a risk factor for cardiovascular disease (CVD) is supported by observations of enhanced expression of systemic inflammatory mediators related to periodontitis and further, that microorganisms found in the oral cavity may be present in the circulation and localized to atherosclerotic lesions (Marques da Silva et al., 2006; Schenkein et al., 2020). Higher levels of high-sensitivity CRP in patients with both cardiovascular disease and periodontitis compared with either of these alone, have been demonstrated (Kumar et al., 2014). Moreover, an increased production of reactive oxygen species in peripheral neutrophils are observed in periodontitis patients (Ling et al., 2016). In human specimens, periodontal pathogens have been found in atherosclerotic lesions,

however, in a complex microbiome with organisms originating from not only the oral cavity, but also from other tissues, such as the intestines (Armingohar et al., 2014). These findings are supported by murine models demonstrating that bacterial infection contribute to atherosclerosis pathogenesis. An increase in inflammatory serum markers as well as increased size of atherosclerotic plaques, were observed in apolipoprotein E-deficient mice infused with *A. actinomycetemcomitans* (Zhang et al., 2010). In a similar model, altered expression of multiple atherosclerosis-related genes were observed after oral inoculation with *T. denticola* (Chukkapalli et al., 2014). Moreover, infusion with *P. gingivalis* induced myocardial infarction or myocarditis in the presence of IL-17A in mice (Akamatsu et al., 2011). The link between periodontitis and CVD is further supported by an RCT testing endothelial dysfunction by flow mediated dilatation of the brachial artery in periodontitis patients (Tonetti et al., 2007). Endothelial dysfunction is regarded a pathway to atherogenesis and cardiovascular events. Severe periodontitis patients were allocated to either community-based care (control) or to intensive periodontal treatment (test). Patients were followed for 6 months, and the results demonstrated improved endothelial function and reduced inflammatory markers in the test group, compared to the control-group.

Diabetes mellitus

The comorbidity of diabetes mellitus and periodontitis involves hyperglycemia and a pro-inflammatory state, thought to act directly and through advanced glycation end products to upregulate immune reactions (Polak et al., 2020). Poorly controlled diabetes has been shown to cause alterations to the composition of the oral microbiota favoring pathogens (Merchant et al., 2014). Diabetes has an impact on a large number of molecules and cell types. Elevated levels of inflammatory markers (interleukins, TNF-alpha) (G. E. Salvi et al., 1998) and immune receptors such as toll-like receptors (Rojo-Botello et al., 2012), impaired new bone formation and increased expression of RANKL (Santos et al., 2010), are seen in hyperglycemic diabetics with periodontitis. Animal- and experimental studies also indicate that the host response is aggravated in the presence of concomitant hyperglycemia and periodontitis, with an increased inflammatory response, compared to periodontitis without hyperglycemia (Fu & He, 2013; Kim et al., 2014). These elements may point in the direction that the increased inflammation in periodontal tissues observed with hyperglycemia increases periodontal deterioration in susceptible hosts (Graves et al., 2020; Polak et al., 2020), Figure 3. Although several pathogenic mechanisms are suggested and supportive of an association between periodontitis and diabetes, there are clinical studies both in favor and in disfavor of a clinically relevant effect of periodontitis treatment on diabetes outcome. Periodontal therapy did not prove to reduce the HbA1c-levels in a 6-month RCT from 2013 (Engebretson et al.). On the other hand, and in support of periodontal therapy in diabetes management, D'Aiuto and coworkers (2018) found intensive periodontal treatment to reduce HbA1c-levels, which were significantly lower than the HbA1c-levels in the control group who received supragingival scaling, after 12 months. This is further supported by a recent Cochrane-review (Simpson et al., 2022).

Rheumatoid disorders

Certain systemic conditions, such as rheumatoid disorders may be associated with specific periodontal pathogens. Protein modification caused by the ability of *P.gingivalis* to induce conversion of protein arginins into citrulline via peptidylarginine deiminase activity, results in production of RA autoantibodies, targeting citrullinated proteins (Hajishengallis, 2015). Further modulation of immune responses in RA has been suggested. de Aquino and co-workers (2014) demonstrated that periodontal pathogens can induce T-cell response involved in the pathogenesis of experimental arthritis. Genetic susceptibility through shared epitope human leukocyte antigen (HLA-DRB1) allele, in individuals with RA and in individuals with periodontitis, and enhancement of periodontal inflammation from increased serum levels of RA inflammatory mediators, are also believed to play a role in the association between periodontitis and rheumatoid conditions (Gehlot et al., 2016; Golub et al., 2006; James et al., 2010). Intervention studies have proven to decrease RA disease activity scores, in terms of DAS28-CRP and musculo-skeletal ultrasound, 6 months after periodontal therapy, compared to oral hygiene instructions (control) (de Pablo et al., 2023; Nguyen et al., 2021).

Chronic obstructive pulmonary disease

The oral-lung microbiome interaction is suggested as a link between pulmonary disease and periodontitis (Mammen et al., 2020). Isolates of oral bacteria, including periopathogens, have been found in aspirated bronchial and peripheral lung samples from COPD-patients (Pragman et al., 2018). It is thought that P. gingivalis in co-infection with respiratory pathogens, such as Pseudomonas Aeruginosa, inhibits apoptosis of epithelial cells thereby reducing bacterial clearance and promoting infection (Li et al., 2014). The “vicious circle” is often given as a visual image of the continuous interaction of the oral-lung microbiome, and describes the flourishing of pathogens through the airways after alterations caused by for instance smoking. An aberrant immune response to these microorganisms further leads to chronic inflammation, bacterial dysbiosis and epithelial damage in the respiratory tract (Sethi & Murphy, 2008).

Coeliac disease

Individuals with coeliac disease may be more at risk of having additional autoimmunity (Bibbò et al., 2017). Coeliac disease has been found to be associated with Hashimoto thyroiditis, psoriasis, type 1 diabetes, Sjögren syndrome, inflammatory bowel diseases, arthritis, thyroid diseases and reduced bone mineral density (Assa et al., 2017; Bibbò et al., 2017; Valdimarsson et al., 1994). There is no abundance of literature on associations between periodontitis and coeliac disease. The authors of an NHANES study (Spinell et al., 2018) reported that coeliac disease was associated with lower levels of mean pocket depths and attachment loss, although the latter was not statistically significant. Coeliac disease and periodontitis may have resembling inflammatory features, but the potential mechanistic links between these two inflammatory entities are not clear. A distinct phenotype of $CD4^+$ T

cells driving celiac disease was identified in multiple autoimmune conditions (Christophersen et al., 2019). When considering the possibility of an association between coeliac disease and periodontitis, one may speculate that differences in type of $CD4^+$ T cells in in these two diseases may be a contributing factor. Another possibility resides in differences in the microbiome of coeliacs as compared to periodontitis individuals (Tian et al., 2017).

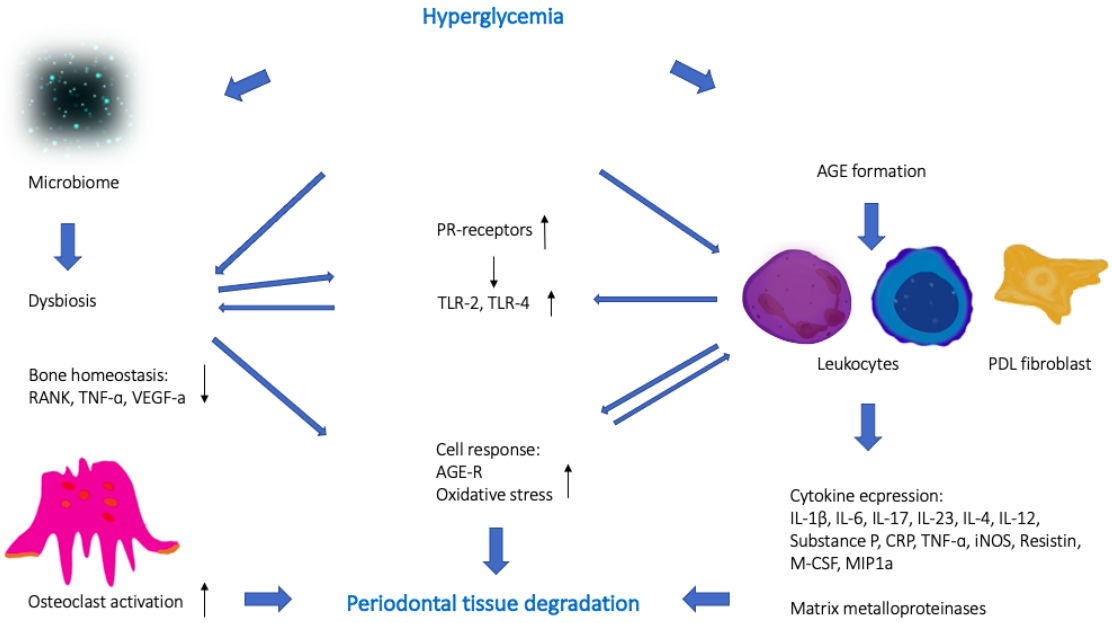

Figure 3. Association between periodontitis and diabetes. Adapted from Polak et al. (2020).

RANK, receptor activator of nuclear factor kappa-B; VEGF-a, vascular endothelial growth factor-a; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; iNOS, inducible nitric oxide synthases; M-CSF, macrophages colony stimulating factor; MIP1a, macrophage inflammatory protein 1-alpha; PR-receptors, pattern recognition receptors; TLR, toll-like receptor; AGE, advanced glycation end product; Interleukin, IL

Changing disease classification

Changing disease classification redefines who and how many meet the diagnostical thresholds. Lowering the threshold criteria for disease increases prevalence. Identification of patients with disease at an earlier stage offer an opportunity for early intervention, may prevent disease development or reduce the number of individuals with severe disease and complications. However, there are also other consequences from changing disease classification. From increased prevalence of disease, there may be an increased need for resources to treat and monitor a higher number of individuals. In turn, this will have significance in a socio-economic perspective (Schwartz & Woloshin, 1999). Having received a diagnosis may also carry a negative impact, such as psychological distress or from additional medical costs (Feldman, 1990). Hence, change in prevalence and incidence, potential benefits or harms and prognostic ability and reproducibility should be evaluated prior to modification of disease definitions. It remains unknown if the use of the new classification of periodontitis will provide more benefits, both individually and on a societal level (Raittio & Baelum, 2023). The purpose of redefining disease classification is to strive against a set of criteria that closely captures those who fulfill the diagnostical terms, and who will benefit from diagnosis and treatment, without over- or underdiagnosing (Doust et al., 2020). The rationale of the present thesis relates to the 2017 Classification, and how it will affect periodontitis prevalence and distribution of severity, and further prevalence of periodontitis in subgroups who suffer from common NCDs.

Aims and Hypotheses

Overall aim of the thesis

The overall aim of this thesis was to identify potential associations between periodontitis and common non-communicable diseases (NCDs), related to periodontitis severity, in a large Norwegian population, by using the 2017 Classification of Periodontal and Peri-implant Diseases and Conditions (paper 1, 2 & 3).

Overall hypothesis

The 2017 Classification will confirm the prevalence of periodontitis and associations between periodontitis and NCDs, equivalent to previous findings

Specific aims and hypotheses

Aim 1

To assess the prevalence of periodontitis in general and the prevalence of the different severities of periodontitis according to the 2017 Classification of Periodontal and Peri-implant Diseases and Conditions. The hypothesis was that assessment of prevalence in a Norwegian population, using the 2017 Classification, corresponded to previous assessments of periodontitis prevalence and distribution of severity

Aim 2

To assess associations between periodontitis and the NCDs CVD, rheumatoid disorders, poorly controlled diabetes and COPD/emphysema, based on the latest classification of periodontitis. The hypothesis was that there are associations between periodontitis based on the 2017 Classification and assessed NCDs, which change with periodontitis severity.

Aim 3

To assess radiographic bone loss in individuals with newly diagnosed coeliac disease compared to a reference group without coeliac disease. The hypothesis was that radiographic bone loss in individuals with newly diagnosed coeliac disease is similar to individuals without coeliac disease.

Material and methods

All studies of the present thesis are based on the HUNT4 Study, and are observational cross-sectional studies.

The HUNT-population

The population of the Nord-Trøndelag Health Study (HUNT) consists of residents in the county of Nord-Trøndelag, Norway (Figure 4). Adult inhabitants (≥20 years) have been invited to four surveys between 1984 and 2019. The HUNT studies represent the most extensive collection of medical data and biological samples in Norway, and the study population is considered representative of the general Norwegian population, except for the lack of larger cities and with lower levels of immigration (Holmen et al., 2003; Krokstad et al., 2013). HUNT1 was intended for research on hypertension, diabetes, lung disease (tuberculosis) and quality of life. The HUNT-studies have gradually expanded the scope of research to include a large range of health and quality of life related topics. More than 230000 participants have been included in the surveys since the beginning. Data collection is performed at field stations throughout the county. In addition to the main studies, Young-HUNT was initiated from 1995, and aims at participants between the age of 13 and 19 years. The HUNT-studies are also supplemented by cross-referencing by regional and national registries. In HUNT4, which was completed in 2019, the total number of participants was 56042. This was a response rate of 54%, and is a decline from 89.4% in HUNT1 (Åsvold et al., 2023; Åsvold et al., 2021).

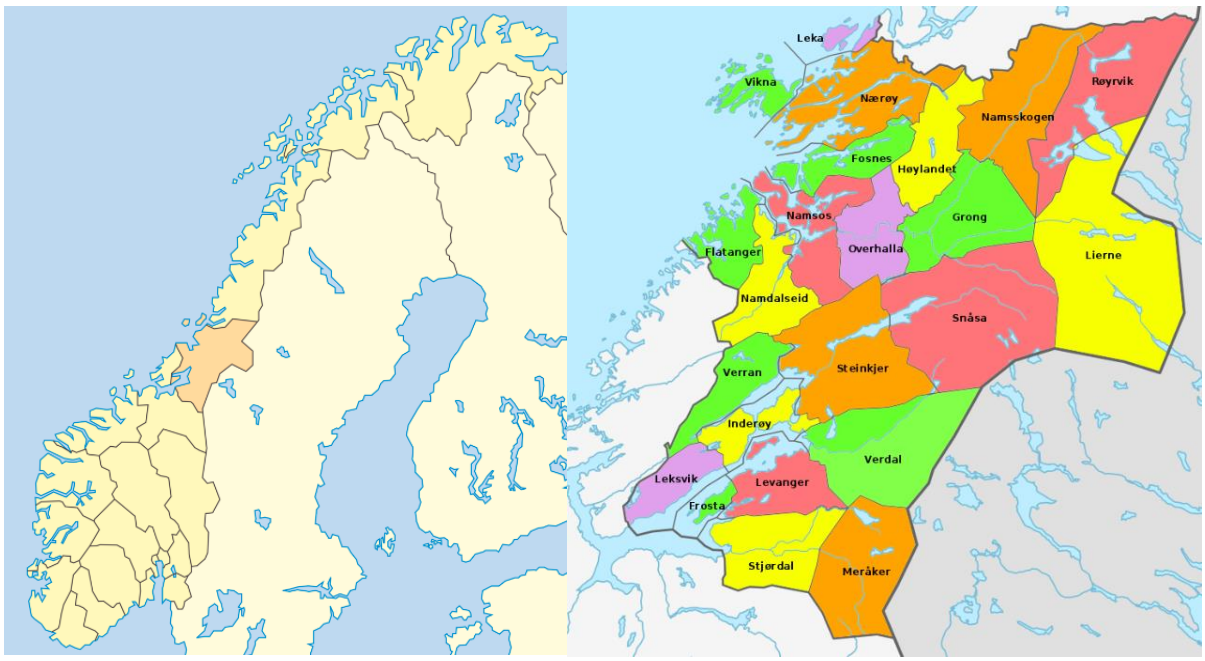

Figure 4. Municipalities of the county of Nord-Trøndelag © Wikipedia.org

Research models

An overview of analyses of the three papers is shown in Table 1.

Table 1. Analyses, outcomes, exposures and independent variables of the three papers

	Paper 1	Paper 2	Paper 3
Design			
Cross-sectional	x	x	x
Outcome			
Prevalence of periodontitis	x		
Cardiovascular disease		x	
Hyperglycemia in diabetics		x	
Rheumatoid disorders		x	
COPD/emphysema		x	
Radiographic bone loss			x
Exposure			
Periodontitis, stage		x	
Periodontitis, grade		(x)	
TG2			x
Marsh grade 3			x
Independent variables			
Age	x	x	x
Sex		x	x
Smoking	x	x	x
BMI		x	
HbA1c	x	x	x
Hb			(x)
Hypertension		x	
Income		x	x
Education		x	x
Physical activity		(x)	(x)
Statistical analyses			
Chi-square	x	x	x
One-way ANOVA	x	x	x
Logistic regression		x	
Poisson regression			x

(x) not included in final analysis

Inclusion to the HUNT4 Study and the HUNT4 Oral Health Study

The invitees to the HUNT4 Study received an invitation letter, information booklet and the first self-administered questionnaire, by mail. Participants were asked to bring written consent when and if attending the examinations. All participants were asked to complete further self-administered questionnaires with a range of health-related questions. Trained nurses and technicians implemented standardized anthropometric and general clinical measurements and collected biological samples. Oral health was first included in HUNT3 (2006-2008) in a smaller scale but was expanded into a large-scale investigation of oral health in HUNT4. The Oral Health Study was performed in six larger municipalities (Stjørdal, Levanger, Verdal, Steinkjer, Nærøy, and Namsos). Inclusion was based on a randomly selected subgroup (approximately 20%) of participants in HUNT4 who attended the HUNT4 Study at one of these six field stations. The number of invited participants was adjusted to fit the capacity at the field stations. The inclusion was successively performed until study completion. Assessment of periodontal conditions was included for the first time in HUNT4. An overview of study participants and populations are shown in Figure 5.

Inclusion to the HUNT4 Coeliac Disease Study

Serum samples were collected from 54541 participants in the HUNT4 Study. Inclusion to the Coeliac Disease Study was based on positive serology, i.e., threshold levels of anti-transglutaminase 2 (TG2) immunoglobulin A (IgA) and G (IgG).

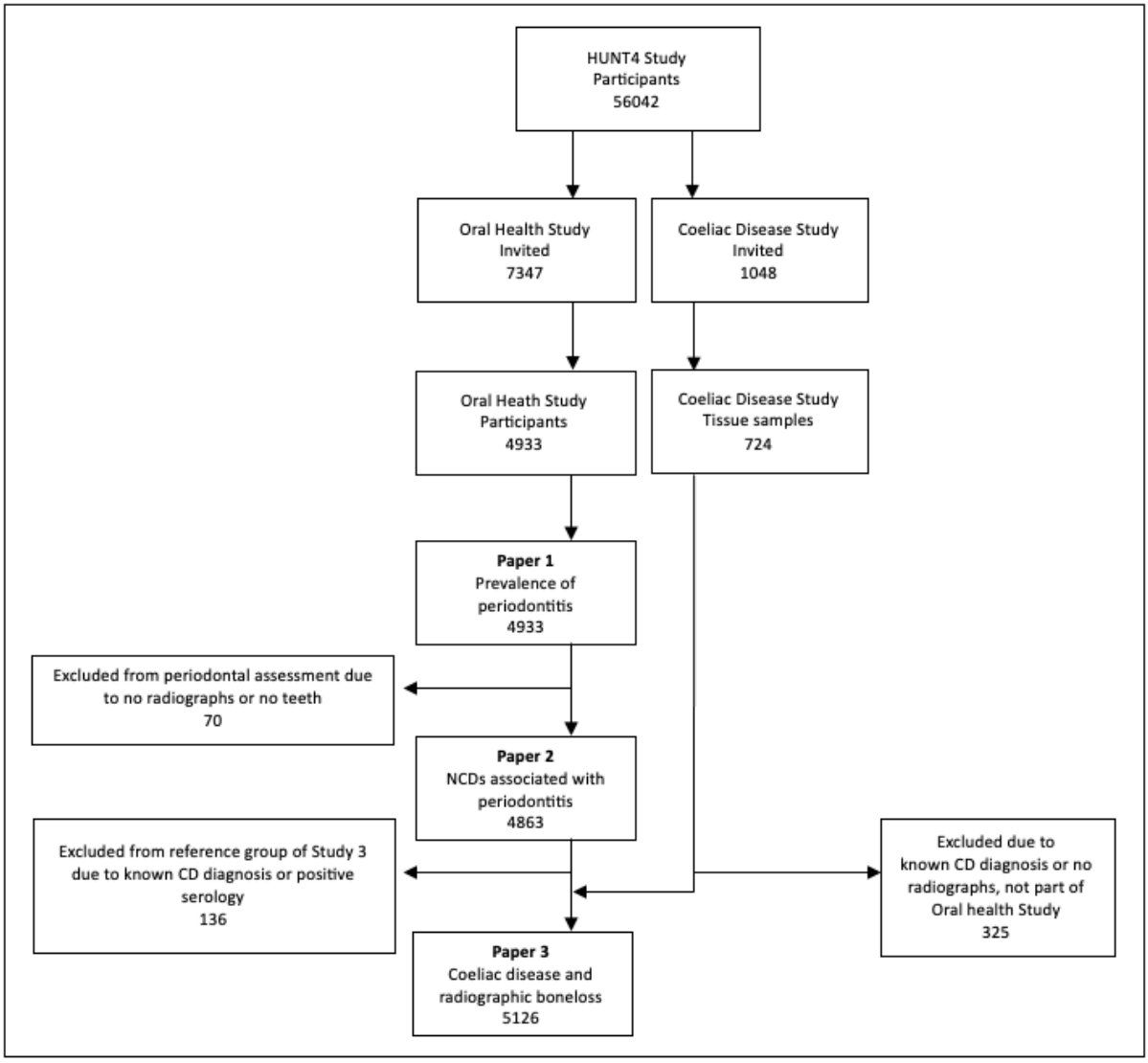

Figure 5. Overview of study populations

Collection of variables

Variables from clinical and radiographic periodontal examination, in addition to data retrieved from HUNT databank, constitute the basis of all analyses in the present thesis. Answers to questions regarding history of disease, education level, level of income, frequency of physical activity and smoking habits were considered in all 3 studies. Participation age and HbA1c-level were included in the analysis in study 1. For the purpose of study 2 and 3, several additional variables were considered, including weight, height, waist circumference, hypertension, serum levels of cholesterol, HDL cholesterol, serum triglycerides, blood glucose and -Hb and level of μCRP. Serum titers of IgA and IgG and results from endoscopic tissue sampling were included for study 3 (Table 1).

Calibration and inter-rater reliability

Clinical assessment

The clinical assessments were performed by calibrated dentists and dental hygienists. The calibration of the clinical examiners was initiated with lectures and demonstrations by experienced specialists in periodontology. The introductory theoretical part of the process consisted of a review of the protocol with introduction to systematic periodontal examination, including sitting position, record keeping and correct use of instruments using sensitive scales to measure a standardized probing pressure of 20 gram. Two separate meetings were arranged, each of which half of the examiners and assistants attended.

Calibration meetings followed the theoretical sessions, at each of the 6 field stations. The calibration consisted of clinical examination performed on voluntary participants (family and friends of the dental health staff, other employees at the clinics). During clinical examination, the examiners received guidance and adjustments of their technique, by the specialist instructors. At each of the field stations 1-5, 9 volunteers were examined. At field station 6, 8 volunteers were examined. Each station had 3 to 4 examiners, and each volunteer was examined 3 times. A total of 20 examiners were calibrated, 19 of whom participated in data collection. No gold standard was applied during the calibration procedures.

Radiographic and periodontal assessment

The radiographic examination and assessment of periodontitis stages and grades were performed by three calibrated specialists in periodontology. Calibration of the specialists was based on a random sample of 70 participants. Radiographs and clinical variables were assessed to determine the percentage of bone loss at the most severely affected mesial or distal site, and to determine stage and grade when identified as periodontitis cases. After calculation of intraclass correlation coefficient (ICC), the cases of disagreement were discussed to increase consistency between examiners.

Inter-rater reliability

Inter-rater reliability was calculated using ICC two-way mixed effect model, assessing absolute agreement for the clinical examiners for measurements of PPD and for the specialists in periodontology in determination of periodontitis stages and grades. Inter-rater reliability of the specialists in periodontology for radiographic bone loss assessment in percentage, was calculated using ICC two-way mixed effects, assessing consistency. The ICC of the PPD-assessment ranged from 0.57-0.79, for each of the field stations. The ICCs of the stage- and grade-assessment were higher; 0.92 (0.88-0.95) for generalized stage and 0.94 (0.91-0.96) for localized stage. The ICC of the grade-assessment was 0.90 (0.85-0.93). The assessment of ICC for percentage bone loss was 0.95 (0.92-0.96).

Assessment of bone loss, periodontitis and modifications to classification

The proceedings of the World Workshop on the Classification of Periodontal and Peri-implant diseases (Caton et al., 2018; Chapple et al., 2018; Papapanou et al., 2018) constituted the basis of the assessments of radiographic bone loss and periodontitis. Four bitewing (BW) and one orthopantomogram (OPG) radiographs were obtained from each participant. The BW radiographs for each participant were screened to identify attachment loss attributable to periodontitis. To be able to separate non-periodontitis cases from periodontitis cases radiographically, a threshold of at >1.5mm between the CEJ and the AC was chosen. This threshold was chosen by the authors, and is not a part of the 2017 Classification. BW radiographs were not considered for the study of coeliac disease and bone loss.

Each participant underwent a clinical examination which consisted of PPD, BoP and suppuration recorded at six sites and tooth mobility. PPD was recorded in intervals with a WHO periodontal probe (LM 550BSI Probe WHO ErgoNorm, LM-Instruments, Parainen, Finland). The criteria for determination of periodontitis for studies 1 and 2, were the clinical recordings, radiographic bone loss in OPG images, number of teeth lost due to periodontitis and complexity factors. Some modification to the classification was required for studies 1 and 2. These modifications included a radiographic evaluation of furcation involvement class II and III (Komšić et al., 2019; Zhang et al., 2018), redefined criteria for vertical bone loss, bite collapse, drifting, flaring and the PPD-registrations, as the WHO probe cannot precisely identify PPD 4, 5 or 6mm. Further, some of the complexity factors, i.e., masticatory dysfunction and secondary occlusal trauma, may be unsuitable for radiographic assessment, or they overlap with other factors, such as tooth loss due to periodontitis in those cases where teeth are missing in such a pattern that occlusion or masticatory function is lost. These were therefore not extensively used, or not at all, for the classification of the present population. The percentage of bone loss at the most severely affected tooth and the age of the participant, were used to determine the initial grade of the periodontitis cases. Final grades were determined by grade modifiers, i.e., self-reported smoking habits and HbA1c measurements in participants with self-reported diabetes.

All participants in the Coeliac Disease Study that attended endoscopy were offered radiographic examination in terms of an OPG. In this study, due to a lack of a clinical examination and BWs, only percentages of bone loss were considered.

Assessment of NCDs

History of disease was assessed by self-administered questionnaires by affirmative answers to the question “Do you or have you ever had any of the following diseases…”. CVD, rheumatoid disorder, COPD/emphysema and hyperglycemia in self-reported diabetics, were used as study endpoints in the study of associations between periodontitis stages and non-communicable diseases (paper 2). CVD was defined as a composite of myocardial infarction and/or angina pectoris and/or apoplexia. Rheumatoid disorder was defined as a composite of RA and/or ankylosing spondylitis. The endpoint hyperglycemia in self-reported diabetes, was a combination of self-reported disease and analysis of HbA1c in serum samples. The exposure coeliac disease was assessed from threshold levels

of anti-TG2 IgA and IgG and from a clinical assessment, including upper endoscopy with small intestinal tissue sampling, with confirmation of coeliac disease when intraepithelial lymphocytosis, crypt hyperplasia and villous atrophy corresponded to Marsh grades 3a, 3b or 3c in either one of the biopsies (Marsh, 1992).

Statistical analyses

Descriptive statistics were used initially to describe the prevalence and distribution of periodontitis.

The mean and standard deviation for continuous variables, and percentages with 95% confidence intervals for categorical variables were presented. The one-way ANOVA test was further used to assess significant differences across group means for continuous variables and Pearson chi-square test was used for categorical variables.

Logistic regression analyses were designed to model the effect of periodontitis stages on the outcomes self-reported CVD, self-reported rheumatoid disorders, self-reported COPD/emphysema and hyperglycemia in self-reported diabetic. Periodontitis was grouped into 3 categories; a combination of no periodontitis and Stage I, Stage II, and a combined group of Stage III and IV. Poisson regression was applied to model the effect of coeliac disease in terms of serum anti-TG2, on percentage of bone loss. Bone loss was categorized corresponding to the stages of severity (<15%, ≥15-33%, >33%) in the 2017 Classification. Coeliac disease determined from small intestinal tissue sampling, and further, coeliac disease where gluten free diet was recommended, were also included as exposures in separate analyses. The statistical models were adjusted for variables known to be associated with periodontitis and/or the outcomes.

Sensitivity analyses

Regression models were the main statistical analyses of study 2 and study 3. Sensitivity analyses were applied to evaluate the influence of alternative analyses on the outcome. Sensitivity analyses increase insight and when consistent with main analyses, increase the validity of the findings (Mowbray et al., 2022). Several sensitivity analyses and supplementary analyses were conducted in the present studies to address validity and strength, and included analyses in never-smokers, analysis with exclusion of participants 75 years and older, analysis of non-diabetics, analysis of participants reporting diabetes diagnosis, but without considering HbA1c-level, propensity score matching to evaluate possible covariate differences and linear regression.

Ethical considerations

At study inclusion, all participants signed a written consent that can be withdrawn if desired. Access to data collected through the HUNT studies are available by application (https://hunt-db.medisin.ntnu.no/hunt-db/), to researchers who are affiliated with a Norwegian institution and who have obtained pre-approval from the Regional Committees for Medical and Health Research Ethics (REC). All data are deidentified with no accessible personal information. A coupling key is stored at HUNT Research Centre. The Norwegian Data Protection Authority has approved and licensed storage and handling of HUNT Data in HUNT Research Centre. All project-specific data are deleted at termination of each project. Original data from HUNT is stored in the HUNT data bank. Coupling of HUNT data to data from other registries can be made given that project-specific approval for such coupling by REC and each registry owner is obtained.

The three studies in the present thesis were approved by the Regional Ethics Committee: 2016/1879/REK, 2020/10417/REK, 2021/264485/REK, 2021/330940/REK.

Summary of results

This thesis includes three cross-sectional studies on periodontitis, in a Norwegian population. The assessment of associations between periodontitis and NCDs are based on the findings from the prevalence study.

The findings from assessment of periodontitis prevalence according to the new classification, revealed that periodontitis affected the majority of the adult Norwegian population (72%). Periodontitis Stage III and IV combined occurred less frequently, in approximately 17% (paper 1). This corresponds to previous studies, with some deviation, because the framework of what defines Stage III and Stage IV overlap with what previous classifications define as moderate and severe. The periodontitis cases were primarily classified as grade B, implying moderate risk. Gingivitis was observed in approximately 12% and periodontal health in 11%.

Further, from the investigations of potential associations with periodontitis stages (paper 2 & paper 3), it was observed that the individuals identified with periodontitis (Stage II-IV) in the prevalence study, more often reported other diseases than participants with no or incipient periodontitis (Stage I). The part of the population affected by Stage III and IV periodontitis, was more likely to suffer from CVD, uncontrolled diabetes and COPD/emphysema, but no association was seen between periodontitis and rheumatoid conditions. Similar relationships were observed for periodontitis Stage II, but the associations were weaker than for periodontitis Stage III/IV. The results placed additional emphasis on differences between stages of periodontitis related to how they occur or act together with certain types of general diseases. Participants with periodontitis had generally lower levels of education and income, were older and used cigarettes more often.

Compared to the associations of the other NCDs, contrasting results were observed for coeliac disease. The present study population (HUNT4 Oral Health) was used as a reference group in a study where radiographically determined bone loss in previously undiagnosed coeliac and non-coeliac participants were compared. The result of this study did not suggest that the periodontal status of individuals with coeliac disease was inferior to that of the non-coeliac individuals. Among participants with newly diagnosed coeliac disease, bone loss ≥15% was a significantly less frequent finding compared to the reference group. This finding was observed when coeliac disease was determined from serum analyses, and when coeliac disease was confirmed by histopathological assessment. When the most severe cases of periodontitis were considered separately (bone loss ≥33%), the associations were not statistically significant. The average bone loss in the groups were 15.9% (coeliacs) and 18.3% (non-coeliacs). Among coeliacs, 54.8% was registered with radiographic bone loss ≥15%, while the corresponding number was 59.3% in the reference group.

Analyses of periodontitis grades and NCDs were performed (Table 2), but not included in paper 2. This analysis demonstrated associations between the different grades of periodontitis and CVD, COPD/emphysema and

rheumatoid disorders. Uncontrolled diabetes was not assessed, due to the direct incorporation of diabetes into grade assessment. Stronger associations with increasing grades, were not observed in this analysis.

Table 2. Association between cardiovascular disease, rheumatoid disorders and COPD/emphysema and periodontitis grades, by logistic regression analysis

NCD [1,2,3]	No. of observations	Crude OR (95% CI)	No. of observations	Adjusted OR (95% CI)
Cardiovascular disease[1]				
Grade A	n=4713	7.09 (3.53-14.23)	n=4039	5.01 (2.35-10.70)
Grade B		7.87 (4.57-13.54)		5.17 (2.83-9.43)
Grade C		12.37 (6.58-23.27)		3.01 (1.40-6.48)
Per unit increase		2.12 (1.80-2.51)		1.51 (1.25-1.82)
p-linear trend		<0.000		<0.000
Rheumatoid disorders[3]				
Grade A	n=4688	3.34 (1.77-6.27)	n=4067	3.95 (1.95-8.01)
Grade B		4.07 (2.67-6.18)		3.83 (2.26-6.49)
Grade C		3.87 (2.14-7.02)		2.75 (1.33-5.67)
Per unit increase		1.67 (1.43-1.95)		1.49 (1.23-1.79)
p-linear trend		<0.000		<0.000
COPD/emphysema[3]				
Grade A	n=4668	4.75 (0.30-76.14)	n=4046	2.84 (0.18-46.11)
Grade B		35.33 (4.91-254.29)		12.88 (1.75-94.53)
Grade C		74.0 (9.77-560.37)		6.26 (0.78-50.47)
Per unit increase		3.19 (2.26-4.49)		1.34 (0.96-1.88)
p-linear trend		<0.000		0.08

Reference: No periodontitis

1 Adjusted for HbA1c-level, BMI, hypertension, sex, smoking (pack years), income and years of education

3 Adjusted for hypertension, sex, smoking (pack years), income and years of education

The overall findings of these studies imply that there are associations between periodontitis and non-communicable diseases with the use of the 2017 classification, and that individuals with severe periodontitis in particular may be at higher risk of concomitant diseases. Increased awareness among all health personnel to increase accessibility of information about prevention, of both periodontitis and life-style related diseases, is justified due to the coincident diseases, prevalence and variance in severity identified in this study.

Discussion

Before a discussion regarding achievement of the aims of this thesis, an evaluation of the methodology is in order.

Methodological considerations

Statistical considerations

Covariate selection

The statistical relationships in the present thesis were assessed by regression analyses. Design of the statistical models may influence the outcomes by a number of different factors, including the choice to use categorical or continuous variables, combination of categories to increase group size and selection of covariates in the multivariable models. Risk factors and indicators are important in the choice of covariates and inflict on the coefficient and the confidence interval of the determination of associations, i.e., affect the proportion of the variance explained by the specific covariates in the models.

Age is frequently stratified based on disease distribution in specific age-groups, when used as an adjusting factor in statistical estimation. This approach was considered for the analyses in this thesis, and may have affected the outcome. To avoid assumptions of age-specific distribution, age was applied as a continuous variable. However, when the relationship between dependent and independent variables are anticipated to be non-linear, a splined model may be appropriate. Splines were incorporated in the present analyses initially, however, there were no substantial divergence from the present results. It is also possible that exclusion of the younger individuals would have been an appropriate approach, as periodontitis and several of the NCDs are infrequent before the age of 40. All individuals included in the Oral Health Study in HUNT4 were included for the analyses of periodontitis to achieve a high number of observations. In a subgroup analysis where all participants younger than 35 years were excluded, result similar to the main results were observed.

Smoking habits were assessed as pack years in study 2. Pack year is a numerical value of lifetime tobacco exposure, independent of variance in smoking intensity over the years. A pack year is defined as twenty cigarettes smoked every day for one year. This variable does not take into account cessation of smoking, and years since cessation, which may have implications for periodontitis pathogenesis. This could have been achieved if the pack year-variable was combined with the smoking status-variable (current, former, never). When choosing between the two, pack year was considered to infer the effect of smoking on the outcome most adequately. The choice of smoking variable is not considered to be decisive, as there was a clear impact from smoking on the outcomes in the statistical analyses.

For the study of bone loss in coeliacs (paper 3), pack years were not assessed, hence smoking status was used.

There is a possibility that the choice of independent variables included in the present analyses of periodontitis and systemic conditions are over-adjusted. There may be an overlapping effect from BMI, hypertension and the HbA1c-concentration, that have led to disturbance of the true relationships. To be noted, the changes in effect sizes and even p-values caused by model design or selection of covariates, may not necessarily be of crucial importance in a clinical perspective, but rather have implications on a theoretical level.

In addition to the applied sensitivity- and supplementary analyses which supported the main findings, *p for linear trend* and *per unit increase* were calculated as a part of the association analyses in study 2. This approach where periodontitis stages are treated as a continuous measure, was performed in order to aid interpretation of the associations with periodontitis as it ranges from no periodontitis to the more severe stages. Although the pathogenesis of periodontitis is not regarded as linear, but rather with episodic progression, the results were in line with the increasing strength of relationships observed in the main analyses.

Model design

Methodological challenges and limitations

There are general limitations related to a cross-sectional design. Neither causal nor temporal relationships between the exposure and the outcome can be determined in a cross-sectional study.

Threshold of bone loss

For the present assessment of prevalence, radiographic bone loss was determined from BW and OPG radiographs, and periodontitis was defined as at least two non-adjacent teeth with a distance of >1.5mm between the CEJ and the AC. This threshold aimed to identify a percentage of the average root length up to, but below 15%, and may be debated. Hausmann and coworkers (1991) claimed that no consistent evidence of bone loss could be determined when the distance between the CEJ and the bone crest in bitewings were less than 2mm. Increasing this threshold in the present study, from >1.5mm to ≥2mm, would likely reduce the prevalence of periodontitis, and would have been possible to defend. It has been argued that in assessment of radiographic bone loss from BW radiographs, 1mm is considered equal to 10% bone loss (Heitz-Mayfield et al., 2020). Still, determination of bone loss from radiographic images is considered to entail underestimation, to a greater extent in OPG images compared to bite wing images (Åkesson et al., 1992), and may have influenced the precision of radiographic bone loss assessment in the least severe cases, in particular.

Clinical assessment

Several additional factors may have influenced the result of the first study. Assessment of CAL, rather than radiographic assessment of bone loss, would have strengthened the reliability of the periodontitis assessment. However, CAL measurement is more demanding for the clinician compared to measurement of PPD, and in particular in a non-specialist setting, and was not feasible due to time limitation in evaluation of the periodontal condition in a large population. Evaluation of CAL rather than radiographic bone loss would have enhanced the assessment of stage distribution.

Furcation involvement was assessed in radiographs. This method is considered to have underestimated the prevalence of furcation class 2, thereby also underestimated the prevalence of individuals with Stage III periodontitis. Moreover, no attempt was made to assess reasons for tooth loss. It is likely that the restrictive attitude in determination of periodontitis as the cause of loss, has led to further underestimation.

The WHO probe is traditionally used for epidemiological purposes, with the intent to efficiently assess periodontal pockets. The selection of probe for the periodontal examination was decided before the 2017 classification was published. A periodontal probe with recording to the nearest mm would have allowed for assessment of periodontal pockets with enhanced accuracy corresponding to the applied classification. This is not, however, considered to have affected the estimated prevalence extensively.

The limited amount of time available for clinical examination may have influenced registration of PPD and BoP. A 10-minute clinical session was the total available time for the periodontal examination, for each patient. In light of this, further underestimations are likely, thereby affecting the distribution of gingivitis, periodontal health and periodontitis stages, in the study population.

Reliability of data

The calibration of the clinical examiners was performed on volunteers, e.g., dental clinic employees and friends and family of the employees. Periodontitis was not a frequent finding among the volunteers. The ICC of the PPD-assessment ranged from 0.57-0.79, indicating moderate to good reliability, but must be considered relative to the low variation in PPD among test subjects. This is in line with the statement that probing to estimate early CAL may be inaccurate (Tonetti et al., 2018), and is thus not necessarily indicative of inferior reliability of measurements of deeper periodontal pockets. The ICC of the periodontitis stage-assessments and the assessments of radiographic bone loss were higher; in the range of 0.92-0.95, indicating excellent reliability.

Self-reported variables

Recall bias is of relevance in the present thesis. The majority of the assessed NCDs and covariates were based on answers to questionnaires. Recall-bias may be relevant in terms of interpretation of questions, e.g., what one defines as physical activity when reporting frequency of physical activity, and in terms of the ability to recall the correct answers, e.g., when reporting number of cigarettes for someone who is a former smoker. The ability to

recall the correct answers is anticipated to entail both over-and underestimation. Further, it is expected that information which is socially undesirable and related to known health hazards are underreported, e.g., smoking habits (Coughlin, 1990). Importantly, well-defined self-reported disease have been found to be reliable in epidemiological research (Midthjell et al., 1992).

Bias towards the healthy

The HUNT populations are selected from a wide geographical area. For some, participation at the field stations may therefore be hindered by physical accessibility. This may imply "bias towards the healthy", where participants without physical or psychological challenges may be able to participate with less difficulty. This is supported by a HUNT cohort profile which identified that good health was reported more frequently among participants compared to non-participants (Åsvold et al., 2021). The implication for the periodontal assessment is unknown, but may have led to underestimation of the most severe periodontitis cases. Likewise, underreporting of general diseases may have affected the estimation of associations between periodontitis and NCDs.

Generalizability

The investigated population of Norwegian adults is considered representative of a general Norwegian small-town and country-side population (Holmen et al., 2003). However, there are some limitations to consider when assuming generalizability.

Cross-sectional studies are characterized by data collection from observations at a certain point of time. Bias known to be associated with cross-sectional studies include selection bias. Sampling bias is usually classified as a subtype of selection bias. Sampling bias occurs when the study participants are systematically different in characteristics compared to individuals eligible for participation, who were not selected. Analyses of non-participants are recommended to enable comparison of background characteristics of non-participants and participants to identify potential sampling bias. Differences among participants and non-participants were identified through primary health care diagnostic codes and health care-use in health registries, and reported in the cohort profile (Åsvold et al., 2023). Hence, some degree of selection bias is expected for the inclusion to the studies in HUNT4. This may have inflicted on the representativity of the study population and thereby the generalizability. In accordance with "bias towards the healthy" disease may be underreported in the Oral Health study, which infers a limitation to the external validity. The response rate of the HUNT4 Study was 54%, and the concern for selection bias was judged to be generally lower due to the relatively high participation (Åsvold et al., 2023).

Representativity in terms of prevalence of self-reported NCDs is of further relevance. The national prevalence of cardiovascular disease is difficult to determine accurately, due to the numerous conditions included within this designation. In the present Oral Health Study-population, the prevalence of the composite CVD measure (myocardial infarction and/or angina pectoris and/or apoplexia) was 6.4%, which is slightly higher than the 5.2% reported to suffer from myocardial infarction, heart failure, apoplexia or atrial fibrillation in 2021 (National

Institute of Public Health, 2021). Diabetes (type I and type II, combined) affects 5% of the Norwegian population (Stene et al., 2020). In the study population, 4.5% reported diabetes (without differentiation between type I or type II diabetes). Rheumatoid disorder was defined as a composite of RA and/or ankylosing spondylitis. The prevalence reported in the present study (5.9%) exceeded the national prevalence, which is approximately 1% for RA (Kvien et al., 1997) and 0.1-0.9% for ankylosing spondylitis (Bakland et al., 2005). COPD is reported to affect 6-7% of the Norwegian population above 40 years in Norway (Melbye et al., 2020). In the present population the prevalence in participants above 40 years was 2.8%. The prevalence of coeliac disease is 1-2% in most countries (Singh et al., 2018). Correspondingly, the present prevalence of seropositivity was approximately 1.9% of the total 54000 participants with serum samples, while the prevalence of seropositivity among the individuals in the Oral Health Study was 2.7%.

For CVD, diabetes and coeliac disease among participants in the Oral Health Study, the prevalence is in line with the reported Norwegian national prevalence. The greatest difference in reported prevalence was seen for rheumatoid conditions. As further discussed below, this may be related to the heterogenous group of participants designated to rheumatoid disorders. Nevertheless, divergence in prevalence between source and study population, also entails a limitation to the representativity of the population and the generalizability of the findings.

As for all population studies, the outcome is a product of the population characteristics. The present population is defined by factors such as relatively high levels of education and income in addition to the easily available health resources. The findings are therefore representative to similar populations, only. The population characteristics have inherently contributed to the findings which may differ from that of other studies with different population characteristics. Extrapolation to populations where health care services are less available and where general health and educational level is lower, as well as to population of large cities may be inappropriate.

Discussion of the specific aims

Periodontitis prevalence

Without consideration of severity, periodontitis was a highly prevalent condition, observed in approximately 72%. Periodontal health (<10% BoP, PPD<4mm in non-periodontitis cases) was observed in approximately 11%, while 12% had gingivitis. The observed prevalence and stage distribution in the present assessment largely coincides with prevalence from previous studies and classifications.

Stage I and Stage II periodontitis may be regarded as what has previously been called incipient, mild and moderate periodontitis with some overlap towards more advanced stages, and was detected in 54.9% in the present assessment. The Norwegian study by Holde et al. (2017) reported 9% severe periodontitis and approximately 40% mild to moderate. The divergence between the study from 2017 and the present, relates to the criteria of the latest classification. Compared to "severe" in previous classifications, a higher number of individuals are included in Stage III and IV. Additional clinical and radiological features are included in stage assessment, and is in this respect considered more complex than previous sets of criteria. This may enable identification of individuals with severe periodontitis (mainly Stage III) at an earlier time. In contrast, Stage IV appears to be an even more limited interval than previous "severe". In addition, the classification differs from previous classifications with regard to the lower limit of what constitutes a periodontitis case, which is not directly defined in the latest classification. This contributes to the high prevalence of periodontitis in the present population.

Holde et al. (2017) reclassified the population according to the 2017 Classification, using radiographic bone loss and PPD assessment (Holde, 2019). The results corresponded to the present study with regards to Stage I and Stage III/IV, but divergence was noticed in total prevalence and for Stage II periodontitis, which were reported in 48% and 19.2% of the population. Differentiation of Stage I from no periodontitis is difficult and is expected to contribute to the observed deviation. Differences with regards to Stage II may be related to more comprehensive registration of PPD in the 2017 study, due to type of probe and time used for clinical examination.

The other Norwegian studies using the 2017 classification are also in agreement with regards to Stage III and/or Stage IV. Bongo et al. reported periodontitis Stage III/IV combined in 20% of the population (2020). The total prevalence of periodontitis was lower (50%) compared to the present, but bone loss was assessed on BWs, which may render underestimation. The most recent Norwegian study (Sødal et al., 2022) assessed full mouth PPD, furcation involvement and radiographically determined bone loss (OPG), and reported a prevalence of 3.3% Stage IV periodontitis. This study was limited to 65-year-olds, and based on several thresholds for defining periodontitis. When analyzing 65-year-olds in the HUNT4 population, Stage III was observed in 26.4%, corresponding to 32.8% in the assessment by Sødal and co-workers (2022). The slightly lower prevalence, may very well be due to lack of clinical furcation assessment in the HUNT4 study.

Some uncertainty with regards to prevalence of periodontitis stages linger, and may be related to several factors. Determination of periodontitis stage relies upon the examiners clinical judgement assessing the totality of the

patient (Kornman & Papapanou, 2020). More severe periodontitis stages are determined with increased accuracy, compared to less pronounced attachment loss (Tonetti et al., 2018). Stage I periodontitis has no quantification of the lower limit of radiographic bone loss. The limiting features of Stage I include maximum PPD 4mm and CAL 1-2mm or less than 15% radiographic bone loss. Based on this diagnostic frame, differentiation between Stage I periodontitis and no periodontitis is difficult in an epidemiological setting and in a cross-sectional study in particular, balancing the borderline between gingivitis and periodontitis (Tonetti et al., 2018). Moreover, 15% of the total root length may lie within the biological variation of a healthy periodontal attachment apparatus (Hausmann et al., 1991).

In the total population, 60% were identified as having a moderate risk of progression of periodontitis (Grade B). This is in accordance with Tonetti et al. (2018), stating that Grade B is to be assumed initially in all cases, until the presence of specific evidence, i.e., longitudinal data, phenotype, bone loss relative to age or risk factors, points towards Grade C, and conversely, if lack of such, Grade A is indicated. The Periodontal Risk Assessment (PRA) tool is based on bone loss at most affected tooth divided by age, as one of several factors. High-risk has been reported in greater proportions of assessed populations, and moderate-risk in smaller proportions, in studies reporting risk assessed by PRA (Costa et al., 2012; Jansson & Norderyd, 2008; Meyer-Bäumer et al., 2012), compared to the present grade assessment. The 2969 individuals allocated to Grade B, represent approximately 80% of the periodontitis cases. And although different methodology in most aspects, Löe and co-workers (1986) reported 80% moderate progression rate in male Sri Lankan laborers. Sødal et al. (2022) reported a grade-distribution that compares to the present, although in 65-year-olds, only, with approximately 45% Grade B and 8% Grade C.
Until an increased number of studies on grade assessment according to the 2017 Classification is available, direct comparison is difficult.

Associations between periodontitis and non-communicable diseases

Adjusted logistic regression models demonstrated associations between periodontitis stages and cardiovascular disease, hyperglycemia in individuals with diabetes and COPD/emphysema. The associations were generally stronger with increasing stage severity, which was expected, but not previously demonstrated in a large population with the use of periodontitis stages according to the latest classification. The present analysis confirmed previous findings of associations (Herrera et al., 2023), with the exception of association with rheumatoid disorders (Qiao et al., 2020). There may be a number of reasons for this. Rheumatoid disorders in the present investigation, was a combined group that consisted of individuals reporting RA or ankylosing spondylitis. Potential variance in disease severity within this group, both among participants with RA, among those who reported ankylosing spondylitis and between the two entities, may have resulted in a heterogenous group of individuals and with the possibility that disease contributing factors differ substantially within the group. The national prevalence of RA is approximately 1% (Kvien et al., 1997). In the present population almost 6% reported RA or ankylosing spondylitis, perhaps also including osteoarthritis, further substantiating the heterogeneity of this group of participants. Moreover, the use of medication and similarly, disease activity score, was not assessed, and may have prevented identification of specific groups possibly associated with periodontitis.

Associations between periodontitis stages and the assessed NCDs were not observed in sensitivity analyses of never-smokers, except for COPD. It is possible that smoking is a mediator of the observed associations.

The main analysis of diabetes in the present thesis assessed poorly controlled diabetes, i.e., individuals with self-reported diabetes and HbA1c-level above or equal to 48mmol/mol (6.5%), as opposed to all participants reporting diabetes. This threshold is in line with the recommended criterium by the WHO and the American Diabetes Association (ADA)(Association, 2017). Further, this approach is also in line with the risk assessment of periodontitis progression, according to the 2017 Classification, which proposes an anticipated increased risk of periodontitis progression in diabetics with elevated HbA1c level (Tonetti et al., 2018). In sensitivity analyses of diabetes without consideration of HbA1c, no association was observed, emphasizing the divergence of diabetes with and without glycemic control.

HbA1c as an adjusting covariate in analyses of NCDs and periodontitis stages were used in a continuous scale rather than a cut-off diagnosis in risk assessment. The true threshold for what constitutes uncontrolled diabetes and glycemic threshold for assessing risk on an individual level is not known and may differ between individuals, further, it is not diagnosis of diabetes that may affect periodontal health, but rather the level of hyperglycemia (Kocher et al., 2018).

Assessment of radiographically determined bone loss in individuals with newly diagnosed coeliac disease and in individuals without coeliac disease

Compared to a reference group without coeliac disease, bone loss in coeliacs was less pronounced, however, the strength of this relationship was not found to increase with bone loss severity, and when restricting degree of bone loss to >33% (corresponding to Stages III and IV) as outcome, the association was weaker and no statistical significance was observed. The sensitivity analyses of the study did not differ from the main analyses, which is considered to increase validity of the findings, and the findings may be considered consistent with a previous similar study (Spinell et al., 2018).

Increased awareness towards a healthier lifestyle, in particular in terms of diet, is possibly more frequent among participants with undiagnosed coeliac disease compared to participants without coeliac disease. This may especially apply to families with clustering of coeliac disease. Individuals with low or diffuse gastrointestinal symptoms have reported improvements in symptoms from low-carbohydrate diet, and further development of increased and obvious symptoms of coeliac disease when carbohydrates are reintroduced (Van Heel et al., 2005). This is consistent with a lower T-cell response to gluten in untreated coeliac disease, which is clearly detectable after 2 weeks of gluten exposure (Anderson et al., 2005). The effect of a healthier diet is uncertain, also as the role of diet in periodontitis is presently unclear (Altun et al., 2021; Wright et al., 2020).

The impact of the intestinal microbiome in the switch from tolerance towards intolerance to gluten, has been suggested in children with coeliac disease (Olivares et al., 2018). Environmental factors are thought to modify the gut microbiota in genetically susceptible individuals, thereby promoting coeliac disease. Cross-reactivity between microbial peptides and the gluten protein gliadin, in T-cells involved in coeliac disease, has been demonstrated *in vitro* (Petersen et al., 2020). Differences in the microbiome in individuals with coeliac disease compared to individuals without coeliac disease (Collado et al., 2008; Tian et al., 2017; Wacklin et al., 2013), may be related to the inverse association with periodontal bone loss observed in the present investigation. Although, as for behavioral change towards healthier diet, the contribution is unknown.

While highly speculative, a different microbiome in coeliacs compared to that of the non-coeliac individuals, may entail that the conditions for periodontal pathogens are unfavorable in individuals with celiac disease. However, in individuals with celiac disease and extensive plaque accumulations, the pressure from periodontal bacteria may be great enough over time for the microbiome to shift towards selection of periodontal pathogens. In other words, when strong risk factors of periodontitis are present, they possibly "override" mechanisms in coeliacs that have prevented the growth of periodontal pathogens, thereby equalizing prevalence of periodontitis between the groups in strongly susceptible hosts, i.e., those who develop severe periodontitis.

The attempts to explain the relationship between coeliac disease and assessed bone loss is elusive. There is a possibility that unidentified confounding remains and based on the modest differences between the groups, clinical relevance and implications are uncertain.

Periodontitis grades

Periodontitis severity in terms of stages, constitutes the main exposures of the association assessments of the present thesis. Additional analyses of the relationships between modified periodontitis grades and NCDs were also conducted. The statistical models were similarly designed as for estimation of periodontitis stages. Determination of grades were based on the most severe bone loss and the age of the participant, followed by modification by smoking habits and HbA1c. Adjusting for age as well as estimation of relationships between grades and diabetes, were therefore omitted, otherwise keeping the models identical to the stage models. As smoking is also an inherent element of periodontitis grade modification, it may be argued that smoking as a covariate is incorrectly included. Periodontitis grades were found to be associated with CVD, rheumatoid disorders and COPD/emphysema. For the COPD/emphysema model, Grade B was the only statistically significant association observed. The majority of the periodontitis cases were graded B (83% of periodontitis cases), which is assumed to explain the observation in this grade level only. Stronger associations with increasing grades, as for the stage models, was not observed, which is also considered to be related to the high number of participants with Grade B, and accordingly the limited number of participants in the other two grades.

In never-smokers, the association between grades and COPD/emphysema was not observed, but the observations between periodontitis grades and CVD and rheumatoid disorders were similar as for the analyses where smokers were included.

A comparison of stages and grades is not straightforward. For stages, radiographic bone loss (or CAL) is the primary determinant. While determination of stage reflects the current status, grading is an attempt to estimate future development. Grading is used to assess the anticipated progression rate, and whether it is higher or lower compared to cases with moderate rate of progression. Deviation between the initial determination based on bone loss and age, and the true longitudinal progression rate is likely, in particular in cases where risk modifiers in terms of smoking habits or diabetes are absent. The most reliable tool is the assessment of direct evidence by longitudinal data. In cross-sectional studies, grades are based on indirect evidence in terms of bone loss as a function of age. This may render flawed identification of low- and high-risk individuals, as Grade A in elderly, necessitates very low levels of bone loss, and likewise, Grade C in young individuals demands very high levels of bone loss. Grading based on longitudinal data renders increased validity, and it is likely that it would have enabled identification of a different risk distribution in the present population, hence identified a clearer pattern of associations.

Conclusions

Overall, periodontitis was associated with cardiovascular disease, hyperglycemic diabetes and COPD/emphysema, in a population where the majority of the participants had periodontitis, and the majority of the periodontitis cases were identified with moderate risk of progression.
The relationships were particularly evident among participants with periodontitis Stage III and Stage IV. A relationship between newly diagnosed coeliac disease and radiographic bone loss was also observed, but in contrast an inverse relationship was seen, demonstrating periodontal bone loss less frequently in coeliacs compared to non-coeliacs.

The findings of this thesis have implications for similar populations. Epidemiological data from a large population where periodontitis prevalence was found to be high, and associations between periodontitis and other common non-communicable diseases were demonstrated, underpin the importance of further research and collaboration across health professions in Norway. Dentists reach a broad segment of the population and have the opportunity to provide information that will benefit patients in an oral-health related perspective, but importantly also promoting overall systemic health.

Evaluation of hypotheses

Evaluation of the overall hypothesis and the hypotheses for study 1 and study 2

The total prevalence of periodontitis was found to affect a large number of participants. The deviations from previous reports of total periodontitis prevalence are considered an effect of that “detectable attachment loss” is not quantified, and is therefore not regarded as contradictory to previous assessments.
It is possible to imagine that the frame of moderate periodontitis overlaps with cases of both Stage II and Stage III periodontitis. An evaluation of generalized and localized periodontitis was performed. For individuals with Stage II periodontitis, approximately half of the cases were annotated as generalized, unlike for individuals with Stage III, of which less than 20% had clinical signs and/or radiographical bone loss corresponding to generalized Stage III. “Translation” of stages may serve to support the perception that the present prevalence estimation corresponds to earlier estimates. Cases of localized Stage III, perhaps in the intersection between Stage II and Stage III, differs significantly from the most advanced cases of generalized Stage III. The present report of stage distribution is assumed to be affected by the limitations of the assessments, e.g., limited time for clinical examination, assessment of furcation involvements limited to radiographs, and must be interpreted in view of these restrictions. It is expected that an expanded clinical assessment and knowledge of reasons for tooth loss would have identified an increased number of individuals with localized Stage III, who at the same time presented with radiographic bone loss corresponding to a less severe stage as well as an increased number of individuals with generalized Stage III. The most severe stages of periodontitis are considered to be found in approximately

10% of the population. This is based on the assumption that periodontitis previously described as severe corresponds to generalized Stage III combined with Stage IV.

Associations between periodontitis and NCDs were identified. For the assessment of rheumatoid disorders, no association was observed with periodontitis stages. It should be noted that this assessment is assumed to have a limitation in identifying individuals with RA or ankylosing spondylitis, i.e., considerable possibility that participants with similar symptoms to those of RA have answered affirmative to the relevant questionnaire, without having the disease in question. A clear pattern of increasing strengths of relationships between periodontitis stages and NCDs was demonstrated. Similar patterns were not observed for periodontitis grades. Few participants were annotated with Grade A or Grade C, which made inferences about grades difficult.

Based on the results of study 1 and study 2, with the limitations herein, the present findings are supportive of the overall hypothesis and the hypotheses of study 1 and study 2. The overall hypothesis and the hypotheses of study 1 and 2 are thereby accepted.

Evaluation of hypothesis for study 3

Radiographically assessed bone loss in individuals with newly diagnosed coeliac disease was expected to correspond to the radiographically assessed bone loss in the control population. There was identified a difference between the groups in adjusted analyses, and although the difference was small, the hypothesis is rejected.

Conclusions related to specific aims and hypotheses

- Periodontitis assessed according to the 2017 Classification was observed in the majority of the study population
- Periodontitis Stage I was observed in 13.8%, Stage II in 41.1%, while Stage III and Stage IV combined were observed in 17.5% of the study population
- Grade B was observed in the majority of the periodontitis cases, in approximately 60% of the study population, while periodontitis Grade C, implying high risk of progression, was observed in approximately 6%
- Periodontitis was associated with CVD, poorly controlled diabetes and COPD/emphysema in adjusted multivariable analyses
- The strength of the observed associations for CVD, poorly controlled diabetes and COPD/emphysema increased with increasing periodontitis severity
- Coeliac disease was inversely associated with radiographically assessed alveolar bone loss ≥15%.

Future perspectives

A high prevalence of periodontitis was observed in the studied population. These findings are consistent with previous findings from similar studies, although direct comparison is difficult due to different case definitions. Periodontitis grades were not evaluated in depth. Hence, the factors which may influence the progression of disease should be in focus in future studies. Enabling identification of individuals with particular susceptibility and risk of disease progression, will be of significance in a clinical context.

Furthermore, periodontitis was found to be associated with NCDs. This in itself are not surprising findings, but due to application of the 2017 classification, a clear relationship of increasing strength between periodontitis and systemic disease was revealed. This observation will have significant implication in clinical practice. The mentioned observations have previously been identified, but mechanistically still not fully clarified. Further studies of mechanistic relationships are therefore necessary.

An association between celiac disease and periodontitis was observed. There is a lack of knowledge about this association, and further work through longitudinal and prospective studies of a celiac disease cohort will be able to shed light on how this relationship is connected. In turn, this will perhaps also lead to an increased understanding of relationships with other diseases in relation to the development of periodontitis, in susceptible hosts.

HUNT5 is planned between 2027 and 2029. This offers an opportunity to conduct prospective longitudinal studies of periodontitis, as the first in Norway. In the HUNT5 study, there will be an opportunity to improve or expand the clinical examination with respect to time and clinical variables

Coherence

Exploration of associations between periodontitis and common systemic disease in the Norwegian population, were the overall purpose of the research project. The recently consented classification may impact on how these potential associations are disclosed. The investigated population served as a basis and was followed through all three parts of the project. In order to answer the overall purpose of associations and the specific aims in studies 2 and 3, the aim of study 1 was first addressed, which was assessment of prevalence of periodontitis in general, and distribution of severity, in terms of periodontitis stages. Knowing the distribution of stages and NCDs in the total population enabled further assessment of associations in the same population, with selected, explored systemic diseases (CVD, diabetes, rheumatoid disorders, COPD/emphysema) and with other, less explored diseases (coeliac disease), relative to these stages.

Associations between periodontitis and systemic disease were observed for some of the investigated conditions. Often, the relationship between periodontitis and systemic disease was found to be reinforcing, but the opposite relationship was also observed, meaning periodontitis appeared to have a protective effect against systemic disease. However, in the latter case, the effect of periodontitis was small, and the uncertainty is considerable. Overall, associations with importance for the general Norwegian population were identified, but the relationships between other diseases and periodontitis are still not clarified.

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Appendix

HUNT4
HELSEUNDERSØKELSEN I NORD-TRØNDELAG

Invitasjon til HUNT4

Du inviteres til å delta i den fjerde store Helseundersøkelsen i Nord-Trøndelag (HUNT4). Ved å delta får du en enkel undersøkelse av din egen helse, og du gir samtidig et viktig bidrag til medisinsk forskning.

Du deltar ved å fylle ut dette spørreskjemaet og møte til undersøkelser på feltstasjonen.

TID OG STED FOR OPPMØTE PÅ FELTSTASJON:

Dersom det foreslåtte tidspunktet ikke passer for deg kan du møte når det passer deg innenfor åpningstiden, men det kan da bli noe ventetid. Du kan møte i en annen kommune hvis det er bedre.

Åpningstider for oppmøte utenfor timeavtale:

Spørreskjemaer er en viktig del av HUNT4. Vennligst svar på skjemaet så nøyaktig som mulig.
Du kan svare på nett eller på papirskjema.

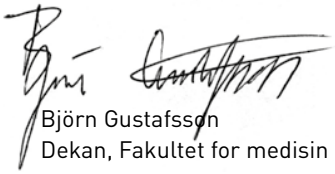
SLIK SVARER DU PÅ NETT: Gå til adressen http://hunt4.no, og velg spørreskjema. Logg deg på med BrukerID og PIN-kode.	BrukerID: PIN-kode:
SLIK SVARER DU PÅ PAPIRSKJEMA: Fyll ut skjemaet slik det er beskrevet på neste side, og kryss av på spørsmålene om samtykke. Lever skjemaet når du møter på feltstasjonen.	

Du kan lese mer om HUNT4 i den vedlagte informasjonsbrosjyren eller på http://hunt4.no.
Om noe er uklart kan du kontakte HUNT forskningssenter på telefon 74 07 51 80 eller på e-post hunt@medisin.ntnu.no.

Vel møtt til undersøkelsen!

Med vennlig hilsen

Steinar Krokstad
Daglig leder, HUNT



Björn Gustafsson
Dekan, Fakultet for medisin og helsevitenskap

I spørreskjemaet finner du spørsmål om plager og sykdommer og om andre forhold som har betydning for helsa. Dersom enkelte spørsmål er uklare, lar du dem bare stå ubesvarte. Hvis du vil, kan du drøfte dem med personalet på feltstasjonen. Flere steder i skjemaet ber vi om antall ganger noe har skjedd, eller alder første gang noe skjedde. Hvis du ikke husker nøyaktig, kan du skrive det tallet du tror er mest riktig.

Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk, er HUNT-veteran eller møter for første gang. Jo flere som blir med, jo mer helhetlig og verdifull blir HUNT. Din deltakelse bidrar til at vi kan finne ut mer om hva som påvirker helse og livskvalitet for alle grupper i samfunnet. For å kunne studere årsaker til, og utvikling av sykdom, er det viktig at også de som tidligere har deltatt møter fram.

LES DETTE FØR DU STARTER

Skjemaet skal leses maskinelt. Følg derfor disse instruksjonene:

- Bruk svart/blå kulepenn eller en god blyant.
- Kryss av slik: ☒
- Krysser du feil, fyller du hele feltet med farge, slik: ■ Sett så kryss i rett felt.
- Sett bare ett kryss for hvert spørsmål om ikke annet er oppgitt.
- Bruk hele tall når du fyller inn antall år eller antall ganger, slik: 5 2

SAMTYKKE TIL HUNT4

Jeg har lest informasjonsbrosjyren om HUNT4 og er kjent med hva det generelle samtykket til å delta innebærer. Jeg har hatt anledning til å spørre om mer informasjon.

Samtykker du til å delta i HUNT4?

☐ Ja, jeg samtykker til å delta i HUNT4

Du kan delta i HUNT4 uansett om du svarer ja eller nei på valgene under.

SPESIFIKKE SAMTYKKER FOR GENETISKE ANALYSER

Nærmere informasjon om dette finner du på side 7 i informasjonsbrosjyren for HUNT4.

Hvis genetiske analyser avdekker økt risiko for sykdom, ønsker du tilbakemelding om slik økt risiko?

Ja ☐ Nei ☐

Ønsker du å bli invitert til oppfølgingsstudier basert på genetiske funn, inkludert varianter som kan gi økt risiko for sykdom?

Ja ☐ Nei ☐

HELSE OG DAGLIGLIV

1 Hvordan er helsa di nå?

Dårlig	Ikke helt god	God	Svært god
☐	☐	☐	☐

2 Har du nå noen langvarig (minst 1 år) sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv?

Nei ☐ Ja ☐

HVIS JA:
Hvor mye vil du si at dine funksjoner er nedsatt?
(Sett ett kryss per linje)

	Ikke nedsatt	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet	☐	☐	☐	☐
Har nedsatt syn	☐	☐	☐	☐
Har nedsatt hørsel	☐	☐	☐	☐
Hemmet pga. kroppslig sykdom	☐	☐	☐	☐
Hemmet pga. psykisk sykdom	☐	☐	☐	☐

3 Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 uker?

Ingen	Meget svake	Svake	Moderate	Sterke	Meget sterke
☐	☐	☐	☐	☐	☐

4 I hvilken grad har din fysiske helse eller følelsesmessige problemer begrenset deg i din vanlige sosiale omgang med familie eller venner i løpet av de siste 4 uker?

Ikke i det hele tatt	En del	Litt	Mye	Kunne ikke ha sosial omgang
☐	☐	☐	☐	☐

5 Har du de siste 2 ukene følt deg:
(Sett ett kryss per linje)

	Nei	Litt	En god del	Svært mye
Trygg og rolig	☐	☐	☐	☐
Glad og optimistisk	☐	☐	☐	☐
Nervøs og urolig	☐	☐	☐	☐
Plaget av angst	☐	☐	☐	☐
Irritabel	☐	☐	☐	☐
Nedfor/deprimert	☐	☐	☐	☐
Ensom	☐	☐	☐	☐
Generelt anspent	☐	☐	☐	☐

6 Føler du deg stort sett sterk og opplagt, eller trøtt og sliten?

Meget sterk og opplagt	☐
Sterk og opplagt	☐
Ganske sterk og opplagt	☐
Både- og	☐
Ganske trøtt og sliten	☐
Trøtt og sliten	☐
Svært trøtt og sliten	☐

SYKDOMMER OG PLAGER

7 Har du, eller har du noen gang hatt, noen av følgende sykdommer/plager? Angi også alder da du fikk dette/disse. *(Sett ett kryss per linje)*

	Nei	Ja	Alder første gang?
Angina	☐	☐	☐☐ år gammel
Hjerteinfarkt	☐	☐	☐☐ år gammel
Hjertesvikt	☐	☐	☐☐ år gammel
Atrieflimmer (forkammerflimmer)	☐	☐	☐☐ år gammel
Hjerneslag (hjerneinfarkt eller blødning)	☐	☐	☐☐ år gammel
Astma	☐	☐	☐☐ år gammel
Kols eller emfysem	☐	☐	☐☐ år gammel
Diabetes (sukkersyke)	☐	☐	☐☐ år gammel
Lavt stoffskifte (hypotyreose)	☐	☐	☐☐ år gammel
Høyt stoffskifte (hypertyreose)	☐	☐	☐☐ år gammel
Kreftsykdom	☐	☐	☐☐ år gammel
Migrene	☐	☐	☐☐ år gammel
Psoriasis	☐	☐	☐☐ år gammel
Nyresykdom, utenom urinveisinfeksjon	☐	☐	☐☐ år gammel
Leddgikt (reumatoid artritt)	☐	☐	☐☐ år gammel
Bechterews sykdom (spondylartritt)	☐	☐	☐☐ år gammel
Urinsyregikt (podagra)	☐	☐	☐☐ år gammel
Psykiske plager som du har søkt hjelp for	☐	☐	☐☐ år gammel

8 **Har du de siste 12 måneder hatt anfall med tung eller pipende pust?** Nei ☐ Ja ☐

9 **Har du de siste 12 måneder hatt smerter i ledd som har vart i mer enn 6 uker?** Nei ☐ Ja ☐

10 **Har du noen gang fått påvist for høyt blodsukker?** Nei ☐ Ja ☐ Alder første gang? ☐☐ år gammel

BRUK AV MEDISINER

11 **Bruker du noen reseptpliktige medisiner nå?**

Nei ☐ Ja ☐

HVIS JA:
Bruker du noen av disse medisinene? Angi også alder da du begynte med slik medisin.

	Nei	Ja	Alder første gang?
Medisin for høyt blodtrykk	☐	☐	☐☐ år gammel
Kolesterolsenkende medisin	☐	☐	☐☐ år gammel
Medisin for astma eller kols	☐	☐	☐☐ år gammel
Medisin for angst eller depresjon	☐	☐	☐☐ år gammel
Medisin for stoffskiftet	☐	☐	☐☐ år gammel
Tabletter eller nesespray mot allergi	☐	☐	☐☐ år gammel

12 **Har du noen gang fått kortisonsprøyte(r)?**

Nei ☐ Ja ☐ Vet ikke ☐

HVIS JA:
Hvorfor har du fått kortisonsprøyte(r)?
(Flere kryss mulig)

Allergi	Sene-betennelse	Leddsmerter	Annet
☐	☐	☐	☐

Hvor mange kortisonsprøyter har du fått siste 12 måneder? ☐☐ Antall

13 **Hvor ofte har du brukt reseptfrie medisiner mot følgende plager i løpet av den siste måneden?**
(Sett ett kryss per linje)

	Sjelden/ aldri	1-3 ganger per uke	4-6 ganger per uke	Daglig
Halsbrann/sure oppstøt	☐	☐	☐	☐
Treg mage	☐	☐	☐	☐
Hodepine	☐	☐	☐	☐
Smerter i muskler og ledd	☐	☐	☐	☐

BRUK AV HELSETJENESTER

14 **Har du i løpet av de siste 12 måneder vært hos:**

	Nei	Ja
Legevakt	☐	☐
Fastlege/allmennlege	☐	☐
Annen lege eller psykolog utenfor sykehus	☐	☐
Konsultasjon uten innleggelse		
- ved psykiatrisk poliklinikk	☐	☐
- ved annen poliklinikk i sykehus	☐	☐
Kommunal psykiatrisk sykepleier	☐	☐
Fysioterapeut/manuell terapeut	☐	☐
Kiropraktor	☐	☐
Naprapat	☐	☐
Akupunktør	☐	☐
Alternativ behandler, homøopat, soneterapeut, håndspålegger eller annen	☐	☐

15 **Har du vært innlagt på sykehus de siste 12 måneder?** Nei ☐ Ja ☐

16 **Har du vært hos tannlege/tannpleier de siste 24 måneder?** Nei ☐ Ja ☐

SYKDOMMER I FAMILIEN

17 **Har du foreldre, søsken eller barn som har, eller har hatt, følgende sykdommer?**

	Nei	Ja	Vet ikke
Astma	☐	☐	☐
Høysnue/neseallergi	☐	☐	☐
Kronisk bronkitt/emfysem/kols	☐	☐	☐
Angst eller depresjon	☐	☐	☐
Hjerteinfarkt før 60-årsalder	☐	☐	☐
Diabetes (sukkersyke)	☐	☐	☐
Hjerneslag (hjerneinfarkt eller blødning) før 60-årsalder	☐	☐	☐
Kreft	☐	☐	☐

18 **Har noen av dine besteforeldre, dine foreldres søsken eller dine søskenbarn hatt diabetes?** Nei ☐ Ja ☐ Vet ikke ☐

TOBAKK

19 Røykevaner *(Sett ett kryss)*

- ☐ Jeg har aldri røykt
- ☐ Jeg har røykt AV OG TIL tidligere
- ☐ Jeg røyker AV OG TIL nå (ikke daglig)
- ☐ Jeg røyker DAGLIG nå:
  - Jeg røyker omtrent..... ☐☐ sigaretter per dag
  - Jeg begynte å røyke daglig da jeg var..... ☐☐ år gammel
- ☐ Jeg har røykt DAGLIG tidligere;
  - Jeg begynte da jeg var..... ☐☐ år gammel
  - Jeg sluttet da jeg var..... ☐☐ år gammel
  - Da jeg røykte, røykte jeg..... ☐☐ sigaretter per dag

SNUS

20 Snusbruk *(Sett ett kryss)*

- ☐ Jeg har aldri brukt snus
- ☐ Jeg har brukt snus AV OG TIL tidligere
- ☐ Jeg snuser AV OG TIL nå (ikke daglig)
- ☐ Jeg snuser DAGLIG nå:
  - Jeg bruker omtrent..... ☐☐ esker per måned
  - Jeg begynte å snuse da jeg var..... ☐☐ år gammel
- ☐ Jeg har tidligere brukt snus DAGLIG:
  - Jeg begynte å snuse da jeg var..... ☐☐ år gammel
  - Jeg sluttet å snuse da jeg var..... ☐☐ år gammel

KOSTTILSKUDD

21 Hvor ofte bruker du noen av følgende kosttilskudd? *(Sett ett kryss per linje)*

	Daglig hele året	Daglig kun i vinter-halvåret	Av og til	Aldri
Tran eller omega 3-kapsler.....	☐	☐	☐	☐
Kalktabletter (kalsium).....	☐	☐	☐	☐
Andre vitamin- og/eller mineraltilskudd.....	☐	☐	☐	☐

MATVARER

22 Tenk på det siste året; hvor mange ganger per uke spiser du disse matvarene?
(Sett ett kryss per linje)

	Mindre enn 1 gang	1-3 ganger	4-6 ganger	7 eller mer
Frukt/bær.....	☐	☐	☐	☐
Grønnsaker.....	☐	☐	☐	☐
Rødt, rent kjøtt (storfe, svin, lam, vilt).....	☐	☐	☐	☐
Hvitt, rent kjøtt (kylling, kalkun).....	☐	☐	☐	☐
Kjøttdeig, pølser og lignende.....	☐	☐	☐	☐
Mager, ren fisk (f.eks. torsk, sei).....	☐	☐	☐	☐
Fet fisk (f.eks. laks, ørret, sild, makrell som pålegg/middag).....	☐	☐	☐	☐

23 Hvor mange glass/beger/kopper drikker/spiser du vanligvis av følgende? *(Sett ett kryss per linje)*

½ liter= 3 glass/ beger/kopper	Aldri eller sjelden	1-6 per uke	1 per dag	2-3 per dag	4 eller flere per dag
Helmelk (søt).....	☐	☐	☐	☐	☐
Lett/skummet melk.....	☐	☐	☐	☐	☐
Hel surmelk (kefir, kultur).....	☐	☐	☐	☐	☐
Lett/skummet surmelk.....	☐	☐	☐	☐	☐
Brus/saft med sukker.....	☐	☐	☐	☐	☐
Brus/saft med kunstig søtning....	☐	☐	☐	☐	☐
Smoothie/ fruktjuice.....	☐	☐	☐	☐	☐
Yoghurt.....	☐	☐	☐	☐	☐
Kaffe (svart).....	☐	☐	☐	☐	☐
Kaffe tilsatt melk/fløte.....	☐	☐	☐	☐	☐

ALKOHOLBRUK

24 Omtrent hvor ofte har du i løpet av de siste 12 måneder drukket alkohol? *(Regn ikke med lettøl)*

- Ikke drukket alkohol siste 12 måneder ☐
- 1 gang i måneden eller sjeldnere ☐
- 2-4 ganger per måned ☐
- 2-3 ganger per uke ☐
- 4 eller flere ganger per uke ☐
- Jeg har aldri drukket alkohol ☐

25 Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av 2 uker?
(Regn ikke med lettøl, sett 0 hvis du ikke drikker alkohol)

	Øl	Vin	Brennevin
Antall glass	☐	☐	☐

26 Hvor ofte drikker du 6 glass eller mer av øl, vin eller brennevin ved samme anledning?

- Aldri ☐
- Sjeldnere enn månedlig ☐
- Månedlig ☐
- Ukentlig ☐
- Daglig eller nesten daglig ☐

SØVN

27 Hvor ofte har det hendt i løpet av de siste 3 måneder at du:

	Aldri/ sjelden	Av og til	Minst 3 ganger per uke
Snorker høyt og sjenerende	☐	☐	☐
Får pustestopp når du sover	☐	☐	☐
Har vanskelig for å sovne om kvelden	☐	☐	☐
Våkner gjentatte ganger om natta	☐	☐	☐
Våkner for tidlig og får ikke sove igjen	☐	☐	☐
Fungerer dårlig på dagtid (sosialt eller yrkesmessig) pga. søvnproblemer	☐	☐	☐
Får ubehag, kribling eller mauring i bein	☐	☐	☐

Omtrent hvor mange timer nattesøvn får du på en vanlig hverdag? ☐ timer

MOSJON/FYSISK AKTIVITET

28 Hvor ofte driver du mosjon? *(Ta et gjennomsnitt)*
Med mosjon mener vi at du f.eks. går tur, går på ski, sykler, svømmer eller driver trening/idrett.

- Aldri ☐
- Sjeldnere enn en gang i uka ☐
- En gang i uka ☐
- 2-3 ganger i uka ☐
- Omtrent hver dag ☐

29 Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? *(Ta et gjennomsnitt)*

- Tar det rolig uten å bli andpusten eller svett ☐
- Tar det så hardt at jeg blir andpusten eller svett ☐
- Tar meg nesten helt ut ☐

30 Hvor lenge holder du på hver gang?
(Ta et gjennomsnitt)

- Mindre enn 15 minutter ☐
- 15-29 minutter ☐
- 30-60 minutter ☐
- Mer enn 60 minutter ☐

31 Omtrent hvor mange timer sitter du i ro på en vanlig hverdag? Regn med både jobb og fritid.
(Ved PC, TV, nettbrett, lesing, bil/buss/togkjøring o.l.)

Antall timer ☐

SKJERMBASERT AKTIVITET

32 Anslå hvor lang tid du vanligvis bruker til skjermbaserte aktiviteter per dag i fritiden.
Med skjermbaserte aktiviteter menes PC, nettbrett, smarttelefon, spillkonsoll, TV, lesebrett.

	Ingen tid	Mindre enn 1 time	1-3 timer	4-6 timer	Mer enn 6 timer
Ser på TV/videoer/ annen skjermbasert underholdning	☐	☐	☐	☐	☐
Spiller spill (alene/ med andre)	☐	☐	☐	☐	☐
Kontakter venner eller nettverk	☐	☐	☐	☐	☐
Innhenting av kunnskap/ informasjon	☐	☐	☐	☐	☐
Jobbrelaterte aktiviteter i fritiden	☐	☐	☐	☐	☐

LIVSSTIL

33 Hvor viktig er det for deg å leve sunt?

- Svært viktig ☐
- Viktig ☐
- Lite viktig ☐
- Ikke viktig ☐

34 Hvor fornøyd er du med din egen livsstil (kosthold, mosjon, røyke- og drikkevaner)?

- Svært fornøyd ☐
- Fornøyd ☐
- Lite fornøyd ☐
- Ikke fornøyd ☐

35 Er du fornøyd med vekta di nå?

- Ja ☐
- Nei, altfor tung ☐
- Nei, litt for tung ☐
- Nei, litt for lett ☐
- Nei, altfor lett ☐

36 Hvor mange ganger har du med hensikt gått ned mer enn 5 kg i vekt i løpet av de siste 5 år?

- Aldri ☐
- 1-2 ganger ☐
- 3 ganger eller mer ☐

37 Har du ufrivillig gått ned mer enn 5 kg i vekt siste 6 måneder?

Nei	Ja
☐	☐

OPPVEKST, DA DU VAR 0-18 ÅR

38 Hvem vokste du opp sammen med?
(Flere kryss mulig)

- Mor ☐
- Stemor ☐
- Far ☐
- Stefar ☐
- Foster-/pleieforeldre ☐
- Søsken ☐
- Andre barn under 18 år ☐
- Andre voksne ☐

39 Ble dine foreldre skilt, eller flyttet de fra hverandre, da du var barn?

Nei	Ja, før jeg var 7 år	Ja, da jeg var 7–18 år
☐	☐	☐

40 Døde noen av dine foreldre da du var barn?

Nei	Ja, før jeg var 7 år	Ja, da jeg var 7–18 år
☐	☐	☐

41 Var det mye krangling, uro, konflikter eller vanskelig kommunikasjon i barndomshjemmet?

- I svært høy grad ☐
- I høy grad ☐
- I liten grad ☐
- I svært liten grad ☐
- Ikke i det hele tatt ☐

42 Kunne du i oppveksten søke støtte hos en voksen person som du var trygg på?

- I svært høy grad ☐
- I høy grad ☐
- I liten grad ☐
- I svært liten grad ☐
- Ikke i det hele tatt ☐

43 Sliter du med vonde minner fra oppveksten pga. tap, svik, vanskjøtsel, vold, mishandling eller misbruk?

- I svært høy grad ☐
- I høy grad ☐
- I liten grad ☐
- I svært liten grad ☐
- Ikke i det hele tatt ☐

44 Når du tenker på barndommen/oppveksten din, vil du beskrive den som:

- Svært god ☐
- God ☐
- Middels ☐
- Vanskelig ☐
- Svært vanskelig ☐

UTDANNING OG INNTEKT

45 Hvilken utdanning er den høyeste du har fullført? *(Sett ett kryss)*

Med grunnskole menes barne- og ungdomsskole, framhaldsskole, folkehøyskole.
Med 1-2 årig videregående menes realskole, middelskole, yrkesskole.

- ☐ Grunnskole
- ☐ 1-2 årig videregående skole
- ☐ 3 år i videregående skole
- ☐ Fagbrev eller svennebrev
- ☐ Høyskole/universitet, mindre enn 4 år
- ☐ Høyskole/universitet, 4 år eller mer

46 Hva er din husstands samlede inntekt siste år (brutto-inntekt)? Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende. *(Sett ett kryss)*

- ☐ Under 250 000 kr
- ☐ 250 000-450 000 kr
- ☐ 451 000-750 000 kr
- ☐ 751 000-1 000 000 kr
- ☐ Over 1 000 000 kr

BOSITUASJON

47 Bor du sammen med noen? *(Flere kryss mulig)*

- ☐ Nei, jeg bor alene
- ☐ Ja, ektefelle/samboer/partner
- ☐ Ja, andre personer 18 år eller eldre:

  HVIS JA:
  Hvor mange andre over 18 år? ..... ☐☐ Antall

- ☐ Ja, barn under 18 år:

  HVIS JA:
  Hvor mange barn under 18 år? ..... ☐☐ Antall

ALT I ALT

48 Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd? *(Sett ett kryss)*

- ☐ Svært fornøyd
- ☐ Meget fornøyd
- ☐ Ganske fornøyd
- ☐ Både/og
- ☐ Nokså misfornøyd
- ☐ Meget misfornøyd
- ☐ Svært misfornøyd

Lever det utfylte skjemaet når du møter på feltstasjonen.

Takk for hjelpen!

SAMTYKKEERKLÆRING

Samtykke til å delta i Helseundersøkelsen i Nord-Trøndelag 2017-19, HUNT4

Jeg har lest informasjonsbrosjyren om HUNT4, og har hatt anledning til å spørre om mer informasjon.

☐ Ja, jeg samtykker til å delta i HUNT4

Samtykkevalg

Nærmere informasjon om bakgrunnen for disse valgene finner du i informasjonsbrosjyren. Du kan delta i HUNT4 uansett om du svarer ja eller nei på valgene under.

Hvis genetiske analyser avdekker at du har høy risiko for en sykdom som kan forebygges eller behandles: Ønsker du tilbakemelding om dette?

JA NEI

Ønsker du å kunne bli invitert til oppfølgingsstudier basert på genetiske analysesvar som innebærer informasjon om sykdomsrisiko?

JA NEI

STED OG DATO

NAVN

Skole: Klasse:

Navn: Født:

SAMTYKKEERKLÆRING

Samtykke til å delta i Helseundersøkelsen i Nord-Trøndelag 2017-19, Ung-HUNT 4

Jeg har lest informasjonsbrosjyren om Ung-HUNT 4, og har hatt anledning til å spørre om mer informasjon.

☐ Ja, jeg samtykker til å delta i Ung-HUNT4

STED OG DATO

NAVN

Til foresatte for

SAMTYKKEERKLÆRING

Helseundersøkelsen i Nord-Trøndelag 2017-19, Ung-HUNT4

Jeg har lest informasjonsbrosjyren om Ung-HUNT4, og har hatt anledning til å spørre om mer informasjon.

- ☐ Ja, jeg samtykker til at mitt barn deltar i undersøkelsen
- ☐ Nei, jeg samtykker ikke til at mitt barn deltar i undersøkelsen

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STED OG DATO

NAVN

Utfylt samtykke tas med tilbake til skolen og leveres til lærer

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Received: 15 December 2020 | Revised: 10 May 2021 | Accepted: 20 May 2021

DOI: 10.1111/jcpe.13507

ORIGINAL ARTICLE PRE-CLINICAL SCIENCES

Journal of Clinical Periodontology WILEY

Prevalence of periodontitis based on the 2017 classification in a Norwegian population: The HUNT study

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Abstract

Aim: This cross-sectional study assesses the prevalence of periodontitis in a large Norwegian population, based on the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions. The prevalence of periodontitis was determined by bone loss recorded on radiographs (orthopantomogram [OPG] and bitewing [BW]) and by clinical examination.

Materials and methods: As part of a large population health study (The HUNT Study), 7347 participants aged 19 years and older were invited to the HUNT4 Oral Health Study. Radiographic bone loss (RBL) and periodontal stage and grade were assessed in 4863 participants.

Results: Periodontal examination was performed in 4863 participants. RBL and clinical registrations corresponding to periodontitis as defined were observed in 72.4%. The prevalence of periodontitis increased after 40 years of age, with severe forms occurring primarily after 60 years of age. Stage I was observed in 13.8%, Stage II in 41.1%, Stage III in 15.3%, and Stage IV in 2.3% of the population. Grade A, B, and C was observed in 5.7%, 60.2%, and 6.2%, respectively.

Conclusion: Periodontitis was frequently observed in the investigated population. The prevalence of periodontitis Stage III and Stage IV combined was observed in 17.6% of the study population.

KEYWORDS

bone loss, classification, HUNT, HUNT4, periodontal diseases, periodontitis, prevalence

Clinical Relevance

Scientific rationale for the study: Periodontitis affects a large part of the world's population and has significant social and economic impact. The 2017 classification promotes a universal approach to determine disease prevalence.

Principal findings: Periodontitis was a common finding, and even the more severe stages were seen in a considerable proportion of the investigated population.

Practical implications: Assessment of periodontitis in a large population using the 2017 classification demonstrated that periodontitis Stage II and grade B was the most common combination.

Differentiation between Stage I and periodontal health is cumbersome in a cross-sectional design.

1 | INTRODUCTION

Periodontitis is an inflammatory disease affecting the supportive tissues of the teeth and may cause extensive tooth loss if left untreated (Pihlstrom et al., 2005; Kassebaum et al., 2014b). Periodontitis affects more than 40% of the U.S. adult population (Eke et al., 2018), and severe periodontitis has been reported as the sixth most prevalent disease worldwide (Kassebaum et al., 2014a). In 2017, severe periodontitis was estimated to affect 7.4% of the world's population (Kassebaum et al., 2017).

Previous epidemiological studies on periodontitis in Scandinavia include a study performed in the 1970s by Löe and co-workers (Schätzle et al., 2003), a repeated cross-sectional study of 35-year-olds in Oslo (Skudutyte-Rysstad et al., 2007), and more recent cross-sectional studies (Holde et al., 2017; Wahlin et al., 2018; Bongo et al., 2020).

Reported prevalence of periodontitis varies with geographical location, ethnicity, age, educational level, availability of health services, and systemic health (Kassebaum et al., 2014a; Eke et al., 2015; Carasol et al., 2016; Jepsen et al., 2018) and is also influenced by different thresholds and case definitions used in the surveys (Costa et al., 2009; Holtfreter et al., 2015; Jin et al., 2016). It has been demonstrated that different diagnostic criteria may affect the association of periodontitis to other diseases and conditions (Manau et al., 2008), thereby substantiating the need for more conformity in periodontal diagnostics. In the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions (Caton et al., 2018; Chapple et al., 2018; Papapanou et al., 2018), new criteria and case definitions were introduced.

The aim of the present study was to investigate the prevalence of periodontitis in a Norwegian population based on the 2017 classification suggested by the 2017 World Workshop.

2 | MATERIALS AND METHODS

2.1 | Study sample: The fourth Trøndelag health survey (HUNT4)

The investigated population was a part of The Trøndelag Health Study (HUNT). HUNT is a repeated population-based study that constitutes a large database for medical and health-related research (Holmen et al., 2003; Krokstad et al., 2013). Data from four surveys have been derived from 230,000 participants in total. The first survey was initiated in 1984 (HUNT1). The present cross-sectional study was based on data from HUNT4, which was conducted between 2017 and 2019. The county of Nord-Trøndelag had 137,233 residents in 2017.

For the fourth HUNT survey (HUNT4), all residents in the county turning 20 years within the year of participation and older were invited to participate. A sub-population was invited for oral examination, which was included in large scale for the first time.

The periodontal examination was part of the HUNT4 Oral Health Study and was performed in mobile dental units at field stations during the period September 2017–February 2019. In HUNT4, the total number of invited residents was 103,734. Of these, 7347 randomly selected participants were invited to the Oral Health Study. Finally, 4933 were included for clinical and radiographic oral examination, (Figure 1).

2.2 | Questionnaires and blood samples

All participants answered questionnaires regarding systemic health, which included self-reported diabetes and smoking habits. Blood samples were collected from all participants and analysed for HbA1c values.

2.3 | Clinical periodontal examination

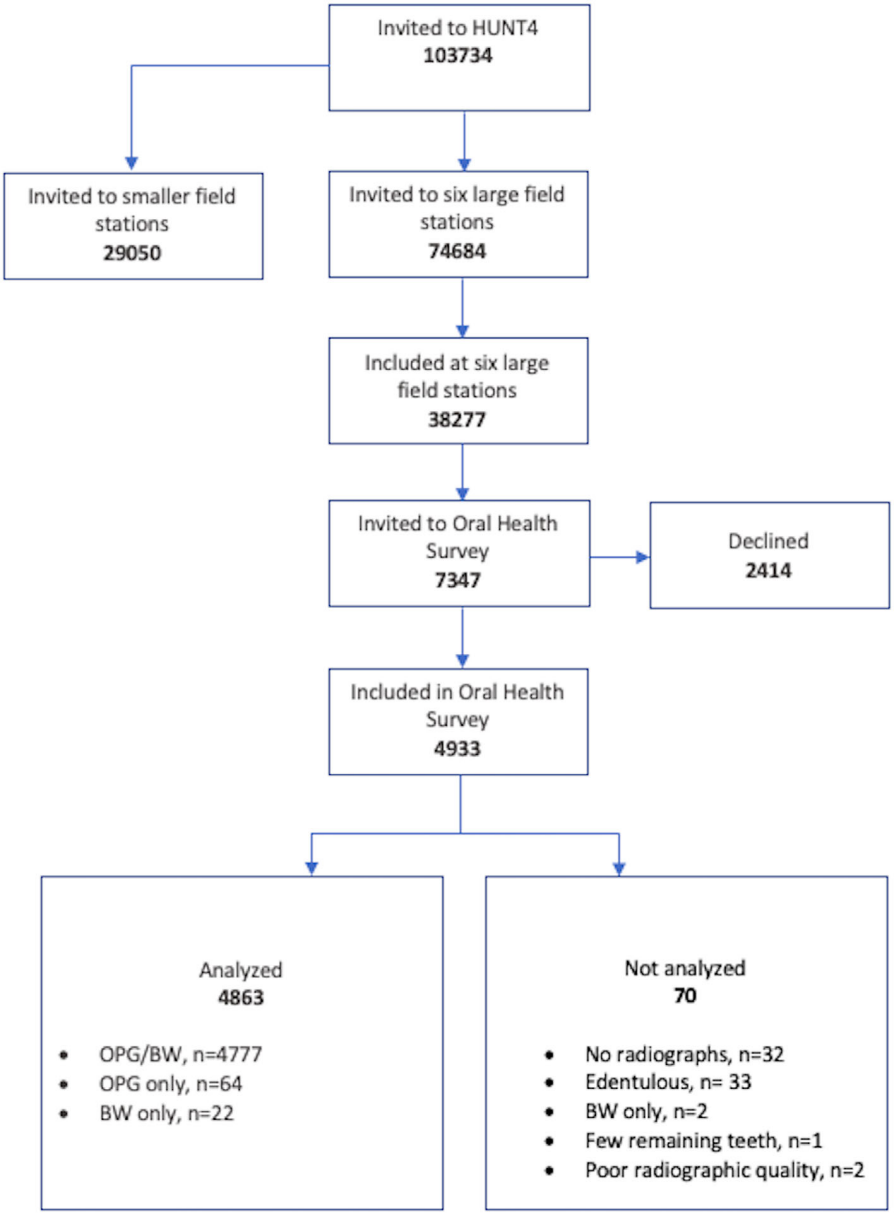
Trained, calibrated dentists ($n = 12$) and dental hygienists ($n = 7$) performed all clinical examinations. Periodontal probing depths (PPDs), bleeding on probing (BoP), suppuration, and mobility grades 2 and 3 (Miller, 1950; Nyman et al., 1975) were registered at six surfaces per tooth. PPD was measured with a World Health Organisation (WHO) periodontal probe (LM 550BSI Probe WHO ErgoNorm, LM-Instruments, Parainen, Finland) and was recorded in the following intervals: 0–3.5, >3.5–5.5, >5.5–8.5, >8.5–11.5, and >11.5 mm.

Calibration of the clinical examiners consisted of theoretical lectures and clinical practical training. This was supervised by experienced, certified periodontists (OCK and AV) and followed by an additional supervised session of training, in groups of three examiners examining nine individuals. The clinical training was repeated after 1 week for recording calibration measurements (PPD).

2.4 | Radiographic examination and calibration

The radiographic examination consisted of bitewing (BW) and orthopantomogram (OPG) radiographs. OPGs were obtained with a panoramic imaging unit, Planmeca ProOne (Planmeca Oy, Helsinki, Finland). In addition, four BW radiographs were obtained per participant using an intraoral imaging unit, Planmeca Intra (Planmeca Oy), with a rectangular collimator (length 35 cm) and an intraoral sensor, ProSensor HD (Planmeca Oy). Examination of the radiographs was performed by three calibrated specialists in periodontology (IHS, AV, and OCK). Inter-investigator calibration was performed on radiographs from 70 participants. Each of the investigators evaluated the

FIGURE 1 Study participants



70 radiographs separately and registered the percentage of bone loss for every tooth in the dentition. This was followed by a review of the results. In cases of disagreement, consensus was reached by discussions in the plenary.

2.5 | Definitions

- Periodontitis case: A subject with a distance between the cementum enamel junction (CEJ) and the alveolar bone crest (AC) exceeding 1.5 mm at ≥2 non-adjacent teeth. This was determined from BW radiographs and was considered "detectable interproximal bone loss". If BW examination was not performed, the distance between CEJ and AC was determined from OPGs ($n = 64$).
  - Periodontitis case, stable: <10% BoP, <4 mm PPD (modification of the 2017 classification)
  - Periodontitis case, some inflammation/unstable: ≥10% BoP, ≥4 mm PPD (modification of the 2017 classification)
- Periodontal health: <10% BoP, ≤3 mm PPD, in non-periodontitis cases
- Localized gingivitis: 10–30% BoP, ≤3 mm PPD, in non-periodontitis cases
- Generalized gingivitis: >30% BoP, ≤3 mm PPD, in non-periodontitis cases
- Tooth loss due to periodontitis: Missing teeth were annotated accordingly if this was considered the most likely cause for tooth loss, that is, cases with limited decay and restorations, few endodontic lesions or root canal treatments, and where the general bone level in the remaining dentition suggested periodontal tooth loss.
- Bone loss plausible by reasons other than periodontitis: Localized bone loss in proximity to impacted teeth or reduced bone level in

areas adjacent to missing teeth was disregarded in the evaluation of the periodontitis cases.

- Complexity: All complexity factors of the 2017 classification were considered. The following complexity factors were defined:
  - Vertical bone loss: Radiographic defects ≥3 mm deep and ≤3 mm wide.
  - Furcation grade ≥2: Overt radiolucency evident in the furcation areas (Zhang et al., 2018; Komšić et al., 2019).
  - Bite collapse/drifting/flaring: ≥3 teeth with obvious change of position and/or mobility grade ≥2 within the same sextant, in combination with presence of periodontal bone loss likely to cause this condition.
  - PPD >5 mm was used to identify Stage III when the radiographic bone level corresponded to Stage II definition.

Staging and grading were assessed only in "periodontitis cases". Determination of stage was based on radiographic bone loss (RBL), on the number of teeth considered lost due to periodontitis, and on all relevant complexity factors. If clinical parameters were not available, determination of stage was based on radiographic evaluation only ($n = 71$). When there was doubt regarding the assignment of a participant to a specific stage and/or grade, the case in question was discussed among the examiners (IHS, AV, and OCK) until consensus was reached.

2.6 | Data extraction

Radiographs were analysed in a room with low ambient light on a computer screen (2560 × 1440 pixel resolution) applying Planmeca Romexis image software, version 4.6.0.R. Periodontal bone loss, stage, and initial grade assessment, based on the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions (Caton et al., 2018; Chapple et al., 2018; Papapanou et al., 2018), were determined from measurements in the OPGs and clinical variables. The distance from the CEJ to the top of the AC where the PDL presented normal width (Bjorn et al., 1969) and the distance from the CEJ to the radiographic apex were measured in millimetres in the entire dentition to calculate the percentage of bone loss. Thereafter, the most severely affected tooth was used to determine the initial grade of the "periodontitis case". Final grades were adjusted by grade modifiers, that is, self-reported smoking habits and HbA1c measurements in participants with self-reported diabetes diagnosis. BWs were used for guidance and verification of the OPG evaluation. For participants with only BW radiographic examination available ($n = 22$), the percentage of bone loss was determined according to a study of average root lengths (Frederiksen, 1972).

The classification of periodontal status included all permanent teeth, except third molars. Root remnants, defined by the examining clinician, were also excluded. Implants and primary teeth were registered accordingly, but were not included in the periodontal evaluation.

2.7 | Ethics

This study was included as a part of The HUNT4 Survey and was evaluated and approved by the regional ethics committee (2016/1879/REK, 2020/10417/REK). The paper was prepared following the STROBE guidelines.

2.8 | Statistics

Descriptive statistics were performed using Microsoft Excel 2016 (16.0.5122.1000) MSO.

3 | RESULTS

3.1 | Participants

Clinical and/or radiographic examination was performed in 4933 participants. The response rate was 67% of the 7347 invited for the Oral Health Study. Seventy participants (1.4%) were not considered in the data analysis. This included participants without radiographic examination, edentulous participants, and three participants who, for different reasons, were considered inappropriate for periodontal evaluation (Figure 1). Another 71 participants (1.5%) were evaluated on radiographs but, for different reasons, did not attend the clinical examination (unknown gingival status).

In the study population, 2174 (44%) were male and 2759 (56%) were female (Table 1). The age distribution ranged from 19 to 94 years. The average age was 51.8 years (SD = ±16.6). The number of edentulous participants was 33 (0.66%), and the average number of teeth present was 25.4 (SD = ±4.3).

3.2 | Periodontal variables in the study population ($n = 4933$)

BoP assessment of the 4933 participants demonstrated that 46.2% had <10% BoP, 36.7% had 10–30% BoP, and 14.8% had >30% BoP. In 2.3% (112 participants), no assessment of BoP was performed. PPD ≥4 mm in at least one site was observed in 2399 participants (48.6%), and PPD ≥6 mm was registered in 466 participants (9.4%).

3.2.1 | Periodontal health and gingivitis

The distribution of periodontal health, gingivitis, and periodontitis is shown in Figure 2. Of the study population, 1290 (26.2%) showed no RBL (i.e., ≤1.5 mm AC-CEJ). Of these, 663 (13.5%) participants were registered with <10% BoP ("no gingivitis") and 608 (12.3%) with gingivitis. Nineteen (0.5%) participants had neither RBL nor data on BoP.

Localized gingivitis was registered in 468 (9.5%) participants and generalized gingivitis in 140 participants (2.8%) (Figure 2).

TABLE 1 Demographic distribution

	Male								Female								
Age	20–29	30–39	40–49	50–59	60–69	70–79	≥80	Male total (%)	20–29	30–39	40–49	50–59	60–69	70–79	≥80	Female total (%)	Total
Number of participants, *N* (%)	274 (12.6)	258 (11.9)	385 (17.7)	442 (20.3)	438 (20.1)	289 (13.3)	88 (4.0)	2174	370 (13.4)	383 (13.9)	515 (18.7)	610 (22.1)	497 (18.0)	307 (11.1)	77 (2.8)	2759	4933
Non-smoker	269 (12.4)	242 (11.1)	360 (16.6)	417 (19.1)	407 (18.7)	274 (12.6)	87 (4.0)	2056 (94.6)	363 (13.2)	362 (13.1)	479 (17.4)	538 (19.5)	452 (16.4)	291 (10.5)	74 (2.7)	2559 (92.8)	4615 (93.6)
Smoker <10/day	1 (0.05)	2 (0.1)	1 (0.05)	2 (0.1)	6 (0.3)	8 (0.4)	1 (0.05)	21 (1.0)	3 (0.1)	13 (0.5)	14 (0.5)	34 (1.2)	21 (0.8)	5 (0.2)	2 (0.1)	92 (3.3)	113 (2.3)
Smoker ≥10/day	4 (0.2)	14 (0.6)	24 (1.1)	23 (1.1)	26 (1.2)	7 (0.3)		98 (4.5)	4 (0.1)	8 (0.3)	22 (0.8)	38 (1.4)	24 (0.9)	11 (0.4)	1 (0.03)	108 (3.9)	206 (4.2)
Non-diabetic HbA1c <7%	272 (12.5)	257 (11.8)	376 (17.3)	412 (19.0)	390 (17.9)	260 (12.0)	73 (3.4)	2040 (93.8)	366 (13.3)	374 (13.6)	504 (18.3)	589 (21.3)	472 (17.1)	275 (10.0)	71 (2.6)	2651 (96.1)	4691 (95.1)
Diabetic HbA1c <7%	1 (0.05)		4 (0.2)	16 (0.7)	24 (1.1)	20 (0.9)	6 (0.3)	71 (3.3)	2 (0.1)	7 (0.3)	9 (0.3)	15 (0.5)	15 (0.5)	17 (0.6)	2 (0.1)	67 (2.4)	138 (2.8)
Diabetic HbA1c ≥7%	1 (0.05)		4 (0.2)	7 (0.3)	23 (1.1)	8 (0.4)	6 (0.3)	49 (2.3)	2 (0.1)	2 (0.1)	2 (0.1)	6 (0.2)	8 (0.3)	13 (0.5)	4 (0.1)	37 (1.3)	86 (1.7)
HbA1c ≥7% wo/diabetes[a]		1 (0.05)	1 (0.05)	7 (0.3)	1 (0.05)	1 (0.05)	3 (0.1)	14 (0.6)					2 (0.1)	2 (0.1)		4 (0.1)	18 (0.4)

[a]Participants without self-reported diabetes diagnosis.

In the "no gingivitis" group, 123 (2.5%) had at least one site with PPD >3 mm, leaving 540 (10.9%) participants with periodontal health (as defined).

3.2.2 | Periodontitis cases

Periodontitis, as defined in Section 2.5, was observed in 3573 participants (72.4% of the study population). BoP was not recorded for 52 periodontitis cases (1.4% of the periodontitis cases).

3.2.3 | Periodontitis cases, stable (health on reduced periodontium)

Of the periodontitis cases ($n = 3573$), 1599 participants (44.8%) were recorded with <10% BoP. Among these 1599, at least one site of PPD ≥4 mm was observed in 593 participants (16.6% of the periodontitis cases), leaving 1006 participants (28.2% of the periodontitis cases) as stable periodontitis cases, as defined in Section 2.5.

3.2.4 | Periodontitis cases, with inflammation/unstable periodontitis

Of the periodontitis cases ($n = 3573$), 1922 (53.8%) showed BoP ≥10%. Of these, 1410 participants (39.4% of the periodontitis cases) also had PPD ≥4 mm, and they were registered as unstable periodontitis cases/periodontitis cases with inflammation.

3.3 | Staging of periodontitis (presented as percentage of the study population, $n = 4933$)

3.3.1 | Severity based on radiographic bone loss

Based on RBL alone, 682 (13.8%) participants defined as periodontitis cases were assigned to Stage I (<15% RBL), 2212 (44.8%) to Stage II (15–33.3% RBL), and 679 (13.8%) to Stage III or IV (>33.3% RBL).

3.3.2 | Tooth loss

For teeth considered "missing due to periodontitis", 247 (5%) of the study population ($n = 4933$) had lost 1–4 teeth (Stage III), whereas 106 (2.1%) had lost 5 teeth or more (Stage IV).

3.3.3 | Complexity (presented as percentage of the periodontitis population, $n = 3573$)

The number of periodontitis cases with at least one site with PPD ≥4 mm was 2003 (56% of the periodontitis cases) and 441 (12.3%) had

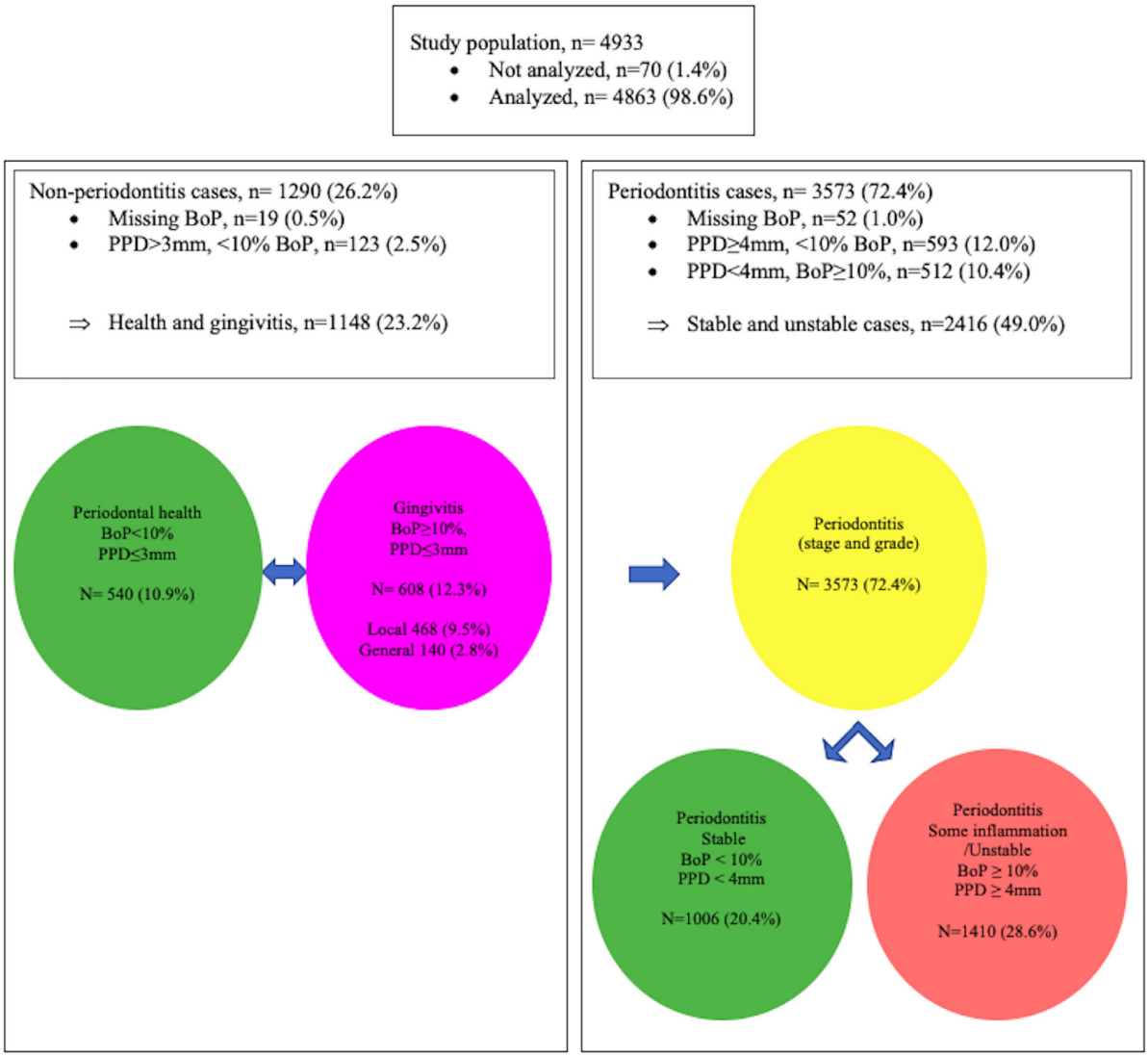


FIGURE 2 Distribution of participants with periodontal health, gingivitis, and periodontitis. All percentages (%) are calculated from the study population. Definitions of stable periodontitis and periodontitis with some inflammation/unstable are modifications of the 2017 classification

at least one site with PPD ≥6 mm. The number of periodontitis cases with less than 10 remaining occluding pairs of teeth, and tooth loss considered caused by periodontitis, was 110 (3.1%). Radiolucency in the furcation area, according to the definition, was registered in 367 participants among the periodontitis cases (10.3%), vertical bone loss was registered in 88 participants (2.5%), and bite collapse/drifting/flaring was observed in 45 (1.3%) participants with periodontitis.

3.3.4 | Extent and distribution

Based on tooth loss and complexity factors in addition to bone-level radiography, Stage II was observed in 2028 participants (41.1%), Stage III in 755 participants (15.3%), and Stage IV in 111 participants (2.3%) of the study population ($n = 4933$). Of the participants who were allocated to Stage III, more than 80% demonstrated localized disease. Stage allocation is displayed in Table 2.

3.4 | Grading of periodontitis (presented as a percentage (%) of the study population, $n = 4933$)

3.4.1 | Primary criterion: percent bone loss divided by age

When the initial grade without grade modifiers was assessed from participants' age and the site of most severe RBL (Table 3), 6.1%, 65%, and 1.4% of the study population were assigned to grade A, B, and C, respectively.

3.4.2 | Grade modifiers

With grade modifiers, the number of participants with grade A and B decreased to 279 (5.7%) and 2969 (60.2%), respectively, while number of participants with grade C increased to 308 (6.2%) (see Table 3) compared to the initial grading.

3.5 | Prevalence of stages and grades

Stages and grades by age groups are displayed in Table 4.

3.6 | Inter-examiner agreement

Inter-rater reliability for measurements of PPD were calculated using intra-class correlation coefficient (ICC) two-way mixed effect model, assessing absolute agreement.

The ICCs (95% CI) for the clinical examiners at the six field stations were as follows: 0.57 (0.52–0.60), 0.68 (0.65–0.71), 0.71 (0.68–0.74), 0.77 (0.75–0.79), 0.77 (0.74–0.79), and 0.79 (0.75–0.82).

Inter-rater reliability for evaluation of grade, generalized stage, and localized stage was calculated using ICC two-way mixed-effect model, assessing absolute agreement.

- Grade: ICC (95% CI) = 0.90 (0.85–0.93).
- Generalized stage: ICC (95% CI) = 0.92 (0.88–0.95)
- Localized stage: ICC (95% CI) = 0.94 (0.91–0.96)

Inter-rater reliability for measures of RBL (percentage of root length) was calculated using ICC two-way mixed effects, assessing consistency.

- Periodontal bone loss: ICC (95% CI) = 0.95 (0.918–0.964)

TABLE 2 Allocation of periodontal stage in number (*N*) and as a percentage (%) of the study population ($n = 4933$)

Stage	Total, *N* (%)	Localized, *N* (%)	Generalized, *N* (%)
Stage I	679 (13.8)	392 (8.0)	287 (5.8)
Stage II	2028 (41.1)	996 (20.2)	1032 (20.9)
Stage III	755 (15.3)	625 (12.7)	130 (2.6)
Stage IV	111 (2.3)		

Note: Seventy ($n = 70$) participants were not analysed (Figure 1).

4 | DISCUSSION

The prevalence of periodontitis as defined and by subsequent classification was comprehensively investigated in this large cross-sectional study based on OPGs, BWs, and clinical assessment of all participants.

Of the study population, 26.2% had no detectable RBL, 13.8% were classified with Stage I, 41.1% with Stage II, 15.3% with Stage III, and 2.3% with Stage IV periodontitis. Grade B was the predominant grade, being diagnosed in 60.2% of the entire study population (83% of the periodontitis cases). Localized and generalized periodontitis were equally distributed in Stage II. In Stage III, the majority of cases (82.8%) demonstrated localized periodontitis.

The National Health and Nutrition Examination Survey (Eke et al., 2018) estimated that about 42% of the U.S. adult population had periodontitis, with 7.8% having severe periodontitis. The Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) case definition (Page & Eke, 2007; Eke et al., 2012) used 6 mm clinical attachment level (CAL) as the threshold for severe periodontitis and 4 mm CAL for moderate periodontitis. Based on reported average root lengths (Frederiksen, 1972), 6 mm corresponds to approximately 40% bone loss. The >33% threshold of RBL for Stages III and IV in the 2017 classification corresponds to approximately 5 mm CAL. Hence, the use of a 5 mm threshold rather than 6 mm included a higher percentage of participants into more severe disease categories and may explain the deviation between severe and moderate periodontitis, compared to Stage III and Stage IV periodontitis.

Findings from the present investigation are in line with those of a Swedish repeated cross-sectional study (Wahlin et al., 2018). The most severe form of periodontitis was defined as alveolar bone loss >1/3 of root length, and/or presence of angular bony defects and furcation grade 2 and 3. This definition has similarities to the diagnostic criteria applied in the present study. The group "no or minor periodontitis" comprised 60% of the sample in the study by Wahlin and coworkers. The corresponding number in the HUNT4 sample was 40% when Stage I and "no periodontitis" were combined. The "moderate and severe" groups in the Swedish study comprised 29% and 11% of the sample, as compared to the present 41% (Stage II) and 17.5% (Stage III and Stage IV). Teeth loss due to periodontitis was

TABLE 3 Distribution of stages and grades with and without modifying factors (smoking, HbA1c, and diabetes diagnosis) in percentage (%) of study population ($n = 4933$)

Grade	Stage I, *N* (%)	Stage II, *N* (%)	Stage III, *N* (%)	Stage IV, *N* (%)	Total, *N* (%)
A	233 (4.7)	65 (1.3)	3 (0.1)		301 (6.1)
A w/modifying factors	220 (4.5)	56 (1.1)	3 (0.1)		279 (5.7)
B	446 (9.0)	1963 (39.8)	712 (14.4)	85 (1.7)	3206 (65.0)
B w/modifying factors	433 (8.8)	1854 (37.6)	618 (12.5)	64 (1.3)	2969 (60.2)
C			40 (0.8)	26 (0.5)	66 (1.3)
C w/modifying factors	23 (0.5)	110 (2.2)	129 (2.6)	46 (1.0)	308 (6.2)

Note: Seventeen participants ($n = 17$) did not provide information on diabetes.

TABLE 4 Periodontal stages and grades distributed by age, $n = 4933$

Age group	*N*	Non-periodontitis cases, *N* (%)	Stage I, *N* (%)	Stage II, *N* (%)	Stage III, *N* (%)	Stage IV, *N* (%)	Periodontitis cases, *N* (%)
20–29	**644**	**573 (89)**	**40 (6.2)**	**21 (3.3)**	**2 (0.3)**		**63 (9.8)**
Grade A			1 (0.15)				
Grade B			38 (5.9)	20 (3.1)	1 (0.15)		
Grade C			1 (0.15)	1 (0.15)	1 (0.15)		
30–39	**641**	**401 (62.6)**	**121 (18.9)**	**101 (15.8)**	**13 (2.0)**		**235 (36.7)**
Grade A			2 (0.3)				
Grade B			113 (17.6)	92 (14.4)	6 (0.9)		
Grade C			6 (0.9)	9 (1.4)	7 (1.1)		
40–49	**900**	**239 (26.6)**	**232 (25.8)**	**372 (41.3)**	**51 (5.7)**	**3 (0.3)**	**658 (73.1)**
Grade A			31 (3.4)	1 (0.1)			
Grade B			191 (21.2)	346 (38.4)	30 (3.3)	1 (0.1)	
Grade C			9 (1.0)	25 (2.8)	21 (2.3)	2 (0.2)	
50–59	**1052**	**66 (6.3)**	**208 (19.8)**	**606 (57.6)**	**155 (14.7)**	**10 (1.0)**	**979 (93.1)**
Grade A			114 (10.8)	1 (0.1)			
Grade B			87 (8.3)	566 (53.8)	112 (10.6)	3 (0.3)	
Grade C			5 (0.5)	35 (3.3)	42 (4.0)	7 (0.7)	
60–69	**935**	**7 (0.7)**	**65 (7.0)**	**550 (58.8)**	**272 (29.1)**	**34 (3.6)**	**921 (98.5)**
Grade A			60 (6.4)	15 (1.6)	1 (0.1)		
Grade B			4 (0.4)	507 (54.2)	227 (24.3)	14 (1.5)	
Grade C			1 (0.1)	27 (2.9)	43 (4.6)	19 (2.0)	
70–79	**596**	**3 (0.5)**	**11 (1.8)**	**308 (51.7)**	**202 (33.9)**	**51 (8.6)**	**572 (96.0)**
Grade A			10 (1.7)	31 (5.2)	2 (0.3)		
Grade B				266 (44.6)	186 (31.2)	35 (5.9)	
Grade C			1 (0.2)	10 (1.7)	12 (2.0)	16 (2.7)	
≥80	**165**	**1 (0.6)**	**2 (1.2)**	**70 (42.4)**	**60 (36.4)**	**13 (7.8)**	**145 (87.9)**
Grade A			2 (1.2)	8 (4.8)			
Grade B				57 (34.5)	56 (33.9)	11 (6.7)	
Grade C				3 (1.8)	3 (1.8)	2 (1.2)	

Note: Seventy ($n = 70$) participants were not analysed (Figure 1). Seventeen participants ($n = 17$) did not provide information on diabetes.

not considered in the Swedish study and might thus be part of the reason for the discrepancy between these two studies.

Recently, two Norwegian studies reported the prevalence of periodontitis. Holde et al. (2017) reported periodontitis in 49.5% of a population ($n = 1911$) in Troms, in the north of Norway. Prevalence of RBL was reported in 72.4% in the study by Holde and coworkers, which was similar to the bone loss in the present study. Interestingly, PPD ≥6 mm was found in 18.7% in the Troms population but only in 9.4% in the HUNT4 population despite a higher mean age of the latter. An underreporting of probing depths in the present study might be possible due to recording of clinical parameters by multiple examiners. Although calibrated, the clinical examiners were not specialists, which might have influenced the clinical assessment. The clinical assessment of this study is acknowledged as weaker than the radiographic assessment that was performed by three calibrated specialists in periodontology.

Another study from northern Norway assessed periodontitis among 2078 individuals aged 18–75 years (Bongo et al., 2020). Periodontitis (Stage II and III/IV combined) was observed in 49.7% of the study population. This number is similar to that in the present study. Bongo et al. (2020) did not consider missing teeth due to periodontitis or furcation involvements. Also, only BWs were used for radiographic evaluation, which may explain the deviating findings.

Stage I has been described as the borderline between gingivitis and periodontitis (Tonetti et al., 2018). Identification of Stage I, in particular, relies on clinical interpretation to be separated from healthy conditions (Kornman & Papapanou, 2020). The prevalence of Stage I periodontitis may have been underestimated in the present study, as clinical attachment level measurements were not performed, which would have more accurately captured incipient periodontitis. Also, the separation of stable periodontitis cases from unstable periodontitis cases according to the 2017 classification had to be modified in the present study. The cross-sectional nature of this study entailed uncertainties and risk of bias with respect to pseudo-pockets. A pretreatment phase to prevent this is generally not feasible in

epidemiological studies. Moreover, participants without bone loss may have been included in Stage I or even Stage II, as 15% of the total root length may lie within the biological variation of a healthy periodontal attachment apparatus (Hausmann et al., 1991).

As measurements of CAL and recessions were not available in this study, RBL was used to identify "periodontal cases" (Tonetti & Sanz, 2019). This is expected to have influenced the distribution of periodontal stages in the present study. A comprehensive assessment of CAL would have enhanced the validity of the present findings, in particular in Stage I and Stage II periodontitis.

The threshold for recording a furcation grade 2 or 3 was met only when furcation involvement was obvious in radiographs. Clinical assessment of furcations would certainly increase the number of participants assigned to Stage III. Grade 2 and grade 3 furcations were observed in 7.4% of the examined HUNT4 population. Although this number is expected to be an underestimation, it is in agreement with the 8.3% found in a radiographic assessment of 329 individuals from the 2003 Jönköping study (Najim et al., 2016).

The prevalence of Stage IV periodontitis was 2.3%. In the present study, teeth were only considered lost for periodontal reasons when the bone loss of the remaining dentition was severe and if there was no other likely cause. Moreover, severe RBL was not registered when reasons other than periodontitis were plausible, such as bone loss on the distal surface of the second molar when the third molar was missing or impacted, or at surfaces with missing adjacent teeth. This approach was intended to avoid overestimation, and the results should be interpreted accordingly. CAL measurements, clinical furcation involvement, and detailed information about missing teeth might have ascertained the distribution of stage allocation in the present study.

The present investigation is limited by lack of buccal and lingual CAL assessment and by lack of detailed radiographs in the front regions of the dentition. The 1.5-mm threshold for identification of periodontitis cases was not determined from OPGs. Periodontitis localized to the anterior regions is likely to be under-reported.

The annotation of RBL was performed by calibrated specialists in periodontology and is considered a strength. Likewise, the large number of participants in an area that resembles both Norway and other Scandinavian countries is a significant strength of this study.

Smoking habits are self-reported and recall bias is possible. Also, diabetes diagnosis is self-reported, but the HbA1c measurement of all participants strengthens this assessment.

The county of Nord-Trøndelag has been described as representative of smaller cities and rural areas in Norway (Holmen et al., 2003). Norway is characterized by the broad availability of healthcare services. This implies that good general and dental health is common, in both cities, coastal, and inland municipalities, such as in the large county of Nord-Trøndelag. An investigation in 2013 (Grytten et al., 2014) demonstrated that 88% of the Norwegian adult population had received dental treatment in the two previous years. Dental treatment is free until 18 years of age, and periodontal treatment is subsidized through Norwegian welfare systems for all citizens.

These aspects may imply that the external validity of this study and the extrapolation to other populations must be considered with caution. However, the present study may be comparable to other countryside populations where welfare services are readily available.

The ICCs for inter-rater reliability of the clinical examiners lay in the range 0.57–0.79. A moderate ICC is not always synonymous with modest measurement agreement, but may reflect low variability in the test sample (Koo & Li, 2016). For calibration procedures, periodontally healthy participants often served as test sample, being in concordance with a population with little variability.

In conclusion, the classification of periodontitis described by the 2017 World Workshop gives opportunities to conduct studies on the prevalence of periodontitis in a more comprehensive manner. In the present study of nearly 5000 participants, periodontitis was common, and Stage III and IV periodontitis combined was observed in approximately 17% of the population.

ACKNOWLEDGEMENTS

The Trøndelag Health Study (HUNT) is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. Dentists and dental hygienists from the public dental health service in the county of Trøndelag performed the clinical examinations. Professor Anne Merete Aass, Head of Department of Periodontology, University of Oslo, Norway, was involved in case discussions and in writing of the manuscript. The authors recognize the contribution of periodontists Odd Bjørn Lutnæs and Olav Inge Larsen during the initial calibration procedures, and all dentists, dental hygienists, and staff involved in collection of clinical data. Funding was provided by The Faculty of Dentistry, University of Oslo, Norway and Center for Oral Health Services and Research, Mid-Norway (TkMidt), Trondheim, Norway, supported the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception of this study. OCK, AV, and IHS contributed to data collection. All authors contributed to data analysis and interpretation of results. IHS, AV, and OCK produced the first draft. HH and AS contributed to critical review and revision of the manuscript. All authors gave final approval of the published version and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from HUNT Databank. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from https://hunt-db.medisin.ntnu.no/hunt-db/ with the permission of HUNT Databank.

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How to cite this article: Stødle, I. H., Verket, A., Høvik, H., Sen, A., & Koldsland, O. C. (2021). Prevalence of periodontitis based on the 2017 classification in a Norwegian population: The HUNT study. *Journal of Clinical Periodontology*, *48*(9), 1189–1199. https://doi.org/10.1111/jcpe.13507

II

Title: Association between Periodontitis Stages and Self-reported Diseases in a Norwegian population: the HUNT Study

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Abstract

Background

The relationships between periodontitis and non-communicable diseases (NCDs) have been investigated through several different case-definitions. The differences in methodology may have hindered the basis of comparison between these studies. The classification from the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions offers a unison platform that may facilitate future comparison of such research. The present study aimed to reproduce associations between periodontitis and other NCDs using the 2017 Classification, in the Trøndelag Health Study (HUNT).

Material and methods

The fourth HUNT-survey was carried out between 2017 and 2019. Clinical variables, blood samples and answers to questionnaires were collected from 4933 participants. Periodontal status was assessed based on the latest staging system, and its associations with NCDs were estimated by logistic regression models adjusted for potential confounders.

Results

Compared to no or Stage I periodontitis, participants with Stage III/IV periodontitis (radiographic bone loss exceeding 33%) were associated with cardiovascular disease, hyperglycemia in participants with diabetes and chronic obstructive pulmonary disease (COPD)/emphysema. Associations with hyperglycemia in participants with diabetes and COPD/emphysema were also observed in participants with Stage II periodontitis. The only observed association when considering never-smokers alone, was with COPD/emphysema.

Conclusion

Periodontitis Stage II and III/IV were associated with major NCDs. Effect sizes increased with increasing periodontitis stages, which implies greater occurrence of coincident comorbidities in patients with severe periodontitis.

Key words

Periodontitis, stage, non-communicable diseases, association, odds ratio, HUNT4

1. INTRODUCTION

Periodontitis is a destructive inflammatory disease, causing loss of supporting bone and soft tissue surrounding the teeth, and may lead to tooth loss if left untreated. Periodontitis has been reported in 40% of the US adult population [1], and severe periodontitis in 7.4% worldwide [2]. In a recent cross-sectional study based on the 2017 Classification, Stage III and Stage IV periodontitis combined was observed in 17% of adults in a Norwegian population [3].

Periodontitis is associated with several non-communicable diseases (NCDs) [4-6]. Shared immunological and inflammatory reactions in the host or bacteremia caused by pathogens of periodontal origin are suggested mechanisms of these associations. Disease activity is modulated through production of inflammatory factors, including interleukins, prostaglandins, and matrix metalloproteinases [7].

The supporting evidence of an association between periodontitis and systemic diseases includes several mechanisms. It is suggested that elevated systemic inflammation, observed through acute-phase proteins and oxidative stress biomarkers is a result of organisms entering the circulation. AGE-RAGE interactions are central in the plausible mechanistic links between periodontitis and diabetes, and leads to the exaggerated inflammatory response and

periodontal tissue destruction seen in diabetics. Moreover, diabetes is associated with elevated levels of several cytokines and other mediators in saliva and gingival crevicular fluid (GCF) [4]. Translocated circulating oral microbiota is also thought to impact on development of atherothrombogenesis through induction of systemic inflammation [5]. *P. gingivalis* has been shown to accelerate atherosclerosis in animal models, and to induce aorta fatty streaks after bacteremia [8, 9]. Further mechanistic evidence includes elevated levels of antibodies that have been shown to cross-react with antigens in cardiovascular tissues and increased production of reactive oxygen species (ROS) in peripheral neutrophils in periodontitis patients [8, 10].

The 2017 Classification redefines the outline of case criteria and disease severities. The aim of this cross-sectional study was to reproduce associations between periodontitis with the use of the 2017 Classification and several prevalent NCDs.

2. MATERIAL AND METHODS

2.1 Study design and population

The investigated population was a part of The Trøndelag Health Study (HUNT). HUNT is a longitudinal population-based study which constitutes a large database of questionnaire data, clinical measurements and biological samples [11-13]. The present cross-sectional study was based on data from HUNT4 which was conducted between September, 2017 and February, 2019. The county of Nord-Trøndelag had 137,233 residents in 2017. All residents in the county, turning 20 years within the year of participation and older (n=103,800), were invited of whom 56,042 (54.0%) participated [13]. At HUNT4 field stations in six larger

municipalities (Stjørdal, Levanger, Verdal, Steinkjer, Nærøy, and Namsos) a random sample were invited to the oral health examination, HUNT4 Oral health study, where periodontal examination was included for the first time. This constituted a subpopulation of 7347 HUNT4 participants. Finally, 4933 (67.1%) participated in clinical and/or radiographic oral examinations (Figure 1).

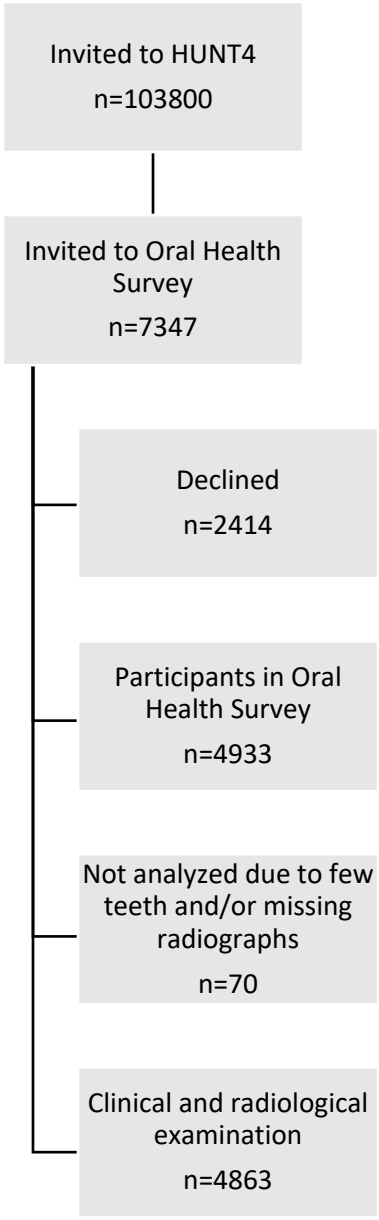

Figure 1. Study participants

2.2 Periodontal examination, questionnaires and blood samples

Periodontal and systemic health status was assessed by clinical and radiological examination, answers to questionnaires and by collection of blood samples. Trained, calibrated dentists/dental hygienists (n=19) performed all clinical examinations, as described in a previous publication [3]. Briefly, periodontal probing depths (PPD), bleeding on probing (BoP) and suppuration were registered at six surfaces per tooth in addition to mobility grade 2 and 3 [14, 15]. Third molars and root remnants were excluded. PPD was measured with a WHO periodontal probe (LM 550BSI Probe WHO ErgoNorm, LM-Instruments, Parainen, Finland), and was recorded in the following intervals: 0-3.5mm, >3.5-5.5mm, >5.5-8.5mm, >8.5-11.5mm, >11.5mm. Calibration of the clinical examiners consisted of theoretical lectures and repeated clinical practical training supervised by experienced, certified periodontists (OCK, AV). The radiographic examination consisted of four bitewings (BW) and one orthopantomogram (OPG) radiograph. The OPGs were obtained with a panoramic imaging unit, Planmeca ProOne (Planmeca Oy, Helsinki, Finland). The BW radiographs were obtained using an intraoral imaging unit, Planmeca Intra (Planmeca Oy, Helsinki, Finland), with a rectangular collimator (length 35 cm) and an intraoral sensor, ProSensor HD (Planmeca Oy, Helsinki, Finland). Examination of radiographs was performed by three calibrated periodontists (IHS, AV and OCK). Inter-investigator calibration was performed on radiographs and clinical variables from 70 participants. Each investigator registered percentage of bone loss for every tooth in the dentition and determined stage. In cases of disagreement, consensus was reached by discussions in plenary [3].

2.3 Periodontitis definition and classification of stages

A description of case definition and periodontitis classification has been published previously [3], in short; A periodontitis case was defined as a subject with a distance between the cementum enamel junction (CEJ) and the alveolar bone crest (AC) exceeding 1.5mm at ≥2 non-adjacent teeth. This was determined from BW radiographs and was considered "detectable interproximal bone loss". The distance from the CEJ to the top of the AC where the periodontal ligament (PDL) presented normal width [16], and the distance from the CEJ to the radiographic apex were measured in mm in the entire dentition to calculate the percentage of bone loss for all teeth. The radiographic bone loss (RBL) for each tooth was recorded in the following intervals: <15%, 15-33%, >33%. The most severely affected tooth was used to determine initial stage. If BW examination was not performed, the distance between the CEJ and the AC was determined from OPGs (n=64). For participants with only BW radiographic examination available (n=22), the percentage of bone loss was determined according to a study of average root lengths [17]. All participants were classified based on the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions [18-20]. Determination of final stage was based on RBL in OPGs, the number of teeth considered lost due to periodontitis and relevant complexity factors. The complexity factors included vertical bone loss (radiographic defects ≥3mm deep and ≤3mm wide), furcation grade ≥2 (overt radiolucency evident in the furcation areas) [21, 22], bite collapse/drifting/flaring (≥3 teeth with obvious change of position and/or mobility grade ≥2 within the same sextant, in combination with presence of periodontal bone loss likely to cause this condition) and PPD>5.5mm (used to identify Stage III when the RBL corresponded to Stage II definition) [3]. The complexity factors vertical bone loss, furcation involvement and bite collapse/drifting/flaring were determined from OPG radiographs. If

clinical parameters were not available, determination of stage was based on radiographic evaluation only (n=71).

2.4 Outcomes

Self-reported history of NCDs (CVD, rheumatoid disorder, COPD/emphysema) and hyperglycemia in self-reported diabetics, were the study endpoints. CVD was defined as a composite of myocardial infarction and/or angina pectoris and/or apoplexia [23]. Rheumatoid disorder was defined as a composite of rheumatoid arthritis and/or ankylosing spondylitis. Hyperglycemia (HbA1c ≥48mmol/mol) was described in subjects with self-reported diabetes.

2.5 Exposure of interest

The exposure periodontitis stage was grouped into three categories (no periodontitis/Stage I, Stage II and Stage III/IV).

2.6 Covariates

Selected confounders included age (continuous), sex, smoking (never smokers, <10, 10-20, >20 pack years), years of education (9-10 years, 11-13 years, college/university), total gross household income (<40000, 40-70000, >70000 EUR), BMI (kg/m^2, continuous), hypertension (>140/90 mmHg) and HbA1c-level (continuous) [24-27]. Information about sociodemographic and lifestyle factors were assessed via self-reported questionnaires. Anthropometric variables including weight, height and blood pressure were measured by trained personnel at HUNT4 field stations. Blood pressure measurements were based on

automatic oscillometric method, using Dinamap CARESCAPE V100 (GE Healthcare, Chicago, US) with GE TruSignal for pulse oximetry. Blood pressure was measured in a sitting position according to standardized methods. Three consecutive automatic oscillometric BP-measurements were recorded at 1-min intervals and the mean of the second and the third readings were calculated. Blood pressure was registered to the nearest 2 mmHg. Blood samples were drawn and analyzed for HbA1c in non-fasting serum or whole blood. Two separate enzymatic analysis; HbA1c and THb, were used to calculate the percentage (NGSP-units) and the hemoglobinfraction (IFCC-units) of HbA1c (Reagent kit; 4P52-21 Hemoglobin A1c, Multigent, Abbot Laboratories, USA). Missing responses in the questionnaires were reported as "Missing information". All variables are listed in Table 1.

2.7 Statistical analyses

Descriptive statistics are presented as mean and standard deviation for continuous variables, and percentages with 95% confidence intervals for categorical variables. The one-way ANOVA test was used to assess significant differences across group means for continuous variables and Pearson chi-square test was used for categorical variables. Logistic regression analyses were used to assess associations between periodontitis stages and CVD (0: no, 1: history of CVD), hyperglycemia in diabetics (0: no, 1: HbA1c ≥48 mmol/mol (6.5%) in self-reported diabetics), rheumatoid disorders (0: no, 1: history of rheumatoid disorders) and COPD/emphysema (0: no, 1: history of COPD/emphysema). All models were adjusted for potential confounders, listed in footnotes of Table 2. Selection of confounders was based on variables known to be associated with periodontitis or any of the outcomes. For testing p for trend, periodontitis stages were included as a continuous variable. Sensitivity analyses were conducted to assess the robustness of the findings by i) exclusion of participants 75 years and

older, ii) separate analysis of non-diabetics, iii) separate analysis of participants reporting diabetes diagnosis, but without considering HbA1c-level and iv) separate analysis of never-smokers. The odds ratios (OR) with corresponding 95% confidence intervals were computed.

Inter-rater reliability for clinical measurement (PPD) was calculated using intraclass correlation coefficient (ICC) two-way mixed effect model, assessing absolute agreement. ICC (95% CI) for the clinical examiners were:
0.57 (0.52-0.60), 0.68 (0.65-0.71), 0.71 (0.68-0.74), 0.77 (0.75-0.79), 0.77 (0.74-0.79), and 0.79 (0.75-0.82). Inter-rater reliability for evaluation of generalized stage and localized stage were calculated using ICC two-way mixed effect model, assessing absolute agreement.

- Generalized stage: ICC (95% CI) = 0.92 (0.88-0.95)
- Localized stage: ICC (95% CI) = 0.94 (0.91-0.96)

Inter-rater reliability for radiographic bone loss assessment (percentage of root length) was calculated using ICC two-way mixed effects, assessing consistency.
Periodontal bone loss: ICC (95% CI) = 0.95 (0.918-0.964). All statistical analyses were based on complete cases and were performed using Stata/MP 16.0 (Stata Corp., TX, USA).

2.8 Ethical approval

The HUNT4 Survey was approved by the Norwegian Data Protection Authority. Informed consent was obtained from all participants and/or their legal guardians. The current study was performed in accordance with relevant guidelines and regulations and was evaluated and approved by the Norwegian Regional Committees for Medical and Health Research Ethics during the conception of the study and when the data collection commenced

(2016/1879/REK, 2020/10417/REK, 2021/264485/REK). The paper was prepared following the STROBE guidelines.

3. RESULTS

Characteristics of the total population by periodontitis stages are presented in Table 1. Of the 4933 participants, 56% were female. The age distribution ranged from 19 to 94 years, and the mean age was 51.8 years (standard deviation (SD) 16.6). The number of edentulous participants was 33 (0.66%), and the average number of teeth present was 25.4 (SD 4.3). PPD ≥4mm in at least one site was observed in 2399 participants (48.6%). PPD ≥6mm in at least one site was observed in 466 participants (9.4%). For teeth considered "missing due to periodontitis", 247 (5.0%) had lost 1-4 teeth, whereas 106 (2.1%) had lost 5 teeth or more. Dental examinations and/or radiographic assessments were not performed in 70 of the participants included in the oral health survey, leaving a total of 4863 participants for statistical analysis (Figure 1). Significant differences across periodontitis stages in relation to demographic-, lifestyle-, anthropometric- and clinical factors was observed (Table 1). Participants with periodontitis Stage II-IV were relatively older, smoked more frequently and had lower levels of education and income compared to participants with no or Stage I periodontitis. Further, comorbid conditions and hypertension were observed more frequently for participants with periodontitis Stage II-IV.

Table 1. Characteristics of study population, by periodontal disease

Characteristics	Total (n=4933) †	No or Stage I periodontitis (n=1969)	Stage II periodontitis (n=2028)	Stage III/IV periodontitis (n=866)	p-value
Age (years)	51.8 (16.6)	38.2 (12.3)	58.5 (11.9)	65.9 (10.8)	<0.001
Sex					
Male	44.1 (42.7-45.4)	43.8 (41.6-46.1)	43.9 (41.8-46.1)	46.0 (42.6-49.3)	0.12
Female	55.9 (54.5-57.3)	56.2 (53.9-58.4)	56.1 (53.9-58.2)	54.0 (50.7-57.4)	
Education					
Primary (9-10 years)	7.3 (6.6-8.1)	2.8 (2.6-3.7)	7.7 (6.6-8.9)	14.8 (12.5-17.3)	<0.001
Secondary (11-13 years)	47.2 (45.8-48.6)	45.1 (42.9-47.3)	47.8 (45.6-50.0)	50.7 (47.3-54.1)	
University/College	45.0 (43.6-46.4)	51.6 (49.3-53.8)	44.1 (41.9-46.3)	33.7 (30.6-37.0)	
Missing information	0.5 (0.3-0.8)	0.5 (0.2-0.9)	0.4 (0.2-0.8)	0.8 (0.3-1.7)	
Income, total household					
<40.000 EUR	25.7 (24.5-26.9)	23.0 (21.1-24.9)	22.7 (20.9-24.6)	37.3 (34.1-40.6)	<0.001
40.000-70.000 EUR	28.4 (27.1-29.7)	24.1 (22.2-26.1)	29.7 (27.7-31.7)	35.8 (32.6-39.1)	
>70.000 EUR	43.8 (42.4-45.1)	50.9 (48.7-53.2)	45.7 (43.5-47.9)	24.1 (21.3-27.1)	
Missing information	2.1 (1.8-2.6)	2.0 (1.4-2.7)	1.9 (1.4-2.6)	2.8 (1.8-4.1)	
BMI (kg/m^2)	27.1 (4.6)	26.6 (4.9)	27.2 (4.3)	27.6 (4.6)	<0.001
Missing information	0.3 (0.2-0.5)	0.2 (0.03-0.4)	0.3 (0.1-0.6)	0.3 (0.1-1.0)	
Smoking					
Never smokers	45.3 (43.9-46.7)	55.9 (53.6-58.1)	43.3 (41.2-45.5)	26.4 (23.5-29.5)	<0.001
Pack years					
>0.0-9.9	24.6 (23.4-25.8)	20.4 (18.7-22.3)	29.0 (27.0-31.0)	24.4 (21.5-27.4)	
10-20	10.9 (10.0-11.8)	4.4 (3.5-5.4)	13.0 (11.6-14.6)	20.6 (17.9-23.4)	
>20	7.7 (7.0-8.5)	1.1 (0.7-1.6)	6.9 (5.8-8.1)	23.6 (20.8-26.5)	
Missing information	11.6 (10.7-12.5)	18.3 (16.6-20.1)	7.7 (6.6-9.0)	5.1 (3.7-6.8)	
HbA1c (mmol/mol)	34.1 (6.0)	32.0 (4.4)	35.0 (6.1)	36.5 (7.0)	<0.001
HbA1c (%)	5.3 (0.5)	5.1 (0.4)	5.3 (0.6)	5.5 (0.6)	
Missing information	1.0 (0.8-1.4)	0.9 (0.5-1.4)	1.2 (0.8-1.8)	1.0 (0.5-2.0)	
Hypertension	20.7 (19.6-21.9)	9.3 (8.1-10.7)	25.5 (23.6-27.4)	35.1 (31.9-38.4)	<0.001
Missing information	0.2 (0.1-0.4)	0.1 (0.01-0.4)	0.2 (0.1-0.5)	0.5 (0.1-1.2)	
Myocardial infarction/apoplexia/angina	6.5 (5.8-7.2)	1.6 (1.1-2.3)	7.5 (6.4-8.7)	14.0 (11.7-16.5)	<0.001
Missing information	2.8 (2.4-3.3)	1.6 (1.1-2.2)	3.2 (2.5-4.1)	4.3 (3.0-5.8)	
HbA1c≥48mmol/mol (6.5%) in diabetics	2.7 (2.2-3.2)	1.7 (1.2-2.4)	5.5 (4.6-6.6)	8.2 (6.5-10.2)	<0.001
Missing information	2.3 (1.9-2.8)	1.1 (0.7-1.6)	1.2 (0.8-1.8)	2.1 (1.2-3.3)	
Rheumatoid disorder	5.9 (5.3-6.6)	3.0 (2.3-3.8)	7.1 (6.0-8.3)	9.2 (7.4-11.4)	<0.001
Missing information	3.4 (2.9-3.9)	1.9 (1.4-2.6)	3.8 (3.0-4.7)	5.0 (3.6-6.6)	
COPD/emphysema	2.1 (1.7-2.5)	0.2 (0.03-0.4)	2.1 (1.2-2.8)	5.9 (4.4-7.7)	<0.001
Missing information	3.8 (3.3-4.4)	2.2 (1.6-2.9)	4.3 (3.5-5.3)	5.7 (4.2-7.4)	
Number of teeth	25.4 (4.3)	27.1 (2.1)	25.5 (3.4)	22.3 (5.3)	<0.001
Number of participants with					
PPD≥4mm in≥1 site	48.6 (47.2-50.0)	32.8 (30.7-34.9)	51.1 (48.9-53.3)	81.2 (78.4-83.7)	<0.001
PPD≥6mm in≥1 site	9.4 (8.6-10.3)	1.7 (1.2-2.4)	3.5 (2.7-4.3)	41.6 (38.3-44.9)	
Missing information	2.3 (1.9-2.7)	1.2 (0.8-1.8)	1.5 (1.0-2.1)	2.0 (1.1-3.1)	

Note: Data are presented as mean (SD) or percentage (95% CI). Differences among groups were analyzed by One-way ANOVA for continuous variables and by x2 for categorical variables.

† 70 participants (1.4%) were considered ineligible for periodontal diagnosis, i.e., edentulous participants or participants missing radiographs.

Abbreviations: SD, standard deviation; CI, confidence interval; PPD, periodontal probing depth

3.1 Association with periodontitis stages

The associations between periodontitis stages and NCDs are presented in Table 2. In the adjusted models, periodontitis Stage III/IV was associated with increased occurrence of CVD (OR, 1.73, 95% CI 1.04-2.89), hyperglycemia in diabetics (OR 2.56, 95% CI 1.17-5.61) and COPD/emphysema (OR 5.40, 95% 1.48-19.78), compared to no/Stage I periodontitis. The effect sizes for periodontitis Stage II, were relatively lower. No association was observed between periodontitis and rheumatoid disorders. Positive linear trends were observed between stages of periodontitis and CVD, hyperglycemia in diabetics, and COPD/emphysema.

Table 2. Association between periodontitis stages and cardiovascular disease, diabetes, rheumatoid disorders and COPD/emphysema, by logistic regression analysis

NCD [1,2,3]	No. of observations	Crude OR (95% CI)	No. of observations	Adjusted OR (95% CI)
Cardiovascular disease[1]				
Stage II	n=4730	4.99 (4.40-7.36)	n=4055	1.39 (0.88-2.22)
Stage III/IV		10.18 (6.83-15.17)		1.73 (1.04-2.89)
Per unit increase		2.84 (2.41-3.35)		1.29 (1.02-1.63)
p-linear trend		<0.001		0.032
Diabetes, HbA1c≥48 mmol/mol (6.5%) in self-reported diabetics[2]				
Stage II	n=4750	4.64 (2.60-8.30)	n=4114	2.12 (1.05-4.30)
Stage III/IV		8.12 (4.45-14.84)		2.56 (1.17-5.61)
Per unit increase		2.52 (1.97-3.23)		1.44 (1.03-2.03)
p-linear trend		<0.001		0.035
Rheumatoid disorders[3]				
Stage II	n=4705	2.53 (1.85-3.45)	n=4083	1.20 (0.79-1.81)
Stage III/IV		3.42 (2.41-4.83)		1.08 (0.66-1.77)
Per unit increase		1.82 (1.55-2.14)		1.01 (0.80-1.28)
p-linear trend		<0.001		0.948
COPD/emphysema[3]				
Stage II	n=4130	14.52 (4.50-46.89)	n=4061	4.17 (1.20-14.57)
Stage III/IV		42.68 (13.28-137.15)		5.40 (1.48-19.78)
Per unit increase		4.22 (3.08-5.78)		1.62 (1.08-2.43)
p-linear trend		<0.001		0.020

Note: Reference: No periodontitis/ periodontitis Stage I

1 Adjusted for HbA1c-level, BMI, hypertension, age, sex, smoking (pack years), income and years of education

2 Adjusted for BMI, hypertension, age, sex, smoking (pack years), income and years of education

3 Adjusted for hypertension, age, sex, smoking (pack years), income and years of education

Abbreviations: NCD, non-communicable disease; OR, odds ratio; CI, confidence interval

3.3 Sensitivity analyses

The analyses of participants below 75 years and of non-diabetics, corresponded to the results of the main analyses (Supplementary tables 1 and 2). In the sensitivity analysis of participants with diabetes regardless of glycemic control, no association was observed (Supplementary table 3). In analysis of never-smokers, associations were observed for periodontitis Stage II (OR 10.79, 95% CI 1.04-111.90) and Stage III/IV (OR 14.58, 95% CI 1.00-212.58) with COPD/emphysema (Supplementary table 4).

4. DISCUSSION

This cross-sectional study of 4933 adult participants assessed associations between self-reported NCDs and periodontitis stages based on the 2017 Classification. The results suggest that periodontitis is associated with CVD, hyperglycemia in participants with diabetes and with COPD/emphysema related to the severity of periodontal disease. The associations were generally stronger with increasing stage severity. No association was observed between periodontitis and rheumatoid disorders.

The observed associations between periodontitis and CVD in the present investigation are consistent with other previous studies [28, 29]. The most recent study [28] used NHANES data to investigate associations between coronary heart disease/stroke (CVD) and periodontitis by the 2017 Classification of Periodontal and Peri-Implant Diseases and Conditions. The authors assessed clinical periodontal attachment loss and reported that Stage III and IV periodontitis were associated with 3.59 times greater occurrence of CVD

compared to Stage I periodontitis. This is higher, but comparable to the present study (OR 1.73 (95% CI 1.04-2.89). Further, the increasing effect sizes of periodontitis stages and CVD in the present study confirm findings by Ngamdu and coworkers with OR 2.58 (95% CI 0.97-6.89) and 3.59 (95% CI 1.12-11.54), for Stage II and Stage III/IV, respectively. Studies with different design are also supportive of these findings. A large longitudinal study of Korean individuals older than 40 years [30], showed that periodontitis assessed from medical records was associated with future cardiac events in individuals without previous cardiac disease and that this association was reduced with good oral hygiene and more frequent dental visits. Improved oral hygiene behavior was suggested as a modifier of the association between periodontitis and CVD. Another follow-up study reported adverse cardiovascular events in individuals who had been treated for severe periodontitis [31]. This association was observed in individuals older than 60 years, only.

Neither sensitivity analyses of participants below 75 years nor analyses of non-diabetics produced results that differed vastly from the main analyses in the present study. The associations between CVD and periodontitis Stage II (OR 1.65, 95% CI 0.99-2.73) and Stage III/IV (OR 1.82, 95% CI 1.03-3.21) in participants younger than 75 years, are in line with a report from the PAROKRANK case-control study [29], despite the differences in study design. In PAROKRANK the association between myocardial infarction and radiologically assessed periodontal bone loss (OR 1.28 (95% CI 1.03–1.60) was assessed in patients <75 years only, to avoid disturbance from accumulation of concomitant disorders.

There is abundant literature on the relationship between periodontitis and diabetes. It has been stated that diabetic patients in general have higher severity of periodontal disease compared to non-diabetics**,** while other studies report comparable periodontal status in

patients with controlled diabetes to that of the general population [32]. A systematic review by Graziani and coworkers [33] concluded that due to heterogeneity among publications, there is still some conflicting evidence, and stated that several studies are unable to confirm periodontitis' impact on diabetes control, incidence and complications, or that type 2 diabetes in individuals with periodontitis is associated with higher levels of HbA1c. The present observations are in line with the aforementioned statements. Stage II and Stage III/IV periodontitis were associated with hyperglycemia in self-reported diabetics in the total population. This association was also observed with Stage III/IV in the subpopulation of participants less than 75 years. When self-reported diabetes was assessed alone without consideration of glycemic control, no association was observed.

Periodontitis was not associated with rheumatoid disorders in the present study, which is in contrast to a recent systematic review and meta-analysis [34]. Hussain and co-workers emphasized that rheumatoid arthritis did not affect periodontal attachment level, but that there is moderate evidence to suggest that individuals with periodontitis have more swollen or tender joints, report more pain on visual analogue scales and have higher erythrocyte sedimentation rates, assessed by a disease activity score tool in 28 joints (DAS28). In the present analysis of rheumatoid disorders, information about joint pain and -motion, functionality, duration of symtoms and use of medication were not assessed, hence the present model design may have inflicted the contrasting findings.

The present analysis of COPD/emphysema is supportive of a Japanese 5-year cohort study [35]. The authors reported an association between severe periodontitis and COPD. Similarly, a systematic review and meta-analysis have validated associations between periodontitis and asthma, COPD and pneumonia [36]. The biological plausibility for such associations include

epithelial damage to lower respiratory tract caused by periodontal pathogens and cytokine release, and neutrophilic inflammation with subsequent proteolytic destruction of connective tissue [6, 37]. It has been suggested that smoking should be considered a modifier of associations between COPD and periodontitis as smoking plays an important role in etiology in both diseases [38]. When analyzing never-smokers in the present investigation, no association with NCDs were observed with the exception of COPD/emphysema. The wide confidence intervals in the present analysis indicates uncertainty of the relationship with COPD/emphysema. Only 2.1% (n=104) of the total population reported COPD/emphysema, and 51 of these 104 individuals (49%) were classified with periodontitis Stage III/IV.

The stages of the 2017 classification reflect severity of periodontitis. Accordingly, it may be used to explore a dose-dependent relationship between periodontitis stages and associated conditions, and perhaps more easily identify if there are certain stages or individuals with increased likelihood of coincident diseases. This is of relevance for patients and dental professionals and may be important in risk factor modification as part of periodontal therapy. Conversely, individuals with systemic diseases may present more severe stages of periodontitis, and awareness of this association for patients and medical doctors is encouraged. The latest staging and grading system may facilitate research on how established and potential risk indicators or determinants of periodontitis are distributed between the different stages of disease. Nevertheless, the suitability of the new classification system in epidemiological research, and its potential benefits for patients' periodontal health has yet to be explored. The cross-sectional design of the present study will not fully reflect disadvantages of the classification in this respect.

The investigated population is representative of smaller cities and rural areas in Norway [11, 13] and the results from the present study may only be generalized to similar populations. Previous findings from the HUNT Study have shown that non-participants had lower socioeconomic status and higher prevalence of chronic diseases and mortality than those who participated [39]. This was confirmed in the latest cohort profile [13] who reported a less healthy lifestyle and inferior self-reported health and higher proportion of cardiovascular diseases, chronic obstructive pulmonary disease, diabetes and antihypertensive medication use, in non-participants. In the present analysis, total household income had a modest effect on the observed associations. Low socioeconomic status has been presented as a risk factor for periodontal disease [40], however, the magnitude may be masked in the present investigation due to inclusion of younger, healthy individuals in a generally healthy, high-income population. There was a tendency of a protective relationship between higher income and NCDs (Supplementary table 5).

Moreover, the magnitude of the crude ORs compared to the adjusted ORs of the statistical estimates suggests that some of the independent variables have a significant effect as determinants of the outcomes, together with periodontitis stages. This should be taken into consideration when interpreting the results.

Self-reported systemic illness is a limitation in the present investigation. HUNT cohort profiles [13] indicate that when compared to hospital journal charts and registries, the sensitivity, specificity and predictive values of the self-reported information varies across diagnoses. In-depth validity studies have been conducted. For self-reported diabetes, Midthjell and co-workers [41] found that patient administered questionnaires regarding a well-defined disease, was highly reliable for epidemiological purposes. The modest inter-examiner reliability of the clinical examiners is also a limitation. On the other hand, the

clinical measurements and biological samples are considered strengths. The large sample size of nearly 5000 individuals and full mouth clinical and radiographical periodontal examination and assessment by the 2017 Classification are also strengths of this study.

5. CONCLUSION

The present investigation demonstrates that associations between periodontitis and history of CVD, diabetes and COPD/emphysema, increases with periodontitis stage severity.

ABBREVIATIONS

AAP: American Academy of Periodontology

AC: Alveolar bone crest

BoP: Bleeding on probing

BW: Bitewing radiograph

CEJ: Cementum enamel junction

CI: Confidence interval

CVD: Cardiovascular diseases

COPD: Chronic obstructive pulmonary disease

EFP: European Federation of Periodontology

HUNT: the Trøndelag Health Study

IFCC: International Federation of Clinical Chemistry and Laboratory Medicine

NCD: Non-communicable disease

NGSP: National Glycohemoglobin Standardization Program

OR: Odds ratio

OPG: Orthopantomogram

PDL: Periodontal ligament

PPD.: Periodontal probing depth

RBL: Radiographic bone loss

SD: Standard deviation

WHF: World Heart Federation

DECLARATIONS

Ethics approval and consent to participate

The HUNT4 Survey was approved by the Norwegian Data Protection Authority. Informed consent was obtained from all participants and/or their legal guardians. The current study was performed in accordance with relevant guidelines and regulations and was evaluated and approved by the Norwegian Regional Committees for Medical and Health Research Ethics (2016/1879/REK, 2020/10417/REK, 2021/264485/REK).

Consent for publication

Not applicable

Availability of data and materials

The Trøndelag Health Study (HUNT) has invited persons aged 13-100 years to four surveys between 1984 and 2019. The data are stored in HUNT databank and biological material in HUNT biobank. HUNT Research Centre has permission from the Norwegian Data Inspectorate to store and handle these data. The key identification in the data base is the personal identification number given to all Norwegians at birth or immigration, whilst de-identified data are sent to researchers upon approval of a research protocol by the Regional

Ethical Committee and HUNT Research Centre. To protect participants' privacy, HUNT Research Centre aims to limit storage of data outside HUNT databank and cannot deposit data in open repositories. HUNT databank holds precise information on all data exported to different projects and can reproduce these on request. There are no restrictions regarding data export given approval of applications to HUNT Research Centre. Provided approval from HUNT Research center, sharing of data from the present investigation will be supported by the corresponding author upon reasonable request. For more information see: www.ntnu.edu/hunt/data.

Inquiries regarding access to data is directed to: kontakt@hunt.ntnu.no

https://biobankregisteret.no/#/biobankDetails/4094, project 2020/26788

Competing interests

The authors declare that they have no competing interests

Funding

The Faculty of Dentistry, University of Oslo, Norway and Center for Oral Health Services and Research, Mid-Norway (TkMidt), Trondheim, Norway, supported the study.

Authors' contributions

All authors contributed to the conception of this study. OCK, AV and IHS contributed to data collection. IHS performed the statistical analysis. All authors contributed in data analysis and in interpretation of results. IHS, AV and OCK produced the first draft. HH and AS contributed to critical review and revision of the manuscript. All authors gave final approval of the published version and agreed to be accountable for all aspects of the work.

Acknowledgements

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. Dental health personnel from the public dental health service in the county of Trøndelag, performed the clinical examinations.

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