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ORIGINAL ARTICLE

Relationship between periodontitis and risk of cardiovascular disease: Insights from the Tromsø Study

Natalia Petrenya[1] | **Laila Arnesdatter Hopstock**[2] | **Gro Eirin Holde**[1,3] | **Nils Oscarson**[4] | **Birgitta Jönsson**[1,5]

[1]The Public Dental Health Service Competence Centre of Northern Norway, Tromsø, Norway

[2]Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[3]Department of Clinical Dentistry, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[4]Clinic of Periodontology, The Public Dental Service, Region Västra Götaland, Skövde, Sweden

[5]Department of Periodontology, Institute of Odontology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Correspondence
Natalia Petrenya, The Public Dental Health Service Competence Centre of Northern Norway (TkNN), P.O. Box 2406, Tromsø N-9271, Norway.
Email: natalia.petrenya@tffk.no

Abstract

Background: Few large-scale studies have investigated the association between periodontitis and cardiovascular risk estimated by risk assessment models; moreover, this association remains unexplored in never-smokers. We aimed to examine the relationship between periodontitis and cardiovascular risk in a Norwegian general population, with a focus on never-smokers and the impact of sex and age.

Methods: The present study included 2623 participants from the seventh survey of the Tromsø Study (Tromsø7, 2015–2016), aged 45–74 years, and without previous myocardial infarction or stroke. Periodontitis was defined according to the 2017 American Academy of Periodontology and the European Federation of Periodontology classification system. Participants were categorized by grade based on percentage bone loss/age as no periodontitis/Grade A (low progression rate) and Grade B/C (moderate-rapid progression rate). Low, medium, and high cardiovascular risk was defined based on the Norwegian risk model NORRISK 2. We used ordered logistic regression analysis to examine the association between periodontitis and cardiovascular risk, adjusting for education, toothbrushing frequency, body mass index, and diabetes. Subanalyses included stratification by sex and age (45–54, 55–64, 65–74 years) and a separate analysis of never-smokers.

Results: Periodontitis Grade B/C was associated with higher cardiovascular risk than no periodontitis/Grade A (odds ratio [OR], 2.13; 95% confidence interval [CI], 1.75–2.61). This association was significant in both men and women, all age groups, and never-smokers. However, when never-smokers were stratified by age, the association remained significant only in those aged 65–74 years (OR, 3.00; 95% CI, 1.50–5.99).

Conclusion: Periodontitis Grade B/C was associated with higher cardiovascular risk overall, and in never-smokers aged 65–74 years.

KEYWORDS
alveolar bone loss, cardiovascular disease(s), epidemiology, inflammation, periodontitis, risk factor(s)

1 | INTRODUCTION

Periodontitis is a highly prevalent chronic inflammatory disease that affects the supporting tissues of the teeth in response to bacterial colonization of dental plaque.[1] Severe forms of the disease affect ≈ 11% of the world population.[2] In Norway, ≈ 50% of the population has periodontitis, and 9% has severe periodontitis.[3]

There is an ongoing debate on whether periodontitis is an independent risk factor for cardiovascular disease (CVD) and therefore contributes to increased cardiovascular risk.[4–6] Some potential pathways may include dysregulated host inflammatory response, prolonged activation of the innate immune system, low-grade chronic inflammation, bacteremia, and dissemination of periodontal pathogens to the endothelial cells of blood vessels and atherosclerotic lesions, cross-reaction of antibodies to periodontal pathogens with antigens in cardiovascular tissues, platelet activation, and endothelial dysfunction.[7]

CVD development depends on a combination of risk factors, such as sex, age, smoking, high blood pressure, an adverse lipid profile, diabetes, and family history of CVD; therefore, model-based risk assessment is a useful tool to identify high-risk individuals.[8] There have been minimal study on the extent to which periodontitis progression rate is associated with cardiovascular risk as estimated by risk assessment model. Although an association between periodontitis and high cardiovascular risk has been reported, evidence from large scale epidemiological studies is still scarce.[9–12] It should be pointed out, however, that different populations might not be equally affected by periodontal disease, and cardiovascular risk profiles might also differ. More recent studies are limited to the United States (i.e., the Hispanic/Latino population) and South Korea.[9–11] To the best of our knowledge, only one study (2008) that used cardiovascular risk as estimated by the systematic coronary risk evaluation (SCORE) risk assessment model has been conducted in a European cohort.[12]

Smoking is a strong risk factor for periodontitis[13,14] and is also associated with increased cardiovascular risk.[8] Epidemiological studies on oral health and cardiovascular risk have shown that the confounding effect of smoking cannot be completely addressed, without restricting the study sample to never-smokers.[15,16] Age[17] and sex[18] can modify the relationship between periodontitis and cardiovascular risk; however, evidence of these modifications is limited and inconsistent. Some prospective studies have reported a significant association between periodontitis and CVD only amongst those aged <65 years.[17,19] However, a large cross-sectional study found a stronger association between periodontitis and atherosclerotic CVD in participants >65 years of age.[20] Further, an association between tooth loss and long-term periodontitis has been related to subclinical atherosclerosis in men, but not women.[18]

Hence, the aim of this study was to examine the relationship between periodontitis and cardiovascular risk in a Norwegian general population, with a focus on never-smokers and the impact of sex and age.

2 | MATERIALS AND METHODS

2.1 | Study population

This study was based on data from the population-based Tromsø Study in Norway.[21] The study consists of seven surveys conducted between 1974 and 2016 that have invited total birth cohorts and representative population samples (attendance 65%–79%); the present report used data from the seventh survey (Tromsø7, 2015–2016). All inhabitants aged ≥40 years and residing in the Tromsø municipality were invited to Tromsø7, and 65% attended (N = 21,083, aged 40–99 years, 53% women). Data collection included questionnaires and interviews, as well as clinical examinations and biological sampling performed with standard methods by trained personnel. A random subsample of 3943 Tromsø7 participants also attended a dental examination. The present cross-sectional analysis included 2623 participants aged 45–74 years who had no previous myocardial infarction or stroke, who attended the dental examination, and had information available for classification of periodontitis and for the calculation of NORRISK 2 score.[22] The definition of NORRISK 2 will be explained later. The age range of 45–74 years was chosen because age-specific thresholds to define levels of cardiovascular risk have been developed and validated for that age range. Edentulous participants and participants with less than two teeth were excluded. The flowchart (Figure 1) shows how the final sample was reached.

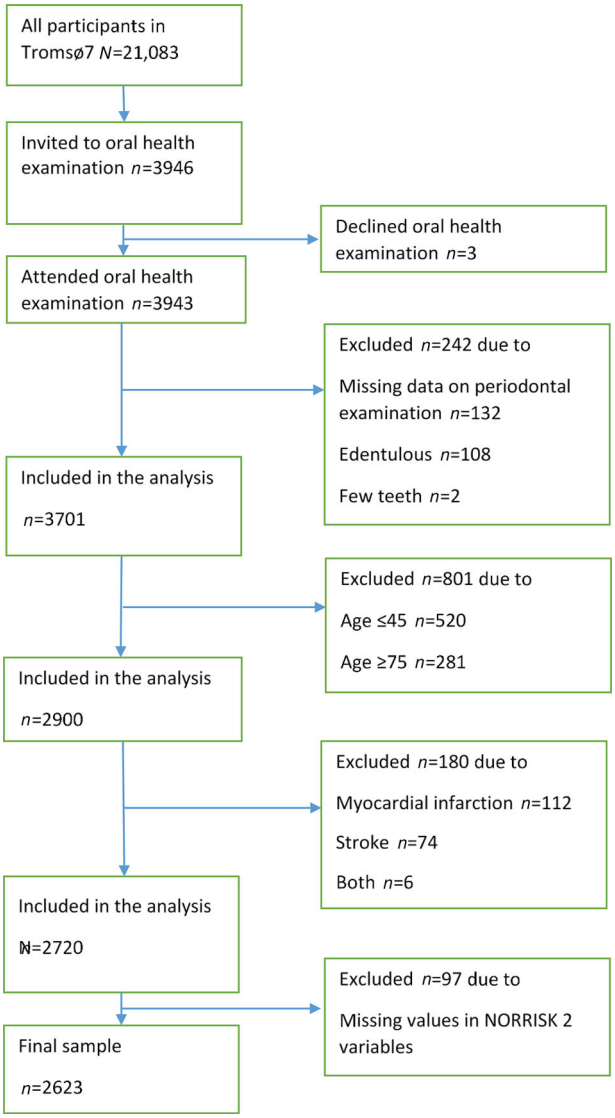

FIGURE 1 Flowchart of the study sample

2.2 | Periodontal assessment, examiner reliability, and case definition of periodontitis

The oral health examination consisted of a clinical and radiographic examination, performed by trained and calibrated dental hygienists. The clinical examination consisted of probing depth (PD), measured to the closest millimeter with a periodontal probe* at four sites per tooth, including all natural teeth, except third molars, and bleeding on probing. An orthopantomogram was used to assess interdental radiographic marginal bone level (RBL). RBL of interproximal surfaces of all teeth, excluding third molars, was measured linearly with a transparent plastic ruler on the orthopantomogram as described by Holde et al.[3] Examiner reliability is described in supplementary material in the online *Journal of Periodontology* under the heading "Examiner reliability".

Case definition of periodontitis was made according to the new American Academy of Periodontology and the European Federation of Periodontology (AAP/EFP) classification system of periodontal diseases and conditions (2017).[23,24] In this study, participants were defined as a periodontitis case if interdental RBL was detectable at ≥2 non-adjacent teeth. Periodontitis cases were further defined by stage, without considering pocket depth and other complexity factors, or grade. Preliminary analyses were performed based on both stage and grade of periodontitis cases. Results of the analyses based on stage, as well as a justification as to why these results were not included in the main results, can be found in online *Journal of Periodontology* under the heading "Analyses based on periodontitis stage" in Table S1 in online *Journal of Periodontology*). In the present article, periodontitis cases were graded A–C, which is an indicator of periodontitis progression. Grade A represents a slow rate of progression, Grade B a moderate rate, and Grade C rapid rate. An indirect estimation of progression was applied by using bone loss as a function of age, that is, radiographic bone loss in percentage of root length divided by the age of the participant.

Two groups were created for the analysis:

- 1) No periodontitis (i.e., individuals with no bone loss or bone loss on one tooth only) or periodontitis Grade A (i.e., individuals with at least two non-adjacent teeth with bone loss, where percentage of bone loss/age is < 0.25)
- 2) Periodontitis Grade B (i.e., individuals with at least two non-adjacent teeth with bone loss, where percentage of bone loss/age is 0.25–1.0) or periodontitis Grade C (i.e., individuals with at least two non-adjacent teeth with bone loss, where percentage of bone loss/age is > 1.0).

We dichotomized the outcome variable rather than using four categories to ensure a sufficient sample size for subgroup analyses and to achieve a more balanced covariate distribution.

Participants were also dichotomized according to the presence of teeth with PD ≥6 mm (no teeth with PD ≥6 mm and ≥1 teeth with PD ≥6 mm).

2.3 | NORRISK 2 assessment

NORRISK 2 is a validated, Norwegian CVD risk prediction model for use in primary prevention,[22] developed to

* UNC15 LM1100-EX, Technomedics Norge, Askim, Norway.

predict acute myocardial infarction and stroke including non-fatal events and death from coronary heart disease (CHD) and stroke. We used the age-specific thresholds for NORRISK 2 risk categories defined by Selmer et al.[22] (45–54 years: low cardiovascular risk < 4.0%, medium cardiovascular risk 4.0–4.9%, high cardiovascular risk ≥5.0%; 55–64 years: low cardiovascular risk < 8.0%, medium cardiovascular risk 8.0–9.9%, high cardiovascular risk ≥10.0%; 65–74 years: low cardiovascular risk < 12.0%, medium cardiovascular risk 12.0–14.9%, high cardiovascular risk ≥15.0%). The risk factors included in the NORRISK 2 score were sex, age, total cholesterol, low high-density lipoprotein (HDL) cholesterol, systolic blood pressure, daily smoking, use of antihypertensives, and family history of premature CHD (first-degree relative with a myocardial infarction before the age of 60 years). NORRISK 2 groups were categorized as low, medium, and high cardiovascular risk.

During the clinical examination, blood pressure was measured* on the right arm of all participants (except in circumstances where this was not possible), three times at 1-min intervals after 2 min seated rest. The mean of the two final readings was used in the analysis. Non-fasting venous blood samples were collected with standard methods, and the samples were analyzed for total and HDL cholesterol within 48 h† at the Department of Laboratory Medicine, University Hospital of North Norway.

Smoking status, use of antihypertensives, and family history of CHD was taken from the Tromsø7 questionnaires. Smoking status was assessed by the question "Do you/did you smoke daily?" (no never, yes now, or yes previously). Use of antihypertensives was assessed by the question "Do you use antihypertensive medication?" (no never, yes now, or yes previously) and by a written list of brand names of regularly used medications, coded by the anatomic, therapeutic, and chemical (ATC) classification system (antihypertensives ATC C02, C03, C07, C08, and C09). Family history of CHD was defined by a question about acute myocardial infarction before the age of 60 years in a first-degree family member (mother, father, child, or sibling). Participants with family history of CHD were classified as having one or at least two family members with family history of premature CHD.

2.4 | High-sensitivity C-reactive protein assessment

High-sensitivity C-reactive protein (hs-CRP) is a marker of systemic inflammation and has been shown to be highly associated with CVD. hs-CRP was measured in blood samples by a particle-enhanced immunoturbidimetric assay§. hs-CRP groups were categorized as low (< 1 mg/L), medium (1-3 mg/L), and high (> 3 mg/L) cardiovascular risk.[25]

2.5 | Covariates

Consistent with previous studies[9,26,27] and existing knowledge, we included education, toothbrushing frequency, body mass index (BMI), and diabetes as covariates in all models. Education was taken from the Tromsø7 questionnaire and categorized as primary/partly secondary (up to 10 years of schooling), upper secondary (minimum of 3 years), and college/university education. Toothbrushing frequency was also taken from the questionnaire and categorized as toothbrushing twice/day or more, or once/day or less. BMI was calculated based on weight and height at the clinical examination (ratio of weight in kilograms and height in meters squared, kg/m^2) and categorized as: underweight/normal weight (< 25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Diabetes was defined by self-reported current diabetes and/or current use of tablets for diabetes and/or insulin and/or HbA1c ≥6.5%. HbA1c was analyzed by high-performance liquid chromatography.‡

The Regional Committee for Medical and Health Research Ethics of Northern Norway (REC North) 10.02.2015 ref.2014/940 approved the Tromsø7 the data collection, including the oral health examination. This study was approved by the Regional Committees for Medical and Health Research Ethics of Northern Norway REC-North; REC-North 05.11.2019 ref.406077, and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. All participants gave written informed consent before participation.

2.6 | Statistical analysis

Characteristics are expressed as numbers (percentages) for categorical variables and as means±SDs for continuous variables. Relationships were tested using *t*-test for continuous variables and Pearson $\chi 2$ test for categorical variables. We estimated the degree to which participants included in the present study were comparable with Tromsø7 participants aged 45–75 years who were eligible for NORRISK 2 estimation but did not attend the oral health examination.

Ordered logistic regression analysis was used to study the association between periodontitis groups and

* Dinamap ProCare 300 monitor, GE Healthcare, Norway.
† Cobas 8000, Roche Diagnostics, Mannheim, Germany.
‡ Tosoh G8, Tosoh Bioscience, San Francisco, CA.

cardiovascular risk, adjusting for education, toothbrushing frequency, BMI category, and diabetes. As the NORRISK 2 score included the risk factors sex, age, and smoking status, these variables were not considered as covariates. The Brant test was used to test that the proportional odds assumption was fulfilled. Results from the ordered logistic regression models are presented as unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Ordered logistic regression models were performed on the total sample, and on men, women, each age group, and never-smokers separately. Regression analysis was also conducted in never-smokers stratified by age group.

Results from ordered logistic regression models are also presented as average marginal effects and 95% CIs. Marginal effects are directly and easily interpretable.[28] The marginal effect represents the difference in the effect of the two groups (no periodontitis/Grade A and Grade B/C) on the change in the probability of having low, medium, and high cardiovascular risk. As the marginal effects of the two groups might be different for men and women, as well as for older and younger participants, the modification effects by sex and age were also presented in the total study sample and in never-smokers.

Ordered logistic regression was also performed in the three hs-CRP groups, adjusting for sex, age, education, smoking status, toothbrushing frequency, BMI category, and diabetes. Models were performed on the same subsamples as for the NORRISK 2 groups. Results are presented as ORs and 95% CIs.

We calculated q-values using the method described by Benjamini and Hochberg (1995) to correct for false discovery rate.[29] The q-values were generally the same as the *p*-values. Therefore, we assumed that multiple testing due to the subgroup analysis did not result in type I error (data not shown).

All analyses were conducted using STATA software.* All tests were two-tailed, and *p*-values < 0.05 were considered to be statistically significant.

3 | RESULTS

The sample characteristics and cardiovascular risk were very similar to the Tromsø7 participants aged 45–75 years, not attending the oral health examination (see Table S2 in online *Journal of Periodontology*).

According to NORRISK 2 groups, 74.8% of participants had low, 11.7% medium, and 13.5% high cardiovascular risk. Regarding periodontitis, 8.3% of the study sample had no periodontitis, 31.6% had Grade A, 58.3% Grade B, and 1.8% Grade C (Table 1).

Those in the periodontitis Grade B/C group had lower mean±SD number of present teeth than the no periodontitis/Grade A group (23.5±5.2 vs. 25.9±4.0, $p < 0.001$, respectively). A significantly higher proportion had deep PD in the periodontitis Grade B/C group than the no periodontitis/Grade A group (21.5% vs. 3.9%, $p < 0.001$, respectively) (Table 1).

Mean age was higher in the periodontitis Grade B/C group. Mean systolic blood pressure was higher ($p < 0.001$) and daily smoking ($p < 0.001$), use of antihypertensives ($p < 0.001$), and having a history of CHD in one ($p = 0.04$) or one or more ($p = 0.01$) relatives was more common in the periodontitis Grade B/C group than the no periodontitis/Grade A group. The distribution of NORRISK 2 groups differed in the periodontitis Grade B/C group (16.6% high, 14.7% medium, 68.8% low cardiovascular risk) and the no periodontitis/Grade A group (9.0% high, 7.3% medium, 83.8% low cardiovascular risk; $p < 0.001$) (Table 1).

The percentage of individuals in the hs-CRP group of high cardiovascular risk was also higher in the periodontitis Grade B/C group (16.6%) than the no periodontitis/Grade A group (11.9%) ($p < 0.001$) (Table 1).

Periodontitis groups in relationship to risk factors included in NORRISK 2 score, NORRISK 2 groups, and hs-CRP groups separately in men and women are presented in Table 2.

The distribution of grade of periodontitis by NORRISK 2 group in all never-smokers and in never-smokers stratified by age is shown in Tables S3 and S4 in online *Journal of Periodontology*.

3.1 | Regression models between periodontitis and NORRISK 2 groups

In regression models, periodontitis Grade B/C was associated with higher cardiovascular risk than no periodontitis/Grade A (OR, 2.13; 95% CI, 1.75–2.61). The result was significant in men (OR, 1.81; 95% CI, 1.42–2.30), women (OR, 3.95; 95% CI, 2.43–6.43), and when the sample was restricted to never-smokers (41.6%) (OR, 2.17; 95% CI, 1.58–2.99) (Table 3).

When stratifying by age group, the association remained significant for participants aged 45–54 (OR, 1.67; 95% CI, 1.20–2.34), 55–64 (OR 1.81, 95% CI 1.29–2.54), and 65–74 years (OR, 2.03; 95% CI, 1.32–3.13) (Table 3). However, when never-smokers were stratified by age, the association remained significant only in participants aged 65–74 years (OR, 3.00; 95% CI, 1.50–5.99); no significant association was found for never-smokers aged 45–54 years (OR, 1.19; 95% CI 0.65–2.20) or 55–64 years (OR, 1.55; 95% CI, 0.92–2.62) (Table 3).

* StataCorp version 16.0, College Station, TX.

TABLE 1 Full study sample and periodontitis groups in relation to sociodemographic, behavioral, and clinical characteristics, the Tromsø Study 2015–2016

Characteristics	Full sample *n* = 2623 (100.0%)	No periodontitis/ Grade A *n* = 1047 (39.9%)	Periodontitis Grade B/C *n* = 1576 (60.1%)	*p*-value*
Sex				
Women	1393 (53.1)	589 (56.3)	804 (51.0)	0.008
Age (years)	57.8 (8.1)	54.8 (7.3)	59.9 (8.0)	0.003
Age group (years)				
45–54	1042 (39.7)	579 (55.3)	463 (29.4)	<0.001
55–64	926 (35.3)	334 (31.9)	592 (37.6)	
65–74	655 (25.0)	134 (12.8)	521 (33.1)	
Education				
Primary/partly secondary education	596 (22.9)	171 (16.4)	425 (27.3)	<0.001
Upper secondary education	797 (30.6)	307 (29.4)	490 (31.5)	
University	1208 (46.4)	565 (54.2)	643 (41.3)	
Smoking status				
Never	1092 (41.6)	569 (54.3)	523 (33.2)	<0.001
Former	1163 (44.3)	387 (37.0)	776 (49.2)	
Current	368 (14.0)	91 (8.7)	277 (17.6)	
Toothbrushing frequency				
1 time/day or less often	498 (19.0)	163 (15.6)	335 (21.3)	<0.001
BMI (kg/m^2)	27.3 (4.5)	27.1 (4.4)	27.5 (4.5)	0.07
BMI category				
Underweight/normal weight	833 (31.8)	349 (33.4)	484 (30.7)	0.361
Overweight	1150 (43.9)	449 (43.0)	701 (44.5)	
Obesity	636 (24.3)	247 (23.6)	389 (24.7)	
Diabetes				
Yes	149 (5.7)	54 (5.2)	95 (6.0)	0.346
No. of present teeth	24.4 (4.9)	25.9 (4.0)	23.5 (5.2)	<0.001
PD ≥6 mm on ≥1 teeth	380 (14.5)	41 (3.9)	339 (21.5)	<0.001
Grade of periodontitis				
No periodontitis	219 (8.3)	–	–	
Periodontitis Grade A	828 (31.6)	–	–	
Periodontitis Grade B	1529 (58.3)	–	–	
Periodontitis Grade C	47 (1.8)	–	–	
Risk factors included in NORRISK 2 score				
Total cholesterol (mmol/L)	5.6 (1.0)	5.6 (1.0)	5.6 (1.1)	0.71
Low HDL-C (men < 1.0 mmol/L; women < 1.3 mmol/L)	342 (13.0)	134 (12.8)	208 (13.2)	0.77
Systolic blood pressure (mm Hg)	130.5 (19.3)	128.0 (0.6)	132.2 (0.5)	<0.001
Daily smoking	368 (14.0)	91 (8.7)	277 (17.6)	<0.001
Use of antihypertensives	594 (22.7)	177 (16.9)	417 (26.5)	<0.001
Family history of CHD: one relative[a]	525 (20.0)	189 (18.1)	336 (21.3)	0.04
Family history of CHD: at least two relatives[a]	94 (3.6)	31 (3.0)	63 (4.0)	0.16
Combined family history of CHD: one or at least two relatives[a]	619 (23.6)	220 (21.0)	399 (25.3)	0.01

(Continues)

TABLE 1 (Continued)

Characteristics	Full sample $n = 2623$ (100.0%)	No periodontitis/ Grade A $n = 1047$ (39.9%)	Periodontitis Grade B/C $n = 1576$ (60.1%)	p-value*
NORRISK 2 groups				
Low cardiovascular risk	1961 (74.8)	877 (83.8)	1084 (68.8)	<0.001
Medium cardiovascular risk	307 (11.7)	76 (7.3)	231 (14.7)	
High cardiovascular risk	355 (13.5)	94 (9.0)	261 (16.6)	
hs-CRP groups				
Low cardiovascular risk (< 1 mg/L)	1312 (50.0)	587 (56.1)	725 (46.0)	<0.001
Medium cardiovascular risk (1-3 mg/L)	925 (35.3)	335 (32.0)	590 (37.4)	
High cardiovascular risk (> 3 mg/L)	386 (14.7)	125 (11.9)	261 (16.6)	

Values are numbers (percentages) for categorical variables and mean (SD) for continuous variables.

*p-values were tested using t-test for continuous variables and Pearson $\chi 2$ test for categorical variables between two periodontitis groups.

[a]First degree family member having suffered an acute myocardial infarction before the age of 60 years.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; PD, probing depth.

Note: No periodontitis/Grade A and Grade B/C classified according to AAP/EFP case definition.

3.2 | Average marginal effects and modification effect by sex and age

The average marginal effects of periodontitis groups on NORRISK 2 groups in the full study sample and by subgroup are presented in Table S5 in online *Journal of Periodontology*.

On average, never-smokers aged 65–74 years with periodontitis Grade B/C were 20.7% less likely than participants with no periodontitis/Grade A to have low, 8.4% more likely to have medium, and 12.3% more likely to have high cardiovascular risk ($p < 0.01$) (see Table S5 in online *Journal of Periodontology*).

In the total sample, men with periodontitis Grade B/C were 5.1% more likely to be in the NORRISK 2 group of high cardiovascular risk than women ($p = 0.01$). However, average marginal effects in never-smokers did not differ by sex. Age effects were observed in never-smokers. Those with periodontitis Grade B/C aged 65–74 years were 10.7% more likely to have high cardiovascular risk than those aged 45–54 years ($p = 0.004$) (see Table S6 in online *Journal of Periodontology*).

3.3 | Regression models between periodontitis and hs-CRP groups

Periodontitis Grade B/C was associated with increased hs-CRP group of cardiovascular risk (OR, 1.30; 95% CI, 1.10–1.54) independent of sex, age, education, toothbrushing frequency, smoking status, BMI category, and diabetes, also in never-smokers (see Table S7 in online *Journal of Periodontology*).

4 | DISCUSSION

The aim of this study was to examine the relationship between periodontitis and cardiovascular risk in a Norwegian general population, with a focus on never-smokers and the impact of sex and age. We found a positive association between periodontitis Grade B/C and higher cardiovascular risk in the total sample, in both men and women, in the three age groups, and in never-smokers. The subanalysis of never-smokers allowed us to eliminate the confounding effect of smoking. In the age-stratified analysis of never-smokers, periodontitis Grade B/C was positively associated with cardiovascular risk only in participants aged 65–74 years.

Our findings support previous research regarding the positive link between periodontitis and high risk for acute cardiovascular events.[30–33] However, it is difficult to compare studies on periodontitis and cardiovascular risk because of large variations in methodology and differences in the definitions of periodontitis. We defined periodontitis based on the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, which is the most recent classification.[24,34–36] Percentage of bone loss/age was used to estimate grade of periodontitis based on orthopantomogram. PD reflects current exposure to periodontal inflammation. Successful treatment commonly results in the elimination or reduction of periodontal pockets; however, alveolar bone loss is continuous over time and is irreversible. Alveolar bone loss could reflect a history of periodontitis, rather than inflammatory activity. However, the periodontitis Grade B/C group in our analysis had significantly fewer teeth and higher presence of deep PD, indicating a higher inflammatory

TABLE 2 Periodontitis groups in relation to risk factors included in NORRISK 2 score, NORRISK 2 groups, and hs-CRP groups in men and women, the Tromsø Study 2015–2016

	Men			Women		
Cardiovascular risk	**No periodontitis/ Grade A**	**Periodontitis Grade B/C**	***p*-value***	**No periodontitis/ Grade A**	**Periodontitis Grade B/C**	***p*-value***
Risk factors included in NORRISK 2 score						
Total cholesterol (mmol/L)	5.6 (1.0)	5.5 (1.1)	0.03	5.7 (1.0)	5.8 (1.0)	0.003
Low HDL-C (men < 1.0 mmol/L; women < 1.3 mmol/L)	51 (11.1)	90 (11.7)	0.78	83 (14.1)	118 (14.7)	0.76
Systolic blood pressure (mm Hg)	130.9 (16.9)	135.2 (18.7)	<0.001	125.7 (19.3)	129.4 (20.2)	0.001
Daily smoking	34 (7.4)	117 (15.2)	<0.001	57 (9.7)	160 (19.9)	<0.001
Use of antihypertensives	75 (16.4)	218 (28.2)	0.001	102 (17.3)	199 (24.8)	<0.001
Family history of CHD: one relative[a]	86 (18.8)	168 (21.8)	0.21	103 (17.5)	168 (20.9)	0.11
Family history of CHD: at least two relatives[a]	13 (2.8)	23 (3.0)	0.89	18 (3.1)	40 (5.0)	0.08
Combined family history of CHD: one or at least two relatives[a]	99 (21.6)	191 (24.7)	0.21	121 (20.5)	208 (25.9)	0.021
NORRISK-2 groups						
Low cardiovascular risk	309 (67.5)	391 (50.6)	<0.001	568 (96.4)	693 (86.2)	<0.001
Medium cardiovascular risk	67 (14.6)	171 (22.2)		9 (1.5)	60 (7.5)	
High cardiovascular risk	82 (17.9)	210 (27.2)		12 (2.0)	51 (6.3)	
hs-CRP groups						
Low cardiovascular risk (< 1 mg/L)	262 (57.2)	343 (44.4)	<0.001	325 (55.2)	382 (47.5)	0.018
Medium cardiovascular risk (1-3 mg/L)	149 (32.5)	297 (38.5)		186 (31.6)	293 (36.4)	
High cardiovascular risk (> 3 mg/L)	47 (10.3)	132 (17.1)		78 (13.2)	129 (16.0)	

Values are numbers (percentages) for categorical variables and mean (SD) for continuous variables.

*p-values were tested using t-test for continuous variables and Pearson $\chi 2$ test for categorical variables between two periodontitis groups.

[a]First degree family member having suffered an acute myocardial infarction before the age of 60 years.

Abbreviations: CHD, coronary heart disease; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein.

Note: No periodontitis/Grade A and Grade B/C classified according to AAP/EFP case definition.

activity compared with the participants in the no periodontitis/Grade A group.

Stages of periodontitis provide information of periodontitis severity, which may be associated with cardiovascular risk. Therefore, in addition to grade, we classified participants according to stage. However, because of the methodological challenges in implementation analyses based on stage in the present study, these results are shown in Table S1 in online *Journal of Periodontology*. Overall, in all age groups and in never smokers, we observed that the severity of periodontitis was associated with a higher cardiovascular risk.

Different mechanisms have been suggested to explain how periodontitis influences CVD: a direct invasion of periodontal pathogens into the host cell cytoplasm,[37] for example, into endothelial cells, and an indirect mechanism by which periodontitis contributes to a systemic inflammatory response which results in chronically elevated levels of different pro-inflammatory cytokines and intravascular plasma proteins such as CRP and fibrinogen. Slightly increased CRP concentration over time, also known as low-grade inflammation,[38] is associated with an increased risk of CVD. In the present study, the percentage of individuals with hs-CRP concentrations > 3 mg/L, which is proposed to be related to high cardiovascular risk,[39] was also higher in participants with periodontitis Grade B/C. Moreover, in parallel with NORRISK2 groups, periodontitis Grade B/C was also positively related to hs-CRP groups of cardiovascular risk, also in never-smokers. These findings suggest that the inflammation of the peri-

JOURNAL OF Periodontology

TABLE 3 Regression models of periodontitis groups and NORRISK 2 groups in the full study sample and by subgroup, the Tromsø Study 2015-2016

	Univariate model			Fully adjusted model		
Subgroup	**OR**	**(95% CI)**	***p*-value**	**OR**	**(95% CI)**	***p*-value**[a]
Full sample						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	2.30	(1.89, 2.79)	<0.001	2.13	(1.75, 2.61)	<0.001
Men						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	1.94	(1.53, 2.45)	<0.001	1.81	(1.42, 2.30)	<0.001
Women						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	4.30	(2.66, 6.94)	<0.001	3.95	(2.43, 6.43)	<0.001
Aged 45–54 years						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	1.84	(1.33, 2.53)	<0.001	1.67	(1.20, 2.34)	0.003
Aged 55–64 years						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	2.01	(1.45, 2.80)	<0.001	1.81	(1.29, 2.54)	0.001
Aged 65–74 years						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	2.03	(1.32, 3.10)	0.001	2.03	(1.32, 3.13)	0.001
Never-smokers						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	2.41	(1.76, 3.30)	<0.001	2.17	(1.58, 2.99)	<0.001
Never-smokers 45–54 years						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	1.46	(0.81, 2.63)	0.205	1.19	(0.65, 2.20)	0.570
Never-smokers 55–64 years						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	1.68	(1.01, 2.81)	0.048	1.55	(0.92, 2.62)	0.103
Never-smokers 65–74 years						
No periodontitis/Grade A	ref			ref		
Periodontitis Grade B/C	3.05	(1.54, 6.05)	0.001	3.00	(1.50, 5.99)	0.002

[a]Models were adjusted for education, toothbrushing frequency, BMI categories, and diabetes.

Abbreviations: CI, confidence interval;OR, odds ratio.

Note: No periodontitis/Grade A and Grade B/C classified according to AAP/EFP case definition.

odontium and the systemic inflammation pathway may be related to increased cardiovascular risk in participants with greater alveolar bone loss. A previous longitudinal study from the Tromsø Study showed that CRP may be linked to CVD; however, not through the mechanism of promoting formation and progression of atherosclerotic plaque.[40]

A causal relationship between periodontitis and CVD is debated, in part because of the confounding effect of shared risk factors, especially smoking. The results of our study contribute to the knowledge of an association between periodontitis and cardiovascular risk in never-smokers. It is well known that smoking has a significant impact on periodontitis; smoking alone may account up to 50% of cases.[13,14] In the present study, smoking status included the categories of current, former, and never-smoker. Characteristics of former smokers, such as time since quitting, age at quitting, and smoking pattern influence both periodontitis and cardiovascular risk, and are difficult to adjust for. Thus, we performed analyses restricted to never-smokers to control for the effect of smoking. We found that periodontitis Grade B/C was associated with higher cardiovascular risk in never-smokers aged 65–74 years; thus, the association was not

explained by confounding due to smoking in this age group. In general, periodontal disease progresses slowly. In the present study, younger participants, although they may have extended inflammation, most likely have not lost as much bone as older participants. There were few participants with periodontitis Grade B/C and medium to high cardiovascular risk amongst never-smokers aged 45–54 years (data are shown in Table S3 in online *Journal of Periodontology*). This may partly explain why the association between Grade B/C and cardiovascular risk was not significant amongst younger never-smokers. Even though smoking is probably the strongest modifiable risk factor for periodontitis, many lifestyle factors can influence both periodontitis and cardiovascular risk. Indeed, unknown or known factors that are difficult to adjust for, such as behavioral factors like diet, may also explain the association we observed.

Our findings of a positive association between periodontitis Grade B/C and high cardiovascular risk as estimated by risk assessment model are consistent with previous, large population-based studies.[9–12] More recent studies from the United States (Hispanic/Latino population groups)[9] and South Korea[10,11] have applied the Framingham general CVD risk score, developed in 2008, which predicts the 10-year risk of general CVD[41] and has been widely used in epidemiological studies.[42,43] NORRISK 2 estimates 10-year risk of fatal and non-fatal cardiovascular events and is based on the European SCORE risk scoring tool.[44] NORRISK 2 has been validated in a Norwegian cohort; and thus has an advantage over other models.[22]

A Mendelian randomization study recently reported that periodontitis is linked to hypertension.[45] In the present study, mean systolic blood pressure and the prevalence of use of antihypertensives were higher in the periodontitis Grade B/C group than those in the no periodontitis/Grade A group. Indeed, periodontitis and cardiovascular risk may be associated through a similar, underlying genetic predisposition.[46] The correlation between periodontitis, cardiovascular risk, and genetic susceptibility is complex. A link between family history of myocardial infarction and increased risk of periodontal disease has been reported by Yu et al.[47] In the present study, significantly more participants in the periodontitis Grade B/C group had a family history of CHD. The Framingham general CVD risk score includes the factors sex, age, systolic blood pressure; use of antihypertensives, total cholesterol, HDL cholesterol levels, smoking, and diabetes status; however, this score is limited by its lack of inclusion of family history of premature CHD. This research contributes to knowledge of a possible link between genetic factors associated with high cardiovascular risk and periodontitis.

The major strength of our study is the possibility to examine relationships between grade of periodontitis and levels of cardiovascular risk based on a reliable and valid model with age-specific thresholds in a large, homogeneous, population-based sample. The Tromsø Study data collection is performed by trained personnel using standardized protocols and validated methods and instruments. We estimated the inflammatory condition of the periodontium using PD, and systemic inflammation using hs-CRP concentrations in relation to periodontitis progression rate groups. Full-mouth periodontal examination protocols and radiographs have been considered to be reliable to study periodontitis in large epidemiological studies when clinical attachment level is not assessed. We examined the potential confounding effect of smoking by running subanalyses restricted to never-smokers. Our study sample was a subsample of the Tromsø7 sample, and the extent to which our results may be generalized to that entire sample is important. The study sample was similar to the Tromsø7 participants who did not attend the oral health examination with respect to sample characteristics and CVD risk. We used ordered logistic regression (proportional odds model) analysis to examine the effects of periodontitis Grade B/C on all cardiovascular risk groups. Ordered logistic regression has an advantage over dichotomization of the ordinal scale.[48] The average marginal effects and the impact of sex and age on these effects are presented in Tables S5 and S6 in online *Journal of Periodontology*, as they are useful for interpreting regression estimates.

The limitations of this study include the cross-sectional nature of the data, meaning we were unable to determine any causal relationship between periodontitis and cardiovascular risk. The possibility of selection bias and bias due to self-reporting should also be considered. People with disability pensions, and with mental and abuse disorders are more likely to have poor oral health and are usually underrepresented in health surveys.[49] A similar population-based study in Norway reported that nonparticipants had lower socioeconomic status, higher mortality, and showed higher prevalence of several chronic diseases, that is, CVD, diabetes, and psychiatric disorders.[50] Even though we applied several methods to account for confounding, such as adjustment and subgroup analyses, we cannot exclude the possibility that the observed association is due to residual confounding related to controlled and unknown factors.

5 | CONCLUSIONS

Periodontitis Grade B/C was associated with higher cardiovascular risk overall, and this association was not

explained by confounding due to smoking in participants aged 65–74 years. The use of NORRISK 2 score for cardiovascular risk assessment should be recommended for patients with periodontitis, especially those with extensive alveolar bone loss. Individuals with a high cardiovascular risk profile should attend regular periodontal check-ups. In addition to adequate, evidence based periodontal treatment, smoking cessation and normalization of blood pressure are important to reduce cardiovascular risk in individuals with periodontitis.

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AUTHOR CONTRIBUTIONS AND CONFLICTS OF INTEREST

Natalia Petrenya was responsible for study conception and design, statistical analyses, data interpretation, and the drafted manuscript; Birgitta Jönsson is a chief investigator for this project, contributed to data collection, study conception and design, data interpretation, the discussion of the data, and critical revision of the manuscript; Laila Arnesdatter Hopstock contributed to the study conception and design, data interpretation, the discussion of the data, and critically reviewed the manuscript; Gro Eirin Holde was responsible for creation of periodontal variables and definition of periodontitis, contributed to data interpretation, and critical revision of the manuscript; and Nils Oscarson was responsible for oral health data collection in Tromsø7, contributed to the study conception and design, and critically reviewed the manuscript. All authors gave final approval and agreed to be accountable for all aspects of this work to ensure integrity and accuracy. The authors declare that they have no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

This research uses data from the seventh survey of the Tromsø Study. The dataset generated and analyzed during the current study is not publicly available. Data are available upon application to the Tromsø Study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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