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Periodontitis is associated with decreased experimental pressure pain tolerance: The Tromsø Study 2015–2016

Elin Hadler-Olsen[1,2] | Natalia Petrenya[1] | Birgitta Jönsson[1,3] | Ólöf Anna Steingrímsdóttir[4,5] | Audun Stubhaug[6,7] | Christopher Sivert Nielsen[6,8]

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

[2]Department of Medical Biology, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

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

[4]Department of Physical Health and Ageing, Norwegian Institute of Public Health, Oslo, Norway

[5]Depertment of Research, Oral Health Centre of Expertise in Eastern Norway (OHCE-E), Oslo, Norway

[6]Department of Pain Management and Research, Oslo University Hospital, Oslo, Norway

[7]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[8]Department of Chronic Diseases, Norwegian Institute of Public Health, Oslo, Norway

Correspondence
Elin Hadler-Olsen, The Public Dental Health Competence Center of Northern Norway, Tromsø, Norway.
Email: elin.hadlerolsen@tromsfylke.no

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Abstract

Aim: To assess the relationship between periodontitis and experimental pain tolerance.

Materials and Methods: Participants from the population-based seventh survey of the Tromsø Study with data on periodontitis were included ($n = 3666$, 40–84 years old, 51.6% women). Pain tolerance was assessed through (i) pressure pain tolerance (PPT) test with a computerized cuff pressure algometry on the leg, and (ii) cold-pressor tolerance (CPT) test where one hand was placed in circulating 3°C water. Cox proportional hazard regression was used to assess the association between periodontitis and pain tolerance adjusted for age, sex, education, smoking and obesity.

Results: In the fully adjusted model using the 2012 Centers for Disease Control/American Academy of Periodntology case definitions for surveillance of periodontitis, moderate (hazard ratio [HR] = 1.09; 95% confidence interval [CI]: 1.01, 1.18) and severe (HR = 1.25, 95% CI: 1.11, 1.42) periodontitis were associated with decreased PPT. Using the 2018 classification of periodontitis, having Stage II/III/IV periodontitis was significantly associated with decreased PPT (HR = 1.09; 95% CI: 1.01, 1.18) compared with having no or stage I periodontitis. There were no significant associations between periodontitis and CPT in fully adjusted models.

Conclusions: Moderate and severe periodontitis was associated with experimental PPT.

KEYWORDS

cold-pressor test, experimental pain tolerance, inflammation, periodontitis, pressure pain test

Clinical Relevance

Scientific rationale for study: Pain tolerance is associated with subjective symptoms of pain and chronic pain conditions. As inflammation can affect pain tolerance, the aim of this study was to assess the association between periodontitis and pain tolerance.

Principal findings: Periodontitis was associated with reduced experimental pain tolerance.

Practical implications: Chronic pain affects about 30% of adults and has huge personal and societal costs. Periodontitis is a prevalent disease that can be treated and kept at bay by meticulous oral hygiene and supportive therapy. Thus, its association with pain tolerance and pain syndromes may have significant clinical relevance.

1 | INTRODUCTION

Chronic pain is a major health problem that causes considerable suffering and reduced quality of life for those affected. It is also a source of huge societal costs through health care expenses, sick leave, early retirement and loss of productivity (Gustavsson et al., 2012). Chronic pain conditions, including fibromyalgia and temporomandibular disorders, have been associated with decreased experimental pain tolerance across body sites, indicating generalized hyperalgesia (Greenspan et al., 2013; Jensen et al., 2009). An increasing body of evidence points to an association between hyperalgesia and chronic inflammation. Elevated levels of pro-inflammatory cytokines have been associated with chronic pain syndromes (DeVon et al., 2014). Furthermore, higher levels of the inflammation marker C-reactive protein (CRP) have been associated with reduced experimental pain tolerance (Schistad et al., 2017), whereas anti-inflammatory mediators have been associated with higher experimental pain tolerance (Iordanova Schistad et al., 2020; Svensson et al., 2007). The mechanisms linking inflammation and pain perception are complex and not fully understood. At the local site of injury or infection, inflammatory cells such as mast cells, macrophages and neutrophils release substances that can bind to receptors on nociceptive nerve endings and cause sensitization. Such injury or infection further activates postsynaptic neurons and glial cells, which may induce central sensitization and a more generalized hyperalgesia (Ren & Dubner, 2010). Experimentally, inflammation induced by lipopolysaccharide (LPS) was shown to increase pressure pain sensitivity and decrease the brain's descending pain-inhibitory pathways (Karshikoff et al., 2016).

Periodontitis is a common chronic disease where periodontal bacteria and the inflammatory host response cause progressive degradation of the tooth-supportive tissues, with tooth loss as the most severe end result (Kinane et al., 2017). The bacteria associated with periodontitis are mainly Gram negative, and both the bacteria and their toxins may enter the circulation through bleeding periodontal pockets and cause endotoxemia (Geerts et al., 2002; Pussinen et al., 2004). Periodontitis is associated with increased concentrations of non-specific inflammatory markers, including CRP (Machado et al., 2021), and the severity of periodontitis has been found to correlate positively with plasma LPS activity and level of CRP (Kallio et al., 2008). This suggests that local inflammation and infection in the gums can induce systemic inflammation. Slightly elevated levels of CRP, commonly in the range of 3–10 mg/L, are often termed low-grade inflammation (Kushner et al., 2010) and have been associated with several other chronic conditions including rheumatoid arthritis, diabetes and hypertension (Pedrinelli et al., 2004; Saltevo et al., 2009; Shrivastava et al., 2015) as well as with decreased pain tolerance (Schistad et al., 2017). Based on previous findings of an association between chronic inflammation and hyperalgesia, we hypothesize that periodontitis is associated with lower experimental pain tolerance. Thus, the aim of the present study was to explore this hypothesis while controlling for possible confounding factors that can be associated with both periodontitis and pain tolerance.

2 | MATERIALS AND METHODS

2.1 | Study design and population

We used cross-sectional data from the seventh survey of the Tromsø Study (Tromsø7), a population-based study conducted in 2015–2016 (Hopstock et al., 2022). All inhabitants 40 years or older in Tromsø municipality in Norway were invited, and 21,083 (65%) participated. The study was conducted in accordance with the Declaration of Helsinki with informed, written consent from all participants. The Regional Committee for Health Research Ethics approved the study (REK320778). The participants answered questionnaires assessing sociodemographic-, lifestyle- and health-related variables. They also underwent clinical examinations, including height and weight measurements and pain tolerance tests, and blood samples were drawn. A random selection ($n = 3946$) of those attending the study were offered a dental examination, and all but three accepted ($n = 3943$). The dental examination included recording of pocket depth (PD) and one panoramic radiograph. Edentulous participants and participants with only one remaining tooth were excluded ($n = 108$) as well as participants lacking data on PD or radiographic bone level ($n = 144$). We also excluded participants with periodontal data who were 85 years or older ($n = 25$) because of a low attendance rate (<25%) in this group. The final study sample included 3666 participants with periodontal status, of whom 3415 had been tested for pressure pain tolerance (PPT) and 3283 had been tested for cold-pressor tolerance (CPT) (Figure 1).

2.2 | Periodontal assessment and periodontal case definition

Six dental hygienists measured periodontal probing depths to the closest millimetre, with a periodontal probe (UNC15 LM1100-EX, Technomedics Norge, Askim, Norway) at four sites per tooth. All natural teeth except third molars were examined. The hygienists were trained by an experienced periodontist prior to the study. The calibration and examiner reliability have been described previously (Petrenya et al., 2022).

The severity of periodontitis was assessed according to a modified version of the joint EU/USA periodontal epidemiology working group's standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies (named CDC/AAP classification in the following) (Eke et al., 2012; Holtfreter et al., 2015), which is based on clinical attachment level (CAL) and PD. As the CAL was not measured, CAL was estimated based on radiographic bone loss (RBL) as per Holde et al. (2017). The three examiners performing the radiographic measurements underwent calibration for the procedure twice with 3-month intervals as previously described (Petrenya et al., 2022). We also re-classified periodontitis based on the 2018 AAP/EFP classification of periodontal and peri-implant diseases and conditions (named 2018 classification in the following) (Caton et al., 2018) to assess whether the association between periodontitis and pain tolerance varied with classification criteria. We used RBL and PD to define

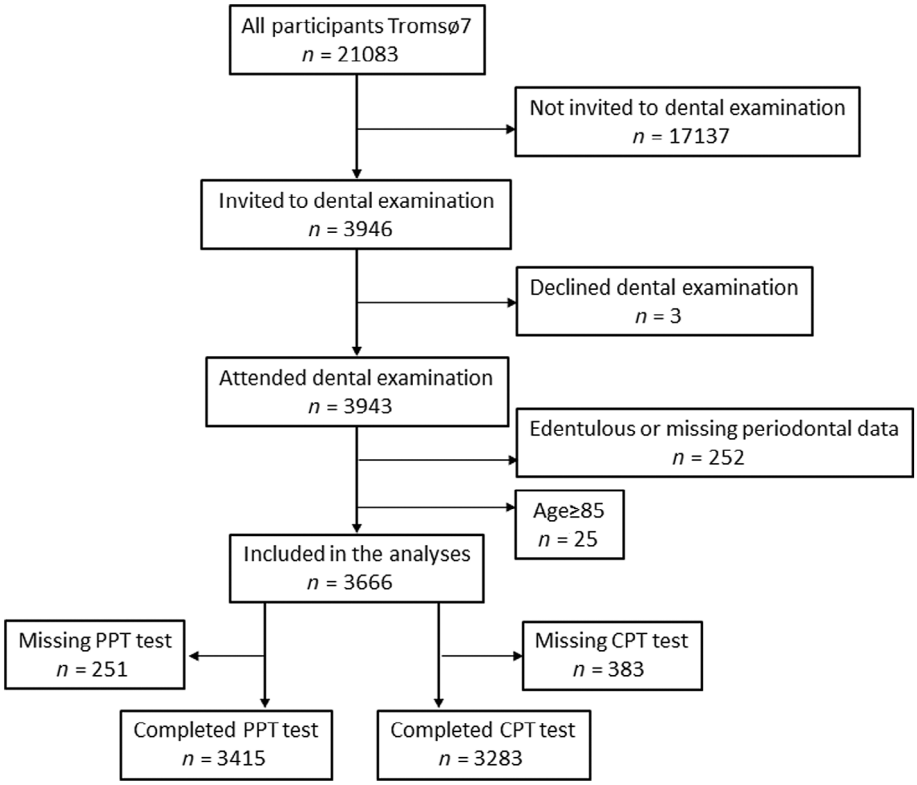

FIGURE 1 Flow chart of the participants included in the study. CPT, cold-pressor tolerance; PPT, pressure pain tolerance.

the stage of periodontitis. The criteria used for both the CDC/AAP and the 2018 classification are described in the Supplementary File Method section. We also assessed the extent of periodontitis, where persons with periodontitis, involving less than 30% of the remaining teeth, irrespective of stage, were defined as having localized disease and those where the disease involved 30% or more of the teeth, irrespective of stage, were said to have generalized disease.

2.3 | Pain tolerance testing

2.3.1 | Pressure pain tolerance

PPT was assessed on the calf by computerized cuff algometry (NociTech, Aalborg, Denmark) (Jespersen et al., 2007), starting the procedure on the non-dominant leg, followed by a test on the opposite leg. A blood pressure cuff was placed around each calf and inflated by 1 kPa/s up to a maximum safety limit of 100 kPa. The participant was instructed to endure the pain as long as possible and press a button if the pain became unbearable, at which point the cuff deflated immediately. Pain tolerance was defined as the maximum pressure endured if the button was pressed, or right censored if the 100 kPa limit was reached. As the pressure increased with 1 kPa/s, the PPT in kPa equals the time to abortion of test in seconds. Participants were asked whether there were any reasons why they should not perform the test, including having open sores, problems with peripheral circulation or hyperalgesia. Only those who stated no reason, were able to understand the instructions and were willing to take the test were included.

The PPT of the two legs was highly correlated (two-way mixed model, intra-class correlation coefficient = 0.92, 95% confidence interval: 0.921, 0.925, absolute agreement). Due to right censoring, averaging the two tests is not indicated and the first test (non-dominant side) with least missing values was therefore used in the analyses.

2.3.2 | Cold-pressor tolerance (CPT)

The cold pressor consisted of a 13-L Plexiglas container with 3°C water. The water temperature was maintained by continuous exchange with a circulating cooling water bath (Julabo PF40-HE, JULABO Labortechnik, GmbH, Germany). The participants were instructed to submerge the hand and wrist of their non-dominant hand in the water for as long as they could stand, to a maximum of 120 seconds. Participants were asked whether there were any reasons why they should not perform the test, including Raynaud syndrome or cold allergy if the participant thought it would affect their performance, bilateral loss of sensation in the hands or breached skin affecting both hands. Only those who stated no reason, were able to understand the instructions and were willing to take the test were included. Pain tolerance was operationalized as time to hand withdrawal in seconds if less than 120 s, and right censored if not.

2.4 | C-reactive protein

Non-fasting blood samples were drawn from all participants and analysed at the Department of Laboratory Medicine, University Hospital

of North Norway, Tromsø, Norway. High-sensitivity (hs) CRP was assessed by a particle-enhanced immunoturbidimetric assay on a Modular P autoanalyzer (Roche Diagnostics, Mannheim, Germany). Reagents were from the manufacturer and the detection limit was 0.12 mg/L.

2.5 | Body mass index

Body height and weight were measured on an electronic scale (Jenix DS-102 scale, DongSahn Jenix, Seol, Korea) with the participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in metres (kg/m^2). BMI was dichotomized into (1) non-obese (BMI < 30) and (2) obese (BMI ≥ 30) (Weir & Jan, 2022).

2.6 | Background characteristics and smoking status

Information on age and sex was obtained from the National Population Register. Age was categorized into three age groups: (1) 40–49 years, (2) 50–59 years and (3) 60–84 years. The highest level of education was recorded from a questionnaire with the following options: (1) primary (up to 10 years), (2) upper secondary (minimum 3 years), (3) tertiary, short (college/university less than 4 years) and (4) tertiary long (college/university 4 years or more). In the statistical analyses, the response options were dichotomized into (1) no college/university education and (2) college/university education. Smoking status was recorded as current, former or never smoker.

2.7 | Statistical analyses

We used the Statistical Package for Social Sciences (SPSS) for Windows version 28 (IMB corporation, Armonk, NY USA) for statistical analyses. Differences between groups were assessed by cross tabulation for categorical variables. CPT was dichotomized into (1) did not abort the test and (2) aborted the test prior to 120 s for cross-tabulation analyses, and PPT was dichotomized into (1) did not abort the test and (2) aborted the test prior to 100 kPa (seconds). Median hs-CRP with interquartile range was calculated, and differences between groups were analysed by Kruskal–Wallis tests.

We used Cox proportional hazard regression (forced entry) to assess the association between periodontitis and pain tolerance with hazard ratios (HRs) and 95% confidence intervals (CIs) presented. In the analyses, we merged the 'no periodontitis' and 'mild periodontitis" groups as they had similar levels of the inflammation marker hs-CRP (Table 1). In additional regression analyses, we used periodontitis re-classified according to the 2018 classification. Here we merged the no periodontitis and the Stage I periodontitis groups. To increase statistical power, we also ran additional analyses where we merged the Stage II and the Stage III/IV periodontitis groups as they showed almost identical effect (HR) on pain tolerance. PPT and CPT were used as continuous variables indicating time to test abortion, where abortion of the tests prior to 100 kPa (seconds) or 120 s, respectively, was defined as the event. We present a model where we adjusted for age and sex only (Model 1), as well as a model where we additionally included education, smoking and obesity (Model 2). Before deciding on the covariates to include in Model 2, we ran explorative analyses where we assessed whether the following factors changed the association between periodontitis and pain tolerance: general health, diabetes, heart disease, emotional distress (Hopkins symptoms scale 10), chronic pain and use of analgesics (all self-reported variables from the questionnaire, further description in Supplementary File Methods), and hs-CRP. None of these variables changed the HR of the associations between periodontitis and pain tolerance by 10% or more, and they were therefore not included in our final model. We examined for multiplicative interactions between periodontitis and each of the covariates by including the cross-product interaction term into the models. For CPT, there was a significant interaction between periodontitis and sex, and sex-stratified analyses were run. Interaction analyses of other covariates were not statistically significant. However, due to the large sex differences in PPT, sex-stratified analyses were also run for this stimulus modality. Fulfilment of the proportional hazard assumption was assessed by studying survival plots for all variables included (data not shown). Missing data were handled with omission. All statistical tests were two-sided; significance level was set at 5%.

3 | RESULTS

3.1 | Characteristics of the study sample

The characteristics of the study sample are described in Table 1 for the whole study sample and stratified on periodontitis classified according to the CDC/AAP classification. Overall, 39% of the participants had moderate periodontitis (of whom 79% had generalized disease) and 11% had severe periodontitis (of whom 98% had generalized disease). Moderate or severe periodontitis was most common among current and former smokers, men, participants 60 years or older and those without university or college education. Also, the proportion of participants with obesity and median hs-CRP concentration was higher with increasing severity of periodontitis. Compared with participants with no or mild periodontitis, a higher fraction of those with moderate or severe periodontitis aborted both the PPT and CPT before the maximum limit, but the differences were only statistically significant for the PPT test (Table 1). Study sample characteristics stratified on periodontitis according to the 2018 classification are shown in Table S1. According to this classification, 22% of the participants had Stage I, 45% Stage II and 21% Stage III/IV periodontitis. In the Stage II group, 70% had generalized disease, and in the Stage III/IV group, 88% had generalized disease (Table S1).

TABLE 1 Characteristics of the study sample.

Characteristics	All	Periodontitis groups CDC/AAP classification				
		No	Mild	Moderate	Severe	
Whole study sample	**3666**	**981 (26.8%)**	**864 (23.6%)**	**1420 (38.7%)**	**401 (10.9%)**	***p***
Age group (years), *n* (%)						
40–49	1053 (28.7)	459 (46.8)	299 (34.6)	267 (18.8)	28 (7.0)	<.001
50–59	1058 (28.9)	275 (28.0)	297 (34.4)	385 (27.1)	101 (25.2)	
60–84	1555 (42.2)	247 (25.2)	268 (31.0)	768 (54.1)	272 (67.8)	
Sex *n* (%)						
Women	1893 (51.6)	585 (59.6)	456 (52.8)	683 (48.1)	169 (42.1)	<.001
Men	1773 (48.4)	396 (40.4)	408 (47.2)	737 (51.9)	232 (57.9)	
Education, *n* (%)						
No college/university	1915 (53.1)	437 (45.1)	398 (46.7)	813 (58.4)	267 (67.8)	<.001
College/university	1691 (46.9)	531 (54.9)	455 (53.3)	578 (41.6)	127 (32.2)	
Smoking, *n* (%)						
Never	1495 (41.1)	542 (55.6)	387 (45.2)	502 (35.7)	64 (16.0)	<.001
Former	1644 (45.2)	369 (37.9)	365 (42.6)	694 (43.9)	216 (54.0)	
Current	499 (13.7)	63 (6.5)	105 (12.3)	211 (15.0)	120 (30.0)	
Aborted PPT test, *n* (%)						
No	263 (7.7)	89 (9.6)	74 (9.0)	85 (6.6)	15 (4.1)	<.001
Yes	3152 (92.3)	842 (90.4)	746 (91.0)	1212 (93.4)	352 (95.9)	
Aborted CPT test, *n* (%)						
No	1242 (37.8)	349 (39.7)	305 (38.4)	473 (37.7)	115 (32.6)	.073
Yes	2041 (62.2)	531 (60.3)	489 (61.6)	783 (62.3)	238 (67.4)	
Obese,[a] *n* (%)						
No	2773 (75.8)	762 (77.9)	655 (76.0)	1074 (75.7)	282 (70.7)	.044
Yes	884 (24.2)	216 (22.1)	207 (24.0)	344 (24.3)	117 (29.3)	
hs-CRP mg/L median (IQR)	0.95 (2)	0.80 (1)	0.93 (1)	1.05 (2)	1.19 (2)	<.001[b]
Generalized periodontitis[c]			306 (37.6)	1119 (79.2)	394 (98.3)	<.001

Note: Numbers for some variables may not add up to the total number of participants due to missing data.
Abbreviations: CPT, cold-pressor tolerance; hs-CRP: high-sensitivity C-reactive protein; IQR, interquartile range; PPT, pressure pain tolerance.
[a]≥30 kg/m^2.
[b]Independent-samples Kruskal–Wallis test, in pairwise comparisons all differences between groups were statistically significant, except between the no and mild periodontitis groups.
[c]Periodontitis, irrespective of stage, affecting ≥30% of remaining teeth.

3.2 | Association between periodontitis and pressure pain tolerance (risk of aborting test)

In univariate analyses, moderate (HR = 1.18, 95% CI: 1.09, 1.27) and severe (HR = 1.39, 95% CI: 1.24, 1.56) periodontitis were significantly associated with lower PPT in the whole study sample. After controlling for confounders, moderate (HR = 1.09; 95% CI: 1.01, 1.18) and severe (HR = 1.25, 95% CI: 1.11, 1.42) periodontitis were still associated with decreased PPT (Table 2, Model 2, Whole study sample). Running sex-stratified analysis had minor effects on the associations between periodontitis and PPT, but the associations with moderate periodontitis were no longer statistically significant (Table 2, Model 2, women and men, respectively).

We ran additional regression analyses using the 2018 periodontitis classifications. In univariate analyses, Stage II (HR = 1.16, 95% CI: 1.07, 1.26) and Stage III/IV (HR = 1.24, 95% CI:1.12, 1.36) periodontitis were significantly associated with lower PPT in the whole study sample. In adjusted models, there were no differences in HR between Stage II and Stage III/IV periodontitis (Table 2). To increase statistical power, we therefore ran additional analyses where these groups were merged. In fully adjusted models, having Stage II or Stage III/IV periodontitis was significantly associated with lower PPT compared with having no or Stage I periodontitis for the whole study sample (HR = 1.09, 95% CI: 1.01, 1.18) and for women (HR = 1.13, 95% CI: 1.01, 1.26), but not for men (Table 2).

TABLE 2 Association between periodontitis and pressure pain tolerance—risk of aborting test.

	Model 1[a]	Model 2[b]	Model 2[c]	Model 2[c]
	Whole study sample	Whole study sample	Women	Men
	Pressure	Pressure	Pressure	Pressure
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Periodontitis (CDC/AAP)				
No/mild	Ref	Ref	Ref	Ref
Moderate	**1.09 (1.01, 1.18)**	**1.09 (1.01, 1.18)**	1.10 (0.98, 1.23)	1.08 (0.96, 1.21)
Severe	**1.27 (1.13, 1.43)**	**1.25 (1.11, 1.42)**	**1.24 (1.02, 1.49)**	**1.24 (1.05, 1.47)**
Periodontitis (2018 AAP/EEP)				
No/Stage I	Ref	Ref	Ref	Ref
Stage II	**1.11 (1.03, 1.21)**	**1.09 (1.00, 1.19)**	**1.15 (1.03, 1.29)**	1.02 (0.90, 1.16)
Stage III/IV	1.11 (1.00, 1.23)	1.09 (0.98, 1.22)	1.07 (0.92, 1.24)	1.09 (0.93, 1.28)
No/Stage I	Ref	Ref	Ref	Ref
Stage II/III/IV	**1.11 (1.03, 1.20)**	**1.09 (1.01, 1.18)**	**1.13 (1.01, 1.26)**	1.03 (0.91, 1.17)

Note: Numbers in bold indicate $p < .05$.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Model 1 adjusted for age group and sex.
[b]Model 2 adjusted for age group, sex, education, smoking and obesity.
[c]Sex-stratified Model 2 adjusted for age group, education, smoking and obesity.

TABLE 3 Association between periodontitis and cold-pressor tolerance—Risk of aborting test.

	Model 1[a]	Model 2[b]	Model 2[c]	Model 2[c]
	Whole study sample	Whole study sample	Women	Men
	Cold-pressor	Cold-pressor	Cold-pressor	Cold-pressor
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Periodontitis				
No/mild	Ref	Ref	Ref	Ref
Moderate	1.02 (0.93, 1.13)	0.99 (0.90, 1.09)	0.93 (0.81, 1.06)	1.08 (0.93, 1.25)
Severe	**1.19 (1.03, 1.38)**	1.10 (0.95, 1.28)	0.99 (0.79, 1.24)	1.21 (0.99, 1.49)
Periodontitis (2018 AAP/EEP)				
No/Stage I	Ref	Ref	Ref	Ref
Stage II	1.11 (1.00, 1.23)	1.07 (0.96, 1.19)	1.08 (0.94, 1.24)	1.09 (0.92, 1.28)
Stage III	1.12 (0.97, 1.27)	1.03 (0.90, 1.17)	0.96 (0.80,1.16)	1.08 (0.89, 1.32)
Periodontitis				
No/Stage I	Ref	Ref	Ref	Ref
Stage II/III/IV	**1.11 (1.01, 1.23)**	1.06 (0.95, 1.17)	1.05 (0.92, 1.20)	1.08 (0.92, 1.26)

Note: Numbers in bold indicate $p < .05$.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Model 1 adjusted for age group and sex.
[b]Model 2 adjusted for age group, sex, education, smoking and obesity.
[c]Sex-stratified Model 2 adjusted for age group, education, smoking and obesity.

3.3 | Association between periodontitis and cold-pressor tolerance (risk of aborting test)

In univariate analyses, severe (HR = 1.20, 95% CI: 1.04, 1.38) periodontitis was significantly associated with lower CPT in the whole study sample. Multiplicative interaction between periodontitis and sex on CPT was significant ($p = .011$). In adjusted models, the associations between periodontitis and CPT were not statistically significant for the whole cohort, nor in sex-stratified analyses (Table 3).

Univariate analyses using the 2018 periodontitis classifications showed that Stage II (HR = 1.11, 95% CI: 1.01, 1.23) but not Stage III/IV (HR = 1.12, 95% CI: 0.99, 1.26) periodontitis was significantly associated with lower CPT in the whole study sample. In fully adjusted models, there were no significant associations between periodontitis and CPT, neither for the whole study sample nor in sex-stratified analyses (Table 3).

4 | DISCUSSION

We tested the hypothesis that periodontitis is associated with lower experimental pain tolerance using data from a large, population-based cross-sectional study. Moderate and severe periodontitis, according to the CDC/AAP classification, was associated with reduced PPT after adjusting for age, sex, education, smoking and obesity. Repeating the analyses with periodontitis according to the 2018 classification gave similar univariate findings, but the associations were generally weaker than with the earlier classification and with no or minor differences in HR between Stage II and Stage III/IV periodontitis. In fully adjusted models, there were no significant associations between periodontitis and CPT.

To the best of our knowledge, this is the first study that evaluates the association between periodontitis and experimental pain tolerance. In contrast to many other chronic diseases, pain is not a common complaint in periodontitis, and the association between periodontitis and pain tolerance is not obvious. Nevertheless, a previous study found an association between the degree of periodontal inflammation and pain upon periodontal probing (Heft et al., 1991), indicative of localized pain sensitization. Loss of the tooth-supportive tissues along with mechanical debridement of the exposed root surfaces may also cause root hypersensitivity with pain upon thermal or mechanical stimuli. However, a systematic review found that such hypersensitivity was typically mild or moderate in nature, and transient (Lin & Gillam, 2012). Thus, to date, there is limited evidence that periodontitis is associated with local pain hypersensitivity. In the present study, periodontitis was associated with decreased PPT assessed on the leg, which may suggest generalized hyperalgesia. Such generalized pain hypersensitivity has been associated with a number of chronic pain conditions, including fibromyalgia (Jensen et al., 2009), temporomandibular disorders (Knuutila et al., 2022) and irritable bowel syndrome (Stabell et al., 2013).

We postulated that periodontitis may affect pain tolerance through induction of systemic inflammation. Mechanisms linking inflammation and pain include local sensitization of nociceptors, central changes in post-synaptic neurons and glial cells, as well as inhibition of descending pain-inhibitory pathways (Karshikoff et al., 2016; Pinho-Ribeiro et al., 2017; Ren & Dubner, 2010). In accordance with previous studies (Machado et al., 2021), we found that the level of the systemic inflammation marker hs-CRP was higher among participants with moderate and severe periodontitis than in participants with no or mild periodontitis. This was also true when periodontitis was classified according to the 2018 case definition. This suggests that inflammation and infection in the tooth-supporting tissues can induce systemic inflammation. However, including hs-CRP in our regression models did not significantly alter the associations between periodontitis and pain tolerance, indicating that the association between periodontitis and pain tolerance is not mediated through this general marker of inflammation. Instead, the association may be through more specific inflammatory or anti-inflammatory mediators, as previous studies have found strong associations between higher levels of anti-inflammatory fatty acids and increased experimental pain tolerance (Iordanova Schistad et al., 2020), and lower levels of osteoarthritis pain (Valdes et al., 2017). These anti-inflammatory fatty acids are precursors of a group of molecules termed specialized pro-resolving lipid mediators (SPM), which coordinate the termination of an acute inflammatory response (Basil & Levy, 2016). SPMs are synthesized at sites of acute inflammation, and inhibit neutrophil migration, stimulate macrophage phagocytosis and promote tissue regeneration (Basil & Levy, 2016). When these processes are disrupted, chronic inflammation follows with tissue destruction and often pain. For periodontitis, there are studies supporting that the microbial dysbiosis associated with the disease is a consequence of, rather than the driver of, a dysregulated immune response (Lee et al., 2016; Van Dyke, 2020). In animal models of periodontitis, local application of SPMs has been found to promote both resolution of the inflammation and tissue regeneration (Osorio Parra et al., 2019). SPMs may alleviate pain by resolving the inflammation, but they are also found to have potent analgesic effects that are independent of their inflammation-resolving roles (Tao et al., 2020). Thus, disrupted SPM synthesis is a putative mechanism linking periodontitis and other chronic inflammatory conditions to hyperalgesia. This could also explain the bidirectional association between periodontitis and fibromyalgia, which was recently found in a large, retrospective cohort study (Ma et al., 2022), as well as the association between periodontitis and rheumatoid arthritis (Bartold & Lopez-Oliva, 2020). However, as we lack data on SPM in the current study, we can only speculate on the role of SPM in the association between periodontitis and pain tolerance, and further studies are needed to establish mechanisms.

In the current study, the association between periodontitis and PPT was weaker when periodontitis was classified according to the 2018 classification than according to the CDC/AAP classification, and there was no difference in the HR between Stage II and Stage III/IV periodontitis. The re-classification caused a substantial drift towards more disease, with 11% versus 26% having no periodontitis, and 21% having Stage III/IV periodontitis compared with 11% having severe periodontitis using the CDC/AAP classification. It is therefore not surprising that the choice of classification affected the results. With the new classification, the Stage II and Stage III/IV periodontitis groups contained more persons with localized disease than the moderate and severe periodontitis groups of the CDC/AAP classification. The extent of the disease, not just the severity, is likely to reflect the systemic effects of periodontitis. Thus, the larger heterogeneity in the Stage II and Stage III/IV groups, with more persons having localized disease, is therefore a possible explanation for the weaker association between PPT and periodontitis classified according to the 2018 classification. In fully adjusted models, there were no significant associations between periodontitis and CPT irrespective of classification. It is a common finding that the sensitivity to different pain modalities varies,

and it is not known whether any specific test is superior in predicting clinical pain (Hastie et al., 2005; Nielsen et al., 2009).

4.1 | Strengths and weaknesses

The Tromsø7 study is the largest study of experimental pain sensitivity worldwide. Sampling is population-based and the study maintains a high response rate and is thus reasonably representative of the general population of Tromsø municipality, though the requirement of meeting on-site in person means that certain groups, including the seriously ill and nursing home patients, are not represented.

All measurements were performed according to research protocols by trained staff. We had objective measurements of both periodontitis and pain tolerance. The methods used to estimate pain tolerance are relatively simple, and therefore widely used in pain research. Periodontitis was assessed with a full-mouth examination protocol performed by trained and calibrated examiners. The number of missing values was negligible. The present study also has some limitations. The study is cross-sectional and does not allow us to make conclusions about longitudinal prediction or causality. Even though we adjusted models for important confounders, some unmeasured confounders could have an impact on the study results. The indirect approach, where CAL was predicted from RBL measurements, may have led to errors in case definitions and potentially resulted in an underestimation of periodontitis. This is because the ability of RBL to predict CAL increases with higher values of CAL. However, by employing threshold values of ≥4 mm and ≥6 mm for CAL, as described by Holde et al., 2017, errors in defining high measures of CAL were minimized. We lacked information on bleeding on probing, which could have added relevant information on the inflammatory state of the periodontium. Though we postulate that specific inflammatory mechanisms, including SPMs, may mediate the relationship between periodontitis and pain tolerance, this study was not designed to test this hypothesis.

4.2 | Clinical relevance and conclusion

Reporting of pain intensity from a given stimulus is subjective but has been found to correspond well to differences in brain activity caused by the pain (Coghill et al., 2003; Raij et al., 2005), suggesting an underlying difference in pain sensitivity. This is also supported by a previous study that found higher pain tolerance in persons with unrecognized compared with recognized myocardial infarction (Ohrn et al., 2016), indicating an association between subjective symptoms and pain tolerance. In further support of the clinical relevance of experimental pain tolerance measures is a recent randomized clinical trial finding that PPT predicted therapy response in patients with fibromyalgia, a chronic pain condition (Bellomo et al., 2020). Chronic pain affects about 30% of the Norwegian adult population (Steingrimsdottir et al., 2017) and is a common reason for reduced quality of life and long-term sick leave (Breivik et al., 2006; Gustavsson et al., 2012). As experimental pain tolerance has been associated with chronic pain conditions, it is important to identify novel factors associated with low pain tolerance, especially modifiable ones. Periodontitis is a highly prevalent chronic disease that can be treated and kept at bay by meticulous oral hygiene and supportive periodontal therapy. Thus, its association with pain tolerance and generalized pain syndromes may have significant clinical relevance. To conclude, this study provides the first report on the association between periodontitis and experimental pain tolerance. The association should be verified in studies on other populations and mechanisms linking periodontitis and pain tolerance explored in future studies.

AUTHOR CONTRIBUTIONS

Conception and design: EHO and CSN; data acquisition: BJ, OAS, AS and CSN; data analyses and interpretation: EHO, NP, OAS and CSN; drafting the manuscript: EHO and NP; critically revising the manuscript, approving the final version and agreeing to be accountable for all aspects of the work: all the authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used are from the seventh survey of the Tromsø Study and are available upon application to the Tromsø Study at https://uit.no/research/tromsoundersokelsen/project?pid=707286.

ETHICS STATEMENT

The Regional Committee for Health Research Ethics approved the study (REK320778).

INFORMED CONSENT

The study was conducted in accordance with the Declaration of Helsinki with informed, written consent from all participants.

ORCID

Elin Hadler-Olsen https://orcid.org/0000-0001-8476-9439
Birgitta Jönsson https://orcid.org/0000-0002-7781-8527

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