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Increased risk of periodontitis in patients with rheumatoid arthritis: A nationwide register study in Norway

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Abstract

Aim: To investigate the risk of periodontitis in rheumatoid arthritis (RA) patients in a nationwide register-based study.

Materials and Methods: Patients and controls were defined using ICD-10 codes registered in the Norwegian Patient Registry (NPR), from 2011 to 2017. The 324,232 included subjects had at least one registered diagnostic code for RA (33,040 patients) or diagnostic codes for non-osteoporotic fractures or hip or knee replacement due to osteoarthritis (controls). The outcome was periodontitis, defined by codes for periodontal treatment from the Norwegian Control and Payment of Health Reimbursements Database (KUHR). Hazard ratios (HRs) were calculated for periodontitis in RA patients compared to controls. Generalized additive model in Cox regressions was estimated to visualize periodontitis occurrences as a function of number of RA visits.

Results: The risk of periodontitis increased with increasing number of RA visits. RA patients having 10 or more visits during the 7-year period had a 50% increased risk of periodontitis compared to controls (HR = 1.48, 95% confidence interval [CI]: 1.39–1.59); also, in patients with assumed new RA, an even higher risk estimate was seen (HR = 1.82, 95% CI: 1.53–2.17).

Conclusions: In this register-based study in which periodontal treatment was used as a surrogate marker for periodontitis, we found an increased risk of periodontitis in RA patients, particularly those with active disease and new RA.

KEYWORDS
autoimmune, nationwide, periodontal, register study, regression analysis

Clinical Relevance

Scientific rationale for study: Data regarding an increased risk of periodontitis in rheumatoid arthritis (RA) patients are conflicting. As these two inflammatory diseases may have mutually negative effect on the host, a connection will have implications for periodontal monitoring of these patients.

Principal findings: The impact of this work lies in the identification of a marked increased risk of periodontitis in RA patients, particularly in patients with active and new RA, in a large nationwide register study of 30,040 RA patients.

Practical implications: This knowledge can increase awareness among healthcare workers about the significance of closely monitoring patients with active RA, ensuring thorough periodontal preventive supervision and treatment.

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that primarily affects peripheral joints. If left untreated, the inflammation eventually leads to destruction of bone and cartilage. However, improved understanding of the pathogenesis, along with the implementation of new treatment strategies and development of new drugs, has markedly improved the prognosis of RA during the last two decades (Klareskog et al., 2009; McInnes & Schett, 2011; Smolen et al., 2018). RA affects approximately 0.35%–0.9% of the population in Europe (Oton & Carmona, 2019). The incidence is 4–5 times higher in women than men under 50 years of age, while at the age of 60–70 years the ratio is approximately 2:1 (Kvien et al., 2006).

An association between RA and periodontitis is well documented (Bartold & Lopez-Oliva, 2020; de Pablo et al., 2008; Demmer et al., 2011; Fuggle et al., 2016; Rutger Persson, 2012), although data regarding an increased risk of periodontitis in RA patients are conflicting (Chen et al., 2013; Eriksson et al., 2016; Fuggle et al., 2016).

Periodontitis is an inflammation in the supporting tissue of the teeth, initiated by microbiota in the dental biofilm (Hajishengallis, 2015). Periodontal tissue destruction requires a susceptible host, and the course is modified by genetic and environmental factors (Leite et al., 2018; Loos & Van Dyke, 2020; Rutger Persson, 2012). Periodontitis can lead to tooth loss, pain and reduced chewing function and negatively affect the aesthetics and quality of life (Ferreira et al., 2017; Kassebaum et al., 2014a). In 2010, severe periodontitis affected nearly 11% of the world population and was the sixth most prevalent health condition in the world (Kassebaum et al., 2014b), while in the Global Burden of Disease 2015 study, the prevalence was 7.4% (Kassebaum et al., 2017). Milder forms of periodontitis affect about 50% of the population (Billings et al., 2018). In a cross-sectional study in Northern Norway, 49.5% of the participants had periodontitis and 9.1% had severe periodontitis (Holde et al., 2017).

The relationships between RA and periodontitis include similarities in genetic risk factors and immunopathogenesis, pathological mechanisms of chronic inflammation and bone destruction as well as increased production of cytokines, prostaglandins and matrix-degrading enzymes (Beyer et al., 2021; Bolstad et al., 2020; Janssen et al., 2013; Rutger Persson, 2012; Stabholz et al., 2010). Among the shared risk factors, cigarette smoking is the most prominent (Klareskog et al., 2006; Papapanou et al., 2018; Razali et al., 2005; Tomar & Asma, 2000). The periodontal pathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have been suggested to be involved in the generation of citrullinated antigens and the subsequent production of anti-citrullinated protein antibody (ACPA), which is crucial in the pathogenesis of RA (Beyer, Lie, et al., 2018; Beyer, Zaura, et al., 2018; Konig et al., 2016; Mikuls et al., 2014; Suzuki et al., 2007). Severe forms of periodontitis in RA patients have been found significantly associated with ACPA positivity, an altered subgingival microbial profile as well as increased levels of systemic and oral inflammatory mediators (Beyer, Lie, et al., 2018; Eriksson et al., 2019; Mikuls et al., 2014). It is suggested that *P. gingivalis* infection may play a role in the early loss of tolerance to self-antigens in RA (Arvikar et al., 2013; Hitchon et al., 2010).

Patients with new-onset RA are treated according to the treat-to-target (T2T) strategy, which implies frequent visits in the first year of disease. After this time, the follow-up is more individual, depending on disease activity and treatment response. This means that patients with ongoing disease activity will have more frequent visits for treatment adjustments and joint injections than those in remission. Based on this, many repeated hospital visits are a reasonable proxy for disease activity, particularly in large patient populations.

The aim of this study was to investigate the association between repeated RA visits and repeated periodontitis occurrences by combining data from two large nationwide registries, namely the Norwegian Patient Registry (NPR) and Norwegian Control and Payment of Health Reimbursements Database (KUHR).

2 | MATERIALS AND METHODS

This is a nationwide, population-based study using data from the 7-year period from 1 January 2011 through December 2017. Our cohorts were defined using the International Classification of Disease (ICD-10) as well as procedure codes registered in the NPR. A total of 324,232 patients were included in the study.

2.1 | The Norwegian Patient Registry

The NPR collects information on all subjects having undergone treatment in a Norwegian hospital or outpatient clinic (Bakken et al., 2020). Data regarding diagnosis, treatment, procedure codes and times of admission and discharge are collected. The information is obtained directly from the institutions' electronic administrative patient registration system, yielding practically 100% data completeness. However, the validity of the single codes to NPR has not been evaluated.

2.2 | Norwegian Control and Payment of Health Reimbursements Database

The KUHR handles reimbursement claims from treatment and health institutions to the state. This is a national system run by the Norwegian Directorate of Health, which manages settlements for dentists and other health professionals. Reimbursement is provided for systematic treatment of periodontitis and peri-implantitis aimed at achieving infection control. There is no reimbursement for gingivitis treatment. For the purpose of this study, the code for systematic periodontal treatment of periodontitis, code 501, and the code for periodontal surgery, code 502, were used as proxies for periodontitis. Code 502 does not provide reimbursement for other periodontal surgeries such as root coverage, implant placement, alveolar bone

augmentation, and so on. It only covers periodontal surgeries carried out as part of systematic treatment of periodontitis and peri-implantitis.

Code 501 can be used only for systematic periodontal treatment. Examination of the patients is covered by a different code. As the KUHR records no information on periodontal disease severity, the use of code 501 (systematic periodontal treatment) was a proxy for the severity of periodontitis in our study.

The 11-digit identification, unique for all Norwegian citizens, was used to merge data on diagnostic and procedure codes from the NPR with data on received reimbursement from KUHR.

2.3 | RA patients

Altogether, 33,040 patients between 20 and 80 years of age at study start had one or more RA visits during the study period (2011–2017). An RA visit was defined as a visit/admission registered in the NPR, with a diagnosis of RA (M05.8, M05.9 and M06.0) as the main diagnosis. From the NPR, we obtained information about the patient's month and year of birth and death, sex and the date of admission/visit. In addition, diagnostic codes (ICD-10) for diabetes mellitus type 2 (DM2) and myocardial infarction (MI) were obtained. These variables were included as covariates in the adjusted regression analyses (see statistics section). Patients with one or more diagnostic codes for systemic lupus erythematosus (SLE) registered were excluded.

Some patients would have had RA before the study start, but because ICD-10 codes were used to identify RA, all patients were treated as controls until the first registered RA visit after study start (1 January 2011) to avoid immortal time bias. Thus, an individual will first be a control and may later shift to the RA group, as illustrated in Figure 1. A total of 12,807 patients had a first RA registration 2 years or later after inclusion in the study. Since no RA visits were registered in this 2-year period, these patients were assumed to be new RA patients.

2.4 | Controls

As control group from the NPR, patients between 20 and 80 years of age at study start and having undergone treatment for assumed non-osteoporotic fractures or hip or knee replacement due to osteoarthritis were included. Patients with fracture were identified using the following procedure codes: NFJ (treatment for femoral fracture), NHJ (treatment for ankle fractures) or NBJ (treatment for fracture of the humerus). ICD-10 codes M15–M19 in combination with procedure codes NFB (hip replacement) or NGB (knee replacement) were used to identify patients who had undergone joint replacements. The large number of individuals, along with no known risk factors for periodontitis associated with these conditions, rendered the groups suitable as controls. The same data as described for the RA patients were obtained for the controls, and patients with SLE were excluded from this group as well.

At study start, all 324,232 patients started out as controls, and by the end of the study 291,192 patients had still no RA registration and were thus controls throughout the study.

2.5 | Outcome

The main outcome of our study was the repeated occurrences of periodontitis, measured as registrations of periodontal treatment codes

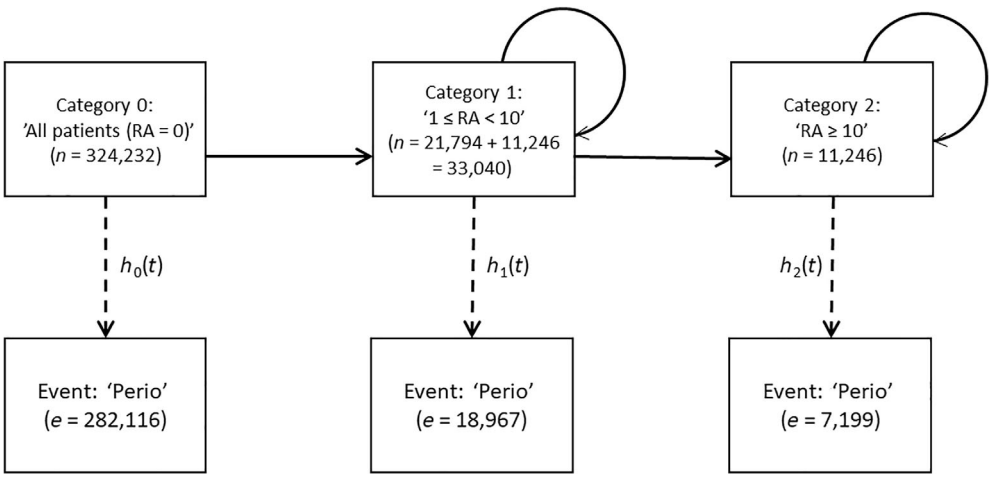

FIGURE 1 Structure for the categorical time-dependent rheumatoid arthritis (RA) variable. All patients start with 0 RA visits (the total cohort), which is the reference category for the time-dependent covariate. The 282,116 periodontitis events took place in patients never having RA or before the first registered RA code, throughout the study period. When RA patients have their first RA visit, the categorical time-dependent covariate changes to category 1. When the RA patients have 10 visits, the categorical time-dependent covariate changes to category 2. The risk of periodontitis is indicated as hazards $[h_k(t), k = 0, 1, 2]$ for each category for the time-dependent covariate. *n* is number of individuals and *e* is the number of periodontitis events. Circle arrows indicate repeated RA visits within each category. Perio means periodontitis.

501 or 502 in KUHR. Although some registrations of 501 might not represent an actual case of periodontitis, all occurrences were included in the analyses. Altogether, 308,282 periodontitis events were registered in 52,049 patients (RA patients or controls) during the 7-year study period. Both patients and controls may have had periodontitis before the study start.

2.6 | Ethics

This study was carried out in compliance with the Helsinki Declaration, and the regional ethics committee (REK) approved the study (reference number 2018/2124/REK vest). As the data were anonymous and thus may not be used to identify individual patients, exemption from obtaining informed consent was granted. The project was evaluated by the Norwegian Data Protection Services (NSD), who recommended that a data protection impact assessment (DPIA) be performed to identify and analyse how data privacy might be affected by our project. The handling of data was considered to be in line with the General Data Protection Regulation (GDPR). This article follows the STROBE statement.

2.7 | Statistical analysis

The Lexis diagram in Figure S1 illustrates the patient flow through the study. As the figure shows, all patients were followed from study start (1 January 2011) or age 20 until the end of study (31 December 2017), reaching 80 years of age or death. For the illustration, 70 patients were randomly selected, and the time of visits for RA and periodontitis procedures was presented at the time of occurrence.

The number of registrations with an RA ICD-10 code (M05.8, M05.9 and M06.0) was used as a measure of disease activity/severity, as patients with high disease activity are likely to have frequent visits while those in remission are not. In some cases, patients participated in rehabilitation or similar programmes in the outpatient clinic, lasting for 1–3 weeks, leading to the use of the same ICD-10 code on several consecutive days. To avoid the interpretation of such cases as illustrating disease activity or severity, only one code per 10 days was counted, because the usual length of such programmes in Norway is 2 weeks (10 working days). For example, for a patient, four visits during a 10-day period were counted as one visit.

Cox proportional hazards regression was performed to analyse the risk (hazard ratio [HR]) for periodontitis according to RA disease activity/severity (0–40 or more registrations). HRs adjusted for sex as well as the presence and severity (as measured by the number of registrations) of DM2 and coronary heart disease were also calculated. The number of RA visits was entered as a time-dependent variable, starting at '0' at inclusion, to avoid immortal time bias. The HRs were furthermore calculated for the categories of patients having 1–9 RA visits and 10 or more RA visits, compared to having none. Age was considered the follow-up time in the analyses. Hence, periodontitis was counted as an event, succeeding the observed number of RA visits, conditioning on the risk set of patients at the specific age. As mentioned previously, no information about diagnostic codes before the study start was available and it is likely that some patients had diagnostic codes before the study period.

To account for the history of periodontitis before RA visits in the Cox regression analysis, inverse probability treatment weights (IPTWs) were applied (Robins et al., 2000). Hence, in this analysis, the HRs were adjusted for previous periodontitis events. The IPTWs were constructed based on predicted probabilities from logistic regressions performed for each 5-year age category. As predictors for RA in these logistic regressions, gender, the history of periodontitis (i.e., number of registered occurrences at that age for the patient) and the history of diabetes and MI were added. In the IPTW analysis, the

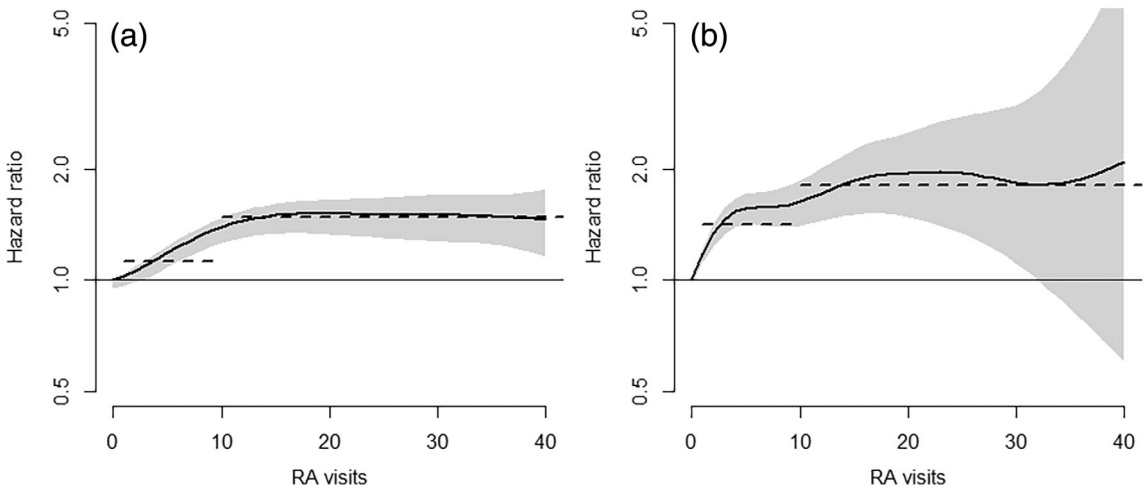

FIGURE 2 Generalized additive model curves with 95% confidence intervals for the hazard ratio (HR) of periodontitis as a function of number of rheumatoid arthritis (RA) visits, from 0 to 40. Patients with more than 40 RA visits were analysed as having 40. (a) All patients, (b) 'new RA' subset (i.e., patients not having RA visits during the first two study years). The dotted lines show HR for periodontitis for the categories of patients with 1–9 RA visits and ≥10 RA visits.

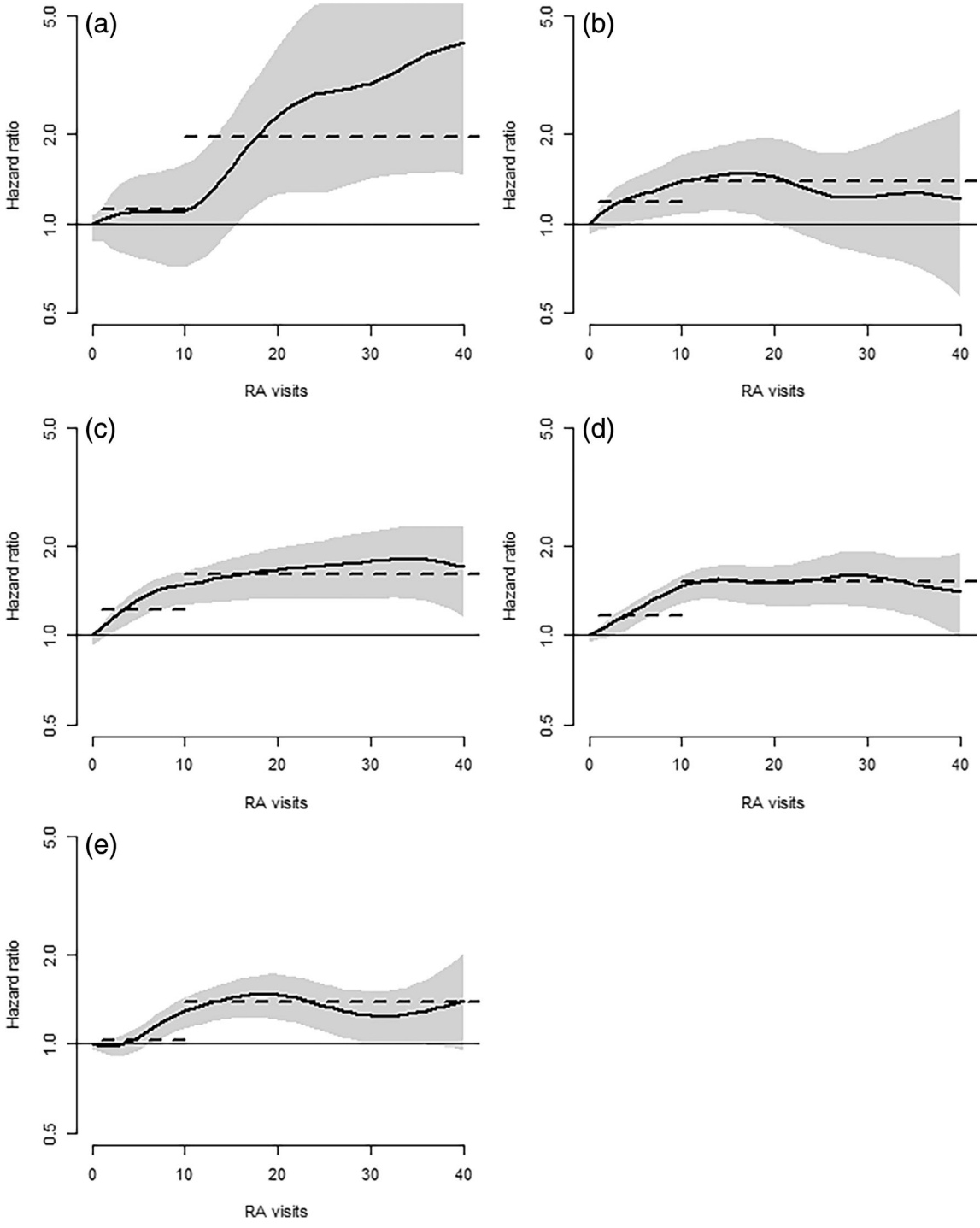

FIGURE 3 Generalized additive model curves with 95% confidence intervals for the hazard ratio (HR) of periodontitis as a function of number of rheumatoid arthritis (RA) visits, from 0 to 40. Patients with more than 40 RA visits were analysed as having 40. (a) Patients ≥20 and <40 years of age, (b) patients ≥40 and <50 years of age, (c) patients ≥50 and <60 years of age, (d) patients ≥60 and <70 years of age, and (e) patients ≥70 and <80 years of age. The dotted lines show the HR for periodontitis for the categories of patients with 1–9 RA and ≥10 RA visits.

interpretation of the effect of RA would be that for an RA patient having a particular number of periodontitis events at the given age, they would be contrafactually compared to controls with the same number of previous events and at the same age. This way, the effect of RA is adjusted for the effect of previous periodontitis.

Separate analyses were performed for each 10-year age category except for the youngest category, which included patients aged 20–40 years, because of the low number of patients in this subgroup. In the analyses, registrations of either periodontitis procedure code 501 or code 502 were used as outcome. A sub-analysis using only

TABLE 1 Characteristics of patients (columns 2–5) and frequency of periodontitis (columns 6–9) within the given subgroups.

	Patients				Periodontitis occurrences			
	Total	RA = 0[a]	1 ≤ RA < 10[a]	RA ≥ 10[a]	Total	RA = 0[a]	1 ≤ RA < 10[a]	RA ≥ 10[a]
Females	189,671	166,773	14,566	8332	198,774	179,707	13,555	5512
Males	134,561	124,419	7228	2914	109,508	102,409	5412	1687
DM2 ≥ 1	5678	4909	502	267	6631	5892	495	244
MI ≥ 1	8134	7119	679	336	9006	8094	703	209
Osteoarthritis ≥1	235,899	229,276	4434	2189	242,534	236,646	4307	1581
Fracture ≥1	54,772	53,798	654	320	43,029	42,284	562	183
Periodontitis[b]	52,049	46,535	3408	2106	308,282	282,116	18,967	7199
Periodontitis (501)	50,793	45,330	3366	2097	301,021	275,693	18,383	6945
Periodontitis (502)	7330	6582	443	305	12,330	11,446	627	257
All patients	324,232	291,192	21,794	11,246				

Abbreviations: DM2, diabetes mellitus type 2; MI, myocardial infarction; RA, rheumatoid arthritis.
[a]RA = 0 means no RA visits, 1 ≤ RA < 10 means 1–9 RA visits, RA ≥ 10 means 10 or more RA visits during study period.
[b]Periodontitis means the total number of individuals/occurrences with periodontitis.

TABLE 2 Subset without RA visits in the first 2 years.

	Patients				Periodontitis occurrences			
	Total	RA = 0[a]	1 ≤ RA < 10[a]	RA ≥ 10[a]	Total	RA = 0[a]	1 ≤ RA < 10[a]	RA ≥ 10[a]
Females	175,453	166,769	7295	1389	183,894	179,191	4193	510
Males	128,541	124,418	3575	548	103,902	102,191	1539	172
DM2 ≥ 1	5191	4909	239	43	6048	5875	155	18
MI ≥ 1	7440	7119	279	42	8319	8068	220	31
Osteoarthritis ≥1	232,177	229,275	2574	328	238,196	236,495	1589	112
Fracture ≥1	54,104	53,798	281	25	42,365	42,255	101	9
Periodontitis[b]	48,717	46,535	1799	383	287,796	281,382	5732	682
Periodontitis (501)	47,495	45,330	1783	382	281,193	274,979	5557	657
Periodontitis (502)	6895	6582	260	53	11,623	11,412	186	25
All patients	303,994	291,187	10,870	1937				

Note: Characteristics of patients (columns 2–5) and frequency of periodontitis (columns 6–9) within the given subgroups.
Abbreviations: DM2, diabetes mellitus type 2; MI, myocardial infarction; RA, rheumatoid arthritis.
[a]RA = 0 means no RA visits, 1 ≤ RA < 10 means 1–9 RA visits, RA ≥ 10 means 10 or more RA visits during study period.
[b]Periodontitis means the total number of individuals/occurrences with periodontitis.

coding 502 was also performed. The standard errors in the analyses were corrected for repeated registrations per patients using cluster robust variances.

Curves for generalized additive Cox models (GAMs) with 95% confidence intervals (CIs) were estimated with the hazard of periodontitis as a function of the number of RA visits, from 0 to 40 or more. As very few patients had more than 40 RA visits during the study period, patients with 40 or more visits were evaluated together. Curves for all patients (Figure 2a), for the 'new RA' subset (i.e., patients not having RA visits during the first two study years) (Figure 2b) and for each of the age strata (≥20 and <40, ≥40 and <50, ≥50 and <60, ≥60 and <70, ≥70 and <80 years) were estimated (Figure 3).

To study only new RA patients, we performed separate analyses including only RA patients not having had a visit during the first 2 years of the study (2011 and 2012). This subgroup is termed 'new RA'. However, the group might contain a few patients who had an RA diagnosis ahead of the study but for some reason not having been followed during 2011 and 2012.

3 | RESULTS

Among the 33,040 patients who had at least one registered RA visit during the study period, there were 22,898 women (69.3%) compared to 57.3% in the never-RA patient group (Table 1). The frequencies of

comorbidities in terms of DM2 and MI in the RA patients and in the never-RA group are shown in Table 1. Of the 33,040 patients with at least one RA visit, 21,794 had 1–9 visits, while 11,246 had 10 or more visits. Altogether, 5514 RA patients (16.7%) had at least one procedure code for periodontitis (501 or 502). The corresponding number in the new RA group was 2182 (17.0%) (Table 2). Furthermore, 748 of the RA patients had at least one 502 registration (periodontal surgery) (Table S1).

There was an elevated risk for periodontitis in RA patients compared to controls, which was highest in patients having 10 or more RA visits during the study period (HR = 1.44, Table 3). Also, for all the age sub-categories, the risk estimates were highest in RA patients with 10 or more RA visits. For the youngest age group (20–40 years), the risk of periodontitis was statistically significantly increased only in patients with 10 or more visits. In the IPTW-adjusted Cox regression, the HRs were even higher. The HR for RA patients 50–60 years of age with 10 or more RA visits became 1.95 (Table S2). The risk of periodontitis also increased with increasing number of DM2 registrations. Similar results were found for MI. In the analyses in which only new RA patients were included, comparable findings were seen (Table 2). For new RA patients with 10 or more RA visits during the study period, the risk for periodontitis was high (HR = 1.77; Table 3). In the sub-analysis in which periodontal surgery alone was the outcome (procedure code 502), the risk estimates were similar but not statistically significant (Table S1).

The risk of periodontitis increased with RA disease activity, as shown in Figure 2a. The same was seen in the new RA subgroup (Figure 2b). The increase in the risk of periodontitis with increasing number of RA visits was seen in all age groups, although most explicitly shown in the three oldest age groups (Figure 3). A plateau in the HR of periodontitis as a function of RA visits was seen between 10 and 20 RA visits for the total cohort and in the four oldest age groups. For the youngest age group, the number of included patients was lower and the results less conclusive (Figure 3).

4 | DISCUSSION

In this large and nationwide study, we found a 50% increased risk of periodontitis in patients with RA. The number of registered RA codes was used as a proxy for disease severity, and the finding of a stronger association for patients with 10 or more visits as well as a gradual increase in HR with increasing number of RA visits strengthens the indication that RA is associated with the risk of periodontitis. As having had periodontitis once increases the risk of a new occurrence, one could argue that if periodontitis is a risk factor for acquiring RA, this could be the cause of the increased risk seen in our RA patients. However, in the IPTW-adjusted Cox regression, the hazards were adjusted for previous periodontitis events (having occurred within the study period, and before the particular age) and the difference in hazard was even higher, showing that the increased risk is indeed associated with RA. Additionally, the risk for periodontitis was higher in the subgroup of new RA patients (not having any RA registration during the first 2 years), further supporting our findings.

An increased incidence of periodontal disease has previously been reported in patients with RA compared to healthy controls (Araujo et al., 2015; Ayravainen et al., 2017; Detert et al., 2010; Pischon et al., 2008), and a meta-analysis including a total of 153,492 participants found a 13% increased risk for periodontitis, increased probing depths and increased attachment loss in individuals with RA (Fuggle et al., 2016). A weak but significant association (odds ratio [OR] = 1.16; 95% CI: 1.12–1.20) was found between RA and periodontitis in a large study in Taiwan based on 13,779 RA patients and 137,790 controls (Chen et al., 2013). Similar results were reported in a Korean population-based registry study (Lee et al., 2015). This agrees with our findings in the less severe RA population, in which a 11% increased risk was found. On the other hand, Eriksson et al. (2016) found no evidence of increased prevalence of periodontitis in patients with established RA compared to healthy controls in their population-based study including 2740 RA cases and 3942 matched controls. In their study, only RA patients diagnosed from 1996 to 2009 were included, while periodontitis was registered from 2008 onwards. Thus, for the majority of patients, periodontitis occurring during early disease would not be registered. We found the highest risk of periodontitis in the new RA subset, with a 77% increased risk for new RA patients with 10 or more visits during a 5 (or less)-year period (as no RA visits could have been registered during the first 2 years). Furthermore, in our total cohort of 33,040 RA patients, there was an association between the number of RA visits, interpreted as a proxy for RA severity, and the number of periodontitis events. Consequently, the increased risk was particularly associated with new and active RA disease, possibly explaining the difference in our results compared to the Swedish study. In this study, patients with assumed new onset RA would have had more RA visits than the rest of the RA group because of the T2T strategy for new RA. We found that within the new onset RA group, those with many visits have more periodontitis than those with new onset RA with fewer visits. Thus, even within a group of patients, where we expect that some visits will only have been routine visits as part of the T2T strategy, having more visits was associated with having more periodontitis treatment.

The risk estimate in our study was somewhat higher than in other studies. Given the very large number of patients and controls in our study, we believe this risk estimate is accurate. Also supporting this is our statistical method ascribing periodontal events to RA only if the event took place after the first registered RA visit. This means that for patients already having RA, periodontal episodes occurring before the first registered RA code in the study were counted within the control group. For this reason, we believe the risk estimate is too low rather than too high.

The causes of increased occurrence of periodontitis in RA patients could be several, including common risk factors such as smoking, but also a general systemic inflammation as well as a possible impact of the medical treatment. We had no data to investigate possible common causes of the association, which should be studied in other settings.

TABLE 3 Unadjusted and adjusted Cox regression analyses for periodontitis in patients with rheumatoid arthritis (RA) versus controls, in the complete dataset and for the 'new RA' subset.

	Complete data				'New RA'[a]			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR[b] (95% CI)	*p*	HR[b] (95% CI)	*p*	HR[b] (95% CI)	*p*	HR[b] (95% CI)	*p*
RA = 0[c]	1	Ref	1	Ref	1	Ref	1	Ref
1 ≤ RA < 10[c]	1.13 (1.08–1.18)	<.001	1.11 (1.06–1.16)	<.001	1.42 (1.33–1.51)	<.001	1.39 (1.30–1.48)	<.001
RA ≥ 10[c]	1.48 (1.39–1.59)	<.001	1.44 (1.35–1.54)	<.001	1.82 (1.53–2.17)	<.001	1.77 (1.49–2.10)	<.001
Female:male			1.21 (1.18–1.24)	<.001			1.22 (1.19–1.25)	<.001
DM2[d]			1.02 (1.02–1.03)	<001			1.02 (1.02–1.03)	<.001
MI[d]			1.09 (1.07–1.12)	<.001			1.10 (1.07–1.13)	<.001
20–40 years								
RA = 0[c]	1	Ref	1	Ref	1	Ref	1	Ref
1 ≤ RA < 10[c]	1.12 (0.87–1.45)	.377	1.06 (0.81–1.37)	.686	1.64 (1.14–2.35)	.007	1.54 (1.07–2.22)	.019
RA≥10[c]	1.96 (1.30–2.95)	.001	1.79 (1.18–2.71)	.006	1.91 (0.75–4.87)	.178	1.72 (0.67–4.41)	.259
Female:male			1.23 (1.05–1.44)	.009			1.24 (1.05–1.46)	.010
DM2[d]			1.02 (0.89–1.17)	.775			1.01 (0.85–1.19)	.948
MI[d]			1.91 (1.08–3.39)	.027			1.93 (1.10–3.40)	.023
40–50 years								
RA = 0[c]	1	Ref	1	Ref	1	Ref	1	Ref
1 ≤ RA < 10[c]	1.18 (1.03–1.35)	.015	1.14 (1.00–1.30)	.059	1.39 (1.12–1.72)	.003	1.33 (1.07–1.65)	.009
RA≥10[c]	1.38 (1.11–1.72)	.003	1.31 (1.06–1.63)	.014	1.94 (1.21–3.11)	.006	1.85 (1.16–2.96)	.010
Female:male			1.20 (1.12–1.30)	<.001			1.22 (1.13–1.32)	<.001
DM2[d]			1.06 (1.03–1.08)	<.001			1.06 (1.04–1.09)	<.001
MI[d]			1.16 (0.92–1.46)	.215			1.18 (0.94–1.48)	.154
50–60 years								
RA = 0[c]	1	Ref	1	Ref	1	Ref	1	Ref
1 ≤ RA < 10[c]	1.22 (1.13–1.31)	<.001	1.18 (1.09–1.27)	<.001	1.33 (1.17–1.5)	<.001	1.28 (1.14–1.45)	<.001
RA≥10[c]	1.61 (1.41–1.83)	<.001	1.53 (1.35–1.74)	<.001	1.86 (1.4–2.47)	<.001	1.78 (1.34–2.37)	<.001
Female:male			1.33 (1.27–1.39)	<.001			1.33 (1.28–1.40)	<.001
DM2[d]			1.03 (1.02–1.04)	<001			1.03 (1.02–1.04)	<.001
MI[d]			1.11 (1.09–1.14)	<.001			1.11 (1.09–1.14)	<.001
60–70 years								
RA = 0[c]	1	Ref	1	Ref	1	Ref	1	Ref
1 ≤ RA < 10[c]	1.16 (1.09–1.23)	<.001	1.14 (1.07–1.21)	<.001	1.47 (1.33–1.62)	<.001	1.45 (1.31–1.60)	<.001
RA≥10[c]	1.51 (1.37–1.68)	<.001	1.48 (1.33–1.63)	<.001	1.74 (1.29–2.35)	<.001	1.70 (1.25–2.29)	.001
Female:male			1.20 (1.16–1.24)	<.001			1.20 (1.16–1.25)	<.001
DM2[d]			1.02 (1.01–1.03)	<.001			1.02 (1.01–1.03)	<.001
MI[d]			1.09 (1.06–1.13)	<.001			1.09 (1.06–1.13)	<.001
70–80 years								
RA = 0[c]	1	Ref	1	Ref	1	Ref	1	Ref
1 ≤ RA < 10[c]	1.02 (0.95–1.10)	.515	1.02 (0.95–1.09)	.645	1.41 (1.26–1.57)	<.001	1.39 (1.24–1.56)	<.001
RA≥10[c]	1.38 (1.23–1.55)	<.001	1.36 (1.21–1.53)	<.001	1.84 (1.24–2.74)	.002	1.82 (1.23–2.70)	.003
Female:male			1.11 (1.06–1.15)	<.001			1.11 (1.07–1.16)	<.001
DM2[d]			1.02 (1.01–1.02)	<.001			1.02 (1.01–1.03)	<.001
MI[d]			1.05 (0.98–1.12)	.196			1.05 (0.99–1.13)	.113

Abbreviations: DM2, diabetes mellitus type 2; MI, myocardial infarction.

[a]RA visits taking place 2 years or later after study start, thus assumed to be new RA.

[b]HR is hazard ratio for the given group compared to the reference group, for example, patients with 1–9 RA visits compared to those having none.

[c]RA = 0 means no RA visits, 1 ≤ RA < 10 means 1–9 RA visits, RA ≥ 10 means 10 or more RA visits during study period.

[d]DM2 and MI are given as increase in HR per number of registrations with DM2 or MI.

Our findings are based on data from two large nationwide registries, rendering a large study population with >300,000 patients including more than 33,000 patients with RA. This provides high power and consistent results, as illustrated by the narrow confidence intervals. Also, the statistical methods used in the study were particularly suited to the study material, as the analyses take into account the order of events (RA visits and periodontitis occurrences). Hence, the number of RA visits, periodontitis occurrences as well as the sequence of these are considered. Some degree of uncertainty and possible miscoding may be present in both databases (NPR and KUHR), but in these analyses one incorrect RA code will have negligible influence on the results. Ten or more hospital visits coded with RA as the main diagnostic code during a 7-year period is highly probable of de facto RA. Thus, our finding of a 50% increased risk of periodontitis among these patients is highly suggestive of an association. Invalid reimbursement claims may happen, but we have no reason to suspect a different degree of such mistakes in RA patients compared to controls.

For periodontitis, reimbursement codes for systematic periodontal treatment were used as a surrogate for periodontal disease. KUHR records no information on periodontal disease severity; therefore, the frequency of systematic periodontal treatment (code 501) was used as a surrogate marker to reflect the severity of periodontitis in our study. Also, we included the use of code 502, which is specific for periodontal surgery. Using register data as surrogate markers for periodontal disease is also known from other studies (Nordendahl et al., 2021).

Patients with RA were included as controls until their first registered RA visit. This was done to avoid immortal time bias. Hence, all patients should be followed from the date of inclusion. Repeated RA visits would then be included as standard time-dependent covariates. Consequently, some periodontitis cases pertaining to RA patients were allocated to the control cohort. Defining the RA patients as controls before the first registered RA visit would, however, tend to erase possible differences between RA patients and controls. The detected risk estimate for RA patients compared to controls may consequently be too low. It is also worth mentioning that the results of the present analysis are based on the fact that periodontitis succeeds RA. This does not mean that RA causes periodontitis, because there may be common causes preceding both RA and periodontitis. However, the analysis in the present study has a stronger design than just using aggregated data for the follow-up period, ignoring the sequence of periodontitis and RA.

The comparative cohort consisted of patients having conditions without a known association to periodontitis: knee and hip arthroplasty due to osteoarthritis and assumed non-osteoporotic fractures. However, one recent study found an increased risk of periodontitis in patients with osteoarthritis (Ma et al., 2022). If this is the case, our reported risk estimate for periodontitis in RA compared to controls should be higher. Even so, the distribution of comorbidities associated with increased periodontitis risk may have been different for the RA patients and controls. To address this, we adjusted for some known risk factors, including DM2 (Loe, 1993; Mealey, 2006; Nascimento et al., 2018; Taylor et al., 2013), MI (Lockhart et al., 2012; Stewart & West, 2016) and age.

Unfortunately, we lacked information on smoking habits for the two study populations. Cigarette smoking is a known risk factor for losing periodontal support and eventual loss of teeth (Chaffee et al., 2021). A common weakness of our study as well as several other studies addressing the connection between RA and periodontitis, is not evaluatng the effect of smoking. Nevertheless, in a stepwise logistic regression including RA status, age, sex, education, smoking, alcohol consumption and BMI, RA status and age remained significant predictors of periodontal disease (Pischon et al., 2008). We argue that the findings of our study represent a true association, although we cannot conclude on the causal mechanisms (Koziel & Potempa, 2022). Nevertheless, we advise taking measures to prevent and adequately treat periodontitis, particularly for patients with newly diagnosed RA.

In conclusion, in this register-based study in which periodontal treatment was used as a surrogate marker for periodontitis, we found an increased risk of periodontitis in patients with RA and particularly in patients with active and new RA. There may be several reasons for the association, but as these two inflammatory diseases may have a synergistic negative effect on the host, it is important that health practitioners are aware of this.

AUTHOR CONTRIBUTIONS

Anne Isine Bolstad was responsible for study conception and design, data interpretation and drafting of the manuscript. Bjørg-Tilde Svanes Fevang was responsible for the study design, data interpretation, and drafting of the manuscript. Stein Atle Lie was responsible for the design, statistical analysis and data interpretation. All authors critically reviewed the work and gave final approval and agreed to be accountable for all aspects of it to ensure integrity and accuracy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Norwegian Patient Registry (NPR) and Norwegian Control and Payment of Health Refunds (KUHR), The Norwegian Directorate of Health (HDIR), at https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/kuhr and https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr.

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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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