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# Association Between Rheumatoid Arthritis Disease Activity and Periodontitis Defined by Tooth Loss: Longitudinal and Cross-Sectional Data From Two Observational Studies

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**Objective.** To analyze the effect of tooth loss/periodontitis on disease activity in early and established rheumatoid arthritis (RA).

**Methods.** Participants of the Course And Prognosis of Early Arthritis (CAPEA) early arthritis cohort reported their number of teeth at baseline. The number of teeth had been validated as a predictor of periodontitis. Clinical end points, including disease activity score (Disease Activity Score in 28 joints using the erythrocyte sedimentation rate [ESR]), swollen joint count (SJC), ESR, and C-reactive protein level were collected at baseline, 3, 6, 12, 18, and 24 months. We used linear mixed regression models to estimate the association between tooth loss and clinical end points over time in early arthritis. For established RA, we analyzed cross-sectional data from the German National Database (NDB). All models accounted for age, sex, smoking, seropositivity, education level, and disease duration (only NDB).

**Results.** Among 1,124 CAPEA participants with early arthritis, those with higher tooth loss were older, more often male, smokers, and seropositive, and they had higher disease activity and inflammation markers at baseline. Tooth loss was associated with higher disease activity and ESR values over time. Inflammatory markers decreased comparably across tooth loss categories. Glucocorticoid use was higher among those with more tooth loss, whereas dose reduction was similar across tooth loss categories. Among 7,179 NDB participants with longstanding RA, disease activity and inflammation markers but not SJC were significantly higher in patients with more tooth loss.

**Conclusion.** Although we observed an association between tooth loss and disease activity scores and inflammation markers in early and established RA, longitudinal results suggest that tooth loss does not hamper treatment response.

## INTRODUCTION

Rheumatoid arthritis (RA) and chronic periodontitis are common chronic inflammatory diseases linked by clinical and pathobiologic similarities (1). In patients with RA, tooth loss and periodontitis are highly prevalent (1–5). A population-based study resulted in a more than 2-fold increased rate of complete tooth loss in patients with RA compared with patients without RA after adjusting for confounders (3). Tooth loss, periodontitis, and arthritis have common underlying proinflammatory mechanisms, triggering inflammatory processes in the periodontium as well as in the synovium. Chronic periodontitis leads to the loss of the periodontal ligament and alveolar bone, which ultimately causes tooth loss. Several characteristics are found in the pathogenesis of RA

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**SIGNIFICANCE & INNOVATIONS**

- Tooth loss and/or periodontitis are frequent in patients with rheumatoid arthritis (RA).
- Increased disease activity scores and inflammation markers are associated with periodontitis as defined by tooth loss in both early and established RA.
- Response to therapy is not hampered by periodontitis as defined by tooth loss.
- Periodontitis/tooth loss has a clinical impact on RA and should be considered in the evaluation of RA disease activity.

as well as in periodontitis, including the presence of cytokine profiles, citrullinated proteins, peptide epitopes, and an association with HLA–DRB1, interleukin 1ß, and tumor necrosis factor-α polymorphisms (3). Various theories related to common risk factors, genetic links, bacterial citrullination, and cytokine imbalance exist to explain a biological link between RA and periodontitis (6). In terms of clinical relevance, results of cross-sectional studies suggest a relationship between the presence of tooth loss or periodontitis and disease activity in patients with RA (7,8). Tooth loss and the severity of periodontal disease were found to be associated with the presence and levels of anti–citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) (9,10). There is still insufficient evidence whether and how periodontitis influences the course of arthritis and response to therapy (11,12). Preliminary data from our study have shown a higher need for glucocorticoids in patients with RA and tooth loss. Using tooth loss as an indicator of periodontitis, we hypothesized that tooth loss is a predictor of higher inflammatory activity in early arthritis. The purpose of our study was to investigate the influence of the number of teeth on RA disease activity and individual disease activity markers within the first 2 years after symptom onset in patients with early arthritis enrolled in the Course And Prognosis of Early Arthritis (CAPEA) cohort study (13). To investigate this association in patients with established RA, we also used cross-sectional data from the German National Database (NDB) in which high numbers of real-life patients with RA are recorded annually (14).

## PATIENTS AND METHODS

**Data sources.** We used longitudinal data from the CAPEA early arthritis cohort to analyze the effect of the number of teeth on disease activity markers within the first 2 years of early arthritis. CAPEA is a prospective, multicenter, longitudinal, observational study, conducted between 2010 and 2013 (13). Eligible patients had inflammatory arthritis for less than 6 months, confirmed by a physician at enrollment. They were consecutively enrolled in rheumatology clinics and practices in Germany and observed for 2 years in order to investigate the prognostic value of early symptoms for the development of persistent disease. Study visits were performed at 0, 3, 6, 12, 18, and 24 months. Ethical approval for the CAPEA study was obtained from the Ethics Committee of the Charité University Medicine, Berlin, in May 2009 (EA1/091/09).

Cross-sectional data of patients with established RA were derived from the NDB of the German Collaborative arthritis

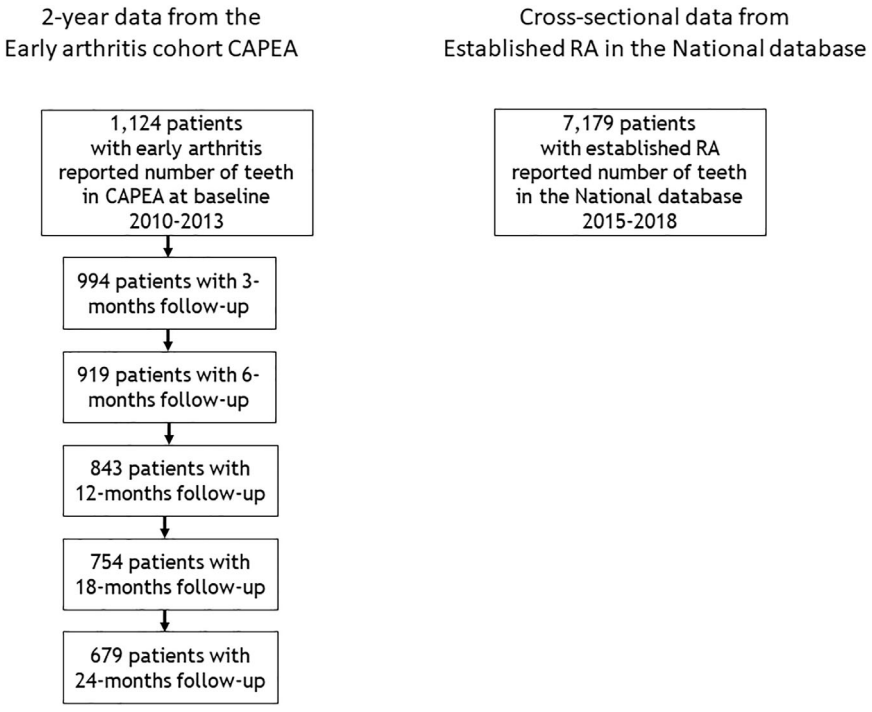


**Figure 1.** Flow chart. CAPEA = Course And Prognosis of Early Arthritis; RA = rheumatoid arthritis.

**Table 1.** Early arthritis cohort (CAPEA) baseline characteristics*

| Characteristics | Number of teeth present | | | | Total |
|---|---|---|---|---|---|
| | 0 | 1–19 | 20–27 | All 28 | |
| N | 89 | 315 | 452 | 268 | 1,124 |
| Female, %† | 57 | 65 | 64 | 69 | 65 |
| Age, mean ± SD years† | 69 ± 11 | 64 ± 10 | 54 ± 12 | 45 ± 15 | 56 ± 15 |
| ESR, mm, mean ± SD‡ | 42 ± 28 | 38 ± 25 | 28 ± 20 | 24 ± 21 | 31 ± 23 |
| Median (IQR) | 32 (40) | 32 (38) | 23 (28) | 18 (19) | 24 (32) |
| CRP (mg/liter), mean ± SD§ | 25 ± 30 | 24 ± 41 | 15 ± 22 | 15 ± 33 | 19 ± 32 |
| Median (IQR) | 13 (26) | 12 (25) | 7 (15) | 5 (11) | 8 (17) |
| TJC, mean ± SD¶ | 9.4 ± 6.6 | 9.6 ± 6.8 | 7.6 ± 6.4 | 7.7 ± 6.7 | 8.3 ± 6.7 |
| SJC, mean ± SD# | 6.1 ± 4.9 | 6.9 ± 5.6 | 5.6 ± 4.9 | 5.2 ± 5.0 | 5.9 ± 5.2 |
| DAS28-ESR, mean ± SD** | 5.5 ± 1.2 | 5.2 ± 1.2 | 4.7 ± 1.2 | 4.5 ± 1.3 | 4.9 ± 1.3 |
| Global Health, 0–10, mean ± SD† | 5.7 ± 2.4 | 5.6 ± 2.3 | 5.1 ± 2.2 | 5.1 ± 2.3 | 5.3 ± 2.3 |
| BMI, kg/m$^2$, mean ± SD†† | 28 ± 5 | 28 ± 5 | 27 ± 5 | 26 ± 5 | 27 ± 5 |
| RF positive, %† | 63 | 53 | 52 | 54 | 54 |
| ACPA positive, %‡‡ | 45 | 36 | 39 | 41 | 39 |
| GCs, %† | 75 | 77 | 71 | 67 | 72 |
| csDMARDs, %§§ | 56 | 60 | 54 | 60 | 58 |
| Education, %¶¶ | | | | | |
| ≤8 years | 80 | 58 | 35 | 21 | 42 |
| 9–10 years | 16 | 30 | 43 | 46 | 38 |
| 11–13 years | 4 | 12 | 22 | 33 | 20 |
| Smoking (ever), %## | 73 | 64 | 61 | 56 | 61 |

* N = 4 patients had initial biologic DMARD therapy. ACPA = anti-citrullinated peptide antibodies; BMI = body mass index; CAPEA = Course And Prognosis of Early Arthritis; CRP = C-reactive protein; csDMARDs = conventional synthetic disease-modifying antirheumatic drug (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine A); DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; GC = glucocorticoid; IQR = interquartile range; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count.
† Data are from 1,124 patients.
‡ Data are from 1,074 patients.
§ Data are from 1,069 patients.
¶ Data are from 1,121 patients.
# Data are from 1,120 patients.
** Data are from 983 patients.
†† Data are from 1,114 patients.
‡‡ Data are from 1,123 patients.
§§ Data are from 1,118 patients.
¶¶ Data are from 1,020 patients.
## Data are from 1,102 patients.

centers. The NDB is a long-term monitoring database for German rheumatology practice. Participating rheumatologists from private practices and tertiary outpatient clinics consecutively include unselected patients with inflammatory rheumatic diseases. The database provides annually updated information on patients with inflammatory rheumatic diseases under rheumatologic care, covering data on laboratory test results, clinical and patient-reported outcomes, and antirheumatic therapy (14). Patients who had documented their tooth count between 2015 and 2018 were included, selecting the most recent data if several entries were available. Ethical approval for the NDB was obtained from the Ethics Committee of the Charité University Medicine, Berlin, in February 2007 (EA1/196/06), which was updated in May 2019. Both research projects were conducted in agreement with the Declaration of Helsinki.

**Definition of periodontitis.** We had previously developed a patient-reported questionnaire to assess periodontitis in patients with early arthritis, validated by radiographs and blinded dentists' assessment within CAPEA (15). A 6-item score turned out to be suitable for investigating periodontitis in RA with moderate diagnostic properties. However, missing teeth challenge the validity of self-reported periodontitis, especially in the case of increased occurrence as in RA (16). In CAPEA, 8% of the patients were edentulous and could not provide additional information on the periodontitis questionnaire. The periodontitis questionnaire was completed by a subset of patients (n = 353). During the validation process, we found that the number of teeth alone was a good predictor of periodontitis. We therefore used the number of teeth as a surrogate for periodontitis, as previously done by Coburn et al (16). The number of teeth has a further advantage because it can easily be included in additional data collections. As a result, we could use data from the NDB for a comparative sensitivity analysis.

**Data assessment.** Study participants reported the number of teeth at baseline in CAPEA and at the annual visit in the NDB,

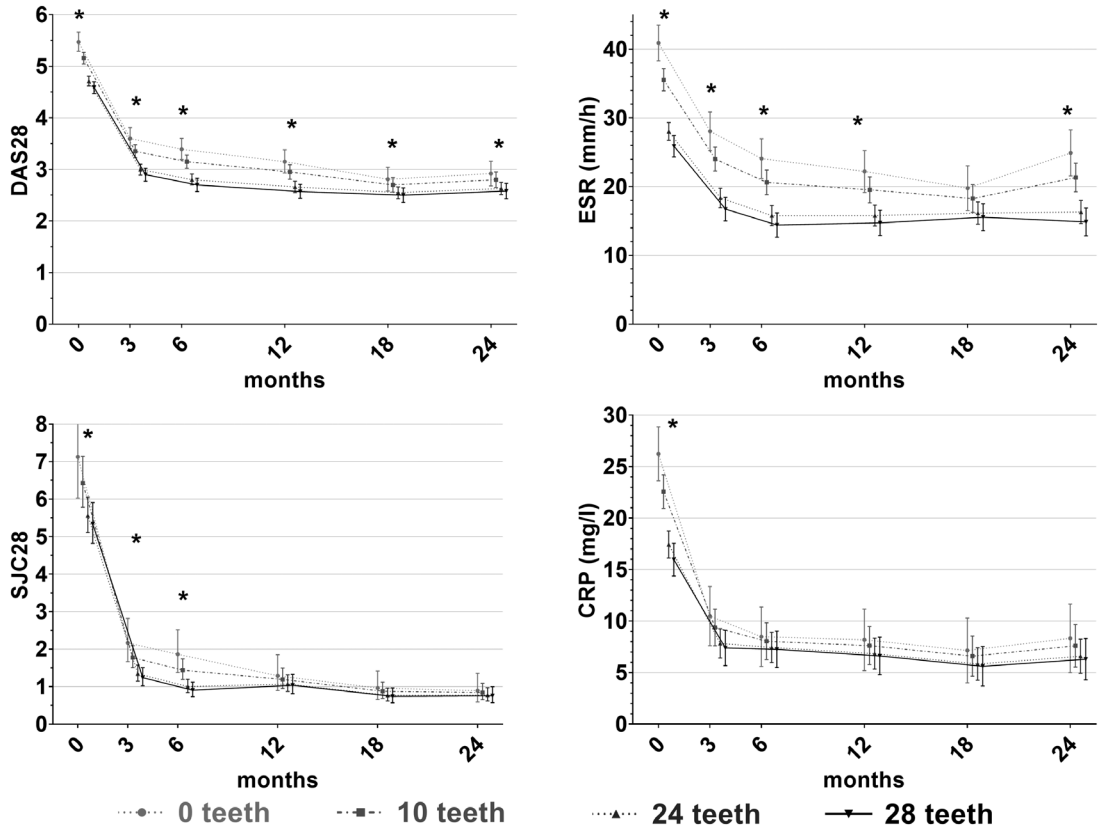


**Figure 2.** Disease activity and inflammatory markers during 2 year follow-up, stratified by number of teeth. CAPEA results from linear mixed models for DAS28, ESR, and CRP and from generalized linear models with negative binomial distribution for SJC28 adjusted for age, sex, smoking, RF, ACPA, and education level. Bars show 95% confidence intervals. * = $P < 0.05$ for the effect of number of teeth at this time point. Number of teeth was entered as a continuous variable in the models. For illustrative purposes, we show the least square means for selected number of teeth at all time points. ACPA = anti-citrullinated peptide antibodies; CAPEA = Course And Prognosis of Early Arthritis; CRP = C-reactive protein; DAS28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; SJC28 = swollen joint count for 28 joints.

based on the following questionnaire item: "How many of your own teeth do you have (including crowned teeth)," and a number between 0 to 28 was requested. For the NDB data analyses, the first recorded number of teeth that was available for a patient was used.

Baseline characteristics reported in both databases included age, sex, disease duration, smoking (no/current/ever), education (≤8/9–10/11–13 years of school), body mass index (in mg/kg$^2$), and the presence of RF and ACPA. Both were assessed and reported by the rheumatologists.

In both databases, rheumatologists reported disease activity markers at each visit, including erythrocyte sedimentation rate (ESR in mm/hour), C-reactive protein (CRP in mg/liter) level, the number of tender (TJC) and swollen joints based on 28 joints (SJC28), patient-reported global health (from 0–10, 10 being the worst rating), and the Disease Activity Score in 28 joints using the ESR (DAS28-ESR). Antirheumatic therapy, including conventional synthetic and biologic disease-modifying antirheumatic drugs (cs/bDMARDs) and glucocorticoid (GC) use, were reported at each visit (yes/no), with the daily prednisolone equivalent dose in mg/day.

**Statistical analysis.** Baseline data are reported as categories of the number of teeth (0, 1–19, 20–27, 28), based on Kim et al (17). The number of available data are reported for each parameter. Missing values from the NDB were replaced by multiple imputation using a fully conditional sampling method with 20 imputations.

For the CAPEA study, we used linear mixed models to assess the influence of the number of teeth at each study visit (0, 3, 6, 12, 18, and 24 months) on disease activity (DAS28) and inflammation markers (ESR and CRP). A generalized linear model with negative binomial distribution was used to assess the influence of number of teeth on swollen joint counts (SJC28), because this distribution models count data. The percentage of patients with GC use was estimated using a generalized linear mixed model, and the mean dosage of patients who were taking GCs was estimated with a linear mixed model. All models were adjusted for age, sex, RF positivity, smoking (ever vs. never) and education level, defined as years in education. The confounders were selected by clinical relevance as reported previously (3,8,16). The exposure, number of teeth, was entered as a

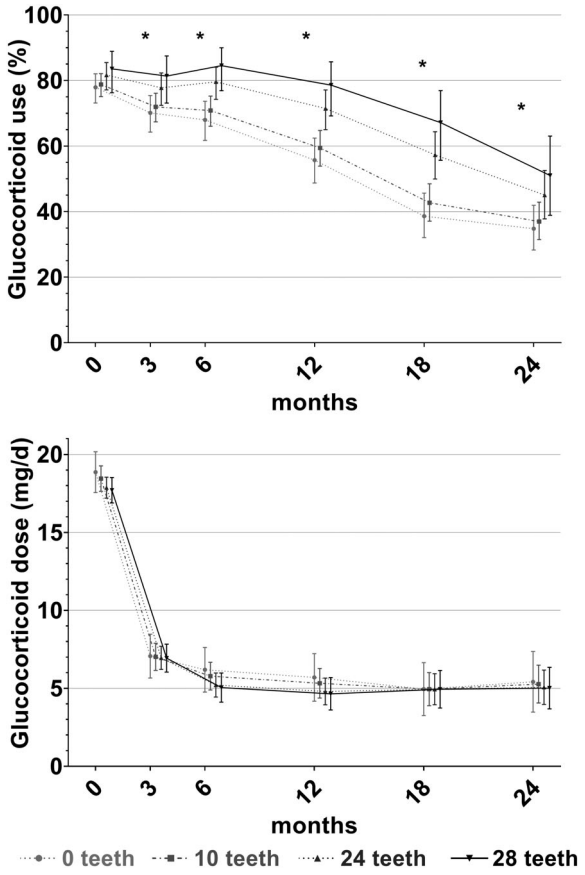


**Figure 3.** Glucocorticoid use during 2-year follow-up, stratified by number of teeth. CAPEA results from generalized linear mixed model and binomial distribution for the proportion of patients with glucocorticoid therapy and from a linear mixed model adjusted for age, sex, smoking, RF, and education level. Bars show 95% confidence intervals. * = $P < 0.05$ for the effect of number of teeth at this time point. Number of teeth was entered as a continuous variable in the models. For illustrative purposes, we show the least square means for selected number of teeth at all time points. CAPEA = Course And Prognosis of Early Arthritis; RF = rheumatoid factor.

continuous variable in all models. For visualization purposes, we chose to show least square means for selected number of teeth (0, 10, 24, and all 28). The influence of tooth loss on the outcomes was tested for each time point, and *P* less than 0.05 was considered statistically significant.

For the NDB data, linear regression models were used to adjust DAS28, ESR, and CRP level for age, sex, disease duration, RF, smoking, and education level. A generalized linear model with negative binomial distribution was used to adjust SJC28 for the same variables. We used box plots to illustrate the association between the number of teeth and DAS28, ESR, CRP, and SJC at the first time point the number of teeth was collected in this sample. Additionally, we used linear mixed models (for DAS28, CRP, and ESR) and a generalized linear mixed model with negetive binomial distribution for SJC to assess if tooth loss had an influence on these parameters over the course of up to 3 years. These models were adjusted for age, sex, presence of RF, presence of ACPA, smoking (ever vs. never), disease duration, and education level, defined as years in education.

The data sets analyzed in the current study are not publicly available because we respect our patients' right to privacy. Consent for publication of the data set was not obtained at the start of recruitment to the studies.

## RESULTS

**Early arthritis cohort (CAPEA) baseline characteristics.** Among 1,124 CAPEA participants included, the mean disease duration was 13 ± 7 weeks, 65% were female, and the mean age was 56 years. Complete 24-month follow-up data were available for 679 patients (Figure 1).

RA diagnosis was confirmed in 91% of participants during follow-up via a clinical diagnosis by a rheumatologist. American College of Rheumatology (ACR)/European League Against Rheumatism 2010 criteria were fulfilled by 74% and ACR 1987 criteria by 57%. At baseline, of the 1,124 participants, 24% had all 28 teeth present, 40% had 20–27 teeth, 28% had 1–19 teeth, and 8% were edentulous. Those with higher tooth loss were older, more often male, more frequently smokers, and more often seropositive, and they had higher disease activity (DAS28-ESR) and inflammation marker (both ESR and CRP) values at baseline. In the edentulous group, 80% had less than 8 years of school education, whereas only 21% in the group with all teeth present had this level of education. Participants with early RA and complete dentition had the highest level of education. Tooth loss was associated with more GCs use (Table 1).

**Disease activity and inflammatory markers during 2-year follow up.** The number of teeth had a statistically significant influence on disease activity (DAS28) at every study visit during follow-up. There was a significant association between the number of teeth and ESR at every visit, except for the 18-month visit, and with CRP level at baseline. The influence on CRP level and SJC disappeared over time. There was a significant association between the number of teeth and SJC in the first 6 months of follow-up and no difference in the joint counts between groups afterward (Figure 2). The coefficients for the influence of tooth loss on the respective outcomes are shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24799.

**GC use during 2-year follow-up.** Tooth loss was significantly associated with a higher percentage of GC use at all study visits after baseline, based on the generalized linear mixed model analysis. The mean adjusted starting doses were 18 mg/day in patients with all teeth and 19 mg/day in patients with no teeth. In general, GC doses were reduced to a mean dose of 5 mg/day in the first 3 months for all patients, independent of their number

of teeth. GC dose was not associated with tooth loss (Figure 3). The coefficients for the influence of tooth loss on GC use and GC dose are shown in Supplementary Tables 2 and 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24799.

**NDB patient characteristics.** Among 7,179 NDB participants included, mean disease duration was 13 years, 74% were female, and the mean age was 62 years. Of those, 21% had all 28 teeth, 41% had 20–27 teeth, 27% had 1–19 teeth, and 11% were edentulous. Patients with higher tooth loss were older, more often male, more frequently smokers, and more often seropositive, and they had higher ESR, CRP level, DAS28, TJC, SJC, and patient global assessments. In the edentulous group, 62% had up to 8 years of school education, whereas only 19% in the group with all teeth had this level of education. Participants with established RA and complete dentition had the highest level of education. Edentulous patients received GCs and csDMARDs more often, whereas bDMARDs were used less frequently (Table 2).

**Association between tooth loss and disease activity markers in established RA.** After adjusting for age, sex, disease duration, RF, smoking, and education level with generalized linear models, disease activity score and inflammatory markers were linearly associated with tooth loss categories (DAS28 no teeth 2.7, all teeth 2.4; ESR no teeth 23 mm/hour, all teeth 17 mm/hour). For all outcomes considered in Figure 4, there was a statistically significant association of tooth loss with the

**Table 2.** NDB patient characteristics*

| | Number of teeth present | | | | |
|---|---|---|---|---|---|
| | 0 | 1–19 | 20–27 | All 28 | Total |
| N | 793 | 1,922 | 2,928 | 1,536 | 7,179 |
| Female, %† | 69 | 72 | 74 | 80 | 74 |
| Age, mean ± SD years† | 73 ± 9 | 67 ± 12 | 62 ± 12 | 52 ± 16 | 62 ± 15 |
| Disease duration, mean ± SD years† | 15.2 ± 12 | 14.4 ± 11 | 12.8 ± 10 | 11.0 ± 9 | 13.1 ± 11 |
| Median (IQR) | 13.0 (16.2) | 12.0 (15.3) | 10.3 (14.4) | 8.4 (11.7) | 10.6 (14.4) |
| ESR, mm/hour, mean ± SD‡ | 26 ± 20 | 21 ± 17 | 18 ± 16 | 16 ± 14 | 19 ± 17 |
| Median (IQR) | 20 (25) | 16 (20) | 14 (18) | 11 (14) | 14 (19) |
| CRP, mg/liter, mean ± SD§ | 10 ± 17 | 8 ± 12 | 7 ± 21 | 7 ± 18 | 8 ± 18 |
| Median (IQR) | 5 (7) | 4 (6) | 4 (5) | 3 (4) | 4 (5) |
| TJC, mean ± SD¶ | 2.3 ± 3.9 | 2.2 ± 3.9 | 1.8 ± 3.6 | 1.5 ± 3.2 | 1.9 ± 3.7 |
| SJC, mean ± SD# | 1.4 ± 2.5 | 1.4 ± 2.8 | 1.1 ± 2.4 | 1.0 ± 2.4 | 1.2 ± 2.5 |
| DAS28-ESR, mean ± SD** | 3.5 ± 1.3 | 3.2 ± 1.2 | 3.0 ± 1.2 | 2.7 ± 1.2 | 3.0 ± 1.2 |
| Patient global, 0–10, mean ± SD†† | 4.7 ± 2.3 | 4.3 ± 2.2 | 4.1 ± 2.2 | 3.5 ± 2.2 | 4.1 ± 2.3 |
| BMI, kg/m$^2$, mean ± SD‡‡ | 27 ± 5 | 27 ± 5 | 27 ± 5 | 25 ± 5 | 26 ± 5 |
| RF positive, %§§ | 61 | 60 | 56 | 54 | 57 |
| ACPA positive, %¶¶ | 59 | 61 | 53 | 55 | 56 |
| GCs, %## | 49 | 47 | 40 | 33 | 41 |
| csDMARDs, %*** | 72 | 70 | 70 | 67 | 70 |
| bDMARDs, %††† | 23 | 28 | 27 | 28 | 27 |
| Education, %‡‡‡ | | | | | |
| ≤8 years | 62 | 41 | 32 | 19 | 35 |
| 9–10 years | 25 | 37 | 38 | 34 | 36 |
| 11–13 years | 13 | 22 | 30 | 47 | 30 |
| Smoking (ever), %§§§ | 61 | 58 | 56 | 46 | 55 |

* ACPA = anti-citrullinated peptide antibodies; bDMARDs = biologic disease-modifying antirheumatic drugs (TNF inhibitors, abatacept, rituximab, tocilizumab); BMI = body mass index; CRP = C-reactive protein; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine); DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; GC = glucocorticoid; IQR = interquartile range; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count.
† Data are from 7,179 patients.
‡ Data are from 5,885 patients.
§ Data are from 6,845 patients.
¶ Data are from 6,881 patients.
# Data are from 6,880 patients.
** Data are from 5,718 patients.
†† Data are from 7,015 patients.
‡‡ Data are from 6,147 patients.
§§ Data are from 7,017 patients.
¶¶ Data are from 4,489 patients.
## Data are from 7,133 patients.
*** Data are from 5,239 patients.
††† Data are from 7,134 patients.
‡‡‡ Data are from 6,340 patients.
§§§ Data are from 6,732 patients.

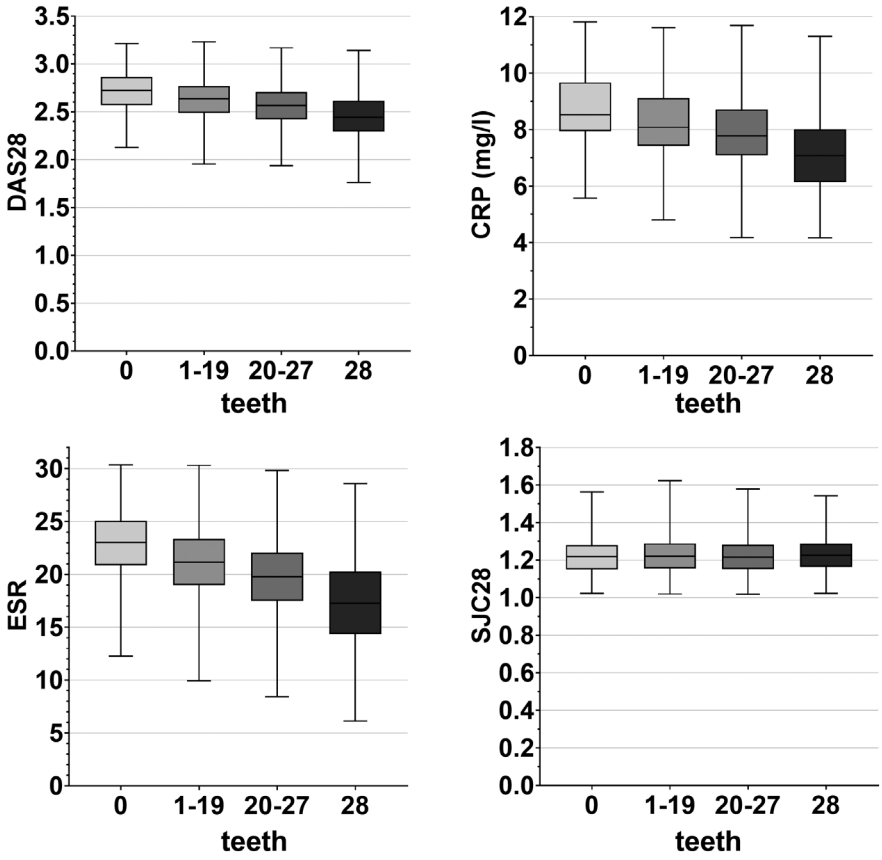


**Figure 4.** Association between number of teeth and disease activity and inflammatory markers in established RA. National database predicted values from generalized linear models, adjusted for age, sex, disease duration, RF, ACPA, smoking, and education level. Boxes show 25th percentile, median, and 75th percentile. Whiskers range from minimum to maximum. ACPA = anti-citrullinated peptide antibodies; CRP = C-reactive protein; DAS28 = disease activity score of 28 joints; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor; SJC28 = swollen joint count for 28 joints.

outcome. But there was no clinically meaningful association between groups of tooth loss and SJC (Figure 4).

## DISCUSSION

To investigate the clinical relevance of a relationship between periodontitis and RA, we analyzed the impact of tooth loss on inflammatory markers and disease activity scores using data of two separate national cohorts, representing both participants with early and established RA. Our results show a significant association between tooth loss severity and increased inflammatory markers, in particular ESR, as well as higher disease activity scores over time. However, there was no relationship between tooth loss and joint swelling. Longitudinal data indicate successful reduction of disease activity, independent of tooth loss.

In early arthritis, tooth loss was differentially associated with various inflammatory markers. Whereas ESR values were significantly higher in patients with fewer teeth and remained higher throughout the 2-year course of treatment, a difference in CRP values was only present before the start of treatment. Increased ESR values do not necessarily reflect solely RA activity. The composite activity score DAS28-ESR reflected the association with ESR. Patients with fewer teeth had slightly more swollen joints in the first year, but there was no difference thereafter because disease activity levels were similar between groups, likely because of response to therapy. NDB data confirmed the association with elevated ESR and CRP levels and tooth loss categories, but no clinically relevant difference in the number of swollen joints in participants with long-standing RA, who have an average disease duration of more than 10 years. Ultimately, none of the differences are clinically important.

The relationship found between tooth loss and inflammatory markers or disease activity indices is in line with data from a recent case-control study by Rodríguez et al that confirmed a significant association between severe periodontitis, assessed by periodontal examination, and RA disease activity, as assessed by different disease activity indices (8). In a recent review, Manzo and Kechida suggested that severe periodontitis should always be treated before evaluating RA disease activity to avoid unnecessary therapeutic modifications (18). We partly agree on this point, because

the more frequent use of GC in patients with tooth loss, which was present in both cohorts, may have been caused not only by more active disease but also extra-articular inflammation. Further to a successful reduction of disease activity, GC tapering was achieved in almost all patients regardless of their number of teeth, so that we found no evidence of a worse response to therapy or refractory disease activity in relation to tooth loss. The lack of association between tooth loss and joint swelling also fits with the findings of Rodríguez et al in that functional disability, as measured by the Health Assessment Questionnaire, was not associated to presence of periodontitis in RA (8).

There have been discussions and studies on whether nonsurgical periodontitis therapy leads to an improvement in RA outcomes (19,20). Results of clinical studies suggest a beneficial effect of periodontitis therapy on RA disease activity (1). A meta-analysis of five clinical trials showed significant improvement in ESR values only. All studies had small case numbers with a study duration of no longer than 6 months (21). The effect shown on ESR matches our results suggesting that inflammatory activity from periodontitis is reflected in increased ESR but does not necessarily lead to increased activity in the joint. In a recent small randomized controlled trial (n = 22), periodontal treatment resulted in significant improvements of periodontal health but had no effects on the DAS28-ESR within 3 months (22).

Tachibana et al investigated the response to biologic therapy using fluorodeoxyglucose-positron emission tomography/computed tomography for periodontitis assessment (11). They found a negative correlation between periodontitis activity and DAS28-CRP reduction within 6 months, but correlations were not significant when adjusted for smoking and ACPA values.

A relative limitation of our study is that we used the patient-reported number of teeth as an indicator for periodontitis, and the periodontal/tooth status was not assessed by a dentist. However, self-reported number of teeth has been shown to be a valid indicator of the true number of teeth present on dental examination (23). Furthermore, we performed dental assessments and x-rays in a subset of CAPEA participants. When validating the periodontitis score, the number of remaining teeth was the item correlating best with the different assessments of periodontitis. Using age and the patient-reported number of remaining teeth resulted in a sensitivity of 86% to detect any periodontitis and a specificity of 78% to detect severe periodontitis (15). Major strengths of our study are that it includes data from two large national patient samples including both early as well as longstanding RA. Because of similar data collection strategies in both cohorts, important risk factors contributing both to periodontitis and RA, such as age, male sex, smoking, RF, and education level, were entered as confounders in all models. The CAPEA data were collected 10 years ago, and treatment options have improved since then. This should be taken into account in the interpretation.

To conclude, our data suggest a clear independent association between increased inflammation markers and periodontitis as defined by tooth loss but not with swollen joint counts as a measure of synovitis, in both patients with early arthritis and longstanding established RA over time. The patient-reported tooth count may be a helpful tool to consider periodontitis when evaluating RA disease activity and raised inflammatory markers. Longitudinal data suggest that periodontitis/tooth loss does not hamper response to therapy because reduction of disease activity and tapering of GCs were successful regardless of the number of teeth.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Callhoff had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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