# Is tooth extraction as proxy for periodontal disease related to the development of RA? Lessons from a longitudinal study in the at-risk stage of clinically suspect arthralgia

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# Is tooth extraction as proxy for periodontal disease related to the development of RA? Lessons from a longitudinal study in the at-risk stage of clinically suspect arthralgia

Emerging evidence points to the involvement of periodontal disease (PD) in the pathogenesis of rheumatoid arthritis (RA), especially in anti-citrullinated protein antibodies (ACPA)-positive RA. The bacteria *Porphyromonas gingivalis*, involved in oral mucosal inflammation and PD, can citrullinate proteins via prokaryotic peptidylarginine deiminase.[1] Systemic translocation of oral bacteria has been found in RA-patients with PD. These bacterial translocations have been implicated in the generation of anti-modified protein antibodies (AMPAs) as ACPA can also recognise modified bacterial proteins.[2] Nevertheless, the 'cause-consequence' relation between PD and RA remains debatable as PD may be a risk factor (PD→RA; scenario 1; figure 1A) but also a consequence of RA (RA→PD; scenario 2).[3] Additionally, the relation PD→RA may be confounded by related factors (eg, body mass index (BMI), smoking or other factors related to socioeconomic status (SES); scenario 3). Increased prevalence of periodontitis and *P. gingivalis* were reported in ACPA-positive/autoantibody-positive at-risk individuals in case–control/cross-sectional studies.[4 5] Longitudinal studies on PD in at-risk individuals could elucidate temporal relationships and provide further insight into the relation of PD in RA-development. Therefore, we longitudinally analysed the relation between tooth loss as proxy for (preceding) PD and progression to clinically apparent inflammatory arthritis (IA) and RA in patients with clinically suspect arthralgia (CSA). We also studied whether this relation is independent of SES and SES-related factors.

700 CSA-patients consecutively included in the Leiden CSA-cohort or placebo arm of the TREAT EARLIER-trial were studied (online supplemental S1). Patients completed a questionnaire at study-entry determining if they had teeth and/or molars extracted other than wisdom teeth. Because PD is a prevalent reason for tooth extraction, tooth extraction was considered a proxy for preceding PD or

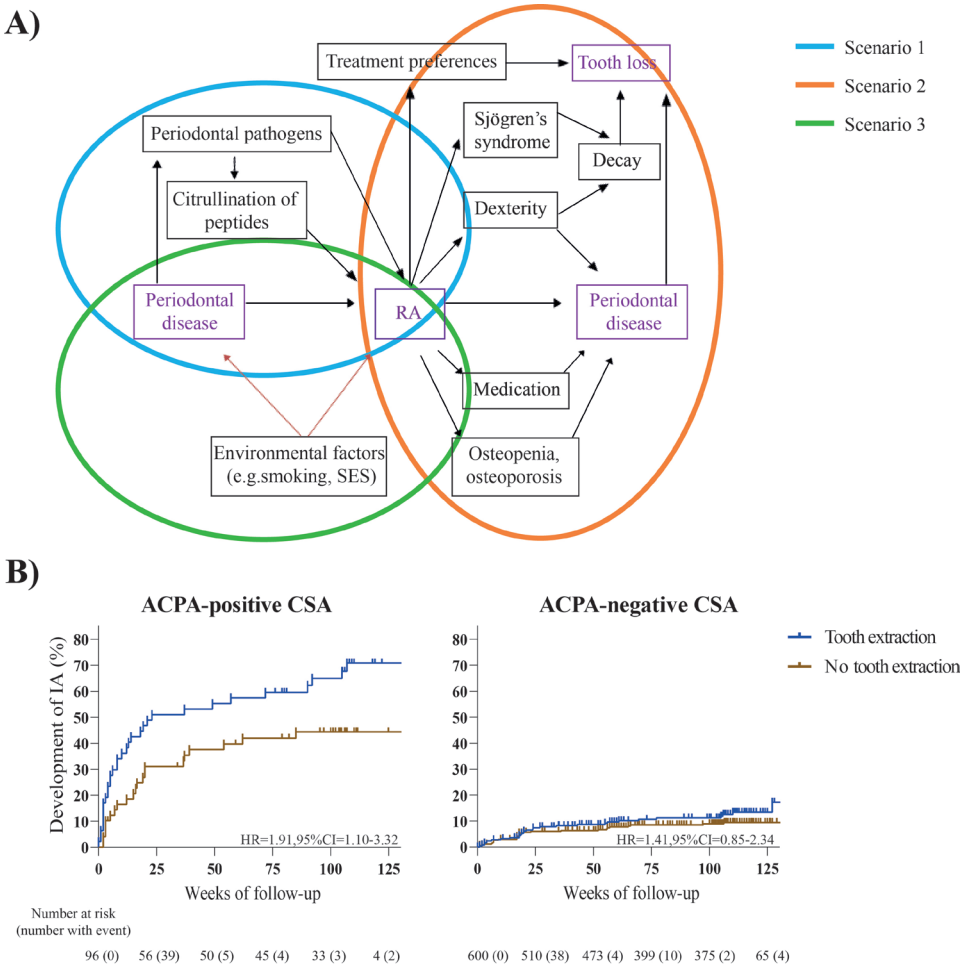


**Figure 1** Conceptual framework of hypotheses on periodontal disease and RA (A) and the development of inflammatory arthritis in ACPA-positive and ACPA-negative clinically suspect arthralgia according to tooth extraction (B). (A) The coloured circles represent the three hypotheses on the relation between PD and RA, inspired by de Pablo *et al*.[3] Scenario 1 in blue: PD is a risk factor for RA. Scenario 2 in orange: RA is a risk factor for PD. Scenario 3 in green: the association between PD and RA is driven by confounding factors such as smoking and SES. (B) Development of IA in ACPA-positive and ACPA-negative patients with clinically suspect arthralgia is shown according to tooth extraction, which is a late-stage of periodontal disease, showing a relation between tooth extraction and IA-development in ACPA-positive CSA-patients. ACPA, anti-citrullinated protein antibody; CSA, clinically suspect arthralgia; IA, inflammatory arthritis; PD, periodontal disease; RA, rheumatoid arthritis; SES, socioeconomic status.

late-stage of PD.[6] CSA-patients were followed for 2 years for IA-development. RA-development was also studied, defined as IA plus fulfilment of 2010/1987-classification criteria. ACPA-stratified Cox-regression was used with adjustments for educational attainment (as proxy for SES), smoking, BMI and age, and additionally for presence of MRI-detected subclinical joint-inflammation.

At baseline, 306 CSA-patients (44%) had previous tooth extraction. These patients were older than patients without tooth extraction (48.7 vs 41.4 years; online supplemental S2), more often had a low educational attainment (15% vs 8%), a higher BMI (27.8 vs 26.3), more often smoked (66% vs 51%) and had subclinical joint-inflammation (57% vs 47%). ACPA-positive CSA-patients with tooth extraction more often progressed to IA than ACPA-positive patients without tooth extraction (HR=1.91, 95% CI 1.10–3.32, p=0.022), while this association was not significant in ACPA-negative CSA (HR=1.41, 95% CI 0.85–2.34, p=0.19; figure 1B). After correcting for SES, smoking, BMI and age, tooth extraction remained significantly associated with IA-development in ACPA-positive CSA-patients (HR=2.22, 95% CI 1.23–4.00, p=0.008). This association remained after additional adjustment for subclinical joint-inflammation (HR=3.10, 95% CI 1.57–6.10, p=0.001). The association between tooth extraction and RA-development was similar, as every ACPA-positive CSA-patient who developed IA also developed RA according to classification criteria. Within ACPA-positive CSA-patients (n=96), ACPA-levels, RF-positivity and number of AMPA-isotypes did not differ between individuals with and without tooth extraction (online supplemental S3). Analyses stratified for autoantibody-positivity/autoantibody-negativity (negative for ACPA and RF) showed similar findings (online supplemental S4).

To our best knowledge, this is the first study that longitudinally evaluates individuals with arthralgia at-risk of RA. We show that tooth extraction is a risk factor for progression to ACPA-positive RA and that this association is not confounded by environmental or SES-related factors. We acknowledge that tooth extraction has different causes among which end-stage periodontitis. This means it is a proxy, but not a perfect proxy. The finding that the risk effect is only present in developing ACPA-positive RA and not in ACPA-negative RA, suggests that tooth loss is partly related to prior PD (potentially present long before CSA-onset or recently). Future clinical and translational studies are needed to substantiate this finding. Interestingly, there were no differences in ACPA-levels and number of AMPA-isotypes as markers of autoantibody-maturation between ACPA-positive patients with and without tooth extraction. Whether antigenic triggering of autoreactive B-cells by bacteraemia plays a role in the trajectory towards ACPA-positive RA remains to be determined.[7]

In conclusion, this is the first longitudinal study with data on tooth extraction as proxy for late-stage PD in both ACPA-positive and ACPA-negative at-risk patients. Tooth extraction, a late-stage of PD, associated with RA-development in ACPA-positive CSA-patients. Although our study does not show causality, it deductively supports the hypothesis that PD could confer risk for ACPA-positive RA and provides clues for future clinical and translational studies.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and the study was conducted in compliance with the Declaration of Helsinki. Research protocols for the Leiden CSA-cohort (P11.210) and the TREAT EARLIER-trial (Trial NL4599) were approved by the local Medical Ethical Committee of the Leiden University Medical Center (LUMC). Written informed consent was obtained from all patients before taking part.

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