## Comments and perspectives on the TREAT EARLIER study

Sir,

I thoroughly enjoyed reading the article presenting the 4-year follow-up data of the TREAT EARLIER study conducted by Dumoulin *et al*. (1). I would like to express my gratitude to the authors on behalf of the scientific community for their valuable contribution to the literature. This ambitious project aimed to shed light on the early phases of rheumatoid arthritis (RA). This commentary aims to offer a different perspective and provide an epidemiological context.

In the TREAT EARLIER study, the inclusion criteria required the presence of "clinically suspected arthralgia (CSA)" and evidence of synovitis on MRI. On the other hand, according to the 2010 ACR/EULAR classification criteria for rheumatoid arthritis, joint involvement is defined as "joint involvement refers to any swollen or tender joint on examination or evidence of synovitis on MRI or ultrasonography" (2). Importantly, these criteria necessitate the observation of "swollen" joints as a prerequisite for application and are recommended for use to ensure the "homogenisation" of study populations (2). Although the CSA group does not exhibit swollen joints, the initial data from the TREAT EARLIER project revealed a median (IQR) number of tender joints of 4 (1–8) in the treatment group and 3 (1–9) in the placebo group (3). While this does not meet the definition of arthritis, it suggests that some patients in the TREAT EARLIER study may fulfill the "joint involvement" definition according to the 2010 RA criteria.

Several critical points warrant attention in this context. Medications that patients were using but were not exclusionary for the study, such as NSAIDs, may have confounded the assessment of joint swelling. While NSAIDs do not have disease-modifying effects, they can suppress joint tenderness and swelling. Additionally, a patient whose joint swelling resolves after NSAID use may be misclassified due to recall bias. Further confounders may include variability in evaluator assessments and differences in patients' perceptions of pain, tenderness, and swelling.

Another possibility is that CSA and established RA represent stages beyond the point of initial irreversible RA trigger activation. This may partly explain the challenges in achieving desired outcomes in prevention studies. Patients identified during the CSA phase might need to be considered from a secondary prevention perspective rather than primary prevention. Achieving primary prevention may require defining an even earlier stage and intervening before that point to reach our goal.

Although shared epitope positivity, smoking, obesity, and oral dysbiosis are well-established risk factors for the development of ACPA-positive RA, there is also evidence suggesting that gut dysbiosis and these factors may play a role in the development of ACPA-negative RA (4). It is plausible that these factors, as confounders or through changes over time, could influence the outcomes of this and other "prevention" studies. Investigating the role of these factors, or at the very least maintaining a dialogue on their potential impact, would undoubtedly add significant value to the study.

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*Competing interests: none declared.*

*Clin Exp Rheumatol 2025.*



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