Intestinal dysbiosis in RA development: difficulty of establishing causality. Response to: 'Non-causal association of gut microbiome on the risk of rheumatoid arthritis: a Mendelian randomisation study' by Inamo

We are grateful to Dr Inamo[1] for his interest in our article. We agree and acknowledged in our manuscript that our study design did not allow us to assess a causal association. Our study described an increased relative abundance in *Prevotella* spp. in individuals in 'preclinical rheumatoid arthritis (RA) stages' using participants enrolled in a first-degree relatives of patients with RA (FDR-RA) cohort.[2] The microbiota of individuals in preclinical RA stages were significantly altered compared with FDR-RA controls. In particular, bacteria of the Prevotellaceae family and associated taxa were enriched among individuals in preclinical stages of RA.

Dr Inamo concludes from his analysis that intestinal dysbiosis is probably only secondary phenomenon and unlikely to trigger the pathogenesis of RA. We respectfully disagree with this conclusion for several reasons:

- As Inamo points out, it is indeed impossible to make causal inferences from cross-sectional studies. Furthermore, the author rightfully notices that the scientific community still does not know whether 'dysbiosis comes first or RA comes first', which is precisely the reason we focused our analysis not on patients with RA but on individuals in different preclinical stages of the disease. While our findings are certainly not yet a proof for a causal role of intestinal dysbiosis in RA development, the demonstration of a large proportion of individuals in preclinical stages of RA with a significant dysbiosis is certainly consistent with the mucosal origins hypothesis of RA development.[3]
- Inamo used Mendelian randomisation analyses to assess causal association of dysbiosis with RA, taking advantage of two large datasets of genome-wide association studies (GWASs).[4 5] Inamo obtained 26 SNPs from gut microbiome GWASs associated with reduced bacterial taxa (see online supplementary table 1, Inamo's correspondence letter) . However, recent data strongly suggest only a minor influence of genetics on microbiota composition.[6] Furthermore, no studies have ever found significant differences in alpha or beta diversities between RA cases and controls, despite significant differences in specific bacterial taxa (ie, *Prevotella copri*).[2 7] Thus, the exposure analysed by the author does not represent a relevant measure of dysbiosis in RA. It would have been more appropriate for Inamo to analyse, for instance, *Prevotella* spp. abundance instead of reduced bacterial taxa.

To formally establish a causal role of intestinal dysbiosis in RA development, longitudinal studies prior to the onset of RA are required to demonstrate that specific dysbiosis precedes the development of RA, which then would have to be further validated by relevant *in vivo* studies and microbiome-centred intervention trials.

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