Response to: ‘Correspondence on ‘Prevotella copri’ in individuals at risk for rheumatoid arthritis’ by Sun and Ni

We read with great interest the letter by Sun and Ni. Our study described an increased relative abundance in Prevotella spp in individuals at risk of rheumatoid arthritis (RA), particularly in ‘pre-clinical RA stages’, among participants enrolled in a cohort of first-degree relatives of patients with RA (SCREEN-RA). Our findings are consistent with the mucosal origins hypothesis of RA development.

Sun et al explored whether single nucleotide polymorphisms (SNPs) associated with gut microbiome and derived from a genome-wide association study (GWAS) were also associated with RA. The authors performed a Mendelian randomisation (MR) analysis to assess potential associations of ‘gut microbiome–associated’ SNPs with RA and concluded that there was no causal relation between gut microbiome and RA. We respectfully would like to highlight some substantial differences between our study and Sun et al’s study and comment on potential limitations that we believe are important to consider:

► Sun et al used as their exposure of interest a number of SNPs associated with specific bacterial abundances in a European population. The rationale for the MR study hypothesises a causal link between these selected SNPs and the observed phenotype (ie, each SNP should be selectively and permanently associated with a variation in the relative abundance of a given bacterial taxa, and without directly affecting the risk of RA). Part of the microbiome composition (including Prevotella species) has been suggested to be heritable. Yet, it remains unclear if the observed heritability is the consequence of specific genetic factors or of shared environmental factors. Therefore, the underlying assumption of a direct causal link between particular SNPs and a specific microbiota alteration is controversial, which should be kept in mind. Performing an MR study also assumes this association (between a given SNP and microbiota composition) to be permanent; while the mucosal hypothesis paradigm presumes that the overexpansion of ‘arthritogenic’ bacteria occurs at a specific time to trigger the immune onset of RA, but may no longer be present once the disease has developed. Overall, because genetics are not the only driver for microbiota composition, it is, to us, very unclear if a SNP can reliably reflect real-life exposure to a bacterial taxon.

► Sun et al’s rightfully examined SNPs associated with increased abundance of particular bacterial taxa, including Bacteroidetes. A recent British study found that gut microbiota and RA genetic risk were associated in the absence of clinically detectable RA disease. The strongest association was with Prevotella spp. We regret that Sun et al did not have taxonomic data on Prevotella species to confirm the previous findings. Sun et al MR analysis would have been more interesting if focused on SNPs related to previously identified microbes associated with RA (particularly those with available mice model derived evidence, such as Collinsella aerofaciens, Prevotella copri or Prevotella histicola).

► We do not know whether the characteristics of the participants enrolled in the two cohorts were totally comparable. The population of healthy volunteers used for the MR analysis was 45% male, and, while no information on the sex ratio in the RA cases is provided, we can assume that patients with RA are usually around 70% female. However, authors did not report any adjustment for sex, which may be relevant as sex is a potential confounder for microbiome analyses.

We strongly believe that in order to establish the causal role of intestinal dysbiosis in the development of RA, longitudinal studies prior to the onset of RA, in well-defined populations, are required.

Benoit Thomas P Gilbert 1, 2, Axel Finckh 1, 2, Deshie Alpizar Rodriguez 1, 2
1Division of Rheumatology, Department of Internal Medicine Specialties, University Hospitals of Geneva, Geneva, Switzerland
2Research Unit, Mexican College of Rheumatology, Coyocacan, Ciudad de Mexico, Mexico

Correspondence to: Dr Deshie Alpizar Rodriguez, Research Unit, Mexican College of Rheumatology, Coyocacan, 04318 Ciudad de Mexico, Mexico; deshie_alpizar@hotmail.com

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ORCID iDs
Benoit Thomas P Gilbert http://orcid.org/0000-0001-6037-6470
Axel Finckh http://orcid.org/0000-0002-1210-4347
Deshie Alpizar Rodriguez http://orcid.org/0000-0002-6930-0517

REFERENCES