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.¹ 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).² Our findings are consistent with the mucosal origins hypothesis of RA development.³

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.⁴ 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.⁵ 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,⁶ and, while no information on the sex ratio in the RA cases is provided,⁷ we can assume that patients with RA are usually around 70% female.⁸ However,

authors did not report any adjustment for sex, which may be relevant as sex is a potential confounder for microbiome analyses.^{6,7}

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.

Benoît Thomas P Gilbert ¹, **Axel Finckh** ¹,
Deshire Alpizar Rodriguez ^{1,2}

¹Division of Rheumatology, Department of Internal Medicine Specialties, University Hospitals of Geneva, Geneva, Switzerland

²Research Unit, Mexican College of Rheumatology, Coyoacan, Ciudad de México, Mexico

Correspondence to Dr Deshire Alpizar Rodriguez, Research Unit, Mexican College of Rheumatology, Coyoacan, 04318 Ciudad de México, Mexico; deshire_alpizar@hotmail.com

Handling editor Josef S Smolen

Contributors All authors were involved in writing the manuscript and approved the final version. All the authors had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite Gilbert BTP, Finckh A, Alpizar Rodriguez D. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2020-219365

Received 19 November 2020

Accepted 23 November 2020

► <http://dx.doi.org/10.1136/annrheumdis-2020-219347>

Ann Rheum Dis 2020;0:1. doi:10.1136/annrheumdis-2020-219365

ORCID iDs

Benoît Thomas P Gilbert <http://orcid.org/0000-0001-6037-6470>

Axel Finckh <http://orcid.org/0000-0002-1210-4347>

Deshire Alpizar Rodriguez <http://orcid.org/0000-0002-6930-0517>

REFERENCES

- 1 Sun T, Ni J. Correspondence on 'Prevotella copri' in individuals at risk for rheumatoid arthritis'. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-219347
- 2 Alpizar-Rodriguez D, Lesker TR, Gronow A, *et al*. *Prevotella copri* in individuals at risk for rheumatoid arthritis. *Ann Rheum Dis* 2019;78:590–3.
- 3 Holers VM, Demoruelle MK, Kuhn KA, *et al*. Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. *Nat Rev Rheumatol* 2018;14:542–57.
- 4 Xie H, Guo R, Zhong H, *et al*. Shotgun Metagenomics of 250 adult twins reveals genetic and environmental impacts on the gut microbiome. *Cell Syst* 2016;3:572–84.
- 5 Wells PM, Adebayo AS, Bowyer RCE, *et al*. Associations between gut microbiota and genetic risk for rheumatoid arthritis in the absence of disease: a cross-sectional study. *Lancet Rheumatol* 2020;2:e418–27.
- 6 Wang J, Thingholm LB, Skieceviciene J, *et al*. Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. *Nat Genet* 2016;48:1396–406.
- 7 Okada Y, Wu D, Trynka G, *et al*. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 2014;506:376–81.
- 8 Hunter TM, Boytsov NN, Zhang X, *et al*. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004–2014. *Rheumatol Int* 2017;37:1551–7.