Comment on: The microbiota in axial spondyloarthritis: what have we learned from Mendelian randomisation studies?

Sirs,

We read with great interest the systematic review by Stoll *et al*. entitled "The microbiota in axial spondyloarthritis: what have we learned from Mendelian randomisation studies?" (1). The authors are to be congratulated for synthesising Mendelian randomisation (MR) studies on the relationship between gut microbiota and axial spondyloarthritis (axSpA), effectively highlighting persistent methodological limitations in cross-sectional research, such as reverse causation and confounding bias. This work provides a valuable evidence base for screening potentially pathogenic microbiota and for future mechanistic studies. Here, we offer several constructive comments to further refine the conclusions and to broaden perspectives for future research.

First, according to the latest ASAS classification criteria, axSpA includes radiographic axSpA (r-axSpA, *i.e*. ankylosing spondylitis, AS) and non-radiographic axSpA (nr-axSpA) two subtypes, which representing different stages of the same disease (2). However, the outcome datasets in the eight two-sample MR studies included by Stoll *et al*. are all based on AS, primarily reflecting genetic effects in r-axSpA. Whether these AS datasets inadvertently include patients with early-stage nr-axSpA remains unknown. This issue is not an oversight in the original study design but is constrained by privacy protection and data de-identification requirements in public databases, which limit access to detailed phenotypic information. This inability to separate disease-stage heterogeneity may not only interfere with the interpretation of causal relationships but also challenge the robustness of the microbiota effect estimates and the generalisability of conclusions derived from two-sample MR studies. More importantly, it may represent a key reason for the inconsistent directions of microbial associations observed across different MR studies.

Second, most current MR studies focus on binary causal inference but have difficulty elucidating the specific pathological mechanisms by which microbiota drive disease progression. Introducing mediation Mendelian randomisation (mediation MR) analysis could effectively address this gap (3). For example, Du *et al*. found that actinobacteria may mediate axSpA pathology by regulating IL-23 and IFN-γ (4). Pan *et al*. quantified that the causal mediation effect of Bacillales on AS risk via IL-7 accounted for as much as 13.8% (5). Moreover, Xue *et al*. combined single cell sequencing with mediation MR and showed that $CD14^{-}CD16^{+}$ monocytes delay AS progression and negatively regulate the causal effect of Sutterella on disease susceptibility (6). These findings demonstrate that mediation MR can clarify how specific microbiota trigger core disease mechanisms through inflammatory proteins, cytokines, or immune cell pathways. This approach not only delineates the complete genetic causal pathway but also helps identify microbial taxa and immune targets closer to disease pathogenesis, thereby advancing axSpA research from simple association to mechanistic dissection.

In conclusion, the review by Stoll *et al*. provides an important foundation for causal research on gut microbiota in axSpA. Further clarification of the applicability of the conclusions to AS *versus* axSpA, along with the introduction of mediation MR analysis to strengthen the dissection of microbiota driven pathogenic mechanisms, would make the causal narrative more rigorous and accurate, with greater biological interpretability and clinical relevance.

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