Causal association of gut microbiome on the risk of rheumatoid arthritis: a Mendelian randomisation study

I read with interest the articles by Inamo[1] and Alpizar-Rodriguez *et al*[2] regarding the effects of the gut microbiome on the risk of rheumatoid arthritis (RA). The Mendelian randomisation (MR) study suggested that dysbiosis may be a secondary phenomenon, rather than a trigger, in the pathogenesis of RA,[1] while the cohort study by Alpizar-Rodriguez *et al* suggested a role for intestinal dysbiosis in the development of RA.[2] However, some methodological issues in the MR study must be discussed. First, I applied a two-sample MR analysis in the MR base platform to the same data analysed with the MR by Inamo.[1] From this analysis, I could obtain 32 single nucleotide polymorphisms as instrumental variables. The MR estimates determined using inverse variance weighted (IVW) and MR-Egger regression analyses support a causal association between gut microbiome and the occurrence of RA (IVW: beta=−0.024, SE=0.007, p=0.0006; MR-Egger: beta=−0.027, SE=0.009, p=0.005), while the weighted median approach yielded no evidence of a causal association between gut microbiome and RA (beta=−0.005, SE=0.003, p=0.144). Unlike the MR results by Inamo,[1] a 'leave-one-out' analysis demonstrated that the IVW method without rs1230666 remained significant (p=0.034) and no single single nucleotide polymorphism (SNP) was driving the IVW point estimate. Second, MR studies are susceptible to bias from pleiotropy. Therefore, sensitivity analysis is required to verify the validity of conclusions drawn from the MR study.[3] Two methods are commonly used for sensitivity testing: a weighted median estimator, which provides valid estimates even if 50% of the SNPs are not valid instruments[4] and MR-Egger regression, which tests for unbalanced pleiotropy and estimates the causal effect of an exposure on an outcome.[5] Here, I found that the results of the MR analysis are supported by significant findings of the MR-Egger analysis (also similar to the IVW estimates), thus providing additional confidence in these findings. Considering that the weighted median estimator allowing 50% of the instruments to be invalid may be a conservative method and no method can provide an infallible test of causation,[3] the MR data may provide support for previous observational studies that have shown an association between microbiome and RA.[2]

Thus, I believe that the findings of this MR study should be interpreted by taking the aforementioned methodological concerns into consideration. In conclusion, the MR analysis results may support epidemiological evidence for a relationship between gut microbiome and RA,[2] suggesting further investigation on how much gut microbiome affects the development of RA.

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