Response to: 'Microbiome in Sjögren's syndrome: here we are' by van der Meulen *et al*

We would like to thank van der Meulen *et al* for their interest in our review and their comments regarding the role of the microbiome in Sjögren's syndrome (SS).^{1 2} As they correctly point out, SS was not mentioned in our review primarily because we, along with the editors, have decided to include the most studied rheumatic and autoimmune conditions as they pertain to microbiome research. We agree that SS is a common disorder with an intriguing and yet to be fully elucidated etiopathogenesis, and that the characterisation of the microbiome in this context is indeed worth pursuing. We also note that the disease entities mentioned in our review were meant as examples of the types of studies currently being performed in the field. The purpose of the review is to outline techniques and strategies that can move microbiome research beyond correlative study designs and into the realm of mechanistic approaches that may have significantly more relevance to clinical practice irrespective of the disease process.

Although van der Meulen, *et al* reference valuable studies in SS, we underscore the fact that many of them draw conclusions based on relatively small sample sizes, rely solely on 16S rRNA sequencing, which is limited in scope, and more importantly, are correlative in nature, which restrict their application to clinical practice.^{3–11} As we state in our review, in order for microbiome research to further the understanding of autoimmune disease pathogenesis, stratify patients and lead to the application of personalised therapies, the field must adopt state-of-the-art methods,¹² aim to study mechanisms rather than correlations, and allow for data validation and data sharing.

We further agree with van der Meulen *et al* that microbiome studies should not be restricted to the gut and that interventional studies may be clinically impactful. In fact, both of these points were discussed in our manuscript (see sections on 'Navigating and addressing challenges in microbiome research' and 'What the future holds'). The authors' suggestion that more than one rheumatic disease should be studied at a time is interesting, but would need to be pursued cautiously as there is established heterogeneity within even a single rheumatic disease (eg, systemic lupus erythematosus¹³ or psoriatic arthritis¹⁴). Exploring multiple diseases at a time would introduce additional variables, making it potentially difficult to interpret outcomes. We appreciate the extra dos and don'ts put forward by van der Meulen, *et al*. There are certainly other caveats to microbiome research not covered within the scope of our review, though we have set up a framework for what future studies should strive for in the context of this fluid discipline.

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