Response to: 'response to: irritable bowel syndrome symptoms in axial spondyloarthritis more common than among healthy controls: is it an overlooked comorbidity?' by Proft *et al*.

We appreciate the correspondence by Proft *et al* regarding our study entitled 'Irritable bowel syndrome symptoms in axial spondyloarthritis more common than among healthy controls: is it an overlooked comorbidity?',^{1,2} and thank *Annals of the Rheumatic Diseases* for the opportunity to respond. We also acknowledge the major contributions of Proft *et al* to the field of spondyloarthritis (SpA) research.

Regarding our main result, that irritable bowel syndrome (IBS) symptoms are significantly more common among patients with axial SpA without known inflammatory bowel disease (IBD) (n=182) than in healthy controls (n=50), Proft *et al* point out that the increased prevalence is likely due to other causes than actual clinical IBS (in particular gut inflammation and side effects of non-steroidal anti-inflammatory drug (NSAID) use).

In response to this, we would first like to draw attention to the rule-out character of the ROME III criteria used to diagnose IBS, as also brought up by Proft *et al*. According to these, a clinical IBS diagnosis requires both a typical constellation of gastrointestinal symptoms, as defined by the criteria, and the exclusion of organic causes such as IBD or malignancies. The main finding of our study, that 30% of the axial SpA patients in the well-characterised SPARTAKUS cohort reported IBS symptoms, as opposed to 16% of healthy controls (sex/age-adjusted OR 2.5; p=0.036), refers to self-reported symptoms, as defined by the ROME III criteria, but irrespective of their underlying cause (and hence not per se meeting the exclusion condition). This important distinction—between IBS symptoms and a clinical IBS diagnosis—is made throughout our report.

In the second part of our study, we then performed a hypothesis-generating analysis of potential drivers behind the observed IBS symptoms. Similar to Proft *et al*, a priori we also considered gut inflammation (in the form of microscopic gut inflammation or even undiagnosed IBD) and NSAID side effects among the more plausible explanations behind these symptoms.

Regarding gut inflammation, faecal calprotectin (F-calprotectin) is a standard clinical and highly sensitive biomarker of IBD disease activity. In SpA, F-calprotectin (as well as C-reactive protein) has also been shown to be significantly elevated among patients displaying microscopic (histological) gut inflammation at ileocolonoscopy, with a reported optimal F-calprotectin cut-off of 85 mg/kg for the detection of such cases.³ Moreover, two other studies have demonstrated the presence of macroscopic inflammatory lesions at capsule endoscopy and/or ileocolonoscopy in SpA patients with previously undiagnosed IBD to be significantly associated with elevated F-calprotectin (>100 mg/kg).^{4,5} In our study, adjustment for F-calprotectin levels did not at all change the results of our main analysis, comparing the prevalence of gut symptoms meeting ROME III criteria for IBS between axial SpA patients and controls. Nor did we find any overall association between the presence of IBS symptoms and F-calprotectin elevation in the axial SpA group, when applying different previously suggested F-calprotectin cut-offs, and the geometric means of F-calprotectin in patients with and without IBS symptoms were very similar (31 vs 35 mg/kg). Finally, the association between IBS symptoms and female sex in the

present work (adjusted OR 2.4 vs males; p=0.017) contrasts with the strong male predominance of microscopic (histological) gut inflammation (OR 8.9 vs females; p=0.035) observed by van Praet *et al* among axial SpA patients without diagnosed IBD,⁶ lending further support to the view that undiscovered gut inflammation is unlikely to be the main driver behind the reported IBS symptoms in our study.

In respect to antitumour necrosis factor (TNF) therapy, initiation of adalimumab in axial SpA patients with newly discovered subclinical IBD has been shown to simultaneously reduce macroscopic gut lesions and F-calprotectin levels.⁴ Moreover, ongoing treatment with monoclonal antibody-type anti-TNF agents among axial SpA patients without known IBD has been associated with significantly lower F-calprotectin levels than in patients receiving etanercept or no anti-TNF treatment.⁷ Despite such previously demonstrated effects on potential low-grade gut inflammation, in our study IBS symptoms were reported by 40% (n=19) of the 48 patients with ongoing monoclonal antibody-type anti-TNF therapy, while the corresponding figure among the remaining 134 patients was 27% (n=36), thus rather pointing towards a disconnect between gut inflammation and IBS symptoms in our cohort.

In regards to potential NSAID side effects, adjustment for NSAID-use during the last 3 months only marginally decreased the point-estimate OR for the axial SpA patients versus controls difference in reported IBS symptoms from 2.5 to 2.2, although statistical significance was lost (p=0.067). Within the axial SpA group, there was also a positive univariate association between NSAID-use and the presence of IBS symptoms, but this did not remain statistically significant in the multivariate model. Furthermore, NSAID enteropathy is known to result in elevated F-calprotectin levels,^{7,8} but we found no clear association between IBS symptoms and F-calprotectin.

In our multivariate analysis, the factors most strongly related to the presence of IBS symptoms in the axial SpA group were female sex (which is also over-represented among clinical IBS patients in the general population⁹) and comorbid fibromyalgia (known to be closely associated with clinical IBS in the general population¹⁰). As previously shown for SpA patients with comorbid fibromyalgia,¹¹ all patient-reported outcomes, but not the evaluator's global assessment of disease activity, were also significantly worse in our axial SpA group reporting IBS symptoms.

In light of the various aspects brought up above, we thus hypothesised that clinical IBS, similar to fibromyalgia, may be over-represented in axial SpA, explaining a relevant part of the observed increase in self-reported IBS symptoms relative to controls in our main analysis. We agree with Proft *et al* that the lack of endoscopic examinations is a limitation of this approach and call for future studies including such assessments to try to further elucidate what the increased frequency of IBS symptoms in the axial SpA population really represents. We note, however, that the authors of a previous study, examining SpA patients with capsule endoscopy and ileocolonoscopy, also hypothesise clinical IBS to be relatively frequent in this disease, based on common gastrointestinal complaints among patients with normal endoscopic examinations.⁵ Finally, we fully share the viewpoint of Proft *et al*, that in the clinical setting, when seeing SpA patients presenting with gastrointestinal symptoms, a thorough examination of potential causes should be performed, including (but not limited to) considerations regarding gut inflammation and NSAID enteropathy.

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