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## Authors' Reply: Confounding and mediation to reveal the true association between systemic inflammation and musculoskeletal pain

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## Letters to the editor

### Authors' Reply: Confounding and mediation to reveal the true association between systemic inflammation and musculoskeletal pain

We wholeheartedly agree with Klyne and Hodges [1] who emphasized in response to our Perspective [2] that the association between systemic inflammation and musculoskeletal pain is complex. In our Perspective, we called for a prudent interpretation of the literature because multiple confounders influence the association between low-grade systemic inflammation and musculoskeletal pain. A recent systematic review reiterated our viewpoint (“*The potential role of confounding factors on the association between (pro)inflammatory biomarkers and nonspecific low back pain needs to be better controlled for and/or evaluated in future research*”) [3]. Furthermore, we proposed to create a core set of potentially important confounders to assist researchers with their selection of factors. This was also echoed by the authors of another recent systematic review who “*did not find relevant information in the literature to decide a-priori which confounders would be the most relevant in this field*” [4]. Although we focussed on confounders in our Perspective, Klyne and Hodges [1] appropriately expanded on the topic and highlighted the distinction between confounders and mediators in their Letter-to-the-Editor.

We agree that some factors which influence the association between systemic inflammation and musculoskeletal pain can be mediators rather than confounders. Mediation closely resembles confounding [5]. The difference between a confounder and mediator is that a mediator lies on the causal pathway between, in this case, systemic inflammation and musculoskeletal pain, and a confounder does not [5]. However, very few studies which assess the association between systemic inflammation and musculoskeletal pain have addressed causality. Our current understanding of the biological mechanisms and pathways is therefore insufficient to already know whether a factor belongs to the causal pathway or not. Without such knowledge, it is impossible to distinguish between a mediator and a confounder [5]. In future studies, it is important to evaluate which factors influence the association between systemic inflammation and musculoskeletal pain, and build a body of knowledge to underpin a theoretical rationale. This is possible by conducting and publishing the analyses with and without the (for example) confounder analysis and by using longitudinal study designs which can address mediation.

The ultimate aim is to thoroughly understand the observed association between systemic inflammation and musculoskeletal pain, and the biological pathways, considering confounders, effect modifiers, mediators, and moderators. There are still plenty of challenges ahead in this field.

### References

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