VU Research Portal

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

Lutke Schipholt, Ivo J.; Scholten-Peeters, Gwendolyn G.M.; Bontkes, Hettie J.; Coppieters, Michel W.

published in

Spine Journal
2019

DOI (link to publisher)

[10.1016/j.spinee.2019.06.013](https://doi.org/10.1016/j.spinee.2019.06.013)

document version

Publisher's PDF, also known as Version of record

document license

Article 25fa Dutch Copyright Act

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Lutke Schipholt, I. J., Scholten-Peeters, G. G. M., Bontkes, H. J., & Coppieters, M. W. (2019). Authors' Reply: Confounding and mediation to reveal the true association between systemic inflammation and musculoskeletal pain. *Spine Journal*, 19(11), 1901-1901. <https://doi.org/10.1016/j.spinee.2019.06.013>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

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

- [1] Klyne DM, Hodges PW. Letter to the editor concerning "Multiple confounders influence the association between low-grade systemic inflammation and musculoskeletal pain. A call for a prudent interpretation of the literature". Spine J 2019.
- [2] Lutke Schipholt JJ, Scholten-Peeters GGM, Bontkes HJ, Coppieters MW. Multiple confounders influence the association between low-grade systemic inflammation and musculoskeletal pain. A call for a prudent interpretation of the literature. Spine J 2018;18:2162–3.
- [3] van den Berg R, Jongbloed EM, de Schepper EIT, Bierma-Zeinstra SMA, Koes BW, Luijsterburg PAJ. The association between pro-inflammatory biomarkers and nonspecific low back pain: a systematic review. Spine J 2018;18:2140–51.
- [4] Jungen MJ, Ter Meulen BC, van Osch T, Weinstein HC, Ostelo RWJG. Inflammatory biomarkers in patients with sciatica: a systematic review. BMC Musculoskelet Disord 2019;20:156.
- [5] Babyak MA. Understanding confounding and mediation. Evid Based Ment Health 2009;12:68–71.

Ivo J. Lutke Schipholt, PT, MSc^a
Gwendolyne G.M. Scholten-Peeters, PT, PhD^a
Hettie J. Bontkes, MSc^b
Michel W. Coppieters, PT, PhD^{a,c,*}

^a Amsterdam Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit, Amsterdam, the Netherlands

^b Department of Clinical Chemistry, Laboratory Medical Immunology, Amsterdam UMC, VU Medical Centre, Amsterdam, the Netherlands

^c The Hopkins Centre, Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia

*Corresponding author. Menzies Health Institute Queensland, Griffith University, Gold Coast Campus (G40; LVL 8.82), Parklands Drive, Southport, QLD 4215, Australia. Tel.: +61 7 5552 7680.

E-mail address: m.coppieters@griffith.edu.au (M.W. Coppieters).

Author disclosures: **IJLS**: Nothing to disclose. **GGMSP**: Nothing to disclose. **HJB**: Nothing to disclose. **MWC**: Nothing to disclose.
<https://doi.org/10.1016/j.spinee.2019.06.013>