Accepted Manuscript

Multiple confounders influence the association between low-grade systemic inflammation and musculoskeletal pain. A call for a prudent interpretation of the literature

I.J. Lutke Schipholt , G.G.M. Scholten-Peeters , H.J. Bontkes ,
M.W. Coppieters

PII: S1529-9430(18)31036-2
DOI: [10.1016/j.spinee.2018.07.019](https://doi.org/10.1016/j.spinee.2018.07.019)
Reference: SPINEE 57765

To appear in: *The Spine Journal*

Received date: 16 July 2018
Revised date: 23 July 2018
Accepted date: 23 July 2018

Please cite this article as: I.J. Lutke Schipholt , G.G.M. Scholten-Peeters , H.J. Bontkes , M.W. Coppieters , Multiple confounders influence the association between low-grade systemic inflammation and musculoskeletal pain. A call for a prudent interpretation of the literature, *The Spine Journal* (2018), doi: [10.1016/j.spinee.2018.07.019](https://doi.org/10.1016/j.spinee.2018.07.019)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Multiple confounders influence the association between low-grade systemic inflammation and musculoskeletal pain. A call for a prudent interpretation of the literature.

Authors: I.J. Lutke Schipholt¹, G.G.M. Scholten-Peeters¹, H.J. Bontkes², M.W. Coppieters^{1,3}

Affiliations

- 1: Amsterdam Movement Sciences; Faculty of Behavioural and Movement Sciences; Vrije Universiteit Amsterdam, The Netherlands.
- 2: Department of Clinical Chemistry, Laboratory Medical Immunology; Amsterdam UMC, Location VU Medical Centre; Amsterdam, The Netherlands
- 3: The Hopkins Centre, Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia

Correspondence to

Professor Michel Coppieters, Menzies Health Institute Queensland, Griffith University, Gold Coast Campus (G40; LVL 8.82), Parklands Dr, Southport QLD 4215, Australia; +61 7 5552 7680
m.coppieters@griffith.edu.au

Keywords

Spinal pain, cytokines, low-grade systemic inflammation, multiple regression analysis

Competing Interest

The authors have no competing interests to declare.

Our understanding of the multiple systems and their interactions that contribute to musculoskeletal pain has evolved considerably in recent years. There is a large interest in the role of the immune system in both acute and persistent musculoskeletal pain states.^(1,2) Systemically

elevated levels of proinflammatory cytokines and chemokines have been revealed in people with musculoskeletal pain. This low-grade inflammation has been demonstrated in various musculoskeletal conditions, such as low back pain,⁽¹⁾ neck pain⁽²⁾ and radicular pain.⁽³⁾ In addition, levels of inflammatory biomarkers are associated with pain severity in people with neck and shoulder pain⁽⁴⁾ and low back pain.⁽¹⁾ Moreover, an initial study suggests that inflammatory responses in the acute phase of low back pain may also be related to recovery.⁽⁵⁾

In people with and without musculoskeletal pain, levels of inflammatory biomarkers are influenced by multiple factors, such as demographic variables (e.g., age, gender), lifestyle factors (e.g., physical activity, saturated fat intake, sleep quality), psychological factors (e.g., depression, catastrophizing) and various diseases (e.g., cardiovascular, osteoarthritis).⁽⁶⁻⁸⁾ These factors can increase systemic cytokine concentrations via their direct or indirect action on immune cells and the subsequent release of inflammatory cytokines and chemokines.⁽⁷⁾ Therefore, adjustment for potential confounders is essential to determine the level of association between low-grade systemic inflammation, musculoskeletal pain and recovery.

The importance of adjusting for confounders when measuring systemic cytokine levels is illustrated in a study in people with multisite persistent pain.⁽⁶⁾ In an unadjusted analysis, systemic levels of CRP, IL-6 and TNF- α (all proinflammatory biomarkers) were significantly higher in people with persistent multisite pain. However, after correcting for sociodemographic variables, TNF- α levels were no longer significantly higher. Subsequently, after correcting for lifestyle, disease, anxiety and depression, CRP and IL-6 were no longer significantly associated with pain. Similarly, in a study of people with persistent low back pain, IL-6 levels were no longer significantly associated with affective pain after correction for sleep quality.⁽¹⁾ These studies demonstrate that the association between inflammatory biomarkers and the presence of musculoskeletal pain is potentially confounded by sociodemographic variables, lifestyle and disease, and anxiety and depression.

Levels of inflammatory biomarkers likely arise from a complex interplay between the central nervous system, immune system, endocrine system, psychological factors, sociodemographic factors, lifestyle and behavior. In most studies, it will not be feasible to correct for all possible confounders or to add all effect modifiers in the association model when assessing the relationship between inflammatory biomarkers and musculoskeletal pain or patient recovery. However, we must remain vigilant when assessing and interpreting associations between systemic cytokine concentrations with persistent musculoskeletal pain and recovery. Unfortunately, researchers rarely control for these confounding factors in the analyses, or only control for a small subset of confounders. This may result in incorrect or overly optimistic conclusions. To address the common issue of insufficient power to include all potential confounding variables, we propose to create a core set of confounders which researchers need to correct for in future multiple regression analyses. This set of confounders can also be used when deriving a model to predict musculoskeletal pain or recovery that includes inflammatory biomarkers as possible predictor variables. Further insight in the interplay between pain, low-grade inflammation and confounders will result in a better understanding of pain mechanisms and potential treatment options for people with or at risk of developing persistent musculoskeletal pain.

Competing Interest

The authors have no competing interests to declare.

References

- [1]. Heffner KL, France CR, Trost Z, Ng HM, Pigeon WR. Chronic low back pain, sleep disturbance, and interleukin-6. *The Clinical journal of pain*. 2011;27(1):35-41.
- [2]. Teodorczyk-Injeyan JA, Triano JJ, McGregor M, Woodhouse L, Injeyan HS. Elevated production of inflammatory mediators including nociceptive chemokines in patients with neck pain: a cross-sectional evaluation. *J Manipulative Physiol Ther*. 2011;34(8):498-505.
- [3]. Wang K, Bao JP, Yang S, Hong X, Liu L, Xie XH, et al. A cohort study comparing the serum levels of pro- or anti-inflammatory cytokines in patients with lumbar radicular pain and healthy subjects. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society*. 2016;25(5):1428-34.
- [4]. Matute Wilander A, Karedal M, Axmon A, Nordander C. Inflammatory biomarkers in serum in subjects with and without work related neck/shoulder complaints. *BMC Musculoskelet Disord*. 2014;15:103.
- [5]. Klyne DM, Barbe MF, van den Hoorn W, Hodges PW. ISSLS PRIZE IN CLINICAL SCIENCE 2018: longitudinal analysis of inflammatory, psychological, and sleep-related factors following an acute low back pain episode-the good, the bad, and the ugly. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society*. 2018;27(4):763-77.
- [6]. Generaal E, Vogelzangs N, Macfarlane GJ, Geenen R, Smit JH, Dekker J, et al. Basal inflammation and innate immune response in chronic multisite musculoskeletal pain. *Pain*. 2014;155(8):1605-12.
- [7]. Navarro SL, Kantor ED, Song X, Milne GL, Lampe JW, Kratz M, et al. Factors Associated with Multiple Biomarkers of Systemic Inflammation. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2016;25(3):521-31.

- [8]. Klyne DM, Barbe MF, Hodges PW. Systemic inflammatory profiles and their relationships with demographic, behavioural and clinical features in acute low back pain. *Brain, Behavior, and Immunity*. 2017;60:84-92.

ACCEPTED MANUSCRIPT