

MUSCULOSKELETAL, REHABILITATION & REGENERATIVE MEDICINE SECTION

Identifying the Most Important Confounders When Assessing the Association Between Low-Grade Systemic Inflammation and Musculoskeletal Pain: A Modified Delphi Study

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Funding sources: None declared.

Conflicts of interest: There are no conflicts of interest to report.

Abstract

Objective. The association between low-grade systemic inflammation and musculoskeletal pain may be influenced by multiple factors. However, little is known about the relative importance of these factors, and few studies account for them. This Delphi study aimed to reach consensus on the most important confounders which influence the association between low-grade systemic inflammation and musculoskeletal pain. **Methods.** The panel consisted of 48 experts. In Round 1, the experts proposed what they believed were important confounders. In Round 2, the experts indicated for each confounder whether they believed it was important (*yes/no*). At least 50% of experts had to indicate the confounder was important to be considered in the final round. In Round 3, the experts rated the importance of each confounder on a 7-point Likert scale. Consensus was reached if $\geq 75\%$ of the experts considered the factor either extremely or moderately important. **Results.** In Round 1, 120 confounders were proposed, which were synthesized into 38 distinct factors. In Round 2, 33 confounders met the criterion to be considered important. In Round 3, consensus was reached for 14 confounders: acute illness/trauma, immune disease, medication use, endocrine, nutritional, or metabolic disease, other musculoskeletal conditions, age, handling of blood samples, sex, cancer, body composition, pregnancy, cardiovascular disease, physical activity, and pain characteristics. **Conclusions.** These findings provide insight in the complexity of the association between low-grade systemic inflammation and musculoskeletal pain. Some factors currently listed as confounders may be re-classified as moderators or mediators as insights progress.

Key Words: Chronic Pain; Low Back Pain; Neck Pain; Immune System; Cytokines; Covariate

Introduction

The reciprocal interaction between the immune system and the nervous system is well described, as immune cells can sensitize nociceptors and nociceptors can modulate immune cells [1, 2]. This crosstalk between nociceptors and immune cells occurs under normal conditions, but it

has also become the culprit for pathological conditions [1]. In several musculoskeletal pain conditions, the neuroimmune system plays a role in the development and maintenance of pain [3, 4]. Levels of various inflammatory markers are associated with the pain intensity and disability of back pain [5–7], radicular pain [8],

traumatic and nontraumatic neck pain [9], and work-related neck-shoulder pain [10, 11]. Understanding the biological pathways between the neuroimmune system and musculoskeletal pain is relevant as it is also related to recovery [12, 13]. Additionally, it is clinically relevant to understand this relationship between the neuroimmune system and musculoskeletal pain as it can be influenced by treatment, such as therapeutic exercise [14].

Unfortunately, only a few studies corrected statistically for possible confounders that might influence the association between inflammatory mediators and musculoskeletal pain [15, 16]. For example, in patients with multisite chronic pain, tumor necrosis factor alpha (TNF- α) measured directly from blood samples and interleukin 8 (IL-8) measured after lipopolysaccharide (LPS) stimulation were elevated compared to pain-free individuals. However, both of these differences were no longer significant after controlling for lifestyle and disease factors [15]. When assessing whether low-grade systemic inflammation is associated with musculoskeletal pain, various factors need consideration which could be confounding, mediating or moderating this relationship [17].

Two commonly used methods to quantify low-grade systemic inflammation assess levels of inflammatory markers either directly from blood samples (ex vivo) or indirectly from whole blood cells that are stimulated with an endotoxin to produce an immune response (in vitro) [15, 18]. Currently, there is little literature to help decide a priori which factors are relevant and whether these are different between direct and indirect methods [8]. The number of confounders researchers can correct for is determined by the sample size. A core set of confounders can guide researchers to consider the most relevant ones, as most studies will be unable to correct for multiple confounders [17, 19]. Such core set is currently unavailable.

To generate this recommended core set of confounders, a Delphi study was conducted. The Delphi method is an ideal method to systematically generate ideas and reach consensus on potential confounders from a large number of experts from around the world [20]. Delphi studies are also advantageous for where there is incomplete knowledge in a particular research field [21]. Therefore, this study aimed to identify and reach consensus on the most important confounders when studying the association between low-grade systemic inflammation and musculoskeletal pain.

Methods

A three-round modified Delphi study was conducted to identify and reach consensus on the most important confounders when studying the association between low-grade systemic inflammation and musculoskeletal pain. We considered it a “modified” Delphi because we predetermined the Delphi study to have three rounds and provided no individual feedback to the panel members

between rounds. The study was approved by the local human ethics committee (VCWE-2018-161; Scientific and Ethical Review Board, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, The Netherlands). The study is reported according to the CREDES guidelines for conducting and reporting Delphi studies [22].

Expert Panel

Between December 2018 and February 2019, PubReMiner from the PubMed database was used to identify the experts. Two types of experts were identified: experts in low-grade systemic inflammation in relation to musculoskeletal pain (Category 1) and experts in low-grade systemic inflammation in relation to other domains (Category 2). These domains were factors that influence low-grade systemic inflammation, and could therefore also be possible confounders for the association between low-grade systemic inflammation and pain, such as depression [23], obesity [24], and medication [25]. Relevant domains were identified via literature searches in PubMed and an overview is provided in [Supplementary Data](#). Search strings to identify potential experts were developed with a health-liaison research librarian from the university library of Vrije Universiteit Amsterdam ([Supplementary Data](#)).

Experts were identified via their publication track record. Criteria to define an expert were determined during a focus meeting of four clinical researchers with expertise in musculoskeletal pain, immunology and Delphi methodology. Category 1 experts were invited to join the expert panel if they published at least two articles on low-grade inflammation and musculoskeletal pain in the preceding ten years. Category 2 experts were invited if they published at least two articles on low-grade inflammation and another relevant domain (see [Supplementary Data](#)) in the preceding 10 years. Author positions were not considered (i.e., whether first, last or middle author). Low-grade systemic inflammation was defined as increased inflammatory markers assessed from either direct (ex vivo) or indirect (in vitro) methods. Considering the diverse domains, we aimed for a sufficiently large expert panel [26, 27], with ~30 Category 1 experts and ~20 Category 2 experts who covered various domains. All experts provided consent when they accepted the invitation to participate.

Delphi Rounds

All experts received the same information and online surveys. For each round, anonymous electronic surveys were used to collect the data (Qualtrics Version 2017, Provo, Utah). For all rounds, the provided information and survey were pilot tested to test the clarity. In each round, nonresponders were sent up to two electronic reminders.

Round 1

Electronic surveys were sent to the experts. The experts were asked to list what they believed were the most important confounders when assessing the association between low-grade systemic inflammation and musculoskeletal pain. The term low-grade systemic inflammation was predefined for the experts as elevated levels of inflammatory biomarkers such as cytokines, chemokines, and c-reactive protein (CRP) in the blood circulation (i.e., systemic).

The suggested confounders from Round 1 were discussed in a focus group ($n=4$) to consolidate similar terms into overarching factors to make rating the number of items feasible in subsequent rounds. If what was meant by a listed factor was unclear, experts were contacted to clarify their answer(s).

As described above, to measure low-grade systemic inflammation, inflammatory markers can be measured directly from blood samples or indirectly from whole blood cells that were stimulated with an endotoxin to produce an immune response. Therefore, experts were also asked in Round 1 whether a distinction should be made between confounders for inflammatory marker concentrations measured from direct blood samples or indirectly from stimulated cultured whole blood cells (*yes/no/don't know*). It was an a priori decision that if $\geq 50\%$ of experts would indicate that a distinction should be made, then questions from Round 2 onward would be asked separately for inflammatory markers determined directly from blood samples and indirectly from stimulated cultured whole blood cells.

Round 2

The list of confounders that were suggested in Round 1 was sent to the experts in Round 2. For each suggested confounder, experts were asked (*yes/no/don't know*) whether they considered the factor as an important confounder when studying the association between low-grade systemic inflammation and musculoskeletal pain. Experts were given the option to explain their answer in a text box.

It was decided a priori that at least 50% of experts [28] had to indicate that the suggested confounder was believed to be important for the confounder to be retained for Round 3. Percentages were calculated without considering the “*don't know*” category.

Round 3

For each factor, the experts were asked to rate how important they believed it was to consider the factor as a possible confounder when studying the association between low-grade systemic inflammation and musculoskeletal pain. A 7-point Likert scale was used with the following answering options: extremely important, moderately important, slightly important, neutral, slightly unimportant, moderately unimportant, and extremely

unimportant. In addition, experts were given a “*don't know*” option and the option to explain their selected answer in a text box.

Following Round 3, answers from the experts were dichotomized by combining the answering options extremely important and moderately important (i.e., the top two answering options of the 7-point Likert scale) and by combining all other answering options. We determined a priori that consensus was reached if at least 75% of the experts rated the confounder as extremely or moderately important, provided that at least 50% of experts ranked the confounder [20, 28]. The “*don't know*” answers were excluded from these calculations [28].

Statistical Analysis

Results were analyzed anonymously and presented in percentages. Descriptive statistics and percentage of agreement were used to define consensus. A Spearman's rank-order correlation analysis was performed to compare the rankings of confounders for direct versus indirect methods. All experts who completed Round 1, were contacted to participate in Round 3, irrespective whether they participated in Round 2. This approach increases the chances of having a representative panel of experts making the final decisions [28, 29]. In line with other Delphi studies [28, 29], we had decided a priori, to conduct a sensitivity analysis only considering the data of the experts who completed all three rounds. The analyses were performed in SPSS Version 26 (IBM Corp., Armonk, New York) and Microsoft Excel.

Results

Expert Panel

We identified 281 researchers as potential experts from the PubReMiner results and known experts and invited them to participate (Figure 1). Although, this number was higher than intended, because PubReMiner lists authors alphabetically, we did not want researchers' surnames to determine who would be invited from a group of authors with the same number of publications. Forty-eight experts accepted our invitation to participate. There was overlap between PubReMiner results for Category 1 and Category 2 experts: 29 experts met the criteria for both Category 1 and Category 2; twelve experts met the criteria for Category 1 only; and seven experts met the criteria for Category 2 only (Figure 1). The mean (SD) number of relevant publications experts had was 5.3 (2.7). Collectively, they had 252 authorships on 209 relevant articles pertaining to low-grade systemic inflammation in musculoskeletal pain conditions. The panel consisted of academic researchers, medical doctors, physiotherapists and psychologists, and resided in North America ($n=21$), Europe ($n=23$), Asia ($n=1$), and Australia ($n=3$) (Table 1). The self-reported expertise of the panel members confirmed that our expert panel had

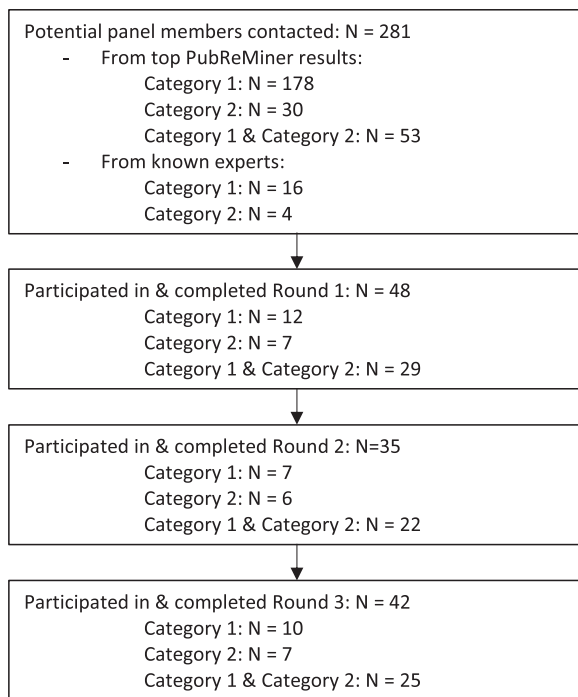


Figure 1. Flowchart of the Delphi study.

knowledge about other domains relevant to low-grade systemic inflammation and musculoskeletal pain (Table 1).

Acceptance and Response Rates

Forty-eight invited experts completed the survey for Round 1, which corresponds with an acceptance rate of 17% (assuming that all email invitations were received). A total of 35 experts completed Round 2 (response rate 72.9%), and 42 experts completed Round 3 (response rate 83.3%). Two additional experts returned a partially completed survey in Round 3 (approximately a quarter of the questionnaire, probably due to a technical issue in the survey that was quickly resolved). The answers of these two experts were included in the analysis, but because only a small number of confounders were rated, we did not include these two experts in the response rate calculations.

Round 1

The expert panel suggested 120 confounders. Seventeen experts were contacted for clarification regarding their response and whether they agreed a confounder they had listed could be merged with other factors suggested by other experts. In the focus group meeting, a list of 38 overarching confounders (Supplementary Data) was created based on the listed factors and additional information from the experts. A majority (77%) of the experts indicated that a distinction should be made between confounders when assessing low-grade systemic inflammation directly from blood samples versus indirectly from stimulated cultured whole blood cells.

Round 2

The 38 suggested confounders were rated by (mean [SD]) 27.6 (3.8) experts. Thirty-three confounders were considered important by at least 50% of the experts when assessing low-grade systemic inflammation directly from blood samples. For indirect measures of low-grade systemic inflammation from stimulated cultured whole blood cells, the same confounders met the cut-off, except one factor, namely dietary intake (Table 2).

Of the 35 experts who participated in this round, 24 provided additional comments in the provided text boxes (326 comments). The majority ($n = 303$) of the comments were simply motivations for their selected choice. Other comments ranged from explanations that the listed factor was influential but not necessarily a confounder ($n = 14$) to explanations that the factor influenced the immune system but was not important ($n = 5$). There were a few comments considering the differences between the two methods of assessing low-grade systemic inflammation ($n = 2$) or that the listed factor is not specific enough/not feasible to measure ($n = 2$).

Round 3

The expert panel reached consensus that 14 confounders were important to consider for the association between low-grade systemic inflammation and musculoskeletal pain: acute illness/trauma, immune disease, medication use, endocrine, nutritional or metabolic disease, other musculoskeletal conditions, age, experimental handling of blood samples, sex, cancer, body composition, pregnancy, cardiovascular disease, pain characteristics, and physical activity (Figure 2). For confounders when indirectly assessing low-grade systemic inflammation from stimulated cultured whole blood cells, consensus was reached for 10 important confounders: immune disease, acute illness/trauma, endocrine, nutritional or metabolic disease, other musculoskeletal conditions, experimental handling of blood samples, medication use, pregnancy, body composition, cardiovascular disease, and age (Figure 2). There were no major differences between the confounders' rank for direct and indirect methods: (1) there was a strong correlation between the two rankings (direct and indirect) ($r_s = 0.95$, $P < .01$) and (2) the mean (SD) difference for the confounder's rank between using direct and indirect methods was 2.4 (1.7) positions. Only 14 experts provided a comment in the optional text box (48 comments). Forty-three of the comments simply supported their selection, while 2 comments mentioned how the listed factor was not a confounder but a mediator. There were also a few comments about the listed factor not being feasible to measure ($n = 2$) or that it is still not clear how important the factor is ($n = 1$).

Sensitivity Analysis

Eight experts who participated in Round 1 and Round 3 did not participate in Round 2. A sensitivity analysis of

Table 1. Expert panel characteristics

Expert Panel (N = 48)	N (%)
Mean (SD) age	50 (12) years
Female/Male	23/25 (48%/52%)
Education degree ^a	
Doctor of philosophy	43
Medical doctor or doctor of chiropractic	6
Master's degree	1
Occupation ^a	
Professor	23 (48%)
Associate professor	11 (23%)
Assistant professor/senior lecturer	4 (8%)
Post-doctoral researcher	7 (15%)
PhD candidate	1 (2%)
Staff scientist	1 (2%)
Medical doctor (clinical)	7 (15%)
Physiotherapist (clinical)	2 (4%)
Psychologist (clinical)	1 (2%)
Years of work experience, mean (SD)	
In research	24 (13) years
In clinical practice	18 (6) years
Self-identified areas of expertise ^a	
Low-grade systemic inflammation	26 (54%)
Immunology	17 (35%)
Musculoskeletal pain	38 (79%)
Aging	10 (21%)
Sex	9 (19%)
Medication	5 (10%)
Physical activity/exercise	11 (23%)
Seasons	2 (4%)
Alcohol	4 (8%)
Smoking	2 (4%)
Stress	15 (31%)
Depression/anxiety	18 (38%)
Body composition	15 (31%)
Menstrual cycle	3 (6%)
Sleep	3 (6%)
Nutrition	3 (6%)

^aMore than one option could be selected; therefore, the sum of percentages exceeded 100%.

the Round 3 results was performed, in which the responses of these eight experts were not considered. The sensitivity analysis results were comparable with the main results ([Supplementary Data](#)). The same 14 confounders for direct methods met the criteria for consensus in the sensitivity analysis compared to the total group, except for “physical activity.” Similarly, for confounders when using inflammatory marker concentrations after stimulated cultured whole blood cells, consensus in the sensitivity analysis was reached for the same confounders, except for “body composition” ([Supplementary Data](#)).

Discussion

The aim of this Delphi study was to identify the most important confounders when studying the association between low-grade systemic inflammation and musculoskeletal pain. A representative group of experts (n = 48) suggested multiple factors (n = 120) in Round 1,

which could be distilled to 38 distinct factors. Following two additional rounds, the panel reached consensus on 14 confounders that were important to consider when assessing the association between low-grade systemic inflammation and musculoskeletal pain ([Figure 2](#)). This overview and ranking of confounders can assist researchers when deciding which factors to select when trying to elucidate the complex interplay between low-grade systemic inflammation and musculoskeletal pain. Finite sample sizes make it typically impossible to consider multiple possible confounders and the findings of this Delphi study can assist in making these a priori selections.

Interestingly, suggested factors such as psychological status, sleep and diet did not reach the threshold for consensus, despite recent research suggesting their importance (e.g., psychological status [12, 30–33], sleep [12, 16, 34], and diet [35–38]). This may be partially due to the a priori defined methodology. We had predetermined that a factor would be considered important if at least 75% of experts would rate the factor as either “extremely important” or “moderately important”. Although in line with recommendations [28] and current practice [28, 29, 39, 40], both criteria (75% and only the highest categories on the Likert scale) are somewhat arbitrary. Other cut-off values could have resulted in a different selection and ranking of confounders. We therefore consider the results of this study as a fluid collection of important confounders, that reflects current knowledge and thinking, which is likely to evolve over time as insights progress. Similarly, some factors reflect a collection of possible items, such as the confounders medication and genetics. Following Round 1, we decided to merge the suggested medications (analgesics, anti-inflammatory medication, anti-depressants, and antibiotics) and the suggested genetic elements (epigenetics, genetic risk, and polymorphisms) into one factor to make the list manageable for experts. Based on the research question and population, researchers will have to make informed decisions on the selection of possible confounders. We believe the findings of the Delphi study can assist researchers in making these decisions.

As indicated above, composing a representative panel of true experts is important in Delphi studies. Identification of experts in a novel and rapidly developing field, such as low-grade systemic inflammation and musculoskeletal pain, is challenging. The PubReMiner searches revealed that in order to be able to invite a sufficient number of experts, the minimum criterion to be considered as an expert was determined at two relevant international peer-reviewed publications. This is lower than other Delphi studies which use publication track records to identify experts [28, 29]. Among other reasons, this minimum criterion may explain the relatively low acceptance rate (17%, assuming all electronic invitations would have reached the experts), because not all people invited to participate may have considered themselves experts in this complex domain. However, on average, experts who joined the panel had five relevant international peer-reviewed publications,

Table 2. Percentage of experts who considered the confounder to be important for the association between low-grade systemic inflammation and musculoskeletal pain in Round 2

Confounder ^a	Directly from Blood Samples	Indirectly Following Whole Blood Stimulation
Medication use	100%	100%
Body composition	100%	93%
Acute illness or trauma	97%	93%
Pregnancy	96%	92%
Immune disease	94%	93%
Physical activity	94%	86%
Sex	93%	89%
Endocrine, nutritional, or metabolic diseases	93%	90%
Psychological status	93%	88%
Experimental handling of blood samples	93%	92%
Smoking	91%	86%
Recreational drug use	90%	85%
Age	90%	88%
Cancer	89%	85%
Sleep	89%	84%
Cardiovascular disease	87%	71%
Additional musculoskeletal conditions	86%	79%
Pain characteristics	85%	75%
Early life events	83%	80%
Genetics	81%	85%
Alcohol	79%	75%
Fatigue	78%	72%
Neurological disease	75%	70%
General health	73%	71%
Number of comorbidities	72%	68%
Ethnicity	71%	71%
Disease burden	71%	62%
Medical history	68%	70%
Seasonal changes	65%	63%
Socioeconomic status	64%	67%
Nutritional supplements	60%	58%
Exposure to environmental hazards	55%	58%
Dietary intake	52%	-----
Occupation	-----	46%
Education level	42%	44%
Early life development	37%	32%
Hygiene	33%	37%
Personal care products	13%	14%
	4%	4%

^aConfounders have been ranked based on percentage results in the direct inflammatory markers column. The dashed line indicates the cutoff criteria (>50%) for a confounder to proceed to Round 3.

which is in line with the criterion utilized in other Delphi studies [28, 29]. Because (1) more than half of the experts ($n = 30$) were in the top of the Category 1 PubReMiner search and authored on average five relevant publications, and because (2) we exceeded our a priori determined number of experts for each category because many experts could be considered experts for both Category 1 and Category 2, we believe the expert panel had appropriate expertise. With high response rates (73% and 83%), this expertise was maintained throughout the study. Each factor was rated by at least the number of experts that is considered required in Delphi studies to result in reliable and stable results [26, 27, 41].

Regarding the two commonly used methods to measure inflammatory marker concentrations (i.e., directly from blood samples or indirectly from stimulated cultured whole

blood cells), a majority of experts indicated in Round 1 that confounders had to be determined separately for direct and indirect methods. However, the results revealed no major differences and the correlation between the ranking of the confounders for the two methods was very strong. We believe this high correlation is logical as we are not aware of biological reasons why confounders would influence the association between low-grade systemic inflammation and musculoskeletal pain differently for direct and indirect methods. The justification for asking this question in Round 1 was that there is literature which evaluated both direct and indirect methods of assessing inflammatory markers in chronic multisite musculoskeletal pain and suggested differences in confounders [15].

It is unclear whether (and perhaps unlikely that) all identified factors are truly confounders. A confounder is

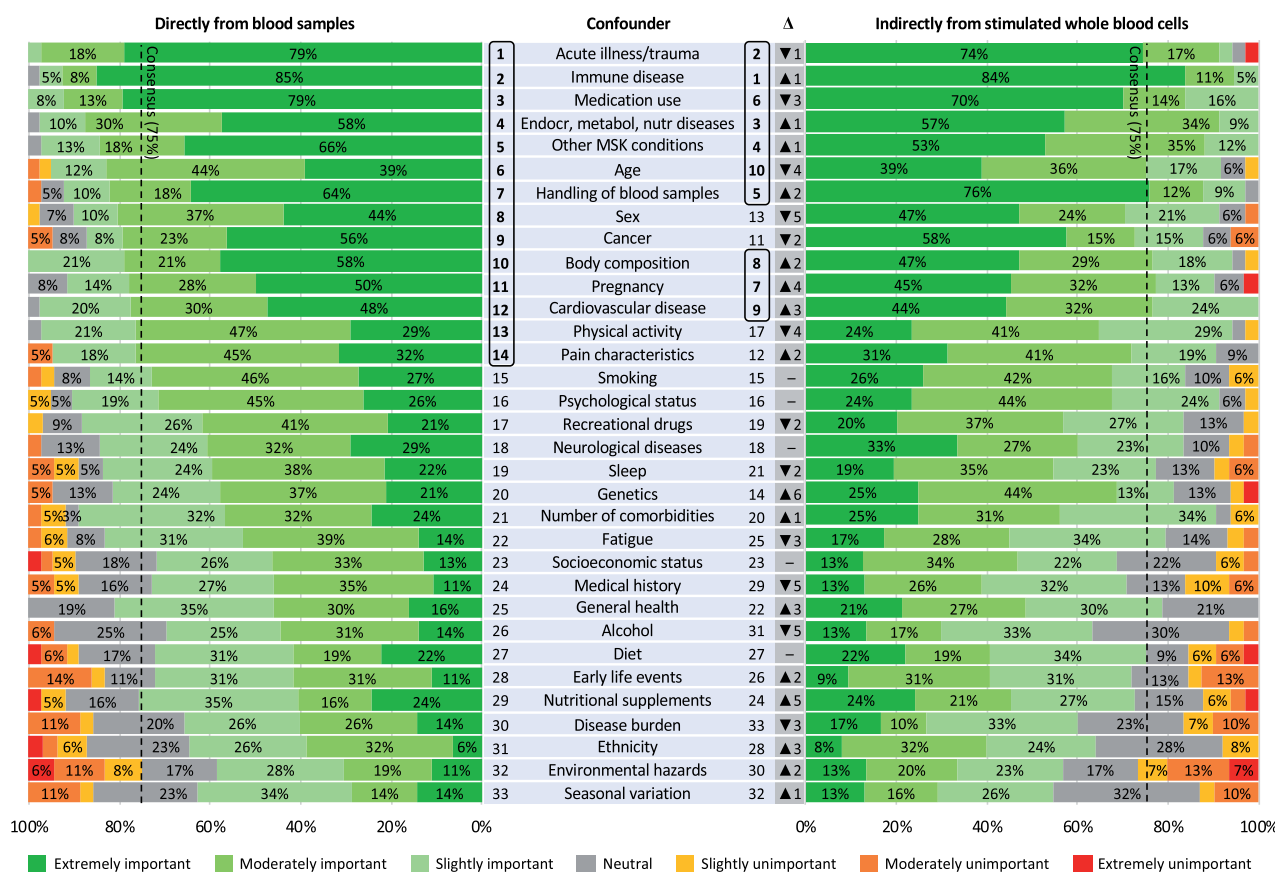


Figure 2. Ranking of the confounders following Round 3. Confounders are ranked based on the percentage of experts that considered the confounder important for the association between low-grade systemic inflammation and musculoskeletal pain when using direct methods to evaluate inflammatory markers. Rank numbers of confounders that reached the consensus threshold (75%) are boxed and highlighted in bold. Percentages < 3% are not labeled. Δ: Change in ranking between the direct and indirect methods. Endocr, metabol, nutr = Endocrine, metabolic, nutritional; MSK = Musculoskeletal.

a third variable that is related to the two variables of interest but does not lie within the causal pathway [42]. Factors, such as body composition, indeed influence both low-grade systemic inflammation and musculoskeletal pain [15], but could be playing more of a mediating role (i.e., part of the causal pathway) [43]. Actually, several factors listed as confounders in this Delphi study may be mediators considering their high comorbidity in persistent pain (e.g., sleep disturbance [44, 45], comorbid inflammatory disorders [46, 47], and psychological status [48–51]). Additionally, sex can be considered as a moderator (influencing the strength/direction of a relationship) as different associations can be found between low-grade systemic inflammation and musculoskeletal pain for males and females [52]. Methodologically, it is difficult to distinguish whether a factor is a confounder, mediator or moderator [42, 53]. The term “confounder” was used in the present study because it is often uncertain whether there is a causal relationship. Future research may reveal that some factors might be best considered mediators. For example, cross-sectional studies suggest that psychological variables are confounders, as the variable diminishes the association between levels of inflammatory

markers from indirect (in vitro) methods and chronic pain [15]. Additionally, mood disorders were considered key potential confounder in a recent systematic review on low back pain and inflammation [5]. However, longitudinal studies suggest that psychological factors act as mediators [12]. Further longitudinal studies with measurements at multiple time points and using statistics that can handle both mediation and confounding analysis (such as marginal structural models [54]) are warranted in order to gain better insight whether a factor lies in the causal pathway or not [19, 55].

Conclusions

In this study, the expert panel recommended 14 factors to consider when studying the association between low-grade systemic inflammation and musculoskeletal pain. This coreset of confounders is a starting point to guide future research, but more research is needed to explore the complex relationships these factors have with low-grade systemic inflammation and musculoskeletal pain.

Author Contributions

MK, ILS, GS and MC conceptualised and designed the study. MK collected the data, and performed the initial data analysis together with ILS. All authors further analysed and interpreted the data. MK and MC prepared the different drafts of the manuscript, and ILS and GS provided important intellectual content and revised the drafts. All authors approved the final version of the manuscript.

Acknowledgments

The authors thank Ralph de Vries from the Medical Library of the VU University for the assistance with the literature search. We would like to thank all the members of the expert panel for their input. The following experts provided consent to be listed: Massimo Allegri, Emmanuel Bäckryd, Sven Benson, Geoffrey Bove, Nadeen Chahine, David Clark, Chris Coe, Robert Dantzer, Niels Eijkelkamp, Sigrid Elsenbruch, Malin Ernberg, Maria Fitzgerald, Rinie Geenen, Ellen Generaal, Bijar Ghafouri, Sean Gibbons, Burel Goodin, Kathi Heffner, Camila Hirotsu, Mark Hutchinson, Kelly Ickmans, Tracey Ignatowski, Bianka Karshikoff, Annemieke Kavelaars, Thomas Kinfe, David Klyne, Anders Larsson, Michael Maes, Mira Meeus, Harvey Moldofsky, Sandi Navarro, Wilfred Pigeon, Andrea Polli, Heike Rittner, Michelle Roche, Andrew Schrepf, Barry Sessle, Shad Smith, Marc Suter, Julita Teodorcyk-Injeyan, Rolf-Detlef Treede, Désirée van der Heijde, Haili Wang, Wei Wang, and Hanneke Willemen.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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