PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	MICROSCOPIC CHANGES IN THE SPINAL EXTENSOR MUSCULATURE IN PATIENTS EXPERIENCING CHRONIC SPINAL PAIN: PROTOCOL FOR A SYSTEMATIC REVIEW
AUTHORS	Purushotham, Shilpa; Stephenson, Robert; Sanderson, Andy; Falla, Deborah

VERSION 1 – REVIEW

REVIEWER	xue Cina
REVIEW RETURNED	29-Sep-2020

GENERAL COMMENTS	Search process is not clear and topic is too old

REVIEWER	Thomas Osinski UR 20201 ERPHAN, Université Versailles Saint Quentin (FRANCE)
REVIEW RETURNED	07-Oct-2020

GENERAL COMMENTS	Thank you for your interesting work. I would like to suggest you some little modifications that I list below: 1-update your prospero number line 48 and 166 : CRD42020198087 2-in risk of bias you describe the NOS for cohort studies (line 265) but in discussion (line 344) you expect to include principally case-control studies. I think you must clarify this discrepancy. If you anticipated the inclusion of case-control studies you should change criteria of inclusion to be more explicit than :" Observational studies will likely constitute the highest level of evidence for this review, as ascertained by scooping searches." (line 181). 3- Moreover you present your review with the interest to help in prescription of exercise but if you expect principally case-control you risk having difficulty to infer who came first between egg and chicken. Do you think that a potential meta-regression will be useful for you? 4-As you concentrate your investigation on extensor muscle, maybe you should clarify title and present this point earlier in text. It isn't present in the abstract. Globally your text is interesting and pleasant to read, in submission of article I think that a short explanation of difference between macro and microscopic muscular changes would help the readers. Regards.

REVIEWER	Sjoerd Stevens Hasselt University
REVIEW RETURNED	25-Dec-2020

GENERAL COMMENTS	Dear Authors, I would like to complement the authors on establishing this strong methodology. I would recommend the authors to speak of non-specific chronic spinal pain from the beginning of their introduction to clearly identify the population of interest. I think the research question very interesting, however, I'm convinced it will be very difficult to get clear answers on the proposed research question, simply because there is very little research (literature) in the area of microscopic muscle changes (especially in aspecific low back pain). In my opinion this will just be another systematic review on paraspinal muscle structure without a clear conclusion, however, I would like to give the authors the benefit of the doubt because their methodology is of good quality, and they take into account multiple spinal regions. I which the authors the best of luck with this systematic review, (and hopefully a meta-analyses with a clear conclusion). I thing it i would like the authors to consider, is the clinical relevance of assessing muscle fiber type composition in relation to its clinical relevance. In other words " What will be the benefit of assessing muscle composition in aspecific low back pain" do the authors think this will lead to finding a structural cause of aspecific pain or a consequence? This is just something to reflect on, because this is often a problem we (as fellow researchers) run into when providing research (results) on this type of topic.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Jun Wu, People's Hospital of Ningxia Hui Nationality Autonomous Region

Competing interests of Reviewer: none

Comments to the Author:

Search process is not clear and topic is too old

Thank you for your feedback, however we disagree with the sentiment.

To clarify the search process, as per the manuscript, the search will be completed by the lead reviewer, and screening completed in duplicate by two reviewers. To conduct the searches, keyword strategies have been identified and optimised for each database as shown in the supplementary files. For example, the search terms used in Medline database under MESH headings are:

- spinal pain, chronic back pain, persistent back pain, cervical spinal pain, neck pain, chronic neck pain, persistent neck pain, thoracic spinal pain, persistent thoracic spine pain, lumbar spinal pain, lumbago, low* back pain, chronic low* back pain, persistent low* back pain, LBP, CLBP.
- muscle fibre type, muscle fiber type, fibre size, fiber size, fibre distribution, fibre area, fiber characteristics, fibre characteristics, fibre proportion, muscle fibre density, fibre type composition, microscopy of back muscle.
- The pain related search terms will be combined using the Boolean term ‘or’ to yield maximum studies and similarly, the muscle fibre related terms will be combined using ‘or’ to yield maximum results. The pain search terms and muscle search terms will then be combined by ‘and’ to yield the final results and study will be limited to humans only.

Per your second point, we would like to clarify that while the topic of back pain is not new, there is no conclusive evidence to date to explain if there are any structural changes in the spinal extensor muscles in patients with chronic back pain. Moreover, no previous systematic review has considered microscopic changes in the musculature and the relationship to chronic pain across all spinal levels (cervical, thoracic and lumbar regions). As discussed in the background section of our protocol, previous systematic reviews have exclusively focussed on macroscopic features/changes using imaging techniques in the cervical region or lumbar region for chronic pain. There has only been one systematic review six years ago which has considered microscopic changes in people with low back pain (but not restricted to chronic non-specific pain as this review considered back pain associated with pathology as well) and these results were inconclusive (Cagnie et al, 2015). Furthermore, this previous review also considered many cadaveric studies which will be excluded in this review as we are only considering studies conducted on living populations and as such, the results of this review will be more immediately applicable to healthcare settings. The results of this review will identify if there is evidence to indicate that there are microscopic changes in the extensor muscle of the spine in (non-specific) chronic pain conditions; and compare these changes across different regions of the spine. If we can gather enough data from all the eligible primary studies to see that microscopic changes or transformations in muscle fibres do happen, then we will be able to present evidence which can further help to develop novel approaches to therapeutic management, prevention or reversal of these changes with an ultimate aim of improving trunk muscle function.

Reviewer: 2

Dr. Thomas Osinski, Université Versailles Saint-Quentin

Competing interests of Reviewer: None declared

Comments to the Author:

Thank you for your interesting work.

I would like to suggest you some little modifications that I list below:

1-update your prospero number line 48 and 166 : CRD42020198087

Thank you for this suggestion, we have made this change.

2-in risk of bias you describe the NOS for cohort studies (line 265) but in discussion (line 344) you expect to include principally case-control studies. I think you must clarify this discrepancy. If you anticipated the inclusion of case-control studies you should change criteria of inclusion to be more explicit than :" Observational studies will likely constitute the highest level of evidence for this review, as ascertained by scooping searches." (line 181).

Thank you for raising this point. While scoping searches have identified the evidence base in observational literature, until the screening and data extraction process is complete we are not sure if this evidence will be from solely observational case-control, cross sectional or cohort studies. We do not anticipate evidence being derived from RCTs or other clinical trials. As such, in the methods section we describe the use of a generic NOS tool at this stage. When we identify the study designs used, we will ensure that the version of the NOS used matches the design of the evidence (e.g. using the case-control or cohort versions).

3- Moreover you present your review with the interest to help in prescription of exercise but if you expect principally case-control you risk having difficulty to infer who came first between egg and chicken. Do you think that a potential meta-regression will be useful for you?

As most of the primary studies that will meet the eligibility criteria are expected to present their results as a binary outcome (i.e., changes in muscle fibres present or absent), we consider meta-analysis as the most appropriate form of analysis. However, we will consider the possibility of conducting a meta-regression analysis as per your suggestion. It is difficult to commit at this stage. The probability of including study level covariates to adjust for systematic differences between the studies for meta-regression can only be ascertained after data extraction from all the included primary studies.

Furthermore, while we agree that there is an element of uncertainty due to the chicken-egg argument, at this stage we are only intending to identify if there is evidence for these changes being present at all. When this is ascertained we then hope that further research will be conducted to investigate if the reversal of these changes can improve symptoms, regardless of whether they are a cause or effect. Additionally, we expect longitudinal studies could be conducted to understand the time course of these changes.

4-As you concentrate your investigation on extensor muscle, maybe you should clarify title and present this point earlier in text. It isn't present in the abstract

Thank you for this suggestion, we have changed spinal to paraspinal in the title to reflect this point.

Globally your text is interesting and pleasant to read, in submission of article I think that a short explanation of difference between macro and microscopic muscular changes would help the readers.-

Thank you for this compliment, we have added some additional text to reflect this suggestion (lines 105-108)

Reviewer: 3

Dr. S Stevens, Hasselt University

Competing interests of Reviewer: No conflict of interest

Comments to the Author:

Dear Authors,

I would like to complement the authors on establishing this strong methodology.

Thank you very much for your kind words.

I would recommend the authors to speak of non-specific chronic spinal pain from the beginning of their introduction to clearly identify the population of interest. I think the research question very interesting, however, I'm convinced it will be very difficult to get clear answers on the proposed research question, simply because there is very little research (literature) in the area of microscopic muscle changes (especially in aspecific low back pain). In my opinion this will just be another systematic review on paraspinal muscle structure without a clear conclusion, however, I would like to give the authors the benefit of the doubt because their methodology is of good quality, and they take into account multiple spinal regions. I which the authors the best of luck with this systematic review, (and hopefully a meta-analyses with a clear conclusion). I thing it i would like the authors to consider, is the clinical relevance of assessing muscle fiber type composition in relation to its clinical relevance. In other words " What will be the benefit of assessing muscle composition in aspecific low back pain" do the authors think this will lead to finding a structural cause of aspecific pain or a consequence? This is just something to reflect on, because this is often a problem we (as fellow researchers) run into when providing research (results) on this type of topic.

Thank you for your suggestions and comments on our topic and the review protocol.

While we recognise that there are a lot of inconclusive reviews due to lack of evidence, we hope that our methodology will help to identify all of the evidence which might confirm or dispute the presence of any microscopic changes in the paraspinal muscles in non-specific CSP population. There are no systematic reviews which bring existing studies on the lumbar, thoracic and cervical regions together to provide researchers and clinicians a full summary of the evidence.

We also agree with your second point as we will not be able to conclude that any microscopic changes are a cause or consequence of pain. But irrespective of cause or consequence, this review would aim to provide evidence regarding the presence or absence of these changes. This evidence would still be relevant to develop novel approaches, targeting these specific changes (if present), to determine whether this changes function.

VERSION 2 – REVIEW

REVIEWER	Osinski Thomas Hopital Raymond Poincaré, Garches, FRANCE UR ERPHAN 20201, Université Versailles Saint-Quentin
REVIEW RETURNED	28-Jan-2021

GENERAL COMMENTS	Excellent second version. All items of PRISMA-Protocol are respected, at the exception to meta-bias but it didn't justify revision. I suggest to authors to perform it to improve their work. In same vein, explanation about threshold for meta-analysis should be presented earlier in final text. Pleasant text on a subject of interest.

REVIEWER	Sjoerd Stevens Hasselt University
REVIEW RETURNED	30-Jan-2021

GENERAL COMMENTS	Dear Author(s), My issues were sufficiently addressed by the authors, I therefore have no further comments. I look forward to the results from this review. I think it will be a nice addition to the sparse literature on muscle structure and muscle microscopy. I hope this will open doors to a more substantial analyses of muscle microstructure in individuals experiencing low back pain such as capillarisation, inflammation.... to expand our view on the contributing mechanism of microstructural alterations in this population. yours sincerely, S. Stevens