PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Differences in chronic pain prevalence between men and women at mid-life: a systematic review protocol
AUTHORS	Borra, Catherine; Hardy, Rebecca

VERSION 1 – REVIEW

REVIEWER	Rovner, Graciela Karolinska Institute
REVIEW RETURNED	16-Jun-2022

GENERAL COMMENTS	It is a pleasure to read this protocol. This review is so needed! Moreover, I agree that the narrative model will help us understand the different prevalence among sex and ages, thus guiding us to adapt interventions more personalized manner. I appreciate the comparisons by country since different cultures and health care services impact how their population report or handles long-term pain. One question: why are you interested only in the general population? Could that be interesting also to include patients and then see if there is any difference between population-based studies and studies with patients? Sometimes I wonder if men may not seek help as women do.

REVIEWER	Aaron, Rachel Johns Hopkins University
REVIEW RETURNED	26-Aug-2022

GENERAL COMMENTS	This paper presents a protocol to determine rates of chronic pain in men versus women at midlife (defined as 40-60). The authors suggest that there are considerations (e.g., increase wealth, onset of menopause) that might contribute to distinct prevalence rates. This is an interesting question, and the authors propose a sound methodological approach to address it from a systematic review perspective. Strengths include a clearly defined research question, a robust approach to assessing risk of bias, and clear screening and data extraction templates. However, it is unclear how the age range was specified, how this is justified by the literature. A minor concern is how many studies will report prevalence rates in this particular bracket, and how authors will approach overlapping age ranges (e.g., 35-55), which could limit the inclusion of relevant studies. Requiring that papers report prevalence by man v. woman further limit the available studies. There also does not seem to be a plan to account for the factors (e.g., SES, menopause status) the

	authors hypothesize account for different prevalence rates in the data extraction process, which could limit interpretation of findings. Introduction P.6 Line 76. "a period with distinct social and physical challenges where growth is balanced with decline [33], related to heightened socioeconomic responsibilities and physiological changes, like the menopause." This line could use more clarity, specifically the sentiment "growth is balanced with decline." P. 4. Line 29: “The aim of this study is to describe the prevalence of CP at midlife in men and women, and to identify how these differences relate to prevalence rates in other periods of the life-course.” This aim does not seem to match the methods, as the authors plan only to include studies with a sample aged between 40-60; it will not be possible to systematically compare prevalence rates in this population with other age ranges. Methods P. 11, line 138. Additional detail about how the age window for midlife was determined, based on the available literature, is necessary. P. 11, line 144. I was surprised to see that identifying country where data was included is an inclusion criteria. This may limit relevant studies, and the authors can address this in their sensitivity analysis by country (i.e., eliminating studies that do not report from sensitivity analysis). P. 11, line 152. "Are samples of specific groups, eg. clinical samples, population minorities." Could the authors please provide more information about what groups they have in mind here, and why they are excluded? Table 1, search Strategy. There are some minor concerns about searching based on "male or female" or "man or woman." It seems possible that studies will be overlooked because they use slightly different terms. The above point relates to a broader question for clarification. Presumably, there are many prevalence studies where rates by sex or gender are not necessarily reported, but are available by author request. How will the authors approach this situation? Given the overarching aims of this paper, the authors might consider a primary aim of establishing prevalence (across gender and/or sex) in mid-life, and a secondary aim of differentiating by gender and/or sex. Another question/concern relates to the author’s premise, that rates of chronic pain may be impacted by changing SES and menopause status. However, there does not appear to be an effort to gather this information in the data extraction stage, which will hinder the teams ability to make conclusions about the data. P. 19, l 225. Please clarify what is meant by "UN, WHO and HDI," in relation to geographic location. (this is defined later, but would be helpful to introduce with first use of the acronyms)

REVIEWER	Steultjens, Martijn Glasgow Caledonian University, Institute of Applied Health Research
REVIEW RETURNED	20-Dec-2022

GENERAL COMMENTS	This is a solid protocol for a systematic review into the prevalence of chronic pain at mid-life. The methods are adequate and follow established procedures for this type of review. I have a few comments relating to the protocol. Comments 1-3 relate to the heterogeneity of chronic pain and defining the scope of the review: 1) Chronic pain comes in many forms, and can occur as a stand-alone condition or as a symptom of another long-term condition. Only in the in- and exclusion criteria does it emerge that some forms of chronic pain (neuropathic, cancer and diabetes-related) are excluded from the review. First of all, I would like the authors to address this issue early on in their review – please clarify which types of chronic pain are in- and excluded from this review, with justification, as part of the Background section. 2) Related to comment #1, I was surprised that there is no mention of arthritis pain. The two most common forms of arthritis typically emerge in early (in the case of rheumatoid arthritis) to late (in the case of osteoarthritis) mid-life, have chronic pain as a hallmark feature, and have been shown to be more prevalent in women than men. Osteoarthritis in particular has a high prevalence, will therefore significantly affect overall chronic pain prevalence, and will magnify sex differences in chronic pain. I would like the authors to clarify whether pain prevalence specifically related to arthritis pain is in or out of scope for this review, with justification. 3) Although it is acknowledged early on that chronic pain comes in various guises – from localised pain, e.g. low back pain to widespread pain, e.g. fibromyalgia – there is no mention of how this heterogeneity will be dealt with in the narrative review or meta-analysis. From the research questions, it appears that the aim is to provide one overall prevalence figure encompassing all types of chronic pain that are deemed in scope (so only excluding the aforementioned neuropathic, cancer and diabetes pain), with only sex- and age-specific estimates given. I would suggest that it would be beneficial to add prevalence estimates for type of chronic pain, as meaningful differences might be obscured if the review only lumps together all types of chronic pain. I have some additional comments on various topics: 4) Please provide a definition of mid-life earlier in the introduction, as the term is used a number of times before it is clarified as meaning 40-65 years of age. I do wonder if this definition of mid-life is exclusively informed by life expectancy in the West. In some of the most populous nations on Earth, such as Nigeria and Pakistan, life expectancy is barely above 65 years, meaning the age bracket of 40-65 can hardly be classified as mid-life in those countries. At the very least, this should be acknowledged and reflected upon in the Discussion of this protocol, and should be discussed once the results of the review are reported as well. 5) I note that the authors propose to include publications up to January 2022. Given that we are now at the end of 2022, and the

	completed review will probably not be published until well into 2023, it would probably be good to move this inclusion cut-off date forward. 6) The statement on public and patient involvement is not very informative and suggests only minimal input was had through PPI activity. Could the authors expand on what PPI activity was undertaken for the 'sister study' (what was that study?) and how that specifically informed this systematic review?

VERSION 1 – AUTHOR RESPONSE

	Reviewer comment	**Response**
	Editor's comments	
1	Please include the planned start and end dates for the study in the methods section	As requested, we have included our start and end dates. Given that this proposed systematic review is part of a PhD programme, and the time taken from submission of this protocol to receiving review was 8 months, the systematic review process has been started. We aim to submit the systematic review results by July 2023 – which we have marked as our end date. These changes have been added (page 9 line 175-176).
2	Please ensure that the main text contains an ethics and dissemination section as per our instructions for authors	We have amended the abstract and the body of the review to include an ethics statement. This has been added (page 3 line 44-45; page 15 line 274).
	Reviewer 1 Dr. Graciela Rovner, Karolinska Institute	
1	Why are you interested only in the general population? Could that be interesting also to include patients and then see if there is any difference between population-based studies and studies with patients? Sometimes I wonder if men may not seek help as women do.	We aimed to study the overall the extent of the sex difference in chronic pain (CP) at mid-life, because we feel it is important to establish what evidence exists in the general population, before looking at specific population groups. The protocol in addition proposes to understand how sex differences may vary by geographic region and pain type. Opening this international review up to specific population sub-samples - like clinical samples, ethnic minorities or work-based samples - would increase the heterogeneity to a point at which we feel we would be unable to comment on sex differences due to inability of accounting for all overlapping intersectional characteristics. We would like to clarify, however, that general population samples do not exclude people from specific groups, so these will be included within this review. We hope our study will provide a general population comparator for future work looking at sex

		differences in CP within specific population sub-samples. We expect that recommendations for further research in this area looking at sub-samples of the general population will be discussed within our study report – particularly in the case of high heterogeneity by geographic region. We have added this to the protocol (page 5 line 95-98).
	Reviewer 2: Dr. Rachel Aaron, Johns Hopkins University	
1	It is unclear how the age range was specified, how this is justified by the literature.	We acknowledge that the age ranges for mid-life vary in the literature (page 13 line 244-247). We have clarified how we selected the age range for this study, and changes have been added (page 7 line 144-148). Clarifications have been added throughout the text to reference the age range we use in relation to mid-life (page 2 line 30-31; page 4 line 73-74; page 15 line 280-282). We chose ages 40-60 based on the work of Lachman et al [see Lachman et al (2015)] who identified specific characteristics (differences in life satisfaction, caring for an elderly parent) in this age group. An additional practical justification is that this age bracket seemed to harmonise with age categorisations in most of the relevant articles that we scoped whilst developing the protocol.
2	A minor concern is how many studies will report prevalence rates in this particular bracket, and how authors will approach overlapping age ranges (e.g., 35-55), which could limit the inclusion of relevant studies.	We acknowledge that age brackets have limitations and we have clarified how the inclusion of studies will be determined -changes have been added (page 7 line 144-148). Studies that report on samples that fall within the 40-60 bracket (e.g. 45-55, 40-50) will be included, while those which fall outside of the bracket will be excluded (e.g. 30-50, 50-70). As you suggest, this criteria will limit the inclusion of studies that could potentially contribute to knowledge around sex differences in chronic pain incidence –this has been added to the limitations (page 3 line 50; page 15 line 280-282).
3	Requiring that papers report prevalence by man v. woman further limit the available studies.	We plan to review papers that report on chronic pain (CP) prevalence by sex and/or sex difference estimates, in line with our study's objectives – clarifications have been added (page 2 line 30-31; page 2 line 35-37; page 3 line 47-48; page 5 line 94-95; page 5 line 101-103; page 7 line 144). We acknowledge that including papers

		that report chronic pain estimates by sex/gender will limit the number of CP epidemiological studies available, so we will report this as a limitation – changes have been added (page 15 line 280-282).
4	There also does not seem to be a plan to account for the factors (e.g., SES, menopause status) the authors hypothesize account for different prevalence rates in the data extraction process, which could limit interpretation of findings.	We have rephrased the rationale section of the protocol to clarify that references to socioeconomic and physical changes are part of the rationale for the study rather than an objective (page 4-5, line 74-83; page 5 line 94-98). We have also clarified our objectives to ensure readers understand that the aims of the study are to analyse sex differences in the prevalence of chronic pain (CP) at a population level (page 5, line 101-103). We hope that this study will provide useful background information for future studies investigating factors associated with differences in CP prevalence by sex.
5	P.6 Line 76. "a period with distinct social and physical challenges where growth is balanced with decline [33], related to heightened socioeconomic responsibilities and physiological changes, like the menopause." This line could use more clarity, specifically the sentiment "growth is balanced with decline."	We acknowledge your comment and this line has now been rephrased, and additional changes have been made (page 4-5, line 74-83). The phrasing 'growth is balanced with decline' is derived from the paper 'Mid-life as a pivotal in the life course: balancing youth and decline at the crossroads between youth and old age', by Lachman et al (2015), which reviews a body of work around the physical and social changes at mid-life. Within this sentence we would like to convey the degree of change and the particular features of mid-life that could be associated with sex/gender differences in chronic pain (CP). While these changes are not the object of this study, we hope they clarify the rationale for studying sex differences in CP prevalence at mid-life.
6	P. 4. Line 29: "The aim of this study is to describe the prevalence of CP at midlife in men and women, and to identify how these differences relate to prevalence rates in other periods of the life-course." This aim does not seem to match the methods, as the authors plan only to include studies with a sample aged between 40-60; it will not be possible to systematically compare prevalence rates in this population with other age ranges.	We have clarified the scope of our review based on your comment, to specify that mid-life is measured within the age bracket 40-60 (page 2 line 30-31; page 3 line 50; page 4 line 73-74; page 7 line 144-148; page 15 line 280-282) and we have removed the sentence saying we will compare results with ones from other age groups since this is beyond the scope of this review.

7	Methods P. 11, line 138. Additional detail about how the age window for midlife was determined, based on the available literature, is necessary.	We have added the details for how the age window for midlife was determined in the inclusion criteria (page 7 line 144-148). The criteria was based on literature, as discussed in the response to comment 1.
8	P. 11, line 144. I was surprised to see that identifying country where data was included is an inclusion criteria. This may limit relevant studies, and the authors can address this in their sensitivity analysis by country (i.e., eliminating studies that do not report from sensitivity analysis).	A preliminary search during the development of this protocol has shown that most eligible studies report country since they are population-level epidemiological studies, which helped justify our methods. The STROBE guidelines for the reporting of observational studies in epidemiology (von Elm et al 2007) state that good quality studies should provide the setting in which data was collected, which may account for the frequency with which the study country is reported. Since geographic region is a key hypothesised source of heterogeneity for our study we propose to maintain this as an inclusion criteria. We do not therefore believe that few (if any) studies will be excluded on the basis of this criteria – but we have added your consideration to our limitations (page 15 line 280-282).
9	P. 11, line 152. "Are samples of specific groups, eg. clinical samples, population minorities." Could the authors please provide more information about what groups they have in mind here, and why they are excluded?	We have clarified our intentions in this line which has now been rephrased, changes added (page 8 line 161-163). Specific groups, e.g. ethnic minorities, sexual minorities or profession-based groups will have characteristics that are different from the general population meaning that the prevalence of pain and the estimated sex difference in pain are unlikely to be representative of the general population – please see our response to reviewer 1, comment 1. For example, clinical groups are likely to have higher prevalence of pain than the general population and sex differences could be biased by sex differences in selection into that group. Since this review aims at estimating the sex difference in chronic pain prevalence in nationally representative data, estimates in specific groups would be biased and increase the heterogeneity in the review. Prior reviews have also used this criteria (Hoy et al 2012, Andrews et al 2018; Fayaz et al 2016). Lastly, general population samples are expected to include individuals from specific groups (e.g. ethnic minorities) so we do not exclude individuals from population sub-samples that take part in population-level surveys.

10	Table 1, search Strategy. There are some minor concerns about searching based on "male or female" or "man or woman." It seems possible that studies will be overlooked because they use slightly different terms.	We included both sex and gender qualifiers to acknowledge that epidemiological literature often uses these interchangeably (Krieger 2003). We based the search strategy on other systematic review protocols looking at sex difference (e.g. Gasbarrino et al 2020) . Although it is common practice to use key phrases like 'sex differences' in the search strategies for such reviews it was thought that this would limit inclusion to only articles that comment on sex difference, while we aim to also include articles that report prevalence. As such we have not made changes to Table 1.
11	The above point relates to a broader question for clarification. Presumably, there are many prevalence studies where rates by sex or gender are not necessarily reported, but are available by author request. How will the authors approach this situation? Given the overarching aims of this paper, the authors might consider a primary aim of establishing prevalence (across gender and/or sex) in mid-life, and a secondary aim of differentiating by gender and/or sex.	We have clarified that we will only be analysing published data (page 5 line 101-103). We have added this as a possible limitation (page 15 line 280-282). We have clarified that we will include studies which report on chronic pain prevalence by gender/sex, and studies which report sex-differences in prevalence (difference in prevalence or odds ratio or relative risk) and so we feel there will be few studies which do not report any of this information. We think that differentiating gender and sex is an important point and as part of our study we will review whether sex or gender (or both) have been used in each study and how this information has been collected – we have clarified this (page 10 line 204-205). While we anticipate that it will not be possible to differentiate between gender and sex, collecting information on how it is collected/reported will be an important first step.
12	Another question/concern relates to the author's premise, that rates of chronic pain may be impacted by changing SES and menopause status. However, there does not appear to be an effort to gather this information in the data extraction stage, which will hinder the teams ability to make conclusions about the data.	We acknowledge that within our background section we discuss various physical and social changes that occur at mid-life. We have clarified that these are not the subject of our study but inform the rationale only. We have now rephrased our rationale and objectives sections to ensure that readers are clear with our aims – changes added (page 4-5 line 78-83; page 5, line 101-103). We draw on claims that socioeconomic and physical changes occur in mid-life as the premise for studying sex differences in chronic pain in this group.
13	P. 19, l 225. Please clarify what is meant by "UN, WHO and HDI," in relation to geographic location. (this is defined later, but would be helpful to introduce with first use of the acronyms)	This line has now been rephrased, please see tracked changes protocol (page 12 line 222-224).

	Reviewer 3: Prof. Martijn Steultjens, Glasgow Caledonian University	
1	Chronic pain comes in many forms, and can occur as a stand-alone condition or as a symptom of another long-term condition. Only in the in- and exclusion criteria does it emerge that some forms of chronic pain (neuropathic, cancer and diabetes-related) are excluded from the review. First of all, I would like the authors to address this issue early on in their review – please clarify which types of chronic pain are in- and excluded from this review, with justification, as part of the Background section.	Reflecting on your comment, we have removed the exclusion criteria for neuropathic pain, diabetes and cancer pain as it is misleading (page 8 line 161-163) and have clarified within the rationale and objectives that our study is of *generic* chronic pain (CP) (page 5 line 94-95; page 6 line 111-114; page 8 line 150-152). We feel that, as you suggest, this acknowledges that CP may be related to many different conditions. Since our proposed review is of general population samples, we expect that people with a variety of conditions (including diabetes, cancer etc.) will be included and contribute to the sex differences in chronic pain prevalence in mid-life. The inclusion criteria specifies that we only include studies of general population samples, which automatically excludes studies of population sub-samples, such as diabetes or cancer patients – where prevalence of pain and sex differences may be different to that in the general population.
2	Related to comment #1, I was surprised that there is no mention of arthritis pain. The two most common forms of arthritis typically emerge in early (in the case of rheumatoid arthritis) to late (in the case of osteoarthritis) mid-life, have chronic pain as a hallmark feature, and have been shown to be more prevalent in women than men. Osteoarthritis in particular has a high prevalence, will therefore significantly affect overall chronic pain prevalence, and will magnify sex differences in chronic pain. I would like the authors to clarify whether pain prevalence specifically related to arthritis pain is in or out of scope for this review, with justification.	Based on our response to comment 1, we have removed the exclusion criteria based on pathology (page 8 line 161-163), and we have acknowledged in the rationale that different factors such as osteoarthritis are often associated with the increased chronic pain (CP) burden in midlife – we have added a reference to this (page 4 line 78-81). Our study will address the sex differences in *generic* CP, so with a focus on the presence of CP rather than its correlation with other organic disease processes. Our definition of CP is in line with the International Association for the Study of Pain and is described as pain lasting for longer than three months (Treede et al, 2019), irrespective of a given cause or disease process. We expect people with arthritis to be included within the studies we review and acknowledge that the higher prevalence of the condition in women may affect sex differences in CP. As in our response to point 2 in relation to diabetes and cancer, epidemiological studies of pain in samples of only patients with arthritis will not be included.
3	Although it is acknowledged early on that chronic pain comes in various guises – from localised pain, e.g. low back pain to widespread pain, e.g. fibromyalgia – there is no mention of how this heterogeneity will be dealt with in	We agree that the type of CP is important, and that the prevalence and sex difference are likely to vary according to type. We are planning on exploring heterogeneity in sex-specific prevalence and sex-differences by pain type (generic, regional, widespread) in our narrative review and analysis – clarifications added (page 13 line 226-228). If numbers allow, we will

	the narrative review or meta-analysis. From the research questions, it appears that the aim is to provide one overall prevalence figure encompassing all types of chronic pain that are deemed in scope (so only excluding the aforementioned neuropathic, cancer and diabetes pain), with only sex- and age-specific estimates given. I would suggest that it would be beneficial to add prevalence estimates for type of chronic pain, as meaningful differences might be obscured if the review only lumps together all types of chronic pain.	carry out subgroup analyses and/or meta-regression to investigate heterogeneity (page 14 line 260-264).
4	Please provide a definition of mid-life earlier in the introduction, as the term is used a number of times before it is clarified as meaning 40-65 years of age. I do wonder if this definition of mid-life is exclusively informed by life expectancy in the West. In some of the most populous nations on Earth, such as Nigeria and Pakistan, life expectancy is barely above 65 years, meaning the age bracket of 40-65 can hardly be classified as mid-life in those countries. At the very least, this should be acknowledged and reflected upon in the Discussion of this protocol, and should be discussed once the results of the review are reported as well.	We have added a definition of mid-life earlier on in the text as requested (page 2 line 30-31; page 4 line 73-74) – please also see our response to reviewer 2, comments 1 and 2 where we address the choice of age range (page 7 line 144-148). We acknowledge that mid-life will have different 'age brackets' according to country, life expectancy, period in history, socioeconomic position and culture (Lachman et al 2015). We have added the limits of age categorisation to the manuscript (page 3 line 50; page 13 line 224; page 15 line 280-282). We will comment on the limitations of age categorisation of mid-life within our narrative analysis, particularly if results differ significantly by geographic region.
5	I note that the authors propose to include publications up to January 2022. Given that we are now at the end of 2022, and the completed review will probably not be published until well into 2023, it would probably be good to move this inclusion cut-off date forward.	Please see our response to the editor / comment 1. Due to this study being part of an educational programme and the length of time between submission of our protocol and review (8 months), we have been pressed to start the review before receiving feedback. Our current work is based on studies published up to 10 January 2022. However, if this is conditional for the acceptance of our protocol we will consider updating the review to include an additional year of publications.
6	The statement on public and patient involvement is not very informative	We have amended the PPI section to include details about our public involvement activity (page 7 line 135-

	and suggests only minimal input was had through PPI activity. Could the authors expand on what PPI activity was undertaken for the 'sister study' (what was that study?) and how that specifically informed this systematic review?	139). The public involvement for this review centred around research question validation.

References:

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VERSION 2 – REVIEW

REVIEWER	Steultjens, Martijn Glasgow Caledonian University, Institute of Applied Health Research
REVIEW RETURNED	13-Mar-2023

GENERAL COMMENTS	Thank you for your comprehensive revision, I have no further comments.