BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065497
Article Type:	Protocol
Date Submitted by the Author:	09-Jun-2022
Complete List of Authors:	Borra, Catherine; UCL Hardy, Rebecca; Loughborough University; UCL
Keywords:	Pain management < ANAESTHETICS, EPIDEMIOLOGY, PUBLIC HEALTH

Differences in chronic pain prevalence between men and women at mid-life: a systematic review protocol

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Word count: 1977

ABSTRACT

Introduction

Epidemiological literature has revealed differences in chronic pain (CP) prevalence in men and women. Women have been found to be more likely to develop CP compared to men at different points of the life-course, such as childhood and old age. Less is known about differences in prevalence by sex during mid-life, when biological and physical changes may predispose to an earlier differentiation in CP

distribution – for example due to the menopause. 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.

Methods and analysis

This systematic review follows PRISMA guidelines. An electronic search will identify appropriate studies in the following databases: MEDLINE, EMBASE, AMED and PSYCHinfo. Two reviewers will independently screen each title and abstract. Studies eligible for data extraction will report estimates of CP prevalence, of prevalence for each sex, and difference in prevalence between sexes. The findings will be reported in a narrative synthesis following the Social Research Council Methods Programme guidelines. A random effects meta-analysis will be conducted where the reviewers can justify combining results.

Ethics and dissemination

This review will summarise the prevalence of CP in men and women at mid-life, based on existing evidence. It is expected that the results will identify gaps in

knowledge and areas for further research. The review will be submitted for publication in topic specific journals and disseminated to professional networks.

Strengths and limitations

- This protocol offers a systematic approach to determining the prevalence of chronic pain in men and women at mid-life
- Additional analyses will explore prevalence by country, offering the opportunity for comparison
- Articles in English language only will be reviewed

SYSTEMATIC REVIEW REGISTRATION

PROSPERO: CRD42021295895

KEYWORDS

chronic pain; persistent pain; prevalence; sex; sex inequalities; gender inequalities

BACKGROUND

Rationale

Chronic pain (CP) – pain that lasts for longer than three months [1] – is becoming increasingly common [2–4], and threatens the physical, social and psychological wellbeing of those who suffer with it [5–11]. While pain is a common experience, there is inequality in CP distribution between men and women, with women being more likely to experience CP at various stages of the life-course [12–19]. There are different hypotheses around the rationale for this inequality: one is sex-linked factors,

like hormones and reproductive factors [20–22], another is it related to discrepancies in the social and cultural experiences between genders [23–25], leading to forms of gendered stress. While systematic reviews have attested to the unequal distribution of CP in childhood and adolescence [26,27] and older age [13,17,18,28–32], the evidence is less clear about the prevalence of CP by sex at mid-life – 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. CP prevalence increases with age [19,34], yet some evidence shows that the burden of pain is increasing for increasingly younger cohorts [35].The mid-life is a potentially sensitive period that may provide an arena for prevention and management interventions to decrease the burden of CP later in life.

Changes at mid-life may be associated with the emergence of CP, leading to significant impact on a person's ability to work [2,36] and lead a fulfilling life [37–39]. The mid-life –the period variously defined between ages of 40-65 [33,40–44]- is a period in which both sex-linked and gender factors converge, and can be a period of stress [33,45–50], at the same time as it is a time of social [33,51] and physical

[3,33,46] change. For example, there is epidemiological evidence suggesting that women experience more musculoskeletal pain around the perimenopause compared with pre-menopausal women, and that the pain persists into later life [31].

Previous systematic reviews have addressed the prevalence of CP by sex in the adult population spanning from 18 years to older age [16–19,34]. Mansfield *et al* (2016), for example, identified that prevalence of chronic widespread pain was higher in women over 40, while Fayaz et al (2016) reported an increase in prevalence of CP with age in the pooled sample. In summary, current systematic reviews of CP prevalence in adults either fail to differentiate between phases of adulthood [17,18,29,34] or have not stratified results by sex at mid-life [15,52,53]. By comparing CP prevalence at mid-life by sex, this review aims at addressing this gap in the literature.

Objectives

We will therefore carry out a systematic review to update the work of previous reviews to investigate CP prevalence by sex in midlife in the general population. It aims at answering the following questions:

- What is the prevalence of CP in men and women in the general population at mid-life?
- What is the difference in CP prevalence between men and women in the general population?

Heterogeneity in the results and variation across studies will be explored by geographic region, pain definition, and pain type. Geographic region has been shown to be related to differences in pain prevalence in other systematic reviews of CP incidence, with higher prevalence in lower-income countries [16,34]. Similarly, differences in pain definition (eg. the IASP definition of pain for 3 months or longer; pain duration for six months or longer; pain duration for 1 month or longer) have shown to have an effect on CP prevalence estimates [54]. Lastly, the type of CP (eg. widespread chronic pain; fibromyalgia; chronic pelvic pain; chronic lower back pain)

will represent further sources of heterogeneity since different conditions have different sex prevalence [55].

Study quality will be assessed using a tool developed for prevalence studies by Hoy et al [56], and previously used in reviews of pain prevalence literature [57].

METHODS

This protocol is registered with the PROSPERO database and will be recorded using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [58] (see Supplementary material). PROSPERO will be updated with significant protocol amendments.

Patient and public involvement

The research questions were determined with input from the patient and public involvement activities for a sister study.

Eligibility criteria

Studies will be included if they:

- Are original studies published in peer reviewed journals.
- Examine the prevalence of CP in the 40-60 age group in men and women separately.
- Use samples selected from the general population.
- Use any clearly stated CP definition in line with the International Association for the Study of Pain (IASP) definition of pain lasting longer than three months [59], including both local and widespread CP.
- Clearly state the country in which data was collected.
- Use data from an observational study, such as prospective and retrospective cohorts, cross-sectional and case control studies.
- Are written in English.

Studies will be excluded if they:

- Do not meet inclusion criteria.
- Are reviews, conference proceedings, editorials and letters.
- Are samples of specific groups, eg. clinical samples, population minorities.

- Are specifically about neuropathic, diabetic or cancer pain.

Information sources and search strategy

An electronic search will identify appropriate studies. The selected databases are MEDLINE, to be accessed through Web of Science as an interface; and EMBASE, AMED and PSYCHinfo to be accessed through Ovid as an interface. These databases will be searched from earliest entries to 10 January 2022. The search strategy is based on CP terms, study terms, moderators, and limits. Different techniques will be followed to ensure the search terms identify all relevant articles, and the search strategy will be piloted to make sure it is selecting relevant articles. The search terms and various search tools used for the different databases are outlined in Table 1. The reference lists of fully eligible texts will also be screened to identify potential inclusions.

Table 1: Search strategy

	MEDLINE (Web of Science)	*EMBASE + AMED + PSYCHinfo (Ovid)*
Pain terms	Chronic pain (MeSH Heading) OR fibromyalgia (MeSH Heading)	Chronic pain OR persistent pain OR fibromyalgia (abstract) NOT cancer OR diabetes OR

	NOT cancer OR diabetes OR neuropath* OR paed* OR child* OR adolescen*	neuropath* OR paed* OR child* OR adolescen* (abstract)
Study terms	epidemiology OR cohort stud* OR cohort analys* OR cross sectional stud* OR cross sectional analys* OR observational analys* OR prevalence OR disease frequency	Epidemiolog* OR cohort stud* OR cohort analys* OR cross sectional stud* OR cross-sectional* OR cross sectional analys* OR observational analys* OR prevalence OR disease frequency NOT trial OR clinical trial (abstract)
Moderators	Women OR female Men OR male	AND Male OR men (all fields) AND Female OR women (all fields)
Limits	Excluding RCTs and clinical studies/reviews English language only Journal articles only	English language only

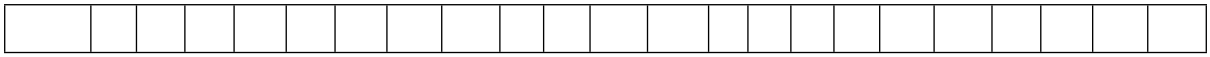
*Legend: MeSH terms are the Medical Subject Headings used for indexing articles in MEDLINE; The truncation command * is used to capture search terms which may have alternative endings; The Boolean logic operator AND combines results from the different search terms; The Boolean logic operator OR identifies results which include at least one of the search terms.*

Study selection

Duplicate search results will be removed from the final search list, which will be stored in Rayyan QCRI – a free systematic review software. The review team will consist of three researchers and two of these will independently screen each title and abstract for eligibility using a template (Table 2). The full text of the remaining articles will be retrieved using the UCL findit@UCL linking service. Inaccessible articles will be dealt with by contacting the authors directly. Each full text will be independently reviewed by two of the three researchers for final eligibility. Reasons for exclusion will be recorded and documented. At each stage of screening, any differences between researchers will be resolved through discussion. Figure 1 represents a flow diagram of the study selection process.

Table 2: Eligibility template

	Inclusion														**Exclusion**							
Article reference	Original studies published in peer reviewed journals		Prevalence of CP in the 40-60 age group in men and women separately		Sample selected from the general population		CP definition in line with the International Association for the Study of Pain (IASP) definition		Clearly state the country in which data was collected		Observational studies		Written in English		Do not meet inclusion criteria		Reviews, conference proceedings, editorials and letters		Samples of specific groups, eg. clinical samples, population minorities		Neuropathic, diabetic or cancer pain.	
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N



[FIGURE 1]

Data extraction and quality assessment

Data extraction will be conducted by the three reviewers for the following data items: citation details (including year of publication and title), study design, country, sample size, CP definition, CP type, CP measurement, age measurement, sex measurement, estimates of CP, estimates of sex difference, estimates of CP prevalence for each sex.

A data extraction form (Table 3) will be used and data will be extracted for each paper by two independent reviewers, who will resolve any discrepancies by discussion and supervision of an experienced member of the team (RH).

Table 3: Data extraction form

Screening form:

Bibliographic reference details:	
First author	
Title	
Journal	

Volume			
Year of publication			
Reviewer	CB	JP	RH
Date			
Inclusion	Yes	No	
Reasons for exclusion:			
Ineligible population	Yes	No	
Ineligible study design	Yes	No	
Ineligible outcome	Yes	No	
Ineligible publication type	Yes	No	
Not in English	Yes	No	
Duplicate	Yes	No	
Other			

Data extraction form:

Bibliographic reference details:			
First author			
Title			
Journal			
Volume			
Year of publication			
Reviewer	CB	JP	RH
Study characteristics:			
Study design	Cohort study	Cross-sectional study	Other:
Sample size			
Country			
Measurements:			
CP definition	IASP	Other:	
CP measurement			
Sex measurement	Self-reported sex	Self- reported gender	
Age measurement			

Outcomes:			
Outcome type	OR	%	Other:
Estimates of CP			
Estimates of sex difference			
Estimates of CP prevalence for each sex			

Risk of bias:		
External validity:		
Was the study's target population a close representation of the national population in relation to relevant variables?	Yes	No
Was the sampling frame a true or close representation of the target population?	Yes	No
Was some form of random selection used to select the sample, OR was a census undertaken?	Yes	No
Was the likelihood of nonresponse bias minimal? Internal	Yes	No
Were data collected directly from the subjects (as opposed to a proxy)?	Yes	No
Was an acceptable case definition used in the study?	Yes	No
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	Yes	No
Internal validity:		
Was the same mode of data collection used for all subjects?	Yes	No
Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	No
Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	No

Summary item on the overall risk of study bias	Low	Moderate	High

The primary estimates of interest are CP prevalence by sex and an estimate of the sex difference in pain (e.g. difference in prevalence or relative risk or odds ratio).

Quality assessment

Study quality will be addressed using a tool for risk of bias assessment for prevalence studies which explores internal and external validity and scores studies as low, moderate or high risk of bias [56]. This tool has high interrater agreement, and it has previously been used in pain prevalence systematic reviews [57]. For this review, two independent reviewers will use a checklist bases on this tool, which can be found in Table 3.

Synthesis

Narrative synthesis

A descriptive summary of studies will be provided using tables and addressing the following domains: primary outcomes, CP definition, CP type, sex/gender, age, geographic location (UN, WHO and HDI); and study quality assessment. It will comment on the similarity of the methods used by the different studies and on the possibility for meta-analysis.

Geographic region will be classified according to – the United Nations (UN) and World Health Organisation (WHO) region classification [60][61], and the Human Development Index (HDI) for each country – a measures of population wealth [62], which has previously used in CP prevalence reviews [16,34].

The narrative synthesis will follow the Social Research Council Methods Programme guidelines [63], with a focus on identifying and exploring the prespecified sources of heterogeneity.

Meta-analysis

A meta-analysis will be conducted if enough studies provide the relevance prevalence information by sex for the defined age group, and where the reviewers can justify combining results.

A random effects meta-analysis will be used to combine estimates of CP prevalence by sex and a measure of difference in CP prevalence between sexes. These will be presented in a Forest plot. The I^2 will be used to assess the extent of heterogeneity in estimates. If there are enough studies included, sub-group analysis or meta-regression will be performed to establish the extent of heterogeneity related to (i) geographic region (coded in three ways: UN, WHO and HDI), (ii) pain definition and (iii) pain type.

Publication bias will be assessed separately using a funnel plot. A sensitivity analysis excluding low quality studies will be carried out.

Reporting

The results of this systematic review will be shared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) 2020 guidelines [64].

DISCUSSION

This study will review existing literature estimating CP prevalence and considers the differences by sex/gender at mid-life, contributing to the literature about sex differences in CP prevalence. Heterogeneity in results will be assessed according to geographic region, CP definition and type. The strengths and limitations will be considered, and measurements of sex (and gender) will be discussed in the context of similar reviews. The results of this review will provide a significant step towards identifying CP inequalities in mid-life between the sexes and identify areas for further research. A better understanding of the relationship of CP emergence, sex and the middle years in the general population may inform better early-prevention-and-treatment strategies that tackle the distinct pathways for men and women.

LIST OF ABBREVIATIONS

CP: Chronic Pain

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Catherine Borra is supported by a PhD studentship funded by the Economic and

Social Research Council (ESRC) and the Biotechnology and Biological Sciences Research Council (BBSRC) (award reference: ES/T00200X/1). Rebecca Hardy is Director of the CLOSER consortium, which is supported by the Economic and Social Research Council (ESRC) (award reference: ES/K000357/1).

Roles of funder: none.

Guarantor: Catherine Borra

Authors' contributions

CB is the main author of the draft of this manuscript. RH contributed with edits and methodological guidance, resulting in two further drafts. All authors read and approved the final manuscript.

Acknowledgements

Dr. Nazlin Bhimani provided search term guidance which was instrumental in developing the search strategy for this protocol.

REGISTRATION

PROSPERO: CRD42021295895

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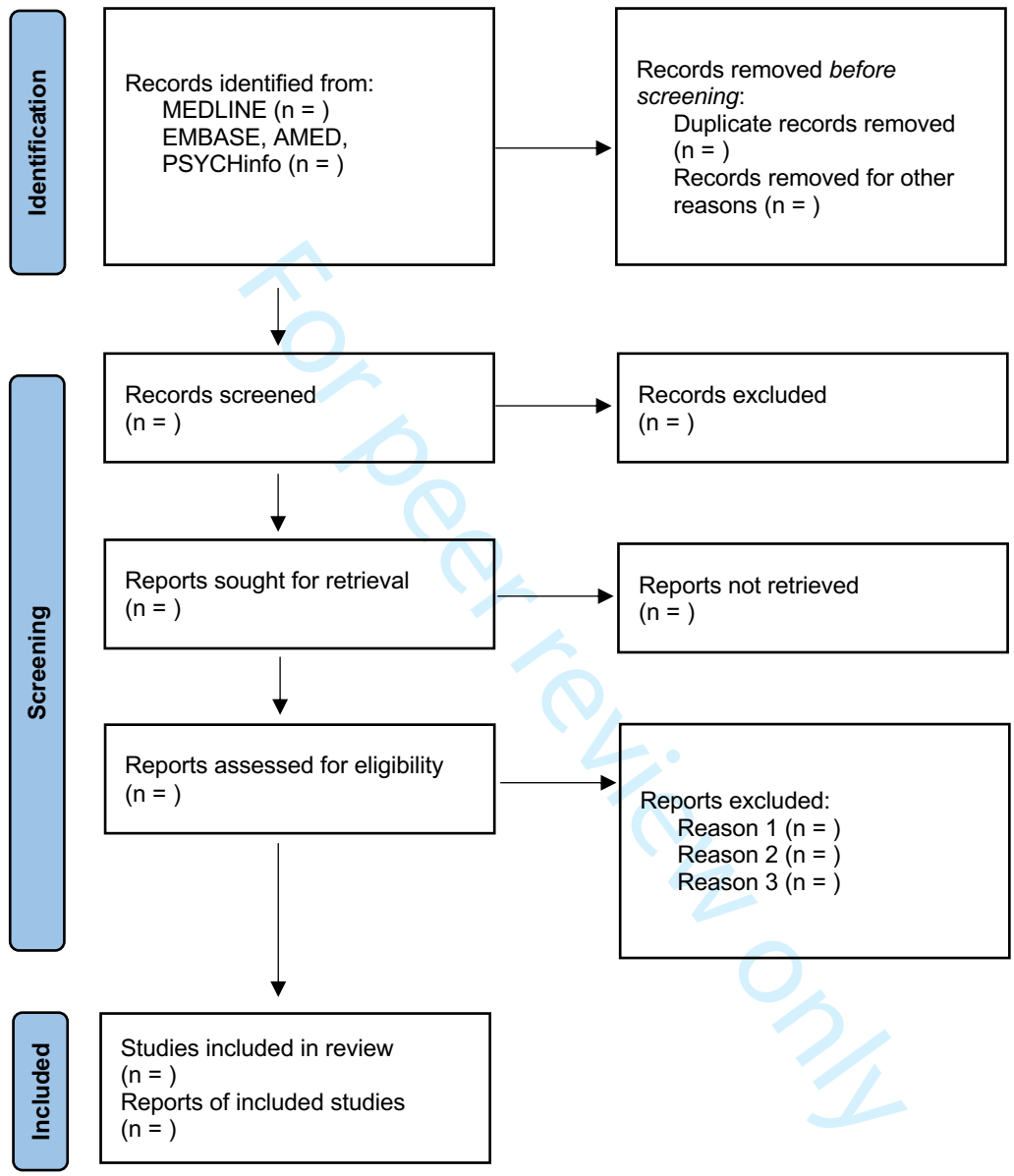
Additional materials

Parts of this manuscript refer to the following additional material, which will be presented on submission:

Material type	File name
Figure 1: Search Strategy Flow Diagram	Figure 1_search strategy.pfd
Supplementary material	Supplementary material.pfd

Figure 1: Study selection strategy – PRISMA 2020 Flow Diagram
From: Chronic pain prevalence in men and women in mid-life: a systematic review.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

This checklist has been adapted for use with the systematic review protocol submissions to BioMed Central Journals from Table 3 in:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev [Internet]. 2015;4 (1):1. Available from: https://doi.org/10.1186/2046-4053-4-1

It was adapted following guidelines from the editors-in-chief of *Systematic Reviews*:

Moher D, Stewart L, Shekelle P. Implementing PRISMA-P: Recommendations for prospective authors. Syst Rev [Internet]. 2016;5(1):4–5. Available from: http://dx.doi.org/10.1186/s13643-016-0191-y

Section and topic	Item No	Checklist item	Information reported (Y/N)	Line number(s)
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Y	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y	53
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y	5-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y	276-279
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol,	NA	N/A

		identify as such and list changes; otherwise, state plan for documenting important protocol amendments		
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Y	268-273
Sponsor	5b	Provide name for the review funder and/or sponsor	Y	268-273
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Y	274
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Y	62-96
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y	98-119
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y	127-147
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y	169-178
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y	149-165
Study records:				

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y	168-179
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y	168-179
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y	183-209
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y	192-198
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y	183-202
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y	204-209
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y	227-239
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Y	227-239
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Y	234-239
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y	212-225

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Y	238-239
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Y	204-209

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Differences in chronic pain prevalence between men and women at mid-life: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065497.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Mar-2023
Complete List of Authors:	Borra, Catherine; UCL Hardy, Rebecca; Loughborough University; UCL
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Global health, Public health, Sociology, Anaesthesia
Keywords:	Pain management < ANAESTHETICS, EPIDEMIOLOGY, PUBLIC HEALTH

Differences in chronic pain prevalence between men and women at mid-life: a systematic review protocol

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Word count: 2024

ABSTRACT

Introduction

Epidemiological literature shows differences in chronic pain (CP) prevalence in men and women. Women have been found to be more likely to develop CP at different points of the life-course, such as childhood and old age. Less is known about the

prevalence of CP by sex and the difference in prevalence during mid-life, when changes may predispose to an earlier differentiation in CP distribution. The aim of this study is to describe the difference in prevalence of CP at mid-life (ages 40-60) in men and women in the general population.

Methods and analysis

This systematic review follows PRISMA guidelines. Appropriate studies will be identified in the following databases: MEDLINE, EMBASE, AMED and PSYCHinfo. Two reviewers will independently screen each title and abstract. Studies eligible for data extraction will report estimates of CP prevalence for each sex, and/or a measure of the difference in prevalence between sexes. The findings will be reported in a narrative synthesis following the Social Research Council Methods Programme guidelines. A random effects meta-analysis will be conducted where the reviewers can justify combining results.

Ethics and dissemination

This review will summarise the prevalence of CP in men and women at mid-life, based on existing evidence. It is expected that the results will identify gaps in

knowledge and areas for further research. The review will be submitted for publication in topic specific journals and disseminated to professional networks.

Individual patient data is not included, so ethical approval is not required.

Strengths and limitations

- This protocol offers a systematic approach to determining the difference in chronic pain prevalence in men and women at mid-life
- Sex difference is explored by geographic region, chronicity threshold and pain type
- Mid-life categorisation is limited to people aged 40-60
- Articles in English language only will be reviewed

SYSTEMATIC REVIEW REGISTRATION

PROSPERO: CRD42021295895

KEYWORDS

chronic pain; persistent pain; prevalence; sex; sex inequalities; gender inequalities

BACKGROUND

Rationale

Chronic pain (CP) – pain that lasts for longer than three months [1] – is becoming increasingly common [2–4], and threatens the physical, social and psychological wellbeing of those who suffer with it [5–11]. While pain is a common experience, previous research has pointed at inequality in CP distribution between men and

women, with women being more likely to experience CP [12–19]. There are different hypotheses explaining this inequality: one relates to sex-linked factors, like hormones and reproductive factors [20–22], and another relates CP to discrepancies in the social and cultural experiences of pain between genders [23–25]. While systematic reviews have attested to the unequal distribution of CP in childhood and adolescence [26,27] and older age [13,17,18,28–32], the evidence is less clear about the difference in prevalence of CP at mid-life – the period defined between ages of 40-60, although definitions of exact age range vary [33–38]. CP in mid-life may have significant impact on a person's ability to work [2,39] and to lead a fulfilling life [40–42], so acknowledging the differences in CP distribution among the sexes may provide an arena for targeted prevention and management interventions to decrease CP burden later in life. Moreover, mid-life may be an important period for the experience of CP as it can be a period of stress [37,43–49] when the first physical signs of ageing [3,37,44], degenerative changes (like those linked to osteoarthritis) [50,51] and sex-specific changes (like menopause) are met with changes in an individual's social structure [37,52]. Such changes in mid-life may thus affect men

and women differently, exacerbating the difference in chronic pain prevalence between the sexes.

For example, there is epidemiological evidence suggesting that women experience more musculoskeletal pain around the peri-menopause compared with pre-menopausal women, and that the pain persists into later life [31].

Previous systematic reviews have addressed the prevalence of CP by sex in the adult population spanning from 18 years to older age [16–19,53]. Mansfield *et al* (2016), for example, identified that prevalence of chronic widespread pain was higher in women over 40, while Fayaz et al (2016) reported an increase in prevalence of CP with age in the pooled sample. In summary, current systematic reviews of CP prevalence in adults either fail to differentiate between phases of adulthood [17,18,29,53] or have not stratified results by sex at mid-life [15,54,55]. By considering the sex-difference in prevalence of CP at mid-life in the general population, this review aims at addressing this gap in the literature. The evidence summarised in this review will provide background for further work evaluating sex-

and gender-based factors for CP in mid-life, and comparing sex differences in CP prevalence in specific patient groups and population sub-groups.

Objectives

We will therefore carry out a systematic review to update the work of previous reviews and investigate CP prevalence by sex and sex-differences in CP in mid-life in the general population, drawing from available published data. The review aims at answering the following questions:

- What is the prevalence of CP in men and in women in the general population at mid-life?
- What is the difference in CP prevalence between men and women in the general population?

This review will consider CP as defined by the International Association for the Study of Pain [1]. While people who are suffering from pain due to other diseases (e.g.

diabetes, cancer) might be included within general population surveys of pain, the review will not include studies that only investigate CP specific to a disease process. Heterogeneity in the results and variation across studies will be explored according to three characteristics - geographic region, chronicity threshold, and pain type. Geographic region has been shown to relate to differences in pain prevalence in other systematic reviews of CP incidence, with higher prevalence in lower-income countries [16,53]. Similarly, differences in chronicity threshold (e.g. pain for 3 months or longer [1]; pain for six months or longer; pain for 1 month or longer) have shown to have an effect on CP prevalence estimates [56]. Lastly, the type of CP (e.g. generic, regional, widespread) will represent further sources of heterogeneity since conditions associated with certain types of CP have different sex prevalence [57].

Study quality will be assessed using a tool developed for prevalence studies by Hoy et al [58], and previously used in reviews of pain prevalence literature [59].

METHODS

This protocol is registered with the PROSPERO database and will be recorded using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [60] (see Supplementary material). PROSPERO will be updated with significant protocol amendments.

Patient and public involvement

The research aims were determined with input from the patient and public involvement activities for an ethnographic study about the experiences of perimenopausal women with chronic pain conducted by the same research team. Participants commented on the relevance of sex differences in CP distribution and the importance of mid-life in relation to CP development.

Eligibility criteria

Studies will be included if they:

- Are original studies published in peer reviewed journals.

- Examine the prevalence of CP for each sex and/or sex difference in the 40-60 age group (determined according to Lachman (2011) and as age categorisations commonly used in studies are in 5 or 10 year age bands) in men and women separately [37]. Only estimates from studies where an entire sample falls within the band will be included.
- Use samples selected from the general population.
- Use any clearly stated CP definition in line with the International Association for the Study of Pain (IASP) definition of pain lasting longer than three months [61], including generic, regional and widespread CP.
- Clearly state the country in which data was collected.
- Use data from an observational study, such as prospective and retrospective cohorts, cross-sectional and case control studies.
- Are written in English.

Studies will be excluded if they:

- Do not meet inclusion criteria.
- Are reviews, conference proceedings, editorials and letters.

- Are samples of specific groups or sub-samples of the general population that are not representative of the general population eg. clinical or disease-specific samples, ethnic minority samples, employment-based samples etc.

Information sources and search strategy

An electronic search will identify appropriate studies. The selected databases are MEDLINE, to be accessed through Web of Science as an interface; and EMBASE, AMED and PSYCHinfo to be accessed through Ovid as an interface. These databases will be searched from earliest entries to 10 January 2022. The search strategy is based on CP terms, study terms, moderators, and limits. Different techniques will be followed to ensure the search terms identify all relevant articles, and the search strategy will be piloted to make sure it is selecting relevant articles. The search terms and various search tools used for the different databases are outlined in Table 1. The reference lists of fully eligible texts will also be screened to identify potential inclusions.

The study will start in January 2022 and end upon submission of the study report for publication – expected in July 2023.

Table 1: Search strategy

	MEDLINE (Web of Science)	*EMBASE + AMED + PSYCHinfo (Ovid)*
Pain terms	Chronic pain (MeSH Heading) OR fibromyalgia (MeSH Heading) NOT cancer OR diabetes OR neuropath* OR paed* OR child* OR adolescen*	Chronic pain OR persistent pain OR fibromyalgia (abstract) NOT cancer OR diabetes OR neuropath* OR paed* OR child* OR adolescen* (abstract)
Study terms	epidemiology OR cohort stud* OR cohort analys* OR cross sectional stud* OR cross sectional analys* OR observational analys* OR prevalence OR disease frequency	Epidemiolog* OR cohort stud* OR cohort analys* OR cross sectional stud* OR cross-sectional* OR cross sectional analys* OR observational analys* OR prevalence OR disease frequency NOT trial OR clinical trial (abstract)
Moderators	Women OR female Men OR male	AND Male OR men (all fields) AND Female OR women (all fields)
Limits	Excluding RCTs and clinical studies/reviews English language only Journal articles only	English language only

*Legend: MeSH terms are the Medical Subject Headings used for indexing articles in MEDLINE; The truncation command * is used to capture search terms which may have alternative endings; The Boolean logic operator AND combines results from the different search terms; The Boolean logic operator OR identifies results which include at least one of the search terms.*

Study selection

Duplicate search results will be removed from the final search list, which will be stored in Rayyan QCRI – a free systematic review software. The review team will consist of three researchers and two of these will independently screen each title and abstract for eligibility using a template (Tables 2a-2b). The full text of the remaining articles will be retrieved using the UCL findit@UCL linking service. Inaccessible articles will be dealt with by contacting the authors directly. Each full text will be independently reviewed by two of the three researchers for final eligibility. Reasons for exclusion will be recorded and documented. At each stage of screening, any differences between researchers will be resolved through discussion. Figure 1 represents a flow diagram of the study selection process.

Table 2a: Eligibility template - inclusion

	Inclusion						
Article reference	Original studies published in peer reviewed journals	Prevalence of CP in the 40-60 age group in men and women separately	Sample selected from the general population	CP definition in line with the International Association for the Study of Pain	Clearly state the country in which data was collected	Observational studies	Written in English

				(IASP) definition			
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N

Table 2b: Eligibility template - exclusion

	Exclusion		
Article reference	Do not meet inclusion criteria	Reviews, conference proceedings, editorials and letters	Samples of specific groups, eg. clinical samples, population minorities
	Y/N	Y/N	Y/N

[FIGURE 1]

Data extraction and quality assessment

Data extraction will be conducted by the three reviewers for the following data items: citation details (including year of publication and title), study design, country, sample size, CP definition, CP type, CP measurement, age measurement, sex measurement (sex and/or gender), estimates of CP, estimates of sex difference, estimates of CP prevalence for each sex.

A data extraction form (Tables 3a-3b) will be used and data will be extracted for each paper by two independent reviewers, who will resolve any discrepancies by discussion and supervision of an experienced member of the team (RH).

Table 3a: Data extraction form

Screening form:

Bibliographic reference details:			
First author			
Title			
Journal			
Volume			
Year of publication			
Reviewer	CB	JP	RH
Date			
Inclusion	Yes	No	
Reasons for exclusion:			
Ineligible population	Yes	No	
Ineligible study design	Yes	No	
Ineligible outcome	Yes	No	
Ineligible publication type	Yes	No	
Not in English	Yes	No	
Duplicate	Yes	No	
Other			

Table 3b: Data extraction form:

Bibliographic reference details:			
First author			
Title			
Journal			
Volume			
Year of publication			
Reviewer	CB	JP	RH
Study characteristics:			
Study design	Cohort study	Cross-sectional study	Other:
Sample size			
Country			
Measurements:			
CP definition	IASP	Other:	
CP measurement			
Sex measurement	Self-reported sex	Self- reported gender	
Age measurement			
Outcomes:			
Outcome type	OR	%	Other:
Estimates of CP			
Estimates of sex difference			
Estimates of CP prevalence for each sex			
Risk of bias:			
External validity:			
Was the study's target population a close representation of the national population in relation to relevant variables?	Yes	No	
Was the sampling frame a true or close representation of the target population?	Yes	No	
Was some form of random selection used to select the sample, OR was a census undertaken?	Yes	No	

Was the likelihood of nonresponse bias minimal? Internal	Yes		No
Were data collected directly from the subjects (as opposed to a proxy)?	Yes		No
Was an acceptable case definition used in the study?	Yes		No
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	Yes		No
Internal validity:			
Was the same mode of data collection used for all subjects?	Yes		No
Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes		No
Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes		No
Summary item on the overall risk of study bias	Low	Moderate	High

The primary estimates of interest are CP prevalence by sex and an estimate of the sex difference in pain (e.g. difference in prevalence or relative risk or odds ratio). Geographic region will be classified according to – the United Nations (UN) and World Health Organisation (WHO) region classification [62][63], and the Human Development Index (HDI) for each country – a measures of population wealth [64], which has previously used in CP prevalence reviews [16,53]. Chronicity threshold

will be classified as over 3 months or over 6 months [1,65]. Pain type will be categorised as generic, regional (in one body part only) or widespread (in multiple body parts according to the American College of Rheumatology's definition of chronic widespread pain) [66].

Quality assessment

Study quality will be addressed using a tool for risk of bias assessment for prevalence studies which explores internal and external validity and scores studies as low, moderate or high risk of bias [58]. This tool has high interrater agreement, and it has previously been used in pain prevalence systematic reviews [59]. For this review, two independent reviewers will use a checklist bases on this tool, which can be found in Table 3.

Synthesis

Narrative synthesis

A descriptive summary of studies will be provided using tables and addressing the following domains: primary outcomes, CP definition, CP type, sex/gender, age,

chronicity threshold, pain type, geographic location; and study quality assessment. It will comment on the similarity of the methods used by the different studies and on the possibility for meta-analysis.

The correspondence between mid-life and the age category utilised in this study is based on life-expectancy in the global north. Countries with lower life expectancy may have different thresholds for midlife, and we will address this when discussing geographical differences in prevalence.

The narrative synthesis will follow the Social Research Council Methods Programme guidelines [67], with a focus on identifying and exploring the prespecified sources of heterogeneity.

Meta-analysis

A meta-analysis will be conducted if enough studies provide the relevance prevalence information by sex for the defined age group, and where the reviewers can justify combining results.

A random effects meta-analysis will be used to combine estimates of sex difference in CP (e.g. difference in prevalence, odds ration or relative risk). These will be presented in a Forest plot. The I^2 statistic will be used to assess the extent of heterogeneity in estimates. If there are enough studies included, sub-group analysis or meta-regression will be performed to investigate heterogeneity related to (i) geographic region (coded in three ways: UN, WHO and HDI), (ii) chronicity threshold (over 3 months, over 6 months) and (iii) pain type (generic, regional, widespread). Publication bias will be assessed separately using a funnel plot. A sensitivity analysis excluding low quality studies will be carried out.

Reporting

The results of this systematic review will be shared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) 2020 guidelines [68].

Ethics

The data will not include individual patient data so ethical approval is not required.

DISCUSSION

This study will review existing literature estimating CP prevalence and considers the differences by sex/gender at mid-life, contributing to the literature about sex differences in CP prevalence. Heterogeneity in results will be assessed according to geographic region, chronicity threshold and CP type. The strengths and limitations will be considered – for example, the restrictions posed by the inclusion criteria on a particular age bracket, published sex data and the need for country to be stated. Measurement ad reporting of sex (and gender) will be discussed. The results of this review will provide a significant step towards identifying CP inequalities in mid-life between the sexes and identify areas for further research. A better understanding of the relationship of CP emergence, sex and the middle years in the general population may inform better early-prevention-and-treatment strategies that tackle the distinct pathways for men and women.

LIST OF ABBREVIATIONS

CP: Chronic Pain

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Catherine Borra is supported by a PhD studentship funded by the Economic and Social Research Council (ESRC) and the Biotechnology and Biological Sciences Research Council (BBSRC) (award reference: ES/T00200X/1). Rebecca Hardy is Director of the CLOSER consortium, which is supported by the Economic and Social Research Council (ESRC) (award reference: ES/K000357/1).

Roles of funder: none.

Guarantor: Catherine Borra

Authors' contributions

CB is the main author of the draft of this manuscript. RH contributed with edits and methodological guidance, resulting in two further drafts. All authors read and approved the final manuscript.

Acknowledgements

Dr. Nazlin Bhimani provided search term guidance which was instrumental in developing the search strategy for this protocol.

REGISTRATION

PROSPERO: CRD42021295895

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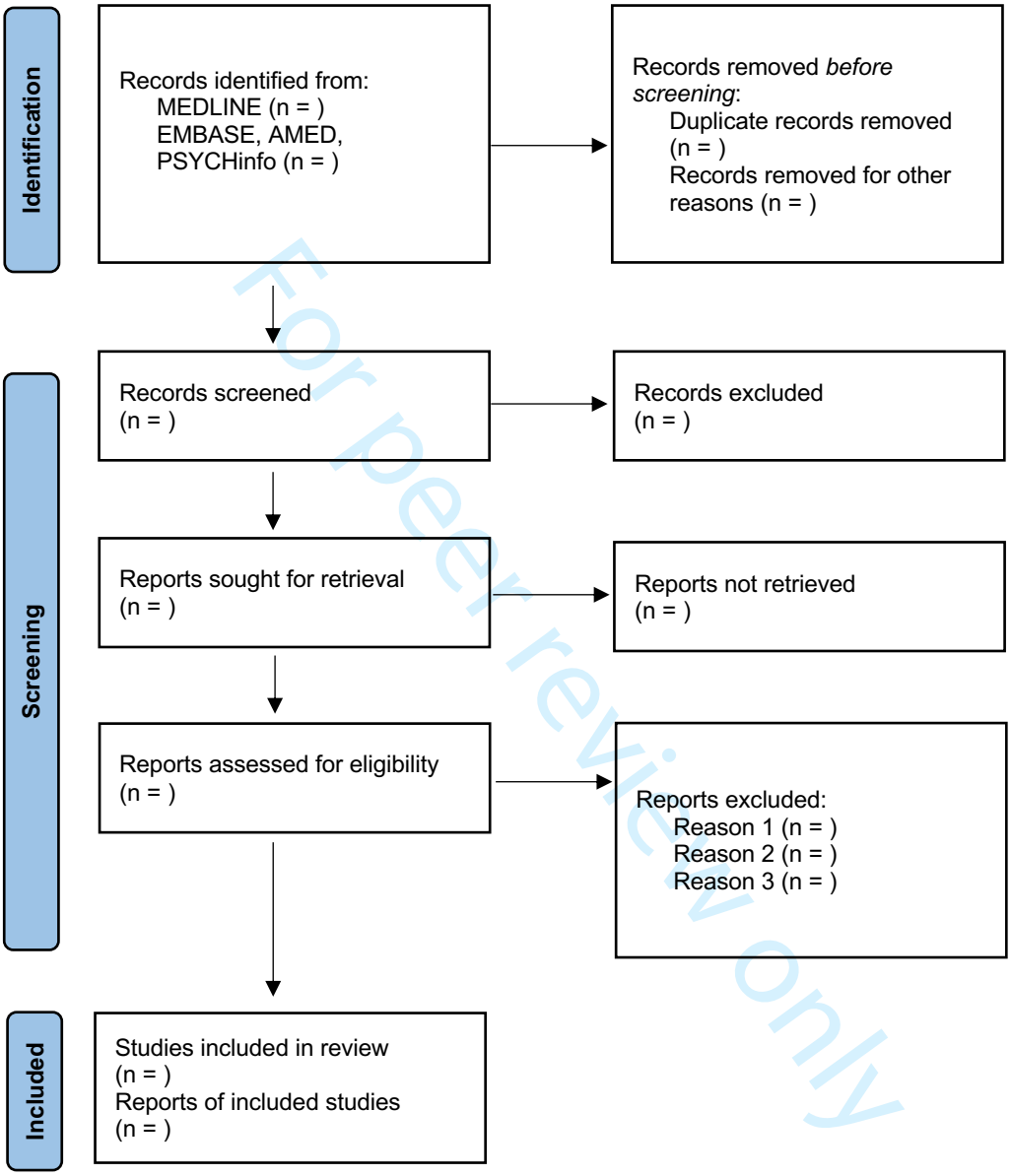
Additional materials

Parts of this manuscript refer to the following additional material, which will be presented on submission:

Material type	File name

Figure 1: Search Strategy Flow Diagram	Figure 1_search strategy.pfd
Supplementary material	Supplementary material.pfd

Figure 1: Study selection strategy – PRISMA 2020 Flow Diagram
From: Chronic pain prevalence in men and women in mid-life: a systematic review.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

This checklist has been adapted for use with the systematic review protocol submissions to BioMed Central Journals from Table 3 in:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev [Internet]. 2015;4 (1):1. Available from: https://doi.org/10.1186/2046-4053-4-1

It was adapted following guidelines from the editors-in-chief of *Systematic Reviews*:

Moher D, Stewart L, Shekelle P. Implementing PRISMA-P: Recommendations for prospective authors. Syst Rev [Internet]. 2016;5(1):4–5. Available from: http://dx.doi.org/10.1186/s13643-016-0191-y

Section and topic	Item No	Checklist item	Information reported (Y/N)	Line number(s)
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Y	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y	54
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y	5-19
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y	309-312
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol,	NA	N/A

		identify as such and list changes; otherwise, state plan for documenting important protocol amendments		
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Y	268-273
Sponsor	5b	Provide name for the review funder and/or sponsor	Y	301-306
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Y	307
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Y	63-98
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y	100-126
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y	141-156
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y	166-169
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y	169-174
Study records:				

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y	186-190
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y	187-194
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y	202-210
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y	203-206
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y	220-228
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y	231-235
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y	254-266
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Y	258-266
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Y	260-264
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y	238-251

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Y	265-266
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Y	231-235

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.