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

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ABSTRACT

Introduction Epidemiological literature shows differences in chronic pain (CP) prevalence in men and women. Women are more likely to develop CP at different points of the life course, such as adolescence 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Appropriate studies will be identified in the following databases: MEDLINE, EMBASE, AMED and PsycINFO. 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 are not included, so ethical approval is not required.

PROSPERO registration number CRD42021295895.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ 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 geographical region, chronicity threshold and pain type.
⇒ Mid-life categorisation is limited to people aged 40–60.
⇒ Articles in English language only will be reviewed.

BACKGROUND

Rationale

Chronic pain (CP)—that lasts for longer than 3 months[1]—is becoming increasingly common,[2–4] and threatens the physical, social and psychological well-being 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, such as 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 will affect men and women differently, exacerbating the difference in CP prevalence between the sexes. For example, there is epidemiological evidence suggesting that women experience more musculoskeletal pain around the perimenopause compared with premenopausal 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*[53] identified that prevalence of chronic widespread pain was higher in women over 40, while Fayaz et al (2016)[19] 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-bsed and gender-based factors for CP in mid-life, and comparing sex differences in CP prevalence in specific patient groups and population subgroups.

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 (IASP).[1] While people who are suffering from pain due to other diseases (eg, 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—geographical region, chronicity threshold and pain type. Geographical 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 (eg, pain for 3 months or longer[1]; pain for 6 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 (eg, 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 (PRISMA) Protocols[60] (see online supplemental 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 CP 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 *et al* and as age categorisations commonly used in studies are in 5-year 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 IASP definition of pain lasting longer than 3 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 subsamples of the general population that are not representative of the general population, for example, clinical or disease-specific samples, ethnic minority samples, employment-based samples.

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 PsycINFO 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 on submission of the study report for publication—expected in July 2023.

Table 1 Search strategy

	MEDLINE (Web of Science)	EMBASE+AMED + PsycINFO (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

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 2A,B). 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.

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 (table 3A,B) 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).

The primary estimates of interest are CP prevalence by sex and an estimate of the sex difference in pain (eg, difference in prevalence or relative risk or OR).

Geographical region will be classified according to—the United Nations (UN) and 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

Table 2 Eligibility template - inclusion and exclusion

	(A)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 definition	Clearly state the country in which data was collected	Observational studies	Written in English
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
		(B)Exclusion					
Article reference		Do not meet inclusion criteria		Reviews, conference proceedings, editorials and letters		Samples of specific groups, for example, clinical samples, population minorities	
		Y/N		Y/N		Y/N	

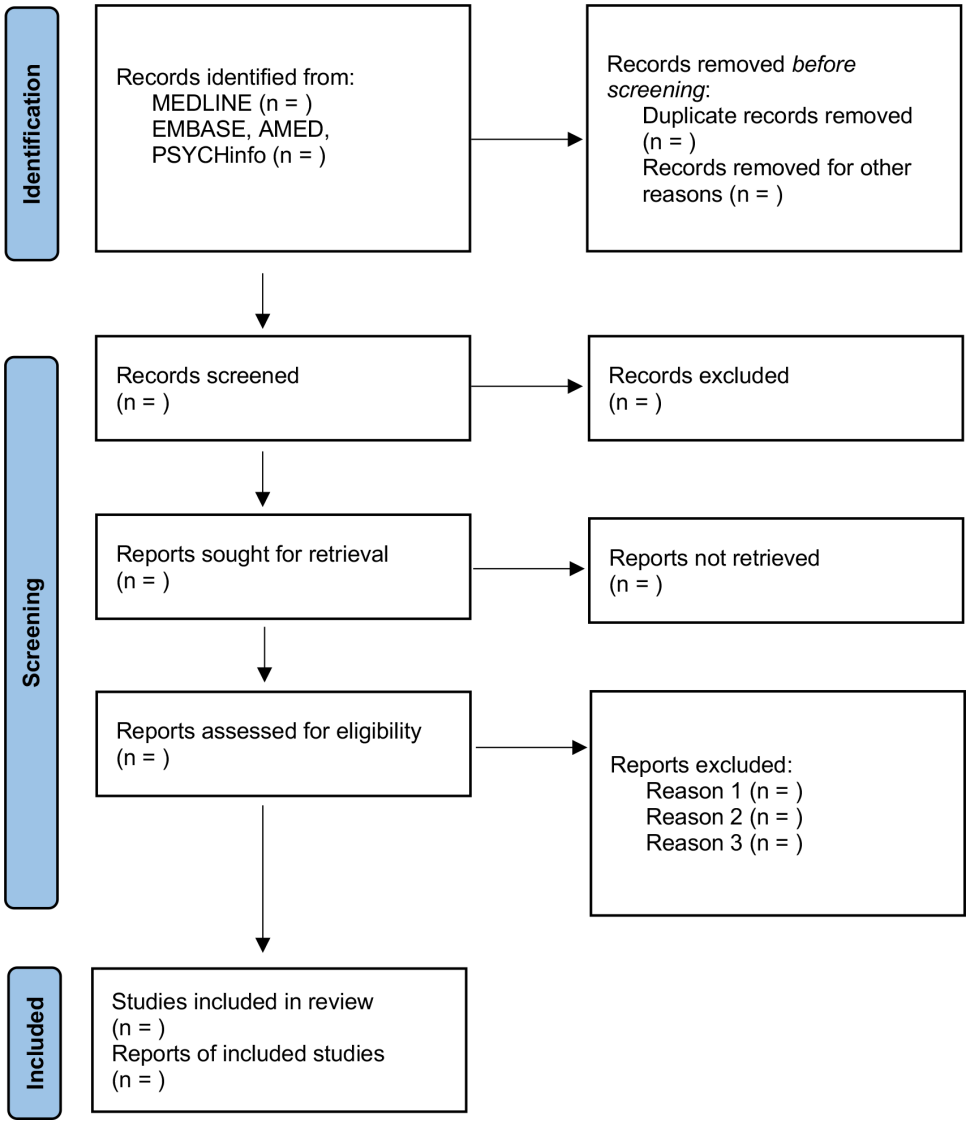

Figure 1 Study selection strategy—PRISMA 2020 Flow Diagram. From: Chronic pain prevalence in men and women in mid-life: a systematic review.[68]. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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 inter-rater 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, geographical 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 used in this study is based on life expectancy in the global north. Countries with lower life expectancy may have different thresholds for mid-life, 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.

Table 3 Data extraction form

Bibliographic reference details:			
First author			
Title			
Journal			
Volume			
Year of publication			
Reviewer	1	2	3
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			
Bibliographic reference details:			
First author			
Title			
Journal			
Volume			
Year of publication			
Reviewer	1	2	3
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

Continued

Table 3 Continued

Bibliographic reference details:			
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

CP, chronic pain.

A random effects meta-analysis will be used to combine estimates of sex difference in CP (eg, 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, subgroup analysis or meta-regression will be performed to investigate heterogeneity related to (1) geographical region (coded in three ways: UN, WHO and HDI), (2) chronicity threshold (over 3 months, over 6 months) and (3) 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 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 geographical 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.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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