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# BMJ Open

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

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SCHOLARONE™  
Manuscripts

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21 19 Word count: 1977

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28 21 **ABSTRACT**

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38 23 **Introduction**

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43 24 Epidemiological literature has revealed differences in chronic pain (CP) prevalence

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46 25 in men and women. Women have been found to be more likely to develop CP

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50 26 compared to men at different points of the life-course, such as childhood and old

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52  
53 27 age. Less is known about differences in prevalence by sex during mid-life, when

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57 28 biological and physical changes may predispose to an earlier differentiation in CP

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4 29 distribution – for example due to the menopause. The aim of this study is to describe  
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6  
7 30 the prevalence of CP at midlife in men and women, and to identify how these  
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11 31 differences relate to prevalence rates in other periods of the life-course.  
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## 14 32 **Methods and analysis**

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19 33 This systematic review follows PRISMA guidelines. An electronic search will identify  
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21  
22 34 appropriate studies in the following databases: MEDLINE, EMBASE, AMED and  
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25  
26 35 PSYCHinfo. Two reviewers will independently screen each title and abstract. Studies  
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28  
29 36 eligible for data extraction will report estimates of CP prevalence, of prevalence for  
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32  
33 37 each sex, and difference in prevalence between sexes. The findings will be reported  
34  
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36 38 in a narrative synthesis following the Social Research Council Methods Programme  
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39 39 guidelines. A random effects meta-analysis will be conducted where the reviewers  
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42  
43 40 can justify combining results.  
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## 46 41 **Ethics and dissemination**

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51 42 This review will summarise the prevalence of CP in men and women at mid-life,  
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54 43 based on existing evidence. It is expected that the results will identify gaps in  
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4 44 knowledge and areas for further research. The review will be submitted for  
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7 45 publication in topic specific journals and disseminated to professional networks.  
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## 10 46 **Strengths and limitations**

- 15 47 • This protocol offers a systematic approach to determining the prevalence of  
16  
17  
18 48 chronic pain in men and women at mid-life
- 22 49 • Additional analyses will explore prevalence by country, offering the  
23  
24  
25 50 opportunity for comparison
- 29 51 • Articles in English language only will be reviewed

## 33 52 34 35 36 37 53 **SYSTEMATIC REVIEW REGISTRATION**

41 54 PROSPERO: CRD42021295895

## 45 55 **KEYWORDS**

50 56 chronic pain; persistent pain; prevalence; sex; sex inequalities; gender inequalities  
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28 61 **BACKGROUND**  
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36 63 **Rationale**  
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40 64 Chronic pain (CP) – pain that lasts for longer than three months [1] – is becoming  
41  
42  
43 65 increasingly common [2–4], and threatens the physical, social and psychological  
44  
45  
46  
47 66 wellbeing of those who suffer with it [5–11]. While pain is a common experience,  
48  
49  
50  
51 67 there is inequality in CP distribution between men and women, with women being  
52  
53  
54 68 more likely to experience CP at various stages of the life-course [12–19]. There are  
55  
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57  
58 69 different hypotheses around the rationale for this inequality: one is sex-linked factors,  
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4 70 like hormones and reproductive factors [20–22], another is it related to discrepancies  
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6  
7 71 in the social and cultural experiences between genders [23–25], leading to forms of  
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9  
10 72 gendered stress. While systematic reviews have attested to the unequal distribution  
11  
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13  
14 73 of CP in childhood and adolescence [26,27] and older age [13,17,18,28–32], the  
15  
16  
17 74 evidence is less clear about the prevalence of CP by sex at mid-life – a period with  
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20  
21 75 distinct social and physical challenges where growth is balanced with decline [33],  
22  
23  
24 76 related to heightened socioeconomic responsibilities and physiological changes, like  
25  
26  
27  
28 77 the menopause. CP prevalence increases with age [19,34], yet some evidence  
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31 78 shows that the burden of pain is increasing for increasingly younger cohorts [35]. The  
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35 79 mid-life is a potentially sensitive period that may provide an arena for prevention and  
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38 80 management interventions to decrease the burden of CP later in life.  
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42 81  
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45 82 Changes at mid-life may be associated with the emergence of CP, leading to  
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49 83 significant impact on a person’s ability to work [2,36] and lead a fulfilling life [37–39].  
50  
51  
52 84 The mid-life –the period variously defined between ages of 40-65 [33,40–44]- is a  
53  
54  
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56 85 period in which both sex-linked and gender factors converge, and can be a period of  
57  
58  
59 86 stress [33,45–50], at the same time as it is a time of social [33,51] and physical



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4 87 [3,33,46] change. For example, there is epidemiological evidence suggesting that  
5  
6  
7 88 women experience more musculoskeletal pain around the perimenopause compared  
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11 89 with pre-menopausal women, and  
12  
13  
14 90 that the pain persists into later life [31].  
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17 91  
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21 92 Previous systematic reviews have addressed the prevalence of CP by sex in the  
22  
23  
24 93 adult population spanning from 18 years to older age [16–19,34]. Mansfield *et al*  
25  
26  
27  
28 94 (2016), for example, identified that prevalence of chronic widespread pain was  
29  
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31 95 higher in women over 40, while Fayaz *et al* (2016) reported an increase in  
32  
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34  
35 96 prevalence of CP with age in the pooled sample. In summary, current systematic  
36  
37  
38 97 reviews of CP prevalence in adults either fail to differentiate between phases of  
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41  
42 98 adulthood [17,18,29,34] or have not stratified results by sex at mid-life [15,52,53]. By  
43  
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45 99 comparing CP prevalence at mid-life by sex, this review aims at addressing this gap  
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49 100 in the literature.  
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## 53 54 55 56 102 **Objectives** 57 58 59 60

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4 103 We will therefore carry out a systematic review to update the work of previous  
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7 104 reviews to investigate CP prevalence by sex in midlife in the general population. It  
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9  
10 105 aims at answering the following questions:

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14 106  
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16  
17 107 • What is the prevalence of CP in men and women in the general population at  
18  
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21 108 mid-life?  
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23  
24 109 • What is the difference in CP prevalence between men and women in the  
25  
26  
27  
28 110 general population?  
29  
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32 111

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35 112 Heterogeneity in the results and variation across studies will be explored by  
36  
37  
38 113 geographic region, pain definition, and pain type. Geographic region has been  
39  
40  
41  
42 114 shown to be related to differences in pain prevalence in other systematic reviews of  
43  
44  
45 115 CP incidence, with higher prevalence in lower-income countries [16,34]. Similarly,  
46  
47  
48  
49 116 differences in pain definition (eg. the IASP definition of pain for 3 months or longer;  
50  
51  
52 117 pain duration for six months or longer; pain duration for 1 month or longer) have  
53  
54  
55  
56 118 shown to have an effect on CP prevalence estimates [54]. Lastly, the type of CP (eg.  
57  
58  
59 119 widespread chronic pain; fibromyalgia; chronic pelvic pain; chronic lower back pain)

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4 120 will represent further sources of heterogeneity since different conditions have  
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7 121 different sex prevalence [55].  
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14 123 Study quality will be assessed using a tool developed for prevalence studies by Hoy  
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17 124 et al [56], and previously used in reviews of pain prevalence literature [57].  
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## 24 25 126 **METHODS** 26 27

28  
29 127 This protocol is registered with the PROSPERO database and will be recorded using  
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31  
32 128 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols  
33  
34  
35 129 (PRISMA-P) [58] (see Supplementary material). PROSPERO will be updated with  
36  
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38  
39 130 significant protocol amendments.  
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### 42 43 131 **Patient and public involvement** 44 45

46  
47 132 The research questions were determined with input from the patient and public  
48  
49  
50 133 involvement activities for a sister study.  
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### 57 135 **Eligibility criteria** 58 59 60

1  
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4 136 Studies will be included if they:

- 5  
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7 137 • Are original studies published in peer reviewed journals.  
8  
9  
10 138 • Examine the prevalence of CP in the 40-60 age group in men and women  
11  
12  
13  
14 139 separately.  
15  
16  
17 140 • Use samples selected from the general population.  
18  
19  
20  
21 141 • Use any clearly stated CP definition in line with the International Association  
22  
23  
24 142 for the Study of Pain (IASP) definition of pain lasting longer than three months  
25  
26  
27  
28 143 [59], including both local and widespread CP.  
29  
30  
31 144 • Clearly state the country in which data was collected.  
32  
33  
34  
35 145 • Use data from an observational study, such as prospective and retrospective  
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37  
38 146 cohorts, cross-sectional and case control studies.  
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40  
41  
42 147 • Are written in English.  
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49 149 Studies will be excluded if they:

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52 150 • Do not meet inclusion criteria.  
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55  
56 151 • Are reviews, conference proceedings, editorials and letters.  
57  
58  
59 152 • Are samples of specific groups, eg. clinical samples, population minorities.  
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4 153      • Are specifically about neuropathic, diabetic or cancer pain.  
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11 155      **Information sources and search strategy**  
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14 156      An electronic search will identify appropriate studies. The selected databases are  
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18 157      MEDLINE, to be accessed through Web of Science as an interface; and EMBASE,  
19  
20  
21 158      AMED and PSYCHinfo to be accessed through Ovid as an interface. These  
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24  
25 159      databases will be searched from earliest entries to 10 January 2022. The search  
26  
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28 160      strategy is based on CP terms, study terms, moderators, and limits. Different  
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32 161      techniques will be followed to ensure the search terms identify all relevant articles,  
33  
34  
35 162      and the search strategy will be piloted to make sure it is selecting relevant articles.  
36  
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38  
39 163      The search terms and various search tools used for the different databases are  
40  
41  
42 164      outlined in Table 1. The reference lists of fully eligible texts will also be screened to  
43  
44  
45  
46 165      identify potential inclusions.  
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49 166      *Table 1: Search strategy*  
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51 167

	<i>MEDLINE (Web of Science)</i>	<i>EMBASE + AMED + PSYCHinfo (Ovid)</i>
<i>Pain terms</i>	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)
<i>Study terms</i>	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)
<i>Moderators</i>	Women OR female Men OR male	AND Male OR men (all fields) AND Female OR women (all fields)
<i>Limits</i>	Excluding RCTs and clinical studies/reviews English language only Journal articles only	English language only

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

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## 175 Study selection

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4 176 Duplicate search results will be removed from the final search list, which will be  
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6  
7 177 stored in Rayyan QCRI – a free systematic review software. The review team will  
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9  
10 178 consist of three researchers and two of these will independently screen each title  
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13  
14 179 and abstract for eligibility using a template (Table 2). The full text of the remaining  
15  
16  
17 180 articles will be retrieved using the UCL findit@UCL linking service. Inaccessible  
18  
19  
20  
21 181 articles will be dealt with by contacting the authors directly. Each full text will be  
22  
23  
24 182 independently reviewed by two of the three researchers for final eligibility. Reasons  
25  
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28 183 for exclusion will be recorded and documented. At each stage of screening, any  
29  
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31 184 differences between researchers will be resolved through discussion. Figure 1  
32  
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34  
35 185 represents a flow diagram of the study selection process.

36  
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38 186 *Table 2: Eligibility template*  
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40 187

Article reference	Inclusion												Exclusion									
	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



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[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:*

<b>Bibliographic reference details:</b>	
First author	
Title	
Journal	



Volume			
Year of publication			
Reviewer	CB	JP	RH
Date			
<b>Inclusion</b>	Yes	No	
<b>Reasons for exclusion:</b>			
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			

204

205 *Data extraction form:*

206

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

<b>Outcomes:</b>			
Outcome type	OR	%	Other:
Estimates of CP			
Estimates of sex difference			
Estimates of CP prevalence for each sex			
<b>Risk of bias:</b>			
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?	Yes	No	
Internal			
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
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209

210 The primary estimates of interest are CP prevalence by sex and an estimate of the

211 sex difference in pain (e.g. difference in prevalence or relative risk or odds ratio).

212

213 **Quality assessment**

214 Study quality will be addressed using a tool for risk of bias assessment for

215 prevalence studies which explores internal and external validity and scores studies

216 as low, moderate or high risk of bias [56]. This tool has high interrater agreement,

217 and it has previously been used in pain prevalence systematic reviews [57]. For this

218 review, two independent reviewers will use a checklist bases on this tool, which can

219 be found in Table 3.

220

221 **Synthesis**

222 **Narrative synthesis**

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4 223 A descriptive summary of studies will be provided using tables and addressing the  
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6  
7 224 following domains: primary outcomes, CP definition, CP type, sex/gender, age,  
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9  
10 225 geographic location (UN, WHO and HDI); and study quality assessment. It will  
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14 226 comment on the similarity of the methods used by the different studies and on the  
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18 227 possibility for meta-analysis.  
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23  
24 229 Geographic region will be classified according to – the United Nations (UN) and  
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26  
27  
28 230 World Health Organisation (WHO) region classification [60][61], and the Human  
29  
30  
31 231 Development Index (HDI) for each country – a measures of population wealth [62],  
32  
33  
34  
35 232 which has previously used in CP prevalence reviews [16,34].  
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42 234 The narrative synthesis will follow the Social Research Council Methods Programme  
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45 235 guidelines [63], with a focus on identifying and exploring the prespecified sources of  
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49 236 heterogeneity.  
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56 238 **Meta-analysis**  
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4 239 A meta-analysis will be conducted if enough studies provide the relevance  
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6  
7 240 prevalence information by sex for the defined age group, and where the reviewers  
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10 241 can justify combining results.  
11  
12  
13  
14 242  
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17 243 A random effects meta-analysis will be used to combine estimates of CP prevalence  
18  
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20  
21 244 by sex and a measure of difference in CP prevalence between sexes. These will be  
22  
23  
24 245 presented in a Forest plot. The I<sup>2</sup> will be used to assess the extent of heterogeneity  
25  
26  
27  
28 246 in estimates. If there are enough studies included, sub-group analysis or meta-  
29  
30  
31 247 regression will be performed to establish the extent of heterogeneity related to (i)  
32  
33  
34  
35 248 geographic region (coded in three ways: UN, WHO and HDI), (ii) pain definition and  
36  
37  
38 249 (iii) pain type.  
39  
40  
41  
42 250 Publication bias will be assessed separately using a funnel plot. A sensitivity analysis  
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44  
45 251 excluding low quality studies will be carried out.  
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## 52 253 **Reporting**

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4 254 The results of this systematic review will be shared in accordance with the Preferred  
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6  
7 255 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020  
8  
9  
10 256 guidelines [64].  
11  
12

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14 257

## 17 258 **DISCUSSION**

21 259 This study will review existing literature estimating CP prevalence and considers the  
22  
23  
24  
25 260 differences by sex/gender at mid-life, contributing to the literature about sex  
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27  
28 261 differences in CP prevalence. Heterogeneity in results will be assessed according to  
29  
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31  
32 262 geographic region, CP definition and type. The strengths and limitations will be  
33  
34  
35 263 considered, and measurements of sex (and gender) will be discussed in the context  
36  
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39 264 of similar reviews. The results of this review will provide a significant step towards  
40  
41  
42 265 identifying CP inequalities in mid-life between the sexes and identify areas for further  
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46 266 research. A better understanding of the relationship of CP emergence, sex and the  
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49 267 middle years in the general population may inform better early-prevention-and-  
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52  
53 268 treatment strategies that tackle the distinct pathways for men and women.  
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4 270 **LIST OF ABBREVIATIONS**

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8 271 CP: Chronic Pain

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16 273 **DECLARATIONS**

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21 274 **Ethics approval and consent to participate**

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25 275 Not applicable.

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29 276 **Consent for publication**

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37 278 **Availability of data and materials**

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## 22 23 24 25 290 Authors' contributions

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## 56 57 58 299 REGISTRATION



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56 501 **Additional materials**

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4 502 Parts of this manuscript refer to the following additional material, which will be  
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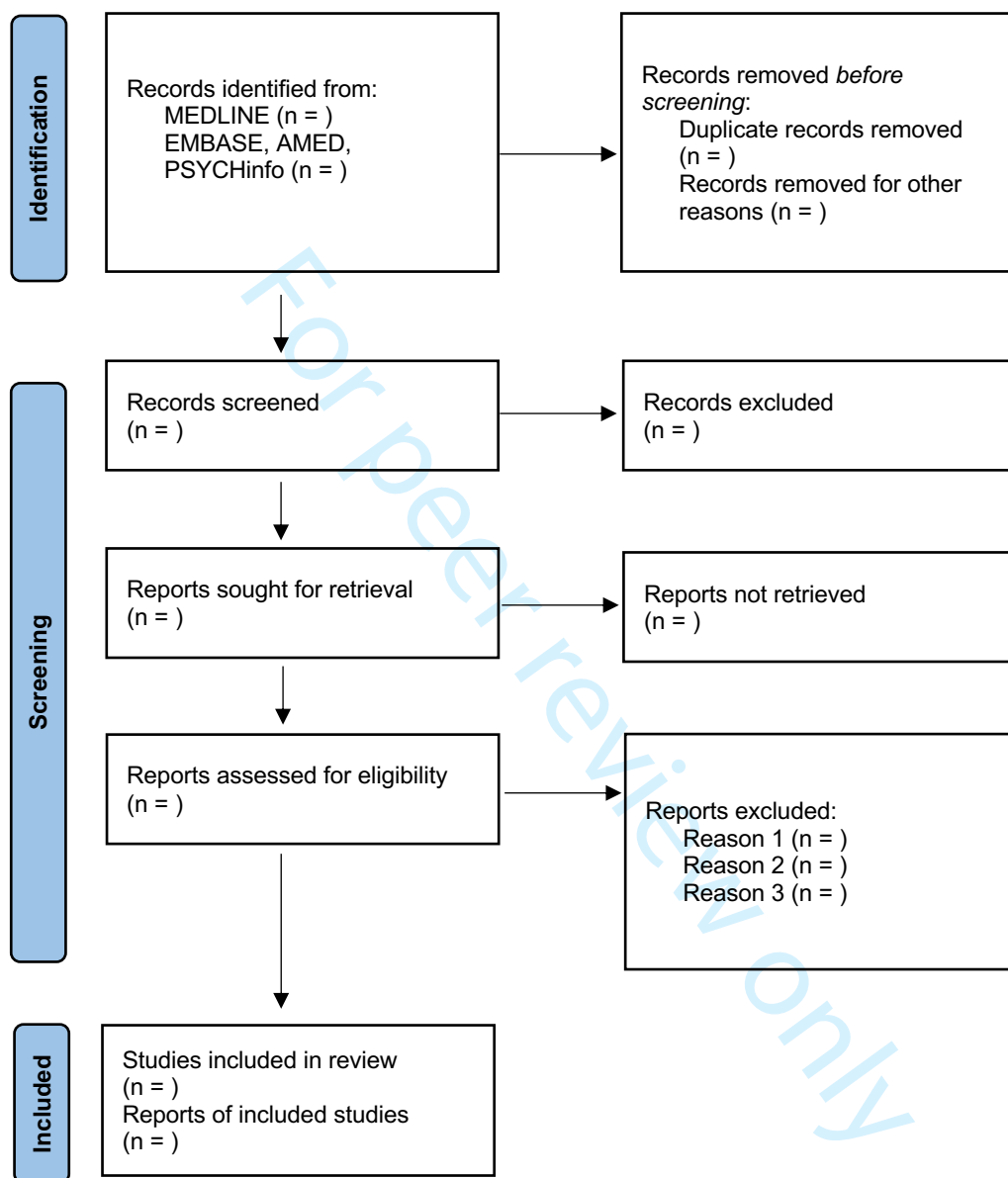
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Material type	File name
Figure 1: Search Strategy Flow Diagram	Figure 1_search strategy.pfd
Supplementary material	Supplementary material.pfd

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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)
<b>ADMINISTRATIVE INFORMATION</b>				
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
<b>INTRODUCTION</b>				
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
<b>METHODS</b>				
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:				



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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 <sup>2</sup> , Kendall's $\tau$ )	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

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3	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
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5				
6	Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Y 204-209
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9				

10 **\* The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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12 *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-*  
13 *analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*  
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# BMJ Open

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

Journal:	<i>BMJ Open</i>
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
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Epidemiology, Global health, Public health, Sociology, Anaesthesia
Keywords:	Pain management < ANAESTHETICS, EPIDEMIOLOGY, PUBLIC HEALTH

SCHOLARONE™  
Manuscripts

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## 23 **ABSTRACT**

### 25 **Introduction**

26 Epidemiological literature shows differences in chronic pain (CP) prevalence in men  
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53 27 and women. Women have been found to be more likely to develop CP at different  
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57 28 points of the life-course, such as childhood and old age. Less is known about the

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4 29 prevalence of CP by sex and the difference in prevalence during mid-life, when  
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7 30 changes may predispose to an earlier differentiation in CP distribution. The aim of  
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10 31 this study is to describe the difference in prevalence of CP at mid-life (ages 40-60) in  
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14 32 men and women in the general population.  
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## 17 33 **Methods and analysis**

18  
19  
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22 34 This systematic review follows PRISMA guidelines. Appropriate studies will be  
23  
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25 35 identified in the following databases: MEDLINE, EMBASE, AMED and PSYCHinfo.  
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28  
29 36 Two reviewers will independently screen each title and abstract. Studies eligible for  
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32 37 data extraction will report estimates of CP prevalence for each sex, and/or a  
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36 38 measure of the difference in prevalence between sexes. The findings will be reported  
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39 39 in a narrative synthesis following the Social Research Council Methods Programme  
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42 40 guidelines. A random effects meta-analysis will be conducted where the reviewers  
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46 41 can justify combining results.  
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## 50 42 **Ethics and dissemination**

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54 43 This review will summarise the prevalence of CP in men and women at mid-life,  
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58 44 based on existing evidence. It is expected that the results will identify gaps in  
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4 45 knowledge and areas for further research. The review will be submitted for  
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7 46 publication in topic specific journals and disseminated to professional networks.  
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11 47 Individual patient data is not included, so ethical approval is not required.  
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## 14 48 **Strengths and limitations**

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19 49 • This protocol offers a systematic approach to determining the difference in  
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22 50 chronic pain prevalence in men and women at mid-life  
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25  
26 51 • Sex difference is explored by geographic region, chronicity threshold and pain  
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28  
29 52 type  
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33 53 • Mid-life categorisation is limited to people aged 40-60  
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36 54 • Articles in English language only will be reviewed  
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## 41 42 43 56 **SYSTEMATIC REVIEW REGISTRATION**

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47 57 PROSPERO: CRD42021295895  
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## 50 51 58 **KEYWORDS**

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56 59 chronic pain; persistent pain; prevalence; sex; sex inequalities; gender inequalities  
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36 64 **BACKGROUND**  
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44 66 **Rationale**  
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48 67 Chronic pain (CP) – pain that lasts for longer than three months [1] – is becoming  
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51 68 increasingly common [2–4], and threatens the physical, social and psychological  
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55 69 wellbeing of those who suffer with it [5–11]. While pain is a common experience,  
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59 70 previous research has pointed at inequality in CP distribution between men and  
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4 71 women, with women being more likely to experience CP [12–19]. There are different  
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7 72 hypotheses explaining this inequality: one relates to sex-linked factors, like  
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10 73 hormones and reproductive factors [20–22], and another relates CP to discrepancies  
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14 74 in the social and cultural experiences of pain between genders [23–25]. While  
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17 75 systematic reviews have attested to the unequal distribution of CP in childhood and  
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21 76 adolescence [26,27] and older age [13,17,18,28–32], the evidence is less clear about  
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24 77 the difference in prevalence of CP at mid-life – the period defined between ages of  
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28 78 40-60, although definitions of exact age range vary [33–38]. CP in mid-life may have  
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31 79 significant impact on a person’s ability to work [2,39] and to lead a fulfilling life [40–  
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35 80 42], so acknowledging the differences in CP distribution among the sexes may  
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39 81 provide an arena for targeted prevention and management interventions to decrease  
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42 82 CP burden later in life. Moreover, mid-life may be an important period for the  
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45 83 experience of CP as it can be a period of stress [37,43–49] when the first physical  
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49 84 signs of ageing [3,37,44], degenerative changes (like those linked to osteoarthritis)  
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52 85 [50,51] and sex-specific changes (like menopause) are met with changes in an  
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56 86 individual’s social structure [37,52]. Such changes in mid-life may thus affect men  
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4 87 and women differently, exacerbating the difference in chronic pain prevalence  
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7 88 between the sexes.  
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10 89 For example, there is epidemiological evidence suggesting that women experience  
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14 90 more musculoskeletal pain around the peri-menopause compared with pre-  
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17 91 menopausal women, and that the pain persists into later life [31].  
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24 93 Previous systematic reviews have addressed the prevalence of CP by sex in the  
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28 94 adult population spanning from 18 years to older age [16–19,53]. Mansfield *et al*  
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31 95 (2016), for example, identified that prevalence of chronic widespread pain was  
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35 96 higher in women over 40, while Fayaz *et al* (2016) reported an increase in  
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38 97 prevalence of CP with age in the pooled sample. In summary, current systematic  
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42 98 reviews of CP prevalence in adults either fail to differentiate between phases of  
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45 99 adulthood [17,18,29,53] or have not stratified results by sex at mid-life [15,54,55]. By  
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49 100 considering the sex-difference in prevalence of CP at mid-life in the general  
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52 101 population, this review aims at addressing this gap in the literature. The evidence  
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56 102 summarised in this review will provide background for further work evaluating sex-  
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4 103 and gender-based factors for CP in mid-life, and comparing sex differences in CP  
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7 104 prevalence in specific patient groups and population sub-groups.  
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## 13 14 106 **Objectives** 15 16

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18 107 We will therefore carry out a systematic review to update the work of previous  
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21 108 reviews and investigate CP prevalence by sex and sex-differences in CP in mid-life  
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25 109 in the general population, drawing from available published data. The review aims at  
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28 110 answering the following questions:  
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35 112 • What is the prevalence of CP in men and in women in the general population  
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39 113 at mid-life?  
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- 42 114 • What is the difference in CP prevalence between men and women in the  
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46 115 general population?  
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53 117 This review will consider CP as defined by the International Association for the Study  
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56 118 of Pain [1]. While people who are suffering from pain due to other diseases (e.g.  
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4 119 diabetes, cancer) might be included within general population surveys of pain, the  
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7 120 review will not include studies that only investigate CP specific to a disease process.  
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10 121 Heterogeneity in the results and variation across studies will be explored according  
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14 122 to three characteristics - geographic region, chronicity threshold, and pain type.  
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17 123 Geographic region has been shown to relate to differences in pain prevalence in  
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21 124 other systematic reviews of CP incidence, with higher prevalence in lower-income  
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24 125 countries [16,53]. Similarly, differences in chronicity threshold (e.g. pain for 3 months  
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28 126 or longer [1]; pain for six months or longer; pain for 1 month or longer) have shown to  
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31 127 have an effect on CP prevalence estimates [56]. Lastly, the type of CP (e.g. generic,  
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35 128 regional, widespread) will represent further sources of heterogeneity since  
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38 129 conditions associated with certain types of CP have different sex prevalence [57].  
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45 131 Study quality will be assessed using a tool developed for prevalence studies by Hoy  
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49 132 et al [58], and previously used in reviews of pain prevalence literature [59].  
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## 135 **METHODS**

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

### 140 **Patient and public involvement**

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

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### 147 **Eligibility criteria**

148 Studies will be included if they:

- 149 • Are original studies published in peer reviewed journals.

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4 150 • Examine the prevalence of CP for each sex and/or sex difference in the 40-60  
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7 151 age group (determined according to Lachman (2011) and as age  
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10 152 categorisations commonly used in studies are in 5 or 10 year age bands) in  
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14 153 men and women separately [37]. Only estimates from studies where an entire  
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17 154 sample falls within the band will be included.
- 18  
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21 155 • Use samples selected from the general population.
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24 156 • Use any clearly stated CP definition in line with the International Association  
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28 157 for the Study of Pain (IASP) definition of pain lasting longer than three months  
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31 158 [61], including generic, regional and widespread CP.
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35 159 • Clearly state the country in which data was collected.
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38 160 • Use data from an observational study, such as prospective and retrospective  
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42 161 cohorts, cross-sectional and case control studies.
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45 162 • Are written in English.

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52 164 Studies will be excluded if they:

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56 165 • Do not meet inclusion criteria.
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59 166 • Are reviews, conference proceedings, editorials and letters.
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4 167       • Are samples of specific groups or sub-samples of the general population that  
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7 168       are not representative of the general population eg. clinical or disease-specific  
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10 169       samples, ethnic minority samples, employment-based samples etc.  
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## 171 **Information sources and search strategy**

172 An electronic search will identify appropriate studies. The selected databases are  
173 MEDLINE, to be accessed through Web of Science as an interface; and EMBASE,  
174 AMED and PSYCHinfo to be accessed through Ovid as an interface. These  
175 databases will be searched from earliest entries to 10 January 2022. The search  
176 strategy is based on CP terms, study terms, moderators, and limits. Different  
177 techniques will be followed to ensure the search terms identify all relevant articles,  
178 and the search strategy will be piloted to make sure it is selecting relevant articles.  
179 The search terms and various search tools used for the different databases are  
180 outlined in Table 1. The reference lists of fully eligible texts will also be screened to  
181 identify potential inclusions.  
182 The study will start in January 2022 and end upon submission of the study report for  
183 publication – expected in July 2023.

184 *Table 1: Search strategy*

185

	<i>MEDLINE (Web of Science)</i>	<i>EMBASE + AMED + PSYCHinfo (Ovid)</i>
<i>Pain terms</i>	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)
<i>Study terms</i>	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)
<i>Moderators</i>	Women OR female Men OR male	AND Male OR men (all fields) AND Female OR women (all fields)
<i>Limits</i>	Excluding RCTs and clinical studies/reviews English language only Journal articles only	English language only

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

191



## 192 Study selection

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

203

204 *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

205

206 *Table 2b: Eligibility template - exclusion*

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

207

208 [FIGURE 1]

209

210 **Data extraction and quality assessment**

211 Data extraction will be conducted by the three reviewers for the following data items:

212 citation details (including year of publication and title), study design, country, sample

213 size, CP definition, CP type, CP measurement, age measurement, sex measurement

214 (sex and/or gender), estimates of CP, estimates of sex difference, estimates of CP

215 prevalence for each sex.

216

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

220

221 *Table 3a: Data extraction form*

222 *Screening form:*

223

<b>Bibliographic reference details:</b>			
First author			
Title			
Journal			
Volume			
Year of publication			
Reviewer	CB	JP	RH
Date			
<b>Inclusion</b>	Yes	No	
<b>Reasons for exclusion:</b>			
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			

224

225 *Table 3b: Data extraction form:*

226

<b>Bibliographic reference details:</b>			
First author			
Title			
Journal			
Volume			
Year of publication			
Reviewer	CB	JP	RH
<b>Study characteristics:</b>			
Study design	Cohort study	Cross-sectional study	Other:
Sample size			
Country			
<b>Measurements:</b>			
CP definition	IASP	Other:	
CP measurement			
Sex measurement	Self-reported sex	Self-reported gender	
Age measurement			
<b>Outcomes:</b>			
Outcome type	OR	%	Other:
Estimates of CP			
Estimates of sex difference			
Estimates of CP prevalence for each sex			
<b>Risk of bias:</b>			
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

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228

229 The primary estimates of interest are CP prevalence by sex and an estimate of the

230 sex difference in pain (e.g. difference in prevalence or relative risk or odds ratio).

231 Geographic region will be classified according to – the United Nations (UN) and

232 World Health Organisation (WHO) region classification [62][63], and the Human

233 Development Index (HDI) for each country – a measures of population wealth [64],

234 which has previously used in CP prevalence reviews [16,53]. Chronicity threshold

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4 235 will be classified as over 3 months or over 6 months [1,65]. Pain type will be  
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6  
7 236 categorised as generic, regional (in one body part only) or widespread (in multiple  
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10 237 body parts according to the American College of Rheumatology's definition of  
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14 238 chronic widespread pain) [66].  
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## 21 240 Quality assessment

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24 241 Study quality will be addressed using a tool for risk of bias assessment for  
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28 242 prevalence studies which explores internal and external validity and scores studies  
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30  
31 243 as low, moderate or high risk of bias [58]. This tool has high interrater agreement,  
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34  
35 244 and it has previously been used in pain prevalence systematic reviews [59]. For this  
36  
37  
38 245 review, two independent reviewers will use a checklist based on this tool, which can  
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42 246 be found in Table 3.  
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45 247

## 49 248 Synthesis

### 53 249 Narrative synthesis

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56 250 A descriptive summary of studies will be provided using tables and addressing the  
57  
58  
59  
60 251 following domains: primary outcomes, CP definition, CP type, sex/gender, age,

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4 252 chronicity threshold, pain type, geographic location; and study quality assessment. It

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6  
7 253 will comment on the similarity of the methods used by the different studies and on

8  
9  
10 254 the possibility for meta-analysis.

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13  
14 255 The correspondence between mid-life and the age category utilised in this study is

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16  
17 256 based on life-expectancy in the global north. Countries with lower life expectancy

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20  
21 257 may have different thresholds for midlife, and we will address this when discussing

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24 258 geographical differences in prevalence.

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31 260 The narrative synthesis will follow the Social Research Council Methods Programme

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34 261 guidelines [67], with a focus on identifying and exploring the prespecified sources of

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38 262 heterogeneity.

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45 264 **Meta-analysis**

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48 265 A meta-analysis will be conducted if enough studies provide the relevance

49  
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51  
52 266 prevalence information by sex for the defined age group, and where the reviewers

53  
54  
55 267 can justify combining results.

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4 269 A random effects meta-analysis will be used to combine estimates of sex difference  
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6  
7 270 in CP (e.g. difference in prevalence, odds ration or relative risk). These will be  
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9  
10 271 presented in a Forest plot. The  $I^2$  statistic will be used to assess the extent of  
11  
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13  
14 272 heterogeneity in estimates. If there are enough studies included, sub-group analysis  
15  
16  
17 273 or meta-regression will be performed to investigate heterogeneity related to (i)  
18  
19  
20  
21 274 geographic region (coded in three ways: UN, WHO and HDI), (ii) chronicity threshold  
22  
23  
24 275 (over 3 months, over 6 months) and (iii) pain type (generic, regional, widespread).  
25  
26  
27  
28 276 Publication bias will be assessed separately using a funnel plot. A sensitivity analysis  
29  
30  
31 277 excluding low quality studies will be carried out.  
32  
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## 38 279 **Reporting**

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42 280 The results of this systematic review will be shared in accordance with the Preferred  
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46 281 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020  
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49 282 guidelines [68].  
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## 285 Ethics

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

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## 288 DISCUSSION

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

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## LIST OF ABBREVIATIONS

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11 303 CP: Chronic Pain  
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## DECLARATIONS

20 305  
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24 306 Ethics approval and consent to participate  
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27

28 307 Not applicable.  
29  
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32 308 Consent for publication  
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36 309 Not applicable.  
37  
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40 310 Availability of data and materials  
41  
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43

44 311 Not applicable.  
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47

48 312 Competing interests  
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52 313 The authors declare that they have no competing interests.  
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## 322 Authors' contributions

323 CB is the main author of the draft of this manuscript. RH contributed with edits and

324 methodological guidance, resulting in two further drafts. All authors read and

325 approved the final manuscript.

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## 544 Additional materials

545 Parts of this manuscript refer to the following additional material, which will be  
546 presented on submission:  
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Material type	File name



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

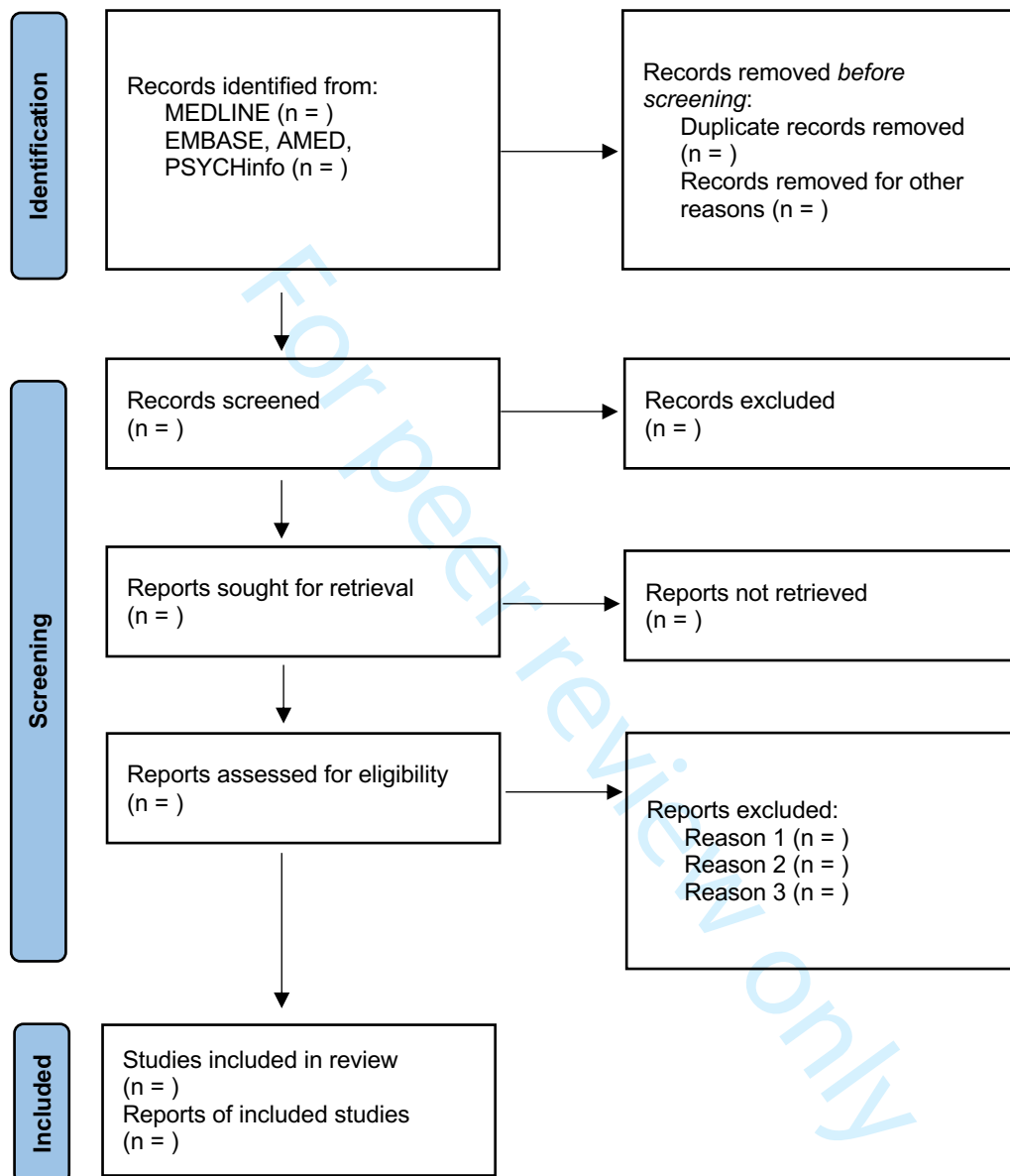
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For peer review only

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)
<b>ADMINISTRATIVE INFORMATION</b>				
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

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		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
<b>INTRODUCTION</b>				
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
<b>METHODS</b>				
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:				

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4	Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y 186-190
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6	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
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11	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
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15	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
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19	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
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23	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
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28	Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y 254-266
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30		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 $\tau$ )	Y 258-266
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35		15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Y 260-264
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39		15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y 238-251
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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

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*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.*