Role of kinesiophobia on pain, disability and quality of life in people suffering from chronic musculoskeletal pain:

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THE ROLE OF KINESIOPHOBIA ON PAIN, DISABILITY, AND QUALITY OF LIFE IN PEOPLE SUFFERING FROM CHRONIC MUSCULOSKELETAL PAIN: A SYSTEMATIC REVIEW

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DISCLOSURES

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the paper, or part of the paper, is found to be faulty or fraudulent, all authors share responsibility. Data can be obtained from the corresponding author.

ABSTRACT

Objective (i) to explore the level of association between kinesiophobia and pain, disability, and quality of life in people with chronic musculoskeletal pain detected via cross-sectional analysis; (ii) to analyse the prognostic value of kinesiophobia on pain, disability, and quality of life in this population detected via longitudinal analyses.

Design A systematic review of the literature including an appraisal of the risk of bias using the adapted Newcastle Ottawa Scale. A synthesis of the evidence was carried out.

Data sources An electronic search of PubMed, AMED, CINAHL, PsycINFO, PubPsych, and grey literature was undertaken from inception to July 2017.

Eligibility criteria for selecting studies Observational studies exploring the role of kinesiophobia (measured with the Tampa Scale for Kinesiophobia) on pain, disability, and quality of life in people with chronic musculoskeletal pain.

Results Sixty-three articles (mostly cross-sectional) (total sample = 10,726) were included. We found strong evidence for an association between a greater degree of kinesiophobia and greater levels of pain intensity and disability, and moderate evidence between a greater degree of kinesiophobia and higher levels of pain severity and low quality of life. A greater degree of kinesiophobia predicts the progression of disability overtime, with moderate evidence. A greater degree of kinesiophobia also predicts greater levels of pain severity and low levels of quality of life at six months, but with limited evidence. Kinesiophobia does not predict changes in pain intensity.

Summary/conclusions The results of this review encourage clinicians to consider kinesiophobia in their preliminary assessment. More longitudinal studies are needed, as most of the included studies were cross-sectional in nature.

PROSPERO: **CRD 42016042641**

Key Words: musculoskeletal pain; chronic pain; fear; systematic review

WHAT IS ALREADY KNOWN

- There is no review on the association between kinesiophobia and pain and disability
- A systematic review reporting this relationship has not been conducted.
- The prognostic role of kinesiophobia on pain and disability is also unknown.

WHAT ARE THE NEW FINDINGS

- A greater degree of kinesiophobia at baseline predicts the progression of disability overtime.
- A greater degree of kinesiophobia is associated with greater pain and disability.
- A greater degree of kinesiophobia is associated with lower quality of life.

INTRODUCTION

Most people suffer from musculoskeletal pain at least once in their lifetime [1]. As such, musculoskeletal pain is a highly prevalent and costly condition [1]. It is the second most common cause of disability in the general population [2]. There are many established factors (physical, biological, cognitive, behavioural, social, occupational) associated with poor prognosis following the onset of musculoskeletal pain [1,3] which helps to explain why many people do not recover after an episode of acute musculoskeletal pain often resulting in a downward spiral of negative physical, social, and psychological consequences [4]. Among the many biopsychosocial factors which contribute to the experience and impact of pain, negative or maladaptive psychological factors (e.g., fear) are amongst the most important [5–8].

Fear is considered to be a relevant factor in order to understand how acute pain becomes chronic for some people, and why pain and associated outcomes (e.g. disability) persist once the tissue damage has healed [9,10]. In this sense, the fear-avoidance (FA) model of pain is one of the frameworks which has received more empirical attention in order to explain the development and persistence of disability following an acute episode of musculoskeletal pain [9,11]. According to this model, individuals with a trait tendency to have fear and catastrophic thoughts in response to pain are more at risk of developing chronic musculoskeletal pain (CMP) after an injury compared to individuals who do not have this tendency [9]. These individuals overreact in response to actual or potential threats, developing avoidance behaviours (e.g. hypervigilance) which aim to prevent a new injury/re-injury [9]. Fear in relation to pain has been described with a variety of conceptual definitions among which pain-related fear, fear-avoidance beliefs, fear of movement, and kinesiophobia are the most commonly used [12].

Physical inactivity is a potential factor for developing and maintaining CMP [13]. Whereas physical activity has positive benefits in decreasing pain and disability in some CMP conditions, e.g., lower limb osteoarthritis [14]. However, people with CMP often show fear of movement [15,16], which limits the adequate execution of a movement or exercise and leads to more sedentary behaviour [17]. Such fear imposes a barrier when exercise is prescribed as part of management resulting in significant clinical implications including reduced adherence to treatment and perseverance of a negative experience with pain [11].

Kinesiophobia (also known as fear of movement) is defined as an excessive, irrational, and debilitating fear to carry out a physical movement, due to a feeling of vulnerability to a painful injury or re-injury [18]. Both constructs are very similar [12], and essentially they have the same clinical relevance. Whilst kinesiophobia is usually assessed with the Tampa Scale of Kinesiophobia (TSK), there is not a specific tool to assess fear of movement [12]. The prevalence of kinesiophobia in persistent pain ranges from 50 to 70% [19,20]. It can be acquired through two forms: a direct aversive experience (e.g. pain or trauma) or social learning (observation and instruction) [21]. Kinesiophobia may be associated with pain and associated outcomes (disability and quality of life) in several ways. First, kinesiophobia alters how people move, possibly with the initial goal to avoid pain. It causes adjustments of motor behaviour which affects the performance of actions related to the management and control of pain and pain-related disability [22]. Second, the processing of pain and pain-related information in people with CMP could be related to how kinesiophobia is perceived [23]. Indeed, a greater degree of kinesiophobia predicts greater levels of pain [24].

The role of kinesiophobia in CMP has been explored extensively. In this regard, a large body of evidence has reported that kinesiophobia is associated with disability [25], pain [26–28], and quality of life [29]. Furthermore, longitudinal studies have shown that high levels of kinesiophobia at baseline, predict negative changes in quality of life [30], and positive changes in disability [31], and pain [30,32]. However, the evidence is inconsistent regarding the strength of the significance and the direction of the findings [33–37]. A synthesis of the evidence of the association between kinesiophobia and pain, disability, and quality of life would contribute to a better understanding and clarification of these relationships in patients with CMP. Moreover, examining the prognostic value of kinesiophobia on the aforementioned outcomes would facilitate a greater understanding of CMP mechanisms, and, thus permit better clinical decision-making. Clinical decision-making requires ongoing reconciliation of studies that provide different answers to the same question, and clinicians and researchers can also benefit from a summary where uncertainty remains [38].

A systematic review of the literature will allow stronger conclusions to be reached compared to those achieved by any one study [39], and will facilitate readers who may have difficulties to capture and review all the evidence provided by primary studies. Hence, the aim of this systematic review was twofold: (i) to explore the level of association between kinesiophobia and pain, disability, and quality of life in people with CMP; (ii) to analyse the prognostic value of kinesiophobia on pain, disability, and quality of life in people with CMP.

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [40]. The systematic

review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD 42016042641). The initial intent of the study, as registered in PROSPERO, was to examine predictive studies only. This approach was abandoned since too few predictive studies existed and we determined that cross-sectional studies and case-control studies were also relevant to include in order to provide additional information on the level of association between kinesiophobia and outcomes related to CMP.

Data Sources and Search Strategy

The following electronic databases from the inception to February 2017 were searched: PubMed, AMED, CINAHL, PsycINFO, and PubPsych. An update of the search strategy was carried out in July 2017 to identify if any new potential studies had been published. A manual search of relevant eligible studies was also carried out. A sensitive search strategy using relevant search terms that were developed from Medical Subject Headings (MeSH), and keywords generated from the subject headings, were used (**Appendix A)**. The following grey literature databases were explored: JBI COnNECT +, NHS Evidence, New York Academy of Medicine Grey Literature Report, Explore the British Library, TRIP database, National Guideline Clearinghouse, and Open Grey.

Eligibility Criteria

The PECOS (P-patient; E-exposure; C-comparator; O-outcome; S-study design) framework was followed to determine which studies to include in the present systematic review. Each study had to meet the following inclusion criteria:

(i) Observational studies (cross-sectional, case-control and longitudinal studies) exploring the predictive role of kinesiophobia in people with CMP, and their associations with the outcomes described below. When prospective studies only

reported findings from the baseline assessment in sufficient detail, analyses between kinesiophobia and outcome measures were limited to the initial assessment and considered as cross-sectional studies.

(ii) Studies whose participants were adults diagnosed with CMP, defined in this review as persistent or episodic pain lasting more than three months, around the axial skeleton (neck, low back, and/or pelvic) or peripheral joints (shoulder, elbow, wrist, knee, and/or ankle). In this regard, the ACCTION-APS Pain Taxonomy (AAPT) for chronic pain was used [41], including people with diagnoses of chronic myofascial pain, fibromyalgia, chronic widespread pain (e.g. chronic fatigue syndrome), rheumatoid arthritis, spondyloarthropathies, and those with a diagnosis of osteoarthritis. Although the AAPT for chronic pain does not consider spinal pain as part of the musculoskeletal pain group, we decided to include people with chronic axial musculoskeletal pain in the present review.

(iii) Only studies measuring kinesiophobia with the Tampa Scale for Kinesiophobia (TSK) were included [12].

(iv) No restrictions were applied on participants' gender, ethnicity, and follow-up duration (in case of longitudinal studies).

(v) Studies recruiting participants from the general population, primary, secondary or tertiary care.

(vi) Only articles written in English were included.

(vii) Studies were only included if there was at least one association between kinesiophobia and one of the following outcome measures: pain, disability and/or quality of life. With regards to the pain construct, the authors of the present review recognise that the differences between pain intensity and pain severity are narrow. However, in order to facilitate the synthesis of results, we divided both constructs based

on a previous literature review [42] which showed that pain intensity is commonly measured with unidimensional instruments (e.g., the numerical rating scale (NRS)), whereas pain severity is mostly measured with multidimensional instruments (e.g., the multidimensional pain inventory (MPI)), where not only intensity of pain is taken into account.

Exclusion criteria were as follows:

(i) Studies of acute pain, subacute pain, and chronic non-musculoskeletal pain according to the AAPT.

(ii) Studies where CMP was associated with a diagnosis of major psychiatric disorders.

(iii) studies evaluating kinesiophobia in CMP attributed to previous fracture or exploring this factor before surgery or post-surgery.

(iv) Studies analysing kinesiophobia in individuals with CMP after trauma.

(v) Studies examining the role of kinesiophobia in experimental models of pain.

(vi) Studies testing kinesiophobia in the context of a behavioural task or treatment (e.g., exposure in vivo).

(vii) Reviews, clinical studies, case reports, editorial, and abstracts.

Study Selection

First, two authors (JMC and ALS) carried out the screening of titles and abstracts. Second, the same authors checked the full text of the included manuscripts. Third, in case of any disagreement, a decision was made by consensus with the participation of a third author (DF). A short checklist was adapted to the present review and was used to guide the selection of relevant studies (see **Appendix B**) [43].

Data Extraction

The following relevant data from each study were extracted: study details (first author, year of publication), sample size, characteristics of participants (mean age, pain duration, pain condition), kinesiophobia measures, outcome (pain, disability, and quality of life) measures, duration of follow-up (in case of longitudinal studies), and study design. When necessary, an email was sent to the original authors to obtain further information regarding a study's findings.

Quality Assessment

The risk of bias of each included study was evaluated using an adapted version of the Newcastle-Ottawa Scale (NOS) [44]. This adapted version includes four domains of risk of bias assessment: methods for selecting study participants (selection bias), methods to control for confounding (performance bias), statistical methods (detection bias), and methods of exposure and outcome assessment (information bias). Seven items compose the four domains. Each item is scored from zero (high risk) to three (low risk) points. Therefore, the maximum score for each study could be twenty-one points. Two researchers (JMC and ALS) were involved at this stage. When any disagreement did appear, a third researcher (DF) was consulted and a decision by consensus was carried out. Qualitative analysis of the evidence was carried out involving a rating system (the Modified Cochrane Back and Neck group) with five levels of scientific evidence [45]. The rating system was based on the methodological quality and the outcome of the studies: (i) strong evidence: consistent findings in two or more low risk of bias studies (score from 14 to 21 on NOS); (ii) moderate evidence: consistent findings in one low risk of bias study or two or more moderate risk of bias studies (score from 8 to 13 on NOS); (iii) limited evidence: consistent findings in one or more high risk of bias studies (score from 0 to 7 on NOS) or one moderate risk of bias study; (iv) lacking evidence: no published studies found; (v) conflicting evidence: inconsistent or contradictory findings

within a quality level. Due to the absence of a cut-off in the adapted NOS scale, the authors decided to divide the scores in three sections (mentioned above) according to the levels of evidence included in the Modified Cochrane Back and Neck Group Criteria (low 0-7 on NOS; moderate 8-13 on NOS; strong 14-21 on NOS).

Statistical Analysis

For the primary analysis, studies were grouped per outcomes: disability, pain, and quality of life. A meta-analysis could not be carried out due to the presence of heterogeneity in terms of participant's age, sample size, pain condition, outcome measures, version of self-reported kinesiophobia questionnaire (e.g. TSK-11 or TSK-17), statistical methods used, and study design in most of the studies potentially eligible for conducting a meta-analysis. Consequently, a descriptive quantitative analysis (the most relevant summary measure with a precision estimate) was provided for each study. For those studies that reported results with several degrees of adjustment for confounders in different models, we extracted the estimate from the model which showed the best adjustment.

Results

Study characteristics

A total of 1,757 articles were identified through electronic databases, with 148 additional studies identified through reference screening. Six hundred and forty-four titles and abstracts were screened with 345 full-text articles evaluated. The number of studies retrieved from each database and the number of studies excluded in each screening phase are shown in **Supplementary Figure 1**. The full reference of excluded studies in the last screening (n=282) is reported in **Appendix C**. The conflict of interests

of included studies are shown in **Appendix D**. Of these, 63 observational studies (eight longitudinal studies; fifty cross-sectional studies; and five case-control studies) with a total of 10,726 participants (chronic low back pain (CLBP)= 2,504; fibromyalgia (FM)= 1,540; chronic neck pain (CNP)= 861; knee osteoarthritis (KOA)= 614; chronic whiplash associated-disorders (CWAD)= 475; chronic fatigue syndrome (CFS)= 385; ankylosing spondylitis (AS)= 194; chronic knee pain (CKP)= 97; mixed= 4,056) satisfied our inclusion criteria and were included in this review. In case of longitudinal studies, duration of follow-up ranged from three to twelve months. Outcomes measures were as follows: disability [15,16,25–32,34,37,46–86], pain (pain intensity [15,25–29,31,34,36,37,46–49,51–53,55–57,59,60,64,66–69,72,76,77,79,80,83–85,87–91], and pain severity [15,30,32,82,92,93]), and quality of life [28–30,47,72,80,82,89,94,95]. The characteristics of the included studies are reported in **Appendix E**. Eight authors were contacted directly by email to gather any non-published data.

Risk of bias

The degree to which studies met the risk of bias criteria varied considerably. The risk of bias assessment of all included studies is presented in **Appendix F**.

The role of kinesiophobia on pain intensity, pain severity, disability, and quality of life in CMP

After analysing the quality of evidence for each outcome included in the present systematic review through the Adapted Cochrane Back and Neck Pain Group Criteria, the evidence was divided between strong and moderate for cross-sectional studies (see **Table 1)** and limited to moderate for longitudinal studies (see **Table 2**). The statistical results for the association between kinesiophobia and pain, disability, and quality of life (cross-sectional analysis) are presented in **Appendix G**, and the predictive value of

kinesiophobia on pain, disability, and quality of life (longitudinal analysis) are presented in **Appendix H.**

Table 1. Modified Cochrane Back and Neck Pain Group criteria for overall level of evidence based on cross-sectional studies

Outcome	Nº Studies	No. of participants	Level of evidence
Kinesiophobia (association with)			
Quality of life	8	1,426	Moderate (negative association)
Disability	46	9,351	Strong (positive association)
Pain intensity	38	6,806	Strong (positive association)
Pain severity	4	767	Moderate (positive association)

Note: strong evidence: consistent findings in two or more low risk of bias studies (score from 14 to 21 on NOS); moderate evidence: consistent findings in one low risk of bias study or two or more moderate risk of bias studies (score from 8 to 13 on NOS); limited evidence: consistent findings in one or more high risk of bias studies (score from 0 to 7 on NOS) or one moderate risk of bias study; lacking evidence: no published studies found; conflicting evidence: inconsistent or contradictory findings within a quality level.

Table 2. Modified Cochrane Back and Neck Pain Group criteria for overall level of evidence based on longitudinal studies

Outcome	Nº Studies	No. of participants	Level of evidence
Kinesiophobia (association with)			
Quality of life	2	289	Limited (negative association)
Disability	7	1,123	Moderate (positive association)
Pain intensity	2	204	Conflicting (positive association)

Pain severity	2	331	Limited (positive association)

Note: strong evidence: consistent findings in two or more low risk of bias studies (score from 14 to 21 on NOS); moderate evidence: consistent findings in one low risk of bias study or two or more moderate risk of bias studies (score from 8 to 13 on NOS); limited evidence: consistent findings in one or more high risk of bias studies (score from 0 to 7 on NOS) or one moderate risk of bias study; lacking evidence: no published studies found; conflicting evidence: inconsistent or contradictory findings within a quality level.

The association between kinesiophobia and pain in people with CMP (cross-sectional analysis)

The association between kinesiophobia and pain intensity based on cross-sectional analyses was evaluated by thirty-eight studies. A total of twenty-one studies showed a significant association between a greater degree of kinesiophobia and greater levels of pain intensity [15,29,46,48,49,51,53,59,64,67–69,72,76,83–85,87–89,91]. There was no significant relationship between kinesiophobia and pain intensity in thirteen studies [25,34,36,37,47,52,55–57,60,77,79,90]. One study did not report statistical results about the association between kinesiophobia and pain intensity [80]. Finally, three studies showed inconsistency in the strength of the significance in their findings [26–28]. Altuğ et al.[28] showed a non-significant association between kinesiophobia and pain intensity at rest, whereas this association was significant and positive during activity. Lamoth et al. [27] showed a non-significant association between kinesiophobia and anticipated pain, whereas this association was significant and positive with regards to actual pain. Lundberg et al. [26] showed a significant and positive association between

kinesiophobia and CLBP, although this association was non-significant when CLBP was diagnosed as non-specific CLBP. Overall the quality of the evidence was strong.

The association between kinesiophobia and pain severity based on cross-sectional analyses was evaluated in four studies. Two studies showed a significant association between a greater degree of kinesiophobia and greater of levels of pain severity [82,92]. There was no significant relationship between kinesiophobia and pain severity in one study [93]. One study showed inconsistency in the strength of the significance in their findings [15]. Bränström et al. [15] showed a non-significant association between kinesiophobia and pain severity in men, whereas this association was significant and positive in women. Overall the quality of the evidence was moderate.

The predictive value of kinesiophobia on pain in people with CMP (longitudinal analysis)

The predictive value of kinesiophobia on pain intensity in people with CMP was explored in two studies based on longitudinal analyses [31,66]. Helminen et al. [31] reported that the degree of kinesiophobia at baseline did not predict changes in pain intensity at twelve months after adjusting for age, gender, educational level, comorbidities, body mass index, work status, marital status, and disease severity. Koho et al. [66] reported that kinesiophobia at baseline did not predict changes in pain intensity at twelve months but no covariates were reported. The overall quality of the evidence was conflicting.

The predictive value of kinesiophobia on pain severity in people with CMP was explored in two studies based on longitudinal analyses [30,32]. Wong et al. [30] reported that baseline kinesiophobia significantly predicted positive changes in pain severity at six months, even when adjusted for sociodemographic factors, and pain

variables (number, duration, and intensity). Van den Houte et al. [32] did not report the predictive value of kinesiophobia on pain severity. The overall quality of the evidence was limited.

The association between kinesiophobia and disability in people with CMP (cross-sectional analysis)

The association between kinesiophobia and disability was evaluated by forty-six studies based on cross-sectional analyses. A total of thirty studies showed a significant association between greater degree of kinesiophobia and greater levels of disability [25,27–29,34,46–56,59,64,65,67–69,72,75,76,78,82–84,86]. There was no significant relationship between kinesiophobia and disability in eleven studies [37,57,60,62,63,74,77,79–81,85]. One study did not report statistical results on the association between kinesiophobia and disability [58]. Finally, four studies showed inconsistency in the strength of the significance in their findings [15,26,61,73]. Bränström et al. [15] reported a significant and positive association between kinesiophobia and disability in women, whereas this association was non-significant in men. Heuts et al. [61] found a significant and positive association between kinesiophobia and disability when kinesiophobia was measured with the somatic focus subscale of TSK but not with the activity-avoidance subscale for TSK. Lundberg et al. [26] showed a significant and positive association between kinesiophobia and disability in CLBP, although this association was non-significant when CLBP was diagnosed as non-specific CLBP. De Moraes Vieira et al. [73] reported a significant and positive association between kinesiophobia and moderate-severe disability, whereas this association was non-significant when the level of disability was minimal. The overall quality of the evidence was strong.

The predictive value of kinesiophobia on disability in people with CMP (longitudinal analysis)

The predictive value of kinesiophobia on disability in people with CMP was explored in seven studies based on longitudinal analyses [16,30–32,66,70,71]. A greater degree of kinesiophobia at baseline significantly predicted greater levels of disability immediately after the intervention [32], and at three [32], six [16,30], and twelve [31] months follow-up, even when adjusted for age [30,31], gender [30,31], educational level [31], comorbidities [31], body mass index [31], pain variables (number, duration, severity, and intensity) [16,30], disability at baseline [16], work status [31], marital status [31], and disease severity [31]. One study [32] reported a significant and positive association between kinesiophobia at baseline and disability after the intervention at three months without adjusting for covariates. Furthermore, Lüning Bergsten et al. [70] found a significant and positive association between changes in kinesiophobia after intervention and changes in disability after intervention without adjusting for any covariates. However, the relationship between changes in kinesiophobia at six months and changes in disability at six months was not reported. On the other hand, Matos et al. [71] reported that kinesiophobia at baseline did not predict changes in disability at three months. No covariates were reported. Koho et al. [66] also showed that kinesiophobia at baseline did not predict changes in disability at twelve months. No covariates were reported. The overall quality of the evidence was moderate.

The association between kinesiophobia and quality of life in people with CMP (cross-sectional analysis)

The association between kinesiophobia and quality of life was evaluated in eight studies based on cross-sectional analyses. A total of three studies showed a significant association between a greater levels of kinesiophobia and lower levels of quality of life

[29,72,80]. There was no significant relationship between kinesiophobia and quality of life in one study [96]. Finally, four studies showed inconsistency in the strength of the in their findings [28,47,89,94]. Altuğ et al. [28] found a significant and negative association between kinesiophobia and quality of life according to general health, physical function, social function, roles restricted by physical function and bodily pain. However, this association was not significant according to the role restricted by mental function, vitality, and mental health. Askary-Ashtiani et al. [47] showed a significant and negative association between kinesiophobia and quality of life (physical function), although this association was not significant in relation to mental health. Larsson et al. [97] reported a significant and negative association between kinesiophobia and quality of life when health is poor, whereas this association was not significant when health was very good, good, and fair. Nijs and Thielemans [94] showed a significant and negative association between kinesiophobia and quality of life according to the role limitations due to physical problems, mental health, and general health perception. However, this association was not significant according to physical functioning, role limitations due to emotional problems, social functioning, bodily pain, and vitality. The overall quality of the evidence was moderate.

The predictive value of kinesiophobia on quality of life in people with CMP (longitudinal analysis)

The predictive value of kinesiophobia on quality of life in people with CMP was explored in two studies based on longitudinal analyses [30,95]. Wong et al. [30] reported that greater degree of kinesiophobia at baseline significantly predicted lower levels of quality of life at six months, even after being adjusted for sociodemographic factors, and pain variables (number, duration, and intensity). However, the relationship was only significant with respect to physical function. Orenius et al. [95] reported that

kinesiophobia at baseline did not predict changes in quality of life at twelve months. No covariates were reported. Moreover, the predictive value of changes in kinesiophobia at twelve months and changes in quality of life at twelve months was not reported. The overall quality of the evidence was limited.

DISCUSSION

The synthesis of the data from the included studies in this systematic review showed the following findings: For the cross-sectional analyses: (i) strong evidence of an association between a greater degree of kinesiophobia and greater levels of pain intensity and disability; (ii) moderate evidence for an association between a greater degree of kinesiophobia and greater levels of pain severity; (iii) moderate evidence for an association between greater levels of kinesiophobia and lower quality of life. For the longitudinal analyses: (i) a greater degree of kinesiophobia at baseline predicts the progression of disability overtime, with moderate evidence; (ii) a greater degree of kinesiophobia at baseline predicts greater levels of pain severity at a six month follow-up, with limited evidence; (iii) greater levels of kinesiophobia at baseline predict lower quality of life at six months, with limited evidence; (iv) conflicting evidence was found in support of kinesiophobia as a predictor of changes in pain intensity.

Comparison with other studies

This is the first synthesis of the evidence evaluating the role of kinesiophobia on pain, disability, and quality of life in people with CMP through the analysis of both cross-sectional and longitudinal studies. Fear is a basic emotion, which appears as a reaction to a specific, identifiable, and imminent threat (e.g. a fall) [98]. It is constituted by three components: interpretation of the stimulus as threatening, increased sympathetic arousal, and defensive behaviour [99]. Escape behaviours are a defensive and adaptive response to stimulus (e.g., pain) in the short term (acute phase) [100], and they can

reduce fear levels. However, in the long term (chronic phase), this avoidance activity can become maladaptive. People with CMP are presumed to develop kinesiophobia [15,16]. They often avoid activities which are assumed to provoke a real or potential injury/re-injury, developing in turn, further physical inactivity [9]. This fear to carry out certain movements can cause a negative vicious cycle where people with CMP show greater levels of pain, disability and emotional distress [9], and as a result, poor quality of life [101]. Our results support this statement as we identified moderate and strong evidence of associations between a greater degree of kinesiophobia and greater levels of pain, greater levels of disability and poorer quality of life, and in addition, moderate evidence that a greater degree of kinesiophobia is a predictor of the progression of disability overtime. Other systematic reviews have evaluated the role of other constructs of fear in acute, subacute, and chronic pain [102–105]. Zale and Ditre [102] showed how pain-related fear is associated with more severe disability in different acute and chronic pain conditions. Wertli et al. explored the prognostic value of fear-avoidance in low back pain [104], and also its role as a mediator of the treatment efficacy in this population [103]. Their findings showed that fear-avoidance predicted the delay of recovery in acute and subacute low back pain, favouring the development of chronicity [104]. Furthermore, fear avoidance also predicted poor treatment responses in acute, subacute and early chronic low back pain [103]. Finally, Kroska [105] reported how fear-avoidance is correlated with pain intensity bidirectionally in chronic pain conditions through the analysis of 118 cross-sectional studies.

Strengths and weaknesses of the study

The present systematic review has several strengths and some limitations that should be mentioned. The strengths are as follows: first, the elaboration and registration of a pre-specified protocol on PROSPERO; the use of the PRISMA checklist through the

development of this systematic review; the use of the NOS adapted checklist to evaluate the risk of bias of each included study, and the Modified Cochrane Back and Neck Pain Group Criteria to analyse the overall quality and strength of the evidence. Second, the inclusion of sixty-three articles with a total sample of 10,726 individuals with CMP exploring the role of kinesiophobia on pain, disability, and/or quality of life allows us to establish a general overview about the role of kinesiophobia in musculoskeletal pain chronicity. As a limitation, even though a long variety of MeSH terms, grey literature and a manual search were carried out, it is still possible that not all studies were identified. Heterogeneity was present between all included studies (in terms of population, outcome measures, pain conditions, statistical parameters, and study design) which limits the opportunity to establish comparisons between studies. Moreover, although mediation analysis should be primarily carried out with the aim of identifying causal mechanisms, in order to avoid possible inflation of the results [106], none of the included studies specifically evaluated the possible mediating effect of kinesiophobia in CMP, and confounding variables were not always explored in all included studies. This review assessed one specific construct of fear (kinesiophobia). Although this construct may share similar characteristics and have similar clinical relevance to other fear constructs (e.g., fear avoidance beliefs or fear of pain), they are not necessarily interchangeable, and readers should consider this when interpreting the results. We selected those studies using the TSK to measure kinesiophobia. Although the TSK has been shown to be the most extended tool to assess this construct [12], this may limit the interpretation of our results. We should also recognise several modifications from the initial protocol registered in PROSPERO (CRD 42016042641), as follows: (i) we decided to include cross-sectional and case-control studies, in order to provide information, not only on the prognostic value of kinesiophobia, but also on the level of

association between kinesiophobia and outcomes related to CMP; (ii) The Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Risk of bias assessment of prognostic factor studies (QUIPS) were replaced by the adapted version of NOS and by the Modified Cochrane Back and Neck Pain Group Criteria. In our search strategy we used specific keywords related to pain, (e.g., chronic pain, low back pain), and did not use "pain" alone, so we may have missed useful studies. Moreover, we did not include the keyword "hip pain" in our search strategy, so we may have missed relevant studies here too.

Clinical implications

Kinesiophobia is known to be a barrier to rehabilitation adherence in different chronic pain conditions [23,107]. However, it is also considered to be a modifiable factor that may facilitate earlier achievement of pain relief and functional recovery [108]. In this sense, clinicians should need to identify the presence of kinesiophobia prior to the prescription of any intervention, e.g., exercise therapy, since its presence may require a different and more specific approach than standard rehabilitation programmes. Furthermore, although rather speculative, individuals with CMP showing a greater degree of kinesiophobia could be more inclined to search for biomedical explanations and solutions for their pain disorder, due to fear for carrying out exercise or to understand their pain from a biopsychosocial perspective [23], giving rise to more co-morbid disorders [109]. In this context, kinesiophobia may cause frustration for both patients and therapists, negatively affecting their therapeutic relationship, and limiting rehabilitation efforts [109]. Therefore, ideally the presence of kinesiophobia should be detected during the first assessment, to plan biopsychosocial treatment strategies focused on the modification of kinesiophobia. This could be achieved through the

selection of functional goals, education to manage safe behaviours, and graded exposure to feared activities in the form of behavioural experiments (e.g. exposure in vivo) [9].

Future Research

In future research: (i) further longitudinal studies are needed analysing prospectively the prognostic value and the mediating role of kinesiophobia in people with CMP; (ii) further experimental studies using cognitive-behavioural activities (e.g. learned movements) are warranted in order to manipulate kinesiophobia; (iii) experimental studies applying biopsychosocial approaches that methodically address and reduce kinesiophobia are required; (iv) studies exploring the role of kinesiophobia on rehabilitation adherence in CMP population are needed; (v) as CMP is a complex multifactorial condition, a number of factors (biological, biomechanical, occupational, contextual, environmental, psychological) besides kinesiophobia may be associated with the development and perpetuation of CMP. These factors should be considered during observational and experimental studies, for example through cluster analysis, and mediation analysis, to determine the importance of each factor.

CONCLUSIONS

This systematic review revealed that a greater degree of kinesiophobia is associated with greater levels of pain intensity, pain severity and disability, as well as lower quality of life, based on the analysis of cross-sectional studies. The analysis of the prognostic role of kinesiophobia showed that greater levels of kinesiophobia at baseline predict higher levels of disability, pain severity and lower quality of life at a six month follow-up, while kinesiophobia does not predict changes in pain intensity. The results of this systematic review encourage clinicians to evaluate kinesiophobia in patients with CMP,

as the presence of kinesiophobia can impact on adherence to exercise therapy and may require specific management strategies such as the selection of functional goals, education to manage safe behaviours, and graded exposure to feared activities. Due to the low number of longitudinal studies found in this review, and the low level of the evidence attained in the analysis, causality was not firmly demonstrated, thus, further longitudinal studies are needed.

COMPETING INTERESTS

All authors declare to have no conflicts of interest to declare.

CONTRIBUTORSHIP

All the authors have contributed to the conception of this study and have participated in the writing of this manuscript.

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Figure legends

Table 1 and Table 2. Modified Cochrane Back and Neck Pain Group criteria for overall level of evidence of cross-sectional and longitudinal studies

Note: strong evidence: consistent findings in two or more low risk of bias studies (score from 14 to 21 on NOS); moderate evidence: consistent findings in one low risk of bias study or two or more moderate risk of bias studies (score from 8 to 13 on NOS); limited evidence: consistent findings in one or more high risk of bias studies (score from 0 to 7 on NOS) or one moderate risk of bias study; lacking evidence: no published studies found; conflicting evidence: inconsistent or contradictory findings within a quality level.

Appendix A. Search Strategy

Appendix B. A short question guide for the selection of relevant studies based on inclusion criteria

Appendix C. Excluded studies in the last screening (n=282)

Appendix D. Conflict of interest of included studies.

Appendix E. Characteristics of included studies

Note: CLBP: chronic low back pain; CWAD: chronic whiplash associated-disorders; CNP: chronic neck pain; CKP: chronic knee pain; CFS: chronic fatigue syndrome; FM: fibromyalgia; KOA: knee osteoarthritis; AS: Ankylosing spondylitis; VAS: visual analogue scale; RDQ: Roland and Morris Disability Questionnaire; RMDQ: Roland and Morris Disability Questionnaire; NRS: numeric rating scale; ODI: Oswestry disability index; SF-36 quality of life scale; PDI: Pain Disability Index; DRI: disability rating index questionnaire; MPI: the Multidimensional Pain Inventory; NDI: Neck Disability Index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; QBPDS: the Quebec Back Pain Disability Scale; CFS-APQ: Chronic Fatigue Syndrome Activities and Participation Questionnaire; FIQR: Revised Fibromyalgia Impact Questionnaire; FIQR-pf: Revised Fibromyalgia Impact Questionnaire perceived

function; NPRS: the numeric pain rating scale; MPQ: the McGill Pain Questionnaire; RM: the Roland-Morris Low Back Pain and Disability Questionnaire; DPQ: the Dallas Pain Questionnaire; KOOS-ADL: the knee injury and osteoarthritis outcome scale-activities of daily living subscale; FIQ: Fibromyalgia Impact Questionnaire; DASH: the Disabilities of the Arm, Shoulder and Hand; BPI: the Brief Pain Inventory; CPG: Chronic Pain Grade questionnaire; ASQoL: the Ankylosing Spondylitis Quality of Life Questionnaire; SF-12 version 2: the Medical Outcome Study 12-item Short-Form Health Survey; PCS-12: physical component of the SF-12; MCS-12: mental component of the SF-12; TSK-SF: tampa scale for kinesiophobia-somatic focus; TSK-AA: tampa scale for kinesiophobia-activity avoidance; BASFI: Bath Ankylosing Spondylitis Functional Index; RAND-36-Function: SF-36 item Health Survey RAND-36; C-S: cross-sectional; L: longitudinal.

Appendix F. Assessment of risk of bias of included studies through the NOS.

Note: the Newcastle-Ottawa Quality Assessment Scale: adapted version: A = Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?; B = Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?; C = Did the study identify and adjust for any variables or confounders that may influence the outcome?; D = Did the study use appropriate statistical analysis methods relative to the outcome of interest?; E = Is there little missing data and did the study handle it accordingly?; F = Is the methodology of the outcome measurement explicitly stated and is it appropriate?; G = Is there an objective assessment of the outcome of interest?.

Appendix G and H. Summary of the Statistical results of each outcome measure included in the systematic review.

Suppl Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram of the conducted search.