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Published in:
Rheumatology Advances in Practice

DOI:
10.1093/rap/rkab013

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

RHEUMATOLOGY ADVANCES IN PRACTICE

Rheumatology Advances in Practice 2021;0:1–14
doi:10.1093/rap/rkab013
Advance Access Publication 27 February 2021

Systematic review meta-analysis

Factors associated with fatigue in hip and/or knee osteoarthritis: a systematic review and best evidence synthesis

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Abstract

Objective The aim was systematically to identify and evaluate factors related to fatigue in individuals with hip and/or knee OA.

Methods A systematic literature search was conducted using AMED, CINAHL, MEDLINE, ProQuest and Web of Science Core Collections databases. Inclusion criteria comprised cross-sectional, case–control or longitudinal studies on patients with a diagnosis of hip and/or knee OA that included self-reported fatigue measures. Study quality was assessed using the National Heart, Lung and Blood Institute quality appraisal tool, and factors were synthesized within a bio-behavioural framework. Study designs and quality were combined to determine current evidence levels using best evidence synthesis grading. The full review protocol is available from PROSPERO (PROSPERO 2019: CRD42019138571).

Results Twenty-four studies were included, of which 19 were high, 4 moderate and 1 low quality. There was strong evidence of an association between poor self-reported physical function and high depressive symptoms with higher fatigue. Moderate evidence of an association was found between severe pain, high numbers of co-morbidities and low physical activity levels with higher fatigue. There was moderate or limited evidence of no association between most sociodemographic factors and radiographic OA severity with fatigue.

Conclusion Targets for fatigue management might include improving physical function, reducing depressive symptoms, pain and co-morbidities, and increasing physical activity levels. There is a need for more rigorous longitudinal studies to understand the causal effect of fatigue determinants within the hip and knee OA populations.

Key words: osteoarthritis, fatigue, factors, correlates, predictors, systematic review

Key messages

- Physical function, depression, co-morbidities, pain and physical inactivity are associated with fatigue based on strong to moderate best evidence.
- Sociodemographics, body mass index and radiographic OA severity are not associated with fatigue based on limited to moderate best evidence.
- To manage fatigue, physical function, depressive symptoms, pain, co-morbidities and physical activity could be targeted.

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Submitted 22 October 2020; accepted 22 January 2021

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CLINICAL SCIENCE

Introduction

OA is the most common form of arthritis and accounts for >80% of global arthritis burden [1]. The recent surge in the obesity epidemic and the increase in the global ageing population have contributed to the higher global prevalence of OA [1]. Hip and knee OA is expected to become the ninth leading cause of years lived with disability by 2030 [2] and, consequently, continue to be a major cause of reduced quality of life for those afflicted [3]. Pain is the cardinal symptom of OA and a significant contributor to functional limitations and reduction in physical activity among individuals with OA [4]. Fatigue, however, has recently emerged as an important and prevalent symptom impacting the lives of individuals with OA [5, 6].

Fatigue is generally defined as an unpleasant and subjective feeling of tiredness, exhaustion or lack of energy [7]. Moreover, aside from pain, fatigue is a common symptom and a significant concern for people with OA [8–10]. Fatigue in OA has been identified as a research priority [11] and recommended in rheumatic diseases, including OA, to be considered as a top priority in clinical practice [12]. Between 47 and 90% of those with OA report some levels of fatigue [5, 13, 14], with >40% reporting clinically significant fatigue levels [5, 13]. These levels are higher than those reported for the general population, where fatigue prevalence ranged between 13 and 25% [15–17]. Equally, fatigue levels were found to be higher for those with OA relative to their age- and sex-matched counterparts [18, 19].

With increasing interest in fatigue, the evidence on OA-related symptoms, behaviours and socioeconomic factors that contribute to fatigue preponderance has not been established within the hip and/or knee OA population, the largest population of those with OA. Evaluating the evidence on correlates or predictors for fatigue in hip and/or knee OA can help in identifying treatment plans or interventions for management or reduction of fatigue within these populations, thereby maximizing overall patient outcomes and quality of life. In order to increase the knowledge on fatigue aetiology in individuals with hip or knee OA and to design appropriate targeted fatigue interventions, the use of a conceptual framework might be beneficial in the identification of potential multifactorial correlates of fatigue. Therefore, the overaching aim of this systematic review was to identify and give an overview of predictors or correlates of fatigue in hip and/or knee OA populations using the bio-behavioural conceptual framework [20, 21]. The bio-behavioural conceptual framework was used in this systematic review because it is likely that the aetiology of fatigue is through biological or behavioural contributions [22]. Moreover, the aim of the bio-behavioural model of symptom management is within the context of a health experience that is based on interactions between biological, behavioural and social factors and their effects to explain symptoms or symptom clusters that subsequently affect health outcomes, such as fatigue [22, 23].

Methods

Review

This review was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline [24]; see Supplementary Data S1, available at *Rheumatology Advances in Practice* online. A review protocol was registered with the PROSPERO database in July 2019 (number CRD42019138571).

Search strategy and article selection

Electronic databases were searched from inception to 18 March 2020: AMED and CINAHL (via EBSCOhost); MEDLINE, ProQuest (Health and Medical Collections, Nursing and Allied Health database, PsycINFO) and Web of Science core collection. The search strategy was formulated in Medline and was reviewed using the PRESS guideline assessment form [25] by a researcher experienced in systematic review methodology. Search strings were translated and adapted for each database search engine. The following keywords, medical headings in combinations with specific database search syntax, filters, limiters and Boolean operators were used: 'fatigue' OR 'vitality' OR 'tiredness' AND 'factors' OR 'correlates' OR 'predictors' OR 'determinants' OR 'risk factors' OR 'depression' OR 'sleep' OR 'pain' AND 'osteoarthritis' OR 'knee osteoarthritis' OR 'hip osteoarthritis'. The complete strategy implemented is presented in Supplementary Table S1, available at *Rheumatology Advances in Practice* online. Reference lists of selected studies were searched to identify relevant studies, and citations (using Google Scholar) of all eligible articles and narrative reviews references were checked for further eligible texts.

Study selection criteria

Inclusion and exclusion criteria

Peer-reviewed studies that included a hip and/or knee OA population or sub-sample of hip and/or knee OA diagnosed using radiographic evidence and/or clinical diagnosis (as defined by the American College of Rheumatology criteria) [26] or according to Kellgren–Lawrence (KL) grading [27] or doctor/physician-confirmed diagnosis and that measured fatigue as an outcome or as a predictor or used subscale questionnaires for fatigue measurement (e.g. SF-36 vitality scale) were eligible for inclusion. The following study designs were included: observational studies (cohort, case–control and cross-sectional). Articles that included participants with hip and/or knee joint replacement, review articles or grey literature or abstracts or non-human and non-English studies were excluded.

Study selection

Studies identified by the search were screened independently based on titles and abstracts by two authors

(H.O.F. and O.A.I.). The eligible full texts were screened further by H.O.F. and O.A.I. In cases of disagreement, both authors discussed and reached a consensus. Where consensus could not be reached, a third author (U.O.A.) was consulted for the final decision.

Data extraction

Two authors (H.O.F. and O.A.I.) extracted the following information independently from all included studies using a pre-piloted data extraction form: study setting, study population, study design, sample size, fatigue measurement tool, follow-up time, statistical analysis method, both significant and non-significant factors associated with fatigue and strength of association.

Quality assessment

The National Heart, Lung, and Blood Institute (NHLBI) quality appraisal tool, a widely used assessment tool recommended by Cochrane for evaluating qualities of observational and cross-sectional studies, was used to evaluate internal validity and risk of bias [28, 29]. The NHLBI comprises 14 items, of which 10 are applicable to cross-sectional studies, and all 14 items are applicable to observational cohort studies. Each item was scored independently by two authors (H.O.F. and O.A.I.). The NHLBI tool allowed for assessment of methodological flaws, such as sampling, adjustment for confounders, study power and other relevant factors for each study. The overall assessment of studies was rated as high, moderate or low based on the risk of bias. In order to capture limitations within the current evidence, no studies were excluded based on the quality assessment.

Data synthesis

There was no meta-analysis performed owing to the high heterogeneity levels with regard to study population, identified factors and fatigue outcome measurements. Two authors (H.O.F. and O.A.I.) independently grouped and classified the identified factors into individual, disease-specific, psychosocial, behavioural and biological groups (Supplementary Table S2, available at *Rheumatology Advances in Practice* online) using the bio-behavioural conceptual framework of fatigue in OA [20, 21]. The synthesis decisions were reviewed until both authors reached consensus.

The findings were presented using a narrative synthesis to report factors that were or were not associated with fatigue, and we performed a best evidence synthesis of factors that were investigated in two or more studies and ranked evidence grading based on previous studies [30–32] to grade the level of evidence supporting the associations (Supplementary Table S3, available at *Rheumatology Advances in Practice* online). Equally, we classified studies according to study design, with the preferred design being cohort study followed by case–control design and, lastly, cross-sectional design. We then ranked the studies according to their methodological quality score. Also, identified factors were classified with the direction and strength of association using correlation or standardized coefficient as weak (<0.3), moderate (≥ 0.3 to <0.7) and strong associations (≥ 0.7) [33] or with odds ratios [34] where these were reported. We adjudged results as consistent if the factor was significantly associated with fatigue in the same direction of the association. In studies where only unstandardized coefficients were presented, we calculated the standardized beta (β) coefficient using this formula: β = [(standard deviation of independent variable)/(standard deviation of dependent variable)] $\times$ unstandardized (B) coefficient.

Results

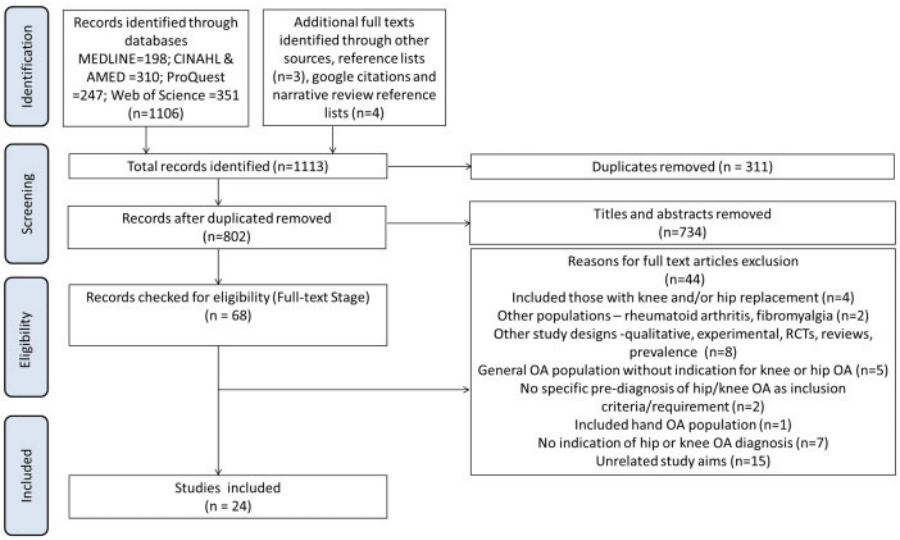
Database searches identified a total of 1106 articles, which were exported to Refworks, where duplicates were removed. Removal of duplicates, screening for title and abstracts yielded a total of 68 articles for full screening. Twenty-four articles met the inclusion criteria and were included in the review (Fig. 1).

The 24 studies included a total of 9475 patients with knee and/or hip OA (Supplementary Table S4, available at *Rheumatology Advances in Practice* online). Diagnosis of OA in most of the included studies ($n = 20$; 83%) was according to ACR criteria or KL grading [6, 9, 10, 13, 18, 19, 35–48]. The remaining four studies confirmed OA based on a physician or rheumatologist diagnosis [49–52]. Included study designs were cross-sectional ($n = 13$, 54.2%), cohort ($n = 9$, 37.5%) or case–control ($n = 2$, 8.3%). However, because the two case–control studies presented either a 5-day repeated longitudinal [18] or cross-sectional design [19] for data on the association between factors identified and fatigue, we used the cohort or cross-sectional quality appraisal for these two studies [18, 19]. Sample size varied considerably across studies, ranging from 68 [35] to 3815 participants [49]. Within the 24 eligible studies, there were 16 fatigue measurement tools used. The visual analog scale (VAS) was the most common outcome measure used (seven studies, 29.2%) to assess fatigue in the studies included; however, VAS anchors varied. Measurement tools for identified factors based on bio-behavioural groupings are presented in Supplementary Table S5, available at *Rheumatology Advances in Practice* online. Statistical analyses methods used in included studies comprised multiple linear regression models (i.e. backwards eliminations, hierarchical), logistic regression, Pearson's correlation, Spearman partial correlation, multilevel modelling, longitudinal mixed modelling and path analysis (Supplementary Table S4, available at *Rheumatology Advances in Practice* online).

Quality assessment

Nineteen studies (nine cross-sectional [6, 9, 10, 19, 37, 44, 46, 49, 51] and 10 longitudinal [13, 18, 38–42, 48, 50, 52]) were rated as having high quality. Four studies

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram



(three cross-sectional [35, 36, 47] and one longitudinal [45]) were of moderate quality, and one had low quality (cross-sectional [43]). The potential risks of bias in most studies were lack of sample size determination or power calculation ($n = 21$) and blinding of outcome assessors ($n = 24$) [Table 1]. The four studies rated as moderate quality lacked clear specification and definition of study populations and inadequate report of the rate of eligible participants [35, 36, 45, 47] or lacked control for confounders [45]. The study rated low quality [43] lacked clarity on the study population, inadequate report of the rate of eligible participants, and lack of adjustment for confounders.

Association between identified factors and fatigue

Factors associated with fatigue, with the direction and strength of association and levels of best evidence, are summarized in Figs 2–4 and Table 2, respectively. Identified factors based on the bio-behavioural framework are depicted in Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online.

Individual factors

Ten studies investigated the association between individual factors (i.e. age, sex, education, BMI, race, living situation, living circumstances, monthly bill payment, financial status, co-morbidities, illness burden, activity-limiting co-morbidities, diabetes, hypertension, back pain, depression, sarcopenia, health status and vitality) and fatigue in five cross-sectional [10, 19, 37, 46, 49] and five longitudinal cohort studies [38, 40, 41, 48, 50]. Two individual factors (age and BMI) had moderate evidence of no association with fatigue. Moderate evidence was found for the association between high co-morbidities/illness burden and higher fatigue. There was limited evidence of no association between race (being Black or non-Hispanic White) and level of education and fatigue, and there was conflicting evidence for the association between sex (being female) and fatigue. The remaining identified individual factors had insufficient evidence on their association with fatigue because results were reported from single studies (Supplementary Table S6, available at *Rheumatology Advances in Practice* online).

Disease-specific factors

Sixteen studies (8 cross-sectional [6, 19, 35, 37, 43, 44, 49, 51] and 8 longitudinal [13, 38, 40–42, 45, 48, 50]) examined the relationship between disease-specifc factors (i.e. pain, momentary pain, hip pain, pain impact, OA symptoms and disability, pain-adjusted physical activity, joint stiffness, disability, knee strength, radiographic OA severity, baseline fatigue and quality of life) and fatigue. There was moderate evidence to support the association between high pain and higher fatigue. Limited evidence was found for the association between high momentary pain, high baseline fatigue and high disability with higher fatigue, and there was limited evidence of no association between radiographic OA severity and fatigue. Conflicting evidence was noted for the association between joint stiffness and fatigue. There was insufficient evidence for the association between fatigue and the remaining disease-specific factors (Supplementary Table S6, available at *Rheumatology Advances in Practice* online).

Psychosocial factors

A total of 11 studies assessed the association between psychosocial factors (i.e. depressive symptoms, anxiety, emotional well-being, pain catastrophizing, coping behaviours and social support) and fatigue, of which five were cross-sectional [9, 19, 37, 44, 49] and six were longitudinal [38, 40–42, 48, 50]. Strong evidence was

TABLE 1 National Heart, Lung and Blood Institute (NHLBI) quality assessment for observational cohort and cross-sectional studies (24 studies)

Authors	Q1	Q2	Q3	*Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall grade
Wolfe (1999) [6]	Y	Y	Y	Y/Y	N	N	N	Y	Y	N/A	Y	NR	N/A	Y	High
Creamer *et al.* (1999) [35]	Y	N	NR	Y/Y	N	N	N	Y	Y	N/A	Y	NR	N/A	Y	Moderate
Creamer *et al.* (2000) [36]	Y	N	NR	Y/Y	N	N	N	Y	Y	N/A	Y	NR	N/A	Y	Moderate
Wolfe *et al.* (2004) [49]	Y	Y	Y	Y/Y	N	N	N	Y	Y	N	Y	NR	N/A	Y	High
Sale *et al.* (2008) [9]	Y	Y	Y	Y/Y	Y	N	N	Y	Y	N/A	Y	NR	N/A	Y	High
Murphy *et al.* (2008) [18]	Y	Y	Y	Y/Y	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	High
Murphy *et al.* (2010) [19]	Y	Y	Y	Y/Y	N	N	N	Y	Y	N	Y	NR	N/A	N	High
Stebbings *et al.* (2010) [37]	Y	Y	Y	Y/Y	Y	N	N	Y	Y	N/A	Y	NR	N/A	Y	High
Snijders *et al.* (2011) [13]	Y	Y	Y	Y/Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	High
Hawker *et al.* (2011) [38]	Y	Y	Y	Y/Y	N	N	Y	Y	Y	Y	Y	NR	Y	Y	High
van Dijk *et al.* (2011) [39]	Y	Y	Y	Y/Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	High
Murphy *et al.* (2013) [40]	Y	Y	Y	Y/Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	High
Murphy & Kratz (2014) [41]	Y	Y	Y	Y/Y	N	N	Y	Y	Y	Y	Y	NR	Y	Y	High
Zullig *et al.* (2015) [10]	Y	Y	Y	Y/Y	N	N	N	Y	Y	N/A	Y	NR	N/A	Y	High
Smith & Parmelee (2016) [50]	Y	Y	Y	N/Y	N	Y	Y	Y	Y	Y	Y	CD	Y	Y	High
Carlesso *et al.* (2016) [42]	Y	Y	Y	Y/Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	High
Huang *et al.* (2017) [43]	Y	Y	NR	Y/Y	N	N	N	Y	Y	N/A	Y	NR	N/A	N	Low
Allen *et al.* (2019) [51]	Y	Y	Y	Y/Y	N	N	N	Y	Y	N/A	Y	NR	N/A	Y	High
Aree-Ue *et al.* (2019) [44]	Y	Y	Y	Y/Y	Y	N	N	Y	Y	N/A	Y	NR	N/A	N	High
Smith et al. 2019 [52]	Y	Y	Y	N/Y	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	High
Fu *et al.* (2019) [45]	Y	NR	NR	Y/Y	N	N	Y	Y	Y	Y	Y	NR	N	Y	Moderate
Vlietstra *et al.* (2019) [46]	Y	Y	Y	Y/Y	N	N	N	Y	Y	N/A	Y	NR	N/A	Y	High
Martinez *et al.* (2019) [47]	Y	N	NR	Y/Y	N	N	N	Y	Y	N/A	Y	NR	N/A	Y	Moderate
Fawole *et al.* (2020) [48]	Y	Y	Y	Y/Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	High

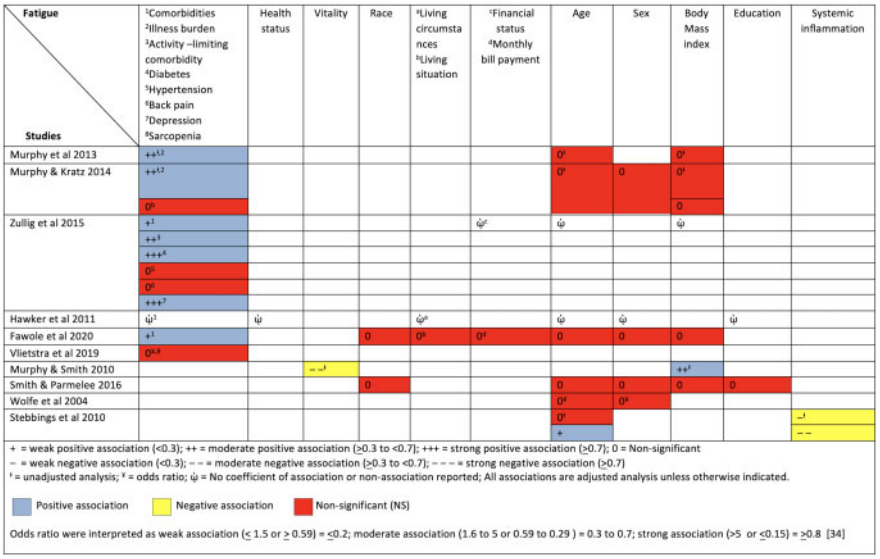
*Same population/uniform eligibility. CD: cannot determine; N: no; N/A: not applicable; NR: not reported; Y: yes. Q1: was the research question or objective clearly stated? Q2: was study population clearly specified and defined? Q3: was the participation rate of eligible persons $\geq$50%? Q4: were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants? Q5: was a sample size justification, power description, or variance and effect estimates provided? Q6: for the analysis, were the exposure(s) of interest measured prior to the outcome(s) being measured? Q7: was the time frame sufficient that one could reasonably expect to see an association between exposure and outcome if it existed? Q8: for exposures that vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)? Q9: were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistently across all study participants? Q10: was the exposure(s) assessed more than once over time? Q11: were the outcome measures (dependent variables) clearly defined, valid, reliable and implemented consistently across all study participants? Q12: were the outcome assessors blinded to the exposure status of participants? Q13: was loss to follow-up after baseline $\leq$20%? Q14: were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

found for the association between high depressive symptoms and higher fatigue. Limited evidence was noted for the association between high pain catastrophizing and higher fatigue. There was conflicting evidence on the association between anxiety and social support with fatigue. Emotonal well-being and coping behaviours had insufficient evidence on their association with fatigue based on findings from single studies.

Behavioural factors

Fifteen studies investigated the association between behavioural factors (i.e. self-reported physical function, performance-based physical function, aerobic function, physical activity, momentary pacing behaviour and sleep) and fatigue in seven cross-sectional [6, 19, 36, 37, 43, 44, 47] and eight longitudinal studies [13, 18, 38–41, 48, 52]. Strong evidence was found for the association between low self-reported physical function and higher levels of fatigue. There was moderate evidence that low physical activity is asociated with higher fatigue. There was conflicting evidence on the association between performance-based physical function and sleep with fatigue. There was insufficient evidence for the association between aerobic function and momentary pacing behaviour with fatigue levels because this was reported in only one study for each of these factors.

Fig. 2 Strength of association between individual and biological factors identified and fatigue



Fatigue / Studies	[1]Comorbidities [2]Illness burden [3]Activity –limiting comorbidity [4]Diabetes [5]Hypertension [6]Back pain [7]Depression [8]Sarcopenia	Health status	Vitality	Race	[a]Living circumstances [b]Living situation	[c]Financial status [d]Monthly bill payment	Age	Sex	Body Mass index	Education	Systemic inflammation
Murphy et al 2013	++[1,2]						0[d]		0[d]		
Murphy & Kratz 2014	++[1,2]						0[d]	0	0[d]		
	0[5]								0		
Zullig et al 2015	+[1]					ψ[c]	ψ		ψ		
	++[3]										
	+++[4]										
	0[5]										
	0[6]										
	+++[7]										
Hawker et al 2011	ψ[1]	ψ			ψ[a]		ψ	ψ		ψ	
Fawole et al 2020	+[1]			0	0[b]	0[c]	0	0	0		
Vlietstra et al 2019	0[a,8]										
Murphy & Smith 2010			– –[d]						++[3]		
Smith & Parmelee 2016				0			0	0	0	0	
Wolfe et al 2004							0[d]	0[a]			
Stebbings et al 2010							0[d]				–[d]
							+				– –

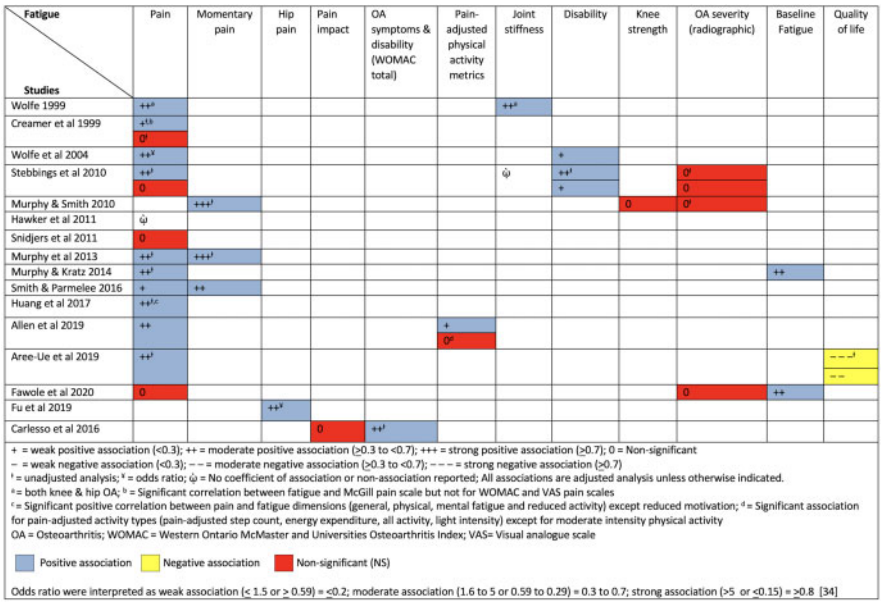
+ = weak positive association (<0.3); ++ = moderate positive association (≥0.3 to <0.7); +++ = strong positive association (≥0.7); 0 = Non-significant
– = weak negative association (<0.3); – – = moderate negative association (≥0.3 to <0.7); – – – = strong negative association (≥0.7)
[1] = unadjusted analysis; [a] = odds ratio; ψ = No coefficient of association or non-association reported; All associations are adjusted analysis unless otherwise indicated.

Positive association | Negative association | Non-significant (NS)

Odds ratio were interpreted as weak association (≤ 1.5 or ≥ 0.59) = ≤0.2; moderate association (1.6 to 5 or 0.59 to 0.29) = 0.3 to 0.7; strong association (>5 or ≤0.15) = ≥0.8 [34]

Associations are presented as correlation (*r*) or standardized (β) coefficients or odd ratios (OR).

Fig. 3 Strength of association between disease-specific factors and fatigue



Fatigue / Studies	Pain	Momentary pain	Hip pain	Pain impact	OA symptoms & disability (WOMAC total)	Pain-adjusted physical activity metrics	Joint stiffness	Disability	Knee strength	OA severity (radiographic)	Baseline Fatigue	Quality of life
Wolfe 1999	++[a]						++[a]					
Creamer et al 1999	+[1,b]											
	0[d]											
Wolfe et al 2004	++[a]							+				
Stebbings et al 2010	++[d]						ψ	++[d]		0[d]		
	0							+		0		
Murphy & Smith 2010		+++[d]							0	0[d]		
Hawker et al 2011	ψ											
Snidjers et al 2011	0											
Murphy et al 2013	++[d]	+++[d]										
Murphy & Kratz 2014	++[d]										++	
Smith & Parmelee 2016	+	++										
Huang et al 2017	++[d,c]											
Allen et al 2019	++					+						
						0[d]						
Aree-Ue et al 2019	++[d]											– – –[d]
												– –
Fawole et al 2020	0									0	++	
Fu et al 2019			++[a]									
Carlesso et al 2016				0	++[d]							

+ = weak positive association (<0.3); ++ = moderate positive association (≥0.3 to <0.7); +++ = strong positive association (≥0.7); 0 = Non-significant
– = weak negative association (<0.3); – – = moderate negative association (≥0.3 to <0.7); – – – = strong negative association (≥0.7)
[1] = unadjusted analysis; [a] = odds ratio; ψ = No coefficient of association or non-association reported; All associations are adjusted analysis unless otherwise indicated.
[a] = both knee & hip OA; [b] = Significant correlation between fatigue and McGill pain scale but not for WOMAC and VAS pain scales
[c] = Significant positive correlation between pain and fatigue dimensions (general, physical, mental fatigue and reduced activity) except reduced motivation; [d] = Significant association for pain-adjusted activity types (pain-adjusted step count, energy expenditure, all activity, light intensity) except for moderate intensity physical activity
OA = Osteoarthritis; WOMAC = Western Ontario McMaster and Universities Osteoarthritis Index; VAS= Visual analogue scale

Positive association | Negative association | Non-significant (NS)

Odds ratio were interpreted as weak association (≤ 1.5 or ≥ 0.59) = ≤0.2; moderate association (1.6 to 5 or 0.59 to 0.29) = 0.3 to 0.7; strong association (>5 or ≤0.15) = ≥0.8 [34]

Associations are presented as correlation (*r*) or standardized (β) coefficients or odd ratios (OR).

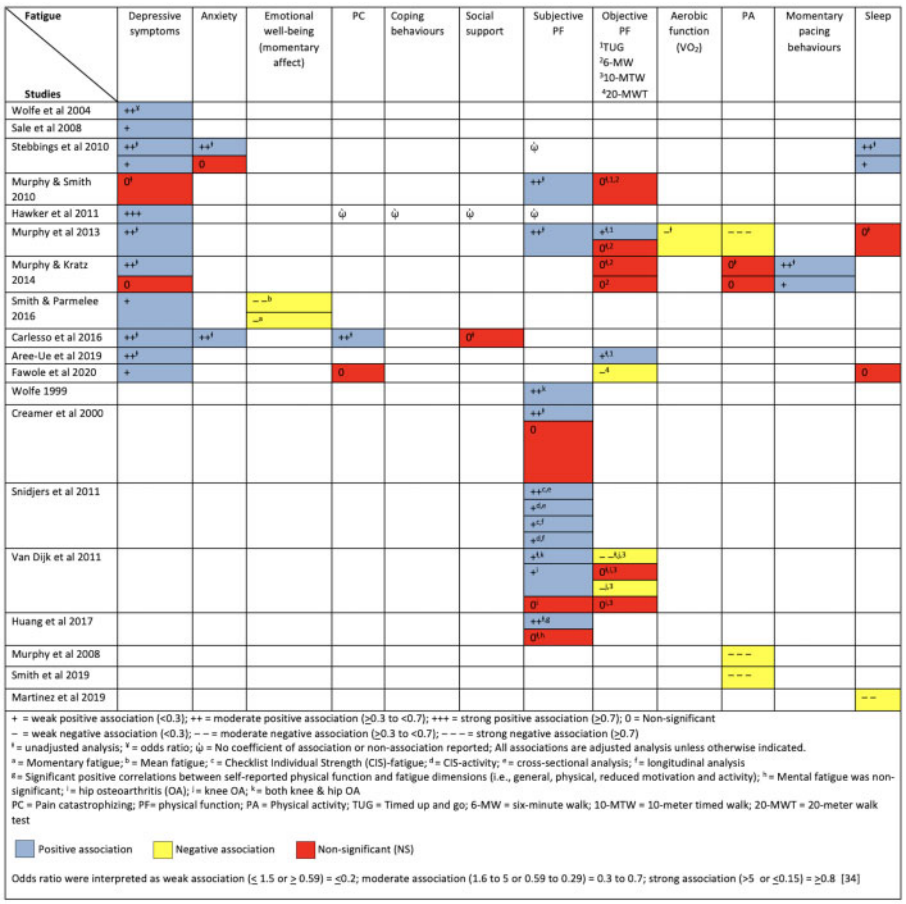
Biological factor

Of the 24 studies, only a cross-sectional study included a biological factor, CRP, a measure of systemic inflammation [37], rendering the evidence on the association between systematic inflammation (CRP) and fatigue to be insufficient (Supplementary Table S6, available at *Rheumatology Advances in Practice* online).

Discussion

The aim of this systematic review was to summarize current epidemiological evidence of potential factors associated (correlates and predictors) with fatigue in people with hip and/or knee OA using the bio-behavioural conceptual framework. Owing to high levels of

Fig. 4 Strength of association between psychosocial and behavioural factors and fatigue



Fatigue / Studies	Depressive symptoms	Anxiety	Emotional well-being (momentary affect)	PC	Coping behaviours	Social support	Subjective PF	Objective PF [1]TUG [2]6-MW [3]10-MTW [4]20-MWT	Aerobic function (VO_2)	PA	Momentary pacing behaviours	Sleep
Wolfe et al 2004	++[3]											
Sale et al 2008	+											
Stebbings et al 2010	++[3]	++[3]					ψ					++[3]
	+	0										+
Murphy & Smith 2010	0[3]						++[3]	0[1,2]				
Hawker et al 2011	+++			ψ	ψ	ψ	ψ					
Murphy et al 2013	++[3]						++[3]	+[4,1]	–[3]	– – –		0[3]
								0[1,2]				
Murphy & Kratz 2014	++[3]							0[1,2]		0[3]	++[3]	
	0							0[3]		0	+	
Smith & Parmelee 2016	+		– –[b]									
			–[a]									
Carlesso et al 2016	++[3]	++[3]		++[3]		0[3]						
Aree-Ue et al 2019	++[3]							+[4,1]				
Fawole et al 2020	+			0				–[4]				0
Wolfe 1999							++[b]					
Creamer et al 2000							++[3]					
							0					
Snidjers et al 2011							++[c,a]					
							+[c,a]					
							+[c]					
							+[c]					
Van Dijk et al 2011							+[a]	– –[1,3]				
							+[c]	0[1,3]				
								–[3]				
							0[c]	0[1,3]				
Huang et al 2017							++[a,g]					
							0[a,h]					
Murphy et al 2008										– – –		
Smith et al 2019										– – –		
Martinez et al 2019												– –

+ = weak positive association (<0.3); ++ = moderate positive association (≥0.3 to <0.7); +++ = strong positive association (≥0.7); 0 = Non-significant
– = weak negative association (<0.3); – – = moderate negative association (≥0.3 to <0.7); – – – = strong negative association (≥0.7)
[a] = unadjusted analysis; [b] = odds ratio; ψ = No coefficient of association or non-association reported; All associations are adjusted analysis unless otherwise indicated.
[a] = Momentary fatigue; [b] = Mean fatigue; [c] = Checklist Individual Strength (CIS)-fatigue; [d] = CIS-activity; [e] = cross-sectional analysis; [f] = longitudinal analysis
[g] = Significant positive correlations between self-reported physical function and fatigue dimensions (i.e., general, physical, reduced motivation and activity); [h] = Mental fatigue was non-significant; [i] = hip osteoarthritis (OA); [j] = knee OA; [k] = both knee & hip OA
PC = Pain catastrophizing; PF= physical function; PA = Physical activity; TUG = Timed up and go; 6-MW = six-minute walk; 10-MTW = 10-meter timed walk; 20-MWT = 20-meter walk test

Positive association Negative association Non-significant (NS)

Odds ratio were interpreted as weak association (≤ 1.5 or ≥ 0.59) = ≤0.2; moderate association (1.6 to 5 or 0.59 to 0.29) = 0.3 to 0.7; strong association (>5 or ≤0.15) = ≥0.8 [34]

Associations are presented as correlation (r) or standardized (β) coefficients or odd ratios (OR).

heterogeneity in study designs, fatigue measurement tools and factors identified, the review used a narrative and best evidence synthesis, which enabled the grading of factors into different levels of evidence. There were 24 studies that evaluated factors associated with fatigue in people with hip and/or knee OA, with the majority having cross-sectional designs.

The best evidence synthesis found strong evidence for the association between poor self-reported physical function and high depressive symptoms with higher fatigue levels. Moderate evidence was found for the association between a high number of co-morbidities or illness burden, high pain and low physical activity with higher fatigue. Moderate or limited evidence was noted for no association between sociodemographic factors (age, education, race, living situation or circumstances), BMI and radiographic OA severity with fatigue. Conflicting evidence was found for the association between poor performance-based physical function, high anxiety, high joint stiffness, poor sleep and low social support with higher fatigue. Limited or insufficient evidence was available for a majority of the disease-specific factors identified, suggesting that it is unclear whether fatigue pathways for those with hip and/or knee OA differ from fatigue pathways in other pathological states. Our discussion will focus on factors identified as having strong, moderate or inconclusive evidence and notable exceptions.

The findings of this review underscore the importance of modifiable factors, including perceived physical function, depressive symptoms, pain and physical activity, as potential targets for consideration in fatigue management in patients with hip and/or knee OA, because the relationships between these factors and fatigue were supported by strong or moderate levels of evidence. Generally, people with hip and knee OA have a high prevalence of low physical function [53], high depressive symptoms [54], severe pain [55] and low physical activity [56]. When present, these modifiable factors are reported to worsen health outcomes and quality of life in this population [57–61]. Thus, their inclusion as potential treatment targets might be important in the design of treatment plans and for optimal fatigue management. A previous review on fatigue interventions identified non-pharmacological interventions, such as exercise and

Table 2 Overview and best evidence synthesis regarding associations with a high level of fatigue in hip and/or knee OA

At least two studies	Association found	No association found	Best evidence
Individual factors			
Older age	One HQ cohort study and one HQ cross-sectional study [37, 38] One HQ cross-sectional study reported an association but did not indicate the direction of association, and this has not been included in the evidence synthesis [10]*	Four HQ cohort studies, two HQ cross-sectional studies [37, 40, 41, 48–50]	Moderate evidence of no association
Sex (being female)	Female One HQ cohort study [38]	Female Two HQ cohort studies [41, 48] One HQ cohort study did not report which of the gender type (male or female) had no association with fatigue [50]*	Conflicting evidence
High BMI	One HQ cross-sectional study [19] One HQ cross-sectional study reported no direction of association, and this has not been included in the evidence synthesis [10]*	Four HQ cohort studies [40, 41, 48, 50]	Moderate evidence of no association
Education levels	–	Two HQ cohort studies [38, 50]	Limited evidence of no association
Race (being Black or non-Hispanic White)	–	Two HQ cohort studies [48, 50]	Limited evidence of no association
Living circumstances/ situation	–	Two HQ cohort studies [38, 48]	Limited evidence of no association
High co-morbidities/illness burden	Four HQ cohort studies [38, 40, 41, 48] and one HQ cross-sectional study [10]	One HQ cohort studies [41]	Moderate evidence of association
Disease-specific factors			
High pain	Three HQ cohort studies and seven HQ, one MQ and one LQ cross-sectional studies [6, 19, 35, 37, 38, 41, 43, 44, 49–51]	Two HQ cohort studies and one HQ, one MQ, and one LQ cross-sectional studies [13, 35, 37, 43, 48]	Moderate evidence of association
High momentary pain	One HQ cohort study and two HQ cross-sectional studies [19, 40, 50]	–	Limited evidence of association
High joint stiffness	Two HQ cross-sectional studies [6, 37]	One HQ cross-sectional study [37]	Conflicting evidence
High disability	Two HQ cross-sectional studies [37, 49]	–	Limited evidence of association
Worse radiographic OA severity (Kellgren–Lawrence scores)	–	One HQ cohort study and two HQ cross-sectional studies [19, 37, 48]	Limited evidence of no association
High baseline fatigue	One HQ cohort study and one HQ cross-sectional study [41, 48]	–	Limited evidence of association
Psychosocial factors			
High depressive symptoms	Six HQ cohort studies and four HQ cross-sectional studies [9, 10, 37, 38, 40–42, 48–50]	One HQ cohort study and one HQ cross-sectional study [19, 41]	Strong evidence of association
High anxiety	One HQ cohort study and one cross-sectional study [37, 42]	One HQ cross-sectional study [37]	Conflicting evidence
High pain catastrophizing	Two HQ cohort studies [38, 42]	One HQ cohort study [48]	Limited evidence of association
Low social support	One HQ cohort study [38]	One HQ cohort study [42]	Conflicting evidence

(continued)

TABLE 2 Continued

At least two studies	Association found	No association found	Best evidence
Behavioural factors			
Poor self-reported physical function	Four HQ cohort studies and six HQ cross-sectional studies, one MQ and one LQ cross-sectional study [6, 13, 19, 36–40, 43, 49]	One HQ, one MQ and one LQ cross-sectional study [36, 37, 43]	Strong evidence of association
Poor performance-based physical function	Three HQ cohort studies and one HQ cross-sectional study [39, 40, 44, 48]	Three HQ cohort studies and one HQ cross-sectional study [19, 39–41]	Conflicting evidence
Low physical activity	Three HQ cohort studies [18, 40, 52]	One HQ cohort study [41]	Moderate evidence of association
Poor sleep	One HQ cross-sectional study and one MQ cross-sectional study [37, 47]	Two HQ cohort studies [40, 48]	Conflicting evidence

*Note that other factors identified from only one study and/or where directions of association have not been stated have not been included in this evidence synthesis. HQ: high quality; LQ: Low quality; MQ: moderate quality.

cognitive behavioural therapies, as the common and likely interventions for reduction of fatigue [62]. Both interventions are also used to decrease the negative impact of high levels of depressive symptoms, severe pain and poor physical function [63, 64] and, as such, might influence fatigue reduction in hip and knee OA. However, owing to limited longitudinal studies in the present review, future studies are warranted to ascertain the predictive nature of these modifiable factors on fatigue.

In general, co-morbidities or illness burden was positively associated with increased fatigue, suggesting that the presence of co-morbidities or illness burden might worsen fatigue. Furthermore, epidemiological evidence indicates that co-morbidities escalate the impact of OA and, accordingly, worsen OA symptoms in the long term [65].

Surprisingly, the radiographic severity of hip or knee OA was not significantly associated with fatigue. This lack of significant association implies that the amount of articular damage around the knee or hip joint seems to be unrelated to fatigue. Likewise, this lack of association between radiographic evidence and fatigue has been reported for the RA population [37]. The premise that radiographic evidence of OA does not always equate to symptoms in OA [66, 67] might be a plausible reason for our finding. Furthermore, there are strong speculations that OA is a multifactorial entity with multiple phenotypes [68, 69], and it is possible that structural phenotypes do not play a role in fatigue symptomology in OA. This finding might be of clinical importance for researchers planning future studies of fatigue and lower limb OA, because this result of no association also suggests that objective measures of hip or knee OA severity or KL score might not be a determinant or prognosticator for fatigue, which has the potential to reduce study costs. However, the current evidence level is limited owing to the availability of two cross-sectional studies and one longitudinal study.

It is important to note that although there was moderate evidence of no association between age, BMI and fatigue, these findings might have been impacted by the variation in fatigue assessment tools in the studies included; nonetheless, our findings are similar to those of prior research in rheumatological conditions [70, 71]. Moreover, four of the six studies included in the best evidence synthesis for BMI and fatigue were longitudinal studies, but only one had a long follow-up time (2 years) [48], with others averaging 5–7 days. It is unlikely that the effect of BMI on fatigue could be detected within such a short temporal scale.

The association of self-reported physical function, depressive symptoms and pain with fatigue is in accordance with previous research [70, 72]. The strong and moderate evidence found for these factors highlights the fact that fatigue is associated with clinical and generic factors that are modifiable and, as such, might have implications for clinical management of fatigue in this population. In contrast, inconclusive evidence was noted for the relationship between performance-based physical function and fatigue relative to the strong evidence found for subjective physical function. One explanation could be attributable to the high numbers of studies that investigated the relationship between subjective physical function and fatigue. Another explanation could be related to the different measures used to evaluate performance-based function (i.e. timed up and go, 6 min walk, and 10 and 20 m timed walk) and the dependence on only two traditional longitudinal studies. The mismatch between objective performance-based findings and subjective measures warrants the need for both physical function measures to be included in fatigue studies until studies elucidate causes and ways to adjust for differences in perception and performance of physical function in the hip and knee OA population.

Likewise, mixed evidence was noted for sleep, female sex and joint stiffness with fatigue. The inconclusive finding for sleep and fatigue is similar to findings for the RA population [70], suggesting that the relationship between sleep and fatigue is not well understood. However, this mixed evidence on the relationship

between sleep with fatigue could be attributable to different sleep constructs measured in the included studies (sleep quality [47, 48] or sleep disturbance [37] or sleep efficiency [40]). Also, variation in fatigue tools could have led to the conflicting evidence, because studies that used more comprehensive fatigue tools (e.g. SF-12 vitality scale or multidimensional assessment of fatigue–global fatigue index) found a significant association relative to those that used a single numerical rating scale or VAS. On the contrary, our conflicting findings between the relationship of female sex and fatigue conflict with that of a previous review [70]. These results between female sex and fatigue might differ because of the different pathways of RA and OA. RA includes both a genetic and an environmental pathway [73], whereas OA also includes other pathways of aetiology, such as traumatic injury or repetitive joint over-use [74]. Moreover, the majority of the studies that reported no association between fatigue and sex used numerical rating scales to measure fatigue. In the future, studies that evaluate fatigue should include information on the type of OA (primary or secondary) and assess fatigue with more comprehensive fatigue instruments. Most of the inconclusive evidence regarding joint stiffness and fatigue might be attributable to the use of different fatigue instruments (15 cm VAS and multidimensional assessment of fatigue–global fatigue index) and studies not including objective measures for joint stiffness, such as joint range of movement or tendon elasticity. Moreover, emerging evidence suggests that altered tendon elasticity owing to structural deformity from pathology might increase the energy requirement during movement and, consequently, lead to fatigue [75, 76]. Although no conclusions have been drawn because work is ongoing, there are debates regarding available quantities of elastin in tendons and its potential role in initiation of fatigue. In OA, the research on systemic inflammation and fatigue is nascent [21], but this emerging evidence creates a basis for further investigation of the relationship between fatigue and OA. However, studies on other chronic diseases (e.g. chronic fatigue syndrome and type 2 diabetes) have evaluated the relationship between systemic inflammation and fatigue, with evidence suggesting that systemic inflammatory makers are positively associated with increased fatigue both cross-sectionally and over time [77, 78]. Thus, it could be hypothesized that systemic inflammation might lead to alteration of molecules that might adversely influence cell functions, thereby distorting cellular energy production and, consequently, leading to subjective feelings of fatigue [79].

Strengths and limitations

Although our review is comprehensive and systematic and the first systematic review to be conducted on factors associated with fatigue in people with knee and/or hip OA, it has some limitations. Our search might have missed some studies that were published in non-English language journals; thus, other factors might not have been identified. Owing to the high levels of heterogeneity with regard to study populations, identified factors and fatigue outcome measurement tools, a meaningful quantitative synthesis (meta-analysis) of effect estimates was not possible. Consequently, the adoption of the best evidence synthesis approach was the most appropriate in this review.

The fatigue measurement tools used in the included studies generally have positive and good psychometric properties [37, 80–82]; nonetheless, many of these fatigue tools have not been validated for the hip and knee OA population. Thus, the use of fatigue instruments designed for other rheumatic and chronic conditions (i.e. RA, multiple sclerosis, cancer) might lead to important issues, such as contamination bias [83]. Thus, there is a need for well-designed and validated fatigue instruments for hip and knee OA populations. Furthermore, the use of diverse fatigue measurement tools and different tools for factors identified might have influenced the associations found, consequently impacting our findings and limiting generalizations. Thus, we suggest that more studies should use uniform measures of fatigue. Although the NHBLI quality appraisal tool is valid for assessing internal validity and risk of bias in observational and cross-sectional studies [28, 29], there were other potential risks of bias that were not considered in the NHBLI. These include pre-definition of key confounders and consideration of adjustment for *a priori* key confounders and attrition bias (handling of missing data). Furthermore, although another study [20] has evaluated fatigue more broadly, there is a need to examine fatigue specifically in those with hip and knee OA and provide a starting point reference on the best evidence available in specific OA-related fatigue literature.

Strengths of this review included the robust classification of factors using the bio-behavioural conceptual framework of fatigue in OA and the best evidence synthesis as a means for amalgamating results. Given that meta-analysis was not possible, the best evidence synthesis and evidence grading of all the data from the systematic review is likely to help streamline future studies of fatigue through identification of factors that need to be researched further in order to deepen our understanding of fatigue within the hip and knee OA population. Although, the approach used for best evidence synthesis is a common one [30–32], this approach does not consider the methodological quality limitation within each study (i.e. whether the weaknesses identified lead to bias), thus results should be interpreted with caution. Furthermore, the use of a more recent Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach might have led to a more robust rating of certainty of evidence [84]; it was not feasible to apply this approach because fatigue was considered in this review as either an outcome or a predictor. This meant that studies differed in the predictors assessed, outcomes assessed and analytical approaches, resulting in heterogeneity in prediction models.

Recommendation for future studies and practice

Current evidence strongly suggests that to manage fatigue in hip and knee OA, modifiable factors, such as physical function, depressive symptoms, pain and physical activity, need to be targeted. However, owing to the potential for circularity *vs* causality of fatigue, depression, pain and physical function, there is a need to investigate the potential longitudinal links between fatigue and these factors to enhance our understanding of fatigue aetiology in hip and knee OA. In contrast, older age, BMI and disease (OA) severity should not be targets for fatigue intervention. More studies that comprise rigorous longitudinal designs, a long-term follow-up period and consistent fatigue measures with adjustment for key confounders are warranted. This could lead to identification of predictors of fatigue and enhancement of current evidence. Also, given that the measurement of fatigue is incomplete without consideration for its multidimensionality, classifying fatigue in relationship to a specific activity with fixed intensity and duration provides a more objective approach to fatigue assessment [19, 85], a concept known as fatigability. Future studies should consider both assessment of fatigability and dimensions of fatigue in those with hip and knee OA. Equally, comprehensive investigations of disease-specific factors and other factors identified using the bio-behavioural conceptual framework are needed to provide more robust and comprehensive evidence on fatigue predictors over time.

Conclusions

There is strong or moderate evidence that high numbers of co-morbidities or illness burden and modifiable factors, such as high depressive symptoms, low levels of self-reported physical function, high pain and low physical activity levels, are associated with greater fatigue, making these factors possible targets for fatigue reduction in hip and/or knee OA populations. More rigorous longitudinal studies are needed in order to substantiate the current evidence and to investigate the causal effect and directionality of other potential identified determinants of fatigue in order to understand the aetiology and mechanisms of fatigue within the knee and/or hip OA populations.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

Data are available upon reasonable request to the corresponding author. All data relevant to the study are included in the article.

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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