Supplementary file 1 Research questions for assembling knowledge about fatigue

Definition fatigue

What is known about:

1. How fatigue is defined in RMDs?
2. What difficulties might occur in defining fatigue?
3. The differences in current or older definitions of fatigue?

Measurement instruments

What is known about:

4. The procedure of identifying fatigue in RMDs?
5. How is fatigue measured in scientific research in RMDs?

Determinants

What is known about:

6. Determinants of fatigue in RMDs?
7. The differences and similarities in determinants of fatigue across RMDs?

Consequences

What is known about:

8. The consequence of fatigue in people with RMDs (for example, on occupation, social contacts or daily functioning)?
9. How the consequences of fatigue are measured?

Interventions

What is known about:

10. Possible interventions for reducing fatigue in RMDs?
11. Differences and similarities of these interventions across RMDs?
12. The effectiveness of these interventions in RMDs?
13. How the effectiveness of these interventions currently measured in RMDs?
14. The feasibility, acceptability or applicability of these interventions for reducing fatigue in practice?
15. The effectiveness for applying (a) combination(s) of interventions for reducing fatigue?

Beckers E, *et al. RMD Open* 2023; 9:e003056. doi: 10.1136/rmdopen-2023-003056

Supplementary file 2 Formulated search strings for the 5 electronic databases

A. OVID Search strategy performed in MEDLINE and EMBASE

$ or * = truncation character (wildcard)
ADJn = search terms within a specified number (n) of words from each other in any order
exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
.tw. = text words, includes title, abstract and drug trade name
.kw. = key words, contains keywords defined by the author of the article

Search string:

1. Exp arthritis, rheumatoid/
2. (Rheumatoid or reumatoid or revmatoid).tw,kw.
3. (Rheumatic or reumatic or revmatic).tw,kw.
4. ((Rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw,kw.
5. OR/1-4
6. Exp spondylitis, ankylosing/
7. Spondylarthritis/
8. (Ankylos$ or spondyl$).tw,kw.
9. (Bekhterev$ or bechterew$).tw,kw.
10. (Marie adj3 struempell$).tw,kw.
11. Sacroiliitis/
12. ((Axial or spin$ or peripheral or vertebral or enthesitis) adj3 (joint$ or spondyloarthritis or arthritis or ankylosing)).tw,kw.
13. Arthritis, Psoriatic/
14. (Psoria$ adj (arthriti$ or arthropath$)).tw,kw.
15. ((Arthriti$ or arthropath$) adj psoria$).tw,kw.
16. OR/6-15
17. Exp osteoarthritis/
18. Osteoarthriti$.tw.
19. Osteoarthros$.tw,kw.
20. (Degenerative adj (joint or arthriti$)).tw,kw.
21. (Arthritis adj1 noninflammatory).tw,kw.
22. (Arthrosis or arthroses).tw,kw.
23. OR/17-22
24. Exp fibromyalgia/
25. Fibromyalg$.tw,kw.
26. OR/24-25
27. Exp fatigue/
28. Fatigue$.tw,kw.
29. (Physical fatigue OR mental fatigue OR muscle fatigue).tw,kw.
30. (Tired$).tw,kw.
31. (Weary or weariness).tw,kw.
32. (Exhaustion or exhausted).tw,kw.
33. (Lassitude or lethargy or lethargy$).tw,kw.
34. ((Lack or loss or lost) adj3 (energy or vigo$ or vital$)).tw,kw.
35. (Feel$ adj3 (drained or sleep$ or sluggish)).tw,kw.
36. Vitality.tw,kw.
37. OR/27-36
38. 5 OR 16 OR 23 OR 26

39. 37 AND 38
40. Limit 41 to ((Dutch or English) and "review")

B. Cochrane library for reviews search strategy

Cochrane Conventions:
.ti. = title
.ab. = abstract
.kw. = key words

Search string:

1. MeSH descriptor: [Arthritis, rheumatoid] explode all trees
2. MeSH descriptor: [Spondylitis] explode all trees
3. MeSH descriptor: [Osteoarthritis] explode all trees
4. MeSH descriptor: [Fibromyalgia] explode all trees
5. #1 OR #2 OR #3 OR #4
6. MeSH descriptor: [Fatigue] explode all trees
7. Fatigue. ti,ab,kw.
8. Tired. ti,ab,kw.
9. Tiredness, ti,ab,kw.
10. Weariness, ti,ab,kw.
11. Exhaustion, ti,ab,kw.
12. Exhausted, ti,ab,kw.
13. Lethargy, ti,ab,kw.
14. Lassitude, ti,ab,kw.
15. Vitality, ti,ab,kw.
16. "Lack of energy": ti,ab,kw.
17. "Loss of energy": ti,ab,kw.
18. AND (OR #6-#17) in Cochrane Reviews

C. CINAHL (*EBSCOhost*) Search strategy

TI = title
AB = Abstract
MJ = Word in Major Subject Heading
* = Truncation character (wildcard)
N = Search terms within a specified number (n) of words from each other in any order
S = Search

Search string:

1. TI AB MJ (Rheumatoid arthritis)
2. TI AB MJ (rheumatoid or reumatoid or revmatoid)
3. TI AB MJ (rheumatic or reumatic or revmatic)
4. TI AB MJ ((rheumat* or reumat* or revmarthrit*) N3 (arthrit* or artrit* or diseas* or condition* or nodule*))
5. S1 OR S2 OR S3 OR S4
6. TI AB MJ spondylitis, ankylosing
7. TI AB MJ Spondylarthritis
8. TI AB MJ (ankylose* or spondyl*)
9. TI AB MJ (bekhterev* or bechterew*)
10. TI AB MJ Sacroiliitis
11. TI AB MJ ((axial or spin* or peripheral or vertebral or enthesitis) N3 (joint* or spondyloarthritis or arthritis or ankylosing))
12. TI AB MJ Arthritis, Psoriatic

13. TI AB MJ (psoria* N (arthriti* or arthropath*))
14. TI AB MJ ((arthriti* or arthropath*) N psoria*)
15. S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
16. TI AB MJ Osteoarthritis
17. TI AB MJ Osteoarthriti*
18. TI AB MJ Osteoarthros*
19. TI AB MJ (degenerative N (joint or arthriti*))
20. TI AB MJ (arthritis N noninflammatory)
21. TI AB MJ (arthrosis or arthroses)
22. S16 OR S17 OR S18 OR S19 OR S20 OR S21
23. TI AB MJ Fibromyalgia
24. TI AB MJ Fibromyalg*
25. TI AB MJ (S23 OR S24)
26. TI AB MJ Fatigue
27. TI AB MJ Fatigue*
28. TI AB MJ ("physical fatigue" OR "mental fatigue" OR "muscle fatigue")
29. TI AB MJ (tired*)
30. TI AB MJ (weary or weariness)
31. TI AB MJ (exhaustion or exhausted)
32. TI AB MJ (lassitude or lethargy or letharg*)
33. TI AB MJ ((lack or loss or lost) N (energy or vigo* or vital*))
34. TI AB MJ (feel* N3 (drained or sleep* or sluggish))
35. TI AB MJ Vitality
36. S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35
37. S5 OR S15 OR S22 OR S25
38. 36 AND 37, Limiters: Publication Type: Review; Language: Dutch, English

D. PsycINFO (*EBSCOhost*) Search strategy

TI = title
AB = Abstract
MJ = Word in Major Subject Heading
* = Truncation character (wildcard)
N = Search terms within a specified number (n) of words from each other in any order
S = Search

Search string:

1. TI AB MJ (Rheumatoid arthritis)
2. TI AB MJ (rheumatoid or reumatoid or revmatoid)
3. TI AB MJ (rheumatic or reumatic or revmatic)
4. TI AB MJ ((rheumat* or reumat* or revmarthrit*) N3 (arthrit* or artrit* or diseas* or condition* or nodule*))
5. S1 OR S2 OR S3 OR S4
6. TI AB MJ spondylitis, ankylosing
7. TI AB MJ Spondylarthritis
8. TI AB MJ (ankylose* or spondyl*)
9. TI AB MJ (bekhterev* or bechterew*)
10. TI AB MJ Sacroiliitis
11. TI AB MJ ((axial or spin* or peripheral or vertebral or enthesitis) N3 (joint* or spondyloarthritis or arthritis or ankylosing))
12. TI AB MJ Arthritis, Psoriatic
13. TI AB MJ (psoria* N (arthriti* or arthropath*))
14. TI AB MJ ((arthriti* or arthropath*) N psoria*)

15. S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
16. TI AB MJ Osteoarthritis
17. TI AB MJ Osteoarthriti*
18. TI AB MJ Osteoarthros*
19. TI AB MJ (degenerative N (joint or arthriti*))
20. TI AB MJ (arthritis N noninflammatory)
21. TI AB MJ (arthrosis or arthroses)
22. S16 OR S17 OR S18 OR S19 OR S20 OR S21
23. TI AB MJ Fibromyalgia
24. TI AB MJ Fibromyalg*
25. TI AB MJ (S23 OR S24)
26. TI AB MJ Fatigue
27. TI AB MJ Fatigue*
28. TI AB MJ ("physical fatigue" OR "mental fatigue" OR "muscle fatigue")
29. TI AB MJ (tired*)
30. TI AB MJ (weary or weariness)
31. TI AB MJ (exhaustion or exhausted)
32. TI AB MJ (lassitude or lethargy or letharg*)
33. TI AB MJ ((lack or loss or lost) N (energy or vigo* or vital*))
34. TI AB MJ (feel* N3 (drained or sleep* or sluggish))
35. TI AB MJ Vitality
36. S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35
37. S5 OR S15 OR S22 OR S25
38. 36 AND 37, Limiters: Publication Type: All Journals; Language: Dutch, English; Document Type: Journal Article; Methodology: SCOPING REVIEW

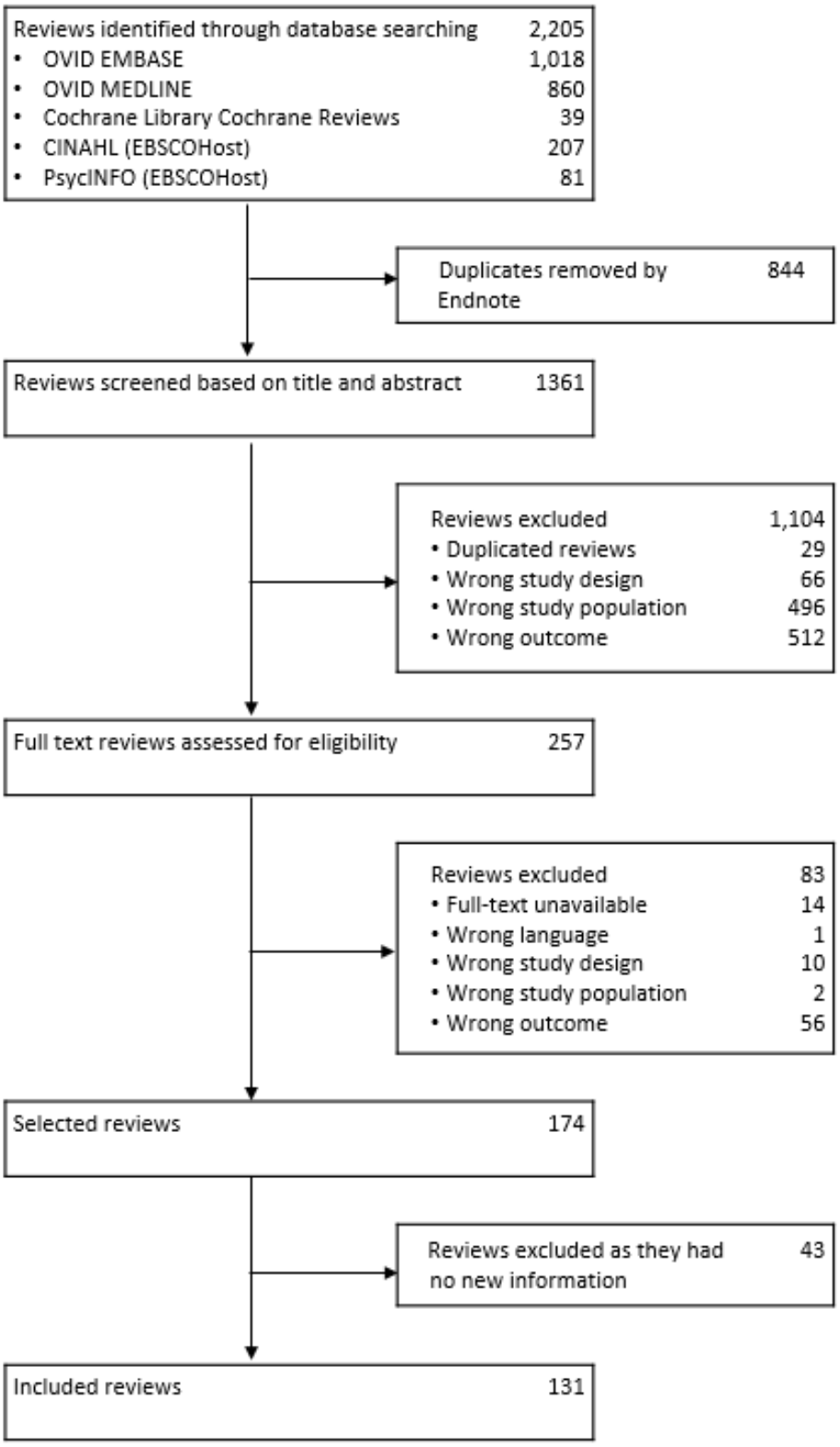
Supplementary file 3 Flowchart of selected and included reviews

The primary literature search was performed in December 2020 and identified 2,205 reviews. Of these, 844 reviews were deleted as they were duplicates. Next, 1,361 reviews were screened based on their title and abstract of which 257 reviews met the eligibility criteria. These reviews were screened on their full-text, after which 83 reviews were excluded and 174 reviews were included in the data extraction phase. During the data extraction, 43 reviews were additionally excluded as their underlying studies (partially) overlapped and only the most complete and recent review was included.

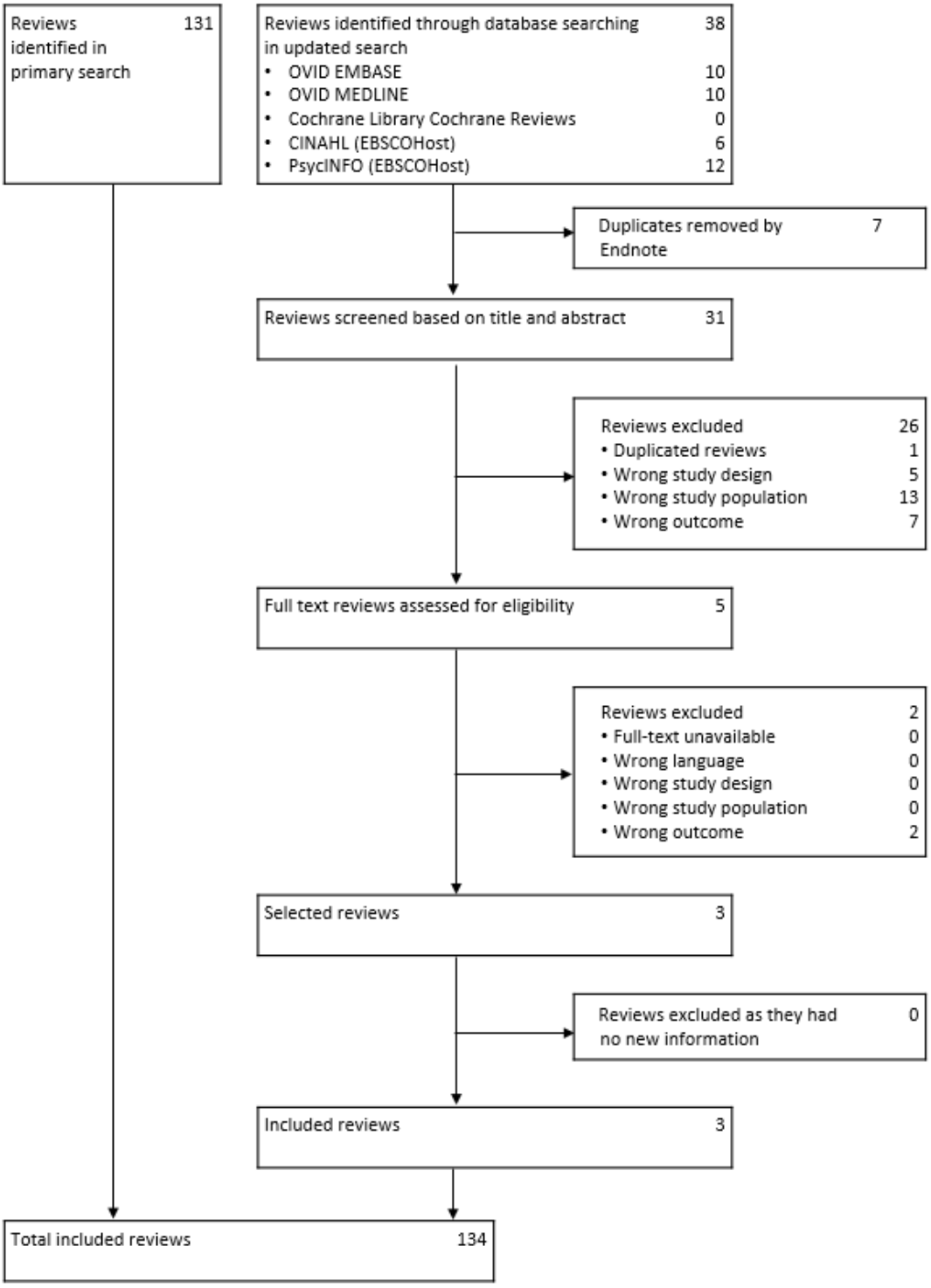
The updated literature search in December 2021 identified 38 additional reviews in the 5 databases. Of these, 31 were screened based on their title and abstract and 5 reviews were screened on their full-text for eligibility. The updated literature search resulted in 3 additional reviews.

In total, 134 reviews were included for this scoping review (19 Cochrane reviews, 44 non-Cochrane systematic reviews and 71 narrative reviews). No additional reviews were identified based on reference lists of included reviews.

A.


Reviews identified through database searching 2,205
• OVID EMBASE 1,018
• OVID MEDLINE 860
• Cochrane Library Cochrane Reviews 39
• CINAHL (EBSCOHost) 207
• PsycINFO (EBSCOHost) 81
Duplicates removed by Endnote 844
Reviews screened based on title and abstract 1361
Reviews excluded 1,104
• Duplicated reviews 29
• Wrong study design 66
• Wrong study population 496
• Wrong outcome 512
Full text reviews assessed for eligibility 257
Reviews excluded 83
• Full-text unavailable 14
• Wrong language 1
• Wrong study design 10
• Wrong study population 2
• Wrong outcome 56
Selected reviews 174
Reviews excluded as they had no new information 43
Included reviews 131

B.



***** No additional reviews were identified based on reference lists of included reviews

Figure 1 Flowchart selected and included reviews by the primary search (A) and updated search (B)

Supplementary file 4 Included reviews covering one or more research areas and/or RMDs

Research areas	Cochrane reviews n=19	Systematic reviews n=44	Narrative reviews n=71
Definition of fatigue n=16*			
▪ RA	-	-	4 (4)[1-4]
▪ SpA	-	-	2 (2)[5, 6]
▪ OA	-	-	2 (2)[4, 7]
▪ FM	-	-	4 (3)[8-11]
▪ Mixed RMDs	-	-	5 (5)[12-16]
Measurement instruments for fatigue n=26*			
▪ RA	-	2 (1)[17, 18]	7 (5)[4, 19-24]
▪ SpA	-	2 (0)[25, 26]	7 (3)[5, 6, 27-31]
▪ OA	-	1 (0)[32]	1 (1)[4]
▪ FM	-	1 (0)[33]	5 (2)[10, 34-37]
▪ Mixed RMDs	-	-	1 (1)[38]
Determinants of fatigue n=28*			
▪ RA	-	4 (4)[39-42]	9 (7)[4, 16, 43-49]
▪ SpA	-	1 (0)[50]	6 (3)[5, 6, 27, 31, 51, 52]
▪ OA	-	-	3 (2)[4, 7, 53]
▪ FM	-	-	6 (3)[9, 10, 54-57]
▪ Mixed RMDs	-	-	-
Consequences of fatigue n=21*			
▪ RA	-	4 (3)[39-41, 58]	11 (7)[4, 16, 19, 44, 45, 47, 49, 59-62]
▪ SpA	-	1 (0)[63]	3 (1)[5, 51, 64]
▪ OA	-	-	3 (2)[4, 7, 53]
▪ FM	-	-	-
▪ Mixed RMDs	-	-	-
Non-pharmacological interventions n=39			
▪ RA	1 (1)[65]	1 (1)[66]	2 (1)[67, 68]
▪ SpA	1 (1)[69]	1 (0)[70]	2 (1)[31, 71]
▪ OA	-	2 (0)[72 73]	1 (1)[7]
▪ FM	10 (5)[74-83]	14 (5)[84-97]	4 (2)[9, 10, 98, 99]
▪ Mixed RMDs	-	-	-
Pharmacological interventions n=39			
▪ RA	1 (1)[100]	3 (1)[101-103]	9 (3)[47, 104-111]
▪ SpA	-	2 (0)[112, 113]	5 (1)[31, 64, 114-116]
▪ OA	-	-	-
▪ FM	6 (1)[117-122]	8 (1)[123-130]	5 (0)[8, 131-134]
▪ Mixed RMDs	-	-	-

Number of included reviews (reviews including fatigue in their primary objective)

*Reported sum of reviews is not equal to the individual number of reviews per research area and review type as some reviews cover one or more research areas and/or RMDs

RA: rheumatoid arthritis, SpA: Spondyloarthritis, OA: Osteoarthritis, FM: Fibromyalgia, RMDs: Rheumatic and musculoskeletal diseases

References of the included reviews can be found below supplementary file 20.

Supplementary file 5 Data synthesis about definitions about fatigue in RMDs

Included reviews		Aim of review	Population	Number of underlying studies in review	Quoted text from reviews on the description of fatigue in patients with RMDs Minor textual adaptations were made for consistency reasons
1	Davies (2021) (NR)[16]	To outline various biological, physiological and psychosocial determinants of fatigue in inflammatory rheumatic diseases, and propose mechanistic and conceptual models of fatigue to summarize current understanding, stimulate debate and develop further research ideas	RMDs	2	▪ Conceptually, no consensus exists on the definition of fatigue. ▪ Most people have experienced fatigue during their everyday life, but qualitative research suggests differences between fatigue associated with chronic diseases and 'usual' or premorbid fatigue. The most distinguishing features of fatigue associated with chronic diseases include the perception of the fatigue as having no obvious 'explanation', a lack of improvement with rest, variability in severity, unpredictability and fatigue being profound or overwhelming. ▪ Patients with fatigue often describe that their muscles feel weak and unable to sustain prolonged or vigorous activity.
2	Seifert (2019) (NR)[15]	To present data about the role of fatigue for the patients' quality of life, tools for diagnosing fatigue, factors contributing to fatigue like disease activity and psychological factors, and some experimental studies to verify the biological background of fatigue	RMDs	2	▪ The symptoms of fatigue are defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases the ability to function and carry out daily activities. ▪ Acute fatigue typically decreases as the effect of the triggering factor is dwindling and a normal homeostatic balance is restored. ▪ Fatigue that persists for 6 months or more is termed chronic fatigue.
3	Dupond (2011) (NR)[12]	To delineate the place of fatigue in rheumatic disorders, most of which involve an inflammatory process	RMDs	3	▪ In contrast to 'pain', 'fatigue' fails to project a clear meaning. Furthermore, fatigue is not sonorous. No specific semiological description of fatigue is available, and neither is there a universally accepted definition of fatigue. Thus, 'fatigue' is a word that robs patients of their ability to communicate their experience. ▪ In a study by Ey et al. described in this review, fatigue was described as "perceiving an

inability and surrendering to it". The concept of surrender is crucial because it embodies the risk of exclusion. Surrendering indicates abdication and evasion, as expressed by the common use of generalizations (major fatigue), globalizations (being fatigued all the time), and stereotypes (having always been fatigued).

- Fatigue encompasses a vast array of manifestations. Fatigue is a multifactorial symptom that reflects closely intertwined physical and psychological factors.
- Physical fatigue – when the spirit is willing but the body is not: "I want to but I can't".
  In physical fatigue, the patient wants to be active but finds activity difficult. Interests are preserved: desire and pleasure are intact but unsatisfied. Resting and sleeping improve physical fatigue. Physical fatigue is least marked in the early morning and increases over the day. Napping is usually restorative. When these features are present, the physician must determine which of the three patterns described below best matches the patient's symptom.
    - Muscle weakness: 'Jelly legs'
      Fatigue due to muscle weakness is closely related to exercise and the post-exercise period. The cause is motor function failure due to neurological or muscle disease. The patient is more likely to say "I tire fast" than "I am tired". The evaluation should include muscle strength testing and assessments of sensation and deep tendon reflexes.
    - Asthenia (tiredness): no energy
      Asthenia, defined as inadequate energy resources, is the second pattern of physical fatigue. Asthenia is present continuously, worsens with physical exertion, and increases as the day wears on. Resting and sleeping help. Asthenia may be related to excessive energy expenditure, deficient energy production, or inadequate recovery.
    - Inadequate recovery: Sleep disorders
      Pain related to rheumatic disease adversely affects sleep and may therefore prevent adequate restoration. However, patients with rheumatic disease may exhibit specific sleep disorders such as restless leg syndrome. Pain related to rheumatic disease adversely affects sleep and may therefore prevent adequate restoration. Firm evidence has been obtained that 15 to 40% of patients with RA meet criteria for FM, a condition associated with specific abnormalities in slow-wave sleep.
- Psychological fatigue (weariness): I don't feel like doing anything
  Weariness is a useful term for psychological fatigue, because the underlying notions of stress and depression are often ill received by patients. Weariness can be described as

					difficulty in reacting, as opposed to difficulty in acting, with a loss of vitality. ▪ Weariness is a difficulty in reacting, with a decrease in vitality. When offered the opportunity of an activity, the weary patient often says "I don't feel like it". The main semiological features of weariness are an inability to cope and the loss of feelings of pleasure or desire. Thus, the clinical picture of weariness-depression can be characterized by the four losses: energy, pleasure, desire, and reaction. Sleep is usually nonrestorative, and patients report being most weary in the morning and feeling better as the day unfolds. Napping provides no relief for weariness.
4	Pan (2009) (NR)[14]	To describe fatigue in rheumatologic diseases*	RMDs	1	▪ There are many definitions of fatigue offered in the medical literature. However, for the purpose of discussing rheumatologic disease, a more global, biopsychosocial orientation is applied. One study offered the following definition: ''The various unmistakably disagreeable sensations commonly referred to the word fatigue are in fact the accompaniment of a great variety of physiologic conditions, which have in common only this, that the physiologic equilibrium of the body is breaking down.'' ▪ A distinction should also be made between fatigue and fatigability, the latter being defined as progressive weakness of muscle with repetitive use followed by recovery after a brief period of rest.
5	Hawley (1997) (NR)[13]	To describe fatigue in musculoskeletal pain conditions*	RMDs	2	▪ Physiologic or muscle fatigue refers to the reduced capacity of muscles to produce tension or shortening resulting from previous activity. ▪ Fatigue is also an internal and subjective feeling of tiredness that may or may not be related to activity. ▪ Acute fatigue is tiredness due to physical or mental exertion or acute conditions such as upper respiratory infections or the flu. ▪ Acute fatigue is self-limiting and ranges from minor to very severe.
6	Marrelli (2018) (NR)[3]	To explore the relationship between RA and fatigue, the different types of fatigue that have been explored in literature, the measures of fatigue that are used to assess both performance and perceived fatigue, what clinicians and researchers are recommending to	RA	7	▪ Because fatigue is often associated with psychological factors such as depression, it can be important to separate whether fatigue is directly or indirectly related to disease progression in RA. ▪ There have been multiple adjectives attached to the term 'fatigue' including: o Definition fatigue: "A state of exhaustion and decreased strength accompanied by a feeling of weariness, sleepiness and irritability, with a cognitive component". o Definition central fatigue: "Difficulty initiating or sustaining voluntary activities, leading to a progressive reduction in the activation of the muscle". In some literature, central fatigue is described as "progressive reduction in voluntary activation of muscle during exercise". Central fatigue is related to the failure of motivational and affective input, leading to a higher perception of effort and

		manage the symptoms of RA, and lastly, future directions of evaluating fatigue			resulting in the sense of fatigue. o Definition peripheral fatigue: "Fatigue produced by changes at or distal to the neuromuscular junction. Peripheral fatigue includes multiple neuromuscular changes affecting the contractility of muscles". o Definition supraspinal fatigue: "A subset of central fatigue produced by failure to generate output from the motor cortex". o Definition muscle fatigue: "A motor deficit, perception or a decline in [...] function, leading to a gradual decrease in the force capacity of muscle or the endpoint of a sustained activity". o Definition pathological fatigue: "Fatigue experienced as a symptom/outcome in acute or chronic diseases, such as RA, that often does not improve with rest". ▪ The expression fatigability denotes 'susceptibility to fatigue'. In other words, individuals who are less fatigable reach the same level of fatigue as others at a much greater demand. ▪ 'Perceptions of fatigue', also referred to as the subjective sensations of fatigue, and fatigability are distinct and possibly independent. ▪ 'Perceptions of fatigue' and 'performance fatigability' are subsections of fatigue that each contain further categories of factors related to fatigue. 'Perceptions of fatigue' contain homeostatic and psychological factors, such as central regulation based on feedback or depression, whereas 'performance fatigability' includes peripheral factors and central factors, similar to the mechanisms involved in peripheral and central fatigue. ▪ Performance fatigability regards "the decline in an objective measure of performance over a discrete period", where perceived fatigability includes "changes in sensations that regulate the integrity of the performer". ▪ Perceived fatigability refers to "homeostatic processes and psychological state, where performance fatigability refers to contractile function and muscle activation". ▪ Perceived fatigability in an individual can be evaluated at both rest as well as during physical activity, where performance is evaluated through strenuous activity.
7	Balsamo (2014) (NR)[1]	To analyse trials assessing fatigue as an outcome measure and as predictor of exercise in RA	RA	3	▪ Fatigue is the enduring sensation of weakness, lack of energy, tiredness or exhaustion, reported by 40%–80% of RA patients as their most disabling symptom. Unlike normal tiredness, fatigue is chronic, typically not related to overexertion and poorly relieved by rest. It is often multifactorial and could be worsened by disease-related components, including comorbid conditions, disease duration, functional status, disease activity, lifestyle factors, level of activity, and inadequate social support.
8	Jaime-Lara (2002)	To better understand the nature of fatigue, a	RA	7	▪ Fatigue was described as omnipresent, uncontrollable, and overwhelming. ▪ Fatigue was depicted as severe and prioritized as one of their most distressing

	(NR)[2]	qualitative meta-synthesis was performed exploring patients' experiences of fatigue across five chronic non-infectious conditions: heart failure, multiple sclerosis, RA, chronic kidney disease, and chronic obstructive pulmonary disease			symptoms, often as distressing as or more distressing than pain. ▪ Descriptions of fatigue explored its profound multidimensional effects (e.g., encompassing physical severity, emotional fatigue, and cognitive fatigue). ▪ People with RA also described feeling misunderstood and how this led to feelings of social isolation and depression. ▪ People with RA also associated fatigue with a loss of cognitive function. ▪ Another symptom co-occurring with fatigue in RA was a sensory experience of heaviness.
9	Stebbings (2010) (NR)[4]	To investigate correlates of fatigue among individuals with RA and OA, including mood, sleep, disease activity and radiographic damage	RA and OA	10	▪ Fatigue can be defined as a state of "extreme tiredness, typically resulting from mental or physical exertion or illness". In a study by Aaronson et al. described in this review several published definitions of fatigue were reported, including the comprehensive definition of fatigue as: "A subjective, unpleasant symptom which incorporates total body feelings, ranging from tiredness to extreme exhaustion, creating an unrelenting overall condition which interferes with an individual's ability to function to their normal capacity". ▪ The suggestion that fatigue is a continuum has been challenged. Fatigue, tiredness and exhaustion have been found to be distinct states with specific clinical meaning at the ends of a continuum of adaptation, where successful adaptation results in tiredness (which can be improved by sleep), and poor adaptation is associated with exhaustion, leading to impaired quality of life and social withdrawal. ▪ Fatigue is recognized as a complex symptom, with both physical aspects (including need for rest and the experience of weakness in muscles) and psychological aspects (including problems with concentration). In qualitative studies of individuals with RA, patients distinguish between systemic fatigue, related to their arthritis, and general tiredness. Fatigue frequently manifests not only as physical fatigue, but also as an inability to think clearly, to concentrate or to motivate oneself. Fatigue is experienced as variable and largely unpredictable, often with sudden onset. Occasionally, an abrupt onset of overwhelming tiredness can occur, which forces people to stop what they are doing and lie down. This characteristic aspect of fatigue has been described in RA, AS and OA.
10	Krajewska (2017) (NR)[5]	To present a definition of chronic fatigue and describes mechanisms	SpA (PsA)	2	▪ Fatigue can be peripheral, which is associated with inability to maintain adequate strength and speed; and central, which is a consequence of unsuccessful initialization of the intended action and physical activity requiring self-motivation

		that may be associated with development of fatigue, highlighting the role of chronic inflammation, selected fatigue measurement methods and relations of fatigue occurrence with clinical aspects of PsA			
11	Rosen (2016) (NR)[6]	To provide an overview of the association between fatigue and psoriatic disease as well as the commonly used metrics for evaluating fatigue	SpA (PsA)	2	▪ Fatigue is defined as "an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work". ▪ Acute fatigue typically is caused by an identified insult (i.e. injury), is self-limiting and is relieved by rest. ▪ Chronic fatigue, which may have multiple unknown causes, may accompany chronic illness and lasts longer than 6 months. ▪ In chronic disease, fatigue can originate peripherally (neuromuscular dysfunction outside of the central nervous system) or centrally (neurotransmitter activity within the central nervous system). ▪ Generally, central fatigue is more relevant in patients with chronic disease; however, both central and peripheral fatigue frequently coexist.
12	Hackney (2019) (NR)[7]	To provide insight into areas of needed research and guide future work toward mechanistic insight of OA fatigue	OA	7	▪ In OA, fatigue is not well explored or defined. In this review, OA fatigue is defined as generalized fatigue and as "an overwhelming, debilitating, and sustained exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles". ▪ Specifically, adults with OA describe fatigue as "complete exhaustion" and feeling like "coming up against a brick wall", that is similar or worse when compared to the fatigue experienced by adults with RA.
13	Ericsson (2016) (NR)[9]	To suggest recommendations for the management of fatigue in fibromyalgia by reviewing and compiling findings of non-pharmacological treatment for fatigue in patients with FM	FM	6	▪ Women with FM have described their fatigue in terms of sleepless nights, social withdrawal, loss of mental energy, physical weakness and overwhelming exhaustion. They have also been shown to report worse symptoms of general, mental and physical aspects of fatigue as well as lack of motivation and reduced activity than have healthy age-matched women. ▪ The subjective experience of fatigue is fluctuating and multidimensional which complicates the assessment of self-reported fatigue.

14	Vincent (2013) (NR)[10]	To 1) provide a general overview of the current knowledge of fatigue in the context of fibromyalgia, 2) suggest a rationale for assessment of fatigue, and 3) describe non-pharmacological and pharmacological management modalities studied in the context of FM that also improve fatigue	FM	6	▪ Patients with fibromyalgia describe fatigue as “an inescapable or overwhelming feeling of profound physical tiredness”, “weakness in the muscles”, “an uncontrollable, unpredictable constant state of never being rested”, “a ghastly sensation of being totally drained of every fiber of energy”, “not proportional to effort exerted”, “not relieved by rest”, “having to do things more slowly”, and “an invisible foe that creeps upon them unannounced and without warning”. Patients also report that fatigue is interwoven, influenced, and intensified by pain, and is sometimes more severe than pain.
15	Casale (2011) (NR)[11]	To provide a definition of fatigue and the modalities of its use in the FM syndrome	FM	4	▪ The definition of fatigue has been modified over time. Fatigue was defined as “a transient phenomenon caused by physical activity and which lead to an inability to maintain the requisite or expected force”. Fatigue is considered a reduction in the force-generating capacity of the neuromuscular system during an isometric maximal voluntary contraction. However, these definitions could not be applied either to the sensation that accompanied a maximal voluntary contraction or to the persistent sensation of fatigue referred to patients with fibromyalgia. ▪ A study by Enoka et al. described in this review, proposed a definition of fatigue that encompassed the main bias in that definition: namely, the perception of the need to increase effort to maintain a given task. Then, fatigue was defined as “an acute impairment in performances that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force”. Indeed, in fibromyalgia, a perception of increased need to enhance the effort required to maintain a given task as well as the feeling of being unable to produce this force were reported. ▪ It is, often, difficult to separate the term ‘fatigue’ from ‘tiredness’ and ‘task failure’, mainly in the clinical setting. The confusion increases when differentiation of these symptoms is applied in patients with fibromyalgia. ▪ The more recently developed, operative definition of fatigue states that fatigue is” a

					condition related to an exercise-induced reduction in the ability to produce force, which determines whether or not the task can be maintained". The most important concept behind this definition is that fatigue appears soon after the beginning of contraction and continues to develop throughout the contraction, although the subject can continue to exercise. In other words, fatigue as a neurophysiological sign commences when the contraction begins and long before the subject reaches the point at which she/he fails to perform the task. ▪ The Merriam-Webster Dictionary defines tiredness to be "a state where one is drained of strength and energy: fatigued often to the point of exhaustion (task failure)". It is obvious that these definitions refer to very different situations and can identify three different moments: the early development of fatigue as noted in the laboratory, the clinical result of the development of fatigue (i.e. the task failure) and the sensation of tiredness which can be perceived without a real physical effort and refers more to a mood than to a physiological condition. ▪ With regard to the dictionary definition of fatigue, from the clinical perspective, one should at least distinguish between the sensation of fatigue or exhaustion and fatigue as possibly measured in the laboratory as well as one cannot compare the sensation of thirst with the level of blood osmolarity or other blood parameters ▪ When the term 'chronic' is added to fatigue, the definition becomes blurred and dangerous as chronic fatigue is, in no circumstance, to be considered a form of 'acute fatigue which persists with time'. Moreover, the term chronic fatigue is clinically employed to define a multisystem syndrome (chronic fatigue syndrome), which is characterised by months of debilitating sensations of fatigue (tiredness) and is frequently associated with myalgia, headache, sore throat, low-grade fever, cognitive complaints, gastrointestinal symptoms and painful lymphadenopathy. It should be clarified that tiredness is not equivalent to fatigue. Thus, a pivotal question arises: Should we deal with two completely separate forms of fatigue, one of central origin (tiredness) and the other more distally localised within the muscle?
16	Guymer (2002) (NR)[8]	To describe treatment of fatigue in FM*	FM	2	▪ Perhaps the most useful distinction in this regard is made between acute and chronic fatigue. In this model, acute fatigue is a normal, protective mechanism in generally healthy individuals, is linked to a single cause, and is often relieved by rest, change in diet, exercise, and stress management. Chronic fatigue, however, is suggested as being

	abnormal, pervasive, and non-functional, occurring in ill clinical populations, having multiple, additive, or unknown causes, and generally, no relief is gained from usual restorative techniques. Chronic fatigue is common, and is a major problem for sufferers of many varied illnesses.

*No clear aim of the review was defined, therefore the aim is formulated based on the title of the review
RA: rheumatoid arthritis, SpA: Spondyloarthritis, PsA: Psoriatic Arthritis, OA: Osteoarthritis, FM: Fibromyalgia, RMDs: Rheumatic and musculoskeletal diseases

Supplementary file 6 Findings for measurement instruments for fatigue in RMDs, excluding instruments that address other health domains but include items on fatigue

	Name of measure	Year of development	Population	N items	Aspects that are covered in the measure	Recall period	Available cut-off values for fatigue states	Usability in research and clinical settings	Reliability evidence	Validity evidence	Ability to detect change
A	**Measurement instruments for fatigue specifically for RMDs**										
1	Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire Numerical Rating Scale (BRAF NRS)	2010	RA	3	**3 items:** Fatigue severity, Effect on life, Coping ability	Preceding week	No	Research	Internal consistency: not reported; Test–retest: strong for BRAF severity and effect; and moderate for BRAF coping	Content validity: strong; construct validity: strong; criterion validity: strong for severity and effect, moderate for coping	Good
2	Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF MDQ)	2010	RA	20	**4 domains:** Physical fatigue, Living with fatigue, Cognitive fatigue, Emotional fatigue	Preceding week	No	Research, may be useful for clinical settings	Internal consistency: strong; test–retest: strong	Content validity: strong; construct validity: strong; criterion validity; strong	Good
3	Multidimensional Assessment of Fatigue (MAF)* *15 items provide a Global Fatigue Index (GFI)*	1991	RA, OA, SpA, and FM	16	**4 domains:** Severity, Distress, Interference in activities of daily living, Frequency and change during the last week.	Preceding week	No	Research	Internal consistency: strong; test–retest: strong	Content validity: moderate; construct validity: strong; criterion validity: strong	Good
B	**Measurement instruments for fatigue for general population, and also used in RMDs**										
4	Binary question: presence or absence fatigue	Not reported	RMDs	1	**Single item:** Presence or absence of fatigue	Not reported	No	Research	N.A.	N.A.	N.A.

5	Brief Fatigue Index (BFI)	1999	PsA	1	**Single item:** Presence or absence of fatigue	Not reported	No	Not reported	Not reported	Not reported	Not reported
6	Chronic Fatigue Index (CFI)	1992	RA	16	**16 items:** Not reported	Not reported	No	Not reported	Internal consistency: strong; test-retest: not reported	Content validity: good; construct validity: not reported; criterion validity: not reported	Not reported
7	Chalder Fatigue Questionnaire (CFQ)	1993	RA, SpA, PsA and FM	11	**2 domains:** Physical fatigue, Mental fatigue	Preceding month	Yes, cut-off values for clinically relevant fatigue	Research	Internal consistency: strong; test–retest: strong in other populations	Content validity: good; construct validity: moderate; criterion validity: moderate	Good
8	Composite Index of Fatigue Impairment (CIFI)	Not reported	Not reported	Not reported	Consists of an 11-point numerical rating scale plus the Nottingham Health Profile (NHP) energy subscale, but it is unclear how these are combined	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
9	Checklist Individual Strength –fatigue (CIS-Fatigue)	1994	RA and FM	20	**4 domains:** Subjective fatigue, Concentration, Motivation, Physical activity	Preceding 2 weeks	Yes, cut-off values for normal experience of fatigue, moderate fatigue and severe fatigue.	Research	Internal consistency: strong; test–retest: strong	Content validity: moderate; construct validity: strong; criterion validity: strong	Good
10	Fatigue Assessment Scale (FAS)	2003	RMDs	10	**2 domains:** Physical symptoms, Mental symptoms	Preceding year	No	Research	Internal consistency: strong; test-retest: strong	Content validity: moderate; construct validity: strong; comparison with other fatigue measures: strong	Not reported
11	Fatigue hours	Not reported	RMDs	1	**Single item:** Fatigue hours	Not reported	No	Not reported	Not reported	Not reported	Good

12	Fatigue intensity	Not reported	RA	1	**Single item:** Fatigue intensity	Not reported	No	Not reported	Not reported	Not reported	Not reported
13	Fatigue effect	Not reported	RA	1	**Single item:** Fatigue effect	Not reported	No	Not reported	Not reported	Not reported	Not reported
14	Fatigue Numeric Rating Scale (Fatigue NRS)	Not reported	RMDs	1	**Single item:** Fatigue aspects, such as intensity, severity, impact time to onset	Generally 1 week	No	Research and clinical settings	Internal consistency: no data; test-retest: strong	Content validity: no standard format; construct validity: strong; comparison with other fatigue measures: no data	Not reported
15	Fatigue Severity Inventory (FSI)	Not reported	RA	14	**3 domains:** Fatigue Intensity, Fatigue interference, Fatigue duration	Preceding week and days with the most and least fatigue	Yes, cut-offs for fatigue interference, more days of fatigue on average, and a greater proportion of each day being fatigued	Research	Internal consistency: strong; test-retest: poor	Content validity: strong; construct validity: strong; criterion validity: not reported	Good
16	Fatigue Severity Scale (FSS)	1989	RA, OA, and SpA with a modified version in PsA	9	**3 domains:** Physical fatigue, Social fatigue, Cognitive effects of fatigue	Preceding weeks	No	Research	Internal consistency: strong; test–retest: strong	Content validity: strong; construct validity: strong; criterion validity: strong	Good
17	Fatigue Visual Analog Scales (Fatigue VAS)	Not reported	RMDs	1	**Single item:** Fatigue aspects, such as intensity, severity or impact	Not reported	Yes, cut-offs for a) Clinically relevant fatigue in RA b) Fatigue as a major symptom in AS c) Substantial or mild fatigue in RA, OA, and FMS	Research and clinical settings	Internal consistency: not reported; Test–retest: strong	Content validity: no standard format; construct validity: strong; criterion validity: variable, moderate to strong	Good
18	Functional Assessment of Chronic Illness	1997	RA and PsA	13	**4 domains:** Physical fatigue, Functional fatigue, Emotional	Preceding week	No	Research and clinical settings	Internal consistency: strong; test–	Content validity: moderate; construct validity: strong;	Good

	Therapy Fatigue (FACIT-F)				fatigue, Social consequences of fatigue				retest: strong	criterion validity: strong	
19	Morning Fatigue scale	Not reported	RMDs	1	**Single item:** Experience of waking unrefreshed	Not reported	No	Not reported	Not reported	Not reported	Not reported
20	Multidimensional Fatigue Inventory (MFI)	1995	RA, SpA and FM	20	**5 domains:** General fatigue, Physical fatigue, Reduced activity, Reduced motivation, Mental fatigue	"Lately"	No	Research	Internal consistency: strong; test–retest: strong	Content validity: moderate; construct validity: strong; criterion validity: moderate and variable	Good
21	Multidimensional Fatigue Symptom Inventory Short Form (MFSI)	1998	FM and OA	83	**Rationally derived subscales** assess global, somatic, affective, cognitive, and behavioural manifestations of fatigue. **Empirically derived subscales** assess general, physical, emotional, and mental manifestations of fatigue as well as vigour	Preceding week	No	Research and clinical settings	Internal consistency: strong; test-retest: strong	Content validity: strong; construct validity: strong; comparison with other fatigue measures: strong	Good
22	Profile of Fatigue (ProF)	2003	RA	16	**6 domains:** Needing to rest, difficulty getting started, low stamina, weak muscles, concentration, memory	Preceding 2 weeks	Yes, cut-offs for fatigue 'cases'	Research	Internal consistency: strong; test–retest: moderate	Content validity: strong; construct validity: moderate; criterion validity: strong	Good
23	Patient-Reported Outcomes Measurement Information System (PROMIS) measures	2005	FM	variable	**2 domains:** Fatigue intensity and fatigue interference/impact	Not reported	No	Not reported	Not reported	Not reported	Not reported

24	Revised Piper Fatigue Self-Report Scale (PFS)	1998	FM	22	**4 domains:** Behavioural/severity of fatigue, affective meaning of fatigue, sensory fatigue, cognitive/mood fatigue	Now	No	Research and clinical settings	Internal consistency: strong; test-retest: strong	Content validity: strong; construct validity: strong; comparison with other fatigue measures: strong	Not reported
25	Short Form 36 Vitality Subscale (SF36 VT)	1992	RA, SpA, FM and OA	4	**4 items:** Full of life, energy, worn out, tired	Preceding month	No	Research, not commonly used in clinical settings	Internal consistency: strong; test–retest: variable, very weak to strong	Content validity: moderate; construct validity: strong; criterion validity: variable, moderate to strong	Good

RA: Rheumatoid arthritis, FM: Fibromyalgia, SpA: Spondyloarthritis, OA: Osteoarthritis, RMDs: Rheumatic and musculoskeletal diseases, N.A.: Not applicable

Supplementary file 7 Summary results determinants of fatigue in RA

	Positive associations
	Positive + absent or inconsistent associations
	Absent or inconsistent associations
	Negative + absent or inconsistent associations
	Negative associations
	Unclear or hypothesized associations

The overall direction of associations between determinants and fatigue across reviews were summarized and color-coded as shown above.
A positive association indicates that an increase in the factors contributes to more severe experiences of fatigue.
Summaries were independent of strength (weak, moderate or strong) and significance of the associations.

Determinants for fatigue	Review type	Reported information on associations between determinants and fatigue Strength and direction of associations were reported whenever available. Minor textual adaptations were made for consistency or clarity reasons.	Overall direction of associations
ICF-model functioning perspective: Body function and structure			
1. Pain	3 SRs and 1 NR	SR[39]: **Consistent associations** between pain and fatigue levels were found and were on average high (median correlation 0.51 (range 0.22-0.75)) in cross-sectional univariable associations. The correlations remained significant in multivariable analyses. The longitudinal bi-directional association between fatigue and pain was **unclear.** SR[41]: **Inconsistent** associations were found between pain and increased levels of fatigue in cross-sectional and longitudinal studies. SR[42]: Pain was **significantly positively** correlated to fatigue. Strength of associations were not reported. NR[49]: A **direct link** between pain and fatigue was found. However, changes in pain and fatigue seem to vary concurrently rather than one predicting the other. Strength of associations was not reported.	Positive and inconsistent
2. Disease activity	2 SRs and 5 NRs	SR[41]: Characteristics of inflammatory activity (e.g. ESR and DAS28) showed an **unclear relationship** with fatigue. SR[42]: DAS28 (CRP or ESR) or ESR were **significantly positively correlated** to fatigue. Strength of associations was not reported. NR[4]: A direct association between raised inflammatory markers (ESR) and fatigue was **not demonstrated**. NR[47]: Disease activity and fatigue **were associated** in many studies, but often associations were weak. When patients with RA flare, usually pain and fatigue increase. NR[43]: The relationship between inflammation and fatigue have yielded **inconsistent results.** NR[45]: Fatigue **occurs independently** of RA disease activity.	Positive, inconsistent and absent

		NR[49]: Inflammatory biomarkers were **linked** to fatigue, particularly TNF-a and IL-6. Strength of associations was not reported.	
3. Disease duration	3 SRs	SR[39]: **No consistent association** between disease duration and fatigue was found. SR[41]: **Inconsistent associations** between longer disease/symptom duration and fatigue were found in cross-sectional and longitudinal studies. SR[42]: Disease duration did **not show any correlation** with fatigue.	Absent and inconsistent
4. Tender and swollen joints	2 SRs and 1 NR	SR[41]: **Inconsistent associations** between the number of tender and swollen joints and fatigue were found in cross-sectional and longitudinal studies. SR[42]: The swollen joints/tender joints ratio (STR) did **not correlate** with fatigue. NR[47]: Disease activity as measured by swollen and tender joint counts was only **weakly correlated** with fatigue.	Positive, inconsistent and absent
5. Morning stiffness	1 SR	SR[41]: **Inconsistent associations** between stiffness and swelling on awakening and fatigue variability were found in cross-sectional studies and **significant positive associations** were found in a longitudinal study. Strength of associations was not reported.	Positive and inconsistent
6. Radiographic joint damage	1 NR	NR[4]: **No association** between radiographic joint damage and fatigue was found.	Absent
7. Sleep (disturbances)	2 SRs and 2 NRs	SR[39]: Cross-sectional univariable and multivariable associations between sleep disturbance and fatigue levels were **consistently found** (cross-sectional univariable associations had median correlation of 0.45 (range 0.21-0.66) and nearly all multivariable analyses remained significant). The evidence for longitudinal associations was **less clear**. SR[41]: **Inconsistent associations** between quality of sleep or sleep disturbances with level of fatigue were found in cross-sectional and longitudinal studies. NR[16]: The association between sleep and fatigue was **not fully defined** but is probably bi-directional, with poor sleep leading to fatigue and day-time fatigue resulting in sleep disturbances. NR[49]: Sleep problems **were linked** to a number of poor health outcomes, including greater fatigue. Sleep problems may also have **indirect effects** on fatigue by lowering pain thresholds and increasing systemic inflammation. Strength of associations was not reported.	Positive and inconsistent
8.Comorbidity	1 SR and 1 NR	SR[41]: A **significant association** between comorbidity and fatigue was found in a cross-sectional study and **inconsistent associations** were found in longitudinal studies. Strength of associations were not reported. NR[49]: Patients with more comorbidities **tend to have** higher levels of fatigue and some comorbid conditions themselves may be associated with fatigue. Strength of associations was not reported.	Positive and inconsistent
9. Depression	3 SRs and 2	SR[39]: In cross-sectional analyses, on average **strong univariable associations** between concurrent depression	Positive and

	NRs	and anxiety with fatigue levels were consistently found (median correlation 0.53 (range 0.29-0.77)) and these associations remained significant in multivariable analyses with only incidental exceptions. Longitudinal associations between depression, anxiety and fatigue levels were **mostly consistently** found in univariable analyses, multivariable associations were **less clear**. SR[40]: Increased levels of depression were univariably **associated** with increased levels of fatigue (range of correlation coefficients 0.15-0.79). One study found **mixed results** in univariable analyses. Neither a lifetime diagnosis of major depressive disorder, nor sub-threshold major depression was significantly associated with current fatigue experience. However, regardless of history of mood disorder, patients experiencing current dysphoria reported significantly higher levels of fatigue than patients not experiencing current dysphoria. This suggests that it is current, rather than previous mood, which is most **reliably associated** with experiences of fatigue. In multivariable analyses, most depression analyses retained their significant associations. One study found that depression was **associated** with increased fatigue in univariable analyses (rs = 0.50). In multivariable analyses, depression remained a **significant predictor** of increased fatigue. SR[41]: **Inconsistent associations** between depression and fatigue were found in a cross-sectional study and longitudinal studies. NR[49]: Depression or depressed mood was a **strong predictor** of fatigue. NR[45]: **Close relationships** between psychological distress and depression with fatigue were found. Fatigue and mood **might mutually influence** each other.	absent
10. Anxiety	3 SRs	SR[39]: In univariable and multivariable analyses **significant associations** between anxiety and fatigue were found in cross-sectional studies and longitudinal studies. Strength of associations were not reported. SR[40]: Increased levels of anxiety were **associated** with increased levels of fatigue in univariable analyses and anxiety **did not retain** a level of statistical significance in multivariable analyses. Strength of associations was not reported. SR[41]: **Inconsistent associations** between being diagnosed at least once during the individual's lifetime with an affective disorder (major depression or generalized anxiety disorder) and fatigue were found in cross-sectional and longitudinal studies.	Positive and inconsistent
11. Mental health	1 SR	SR[39]: **Inconsistent associations** between low mental health and fatigue were found in cross-sectional studies (univariable significant associations had a median correlation of 0.46 (range 0.38-0.76)) and good but not poor mental health at baseline was **associated** with improvement of fatigue in a longitudinal study.	Positive and inconsistent
12. Muscle strength and inflammation	1 NR	NR[16]: Sarcopenia (reduced muscle mass) and myositis (muscle inflammation) **could contribute** to fatigue.	Unknown

13. Vitamin D deficiency	1 NR	NR[46]: An absolute deficiency of vitamin D was a **relatively good predictor** of fatigue.	Positive
14. Functional limitations	1 NR	NR[49]: Individuals with greater functional limitations have **more fatigue**.	Positive
ICF-model functioning perspective B: Activities			
1. Physical functioning	2 SRs	SR[39]: **Moderate positive associations** between reduced physical functioning and fatigue were found in univariable (median correlation 0.49 (range 0.30-0.59)) and multivariable cross-sectional analyses, but associations were **not significant** in all studies. Associations between low physical role functioning (SF-36) and fatigue were **low to moderate** in univariable analyses (median correlation was 0.51 (range 0.29-0.56)) and multivariable analyses, but again associations were not significant in all univariable and multivariable associations. SR[41]: Physical functioning was **significantly related** to fatigue in nearly all cross-sectional studies. Strength of associations was not reported.	Positive and inconsistent
2. Disability	2 SRs	SR[39]: **Associations** between disability and fatigue were found in cross-sectional univariable analyses (median correlation 0.48 (range 0.38-0.61)), but associations were **not significant** in all univariable and multivariable analyses. In longitudinal (univariable and multivariable) analyses, disability was **associated** with fatigue over time. SR[41]: **Inconsistent associations** between indication of disability and fatigue were found in cross-sectional and longitudinal analyses.	Positive and inconsistent
3. Physical capacity	1 SR	SR[39]: **Inconsistent associations** between poorer physical capacity and fatigue were found depending on how physical capacity was assessed (6-min walking test, aerobic capacity, lower limb function and grip strength).	Inconsistent
4. Physical activity	1 SR	SR[39]: **Inconsistent associations** between self-reported physical activity and fatigue were found in cross-sectional univariable and multivariable analyses. Longitudinally, **no significant associations** between physical activity and fatigue were found.	Inconsistent and absent
5. Sedentary time	1 NR	NR[44]: Reductions in sitting time were **associated** with reductions in fatigue. Strength of associations was not reported.	Positive
ICF-model functioning perspective: Participation			
1. Reduced role functioning/	1 SR	SR[39]: Role satisfaction was **associated** with less fatigue. The impact on roles (e.g. with family and friends) and multiple roles were **related** to more fatigue. Strength of associations was not reported.	Positive

satisfaction			
2. Interpersonal events	2 SRs and 1 NR	SR[40]: **Inconsistent associations** between positive and negative interpersonal events and same-day and next-day assessments of fatigue were found. SR[41]: Negative interpersonal events were **associated** with more fatigue. Strength of associations was not reported. NR[45]: Individuals who report frequent positive interpersonal events **might** still experience increased fatigue at a later time. The concurrence of both positive and negative interpersonal events **might** be the most meaningful factor in determining subsequent fatigue states.	Unclear
3. Social functioning	1 SR	SR[39]: **Inconsistent associations** between low social functioning (SF-36) and fatigue were found in cross-sectional univariable analyses (median correlation 0.62 (range 0.50-0.78)) and multivariable analyses.	Inconsistent
ICF-model contextual perspective: Personal factors			
1. Age	2 SRs and 1 NR	SR[39]: **Inconsistent associations** between older age and fatigue were found in cross-sectional and longitudinal studies. SR[41]: **Inconsistent associations** between age and fatigue were found. NR[48]: Age does **not appear to be of major importance** for fatigue.	Inconsistent and absent
2. Sex	2 SRs	SR[39]: **Inconsistent associations** between female sex and greater persistent fatigue were found in cross-sectional and longitudinal studies. SR[41]: **Inconsistent associations** between the sex of the patients and fatigue were found.	Inconsistent
3. Marital status	1 SR	SR[39]: There was **no consistent association** between marital status and persistent fatigue levels.	Absent
4. Educational level	1 SR	SR[39]: There was **no consistent association** between educational level and persistent fatigue levels.	Absent
5. Stress	3 SRs and 1 NR	SR[39]: **Significant associations** between chronic stress and fatigue levels were found in univariable cross-sectional studies (correlations were 0.32, 0.39 and 0.43), but statistical significance only remained in 50% of the multivariable analyses. In a longitudinal study, stress levels were **correlated** with longer-term fatigue levels in univariable but not in multivariable analyses; stress levels **did not predict** a change in fatigue. SR[40]: In cross-sectional univariable analyses, 77.8% of the studies reported a **significant association** between stress and coping variables with fatigue. Increased levels of stress/hassles was **associated** with increased fatigue (rs = 0.43, 0.37, 0.39). In longitudinal analyses, stress/coping variables were found **not to be associated** with fatigue either in univariable or multivariable analyses. SR[41]: Global psychological distress and social stress were **significantly related** to more fatigue. In longitudinal studies **associations** were found between current distress and fatigue and between several social aspects and	Positive and inconsistent

		fatigue, including stress with friends or family were related to fatigue, but stress or enjoyment with co-workers, or stress with the spouse were not related to fatigue. Strength of associations was not reported. NR[49]: An **association** between higher levels of interpersonal stress and fatigue was found. Perceived stress may also have direct and indirect effects on fatigue. Higher levels of self-perceived daily stressors **predicted increases** in fatigue one month later. Strength of associations was not reported.	
6. Low self-efficacy	3 SRs	SR[39]: In cross-sectional studies, univariable associations between low self-reported self-efficacy and fatigue were **significant** (median correlation of 0.46 (range 0.30-0.57)) and multivariable associations were **significant** in 50% of the studies. Low self-efficacy **did not significantly predict** the change of fatigue 1 year later. Strength of associations was not reported. SR[40]: **Low negative univariable associations** between reduced general self-efficacy and levels of fatigue were found in cross-sectional studies and one longitudinal study. Reduced self-efficacy remained **a significant predictor** for increased fatigue in 60% of the studies. For non-RA-related cognitions, increased levels of fatigue were **associated** with reduced fatigue self-efficacy (r=-0.46). A **significant association** between fatigue self-efficacy, and social mobilization self-efficacy and fatigue in a multivariable analysis. In one longitudinal study, increased fatigue at follow-up was **associated** with reduced fatigue self-efficacy at baseline. In multivariable analyses, fatigue self-efficacy at baseline was also **associated** with increased fatigue at follow-up. SR[41]: **Significant negative associations** between self-efficacy and fatigue were found in cross-sectional and longitudinal studies, except for one cross-sectional analysis. Strength of associations was not reported.	Positive and inconsistent
7. Coping	3 SRs	SR[39]: **Inconsistent associations** between coping and fatigue were found in univariable analyses. Coping **did not predict** fatigue level or change 1 year later. SR[40]: In cross-sectional univariable analyses, 77.8% of studies reported **significant associations** between stress and coping variables and fatigue. No significant univariable associations were found between general coping strategies and fatigue, nor praying/hoping coping or distraction coping and fatigue. In multivariable analyses, only worrying coping retained its significant association with fatigue. In longitudinal analyses, stress/coping variables were **not associated** with fatigue either in univariable or multivariable analyses. Strength of associations was not reported. SR[41]: Catastrophizing and avoidant coping were **associated** with higher levels of fatigue. Strength of associations was not reported.	Positive, inconsistent and absent
8. Personality traits	2 SRs and 3 NRs	SR[39]: Several psychological and relational factors were **associated** with less fatigue, including low neuroticism, low helplessness, role satisfaction and greater perceived help at home, optimism, perceiving less severe consequences of the illness, hope, higher self-esteem, lower somatic and higher non-somatic causal attributions, fewer catastrophizing cognitions, resilience and increased public self-consciousness. Strength of	Positive and inconsistent

		associations was not reported. SR[40]: Personality traits were **associated** with fatigue in 50% of the univariable analyses. Increased neuroticism and increased public self-consciousness were **associated** with increased levels of fatigue (r=0.44 and r=0.22, respectively). **Inconsistent results** were found for the relationships between optimism and fatigue. In multivariable level, only public self-consciousness was **associated** with fatigue. Fatigue was **lower** in patients with low public self-consciousness than in those with high public self-consciousness. Neuroticism was **not significantly associated** with fatigue variability. Strength of associations was not reported. NR[45]: Mood and fatigue **might mutually influence** each other and the deleterious effects of fatigue on mood could be attenuated by behavioral responses. NR[47]: An extrovert personality was **associated** with **more** fatigue. However, the association between personality traits and fatigue likely needs verification in other studies. Strength of associations was not reported. NR[48]: Learned helplessness and pain catastrophizing **could also play a role** in a bio-psycho-social model for fatigue.	
9. Positive Beliefs	1 SR	SR[40]: **Weak associations** were found between perceptions of the disease being uncontrollable/incurable and reduced illness acceptance with increased levels of fatigue. High levels of illness acceptance **might help** an individual to manage fatigue levels more effectively. Both increased perceptions of consequences and reduced self-efficacy were **significantly correlated** with more fatigue both at baseline and at 1-year follow-up. Concerns about medication and beliefs about medication necessity had **low significant associations** with increased fatigue, but **inconsistent evidence** was found for the perceptions of medication beliefs and concerns about medication and fatigue.	Positive and inconsistent
10. Obesity	1 SR and 2 NRs	SR[39]: The association between obesity and fatigue was not clear because there were only a few studies, with **inconsistent findings**. NR[49]: A **significant independent relationship** between obesity and fatigue was found. Obesity may have both direct and indirect influences on fatigue. NR[16]: Obesity was **a predictor** of fatigue, however, the relationship has **potentially interacting factors** at the intra-individual, inter-individual and societal levels.	Positive and inconsistent
11. Emotional role functioning	1 SR	SR[39]: **Inconsistent associations** between low emotional role functioning (SF-36) and fatigue levels were found.	Inconsistent
12. Medication use	1 NR	NR[47]: Medications such as methotrexate and even sulfasalazine **can cause** fatigue. Strength of associations was not reported. NR[47]: Virtually all treatments in RA **reduce fatigue**, including csDMARDs, tsDMARDs, bDMARDs and corticosteroids.	Inconsistent
ICF-model contextual perspective: Environmental factors			

1. Positive social support	2 SRs	SR[40]: **Inconsistent associations** between social support and fatigue were found. Some evidence suggests that negative or problematic social support was associated with poorer fatigue outcomes, and that positive social support was associated with reduced fatigue. However the limited number of studies prevents solid conclusions being formed. SR[41]: Less or inadequate social support from the patient's perspective, social stress and less help at home were **significantly related** to less fatigue. However, some studies found that social support was **not related** to fatigue.	Positive and inconsistent
2. Daily/life events	2 SRs	SR[39]: **Inconsistent associations** between daily positive events and less fatigue and negative life events and same-day or next-day fatigue were found. SR[41]: More than average numbers of negative interpersonal events **predicted** same day fatigue. There was **no association** between positive events in men and same day and next day fatigue. A relationship of negative events and fatigue was mediated by negative affect.	Inconsistent
3. Seasonal variation	1 SR	SR[39]: Statistically **significant** seasonal variation in fatigue levels was found, with more fatigue values during the winter, but **inconsistent associations** were found in multivariable analyses.	Positive and inconsistent

ICF-model: International Classification of Functioning, Disability and Health Framework, SR: Systematic review, NR: Narrative review, Rs: Spearman's rank coefficient, DMARD: disease-modifying anti-rheumatic drugs, csDMARDs: conventional synthetic DMARDs, tsDMARDs: targeted synthetic DMARDs, bDMARDs: biologic DMARDs

Supplementary file 8 Summary results determinants of fatigue in SpA

	Positive associations
	Positive + absent or inconsistent associations
	Absent or inconsistent associations
	Negative + absent or inconsistent associations
	Negative associations
	Unclear or hypothesized associations

The overall direction of associations between determinants and fatigue across reviews were summarized and color-coded as shown above.
A positive association indicates that an increase in the factors contributes to more severe experiences of fatigue.
Summaries were independent of strength (weak, moderate or strong) and significance of the associations.

Determinants for fatigue	Review type	Reported information on associations between determinants and fatigue Strength and direction of associations are reported whenever available. Minor textual adaptations were made for consistency or clarity reasons	Overall direction of associations
ICF-model functioning perspective: Body function and structure			
1. Pain	3 NRs	NR[5]: Pain was found to be **associated** with severity of fatigue and **significant associations** between reduced number of painful joints and the presence and severity of fatigue were found. Strength of associations was not reported. NR[6]: Pain can interrupt sleep and thus **may contribute** to symptoms of fatigue. NR[31]: Pain (axial and peripheral), pain intensity and pain duration were **positively associated** with fatigue. Fatigue was found to occur approximately 24h after pain in patients with recurrent low back pain. Strength of associations was not reported.	Positive
2. Disease activity	1 NR	NR[31]: **Inconsistent associations** between disease activity and fatigue were found, as the strength of associations depended on the used outcome measures for disease activity and fatigue.	Inconsistent
3. Psoriasis	1 NR	NR[5]: **Significant associations** between the severity of psoriasis and the presence and severity of fatigue were found. Strength of associations was not reported. NR[5]: Psoriatic skin lesions have an indirect effect on the severity of fatigue.	Positive
4. Pruritus	1 NR	NR[6]: Pruritus can interrupt sleep and thus **may contribute** to symptoms of fatigue.	Unclear
5. Enthesopathy	1 NR	NR[5]: **Significant associations** between the presence of enthesopathy and the presence and severity of fatigue were found. Strength of associations was not reported.	Positive
6. Stiffness	1 NR	NR[31]: Stiffness was often **correlated** with fatigue.	Positive
7. Sleep	2 NRs	NR[31]: A **positive association** between sleep problems and fatigue was found and patients complaining about	Positive

(disturbances)		severe fatigue were **more likely** to have more than 3 awakenings in one night and to feel tired in the morning. Strength of associations was not reported.	
8. Depression	2 NRs	NR[6]: It was **unclear** whether fatigue is a predictor or a result of depression. NR[51]: **Moderate associations** between disease-related factors and depression were found, but it is unknown if fatigue is a cause or consequence of depression.	Unclear
9. Comorbidity	1 SR and 1 NR	SR[50]: A higher score on the Charlson Comorbidity Index was **associated** with more fatigue. Strength of association was not reported. NR[5]: **No associations** between coexistent diseases and of the occurrence of fatigue were found.	Positive and absent
10. Psychological health	1 NR	NR[31]: Fatigue was **related** to psychological health.	Positive
11. Lower general health	1 NR	NR[31]: General health was **significantly associated** with fatigue. Strength of association was not reported.	Positive
12. Quality of life	1 NR	NR[5]: A **strong association** between reduced quality of life associated with illness and fatigue was found.	Positive
ICF-model functioning perspective: Activities			
1. Physical disability	1 NR	NR[5]: Physical disability **can increase** fatigue.	Positive
2. Physical functioning	1 NR	NR[31]: A **positive association** between higher Bath Ankylosing Spondylitis Functional Index (BASFI) scores and higher levels of fatigue was found. Strength of association was not reported.	Positive
ICF-model functioning perspective: Participation			
1. Social functioning	1 NR	NR[31]: Physical role limitations and social functioning were **not significantly associated** with fatigue.	Absent
ICF-model contextual perspective: Personal factors			
1. Demographic factors	2 NRs	NR[5]: **No associations** between of demographic factors the occurrence of fatigue were found. NR[27]: High fatigue was mainly **explained** by disease-related factors and by patient-related characteristics (years of education and female gender).	Unclear
2. Female sex	2 NRs	NR[5]: Fatigue was **more common** in women than in men. NR[52]: Women with PsA tend to suffer from **more severe fatigue** compared to men.	Positive
3. Development level (education)	1 NR	NR[5]: **Significant associations** between reduced development level and the presence and severity of fatigue were described. Strength of associations was not reported.	Positive
4. Vitality	1 NR	NR[31]: Vitality was **significantly associated** with fatigue. Strength of association was not reported.	Positive

5.	Emotional and social aspects of the disease	1 NR	NR[27]: High fatigue **might be more related** to the emotional and social aspects of the disease than to joint inflammatory aspects.	Unclear
6.	Addiction to smoking	1 SR and 1 NR	SR[50]: A **weak correlation** between smoking (past and current) and fatigue was found. NR[5]: Addiction to smoking was **associated** with the severity of fatigue. Strength of association was not reported.	Positive
7.	Alcohol consumption	1 SR	SR[50]: Current alcohol consumption was **weakly correlated** with fatigue.	Positive
8.	Systemic treatment	1 NR	NR[5]: Severe fatigue was present **twice as frequent** in patients treated systemically than in patients treated with phototherapy (appropriately 21% vs. 11%).	Positive
ICF-model contextual perspective: Environmental factors				
1.	Warm weather	1 NR	NR[31]: The weather **could influence** fatigue, as patients with fatigue have a stronger preference for heat and seem to be more disturbed by cold and wet weather. Strength of association was not reported.	Positive

ICF-model: International Classification of Functioning, Disability and Health model, SR: Systematic review, NR: Narrative review, PsA: Psoriatic arthritis

Supplementary file 9 Summary results determinants of fatigue in OA

	Positive associations
	Positive + absent or inconsistent associations
	Absent or inconsistent associations
	Negative + absent or inconsistent associations
	Negative associations
	Unclear or hypothesized associations

The overall direction of associations between determinants and fatigue across reviews were summarized and color-coded as shown above.
A positive association indicates that an increase in the factors contributes to more severe experiences of fatigue.
Summaries were independent of strength (weak, moderate or strong) and significance of the associations.

Determinants for fatigue	Review type	Reported information on associations between determinants and fatigue Strength and direction of associations are reported whenever available. Minor textual adaptations were made for consistency or clarity reasons	Overall direction of associations
ICF-model functioning perspective: Body function and structure			
1. (Joint) pain	3 NRs	NR[4]: **Inconsistent associations** between pain and fatigue were found in both qualitative and quantitative studies. NR[7]: **Inconsistent associations** between joint pain and fatigue were found. NR[53]: Pain was **strongly correlated** with fatigue (correlation 0.51) and increases in pain were related to next-day daily increases in fatigue.	Positive and inconsistent
2. Disease severity	1 NR	NR[7]: **No association** between radiological evidence of disease severity and fatigue was found.	Absent
3. Systemic inflammation	1 NR	NR[7]: There was **a lack of evidence** to characterize the relationship between systemic inflammation and fatigue.	Unclear
4. Radiographic joint damage	1 NR	NR[4]: **No association** between radiographic joint damage and fatigue was found.	Absent
5. Depression	1 NR	NR[7]: **Positive associations** between depression and fatigue were found, but joint pain may alter the relationship. Strength of associations was not reported.	Positive
6. Anxiety	2 NRs	NR[4]: **Inconsistent associations** between anxiety and fatigue were found. NR[7]: **Inconsistent associations** between anxiety and fatigue were found.	Inconsistent
7. Sleep	2 NRs	NR[4]: **Inconsistent** associations between sleep disturbance and fatigue were found. NR[7]: Poor sleep quality or sleep disturbances were **significantly associated** with more fatigue. Short-term	Positive and inconsistent

	(disturbances)		improvements in overall sleep quality result in long-term reductions in fatigue. However, sleep quality **no longer significantly** contributes to fatigue when adjusting for the effect of pain. Strength of associations was not reported.	
8.	Comorbidity	1 NR	NR[7]: Having comorbidities in conjunction with an osteoarthritis diagnosis results in higher levels of fatigue.	Positive
ICF-model functioning perspective: Activities				
1.	Physical activity	2 NRs	NR[7]: Adults with OA were four times **more likely** to have increased fatigue after periods of high activity. Adults with OA who pre-plan activities and alternate between rest and activity have less activity-associated fatigue. Tailored activity pacing had no effect on improving fatigue and most findings suggest an underlying **positive relationship** between physical activity and fatigue. NR[53]: Lower physical activity level was **strongly associated** with fatigue and daily physical activity was related to daily self-reports of fatigue.	Positive
2.	Physical functioning	1 NR	NR[7]: Functional ability **may affect** fatigue. Following performance of various physical function tasks, fatigue initially increases and then there is a decrease in performance of additional tasks. With increased physical function, there is a **negative fatigue-physical activity association**. Despite this, there exists **a close negative association** between physical function and fatigue. Strength of associations was not reported.	Inconsistent
3.	Physical disability	1 NR	NR[4]: Disability **correlates** with fatigue.	Positive
ICF-model functioning perspective: Participation				
1.	Daily activities	1 NR	NR[53]: Patients who do not experience positive effect when engaging in daily activities were **much more likely** to report fatigue than patients who do.	Positive
ICF-model contextual perspective: Personal factors				
1.	Female sex	1 NR	NR[7]: A vast majority of the research suggests female sex is **positively associated** with fatigue. Strength of associations was not reported.	Positive
2.	Age	1 NR	NR[7]: Age is **positively associated** with fatigue in OA. Strength of association was not reported.	Positive
3.	Medication use	1 NR	NR[7]: Drugs commonly prescribed for OA pain management were **positively associated** with fatigue including non-steroidal anti-inflammatory drugs (NSAIDs), sleep aids, and analgesics like opioids. Conversely, pain management through usage of NSAIDS, compared to other pain medications, **may have a protective** effect for fatigue.	Inconsistent

ICF-model: International Classification of Functioning, Disability and Health model, NR: Narrative review

Supplementary file 10 Summary results determinants of fatigue in FM

	Positive associations

Positive + absent or inconsistent associations
Absent or inconsistent associations
Negative + absent or inconsistent associations
Negative associations
Unclear or hypothesized associations

The overall direction of associations between determinants and fatigue across reviews were summarized and color-coded as shown above.
A positive association indicates that an increase in the factors contributes to more severe experiences of fatigue.
Summaries were independent of strength (weak, moderate or strong) and significance of the associations.

Determinants for fatigue	**Review type**	**Reported information on associations between determinants and fatigue** Strength and direction of associations are reported whenever available. Minor textual adaptations were made for consistency or clarity reasons	**Overall direction of associations**
ICF-model functioning perspective: Body function and structure			
1. Pain	3 NRs	NR[9]: High pain intensity was **associated** with different aspects of fatigue. Strength of associations not reported NR[10]: A **positive association** between pain and fatigue was found in cross-sectional and longitudinal studies. Chronic persistent pain was **positively associated** with fatigue. Strength of associations was not reported. NR[54]: A **strong association** between tender points and fatigue was found.	Positive
2. Tenderness	3 NRs	NR[9]: Increased muscular tenderness was **associated** with different aspects of fatigue. Strength of association was not reported. NR[10]: A **positive association** between tenderness and fatigue was found. Strength of association was not reported.	Positive
3. Stiffness	1 NR	NR[10]: A **positive association** between stiffness and fatigue was found. Strength of association was not reported.	Positive
4. Fibromyalgia severity	1 NR	NR[10]: A **positive association** between fibromyalgia severity and fatigue was found. Strength of association was not reported.	Positive
5. Sleep (disturbances)	4 NRs	NR[9]: Poor sleep quality was **associated** with different aspects of fatigue. Strength of associations was not reported. NR[10]: **Inconsistent associations** between sleep duration, sleep quality, sleep disturbances and fatigue were found in cross-sectional and longitudinal studies. NR[54]: Poor self-reported sleep quality **fully mediated the relation** between pain and fatigue in a daily process analysis. Strength of association was not reported. NR[57]: Poor sleep quality **increases** the effect of pain on fatigue and the duration and quality of sleep were	Positive and inconsistent

		associated with depression and fatigue. Strength of association was not reported.	
6. Anxiety and depression	1 NR	NR[10]: **Positive associations** between anxiety and depression with fatigue were found in cross-sectional studies and longitudinal studies. Strength of associations was not reported.	Positive
7. Diurnal rhythmicity	1 NR	NR[10]: **Associations** between diurnal rhythmicity and lag relationships with fatigue were found. Strength of associations was not reported.	Positive
8. Low zinc and magnesium levels	1 NR	NR[56]: Serum zinc and magnesium levels were **associated** with fatigue. Strength of associations was not reported.	Positive
9. Gastro-intestinal complaints	1 NR	NR[10]: A **positive association** between gastro-intestinal complaints and fatigue was found. Strength of association was not reported.	Positive
ICF-model functioning perspective: Activities			
1. Physical activity and physical functioning	2 NRs	NR[9]: Low level of physical activity and physical function were **associated** with different aspects of fatigue and physical activity **induces** markedly more fatigue in women with FM than in healthy women. Strength of associations was not reported. NR[10]: Physical activity levels demonstrate **strong associations** with fatigue.	Unclear
2. Physical disability	1 NR	NR[10]: A **positive association** between disability and fatigue was found. Strength of association was not reported.	Positive
3. Sedentary lifestyle	1 NR	NR[9]: A sedentary lifestyle was **associated** with different aspects of fatigue. Strength of association was not reported.	Positive
ICF-model functioning perspective: Participation			
1. Domestic responsibilities combined with job strain	2 NR	NR[55]: Heavy domestic responsibilities and job strain were separately and in interaction **associated** with tiredness in women and these aspects were **more strongly associated** with fatigue in women exposed to the double burden.	Positive
2. Low working capacity	1 NR	NR[9]: Low working capacity was **associated** with different aspects of fatigue. Strength of associations was not reported.	Positive
ICF-model contextual perspective: Personal factors			
1. Low age	1 NR	NR[9]: Low age was **associated** with different aspects of fatigue. Strength of associations was not reported.	Positive
2. Female sex	1 NR	NR[10]: Men had **less fatigue** compared to women and men tend to focus more on pain and women on fatigue.	Positive
3. Obesity,	1 NR	NR[56]: Obesity and overweight were **related** to worsening of the quality of life through fatigue among other	Positive

	overweight		aspects.	
4.	Psychological distress	3 NRs	NR[9]: Psychological distress was **associated** with different aspects of fatigue. Strength of associations was not reported. NR[10]: A **positive association** between emotional distress and fatigue was found. Strength of association was not reported. NR[54]: The high rate of affective distress might **at least partially explain** the presence of fatigue in some patients.	Positive
5.	Negative affect	2 NR	NR[10]: A **negative association** between positive affect and fatigue and **a positive association** between negative affect and fatigue was found. Strength of associations were not reported. NR[54]: An **association** between lower daily positive affect, relative to a patient's own mean, and higher same-day fatigue was found. Strength of association was not reported.	Positive
6.	Cognitive complaints	1 NR	NR[10]: A **positive association** between cognitive complaints and fatigue was found. Strength of association was not reported.	Positive
7.	Internal and external locus of control	1 NR	NR[10]: A **negative association** between internal and external locus of control and fatigue was found. Strength of association was not reported.	Unclear
ICF-model contextual perspective: Environmental factors				
1.	Positive and negative events	2 NRs	NR[10]: A **positive association** between negative events and fatigue and a **negative association** between positive events and fatigue on the same day and on the next day was found. Strength of associations was not reported. NR[54]: A **positive association** between interpersonal events and lower same-day fatigue was found. Strength of association was not reported.	Unclear

ICF-model: International Classification of Functioning, Disability and Health model, NR: Narrative review

Supplementary file 11 Summary results consequences of fatigue in RA

Consequences of fatigue	**Review type**	**Reported effect of fatigue on other aspects** Strength and direction of associations were reported whenever available. Minor textual adaptations were made for consistency or clarity reasons

ICF-model functioning perspective: Body function and structure		
1. Pain	1 NR	NR[49]: Changes in pain and fatigue **seem to vary concurrently** rather than one predicting the other. Experimental pain thresholds were **more consistently predictive** of subsequent fatigue than current reported pain levels, suggesting that pain sensitization **may** be a crucial factor for fatigue.
2. Disease activity	1 NR	NR[47]: Fatigue at baseline and at 3 months **predicted** disease activity at 12 months.
3. Fatigue	1 SR and 1 NR	SR[41]: Next day fatigue is **predicted** by same day fatigue. NR[47]: Fatigue at baseline and at 3 months **predicted** fatigue at 12 months.
4. Health status	1 NR	NR[4]: Fatigue is a **strong predictor** of overall health status.
5. Depression	2 NRs	NR[49]: Patients viewed depression as a **consequence of fatigue** rather than a cause and on days with more fatigue, positive mood decreases. NR[45]: Fatigue and mood **might mutually influence** each other.
ICF-model functioning perspective: Activities		
1. Physical functioning	1 SR	SR[41]: Fatigue **significantly predicted** physical functioning in a longitudinal study.
2. Physical activity	1 SR and 2 NRs	SR[58]: Fatigue is identified as an **arthritis-specific barrier** to participating in regular physical activity. NR[44]: Fatigue and pain levels **may be perceived** as barriers to participation in activity. NR[16]: Physical fatigue is the **strongest predictor** of reduced physical activity in RA.
3. Sexual activities	1 NR	NR[61]: Higher levels of fatigue were **related** to perceived problems with sexual activity.
ICF-model functioning perspective: Participation		
1. Work performance	2 SRs and 3 NRs	SR[39]: Fatigue was **associated** with reduced performance at work due to ill health (presenteeism), activity impairment, work productivity loss, and absenteeism. A longitudinal, multivariable analysis found that improvements in fatigue were **correlated** with work inside and outside the home. Strength of associations was not reported. SR[41]: Fatigue was **significantly related** to reduced work ability and minor negative work place events (commonly occurring stressful events), but **not** with major workplace events. NR[19]: Work disability is among **the most important consequences** of fatigue. Patients have identified fatigue as the **principal barrier** to employment and reduced productivity. The likelihood of absenteeism at 6 and 12 months was **significantly higher** in those describing more fatigue at baseline. NR[4]: Forty-five percent of the patients with RA cited fatigue as a persistent **threat** to employment and they had made a number of adaptations in order to continue working. NR[60]: Pain and fatigue **affect** patients' ability to attend work and to perform paid and unpaid work and household activities.

2. Social activities and household chores	1 NR	NR[4]: Fatigue **commonly affected** social activities and household chores.
3. Role limitations	1 NR	NR[19]: Fatigue was found to **account** for role limitations, for physical and social functioning problems, mental health symptoms, and the general perception of health worsening.
4. Daily self-care and socially relevant tasks	1 NR	NR[19]: Fatigue has a **significant negative impact** on patients' ability to perform daily self-care and socially relevant tasks and to the detriment of physical and mental or emotional well-being and personal satisfaction.
ICF-model contextual perspective: Personal factors		
1. Stress	1 SR and 2 NRs	NR[19]: Fatigue **results** in higher experienced levels of interpersonal stress, including with friends and family members. SR[40]: Increased fatigue was **associated** with increased levels of stress/hassles. Strength of association was not reported. NR[62]: Fatigue did **not systematically vary** for stressful and non-stressful events. Patients have reported moderate distress from fatigue.
2. Parenting and family size	1 SR and 1 NR	SR[41]: Fatigue was **related** to greater frequency and intensity of daily hassles while parenting as well as having less energy to monitor a child's whereabouts. Fatigue was **not significantly associated** with laxness and/or over-reactivity in mothers with RA. Strength of associations was not reported. NR[59]: Concerns about fatigue **affected** in 20% of the women the decision to have fewer children than they had initially hoped for and these women had concerns about being able to care for a child (including concerns about fatigue).
3. Physical and mental or emotional well-being	1 NR	NR[19]: Fatigue has a **significant negative impact** to the detriment of physical and mental or emotional well-being and personal satisfaction. As a consequence of fatigue, patients experience **higher levels** of interpersonal stress, including with friends and family members. Fatigue was found to **account** for role limitations, physical and social functioning problems, mental health symptoms, and the general perception of health worsening.
4. Coping	1 NR	NR[62]: Increased fatigue was **associated** with increased worrying coping, retreating coping, resting coping, and fatigue transformation coping, reducing demands. Strength of associations was not reported.
ICF-model contextual perspective: Environmental factors		
1. Social support	1 SR	SR[40]: Increased fatigue was **associated** with reduced perceived quantity of social support and increased problematic social support. Strength of associations was not reported.
2. Partner relationships	1 NR	NR[61]: Fatigue **affects** partner relationships.
3. Relational and	1 SR and	SR[39]: Several relational and socioeconomic variables were **related** to more fatigue in RA, including more visits to rheumatologist,

socioeconomic variables	1 NR	the need for help from others, lower income, higher gross domestic product and better human development index of countries. NR[49]: Fatigue is **associated** with greater healthcare utilization. Strength of association was not reported.

ICF-model: International Classification of Functioning, Disability and Health model, SR: Systematic review, NR: Narrative review

Supplementary file 12 Summary results consequences of fatigue in SpA

Consequences of fatigue	Review type	Reported effect of fatigue on other aspects Strength and direction of associations were reported whenever available. Minor textual adaptations were made for consistency or clarity reasons
ICF-model functioning perspective: Body function and structure		
1. Disease severity	1 NR	NR[5]: A **strong association** between fatigue and the severity of the disease by patients was found.
2. Quality of life	1 NR	NR[5]: A **strong association** between fatigue and reduced quality of life associated with illness was found.
3. Depression	2 NRs	NR[5]: The severity of fatigue was **associated** with depression. Strength of association was not reported. NR[51]: An **association** between fatigue and depression severity was found and sleep and fatigue were indirectly **associated** with risk of depression in patients with PsA. Strength of associations was not reported.
ICF-model functioning perspective: Activities		
1. Physical activity	1 SR and 1 NR	SR[63]: Fatigue is **identified** as a barrier to engaging in physical activity. NR[64]: Fatigue **may lead** to reduced activity and poor physical fitness.
ICF-model functioning perspective: Participation		
1. Work performance	2 NRs	NR[5]: The **association** between work productivity loss and fatigue persisted after controlling for cutaneous/musculoskeletal activity. Strength of association was not reported. NR[64]: The combination of pain, fatigue, and anxiety experienced by patients with PsA **can contribute** to work absenteeism and increased disability can result in lost productivity and unemployment.

ICF-model: International Classification of Functioning, Disability and Health model, SR: Systematic review, NR: Narrative review

Supplementary file 13 Summary results consequences of fatigue in OA

Consequences of fatigue	Review type	Reported effect of fatigue on other aspects Strength and direction of associations were reported whenever available. Minor textual adaptations were made for consistency or clarity reasons
ICF-model functioning perspective: Body function and structure		
1. Pain	1 NR	NR[53]: More fatigue is **related** to increased pain and patients who were more fatigued report much higher levels of pain.
2. Health status	1 NR	NR[4]: Fatigue is a **strong predictor** of overall health status.
3. Sleep (disturbances)	1 NR	NR[4]: Some individuals **link** fatigue to difficulties falling asleep or staying asleep.
4. Depression	1 NR	NR[53]: Patients who were more fatigued **reported more** depression.
ICF-model functioning perspective: Activities		
1. Physical activity	3 NRs	NR[4]: Fatigue is **described as** debilitating and occasionally restricting activity. NR[7]: Fatigued adults with OA have **difficulty** with physical activity and function like walking, exercising, and performing chores, and need to take more time, require more rest, and were easily exhausted as compared to adults with RA or when symptoms of fatigue were not present. Fatigue is a **barrier** to participate in physical activity and may explain why those with OA have lower average and peak physical activity over time. NR[53]: Fatigue was **strongly correlated** with lower physical activity level.
2. Physical disability	1 NR	NR[53]: Patients who were more fatigued **reported more** physical disability and more fatigue is **related** to increased pain-related physical and psychological disability.
3. Functional impairment	1 NR	NR[7]: Increased fatigue results in an **increase** in functional impairment and when fatigue is improved there is a **decrease** in functional impairment.
ICF-model functioning perspective: Participation		
1. Work performance	1 NR	NR[4]: Fatigue is a **strong predictor** of work dysfunction in OA.
2. Social activities and household chores	2 NRs	NR[4]: Social activities and household chores were **commonly affected** by fatigue among people with OA. NR[7]: Adults with fatigue **report** having to give up volunteer and social activities, which are essential for maintaining joint function and life engagement for successful aging.

ICF-model: International Classification of Functioning, Disability and Health model, SR: Systematic review, NR: Narrative review

Supplementary file 14 Effectiveness of non-pharmacological interventions on fatigue in RA

Non-pharmacological interventions for RA	Review type	Reported effect of intervention on fatigue	Reported quality of evidence
Physical exercise interventions			
▪ Physical exercise versus usual care (Pool based therapy, yoga, dynamic strength training, stationary cycling, low impact aerobics and Tai Chi)	1 CR[65]	Overall, the interventions had a statistically significant **small effect** on fatigue compared to the control group.	Moderate
▪ Physical exercise versus usual care	1 NR[67]	The intervention resulted in **significant improvements** in fatigue at the end of the intervention in 3 of 4 studies compared to a control arm. The results of the intervention remained **significant** in one study at long-term follow-up.	Not reported
▪ Physical exercise: 'Pedometer' and 'Pedometer plus step count'	1 NR[67]	The intervention had **no effect** on fatigue.	Not reported
▪ Aerobic exercises versus controls (usual care, range of motion exercises or receiving verbal advice about exercise benefits and lifestyle changes)	1 NR[68]	The intervention resulted in **larger improvements** in fatigue scores compared to controls. Sensitivity analyses using studies with a low risk of bias showed **no effect** on fatigue compared to controls.	Not reported
▪ Resistance exercise interventions versus usual cares usual care	1 NR[68]	The intervention **improved** fatigue to a greater extent compared to control.	Not reported
▪ Interventions combining both aerobic and resistance-based exercises versus usual care	1 NR[68]	The intervention resulted in **significant greater reductions** in fatigue compared to control.	Not reported
▪ Tai chi versus education about RA	1 NR[68]	The intervention **improved** fatigue compared to control.	Not reported
Psycho-therapeutic or educational interventions			
Psychosocial interventions			
▪ Psychosocial interventions versus usual care (including benefit finding, expressive writing, cognitive behavioural therapy, mindfulness, lifestyle management, energy conservation, self-management and group education)	1 CR[65]	The intervention had a **statistically significantly small effect** compared to control.	Low
▪ Internet-based cognitive behavioural intervention versus usual care	1 NR[67]	The intervention resulted in a **significant reduction** in fatigue compared to controls.	Not reported

▪ Group course using cognitive behavioural approaches 'Reducing Arthritis Fatigue' intervention versus usual care plus a fatigue self-management booklet	1 NR[67]	The intervention resulted in a **non-significant reduction** in fatigue compared to controls.	Not reported
Complementary interventions and alternative medicine			
Herbal medicine			
▪ Andrographis paniculata versus placebo	1 CR[65]	The intervention had **no effect** on fatigue compared to controls.	Low
Reflexology			
▪ Reflexology versus a non-specific foot massage	1 CR[65]	The intervention resulted in a **greater mean reduction** in fatigue compared to the controls.	Low
▪ Reflexology and aromatherapy versus usual care	1 NR[67]	The interventions resulted in **a significant reduction** in fatigue over time compared to controls. The reflexology intervention resulted in a **greater reduction** in fatigue than the aromatherapy intervention.	Not reported
Lifestyle interventions			
Diet interventions			
▪ Mediterranean diet versus Western diet	1 CR[65]	The intervention resulted in a **statistically significant improvement** on fatigue, whereas no statistically significant change was shown in the controls; between arm comparisons were not reported.	Low
▪ Omega-3 fatty acid supplementation	1 CR[65]	The intervention resulted in **statistically significant improvements** in fatigue between baseline and follow-up.	Low
Providing health information			
▪ Data tracker versus usual care	1 CR[65]	The intervention resulted in **small improvements** in fatigue between baseline and follow-up.	Low
Other			
Nurse-led care			
▪ Nurse-led care versus no nurse-led care, junior hospital doctor's clinic or rheumatologist-led care	1 SR[66]	The intervention significantly **reduced fatigue** in four studies, whilst no statistically significant difference was noted in two other studies.	Not reported

CR: Cochrane review, SR: Systematic review, NR: Narrative review

Supplementary file 15 Effectiveness of non-pharmacological interventions on fatigue in SpA

Non-pharmacological interventions for SpA	Review	Reported effect of intervention on fatigue	Reported

	type		quality of evidence
Physical exercise interventions			
▪ Exercise programs versus no intervention	1 CR[69]	The intervention had **no effect** on fatigue compared to controls at the end of treatment, but **a reduction** in fatigue was found in one study.	Very low
▪ High intensity interval training (HIIT) on a cycloergometer) versus control	1 SR[70]	PsA: The intervention resulted in a **reduction** in in the score of fatigue from 43.5 to 27.9 out of 100 (− 15.8 ± 9.8 vs − 3.03 ± 9.79, p = 0.05) after 3 months of physical activity but **not** after 6 and 9 months.	Not reported
▪ Strength exercise versus control	1 SR[70]	PsA: The intervention **did not result** in differences in fatigue between groups.	Not reported
▪ Rehabilitation programs, including therapeutic education + supervised exercise, therapeutic education + stretch exercises or therapeutic education alone	1 SR[70]	PsA and SpA: The intervention **reduced** fatigue in 2 studies, but **not** in 2 other studies. Positive effects in fatigue appear to **decrease** over time.	Not reported
▪ Physical exercise (e.g. walking, jogging or swimming)	1 NR[31]	The intervention had **conflicting effects** on fatigue as it reduced fatigue in 34% of patients and increased fatigue in 37% of patients. However, 55% of all patients found that exercises specific for ankylosing spondylitis **reduced** their fatigue.	Not reported
▪ Physical exercise combined with spa therapy	1 NR[71]	The intervention **may help** to alleviate fatigue.	Not reported
▪ Weekly leisure activity consisting of aerobic physical exercise	1 NR[31]	The intervention **seems to reduce** fatigue.	Not reported
Psycho-therapeutic or educational interventions			
Cognitive behaviour therapy			
▪ Cognitive behavioural therapy	1 NR[71]	The intervention **may reduce** fatigue.	Not reported
Other			
▪ Changes in work environment	1 NR[71]	The intervention **may help** to alleviate fatigue.	Not reported

CR: Cochrane review, SR: systematic review, NR: Narrative review

Supplementary file 16 Effectiveness of non-pharmacological interventions on fatigue in OA

Non-pharmacological interventions for OA	Review type	Population	Reported effect of intervention on fatigue	Reported quality of evidence
Physical exercise interventions				
▪ (Supervised) physical therapy versus controls not receiving physical therapy	1 SR[73]	Knee OA	The intervention resulted in **greater improvements** in fatigue and significant between-group differences compared to the control at 20-weeks follow-up, but not at week 10 nor week 32 follow-up.	Not reported
▪ Aquatic dance-based exercise versus traditional aquatic exercise (both groups: supervised by a physical therapist)	1 SR[73]	Knee OA	The intervention **improved** fatigue more compared to the control.	Not reported
▪ Physical exercise	1 NR[7]	OA in general	A variety of physical exercises **significantly decreased** fatigue in the short and long term. Light exercises were effective in reducing fatigue immediately post-intervention but had **no long-term effects** on fatigue. Conversely, moderate aerobic exercise such as a dance aquatic program or resistance training resulted in **sustained reductions** in fatigue for three months. These outcomes support the notion that physical exercise is **negatively associated** with fatigue in some fashion. More explicitly, only aerobic or resistance exercises were associated with improving fatigue over the long term when compared to more gentle exercise (e.g., yoga, Tai Chi) or no exercise.	Not reported
Psycho-therapeutic and educational interventions				
▪ Psychological interventions versus no intervention, including: • Pain coping skills training versus usual care • Cognitive-behavioral training versus GP care • Cognitive-behavioral therapy for pain involved pain education compared to education only	1 SR[72]	Hip and/or knee OA	The interventions had **significant effect** compared to the control.	Not reported

SR: Systematic review, NR: Narrative review, OA: osteoarthritis

Supplementary file 17 Effectiveness of non-pharmacological interventions on fatigue in FM

Non-pharmacological interventions for FM	Review type	Reported effect of intervention on fatigue	Reported quality of evidence
Physical exercise interventions			
Resistance exercise therapy			
▪ Resistance training versus usual care	1 CR[79]	The intervention had **large effects** on fatigue compared to the control.	Not reported
▪ Resistance training versus aerobic training	1 CR[79]	The intervention had **no effect** on fatigue compared to the control.	Not reported
▪ Resistance training versus flexibility exercise	1 CR[79]	The intervention had **large effects** on fatigue compared to the control.	Not reported
Whole body vibration therapy (WBV)			
▪ WBV therapy plus mixed exercise versus placebo plus mixed exercise	1 CR[76]	The intervention resulted in a **reduction** in fatigue that met the threshold for **clinical relevance** compared to the control.	Very low
▪ WBV therapy plus mixed exercise versus other exercise	1 CR[76]	The intervention resulted in a **reduction** in fatigue that **did not** meet the threshold for **clinical relevance** compared to the control.	Very low
Meditative movement therapies therapy (MMT) (e.g. Ai Chi, Tai Chi, Yoga awareness, Bat, Qi-Gong, Water yoga)			
▪ MMT versus usual care	1 CR[81]	The intervention resulted in **an advantage** on fatigue compared to the control.	Very low
▪ MMT versus controls (another active therapy (stretching, education, physiotherapy and moderate aerobic exercise), delayed treatment control or treatment as usual)	1 SR[84]	The intervention had a **moderate effect** on fatigue compared to the control at the end of the intervention (5 studies; range 6-12 weeks) and no effect at long-term follow-up (2 studies; 3 and 6 months). Sub-analyses excluding 2 studies with MMT in warm water showed a **moderate effect** for fatigue at follow up.	Not reported
▪ Qigong versus waitlist/usual care	1 SR[86]	The intervention had a **moderate short-term effect** on fatigue compared to the control.	Very low
▪ Qigong versus sham qigong or exercise	1 SR[86]	The intervention had **no effect** on fatigue compared to the control.	Very low
Mixed exercise training (two or more components of physical exercise)			
▪ Mixed exercise training versus no exercise	1 CR[75]	The intervention **improved** fatigue more compared to controls post intervention, but at long-term follow-up only 1 out of 3 studies showed an effect on improving fatigue.	Moderate

▪ Mixed exercise versus self-help programs	1 CR[75]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Mixed exercise versus cognitive-behavioral therapy	1 CR[75]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Mixed exercise plus education versus education alone	1 CR[75]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Mixed exercise versus biofeedback	1 CR[75]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Mixed exercise versus medication	1 CR[75]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Mixed exercise versus aerobic exercise only	1 CR[75]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Mixed exercise (aerobic + flexibility) versus mixed exercise (resistance + aerobic + flexibility)	1 CR[75]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Mixed exercise (calisthenics + aerobic + flexibility) versus mixed exercise (resistance + flexibility + posture exercise)	1 CR[75]	The intervention had **no effect** on fatigue compared to the control.	Very low
Aerobics exercise (e.g. cycling, walking, regardless of frequency, duration, or intensity)			
▪ Aerobics versus controls (treatment as usual, wait list control, daily activities)	1 CR[74]	The intervention had **no effect** on fatigue compared to the control at the end of the intervention and had **no effect** on fatigue (1 study) and a significant effect (2 studies) at long-term follow-up.	Very low
▪ Aerobics (Nordic walking) versus aerobics (low-intensity aerobic training)	1 CR[74]	The intervention had **no effect** on fatigue compared to the control.	Low
▪ Aerobics versus other non-exercise interventions	1 CR[74]	The intervention had **no effect** on fatigue compared to the control.	Low
▪ Aerobic prescribed at American College of Sport Medicine (ACSM) levels	1 CR[78]	The intervention had **no effect** on fatigue.	Very low
Aquatic exercise therapy			
▪ Aquatic exercise versus controls (treatment as usual, balneotherapy or education)	1 CR[77]	The intervention had **no effect** on fatigue compared to the control.	Not reported
▪ Aquatic exercise versus land-based training	1 CR[77]	The intervention had **no effect** on fatigue compared to the control.	Not reported

▪ Aquatic exercise (tai chi) versus aquatic exercise (stretching)	1 CR[77]	The intervention had **no effect** on fatigue compared to the control.	Not reported
▪ Aquatic exercise in outdoor pool versus aquatic exercise in sea water (effects of salinity of water)	1 CR[77]	The intervention had **no effect** on fatigue compared to the control.	Not reported
Flexibility exercise therapy			
▪ Flexibility exercise versus land-based aerobic exercise	1 CR[80]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Flexibility exercise versus untreated controls	1 CR[80]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Flexibility exercise versus resistance training	1 CR[80]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Flexibility exercise versus tai chi	1 CR[80]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Flexibility exercise versus aquatic biodanza	1 CR[80]	The intervention had **no effect** on fatigue compared to the control.	Very low
All types of physical exercises			
▪ All types of physical exercise grouped ▪ (E.g. aerobic exercise, flexibility exercise, land-based exercise, resistance exercise; tai chi, water-based exercise and yoga)	1 SR[87]	Overall, the interventions were **effective in reducing** fatigue compared to the control.	Low-moderate
Psycho-therapeutic or educational interventions			
Mind and body therapy			
▪ Psychological therapies versus attention care	1 CR[81]	The intervention had **no effect** on fatigue compared to the control at the end of the intervention, nor at follow-up.	Very low
▪ Psychological therapies versus usual care	1 CR[81]	The intervention had **no effect** on fatigue compared to the control at the end of the intervention, nor at follow-up.	Very low
▪ Relaxation-based therapies versus usual care	1 CR[81]	The intervention had **no effect** on fatigue compared to the control.	Very low
▪ Mind-body techniques: biofeedback	1 SR[88]	The intervention **did not reduce** fatigue on short term or long-term in comparison to control groups.	Not reported

Mindfulness			
▪ Mindfulness based stress reduction (MBSR) versus waitlist/usual care	1 SR[85]	The intervention resulted in a **significant group difference** for fatigue compared to the control.	Not reported
Cognitive behaviour therapy (CBT)			
▪ CBTs versus controls (waiting list, treatment as usual, attention controls and active non pharmacological therapies) at the end of treatment	1 SR[90]	The intervention had a **small effect** on fatigue compared to the control.	High
▪ CBTs versus controls (waiting list, treatment as usual, attention controls and active non pharmacological therapies) at long-term follow-up	1 SR[90]	The intervention had a **small effect** on fatigue compared to the control.	High
▪ Behavioral strategies that focus on sleep	1 NR[98]	The intervention resulted in **less** fatigue.	Not reported
Educational interventions			
▪ Education as treatment	1 SR[91]	The intervention had a **small effect** on fatigue compared to the control.	Not reported
▪ Combination therapy of exercise and education	1 SR[91]	The intervention had a **small effect** on fatigue compared to the control.	Not reported
Guided imagery			
▪ Guided imagery versus usual care group	1 SR[92]	The intervention resulted in **significantly less** fatigue compared to the control.	Not reported
▪ Written emotional disclosure versus neutral writing condition or usual care	1 SR[92]	The intervention **reduced** fatigue compared to the control at the end of the treatment, but **not** at long-term follow-up.	Not reported
Hypnosis			
▪ Hypnosis versus controls receiving physical therapy	1 SR[89]	The intervention was **superior** in reducing fatigue compared to the control.	Not reported
Complementary interventions and alternative medicine			
Acupuncture			
▪ Real acupuncture versus non-acupuncture treatment	1 CR[82]	The intervention resulted in **significant group difference** for fatigue compared to the control.	Low
▪ Real acupuncture versus placebo or sham	1 CR[82]	The intervention had **no effect** on fatigue compared to the control.	Moderate

acupuncture			
▪ Deep invasive needling with stimulation versus deep invasive needling without stimulation	1 CR[82]	The intervention had **no effect** on fatigue compared to the control.	Not reported
▪ Verum acupuncture versus sham acupuncture	1 SR[93]	The intervention was **not superior** for fatigue compared to the control.	Low
Homeopathy			
▪ Homeopathy versus placebo	1 SR[94]	The intervention had **an effect** on fatigue compared to the control.	Not reported
Electrical nerve stimulation interventions			
Transcutaneous electrical nerve stimulation (TENS)			
▪ TENS versus placebo TENS	1 CR[83]	The intervention **reduced** fatigue with movement, but **not** fatigue at rest compared to the control.	Very low
▪ TENS versus no treatment or waiting list control	1 CR[83]	The intervention **reduced** fatigue with movement, but **not** fatigue at rest compared to the control.	Very low
▪ TENS added to exercise versus exercise alone (usual care)	1 CR[83]	The intervention resulted in **clinically important improvements** in fatigue compared to the control.	Very low
▪ TENS versus other treatment	1 CR[83]	The intervention resulted in **clinically important improvements** in fatigue compared to the control.	Very low
Electronic stimulation			
▪ Electronic stimulation with or without other types of therapy versus control group (Education and exercise, superficial warmth stimulation or S-adenosyl-L-methionine supplements)	1 SR[95]	The intervention had **no effect** on fatigue compared to both control groups.	Moderate
Non-invasive brain stimulation			
▪ Non-invasive brain stimulation versus sham stimulation	1 SR[97]	The intervention resulted in **favourable effects** on fatigue compared to the control.	Not reported
Non-invasive cortical electrostimulation			
▪ Non-invasive cortical electrostimulation	1 NR[10]	The intervention had a **clinically meaningful improvement** on fatigue compared	Not reported

versus placebo		to the control.	
Repetitive transcranial magnetic stimulation			
▪ Repetitive transcranial magnetic stimulation	1 SR[91]	The intervention resulted in a **large effect** on fatigue.	Not reported
Pulsed ultrasound and interferential current therapy			
▪ Pulsed ultrasound and interferential current therapy versus placebo	1 NR[10]	The intervention had a **clinically meaningful improvement** on fatigue compared to the control.	Not reported
Sensory motor rhythm treatment			
▪ Sensory motor rhythm treatment	1 NR[10]	The intervention had a **clinically meaningful improvement** on fatigue.	Not reported
Neuro-therapy			
▪ Neuro-therapy	1 SR[91]	The intervention had **no effect** on fatigue.	Not reported
Lifestyle interventions			
Diet instructions			
▪ Vegetarian diet	1 NR[10]	The intervention had a **clinically meaningful improvement** on fatigue.	Not reported
Sleep hygiene			
▪ Instructions for sleep hygiene	1 NR[9]	The intervention contributed to **improvements** in fatigue.	Not reported
Other			
Massage			
▪ Myofascial release massage versus placebo	1 SR[96]	The intervention resulted in **statistically significant reductions** in fatigue compared to the control.	Moderate
▪ Connective tissue massage versus manual lymphatic drainage	1 SR[96]	The intervention had an **inferior effect** on fatigue compared to the control.	Very low
▪ Shiatsu massage versus educational guidance	1 SR[96]	The intervention resulted in **statistically significant improvements** in fatigue compared to the control.	Very low
Ultra-violet/bright light treatments			
▪ Ultraviolet/bright light treatments	1 SR[91]	The intervention had a **small effect** on fatigue.	Not reported
Low energy laser therapy			
▪ Low energy laser therapy versus placebo	1 NR[10]	The intervention resulted in **clinically meaningful improvements** in fatigue compared to the control.	Not reported

Pulsed ultrasound and interferential current			
▪ Pulsed ultrasound and interferential current versus placebo	1 NR[10]	The intervention had a **clinically meaningful improvement** on fatigue compared to the control.	Not reported
Spa therapy			
▪ Dead Sea balneo-therapy	1 NR[99]	The intervention resulted in a **relief** in the severity of FM symptoms including fatigue.	Not reported

CR: Cochrane review, SR: Systematic review, NR: Narrative review

Supplementary file 18 Effectiveness of pharmacological interventions on fatigue in RA

Pharmacological interventions for RA	Review type	Reported effect of intervention on fatigue *Effect is always favouring fatigue	Reported quality of evidence
Biological DMARDs (bDMARDs)			
▪ bDMARDs versus placebo or usual care (Adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, canakinumab*, rituximab, tocilizumab and an anti-interferon gamma monoclonal antibody*)	1 CR[100]	Treatment with bDMARDs in patients with active RA and moderate to high levels of fatigue might lead to a **small to moderate improvement** in fatigue compared to the controls.	Moderate
▪ bDMARDs versus placebo or usual care (Abatacept, canakinumab*, rituximab, tocilizumab and an anti-interferon gamma monoclonal antibody*)	1 CR[100]	Biologic DMARDs have a **moderate effect** on fatigue compared to the controls.	Moderate
▪ bDMARDs versus placebo or placebo plus a DMARD (Rituximab, abatacept or tocilizumab)	1 SR[103]	The overall effect of non-anti-TNF bDMARDs on fatigue was **moderate** compared to the controls.	Not reported
TNF inhibitors (TNFi)			
▪ **TNFi grouped:** TNFi versus placebo or usual care (Adalimumab, certolizumab, etanercept, golimumab, infliximab)	1 CR[100]	TNF inhibitors have a **moderate effect** on fatigue compared the controls.	Moderate
▪ **TNFi grouped:** TNFi versus placebo or placebo plus a DMARD (Adalimumab, golimumab or certolizumab)	1 SR[103]	The overall effect of TNF inhibitors on fatigue was **small** compared to the controls.	Not reported
▪ Adalimumab versus placebo	1 NR[104]	Three trials showed that adalimumab had a **significantly greater and clinically meaningful improvements** in fatigue compared to the control.	Not reported
▪ Certolizumab versus placebo	1 NR[110]	**Significant and clinically meaningful reductions** in fatigue were reported by patients receiving certolizumab monotherapy compared to the control. These meaningful reductions in fatigue were reported by 46% of certolizumab patients compared to 17% of placebo patients	Not reported
▪ Certolizumab plus methotrexate versus placebo	1 NR[110]	**Statistically significant reductions** in fatigue were reported in patients	Not reported

		receiving certolizumab plus methotrexate compared to the control.
▪ Etanercept plus methotrexate versus methotrexate	1 NR[105]	Etanercept plus methotrexate **improved** fatigue in the first 2 weeks, whereas patients on methotrexate took approximately 10 weeks to achieve this improvement.	Not reported
Immunomodulators			
▪ Abatacept versus placebo	1 NR[111]	Abatacept demonstrated **clinically and statistically significant improvements** in fatigue compared to the controls.	Not reported
Monoclonal anti-CD20 antibodies			
▪ Rituximab versus placebo	1 NR[106]	Rituximab recipients reported **greater improvements** in fatigue compared to the controls.	Not reported
IL-6 inhibitors			
▪ Tocilizumab versus placebo	1 SR[101] and 1 NR[47]	SR[101]: Patients' feelings of fatigue **improved substantially** more than the MCID when treated with tocilizumab, when compared to the controls. NRs[47]: Tocilizumab **improves** signs and symptoms of active RA in RCTs including fatigue. In an observational study, tocilizumab **significantly decreased** fatigue.	Not reported
▪ Sarilumab	1 NR[47]	Sarilumab has shown **improvement** in PROs, with an effect size that was **clinically relevant** for fatigue.	Not reported
▪ Sarilumab versus placebo plus methotrexate or sarilumab versus adalimumab	1 NR[107]	Sarilumab **significantly improved** fatigue compared to the placebo group and both the sarilumab group and adalimumab group showed similar improvements in fatigue.	Not reported
▪ Sarilumab versus other bDMARDs versus tocilizumab	1 NR[108]	Sarilumab had a **moderate effect** on fatigue which was similar to that of other bDMARDs, including tocilizumab.	Not reported
IL-1 inhibitors			
▪ Anakinra	1 NR[109]	Anakinra has been shown to **significantly improve** fatigue in patients with RA.	Not reported
Effect of a second bDMARD in patients with inadequate response to a prior bDMARD			
▪ bDMARDs versus placebo plus methotrexate (Abatacept, golimumab or rituximab)	1 SR[103]	The overall effect of bDMARDs on fatigue was **moderately positive** compared to the controls.	Not reported
▪ Rituximab	1 NR[47]	Half of the patients treated with rituximab started after failure on one or	Not reported

		more TNF inhibitors, had **improvement** in fatigue.	
Targeted synthetic DMARDs (tsDMARDs)			
Janus kinase (JAK) inhibitors			
▪ JAK inhibitors versus adalimumab	1 NR[47]	JAK inhibitors have demonstrated **clinically relevant improvements** in fatigue in patients with active RA in methotrexate naive, methotrexate inadequate responders and bDMARD inadequate responders. JAK inhibitors were more effective in treating pain in active RA than TNF inhibitors (or at least adalimumab), and this may correspond to improved fatigue.	Not reported
▪ Baricitinib versus placebo	1 NR[47]	Treatment with baricitinib in active RA patients who were inadequate responders to methotrexate **improved** fatigue more than the control.	Not reported
▪ Tofacitinib versus placebo or methotrexate	1 NR[108]	Tofacitinib **statistically significantly reduced** fatigue compared to placebo and improvement in fatigue was statistically significantly superior to methotrexate.	Not reported
Cannabinoids			
▪ Nabilone versus placebo	1 SR[102]	**No superiority** of nabilone over placebo in reducing fatigue was found and fatigue was experienced more often as an adverse effect in the treatment arm compared to the control.	Not reported

*These drugs are not prescribed in patients with RA.
CR: Cochrane review, SR: Systematic review, NR: Narrative review, DMARD: disease-modifying anti-rheumatic drugs, tsDMARDs: targeted synthetic DMARDs, bDMARDs: biologic DMARDs, TNF: Tumour Necrosis Factor, JAK: Janus kinase, IL: Interleukin, MCID: Minimal Clinical Important Difference

Supplementary file 19 Effectiveness of pharmacological interventions on fatigue in SpA

Pharmacological interventions	Review type	Population	Reported effect of intervention on fatigue *Effect is always favouring fatigue	Reported quality of evidence
Non-Steroidal Anti-Inflammatory Drug (NSAIDs)				
▪ NSAIDs	1 NR[31]	AxSpA	Patients with AS and fatigue felt that NSAIDs **reduced** their fatigue. NSAIDs were found to be less effective for fatigue than for pain and functional impairment.	Not reported
Conventional synthetic DMARDs (csDMARDs)				
▪ Methotrexate	1 NR[64]	PsA	Methotrexate **improved** fatigue.	Not reported
Biological DMARDs (bDMARDs)				
TNF inhibitors				
▪ Golimumab or etanercept versus placebo	1 SR[112]	AxSpA	Golimumab versus placebo and etanercept versus placebo both resulted in an overall **statistically significant reduction** in fatigue.	Not reported
▪ Etanercept or Infliximab	1 NR[31]	AxSpA	Three-month use of etanercept or infliximab **reduced** the level of fatigue by more than 55%. Infliximab demonstrated an **improvement** in fatigue level by more than 50% after one year.	Not reported
IL17 inhibitors				
▪ Secukinumab	1 SR[113] and 1 NR[116]	AxSpA	SR[113]: Treatment with secukinumab provided **rapid and durable improvement** in fatigue and improvements in fatigue were observed regardless of prior anti-TNF exposure. NR[116]: Fatigue can **effectively** be ameliorated with secukinumab.	Not reported
Targeted synthetic DMARDs (tsDMARDs)				
Janus kinase (JAK) inhibitors				
▪ Tofacitinib versus placebo	1 NR[114]	PsA	Tofacitinib **did not result** in different fatigue levels compared to placebo among TNFi-naïve patients. These results appeared to be maintained over 12 months, although this was not significantly tested.	Not reported
PDE4 inhibitors				
▪ Apremilast	1 NR[115]	PsA	Apremilast **improved** fatigue and the threshold for minimal clinical important difference was achieved in 51% of the patients. Apremilast **improved** fatigue in both bDMARD-naive and bDMARD-experienced patients with active PsA.	Not reported

SR: Systematic review, NR: Narrative review, axSpA: axial spondyloarthritis, PsA: psoriatic arthritis; NSAID: Non-Steroidal Anti-Inflammatory Drug, IL: Interleukin, JAK: Janus kinase

Supplementary file 20 Effectiveness of pharmacological interventions on fatigue in FM

Pharmacological interventions for FM	Review type	Reported effect of intervention on fatigue *Effect is always favouring fatigue	Reported quality of evidence
Anti-depressants			
▪ **All anti-depressants:** TCA, SSRIs, SNRIs, MAOIs versus placebo	1 SR[123]	There was strong evidence for a **negligible reduction** in fatigue compared with controls.	High
Anti-depressant class SNRIs			
▪ **SNRIs grouped:** Duloxetine, milnacipran or desvenlafaxine versus placebo	1 CR[118]	The overall effect of SNRIs on fatigue of was **not substantial** versus the control.	Low
▪ Milnacipran	1 SR[126]	The effect of milnacipran on fatigue was **not substantial**, but statistically significant.	Not reported
▪ Duloxetine	1 SR[126]	The effect of duloxetine on fatigue was **not statistically significant.**	Not reported
Anti-depressant class SSRIs			
▪ **SSRIs grouped:** Citalopram, paroxetine and fluoxetine	2 SRs[125, 127]	SR[125]: The effect sizes of SSRIs on fatigue was **not substantial**. SR[127]: A **reduction** of fatigue was found in 5 (50%) of 10 studies using SSRIs.	Not reported
▪ **SSRIs grouped:** Fluoxetine and paroxetine	1 SR[123]	There was **no effect** of fluoxetine and paroxetine on reducing fatigue.	Not reported
▪ Citalopram versus placebo	1 CR[121]	Citalopram was **not statistically significant superior** for reducing fatigue compared to the control.	Very low
▪ Fluoxetine versus melatonin	1 CR[121]	Fluoxetine was **not statistically significant superior** in reducing fatigue compared to control.	Very low
Anti-depressant class TCAs			
▪ **TCAs grouped:** Amitriptyline, dothiepin, nortriptyline	1 SR[125]	The effect size of TCAs on reducing fatigue was **small**.	Not reported
▪ **TCAs grouped:** Amitriptyline and nortriptyline	1 SR[127]	A **reduction of fatigue** was found in 8 (80%) of 10 studies using TCAs.	Not reported
▪ Amitriptyline versus placebo	3 SRs[123, 124, 128]	SR[123]: There was strong evidence for a **large effect** of amitriptyline in reducing fatigue. SR[124]: Amitriptyline had a significant **small effect** on fatigue. SR[128]: Overall, **improvements** in fatigue were reported in 3 out of 6 studies comparing amitriptyline with placebo. Amitriptyline 25 mg showed a **significant improvement** in	Not reported

		fatigue in 3 out of 5 studies. Amitriptyline 25mg was consistently reported to be **more effective** compared to amitriptyline 50 mg for clinical effects, including fatigue.	
▪ Mirtazapine versus placebo	1 CR[117]	Mirtazapine **did not show** a statistically significant benefit compared to placebo in reduction of fatigue.	Low
▪ Cyclobenzaprine ***** Cyclobenzaprine is a muscle relaxant, structurally related to TCAs	1 SR[129]	The cyclobenzaprine group showed **no improvement** in fatigue at any time point.	Not reported
Anti-depressant class MAOIs			
▪ Moclobemide	1 SR[123]	There was **no evidence** of efficacy for moclobemide on fatigue.	Not reported
Anticonvulsants			
▪ Pregabalin	1 SR[126]	The effect of pregabalin on fatigue was statistically significant, but **not substantial**.	Not reported
Antipsychotics			
▪ Quetiapine versus placebo	1 CR[120]	Participants on quetiapine had a **significant improvement** on fatigue compared to placebo.	Very low
▪ Quetiapine versus amitriptyline	1 CR[120]	There was **no statistically significant difference** in fatigue when using quetiapine versus amitriptyline.	Low
Other			
▪ **Cannabinoids:** Nabilone versus placebo or amitriptyline	1 CR[119]	Nabilone did **not convincingly relieve** FM symptoms including fatigue compared to the controls.	Very low
▪ **Dopaminergic agonist:** Pramipexole	1 NR[131]	Pramipexole **improved** fatigue.	Not reported
▪ **5-HT3 Antagonist:** Tropisetron	1 NR[8]	Tropisetron **significantly improved** fatigue.	Not reported
▪ **Central stimulant:** Modafinil	1 NR[132]	Modafinil showed that on average, two-thirds of patients experienced a 50% **reduction** in fatigue levels. One-third reported **no benefit** from modafinil.	Not reported
▪ **CNS depressant:** Sodium oxybate versus placebo	1 NR[133]	Sodium oxybate **significantly reduced** fatigue compared to the control.	Not reported
▪ **Hypnotics:** Zopiclone and zolpidem	1 NR[132]	Zopiclone and zolpidem **improved** fatigue.	Not reported
▪ **Opioid blocker**: Naltrexone versus placebo	1 NR[131]	Low dose naltrexone was **not superior** in reducing fatigue compared to the control.	Not reported
▪ **Androgen hormone:** Testosterone gel formulation	1 NR[131]	A transdermal testosterone gel formulation **significantly improved** clinical symptoms such as fatigue.	Not reported
▪ **Antiviral agent and COX-2 inhibitor combined:** IMC-1 (Famciclovir and Celecoxib)	1 NR[131]	Famciclovir and Celecoxib **significantly improved** fatigue.	Not reported
▪ **Topical agent:** Capsaicin	1 NR[131]	Capsaicin-treated patients showed a **significant improvement** in fatigue.	Not reported

Combinations of pharmacological interventions for fatigue			
▪ **TCA and SSRI:** Amitriptyline and fluoxetine alone and in combination versus placebo or monotherapy	1 CR[122]	Amitriptyline and fluoxetine alone and in combination had **no statistically significant effect** on fatigue or feeling refreshed upon awaking compared to placebo or monotherapy.	Very low
▪ **TCA:** Amitriptyline either alone or in combination with naproxen	1 CR[122]	Participants receiving amitriptyline either alone or in combination with naproxen exhibited **significantly larger improvements** in VAS scores of sleep difficulty, fatigue, and morning tiredness. There was **no statistically significant effect** of naproxen on any of these outcomes.	Very low
▪ **TCA:** Amitriptyline monotherapy versus combination therapy of amitriptyline and intravenous lidocaine.	1 CR[122]	Amitriptyline monotherapy versus combination therapy of amitriptyline and intravenous lidocaine **did not statistically significantly change** the number of participants experiencing fatigue.	Very low
▪ Anti-depressants combined with melatonin	1 CR[122]	Both low and high doses of melatonin with fluoxetine monotherapy **significantly improved** fatigue and high-dose melatonin monotherapy **did not improve** fatigue.	Very low
Comparative efficacy of pharmacological interventions for fatigue			
▪ **SNRIs:** Duloxetine versus milnacipran	1 CR[118]	There were **no significant differences** between the two drugs in fatigue.	Not reported for subgroup analyses
▪ **SNRIs versus anticonvulsants**: Duloxetine versus milnacipran versus pregabalin	1 NR[134]	**Improvement in fatigue was better** with milnacipran and pregabalin compared to duloxetine.	Not reported
▪ **TCAs versus SNRIs**: Amitriptyline versus duloxetine versus milnacipran	1 SR[124]	In adjusted indirect analyses, amitriptyline was **superior** to duloxetine and milnacipran in reducing fatigue. Milnacipran was **superior** to duloxetine in reducing fatigue.	Not reported
▪ **Different classes of anti-depressants**	1 SR[127]	**Significant improvements** were reported for fatigue in 13 (72%) of 18 studies who studied anti-depressants. There were **no differences** in the percentage of positive outcomes for fatigue between the different classes of antidepressants.	Not reported
Dietary supplements			
▪ S-Adenosylmethionine (SAMe)	1 NR[8]	S-Adenosylmethionine (SAMe) resulted in a **significant improvement** in fatigue.	Not reported
▪ Coenzyme Q10 supplementation (CoQ10) versus placebo	1 SR[130]	Coenzyme Q10 supplementation (CoQ10) resulted in a **significant reduction** of fatigue compared to control.	Not reported

CR: Cochrane review, SR: Systematic review, NR: Narrative review, FM: Fibromyalgia, MAOIs: Monoamine oxidase inhibitors, SNRIs: serotonin and noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants, RCT: Randomized controlled trial

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