Understanding the impact of fatigue management interventions on mental health outcomes among adults with inflammatory rheumatic disease.

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Chapter 1- Systematic Review

An updated review of non-pharmacological interventions for fatigue in rheumatoid arthritis

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Abstract

Objective: This review aimed to update the previous Cochrane (Cramp et al., 2013) review of the benefits and harm of non-pharmacological interventions on fatigue in rheumatoid arthritis. The review also evaluated the effects of non-pharmacological interventions on the outcomes of depression, pain, disability, anxiety, and disease activity in the same population.

Methods and Measures: Studies were included if they were randomised controlled trials that evaluated fatigue as an outcome following non-pharmacological intervention. Studies included only those aged 13 years and above with rheumatoid arthritis.

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, EMBASE, Specialized Register of the relevant Cochrane Review Groups, Web of Science and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched between 25.09.23 and 18.11.2023 for studies published since the period of the Cramp et al. (2013) review.

All results were screened by title and abstract, then by full-text, by two reviewers independently. The Risk of Bias-2 tool was used to appraise the included studies. The studies were presented and synthesised using four meta-analyses, two for physical activity interventions and two for psychosocial interventions for the effect on fatigue. This included two sub-analyses for the intervention types and included only those studies that specified fatigue as the primary outcome. Studies of other intervention types and secondary outcomes were presented with a narrative synthesis.

Results:

There were 29 eligible papers identified that were appraised and synthesised. Data from an additional 17 papers from the previous review by Cramp et al., 2013 were then included in the meta-analysis. This totalled to 4,562 participants across all papers. Both meta-analyses indicated a small effect, psychosocial interventions had a pooled effect size of -0.34 (95% CI -0.49 to -0.19) and physical activity interventions showed a pooled effect size of -0.27 (95% CI -0.43 to -0.10). There was no serious harm reported that was a result of the fatigue interventions. The results across the secondary outcomes were variable. Risk of bias ranged from low to high, with over half of the studies rated as high.

Conclusion:

Physical activity and psychosocial interventions showed some benefit for improving fatigue. Evidence for other interventions was inconclusive, as was the impact of non-pharmacological interventions on the secondary outcomes. The evidence was limited in that most studies were rated as high risk of bias. There was also variation across the interventions and outcome measures used which therefore limits the ability to compare. This review was also limited as it included papers published in English only.

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease (IRD) (Crowson et al., 2011; Symmons, 2002). It has been estimated that the point prevalence is around 500,000 people in the UK, or around 0.87% of the population (Ledingham et al., 2017; Symmons et al., 2002). The lifetime risk for women is more than double that for men, 3.6% versus 1.7% (Crowson et al., 2011).

Fatigue is a significant and common difficulty reported by those with RA (Dures et al., 2020). It can cause significant impact psychologically, socially and cognitively (Dures et al., 2020). A Cochrane systematic review of twenty-four studies of non-pharmacological interventions suggested that psycho-social and physical activity interventions could improve fatigue (Cramp et al., 2013). This was more evident for physical activity interventions but was apparent also for some psycho-social interventions such as cognitive behavioural therapy. The review also included other non-pharmacological interventions such as diet, reflexology, and use of health tracker information and found that the evidence for these was variable (Cramp et al., 2013). The authors also looked at secondary outcomes such as anxiety, depression, pain, disability, tender and swollen joints. It was found that interventions did not lead to a significant improvement in anxiety. The other secondary outcome findings were more varied. For example, depression showed improvements for some interventions such as cognitive-behavioural therapy and tai-chi but not for others. There was a similar pattern across the other secondary outcomes (Cramp et al., 2013). Since that review was conducted, two more large-scale randomised controlled trials have evaluated non-pharmacological fatigue interventions for RA with both showing improvements (Bachmair et al., 2022; Hewlett et al., 2019). Furthermore, other recent reviews have suggested that

physical activity may reduce fatigue compared to comparator groups in the short-term, and that non-pharmacological interventions were effective for improving fatigue, pain and disability in 'difficult to treat' RA. However, the studies included were of mixed quality, with most found to have some to high risk of bias (Roodenrijs et al., 2021; Runge et al., 2023). Although these additional reviews have been somewhat informative, there has not been a fully comprehensive updated review that has included all non-pharmacological interventions for fatigue since the Cramp et al., (2013) review was published, and which have also reviewed the full range of additional outcomes (pain, depression, anxiety, disability and disease activity) that were also included in the Cramp et al. (2013) review.

The present paper is an updated review of non-pharmacological interventions for the treatment of fatigue in RA, designed to build on the prior Cochrane review (Cramp et al., 2013). The present review also includes a meta-analysis of new findings (since November 2012) combined with the data that had already been meta-analysed in Cramp et al. (2013). The aims of this review were as follows:

To evaluate the effects, including both benefits and harm, of non-pharmacological interventions for fatigue on measures of fatigue in adults and adolescents (aged 13 and above) with rheumatoid arthritis.

To evaluate the effects of those non-pharmacological interventions on depression, pain, disability, anxiety, and disease activity in adults and adolescents (aged 13 and above) with rheumatoid arthritis.

Method

The protocol for this review was registered on PROSPERO (ID CRD42023439975). The review follows the PRISMA 2020 reporting guideline (Page et al., 2021).

Inclusion Criteria

Studies were included if they: 1) Were randomised controlled trials; 2) Had participants aged thirteen years and over with a rheumatoid arthritis diagnosis; 3) Involved an intervention that was non-pharmacological (e.g. psycho-social intervention, physical activity, therapeutic procedure etc.); 4) Had fatigue as an outcome measure. Studies were excluded if they had a pharmacological intervention only. If studies had mixed-age (including <13 years) or mixed-diagnosis participant groups, they were only included if results were reported separately for those aged thirteen years and over, and for those with RA diagnosis only.

Review Outcomes

The primary outcome reviewed was fatigue, with the additional secondary outcomes of pain, disease activity, disability/functional impact, depression and anxiety also reviewed.

Context and Scope

New papers that were published from November 2012 onward were included in this review. This was because the review by Cramp et al. (2013) included papers published until October 2012. These new papers are fully described and appraised here. Additionally, for the meta-analysis, data were incorporated from the pre-November 2012 studies that had already been reviewed by Cramp et al. (2013). These earlier studies are not fully described and appraised here, as this information had already been presented by Cramp et al.; their data has only been included in the meta-analysis results here.

Sources

The following electronic databases were searched for peer-reviewed English-language original articles published from October 2012 to the date of the search (18/11/2023):

- The Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE
- PsycINFO
- EMBASE
- Specialized Register of the relevant Cochrane Review Groups
- Web of Science
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

Backward citation searches were also carried out by hand searching previous reviews and reference lists of studies. Forward searching was conducted by using the online 'cited by' function for eligible papers. Unpublished studies were not included.

Search Strategy

The search terms used (see appendix 1.2, page 103) were based upon those used in the previous review (Cramp et al., 2013). Search strategies were also adjusted following discussion with a specialist librarian.

Study Screening

Search results were de-duplicated automatically using Endnote software before further manual de-duplication by the primary reviewer. Records were then screened based upon the inclusion and exclusion criteria by both the primary and second reviewer independently. Records were firstly screened by the title and abstract and then by full-text. Both reviewers screened 100% of records at both stages. Any discrepancies were then discussed between

reviewers to reach consensus, involving a third author if necessary. An excel spreadsheet was used to record decisions and calculate agreement statistics.

Data Extraction

Data was extracted by the primary reviewer using an adapted template from the prior review (Cramp et al., 2013) and the Cochrane website. Information was collected on the following: participant details (number in each treatment group, age and gender); outcome measures used; intervention type and length; main findings, and any harm identified. Extraction accuracy was checked by the second reviewer for 25% of the papers.

Critical Appraisal

The quality of included studies was appraised by the primary reviewer using the Cochrane Risk of Bias-2 (ROB-2) tool for randomized trials (Higgins, Savović, et al., 2022). The second reviewer appraised 100% of the papers independently also. Any discrepancy was discussed and resolved readily. The following domains were assessed for bias as part of the ROB-2: randomisation bias; bias from intended intervention deviations; missing outcome data; outcome measurement bias and selective reporting bias (Higgins, Savović, et al., 2022).

Data Synthesis

Key information from the included studies was presented narratively in text and tables. Results for fatigue outcomes were statistically synthesized in four random effects meta-analyses, two for psycho-social interventions and two for physical activity interventions, with results expressed as standardised mean differences (Cohen's d) with 95% confidence interval (CI) and presented visually in forest plots. These were conducted using SPSS software. Two of the new studies (Katz et al., 2018; Yousefi et al., 2022) included more than

one intervention arm. The two intervention arms were entered separately into the meta-analysis, however both then contained the same control groups as comparators. There was a range of time points for outcome measurements in the study, table 1 highlights the timepoint for which the data was used in the meta-analysis. Heterogeneity was checked using the I-squared statistic (Deeks et al., 2023). Two meta-analyses were sub-analyses conducted using only the studies which identified fatigue as the primary outcome. The studies of other outcomes and interventions were synthesised only using a narrative approach as there were insufficient numbers of studies using similar interventions and/or outcomes to warrant meta-analysis. If standard deviations were unavailable from the text, authors were approached for this information, however none responded, and these were then hand calculated using the methods described in chapter 6 of the Cochrane handbook (Higgins, Li, et al., 2022).

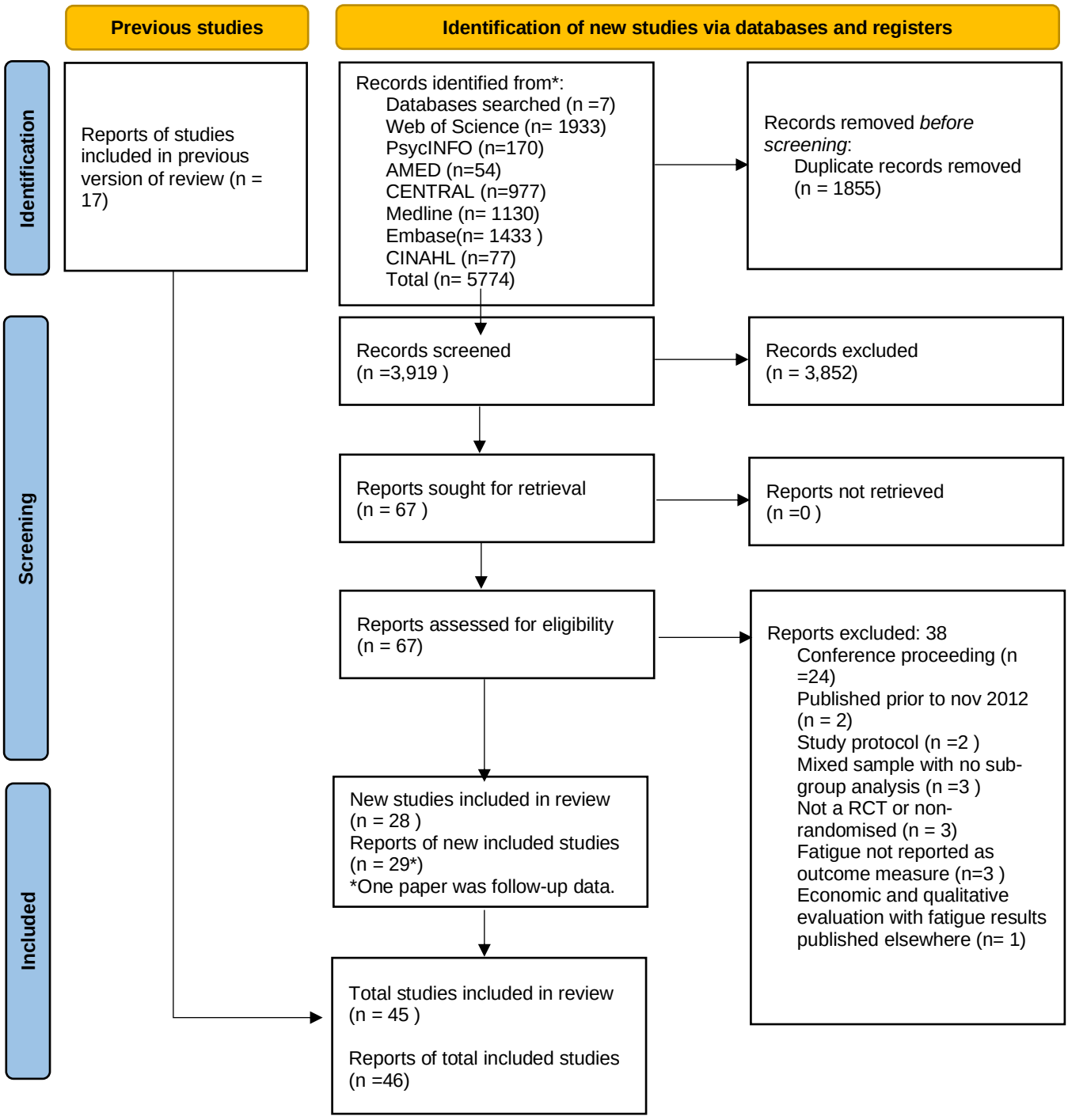
Results

The results of the search process are shown in the PRISMA flow diagram (Figure 1). Following de-duplication, 3919 records were independently screened using the titles and abstracts by the first and second reviewer. There was almost perfect inter-rater reliability agreement (Cohen's Kappa=0.81, agreement 99.3%). Similarly, at full-text screening (67 records) there was almost perfect agreement (Cohen's Kappa= 0.82, 91.2%). Any discrepancies were then discussed and resolved. There were 29 eligible papers that were then quality appraised and synthesised. Data from a further 17 papers previously reviewed by Cramp et al. were added to the meta-analysis.

Study Characteristics

The total participants across all studies was 4,562, comprising 2,635 participants from the new papers identified for this review and a further 1,927 participants from the older studies in the Cramp et al., 2013 review which were incorporated in the meta-analysis. For the new studies found as part of this updated review, most studies reported the mean age of participants to be in the 50s and for female participants to be in the majority. Table 1 below provides an overview of the characteristics of the new studies identified as part of this review. Ten of the new studies specified fatigue as the primary outcome (Bachmair et al., 2022; Durcan et al., 2014; Feldthusen et al., 2016; Ferwerda et al., 2017; Gok Metin & Ozdemir, 2016; Hewlett et al., 2019; Katz et al., 2018; Kiliç & Kiliç, 2023; Lau et al., 2019; SevgiUnal Aslan & Cetinkaya, 2023). Five of the new studies did not specify a primary outcome of interest (Moosavian et al., 2020; Paek et al., 2018; Yentur et al., 2021; Yousefi et al., 2022; Zuidema et al., 2019). The remaining studies included another outcome as the primary outcome as shown in table 1. For the older studies included in the Cramp et al., 2013 review, only 3 studies included fatigue as the primary outcome and one included tiredness. The remaining studies either did not specify the primary outcome or included a different one (Cramp et al., 2013).

Figure 1.
PRISMA flow diagram of search results.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table 1
Overview of the study characteristics

Study	Sample size (n)	Age = Years M (SD) unless specified otherwise	Female n (%)	Country	Intervention type	Specific Intervention	Control	Session number (duration)	Outcomes	Timing and frequency outcome measure
Azeez et al., 2015	Intervention group (33) Control group (33)	Exercise group median age was 58.5 and 63 for TAU.	Over 80% female (did not specify numbers)	Ireland	Physical Activity	Personalised Exercise Program	Treatment as usual (advice on benefits and recommendations of exercise in rheumatoid arthritis by ACSM and American Heart Association guidelines for physical activity in older adults).	3 sessions, one at baseline then 1 every 4 weeks over 12 weeks (duration not given)	Fatigue [b], disability, disease activity, body composition [a], cardiovascular fitness [a], muscle strength [a] and cognitive function [a].	Baseline and week 12 (post-intervention)
Bachmair et al., 2022	Personalised exercise program (PEP) = 67 Cognitive behavioural approach (CBA) =67 Control = 68	PEP = 56.4 (12.3) CBA = 59.3 (13.0) Control 56.8 (12.7)	PEP = 97 (78) CBA = 84 (69) control= 93 (76)	UK	Physical Activity and Psychosocial	Personalised exercise program and cognitive-behavioural intervention	Treatment as usual	7 sessions (up to 45 mins) over 14 weeks, with one booster session at 22 weeks.	Fatigue[a], pain, depression, anxiety, disability, disease activity	Baseline, week 10 (mid-intervention), 28 weeks (post-intervention)[d], 56 weeks (follow-up)
Davis et al., 2015	Mindfulness group=47 Cognitive Behavioural therapy =52 Control n=44	Full sample = 54.28 (13.80). Reported for full sample only.	98 (68.5). Reported for full sample only.	USA	Psychosocial	Mindfulness and cognitive-behavioural intervention	Arthritis education	8 modules over 8 weeks.	Fatigue, pain, stress-related reactivity [a], morning disability, anxious affect	Daily for 4 weeks pre and post-intervention
Durcan et al., 2014	Intervention group (40) control group (38)	Intervention group age =61 (8) Control = 59 (12).	20 females in control (52.6) and 30 in intervention group (75).	Ireland	Physical Activity	Exercise program	Control received advice only	12 week at home exercise program (5 days a week of moderate intensity cardiovascular exercise. Duration and pattern person dependent.	Fatigue[a] , sleep quality[a], disability/functional limitations, pain, stiffness, disease activity	Baseline and 12 weeks (post-treatment)[d]
Feldthusen et al., 2016	Intervention Group (36) Control Group (34)	Intervention group = 54.2 (8.5)	32 females (88.9) for intervention 30 (88.2) in control group.	Sweden	Physical Activity	Person-centered physical therapy	Usual care	12 week intervention with one initial session. Dosage, duration, and	Fatigue [a], disease activity, tender and swollen joints, pain, depression and anxiety	Baseline, 12 weeks (post-intervention)[d] and 6 month follow-up

Study	Sample size (n)	Age = Years M (SD) unless specified otherwise	Female n (%)	Country	Intervention type	Specific Intervention	Control	Session number (duration)	Outcomes	Timing and frequency outcome measure
		Control = 52.7 (10.9)						intensity of exercise dependent on participants as was number of sessions. Median session number = 4. Duration lasting from 10 minutes to 1 hour.		
Ferwerda et al., 2017	Intervention group =62 Control group = 71	Intervention= 55.45 (10.69) Control= 57.14 (9.36)	Intervention= 38 (61) Control = 47 (66)	The Netherlands	Psychosocial	Tailored-guided internet-based cognitive-behavioural intervention	Usual care	Internet based module number varied as they were tailored to participant (range from 1 to 4). Duration also varied and was person specific.	Fatigue [a], depression [a], anxiety [a], mood [a], pain [a], disability [a], Disease activity [b]	Pre-intervention, Post-intervention [d] and 3 months post-intervention. Timing varied on how long it took for participants to go through modules.
Gok Metin & Ozdemir, 2016	Aromatherapy massage = 17 Reflexology = 17 Control group = 17	Mean age was 54.4 (1.2). Not reported for each group.	Aromatherapy massage= 15 (88.2) Reflexology=15 (88.2) Control =15 (88.2)	Turkey	Other	Aromatherapy massage and reflexology	Usual care	Aromatherapy massage was delivered three times a week for 6 weeks (30 minutes duration). Reflexology delivered once a week for 6 weeks (40 minutes duration).	Fatigue[a] and pain[a]	Baseline then weekly for 6 weeks.
Hewlett et al., 2019	Intervention group= 156 Control group =152	Intervention median and IQR = 63.7, IQR 54.2, 69.9 Control median and IQR = 61.8, IQR 54.4, 69.6	Intervention = 125 (80.1) Control = 121 (79.6)	UK	Psychosocial	Cognitive behavioural approach group	Usual care (the Arthritis Research UK fatigue self-management booklet)	7 sessions, weekly for 6 weeks (2 hours durations) and one follow-up session at week 14 (1	Fatigue[a], depression, anxiety, disease activity, pain, disability	Weeks 0, 6, 26[d], 52, 78 and 104.

Study	Sample size (n)	Age = Years M (SD) unless specified otherwise	Female n (%)	Country	Intervention type	Specific Intervention	Control	Session number (duration)	Outcomes	Timing and frequency outcome measure
								hour duration)		
Katz et al., 2018	Pedometer only =34 Pedometer plus step target =34 Control =28	Pedometer only = 59.1 (12.5) Pedometer plus step target = 55.9 (12.4) Control =50.2 (14.1)	Pedometer only = 30 (88.2) Pedometer plus step target = 30 (88.2) Control = 24 (85.7)	USA	Physical Activity	Use of pedometer and step-diary and using both plus step target	Education	No sessions, self-practice with pedometer and step-target.	Fatigue[a], disease activity, disability, pain and depression	Baseline, week 10[d] and week 21
Kılıç & Kılıç 2021	Intervention group= 35 Control group = 37	Intervention= 46.3 (13.4) Control = 56.6 (11.2)	Intervention = 27 (77.1) Control = 29 (78.4)	Turkey	Other	Progressive Muscle Relaxation	No information given	No session, self-practice.	Fatigue [a] and sleep [a]	Baseline and week 6 (post-intervention)
Knittle et al., 2015	Intervention group= 38 Control=40	Intervention = 60.7 (11.9) control =64.7 (11.5)	Intervention = 30 (79) Control=22 (55)	The Netherlands	Psychosocial	Education plus motivational interviewing and self-regulation coaching	Education	4 sessions (40-60minutes duration)	Fatigue [b], physical activity [a], disease activity, disability, depression	Baseline, week 6 (post-intervention)[d], week 32 (follow-up)
Latocha et al., 2023	Intervention group= 31 Control group = 31	Intervention group = 60 (10) Control= 57 (11)	Intervention =28 (90) Control= 27 (87)	Denmark	Psychosocial	Group cognitive behavioural therapy	Usual care	6 sessions (2 hours)	Fatigue [b], sleep efficiency [a] depression, pain, disease activity, functional status	Week 0 (baseline), week 7 for sleep only (post-treatment). and week 26 (longer-term effect)[d].
Lau et al., 2019	Intervention group= 11 Control =10	Mean age for full sample =57.5 (7.1) Not provided for each group separately.	Intervention = 11 (100) Control = 10 (100)	China	Other	Neural Mobilization	Gentle joint mobilization exercises. Same joints as intervention.	Twice daily self-practice	Fatigue[a] , pain [a], functional disability [a]	Pre- and post-intervention. Post-intervention was collected between weeks 4-8.
Li et al., 2020	Intervention group (43) Delay/Control group (43)	Intervention group = 54.8 (15.4) Delay/ Control group= 55.3 (11.5)	Intervention group= 38 (88.4) Delay/control group= 40 (93)	Canada	Physical Activity	Physical activity counselling program with a wearable tracker	Delayed intervention (no intervention until later timepoint)	One in-person session (20 minutes) of group education and individual counseling (30 minutes).	Fatigue [b], depression, time spent in moderate/vigorous physical activity [a] and pain	Baseline, post-intervention week 9 (post-intervention)[d] week 18, and week 27 (follow-up)

Study	Sample size (n)	Age = Years M (SD) unless specified otherwise	Female n (%)	Country	Intervention type	Specific Intervention	Control	Session number (duration)	Outcomes	Timing and frequency outcome measure
								Four biweekly phone calls (20–30 minutes)		
Loeppenthin et al., 2022	Intervention group (17) Control group (21)	Intervention group = 57.8 (9.8) Control group = 54.8 (9.6)	Intervention group =13 (75) Control group =20 (95)	Denmark	Physical Activity	intermittent aerobic exercise	Treatment as usual	3 sessions (20 to 30 minutes) per week for 6 weeks	Fatigue [b], sleep [a], pain, depression and physical function	Baseline and week six (post-intervention)
Moosavian et al., 2020	Intervention group = 35 Control group = 35	Intervention =52.22 (12.61) Control = 51.37 (11.04)	Intervention = 35 (100) Control = 35 (100)	Iran	Other	Garlic supplement	Placebo	N/A –received 500mg garlic powder tablets, twice a day for 8 weeks	Fatigue, pain, disease activity [c]	Baseline and week 8 (post-intervention)
Paek et al., 2018	Intervention group = 35 Control group = 35	Intervention =45.88 (11.66) Control =46.48 (12.74)	Intervention= 30 (90.91) Control= 29 (87.88)	Korea	Psychosocial	Nursing education program	Usual care	4 individualized education sessions (30-40minutes) and 8 telephone sessions (20 minutes)	Fatigue, disease activity, functional disability [c]	Baseline, 3, 6 and 9 months.
Pot-Vaucel et al., 2016	Intervention group = 28	Intervention= 58.2 (10.7) Control = 62.4 (9.8)	Not provided	France	Psychosocial	Customised therapeutic education	Waiting list	5 sessions (1-3 hours)	Fatigue [b], disability, depression, anxiety and problem solving [a]	Baseline and 6 months (post-intervention)[d]
Prioreschi et al., 2016	Intervention group = 16 Control group = 15	Intervention group = 51 (10) Control = 52 (12)	Not provided	South Africa	Other	Whole-body vibration	No information	Two sessions per week (15 minutes), a total of 24 sessions over 12 weeks.	Fatigue [b] , disease activity, functional ability [a] and pain	Baseline, three months (post-intervention) and six months (follow-up)
Pukšić et al., 2021	Intervention group (30) Control group (27)	Intervention group = 52.9 (12.2) control group = 57.9 (9)	Intervention = 30 (100) Control= 24 (89)	Croatia	Physical Activity	yoga	Education (once weekly 60 min lecture by a rheumatologist on arthritis-related topics)	Twice weekly (90 minutes per session) for 12 weeks	Fatigue [b], depression, anxiety, pain, disease activity and health impact [a]	Baseline, 12 weeks (post-intervention)[d] and 24 weeks (follow-up)

Study	Sample size (n)	Age = Years M (SD) unless specified otherwise	Female n (%)	Country	Intervention type	Specific Intervention	Control	Session number (duration)	Outcomes	Timing and frequency outcome measure
SevgiUnal Aslan & Cetinkaya, 2023	Reiki group= 37 in reiki, Hand massage = 39 Control group= 33	Ages reported as group categories: Reiki group= 19 to 35 - 4 (11.4%). 36 to 64 - 29 (82.9%). 65 and over - 2 (5.7%). Hand massage group= 19 to 35- 5 (13.5%). 36 to 64 - 24 (64.9%). 65 and over - 8 in (21.6%) Control group= 19 to 35 - 7 (21.2%), 36 to 64 - 22 (66.7%). 65 and over - 4 (12.1%).	Reiki group = 17 (48.6) Hand massage group= 19 (51.4) Control = 19 (57.6)	Turkey	Other	Reiki and hand massage	No information	Reiki = 6 sessions (30 minutes) Hand massage = 6 sessions (30 minutes)	Fatigue [a] and pain [a]	Baseline and 4 weeks (post-intervention)
Thomsen et al., 2017	Intervention group = 75 Control group= 75	Intervention= 59.7 (10.7) Control = 59.5 (12.7)	Intervention =61 (81) Control= 60 (80)	Denmark	Psychosocial	Individually tailored, behavioural intervention with SMS reminders.	Usual lifestyle	Three individual motivational counselling sessions (duration not stated) and short message service or text messages over 16-week.	Fatigue[b], pain, physical function and disease activity, daily sitting time[a].	Baseline and 16 weeks.
Turesson Wadell et al., 2021	Intervention group = 25 Control group = 22	Median age and IQR as following, intervention group = 62.8 (59.3, 70.2) Control = 64.3 (47.8, 72,4).	Intervention = 20 (80) Control =16 (72.7)	Sweden	Other	Anti-Inflammatory Diet	Control diet that nutritionally corresponds to an average Swedish dietary intake.	anti-inflammatory diet for 10 weeks	Fatigue[b], disability, health-related quality of life[a] and pain.	Baseline and post-intervention
Van Vilsteren et al., 2017	Intervention = 75 Control = 75	Intervention group = 49.8 (8.6)	Intervention = 63 (84) Control= 63 (84)	The Netherlands	Other	Care for Work intervention program	Usual care	Non-applicable as work based adaptions.	Fatigue [b], pain and at-work productivity loss [a].	Baseline, 6 and 12 months

Study	Sample size (n)	Age = Years M (SD) unless specified otherwise	Female n (%)	Country	Intervention type	Specific Intervention	Control	Session number (duration)	Outcomes	Timing and frequency outcome measure
		Control = 49.6 (8.7)								
Ward et al., 2018	Intervention (13) Control (13)	Intervention group = 50 (12) Control group =59 (8)	Intervention group= 13 (100) Control = 12 (92)	New Zealand	Physical Activity	Yoga	Treatment as usual	Eight weekly (75 minutes)	Fatigue [b], pain [a], sleep [a], disease activity, disability, mood including depression and anxiety	Baseline, week 9 (post-intervention), week 12 (follow-up).
Yentur et al., 2021	30 (10 in each group)	Pilates group = 48.2 (9.54), aerobics group = 50.70 (10.66) and combined group = 51.90 (11.52)	Not reported	Turkey	Physical Activity	Pilates , aerobic exercises and combined Pilates/aerobics	Comparator group undertook an aerobics intervention.	Pilates = three times a week (30 minutes) Aerobics = three times a week (45 minutes) Combined = aerobics and pilates three times a week	Fatigue, depression and pain[c]	Baseline and 8 weeks (post-intervention)[d]
Yousefi et al., 2022	Mindfulness-Based Stress Reduction Therapy = 19 Cognitive-Behavioural Therapy = 19 Control Group = 19	MBSR= 51.26 (5.70) CBT =48.73 (7.30) control =50.89 (6.84)	16 (84.2) in each group	Iran	Psychosocial	Mindfulness-Based Stress Reduction Therapy (MBSR) and Cognitive-Behavioural Therapy (CBT)	Treatment as usual	8 sessions of MBSR (90 minutes) and 10 sessions of CBT (90 minutes)	Fatigue and disease activity[c]	Pre and Post-treatment [d], then 3 months follow-up.
Zuidema et al., 2019	Intervention group = 78 Control group =79	Intervention= 62.9 (10.2) Control = 61.0 (11.3)	Intervention group = 51 (65) Control group= 52 (67)	The Netherlands	Psychosocial	Web-based self-management enhancing program	Usual care	Non-applicable: unguided web-based program	Fatigue and pain[c]	Baseline, 6[d] and 12 months

Note [a] denotes primary outcome as specified by original study. [b] denotes fatigue as a secondary outcome as specified by original study. [c] denotes when no primary outcome is identified in the original study. For meta-analysis included studies only: [d] denotes timepoint used in meta-analysis.

There were nine physical activity only interventions and ten psycho-social only interventions in this review. One study included both a physical activity and a psychosocial arm (Bachmair et al., 2022). The remaining studies were of other types of non-pharmacological interventions. One study that was included in the review but is not included in the table is the paper by Thomsen et al., 2020 as this was follow-up data from Thomsen et al., 2017.

Risk of bias

Risk of bias was assessed using information from published reports only and no further information was sought from authors. This meant that there was at times missing information, with the reviewers then needing to rate items as 'no information' and therefore it could not be fully established whether there was evidence of bias or not. Figure 2 below shows the summary of the risk of bias for each study, whilst Figure 3 shows the percentage of risk of bias across all studies for each domain. Only three studies were rated as low risk of bias (Latocha et al., 2023; Turesson Wadell et al., 2021; Ward et al., 2018). Overall, the most common reason for a high risk of bias rating was owing to domain 3 being rated as high due to a lack of information regarding missingness in the outcome data and whether it related to its true value. Furthermore, several studies were rated as overall high risk of bias due to several domains being rated as having some concerns.

Figure 2. Risk of bias rating for each domain for included papers (published since November 2012).

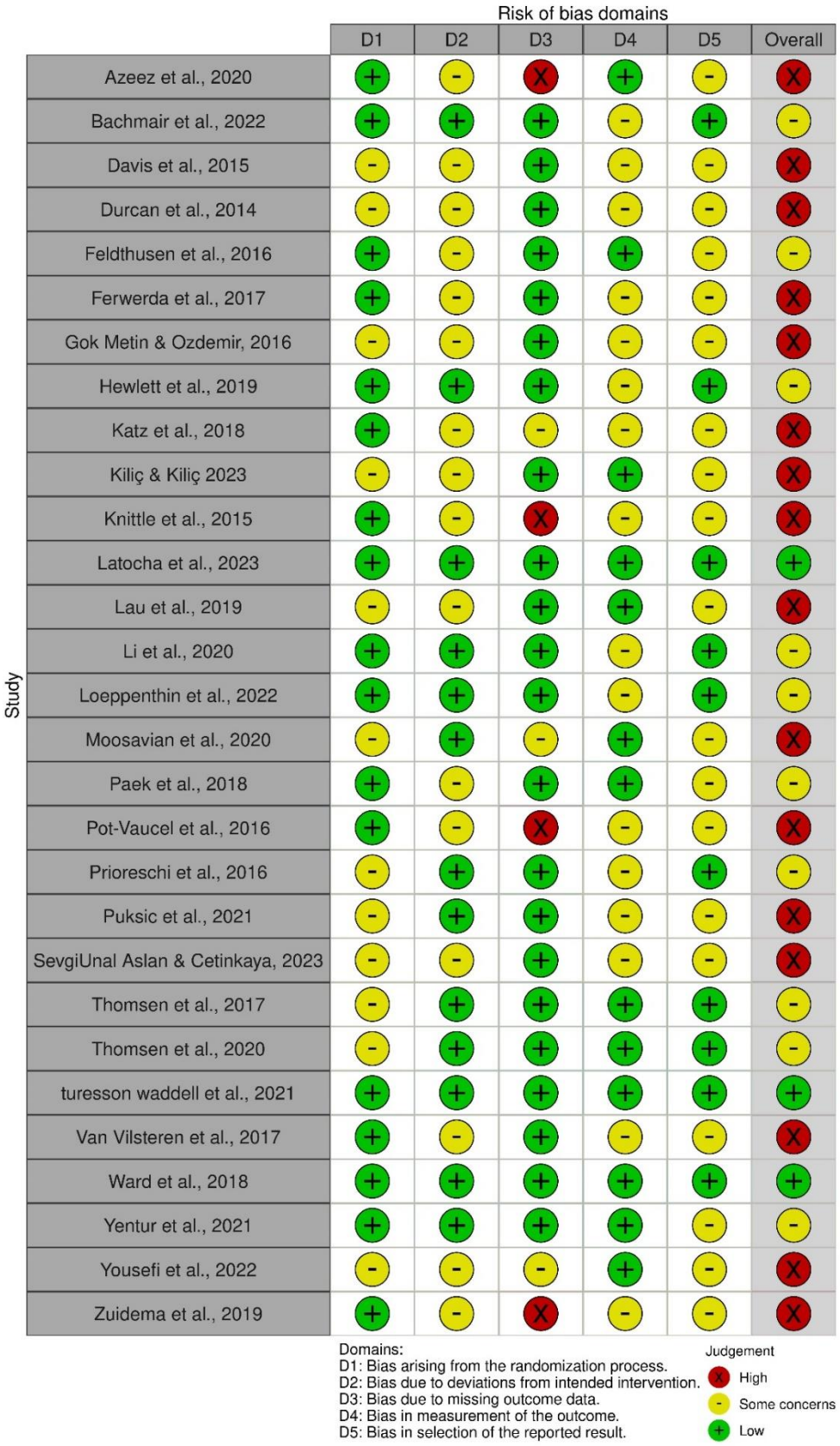
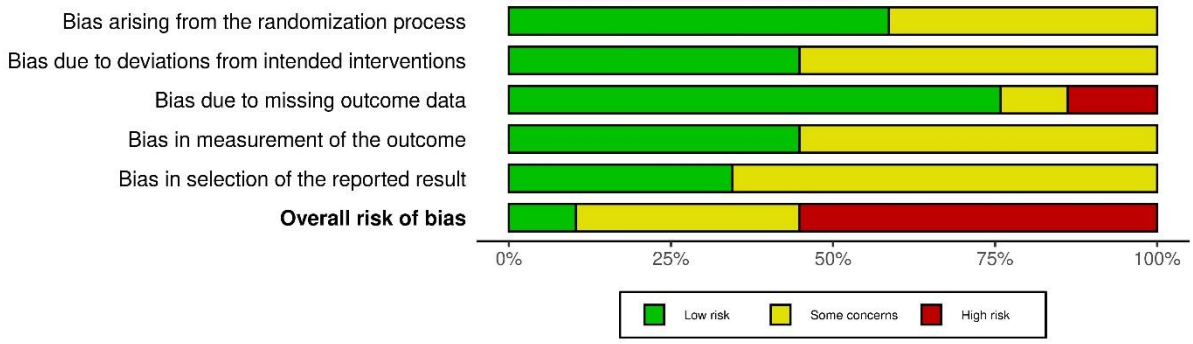


Figure 3. Risk of bias across all papers (published since November 2012) as a percentage.



Fatigue

Across the studies published since November 2012, fatigue was measured using several different tools with some studies using more than one fatigue measure. The Visual Analogue Scale (VAS) or a Numerical Rating Scale (NRS) were used in nine studies (Davis et al., 2015; Feldthusen et al., 2016; Loeppenthin et al., 2022; Pot-Vaucel et al., 2016; Thomsen et al., 2017; Thomsen et al., 2020; Turesson Wadell et al., 2021; van Vilsteren et al., 2017; Zuidema et al., 2019). The Fatigue Severity Scale was used in seven studies (Bachmair et al., 2022; Durcan et al., 2014; Gok Metin & Ozdemir, 2016; Kiliç & Kiliç, 2023; Li et al., 2020; Moosavian et al., 2020; Yentur et al., 2021). The BRAFs (Bristol Rheumatoid Arthritis Fatigue Scales) were used in five studies (Bachmair et al., 2022; Feldthusen et al., 2016; Hewlett et al., 2019; Latocha et al., 2023; Ward et al., 2018). Two studies used the Chalder Fatigue Scale (Bachmair et al., 2022; Yousefi et al., 2022), two used the fatigue scale of the Checklist of Individual Strengths (Ferwerda et al., 2017; Knittle et al., 2015) and the Functional Assessment of Chronic Illness Therapy – Fatigue Scale was used twice also (Paek et al., 2018; Pukšić et al., 2021). The Multi-dimensional Fatigue Inventory (MFI 20) was used to report fatigue in one study and its follow-up results paper (Thomsen et al., 2017; Thomsen et al.,

2020). The remaining studies used the following measures: Multidimensional Assessment of Fatigue Scale (Azeez et al., 2020); Rheumatoid Arthritis Impact of Disease (RAID) questionnaire (Lau et al., 2019); Piper Fatigue Scale (SevgiUnal Aslan & Cetinkaya, 2023); the vitality scale from the 36-Item Short Form Survey (Pukšić et al., 2021); a likert scale rated 0 to 5 (Prioreschi et al., 2016); and the PROMIS fatigue short form 7a (Katz et al., 2018).

Effect of interventions on fatigue outcomes

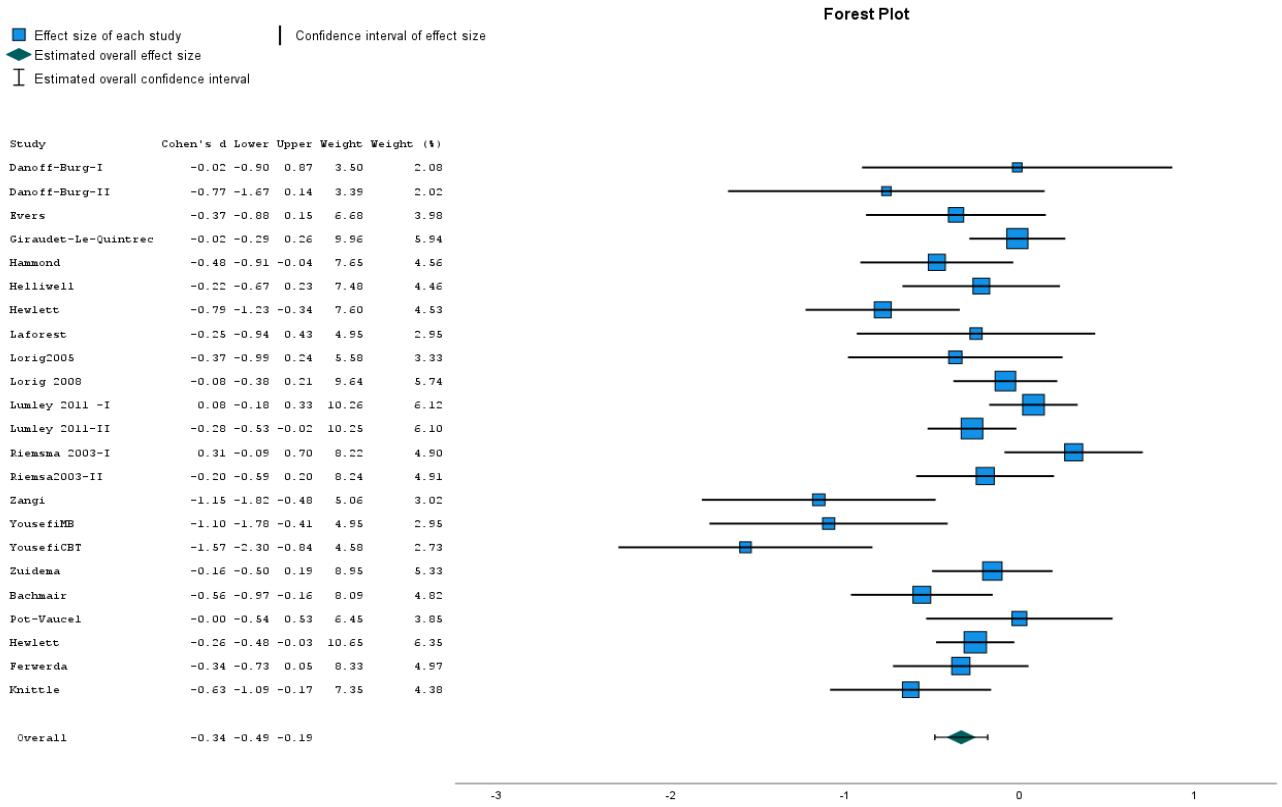
The effect of physical activity and psychosocial interventions on fatigue outcomes were analysed using four separate meta-analyses. Two of which were sub-analyses including only studies that specified fatigue as the primary outcome.

Psychosocial interventions

Nineteen studies were included in the meta-analysis for psychosocial interventions (seven new studies since November 2012, and twelve previous studies from Cramp et al., 2013). Two studies had some concerns of bias and 17 had high risk of bias. Twenty-three comparisons were made as four studies had two arms with an intervention. There was a total of 1152 participants in the control groups and 1252 in the intervention groups. As shown in the forest plot (Figure 4), the pooled effect size was -0.34 (95% CI -0.49 to -0.19), indicating a small overall beneficial effect of psychosocial interventions on fatigue outcomes. By comparison, the pooled effect size previously reported by Cramp et al. for the original subset of studies was -0.24 (95% CI -0.40 to -0.07). Three papers were not included due to the data needed for meta-analysis being unavailable (Davis et al., 2015; Thomsen et al., 2017; Thomsen et al., 2020). There was substantial heterogeneity (I^2 = 66%) found between studies (shown in Figure 4), with the meta-analysis in the prior review also having

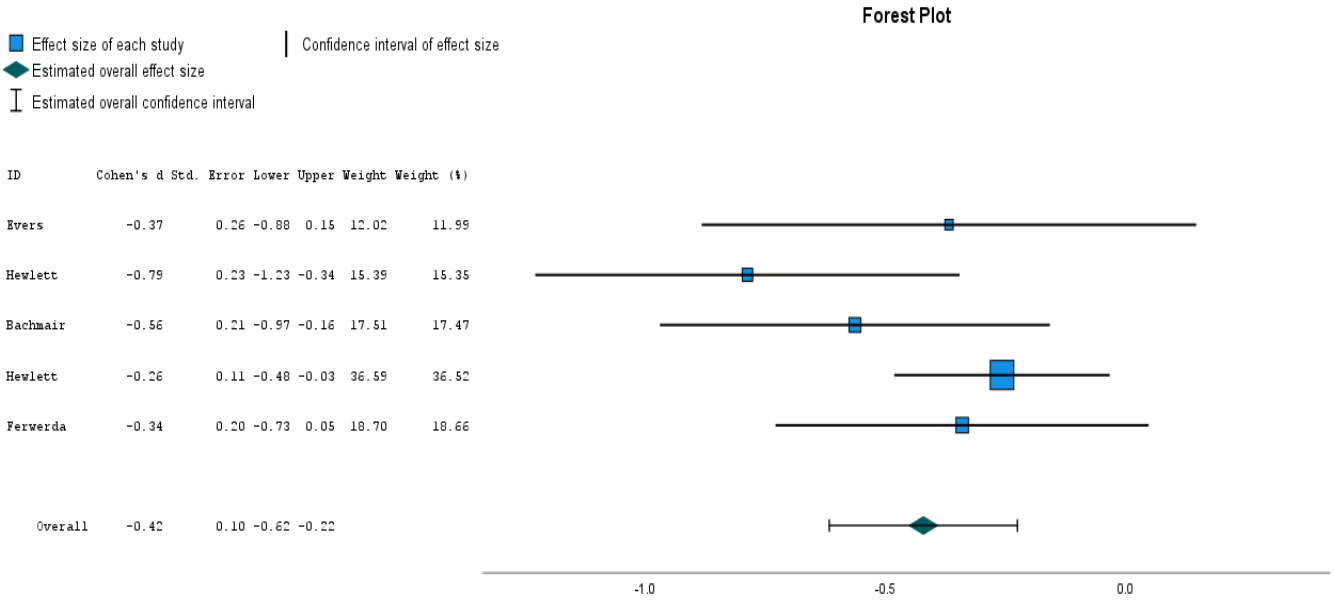
been found to have substantial heterogeneity (I^2 = 55%). The sub-analysis for psychosocial studies that had fatigue as primary outcome included two studies from the previous review by Cramp et al., 2013 and three new studies. There was 321 participants in the intervention groups and 333 in the control groups. As shown in the forest plot (Figure 5), the pooled effect size was -0.42 (95% CI -0.62 to -0.22), indicating a small overall beneficial effect of psychosocial interventions on fatigue outcomes. There was some heterogeneity (I2 = 28%) found between studies (shown in Figure 5), although this was a decrease in comparison to the above meta-analysis that included more of the psychosocial studies. Evidence of harms (serious adverse events) from psychosocial interventions on fatigue outcomes were reported by the authors of two of the new studies (Bachmair et al., 2022; Latocha et al., 2023), however these events were not considered to be related to the intervention. The previous review by Cramp et al. (2013) had reported that none of the psychosocial studies in their review reported serious harms. However, in both the current review and the one undertaken by Cramp et al., (2013), the majority of studies did not include this information so it was therefore unclear whether there was an absence of events or a lack of reporting.

Figure 4. Forest plot for effect of psychosocial interventions on fatigue



Model: Random-effects model
Heterogeneity: Tau-squared = 0.08, H-squared = 2.97, I-squared = 0.66
Test of overall effect size: z = -4.36, p-value = 0.00

Figure 5.
Sub-analysis forest plot for effect of fatigue focused psychosocial interventions on fatigue



Model: Random-effects model
Heterogeneity: Tau-squared = 0.01, H-squared = 1.40, I-squared = 0.28
Test of overall effect size: z = -4.21, p-value = 0.00

Physical activity interventions

Twelve studies were included in the meta-analysis for physical activity interventions (seven new studies since November 2012, and five previous studies from Cramp et al., 2013). None of these studies were rated as low risk of bias, five had some concerns and seven had high risk of bias. Fourteen comparisons were made as two studies had two arms with an intervention. There was a total of 420 participants in the control groups and 497 in the intervention groups. As shown in the forest plot (Figure 6), the pooled effect size was -0.27 (95% CI -0.43 to -0.10), indicating a small overall beneficial effect of psychosocial interventions on fatigue outcomes. By comparison, the pooled effect size previously reported by Cramp et al. for the original subset of studies was -0.36 (95% CI -0.62 to -0.10). One study was not included due to the comparator group being an active (aerobics) intervention (Yentur et al., 2021) and two studies did not have the data needed to include in meta-analysis (Azeez et al., 2020; Ward et al., 2018). There was moderate heterogeneity (I^2 = 32%) found between studies (shown in Figure 6), with the prior review also reporting moderate heterogeneity (I^2 = 27%). The sub-analysis for physical activity interventions that included fatigue as the primary outcome included four of the new studies with five comparisons and none from the previous review by Cramp et al., 2013; this was due to none of the physical activity studies from the older review identifying fatigue as the primary outcome. There was 188 participants in the intervention groups and 177 from the control groups. As shown in the forest plot (Figure 7), the pooled effect size was -0.30 (95% CI -0.51 to -0.09), indicating a small overall beneficial effect of physical activity interventions on fatigue outcomes. There was no heterogeneity (I2 = 0.00%) found between studies (shown

in Figure 7). Evidence of harms (serious adverse events) from physical activity interventions on fatigue outcomes was reported by the authors of one paper, however it was not considered to be due to the intervention (Bachmair et al., 2022). The remaining papers reported no serious adverse events, although some papers did not include this information so it remains unclear whether there was an absence of serious adverse events or absence of reporting. The previous review by Cramp et al. (2013) reported that none of the physical activity studies in their review reported serious harms.

Figure 6. Forest plot for effect of physical activity interventions on fatigue

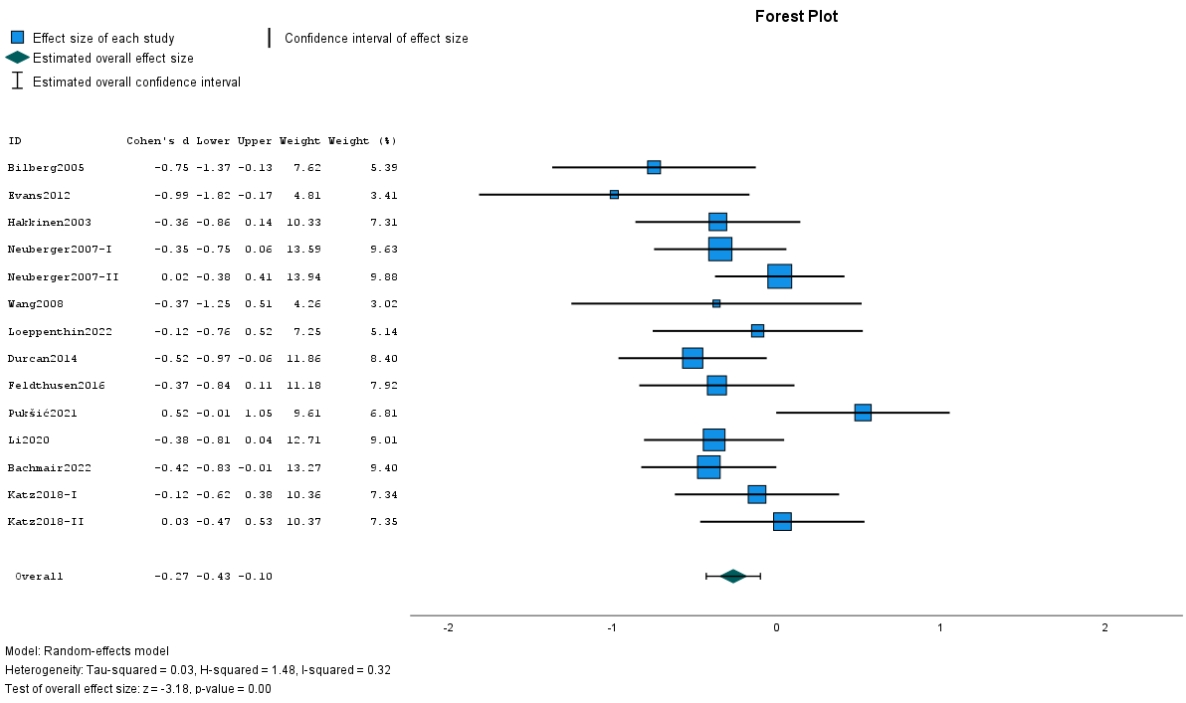
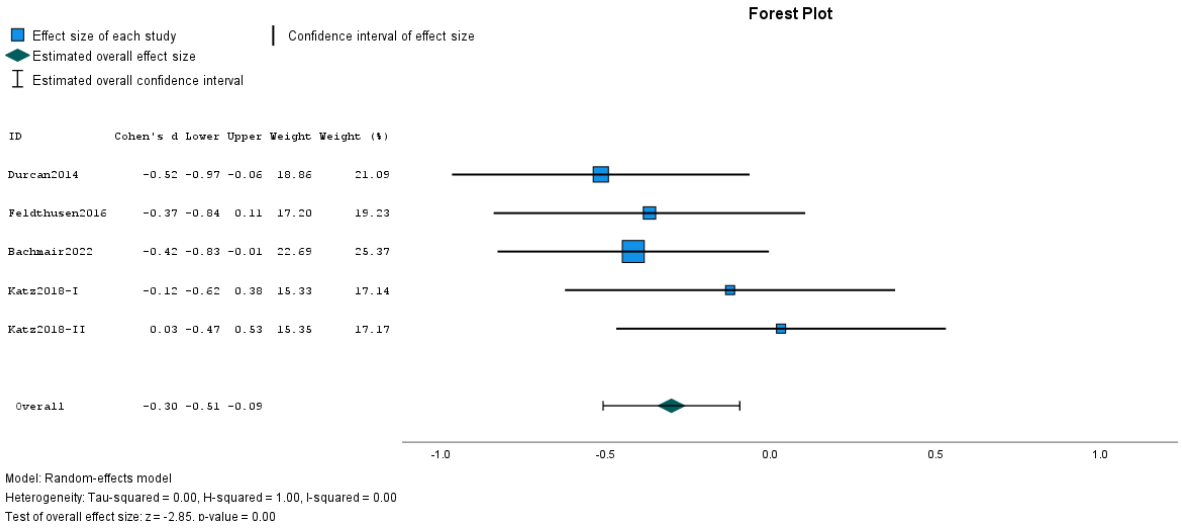


Figure 7. Sub-analysis forest plot for effect of fatigue focused physical activity interventions on fatigue



Other intervention types

Nine studies published since November 2012 investigated a disparate range of other non-pharmacological interventions and it was therefore not feasible to include them in the meta-analyses. The findings of these studies are summarised here. One study with high risk of bias found that the effect of garlic supplements compared to placebo resulted in a statistically significant decrease in scores on the Fatigue Severity Scale after 8 weeks (Moosavian et al., 2020): effect size -0.53, 95% CI -1.00 to -0.05. Another dietary based study, with low risk of bias, found that there was no significant evidence of improvement following the use of an anti-inflammatory diet in a randomised cross-over controlled trial (Turesson Wadell et al., 2021) but the information was not available to calculate effect sizes. Progressive Muscle Relaxation (PMR) was found to have significantly improved fatigue severity from baseline following a six-week intervention in a study with high risk of bias, with this also resulting in a significant difference in fatigue severity when compared to the control group at follow-up (Kiliç & Kiliç, 2023): effect size -3.46, 95% CI -4.14 to -2.69. A

study with some risk of bias found that fatigue significantly improved following a whole-body vibration intervention at 3 months compared to the control group (effect size -3.85, 95% CI -4.92 to-2.58), however these were not maintained to 6 months (effect size 0.00, 95% CI -0.76 to 0.76) (Prioreschi et al., 2016). A study of an educational program, with some risk of bias, delivered by nurses over a 9-month intervention period (4 sessions at 3-month intervals) reported significant differences between groups for fatigue scores at 9 months, with fatigue improving as indicated by a higher score (Paek et al., 2018): effect size 0.51, 95% CI 0.01 to 0.99. A work-based productivity intervention evaluated in a study with high risk of bias showed no significant effect of the intervention on fatigue: effect size 0.15, 95% CI -0.18 to 0.47 (van Vilsteren et al., 2017). Neural mobilization, an intervention that targets the nerves through actions, showed no significant difference between intervention and control group, in a high risk of bias study: effect size 0.13, CI -0.74 to 0.98 (Lau et al., 2019). Reiki and hand massage also appeared to result in a decrease in fatigue severity, in a study with high risk of bias, with the differences found to be statistically significant (SevgiUnal Aslan & Cetinkaya, 2023): Reiki effect size -12.89, 95% CI -14.93 to -10.55, hand massage effect size -7.83, 95% CI -9.11 to -6.38. Finally, both aromatherapy and reflexology were found to lead to a significant decrease in fatigue severity scores at 6 weeks when compared to a control group, in a study with high risk of bias, with fatigue significantly decreasing from baseline at week one for reflexology (effect size -0.91, 95% CI -1.59 to -0.18) and week four for aromatherapy (effect size -0.99, 95% CI -1.47 to -0.48) (Gok Metin & Ozdemir, 2016). Of these nine studies, none reported evidence of serious harms.

Other outcomes

Depression

Depression was an outcome in thirteen studies published since November 2012. There was a range of measures used; the Hospital Anxiety and Depression Scale (HADS) was the most commonly used with six studies using this measure, followed by three studies which used the Beck Depression Inventory and two studies which used the Patient Health Questionnaire-9. One study used the Center for Epidemiological Studies Depression (Loeppenthin et al., 2022) and another used the Brief Symptom Inventory (Knittle et al., 2015).

Seven studies included physical activity interventions and five used psycho-social interventions. One study included both, but depression results were not reported for RA-only participants (Bachmair et al., 2022).

Physical activity interventions showed differing results for the effect on depression. Four studies showed no significant differences between groups for depression score (Feldthusen et al., 2016; Katz et al., 2018; Li et al., 2020; Ward et al., 2018). Results for studies that found no significant effects are given in Supplementary Table S1 in Appendix 1.3, page 111. The bias ranged from low to high risk. The remaining studies' results suggested significant improvements. Yoga showed significant differences between intervention and control group, adjusted mean difference was -1.37 (CI -2.38 to -0.36; effect size 0.58) in a study rated as high risk (Pukšić et al., 2021). Pilates compared to aerobics showed a significant difference (effect size -2.63, 95% CI -3.69 to -1.35), as did Pilates versus a combined aerobics and Pilates group (effect size -5.95, 95% CI -7.67 to -3.73), in a study rated as some concerns of bias (Yentur et al., 2021). A study rated as some concerns of bias, also showed a reduction in scores for the aerobic exercise group compared to the control, however it was

not a statistically significant effect (effect size -0.11, 95% CI -0.74 to 0.54) (Loeppenthin et al., 2022).

For psycho-social interventions, results again varied across studies. One group cognitive-behavioural study, rated as low risk of bias, showed a significant decrease in depression scores for the intervention group compared to control (Latocha et al., 2023). The data was not available to calculate effect sizes. However, another group cognitive-behavioural program found no significant differences between groups, effect size 0.10, 95% CI –0.11 to 0.32 (Hewlett et al., 2019), with this study rated as having some concerns of bias. An online cognitive-behavioural intervention led to a significant reduction in score compared to control (Ferwerda et al., 2017): effect size -0.70, 95% CI -1.10 to -0.30. There was no significant change in scores for either a therapeutic education intervention (effect size 0.40, 95% CI -0.14 to 0.94) or a motivational interviewing and self-regulation intervention group (effect size 0.04, 95% CI -0.40 to 0.48) compared to comparators (Knittle et al., 2015; Pot-Vaucel et al., 2016). However, all three of these studies were rated as high risk of bias.

Anxiety

Seven studies published since November 2012 included anxiety as an outcome. Five studies used the HADS to measure anxiety, with the State-Trait Anxiety Inventory (STAI) instead used in one study (Pot-Vaucel et al., 2016) and the anxiety scale from the Impact of Rheumatic diseases on General health and Lifestyle (IRGL) used in another (Ferwerda et al., 2017).

Three studies were of physical activity interventions. One of these studies reported a significant reduction in anxiety for the intervention group compared to the control and

baseline (Feldthusen et al., 2016): effect size -0.71, 95% CI -1.20 to -0.21. The other reported a reduction in anxiety but that this was not a significant difference compared to control group: effect size -0.33, 95% CI -0.90 to 0.24 (Pukšić et al., 2021). The first study was rated as some concerns of bias and the latter as high risk. A yoga pilot, rated as low risk, reported that there was no group-by-time effect and anxiety remained stable across each of the measured timepoints (Ward et al., 2018); effect size -0.06, 95% CI -0.84 to 0.73.

One of three psycho-social interventions led to no significant change in anxiety: effect size -0.21, 95% CI -0.43 to 0.02 (Hewlett et al., 2019). One study reported that there was no significant effect (Pot-Vaucel et al., 2016), however this did not correspond with the effect size that was calculated using the information from the paper: effect size 0.61, 95% CI 0.06 to 1.15. The studies were rated as some concerns of bias and high risk of bias respectively. An online CBT intervention adapted to the individual found a larger decrease in anxiety for the intervention group compared to the control group, effect size -0.61, 95% CI -1.07 to -0.14 (Ferwerda et al., 2017) in a study rated as high risk of bias. One study had an arm with both physical activity and a psycho-social intervention but did not report separate anxiety results for the RA sub-group (Bachmair et al., 2022).

Pain

Six papers published since November 2012 did not include pain as an outcome measure (Azeez et al., 2020; Kiliç & Kiliç, 2023; Knittle et al., 2015; Paek et al., 2018; Pot-Vaucel et al., 2016; Yousefi et al., 2022), with the remaining 24 papers including it. Most studies used a VAS or numerical rating scale to rate pain. The remaining studies used the McGill Pain

Questionnaire (Li et al., 2020; Yentur et al., 2021), the pain scale of the Impact of Rheumatic diseases on General health and Lifestyle (Ferwerda et al., 2017), the RAID (Lau et al., 2019) and the Pain Interference Questionnaire (Katz et al., 2018). One paper used a Likert scale (rated 0 to 5) to rate pain (Prioreschi et al., 2016).

Most physical activity studies reported no significant differences in pain outcomes between control and intervention groups aside from two studies. Results for the other studies that found no significant effects are given in Supplementary Table S2 in Appendix 1.3, page 111. Both physical activity counselling with an activity tracker (effect size -0.75, 95% CI -1.19 to -0.29) and a home-based physical activity program (effect size -0.78, 95% CI -1.23 to -0.31) showed significant improvements in pain compared to control groups (Durcan et al., 2014; Li et al., 2020). These studies were rated as high risk of bias and some concerns respectively. A Pilates group was found to have significant difference compared to both aerobics and a combined aerobics and Pilates group in a study with some concerns of bias: effect size -2.21, 95% CI -3.22 to -1.02; effect size -2.43, 95% CI -3.47 to -1.19 (Yentur et al., 2021).

For psycho-social interventions, group CBT showed significant improvements in pain for the intervention group as did a motivational counselling program which was also sustained at 22-month follow-up (Latocha et al., 2023; Thomsen et al., 2017; Thomsen et al., 2020). The study by Latocha et al. (2013) was rated as low risk of bias, whereas the latter two were rated as some concerns of bias. It was not possible to calculate effect sizes for either of these findings. A mindfulness-based intervention also showed differences in how participants responded to pain compared to a control group (Davis et al., 2015) in a study rated as high risk of bias. Again, it was not possible to calculate effect sizes. The remaining psycho-social studies did not find significant differences (see Supplementary Table S3 in

Appendix 1.3, page 111, for details). Sub-group analysis results for RA were not available in one relevant study (Bachmair et al., 2022).

Other interventions that were not considered either psycho-social or physical activity had mixed results. A significant improvement in pain (effect size -0.61, 95% CI -1.09 to -0.13) was noted following an 8-week garlic supplement compared to a placebo group, with this reduction also significantly reduced from baseline (Moosavian et al., 2020). There was a significant decrease in pain as measured by the VAS, following 6 weeks of either aromatherapy massage(effect size -1.44, 95% CI -2.16 to -0.66) or reflexology (effect size -2.00, 95%, CI -2.77 to -1.13) when compared to the control group and at baseline (Gok Metin & Ozdemir, 2016). Both reiki and hand massage also showed a significant decrease (effect size -2.68, 95% CI -3.31 to -2.00; effect size -2.14, 95% CI -2.70 to -1.53) in pain (SevgiUnal Aslan & Cetinkaya, 2023). The previous three studies were all rated as high risk of bias. There was a change in pain following whole body vibration compared to control group (Prioreschi et al., 2016) when measured using Likert score (rated 0-5) in a study rated as some concerns (effect size -2.48, 95 % CI -3.34 to -1.49), however the changes were not significant at follow-up between the two groups (effect size 0.00, 95% CI -0.76 to 0.76). There was no significant difference between a control group and a group that received an anti-inflammatory diet in a study with low risk of bias: data was not available to calculate effect sizes (Turesson Wadell et al., 2021). A work-based productivity intervention in a study with high risk of bias, showed a slight increase in pain for both control and intervention groups, with the intervention group mean also higher than control. However, this was not a significant effect: effect size 0.00, 95% CI -0.32 to 0.32 (van Vilsteren et al., 2017). Neural

mobilization in a high risk of bias study, did not show a significant difference between intervention and control group: effect size -0.27, 95% CI -1.12 to 0.60 (Lau et al., 2019).

Disability/functional ability

Fifteen studies included disability or functional ability as an outcome. Most studies used the Health Assessment Questionnaire (HAQ) to measure this. The remaining studies used the following: two studies used the modified HAQ (Hewlett et al., 2019; Prioreschi et al., 2016); one used the RAID (Lau et al., 2019); one used the Multi-dimensional HAQ (Latocha et al., 2023); one used the Short Version - Valued Life Activities Disability scales (Bachmair et al., 2022); another used the Impact of Rheumatic diseases on General health and Lifestyle (Ferwerda et al., 2017). One study used a measure of morning disability that assessed how long it took to reach maximum physical activity, which was proposed to be reflective of disability (Davis et al., 2015).

Two physical activity interventions showed significant improvements. An exercise program showed improvements in HAQ scores (Durcan et al., 2014): effect size -0.50, 95% CI -0.94 to -0.04. Similarly, a PEP also showed improvement in scores (Azeez et al., 2020). Effect size and confidence intervals were not able to be calculated from reported data in the latter study. One study that included an arm using a pedometer and another using both pedometer and target steps reported non-significant improvements for both arms compared to control: effect size -0.09, 95% CI -0.61 to 0.42; effect size -0.35, 95% CI -0.87 to 0.17 (Katz et al., 2018). All three of the studies were rated as high risk of bias. A yoga pilot study, rated as low risk of bias, did not show a significant difference in scores: effect sizes -0.82 , 95% CI -1.61 to 0.02 (Ward et al., 2018). Intermittent aerobic exercise, also showed no

significant improvements in a study rated as some concerns of bias: effect size -0.02, 95% CI -0.60 to 0.57 (Loeppenthin et al., 2022).

The majority of the psychosocial interventions showed no significant improvement for disability/functional ability in the intervention groups compared to the control groups, with risk of bias ranging from low to high in these studies (Hewlett et al., 2019; Knittle et al., 2015; Latocha et al., 2023). The paper by Latocha et al., 2023 did not have the information needed to calculate effect size with the remaining studies effect sizes found in appendix (see Supplementary Table S4 in Appendix 1.3, page 111 for details). One study, rated as high risk of bias, showed significant improvement for the mindfulness only group compared to control (Davis et al., 2015). Another two papers (both rated as some concerns of bias) reported improvement at 16 weeks and at 22 month follow-up (Thomsen et al., 2017; Thomsen et al., 2020). Effect sizes were unable to be calculated for these studies due to required data not being available. Another study, rated as high risk of bias, found an overall significant reduction for the overall impact of rheumatoid arthritis on daily living, effect size –0.62, CI -1.02 to -0.22, when comparing an internet-based cognitive-behavioural intervention and the control group (Ferwerda et al., 2017).

Improvement in functional ability was also observed for a group who undertook WBV compared to baseline and the control group at 6 months, with no improvements observed for the control group (Prioreschi et al., 2016); effect size -1.28, 95% CI -2.02 to -0.48. There was no significant difference between groups for disability following the use of an anti-inflammatory diet (Turesson Wadell et al., 2021), in a study rated as low risk of bias: effect size unable to be calculated. Neural mobilization in a high risk of bias study, also showed no significant difference: effect size -0.13, CI -0.98 to 0.73 (Lau et al., 2019). A nursing

education program over nine months, also showed no significant difference when compared to the control group in a study with some concerns of bias; effect sizes were unable to be calculated due to missing information (Paek et al., 2018).

Disease activity

Sixteen studies measured disease activity impact following intervention with the majority of studies using the DAS-28 to measure change. The RA disease activity index (RADAI) was used in three studies (Ferwerda et al., 2017; Katz et al., 2018; Knittle et al., 2015); the Clinical Disease Activity Index (CDAI) used in two studies (Prioreschi et al., 2016; Ward et al., 2018) ; one study used a measure of global health outcome (Bachmair et al., 2022) and another measured stiffness using a VAS (Durcan et al., 2014).

An exercise program resulted in significant improvements in stiffness compared to control group (effect size -0.65, 95% CI -1.10 to -0.19), however was rated as high risk of bias (Durcan et al., 2014). The remaining physical activity interventions found no significant improvement in disease activity compared to control groups (Azeez et al., 2020; Feldthusen et al., 2016; Katz et al., 2018; Pukšić et al., 2021; Ward et al., 2018), with the risk of bias ranging from low to high risk of bias. It was not possible to calculate the effect sizes for one study (Azeez et al., 2020), the remaining effect sizes are found in Appendix 1.3, page 112, see Supplementary Table S5 for details.

Most psychosocial interventions did not result in a significant improvement in disease activity (Ferwerda et al., 2017; Hewlett et al., 2019; Knittle et al., 2015; Latocha et al., 2023; Thomsen et al., 2020; Yousefi et al., 2022). Effect sizes and confidence intervals can be found in Appendix 1.3, see Supplementary Table S6 for details. Two papers did not have the

information needed to calculate effect sizes (Latocha et al., 2023; Thomsen et al., 2020). Risk of bias ranged from low to high risk for the studies. RA only sub-group analysis was not reported by one study for disease activity (Bachmair et al., 2022).

One study, with some concerns of bias, found a significant effect (effect size -0.53, 95% CI -1.01 to -0.03) on disease activity following participation in a nursing education program (Paek et al., 2018). Moosavian et al. (2020), which was rated as high risk of bias, also found a significant reduction in disease activity as measured by the DAS-28 between the group receiving a garlic supplement compared to the placebo group (effect size -0.78, 95% CI -1.26 to -0.28). No significant improvements were noted for disease activity, as measured by Compound Disease Activity Index (CDAI), following whole body vibration: effect size -0.39, 95% CI -1.14 to 0.39 (Prioreschi et al., 2016).

Discussion

This review evaluated both the benefits and harm of non-pharmacological interventions for fatigue in RA, as well as evaluating benefits on a range of secondary outcomes. In total, 29 papers were identified as published since November 2012. There was a range of interventions used: ten psychosocial interventions; nine physical activity interventions; one that included an arm for both physical activity and psychosocial; aromatherapy massage and reflexology; progressive muscle relaxation; neural mobilisation; garlic supplements; whole body vibration; reiki and hand massage; an anti-inflammatory diet; and a work-based intervention. The quality of evidence ranged from low risk of bias to high. Two meta-analyses conducted (one for psychosocial interventions and one for physical activity, incorporating new data since 2012 and earlier data from a previous review) indicated a small effect size for the impact of interventions on the outcome of fatigue, with psychosocial interventions showing a slightly greater effect size. Similarly, for the sub-analyses that included only the studies that identified fatigue as the primary outcome, there was also a small beneficial effect size observed for both psychosocial and physical activity interventions. However, with the inclusion of fatigue focussed interventions only, the effect size increased and the heterogeneity decreased. Across all four meta-analyses, there was higher heterogeneity between the psychosocial studies than physical activity. The findings differed slightly from the previous review, in which physical activity interventions had shown a somewhat stronger effect (Cramp et al., 2013). Overall, across the secondary outcomes, evidence was not conclusive as findings and risk of bias varied across studies.

Nonetheless, this review also shows the potential for non-pharmacological interventions to improve multiple areas of difficulties.

There was heterogeneity across the interventions and also for the measures used. A range of measures were used both to measure fatigue and the secondary outcomes, suggesting that there is no standard approach to measurement. The previous review also noted this and suggested that a more standardised approach would then allow for easier comparison (Cramp et al., 2013). It could then be recommended that future research should consider the development of perhaps a core set of outcome measures or a gold standard approach to measuring fatigue to allow for better comparison.

Quality appraisal

Risk of bias ranged from low to high across studies with very few studies rated as low. There was a consistent lack of reporting across studies which meant items were often rated as "no information" which impacted overall domain rating of risk of bias. This was similarly identified in the previous review (Cramp et a., 2013), suggesting that more transparent and clear reporting is needed. Many studies showed bias in relation to non-blinding which is difficult to achieve in the interventions included in this review. However, this was again also identified by the previous review and highlighted as limitation in the research (Cramp et al., 2013). Nonetheless, it has clearly not been addressed in the time since the previous review was published and therefore is an area future research should consider to improve on. It could then be helpful to include more active control groups in future, such as comparing with another intervention or one that involves similar therapeutic aspects such as meeting with others or professionals to discuss difficulties etc.,

Additionally, many studies used self-rated outcome (such as VAS) measures which then impacted quality rating. However, again this is likely due to intervention and outcome type which would be difficult to measure without use of self-report measures. This also was highlighted as a limitation within the literature in other similar reviews (Runge et al., 2023) and should be an area for future improvement within the literature.

Clinical Implications

Both physical activity and psychosocial interventions show a benefit for improving fatigue in people with rheumatoid arthritis. Therefore, both should be considered to be offered as interventions. However, the conceptualisation and the mechanisms of fatigue are not yet fully understood with psychosocial, biological and physiological factors such as anxiety, inflammation and physical activity among others, all suggested to influence. Additionally, it has been suggested that these factors are likely to also have varying influence on individuals (Davies et a., 2021). Therefore, it could be suggested that a multi-modal intervention that targets various mechanisms could be more effective as would perhaps a person-centred approach to offering interventions that are best matched to an individual and their difficulties. This may also be an area that future research could consider exploring.

Strengths and limitations of the review

The current review not only adds to the research evidence by updating the literature but has methodological strengths in that it was 100% co-rated at both screening and quality appraisal stages. However, the review was limited in that only 25% of papers were checked for accuracy of data extraction and coverage was limited to papers published in the English language only. Another limitation was that some papers did not report standard deviations

and were then hand calculated from information found in the text. However, not all papers had the information within the text needed to do this and the authors approached for this missing information did not respond to the queries. Additionally, the meta-analyses included two studies that had more than one arm, this then led to “double-counting” within the analysis as the control groups for these studies were entered twice. This then may have led to an overestimate of the effects within these studies.

Conclusions

This review highlights that non-pharmacological interventions can help to improve fatigue in a rheumatoid arthritis population and that there was no serious harm directly related to engaging in these interventions. There was also promise shown for improvements in other domains, however it is difficult to draw conclusive evidence as results remain variable between interventions including those of a similar type. This review has also highlighted that there is a need still for more high quality research, with risk of bias high across most studies included, and there is a need for more for clear and transparent reporting also.

Systematic Review References

Azeez, M., Clancy, C., O'Dwyer, T., Lahiff, C., Wilson, F., & Cunnane, G. (2020). Benefits of exercise in patients with rheumatoid arthritis: a randomized controlled trial of a patient-specific exercise programme [Journal article]. *Clinical rheumatology*, *39*(6), 1783 - 1792. https://doi.org/10.1007/s10067-020-04937-4

Bachmair, E.-M., Martin, K., Aucott, L., Dhaun, N., Dures, E., Emsley, R., Gray, S. R., Kidd, E., Kumar, V., Lovell, K., MacLennan, G., McNamee, P., Norrie, J., Paul, L., Packham, J., Ralston, S. H., Siebert, S., Wearden, A., Macfarlane, G., & Basu, N. (2022). Remotely delivered cognitive behavioural and personalised exercise interventions for fatigue severity and impact in inflammatory rheumatic diseases (LIFT): a multicentre, randomised, controlled, open-label, parallel-group trial. *The Lancet Rheumatology*, *4*(8), e534-e545. https://doi.org/https://doi.org/10.1016/S2665-9913(22)00156-4

Cramp, F., Hewlett, S., Almeida, C., Kirwan, J. R., Choy, E. H. S., Chalder, T., Pollock, J., & Christensen, R. (2013). Non - pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database of Systematic Reviews*(8). https://doi.org/10.1002/14651858.CD008322.pub2

Crowson, C. S., Matteson, E. L., Myasoedova, E., Michet, C. J., Ernste, F. C., Warrington, K. J., Davis III, J. M., Hunder, G. G., Therneau, T. M., & Gabriel, S. E. (2011). The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis & Rheumatism*, *63*(3), 633-639. https://doi.org/https://doi.org/10.1002/art.30155

Davies, K., Dures, E., & Ng, W. F. (2021). Fatigue in inflammatory rheumatic diseases: current knowledge and areas for future research. Nature Reviews Rheumatology, 17(11), 651-664.

Davis, M. C., Zautra, A. J., Wolf, L. D., Tennen, H., & Yeung, E. W. (2015). Mindfulness and cognitive-behavioral interventions for chronic pain: differential effects on daily pain reactivity and stress reactivity [Journal article]. *Journal of consulting and clinical psychology*, *83*(1), 24 - 35. https://doi.org/10.1037/a0038200

Deeks, J., Higgins, J., & Altman, D. (2023). Chapter 10: Analysing data and undertaking meta-analyses. In T. J. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (Ed.), *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023)*. Cochrane. https://training.cochrane.org/handbook/current/chapter-10

Durcan, L., Wilson, F., & Cunnane, G. (2014). The effect of exercise on sleep and fatigue in rheumatoid arthritis: a randomized controlled study [Journal article]. *Journal of rheumatology*, *41*(10), 1966 - 1973. https://doi.org/10.3899/jrheum.131282

Dures, E., Cramp, F., Hackett, K., & Primdahl, J. (2020). Fatigue in inflammatory arthritis. *Best Practice & Research Clinical Rheumatology*, *34*(2), 101526. https://doi.org/https://doi.org/10.1016/j.berh.2020.101526

Feldthusen, C., Dean, E., Forsblad-d'Elia, H., & Mannerkorpi, K. (2016). Effects of Person-Centered Physical Therapy on Fatigue-Related Variables in Persons

With Rheumatoid Arthritis: a Randomized Controlled Trial [Journal article]. *Archives of physical medicine and rehabilitation*, *97*(1), 26 - 36. https://doi.org/10.1016/j.apmr.2015.09.022

Ferwerda, M., Van Beugen, S., Van Middendorp, H., Spillekom-van Koulil, S., Donders, A. R. T., Visser, H., Taal, E., Creemers, M. C. W., Van Riel, P. C. L. M., & Evers, A. W. M. (2017). A tailored-guided internet-based cognitive-behavioral intervention for patients with rheumatoid arthritis as an adjunct to standard rheumatological care: Results of a randomized controlled trial. *Pain*, *158(5)*, 868-878.

Gok Metin, Z., & Ozdemir, L. (2016). The Effects of Aromatherapy Massage and Reflexology on Pain and Fatigue in Patients with Rheumatoid Arthritis: A Randomized Controlled Trial. *Pain management nursing*, *17*(2), 140-149. https://doi.org/10.1016/j.pmn.2016.01.004

Hewlett, S., Almeida, C., Ambler, N., Blair, P. S., Choy, E. H., Dures, E., Hammond, A., Hollingworth, W., Kadir, B., Kirwan, J. R., Plummer, Z., Rooke, C., Thorn, J., Turner, N., & Pollock, J. (2019). Reducing arthritis fatigue impact: two-year randomised controlled trial of cognitive behavioural approaches by rheumatology teams (RAFT). *Annals of the Rheumatic Diseases*, *78*(4), 465-472. https://doi.org/10.1136/annrheumdis-2018-214469

Higgins, J., Li, T., & Deeks, J. (2022). Choosing effect measures and computing estimates of effect. In T. L. Julian PT Higgins, Jonathan J Deeks (Ed.), *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. Cochrane. https://training.cochrane.org/handbook/current/chapter-06#section-6-5

Higgins, J., Savović, J., Page, M., Elbers, R., & Sterne, J. (2022). Assessing risk of bias in a randomized trial. In T. J. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (Ed.), *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. https://training.cochrane.org/handbook/current/chapter-08

Katz, P., Margaretten, M., Gregorich, S., & Trupin, L. (2018). Physical Activity to Reduce Fatigue in Rheumatoid Arthritis: a Randomized Controlled Trial [Journal article]. *Arthritis Care & Research*, *70*(1), 1 - 10. https://doi.org/10.1002/acr.23230

Kiliç, N., & Kiliç, S. P. (2023). The effect of progressive muscle relaxation on sleep quality and fatigue in patients with rheumatoid arthritis: A randomized controlled trial. *International journal of nursing practice*, *29*(3), Article e13015. https://doi.org/10.1111/ijn.13015

Knittle, K., De Gucht, V., Hurkmans, E., Peeters, A., Ronday, K., Maes, S., & Vlieland, T. V. (2015). Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial. *Clinical rheumatology*, *34*(2), 231-238. https://doi.org/10.1007/s10067-013-2425-x

Latocha, K. M., Loppenthin, K. B., Ostergaard, M., Jennum, P. J., Hetland, M. L., Rogind, H., Lundbak, T., Midtgaard, J., Christensen, R., & Esbensen, B. A. (2023). The effect of group-based cognitive behavioural therapy for insomnia in patients with rheumatoid arthritis: a randomized controlled

trial. *Rheumatology*, *62*(3), 1097-1107. https://doi.org/10.1093/rheumatology/keac448

Lau, Y. N., Ng, J., Lee, S. Y., Li, L. C., Kwan, C. M., Fan, S. M., Leung, B. P. L., & Lo, C. N. (2019). Abrief report on the clinical trial on neural mobilization exercise for joint pain in patients with rheumatoid arthritis. *Zeitschrift fur Rheumatologie*, *78*(5), 474-478. https://doi.org/10.1007/s00393-018-0521-7

Ledingham, J., Snowden, N., & Ide, Z. (2017). Diagnosis and early management of inflammatory arthritis. *BMJ*, *358*, j3248. https://doi.org/10.1136/bmj.j3248

Li, L. C., Feehan, L. M., Xie, H., Lu, N., Shaw, C., Gromala, D., Aviña-Zubieta, J. A., Koehn, C., Hoens, A. M., English, K., & et al. (2020). Efficacy of a Physical Activity Counseling Program With Use of a Wearable Tracker in People With Inflammatory Arthritis: a Randomized Controlled Trial [Journal article]. *Arthritis Care & Research*, *72*(12), 1755 - 1765. https://doi.org/10.1002/acr.24199

Loeppenthin, K., Esbensen, B. A., Klausen, J. M., Ostergaard, M., Christensen, J. F., Tolver, A., Thomsen, T., Bech, J. S., & Jennum, P. (2022). Efficacy and Acceptability of Intermittent Aerobic Exercise on Polysomnography-Measured Sleep in People With Rheumatoid Arthritis With Self-Reported Sleep Disturbance: a Randomized Controlled Trial [Journal article]. *ACR open rheumatology*, *4*(5), 395 - 405. https://doi.org/10.1002/acr2.11403

Moosavian, S. P., Paknahad, Z., Habibagahi, Z., & Maracy, M. (2020). The effects of garlic (Allium sativum) supplementation on inflammatory biomarkers, fatigue, and clinical symptoms in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial [Journal article]. *Phytotherapy research : PTR*, *34*(11), 2953 - 2962. https://doi.org/10.1002/ptr.6723

Paek, S. I., Jung, S. M., Lee, J., Kwok, S. K., Kim, W. U., Park, S. H., Ju, J. H., & Sohng, K. Y. (2018). Effects of Individual Education Using a Treating-to-target Strategy in Patients with Rheumatoid Arthritis. *Journal of Rheumatic Diseases*, *25*(4), 255-262. https://doi.org/10.4078/jrd.2018.25.4.255

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., . . . Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Pot-Vaucel, M., Aubert, M. P., Guillot, P., Glémarec, J., Berthelot, J. M., Le Goff, B., & Maugars, Y. (2016). Randomised study versus control group of customised therapeutic education for patients in follow-up for rheumatoid arthritis. *Joint Bone Spine*, *83*(2), 199-206. https://doi.org/10.1016/j.jbspin.2015.05.017

Prioreschi, A., Makda, M. A., Tikly, M., & McVeigh, J. A. (2016). In Patients with Established RA, Positive Effects of a Randomised Three Month WBV Therapy Intervention on Functional Ability, Bone Mineral Density and Fatigue Are Sustained for up to Six Months [Journal article]. *PLoS One*, *11*(4), e0153470. https://doi.org/10.1371/journal.pone.0153470

Pukšić, S., Mitrović, J., Čulo, M. I., Živković, M., Orehovec, B., Bobek, D., & Morović-Vergles, J. (2021). Effects of Yoga in Daily Life program in rheumatoid arthritis: a randomized controlled trial [Journal article]. *Complementary therapies in medicine*, *57*, 102639. https://doi.org/10.1016/j.ctim.2020.102639

Roodenrijs, N. M. T., Hamar, A., Kedves, M., Nagy, G., van Laar, J. M., van der Heijde, D., & Welsing, P. M. J. (2021). Pharmacological and non-pharmacological therapeutic strategies in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. *RMD open*, *7*(1), e001512. https://doi.org/10.1136/rmdopen-2020-001512

Runge, N., Arribas-Romano, A., Labie, C., Mairesse, O., Goossens, Z., Nijs, J., Malfliet, A., Verschueren, S., Van Assche, D., de Vlam, K., & De Baets, L. (2023). The effectiveness of exercise and physical activity programs on fatigue and sleep in people with arthritis – A systematic review with meta-analysis. *Sleep Medicine Reviews*, *71*, 101832. https://doi.org/https://doi.org/10.1016/j.smrv.2023.101832

SevgiUnal Aslan, K., & Cetinkaya, F. (2023). The effects of Reiki and hand massage on pain and fatigue in patients with rheumatoid arthritis [Journal article]. *Explore (New York, N.Y.)*, *19*(2), 251 - 255. https://doi.org/10.1016/j.explore.2022.06.006

Symmons, D., Turner, G., Webb, R., Asten, P., Barrett, E., Lunt, M., Scott, D., & Silman, A. (2002). The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology*, *41*(7), 793-800. https://doi.org/10.1093/rheumatology/41.7.793

Symmons, D. P. M. (2002). Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome. *Best Practice & Research Clinical Rheumatology*, *16*(5), 707-722. https://doi.org/https://doi.org/10.1053/berh.2002.0257

Thomsen, T., Aadahl, M., Beyer, N., Hetland, M. L., Loppenthin, K., Midtgaard, J., Christensen, R., Ostergaard, M., Jennum, P. J., & Esbensen, B. A. (2017). The efficacy of motivational counselling and SMS reminders on daily sitting time in patients with rheumatoid arthritis: a randomised controlled trial [Journal article]. *Annals of the rheumatic diseases. (no pagination), 2017*, *Date of Publication: June 25*. https://doi.org/10.1136/annrheumdis-2016-210953

Thomsen, T., Aadahl, M., Beyer, N., Hetland, M. L., Løppenthin, K. B., Midtgaard, J., Christensen, R., Nielsen, S. M., Østergaard, M., Jennum, P., & et al. (2020). Sustained Long-Term Efficacy of Motivational Counseling and Text Message Reminders on Daily Sitting Time in Patients With Rheumatoid Arthritis: long-Term Follow-up of a Randomized, Parallel-Group Trial [Journal article]. *Arthritis Care & Research*, *72*(11), 1560 - 1570. https://doi.org/10.1002/acr.24060

Turesson Wadell, A., Bärebring, L., Hulander, E., Gjertsson, I., Hagberg, L., Lindqvist, H. M., & Winkvist, A. (2021). Effects on health-related quality of life in the randomized, controlled crossover trial ADIRA (Anti-inflammatory

Diet In Rheumatoid Arthritis) [Journal article]. *PLoS One*, *16*(10), e0258716. https://doi.org/10.1371/journal.pone.0258716

van Vilsteren, M., Boot, C. R., Twisk, J. W., Steenbeek, R., Voskuyl, A. E., van Schaardenburg, D., & Anema, J. R. (2017). One Year Effects of a Workplace Integrated Care Intervention for Workers with Rheumatoid Arthritis: results of a Randomized Controlled Trial [Journal article]. *Journal of occupational rehabilitation*, *27*(1), 128 - 136. https://doi.org/10.1007/s10926-016-9639-0

Ward, L., Stebbings, S., Athens, J., Cherkin, D., & Baxter, G. D. (2018). Yoga for the management of pain and sleep in rheumatoid arthritis: a pilot randomized controlled trial. *Musculoskeletal care*, *16*(1), 39-47. https://doi.org/10.1002/msc.1201

Yentur, S. B., Atas, N., Ozturk, M. A., & Oskay, D. (2021). Comparison of the effectiveness of pilates exercises, aerobic exercises, and pilates with aerobic exercises in patients with rheumatoid arthritis. *Irish journal of medical science*, *190*(3), 1027-1034.

Yousefi, S., Zanjani, Z., Omidi, A., Zamani, B., & Sayyah, M. (2022). Comparison of Mindfulness-Based Stress Reduction Therapy and Cognitive-Behavioral Therapy of Chronic Fatigue, Sleep Quality, Executive Function and Disease Activity in Patients with Rheumatoid Arthritis [Journal article]. *Journal of contemporary psychotherapy*. https://doi.org/10.1007/s10879-022-09558-3

Zuidema, R., van Dulmen, S., Nijhuis-van der Sanden, M., Meek, I., van den Ende, C., Fransen, J., & van Gaal, B. (2019). Efficacy of a Web-Based Self-Management Enhancing Program for Patients with Rheumatoid Arthritis: explorative Randomized Controlled Trial [Journal article]. *Journal of medical Internet research*, *21*(4), e12463. https://doi.org/10.2196/12463

Chapter 2- Major Research Project

Understanding the impact of fatigue management interventions on mental health outcomes among adults with inflammatory rheumatic disease.

Prepared in accordance with the author requirements for Psychology & Health; https://www.tandfonline.com/action/authorSubmission?show=instructions&journalCode=gpsh20

Plain Language Summary

Title

Understanding the impact of fatigue management interventions on mental health outcomes among adults with inflammatory rheumatic disease.

Background

Inflammatory rheumatic diseases (IRD), such as rheumatoid arthritis, are common in the population. Fatigue is a common and significant concern reported by those with an IRD. The "Lessening the Impact of Fatigue in Inflammatory Rheumatic Diseases: a Randomised Trial" (LIFT) study, studied the effects of two fatigue focused interventions (a graded exercise program and a psychological based approach), compared with usual care, on several outcomes. Improvements were shown for the outcomes of fatigue, sleep difficulties, depression and functional ability (Bachmair et al., 2022). It is less clear what influences these changes, what background factors may impact on how or why the changes arise.

Aims and Questions

This study aimed to understand the influence of background and other factors that impacted on how and why interventions have affected the outcomes of mental health quality of life; sleep disturbance; depression and engagement in valued life activities.

Methods

Participants:

Participants came from six rheumatology centres across the UK. Participants could participate if they were over eighteen years old, had a diagnosis of an IRD, and reported fatigue to be a persistent and significant difficulty. They were not able to take part in the study if there was a reason for fatigue that could be reversed by treating an established biomedical cause of fatigue, if their IRD was unstable or if they could not participate in the interventions for physical health reasons. There were 368 participants, with one later withdrawing and another excluded. Most participants had a rheumatoid arthritis diagnosis and were female. Participants were assigned to one of three intervention groups.

Recruitment:

No new participants were recruited for this analysis, as the data was already gathered as part of the LIFT study.

Informed Consent:

Participants had previously provided written informed consent before participation in the original LIFT study. Participants had also consented to future data sharing.

Design of study:

This study was a secondary data analysis of existing data.

Data collection:

There was no further data gathered as part of this study.

Main Findings and Conclusions

The background factors included as part of the analysis in this study - age, gender, employment group, pain, perception of illness, behaviour response to illness and depression - did not appear to influence the change in outcomes after intervention. However, fatigue appeared to impact change in mental health quality of life in the groups who underwent the exercise program and the psychological based approach. Fatigue also influenced change in depression and engagement in valued life activities for those in the exercise group, with behavioural response to illness also seen to influence change in engagement in valued life activities in the same group. However, this only occurred for the fatigue and behavioural response scores after the intervention had finished but not during it. This would suggest that post-intervention scores in fatigue and behavioural response to illness could be related to subsequent change in these other follow-up outcomes.

Abstract

Objective

The “Lessening the Impact of Fatigue in Inflammatory Rheumatic Diseases: a Randomised Trial” (LIFT) found that secondary outcomes of quality of life and sleep disturbance improved following two fatigue interventions (personalised exercise program (PEP) or cognitive behavioural approach (CBA)) vs treatment as usual (TAU), with the PEP group showing improvements on depression and engagement in valued life activities also (Bachmair et al., 2022). This study aimed to understand the impact of moderating and mediating variables on changes in these secondary outcomes in response to the interventions.

Methods and Measures

This was a secondary analysis of data from the LIFT study. Moderation and mediation analyses were conducted to understand the influence of variables on the improved outcomes at 56 week follow-up (timepoint 4). Potential moderators (gender, age, employment group, illness perception, pain, behavioural response and depression) were taken from timepoint 1 (baseline). Potential mediators (fatigue, sleep disturbance, depression and behavioural response) were taken from timepoint 2 (10 weeks – mid-intervention) and timepoint 3 (28 weeks – post-intervention).

Results

There were no significant moderation effects found for any outcomes studied. None of the mediators recorded at timepoint 2 indicated a significant mediation effect.

Fatigue recorded at timepoint 3 showed a significant mediation effect on change in quality of life in response to both interventions vs TAU (indirect effect in PEP group = 1.44, 95% CI 0.53 to 2.60; indirect effect in CBA group = 0.92, 95% CI 0.22 to 1.87), and on change in depression and valued life activities in response to the PEP intervention vs TAU (indirect effect for depression outcome = -0.48, 95% CI -0.87 to -0.17; indirect effect for valued life activities outcome = -0.08, 95% CI -0.16 to -0.03). Behavioural response at timepoint 3 showed a mediating effect on change in valued life activities in response to the PEP intervention vs TAU (indirect effect = -0.07, 95% CI -0.13 to -0.01).

Conclusion

Fatigue and behavioural response at post-intervention appeared to have partly mediated the effect of the interventions on some of the secondary outcomes at longer term follow-up. This work then highlights that fatigue focussed interventions can alter other outcomes via their influence on fatigue and behavioural response in an IRD population. This is an important step in understanding the causal mechanisms of these interventions.

Introduction

Rheumatoid arthritis (RA) and other inflammatory rheumatic diseases (IRD) are common health conditions, with life-time risk of developing an IRD around 1 in 12 for women and 1 in 20 for men (Crowson et al., 2011).

It has been found that both physical activity and cognitive-behavioural interventions have resulted in improvements in quality of life, ability to engage in valued activities, affect, and sleep outcomes in a clinical IRD population (Bachmair et al., 2022; Hewlett et al., 2019). It is less clear how these changes occur, and what the possible moderating and mediating variables could be that may impact these outcomes. A moderator is a third variable which influences the relationship between the independent and dependent variables by affecting the direction and/or strength of their relationship. On the other hand, a mediator variable is on the causal pathway between the independent and dependent variables, and can be the mechanism of change that explains the relationship between them: how or why an effect has occurred (Baron & Kenny, 1986). Therefore, studying moderation and mediation effects can provide further understanding as to why changes in outcomes occur, as well as which pre-disposing factors may influence why changes are more or less likely to arise.

Potential moderators and mediators of quality-of-life outcomes

In an IRD population, it has been found that lower health-related quality of life is more common for women and people who do not have full-time employment (Dean et al., 2018; Matcham et al., 2014). Age has also been related to mental health quality of Life (MHQoL), with older age having a positive association with increased MHQoL (Berner et al., 2018; Matcham et al., 2014). Illness perception has also been found to relate to MHQoL within this clinical population, with increased scores on MHQoL associated with lower illness perception, in particular emotional representation of illness (Berner et al., 2018). In conclusion, it can be suggested that gender, age, employment status and illness perception could be background moderators that influence the association between a clinical intervention and MHQoL outcomes.

Research has also suggested that factors such as fatigue, sleep disturbance, depression and activity impairment are predictive of a lower health-related quality of life in an arthritis population (Berner et al., 2018; Dean et al., 2018; Macfarlane et al., 2020). It could be proposed that these could be potential mediators between clinical interventions and subsequent outcome measures of quality of life.

Potential moderators and mediators of sleep outcomes

Previously, research has suggested that depression, illness perception and pain are associated with sleep disturbance in a RA population, with it being suggested that depression shows partial mediation between pain and sleep disturbance (Nicassio et al., 2012). It could therefore be suggested that depression could be a mediator for the effect of clinical interventions on sleep disturbance, and that perception of illness and pain may be moderators.

Potential moderators and mediators of depression outcomes

Increased depression scores have been found to be associated with sleep disturbance, with research also suggesting that increased sleep disturbance then caused a significant increased change in depression scores in comparison to the control group (Irwin et al., 2012; Luyster et al., 2011). Additionally, fatigue has also been suggested to be predictive of depression (Wolfe & Michaud, 2009). Therefore, it could be suggested that depression outcomes following intervention may be mediated by both sleep disturbance and fatigue. Additionally, illness perception has also been suggested to relate to depression, with an association between increased depression levels and more illness symptoms. Additionally, perception of illness consequence has also been found to correlate with depression (Cordingley et al., 2014; Groarke et al., 2004). Moreover, a review suggested that behavioural response (e.g. how an individual copes or responds behaviourally to illness), illness cognitions, and fatigue may all underlie the relationship between mental health and RA (Sturgeon, Finan, & Zautra, 2016). It can then be suggested that sleep disturbance and fatigue may mediate depression levels in response to intervention, and that moderators for this relationship could be illness perception and behavioural response.

Potential moderators and mediators of valued life activities outcomes

When comparing those with more positive illness perceptions, those with a negative view of illness had worse daily functioning; more positive perceptions of illness were more strongly linked to lower functional impairment (Gwinnutt et al., 2021; Norton et al., 2014). It has also been proposed that in an RA sample, depression may influence the ability to experience positive affect, and this then influences activity participation. This impairment then also influences the effect of pain and the ability to cope, and

negatively affects wellbeing. The researchers proposed that this then causes a prioritisation of more immediate pain relief rather than participation in activity that is meaningful (Sturgeon et al., 2016). In summary, it is proposed that engagement in valued life activities in response to an intervention may be moderated by illness perception and depression. It could also be suggested that behavioural response and pain may act as mediators also. Furthermore, sleep disturbance has also been found to be associated with functional impairment, with fatigue and pain also mediating this relationship (Luyster et al., 2011), which could suggest perhaps serial mediation.

LIFT trial

The "Lessening the Impact of Fatigue in Inflammatory Rheumatic Diseases: a Randomised Trial" (LIFT) study, which was a large randomised controlled trial, investigated the effects of two interventions on fatigue and other physical and mental health outcomes (Bachmair et al., 2022). It compared a graded personalised exercise program (PEP) and a cognitive behavioural approach intervention (CBA) against treatment as usual (TAU). Following randomisation, 368 participants participated in the trial with almost equal numbers in each group. There were 124 participants in the PEP group (one later with withdrew), 122 in CBA (one participant was excluded post-randomisation) and 122 in TAU. Fatigue was the primary outcome of interest in the trial, and both interventions were found to be effective in reducing its severity and impact. Benefits were also seen on several of the secondary outcome measures. Both sleep disturbance and MHQoL showed significant improvements at 56 weeks (final follow-up) for both interventions when compared to TAU. Additionally, there was a significant improvement for sleep at 28 weeks (post-intervention) for PEP compared to

TAU. PEP at 28 and 56 weeks also showed significant improvement for depression and valued life activities (VLA), a measure of functional impairment (Katz et al., 2011) when compared to TAU (Bachmair et al., 2022).

Research is underway by the LIFT study team to analyse the potential mediators and moderators of the primary fatigue outcomes. However, it is also of interest to explore possible moderating and mediating factors for the impact of the interventions on the secondary outcomes, which are therefore the focus of the present study. It is hoped that this research will further our understanding of which individuals may benefit most from interventions, how these interventions may work, and why effects occur.

Aims and Research Questions

Using secondary data from LIFT, this study aimed to explore the underlying mechanisms, specifically the moderating and mediating effect of variables, which led to changes in the outcome variables of MHQoL, sleep disturbance, depression and VLA, after participation in either a personalised exercise program or a cognitive behavioural fatigue focussed intervention. Figure 1 shows a graphic representation of the planned mediation analysis with fatigue used as the example of a mediator. Figure 2, shows a graphic representation of the planned moderation analysis with illness perception as the example of a moderator.

Primary research questions:

1. To what extent do gender, age, employment status and illness perception moderate the effects of fatigue interventions on the outcome of mental health related quality of life?

2. To what extent do fatigue, sleep disturbance and depression mediate the effects of fatigue interventions on the outcome of mental health related quality of life?
3. To what extent do pain and illness perception moderate the effects of fatigue interventions on the outcome of sleep disturbance?
4. To what extent does depression mediate the effects of fatigue interventions on the outcome of sleep disturbance?

Secondary research questions (for the PEP intervention only, as the CBA intervention was not significantly associated with these outcomes):

5. To what extent do illness perception and behavioural response to illness moderate the effects of the PEP intervention on the outcome of depression?
6. To what extent do fatigue and sleep disturbance mediate the effects of the PEP intervention on the outcome of depression?
7. To what extent do illness perception and depression moderate the effects of the PEP intervention on valued life activities?
8. To what extent do sleep disturbance, pain, fatigue, and behavioural response mediate the effects of the PEP intervention on valued life activities?

Figure 8. Graphic representation of moderation analysis with illness perception as a moderator.

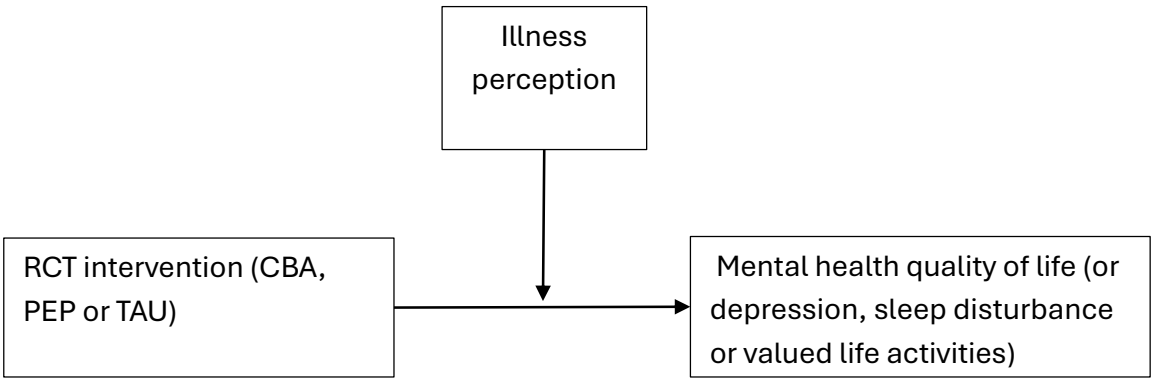
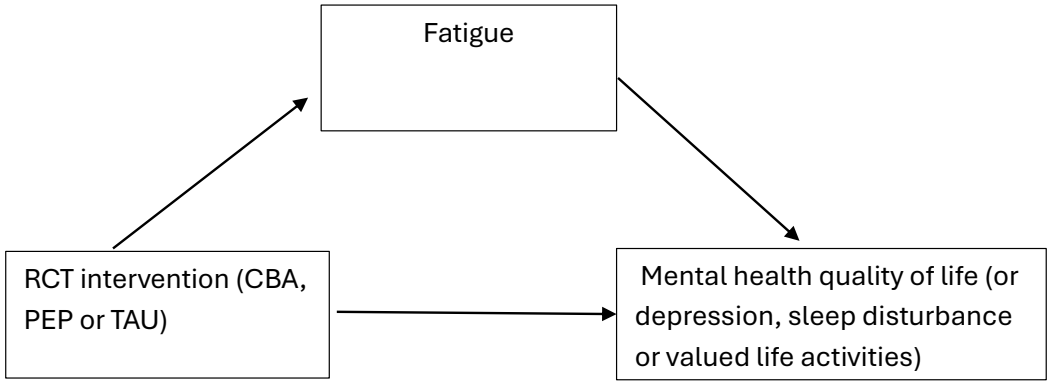


Figure 9. Graphic representation of mediation analysis with fatigue as mediator.



Methods

This paper was written up in accordance with the AGReMA Statement, the guideline for reporting mediation analysis (Lee et al., 2021).

Design

LIFT was a randomised controlled trial with three parallel arms across multiple sites (Martin et al., 2019). The trial protocol and later amendments have been published elsewhere (Bachmair et al., 2022; Martin et al., 2019). This project was a secondary data analysis using quantitative data from the trial.

Participants

Recruitment was conducted in six rheumatology clinics throughout Scotland and England. Participant inclusion criteria were as follows: aged 18 years and over; IRD diagnosis by a Consultant Rheumatologist, and fatigue reported as a concern. Furthermore, fatigue had to be clinically significant and persistent. This was defined as a minimum self-rating of 6/10 for average fatigue level in the prior seven days and had to have occurred for three months. Individuals were excluded if their IRD was unstable, if there was a medical explanation for fatigue which could be changed or if they were unsuitable for the interventions due to physical health reasons. There were 368 participants in the trial, with one later excluded and another withdrawing. Of

those who participated, the majority were female (n=274, 75%) and most had a diagnosis of rheumatoid arthritis (n=202, 55%).

Procedure

Recruitment started in August 2017 and finished in September 2019. Participants were randomly allocated to one of three conditions (CBA, PEP or TAU) using an online randomisation system (Bachmair et al., 2022). All participants received treatment as usual as a minimum, with this being an education booklet focused on fatigue.

The CBA and PEP interventions were telephone-based and delivered one-to-one by trained clinicians (occupational therapists, nurses and a physiotherapist). The interventions were delivered as seven 45-minute sessions over 14 weeks with a further booster session at 22 weeks. Both interventions were based on previous fatigue interventions (Hewlett et al., 2015; White et al., 2011).

Participants were assessed at baseline and at three further time points (week 10 mid-intervention, week 28 post-intervention, and week 56 follow-up). Participants were not blinded to interventions nor to the purpose that interventions were to reduce fatigue. Those delivering the interventions were also not blinded, however all research investigators including those performing assessments were blinded to allocation.

The CBA intervention targeted unhelpful cognitions and behaviours and aimed to replace these with the use of more helpful ones. The PEP intervention was a personalised exercise programme. It gradually increased exposure and amount of exercise, with the aim to also change exercise tolerance and effort perception (Bachmair et al., 2022; Martin et al., 2019).

Materials and measures

The manuals for CBA and PEP interventions are available from the LIFT page on the University of Aberdeen website (Macfarlane, n.d).

Appendix 2.3 (p116), table 1A, summarises the measures collected in the trial and the timepoints for which they were collected. Only a subset of the measures collected were used as part of this project; this included mental and physical health outcomes and demographic information such as age, employment status and gender. Moderator variables were taken from timepoint one (baseline, before intervention) and mediators from both timepoint 2 (10 weeks) and 3 (28 weeks). Mediator variables at timepoint 2 were used for the main analyses, because there was less missing data compared to timepoint 3. Timepoint 3 data was used for additional mediation analyses as reported within the results section also.

The following measures were used in the analysis:

Demographic information

Demographic information such as age, gender and employment status were collected at baseline.

Fatigue

Fatigue was measured using the Chalder Fatigue scale (Cella & Chalder, 2010). It measures fatigue severity and is rated on a 0 to 33 total scale, with higher scores reflecting higher fatigue. It has good internal consistency and discriminative validity

(Cella & Chalder, 2010). This was the primary fatigue outcome in the LIFT study (Bachmair et al., 2022; Martin et al., 2019).

Mental Health Quality of Life

MHQoL was measured using the mental component of the Short Form-12. The Short-Form-12 measures both physical and mental quality of life, and the overall score ranges from 0 to 100, with a higher score suggesting better QoL. It has reasonable test-retest reliability and good validity (Ware et al., 1996). The original LIFT study measured both. However, only the mental component of the Short Form-12 was used in the current study, with scores of 42 or less indicating lower mental health functioning (Bachmair et al., 2022; Ware et al., 1996).

Sleep

Sleep disturbance was measured using the Jenkin's Sleep Scale (Bachmair et al., 2022; Jenkins et al., 1988). It has been found to have good internal and moderate test re-test reliability. The scores range from 0 to 20, with higher scores reflecting higher sleep disturbance (Jenkins et al., 1988).

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety and depression (Bachmair et al., 2022; Zigmond & Snaith, 1983). The depression component only was used in the analysis; scores range from 0 to 21 with scores over 7 indicating presence of depression (Zigmond & Snaith, 1983). A review found that the HADS had good reliability and validity (Bjelland et al., 2002).

Pain

Pain intensity was measured on a numerical 0-10 scale (Bachmair et al., 2022; McCaffery, 1994). It is suggested to be both a valid and reliable measure of pain intensity (Hawker et al., 2011).

Valued Life Activities

Valued life activities, which is a measure of functional impairment/disability, was measured using the Short Form of the Valued Life Activities Disability Questionnaire for Rheumatoid Arthritis (Bachmair et al., 2022; Katz et al., 2011). It rates difficulty of ability to do 14 activities, with response options ranging from 0 (no difficulties) to 3 (unable to perform). The overall score is the mean of the scores rated for difficulty on the activities (Katz et al., 2011). It has good internal consistency, test re-test reliability and has been found to correlate with other measures of disability (Katz et al., 2011).

Behavioural Response to Illness

The Cognitive and Behavioral Responses to Symptoms Questionnaire (CBSQ) was used to measure behavioural response to symptoms/illness. It has an acceptable internal reliability and was found to be both valid and reliable for use within long-term conditions (Picariello et al., 2023; Skerrett & Moss-Morris, 2006). The behavioural component has two sub-scales with 13 items scored on a five-point frequency scale. The two sub-scales are summed to give the total score, with a higher score indicating a stronger behavioural response to symptoms (Bachmair et al., 2022; Macfarlane et al., 2020; Skerrett & Moss-Morris, 2006).

Illness Perception

Illness perception was measured using the Brief Illness Perception Questionnaire (Brief IPQ), a 9-item measure of illness perception. It is rated on a 0-10 scale, with total score calculated by summation of the item response. Higher scores indicate a poorer perception of illness. It has been found to have good test-retest reliability, predictive and concurrent validity (Broadbent et al., 2006).

Ethics, Governance and Data Protection

The LIFT study received approval from NHS Research Ethics Committee Wales 7 (17/WA/065), as well as the Research and Development departments of the NHS health boards that participated in the trial (Bachmair et al., 2022). All participants gave written, informed consent. Additionally, consent for future data sharing was also provided. The data from the study was anonymised, with the trainee having no access to participant identification logs. There was an existent data sharing agreement between the University of Glasgow and the University of Aberdeen (the original study sponsor) prior to this secondary data analysis project.

It was advised by the University of Glasgow Medical, Veterinary and Life Sciences Ethics Committee and NHS West of Scotland Research Ethics Service that further ethical approval would not be required from either organisation due to data being anonymised and not stored within the NHS.

Sample Size

The sample size analysed for the original LIFT study was 366 participants (Bachmair et al., 2022). This was pre-calculated for 90% power to detect a standardised effect size of 0.5 between intervention groups and to include additional participants to account

for an anticipated drop-off rate of 20% (Bachmair et al., 2022). The sample size analysed in this study was lower due to incomplete and missing data on the outcomes, moderators and/or mediators, which meant that the complete-case analysis approach used here (necessary for the PROCESS statistical software) included fewer participants than the original main outcome analyses in LIFT. The final sample size that was analysed for each model is reported in the results tables.

As the sample sizes were already known for this study, sensitivity power analyses were conducted to estimate the minimum effect size that could be reliably detected for the largest moderation and mediation analyses conducted in this study (n=244 and n=228 respectively; see results section). G*Power software showed that a sample of n=244 in a moderation model with 5 predictors would have 80% power (at alpha 0.05) to detect a small moderation effect or above (f-sq = 0.03 or above). Power calculations for mediation analyses are typically based on published estimates taken from simulation models. Estimates published by Fritz and MacKinnon (2007) indicate that at least 162 participants are needed to give 80% power to detect a mediation effect that is small to medium or above (r=0.26 or above), for both the effect of the independent variable on the mediator and the effect of the mediator on the outcome. This minimum sample size was exceeded in the present study (n=228); much larger samples (around 400 or above) would be needed to reliably detect weaker mediation effects involving smaller correlations. Therefore, the largest models in present study were adequately powered to reliably detect small moderation effects and small to medium mediation effects.

Statistical Analysis

Statistical analysis was completed using SPSS and PROCESS macro, an SPSS additional program designed for mediation and moderation analyses (Hayes, 2022). Both mediation and moderation analyses were conducted with adjustment for the treatment centre, the baseline values of the outcome measures that were the focus of that model, the diagnosis, and a HADS score indicative of depression at timepoint one (the latter two were used as part of the stratified randomisation process in the original trial and so must be accounted for in the models). Multi-categorical moderation analysis was conducted using PROCESS with moderator measures collected at time point one (baseline), with the generated conditional effects and confidence intervals being of interest. PROCESS macro was also used to run multi-categorical mediation analysis with bootstrap confidence intervals based on 5000 bootstrap samples, with the indirect effect being the result of interest. This effect is the amount of the total effect that is due to the mediator. PROCESS does not produce a p value for the indirect effect, owing to the assumptions of the percentile bootstrapping method that it uses to generate the confidence intervals. Mediator variables analysed in the main analysis were from timepoint two (10 weeks, mid-intervention). Additional analyses of the mediators at timepoint three (28 weeks, post-intervention) are included in the results also. Due to the study being exploratory, the results of mediation and moderation analysis focused on the effect sizes and 95% confidence intervals, with p-values being of less interest. Results are expressed as unstandardised effect sizes. If zero is within the 95% CI this would suggest that there is not a significant effect (A. F. Hayes, 2022), with the width of the confidence interval indicating the level of precision of the estimate.

Results

Characteristics of the sample

Table 2 shows the baseline descriptives for the full sample (n=367).

Table 2.

Baseline participant information.

	PEP (n=124)	CBA (n=121)	TAU (n=122)
Gender, n (%)			
Female	97 (78.2)	84 (69.4)	93 (76.2)
Male	26 (21.0)	37 (30.6)	29 (23.8)
Missing	1 (0.8%)	0	0
Diagnosis, n (%)			
Rheumatoid Arthrit is	68 (54.8)	67 (55.4)	68 (55.7)
Systemic Lupus Erythematosus	13 (10.5)	12 (9.9)	12 (9.8)
Axial spondyloarthritis	10 (8.1)	9 (7.4)	10 (8.2)
Other	33 (26.6)	33 (27.3)	32 (26.2)
Age n missing	1	0	0
Mean (SD) years	56.39 (12.28)	59.33 (13.02)	56.81 (12.70)
Employment group, n (%)			
Working full-time (30 hrs or more per week)	35 (28.2)	36 (29.8)	38 (31.1)
Working part-time (less than 30 hrs per week)	16 (12.9%)	16 (13.2)	23 (18.9)

Unemployed and looking for work	2 (1.6)	1 (0.8)	1 (0.8)
Unable to work because of illness or Disability	20 (16.1)	14 (11.6)	16 (13.1)
At home and not looking for paid employment	4 (3.2)	2 (1.7)	3 (2.5)
Student	2 (1.6)	2 (1.7)	1 (0.8)
Retired	42 (33.9)	46 (38.0)	36 (29.5)
Other	2 (1.6)	3 (2.5)	2 (1.6)
Missing	1 (0.8)	1 (0.8)	2 (1.6)
Depression score n missing	0	0	0
Mean (SD)	6.66 (3.32)	6.53 (3.36)	6.25 (3.26)
Illness perception score n missing	10	11	9
Mean (SD)	53.12 (11.64)	51.20 (12.33)	51.64 (10.98)
Behavioural Response to Illness score n missing	3	3	3
Mean (SD)	26.59 (7.56)	26.54 (6.94)	26.53 (6.21)
Pain score n missing	3	3	2
Mean (SD)	5.94 (2.52)	5.73 (2.27)	5.75 (2.25)

Table 3.

Scores at each timepoint for variables used as outcome measures in the analysis models.

	PEP (n=124)	CBA (n=121)	TAU (n=122)
MHQoL			
Baseline (n) Mean (SD)	117 40.75 (11.33)	116 41.58 (11.23)	117 42.85 (11.24)
Time 2 (n)	88	92	95

Mean (SD)	42.33 (11.08)	44.29 (10.98)	44.87 (9.51)
Time 3 (n) Mean (SD)	73 45.31 (12.34)	85 44.96 (11.22)	81 44.67 (10.21)
Time 4 (n) Mean (SD)	73 44.83 (10.50)	87 45.31 (10.71)	79 43.23 (11.24)
Sleep disturbance			
Baseline (n) Mean (SD)	120 13.03 (5.25)	115 13.40 (4.93)	119 12.77 (5.32)
Time 2 (n) Mean (SD)	89 12.09 (5.15)	91 11.77 (5.33)	95 11.83 (5.68)
Time 3 (n) Mean (SD)	78 10.55 (5.56)	87 10.95 (5.30)	83 11.73 (5.45)
Time 4 (n) Mean (SD)	75 11.61 (5.85)	89 10.76 (5.82)	81 12.88 (5.65)
Depression			
Baseline (n) Mean (SD)	123 6.656(3.32)	121 6.53 (3.36)	122 6.25 (3.26)
Time 2 (n) Mean (SD)	91 6.56 (3.70)	93 6.34 (3.65)	95 5.99 (3.27)
Time 3 (n) Mean (SD)	78 5.35 (3.65)	88 5.89 (3.27)	83 5.77 (3.10)
Time 4 (n) Mean (SD)	75 5.41(3.56)	88 6.01 (3.43)	85 6.29 (3.46)
Valued life activities			
Baseline (n missing) Mean (SD)	122 1.54 (0.82)	120 1.50 (0.80)	120 1.58 (0.81)
Time 2 (n) Mean (SD)	90 1.32 (0.81)	93 1.42 (0.86)	94 1.46 (0.84)
Time 3 (n) Mean (SD)	78 1.18 (0.82)	88 1.44 (0.85)	84 1.46 (0.88)
Time 4 (n) Mean (SD)	76 1.25 (0.94)	88 1.26 (0.86)	85 1.48 (0.90)

Table 4.

Scores for other variables used as mediators and moderators in the analysis models.

Mediator	PEP	CBA	TAU

Fatigue Baseline (n) Mean (SD)	 122 21.41 (5.57)	 120 20.42 (5.81)	 120 20.68(5.23)
Time 2 (n) Mean (SD)	91 16.54 (7.49)	95 17.19 (6.38)	94 17.90 (6.16)
Time 3 (n) Mean (SD)	79 14.87 (8.16)	88 15.71 (6.68)	82 18.44 (5.72)
Pain Baseline (n) Mean (SD)	 121 5.94 (2.52)	 119 5.73 (2.27)	 120 5.75 (2.25)
Time 2 (n) Mean (SD)	91 5.08 (2.73)	93 5.37 (2.36)	94 5.27 (2.55)
Time 3 (n) Mean (SD)	 77 4.81 (2.86)	 87 5.33 (2.20)	 83 5.23 (2.29)
Behavioural response Baseline (n) Mean (SD)	 121 26.57 (7.56)	 118 26.54 (6.94)	 119 26.53 (6.21)
Time 2 (n) Mean (SD)	91 24.79(7.38)	93 26.08 (7.87)	94 25.89 (6.30)
Time 3 (n) Mean (SD)	77 22.52(7.92)	86 24.43 (7.45)	83 25.28 (6.28)

Baseline differences

One-way ANOVAs were conducted to detect whether there were any baseline differences on the outcome variables, mediators or moderators between the intervention groups. There were no significant differences found (results not shown), indicating that the groups were similar on these measures at timepoint 1 before they commenced the intervention.

Moderation and mediation analyses

Complete-case analysis was run for each of the moderation and mediation models, with the sample size for each detailed in the tables below. All models were run with

TAU as the reference group. The below tables show the results for each of these models with further analysis for mediators at timepoint 3.

Primary research questions

Gender, age, employment status and illness perception as moderators of the impact of fatigue interventions on mental health related quality of life, research question (RQ) 1.

As shown by table 5, there was no significant moderation effect found for gender, age, employment status or illness perception on the relationship between each treatment and the outcome of mental health related quality of life. The coefficients were generally small, with confidence intervals including zero.

Table 5.
Results for potential moderators of the effect of fatigue interventions on mental health related quality of life.

Model	Co-efficient for moderation effect	95% CI; p-value
PEP vs TAU (n=232) Moderator = gender	0.74	-5.82 to 7.29; p=0.83
CBA vs TAU (n= 232) Moderator=gender	-1.40	-0.12 to 0.35; p=0.33
PEP vs TAU (n=232) Moderator=age	-0.15	-0.39 to 0.85; p=0.21
CBA vs TAU (n= 232) Moderator=age	0.09	-0.12 to 0.29; p=0.42
PEP vs TAU (n=232) Moderator=employment group* *Moderator reference group= Full-time employment		
PEP (part-time)	1.86	-7.01 to 10.74; p=0.68
PEP (no job)	1.79	-6.79 to 10.36; p=.68
PEP (retired)	-2.66	-9.83 to 4.51; p=0.47
PEP (other)	-11.30	-32.44 to 9.84; p=0.29
CBA vs TAU (n=232) Moderator=employment group*		

*Moderator reference group= Full-time employment **CBA (part-time)** **CBA (no job)** **CBA (retired)** **CBA (other)**	 1.08 0.80 1.54 -6.80	 -6.68 to 8.84; p=0.78 -7.84 to 9.43; p=0.86 -5.05 to 8.14; p=0.65 -31.03 to 17.44; p=0.58
PEP vs TAU (n=219) Moderator=illness perception	0.10	-0.14 to 0.35;p=0.41
CBA vs TAU (n= 219). Moderator =illness perception	0.12	-0.12 to 0.35; p=0.33

Note: For all models, the dependent variable was mental health quality of life at timepoint 4, and the covariates were baseline mental health quality of life, baseline depression status, diagnosis and study centre.

Abbreviations: CBA = cognitive behavioural approach, PEP = Physical Exercise program, TAU = Treatment as usual.

Fatigue, sleep disturbance and depression as mediators of the effect of fatigue interventions on mental health related quality of life (RQ 2).

As had already been reported by Bachmair et al. (2022), there was a significant overall effect of both PEP and CBA on MHQoL at 56 weeks, compared with TAU. The total effect estimates are reported in Table 6 below; the exact results vary slightly from model to model owing to the differences in samples with complete mediator and covariate data analysed in each model. Fatigue at timepoint 2 only accounted for a small proportion of these overall total effects. The indirect effect via fatigue was 0.45 (CI -0.02 to1.19) for PEP and 0.18 (-0.29 to 0.74) for CBA; this was non-significant for both. At timepoint 3, fatigue indicated a significant mediation effect on MHQoL for both intervention groups. In the PEP group, the indirect effect (=1.44, 95% CI 0.53 to 2.60) accounted for a medium sized proportion (around 40%) of the total effect. Whereas in the CBA group, around a quarter of the total effect was due to the indirect effect (= 0.92, 95% CI 0.22 to 1.87). Sleep disturbance showed no significant mediation effect in either intervention group nor at either timepoint. For timepoint 2, in the PEP group, the indirect effect via sleep disturbance was small (0.23, 95% CI -0.37 to 0.87). This was also similarly observed for the CBA group, where the indirect effect via sleep disturbance (0.26, 95% CI -0.28 to 0.96) again was only a small proportion of the overall total effect. At timepoint 3, sleep disturbance only accounted for a small proportion of the overall total effects in both groups. The indirect effect via sleep disturbance was 0.66 (95% CI -0.02 to 1.60) for PEP and 0.37 (95% CI -0.25 to 1.17) for CBA; this was non-significant for both as zero was within the CI. Depression also did not show a significant mediation effect for either intervention group at timepoint 2,

with a small proportion of the total effect in both groups due to the indirect effect (indirect effect in PEP group =-0.17 95% CI -0.76 to 0.48; indirect effect in CBA group = -0.08 95% CI -0.70 to 0.57). Similarly, at timepoint three, depression did not show a significant mediation effect with only a small proportion of the total effect due to the indirect effect. The indirect effect via depression was 0.48 (-0.10 to 1.44) for PEP and 0.07 (-0.50 to 0.84 for CBA; this was non-significant for both as zero was within the CI.

Timepoint 2 (10 weeks)				Timepoint 3 (28 weeks)			
Model	**Indirect effect via Mediator (95% CI)**	**Direct effect not via Mediator (95% CI; p-value)**	**Total effect (95% CI; p-value)**	**Model**	**Indirect Effect via Mediator (CI)**	**Direct effect not via Mediator (CI; p-value)**	**Total effect on DV (95% CI; p-value)**
PEP vs TAU (n=213) Mediator = fatigue	0.45 (-0.02 to 1.19)	3.71 (0.99 to 6.43; p=.008)	4.160 (1.42 to 6.89; p=.003)	**PEP vs TAU** (n=206) Mediator = fatigue	1.44 (0.53 to 2.60)	2.01 (-0.84 to 4.85; p=0.17)	3.45 (0.61 to 6.28; p=0.02)
CBA vs TAU (n= 213) Mediator=fatigue	0.18 (-0.29 to 0.74)	3.295 (0.74 to 5.85; p=0.01)	3.47 (0.89 to 6.06 ; p=. 01)	**CBA vs TAU** (n=206). Mediator=fatigue	0. 92 (0.22 to 1.87)	2.68 (0.06 to 5.31; p=0.05)	3.60 (0.93 to 6.27; p=0.01)
PEP vs TAU (n= 209) Mediator=sleep	0.23 (-0.37 to 0.87)	3.78 (1.05 to 6.51; p=0.01).	4.01 (1.23 to 6.79; p=.01)	**PEP vs TAU** (n=207) Mediator=sleep	0.66 (-0.02 to 1.60)	2.87 (0.13 to 5.62; p=0.04)	3.53 (0 .73 to 6.34; p=0.01)
CBA vs TAU (n= 209) Mediator=sleep	0.26 (-0.28 to 0.96)	2.94 (0.36 to 5.52; p=0.03)	3.20 (0.57 to 5.83; p=0.02)	**CBA vs TAU** (n=207) Mediator=sleep	0.37 (-0.25 to 1.17)	2.98 (0.43 to 5.53; p=0.02)	3.35 (0.73 to 5.98; p=0.01)
PEP vs TAU (n=213) Mediator=depression	-0.17 (-0.76 to 0.48)	4.16 (1.48 to 6.84; p=0.00)	3.99 (1.25 to 6.72; p=0.01)	**PEP vs TAU** (n=) Mediator=depression	0.48 (-0.10 to 1.44)	3.02 (0.26 to 5.78; p=0.03)	3.50 (0.70 to 6.31; p=0.01)

CBA vs TAU (n=213) Mediator=depression	-0.08 (-0.70 to 0.57)	3.28 (0.74 to 5.82; p=0.01)	3.20 (0.60 to 5.79; p=0.02)	**CBA vs TAU** (n=) Mediator=depression	0.07 (-0.50 to 0.84)	3.41(0.85 to 5.97; p=.01)	3.49 (0.87 to 6.10; p=.01)

Table 6. Results for potential mediators of the effect of fatigue interventions on mental health related quality of life.

Note: PROCESS does not produce a p value for the indirect effect, owing to the assumptions of the percentile bootstrapping method that it uses to generate the CI. For all models, the dependent variable was mental health quality of life at timepoint 4, and the covariates were baseline mental health quality of life, baseline depression status, diagnosis and study centre.

Abbreviations: CBA = cognitive behavioural approach, PEP = Physical Exercise program, TAU = Treatment as usual

Pain and illness perception as moderators of the impact of fatigue interventions on sleep disturbance (RQ 3).

Pain did not show a significant moderation effect on sleep disturbance for either intervention, nor did illness perception for the PEP intervention. The results below in Table 7 for illness perception as a moderator in CBA would suggest that there was not a significant moderation effect (p=0.06). However, the PROCESS macro automatically ran further analysis (not shown) to probe the interaction using a 'pick-and-point approach' at different levels of the moderator variable, which it only does if there is a possible moderation effect detected. These results suggested that there was a moderation effect for illness perception at the 50^{th} and 84^{th} percentiles but not at the 16^{th} percentile, suggesting that among participants with a higher illness perception score (increased perception of threat to illness), this may be moderating the effect of the CBA intervention on sleep disturbance.

Table 7.
Results for potential moderators of the effect of fatigue interventions on sleep disturbance.

Model	Co-efficient for moderation effect	CI 95%; p-value
PEP vs TAU (n=241) Moderator=pain	-0.16	-0.82 to 0.52; p=0.65
CBA vs TAU (n= 241) Moderator=pain	-0.28	-0.95 to 0.40; p=0.42
PEP vs TAU (n=229) Moderator=illness perception	-0.01	-0.14 to 0.12; p=0.90
CBA vs TAU (n= 229) Moderator=illness perception	-0.12	-0.25 to 0.002; p=0.06

Note: For all models, the dependent variable was sleep disturbance at timepoint 4, and the covariates were baseline sleep disturbance, baseline depression status, diagnosis and study centre.

Abbreviations: CBA = cognitive behavioural approach, PEP = Physical Exercise program, TAU = Treatment as usual.

Depression as a mediator of the effect of fatigue interventions on sleep disturbance (RQ 4).

The results in table 8 suggest that depression at timepoint 2 (10 weeks) and 3 (28 weeks) were not significant mediators of the effect of the interventions on sleep disturbance at 56 weeks for either the PEP or CBA group. For both groups, the indirect effect was a small proportion of the overall total effect. Interestingly, it appears that depression at 10 weeks may have inversely impacted the sleep disturbance score (as an increase in scores would reflect higher depression levels and sleep disturbance) .

Table 8.

Results for potential mediators of the effect of fatigue interventions on sleep disturbance.

Timepoint 2 (10 weeks)				Timepoint 3 (28 weeks)			
Model	**Indirect effect via Mediator (95% CI)**	**Direct effect not via Mediator (95% CI; p-value)**	**Total effect (95% CI; p-value)**	**Model**	**Indirect effect via Mediator (95% CI)**	**Direct effect not via Mediator (95% CI; p-value)**	**Total effect (95% CI; p-value)**
PEP vs TAU (n=221) Mediator=depression	0.12 (-0.16 to 0.45)	-2.01 (-3.48 to -0.53; p=0.01)	-1.89 (-3.38 to -0.39; p=0.01)	**PEP vs TAU** (n=214) Mediator=depression	-0.09 (-0.53 to 0.25)	-1.65 (-3.19 to -0.1; p=0.04)	-1.74(-3.31 to -0.17; p=0.03)
CBA vs TAU (n= 221) Mediator=depression	0.03 (-0.26 to 0.33)	-2.39 (-3.81 to -0.97; p=0.00)	-2.36 (-3.80 to -0.92; p=0.00)	**CBA vs TAU** (n=214). Mediator=depression	0.03 (-0.34 to 0.36)	-2.21(-3.67 to -0.76; p=0.00)	-2.19 (-3.67 to -0.70; p=0.00)

Note: PROCESS does not produce a p value for the indirect effect, owing to the assumptions of the percentile bootstrapping method that it uses to generate the CI. For all models, the dependent variable was sleep disturbance at timepoint 4, and the covariates were baseline sleep disturbance, baseline depression status, diagnosis and study centre.

Abbreviations: CBA = cognitive behavioural approach, PEP = Physical Exercise program, TAU = Treatment as usual

Secondary research questions

Illness perception and behavioural response to illness as moderators of the effect of PEP intervention on depression (RQ 5).

As shown by the below table (Table 9), both illness perception and behavioural response to illness did not indicate a significant moderation effect for the effect of PEP on the outcome of depression.

Table 9.

Results for potential moderators of the effect of PEP on depression.

Model	Co-efficient for moderation effect	95% CI; p-value
PEP vs TAU (n=233) Moderator=illness perception	0.01	-0.06 to 0.08; p=0.87
PEP vs TAU (n= 244) Moderator= behavioural response to illness	-0.03	-0.14 to 0.09; p=0.67

Note: For both models, the dependent variable was depression at timepoint 4, and the covariates were baseline depression status, baseline depression score, diagnosis and study centre.

Abbreviations: PEP = Physical Exercise program, TAU = Treatment as usual.

Fatigue and sleep disturbance as mediators of the effect of PEP intervention on depression (RQ 6).

Fatigue at timepoint 2 accounted for a small proportion of the total effect for change in the depression score at 56 weeks for PEP versus TAU. The indirect effect was -0.16 (95% CI -0.44 to 0.04). However, fatigue at timepoint 3 accounted for a larger proportion of the overall total effect, the indirect effect via fatigue was -0.48 (-0.87 to -0.17) for PEP; this was a significant mediation effect. The indirect effect via sleep disturbance was very small (-0.01, 95% CI -0.12 to 0.07) at timepoint 2 as was the indirect effect of sleep disturbance at timepoint 3 (-0.12 , 95% CI -0.34 to 0.05).

Table 10.

Results for potential mediators of the effect of PEP on depression.

Timepoint 2 (10 weeks)				Timepoint 3 (28 weeks)			
Model	**Indirect effect via Mediator (95% CI)**	**Direct effect not via Mediator (95% CI; p-value)**	**Total effect (95% CI; p-value)**	**Model**	**Indirect effect via Mediator (95% CI)**	**Direct effect not via Mediator (95% CI; p-value)**	**Total effect (95% CI; p-value)**
PEP vs TAU (n=228) Mediator=fatigue	-0.16 (-0.44 to 0.04)	-0.95 (-1.76 to -0.14; p=.02)	-1.11 (-1.94 to -0.29; p=0.01	**PEP vs TAU** (n=219) Mediator=fatigue	-0.48 (-0.87 to -0.17)	-0.50 (-0.35 to 0.34; p=0.24)	-0.99 (1.84 to -0.13; p=0.02)
PEP vs TAU (n=224) Mediator =sleep disturbance	-0.01 (-0.12 to 0.07)	-1.01 (-1.83 to -0.18; p=0.02)	-1.02 (-1.85 to -0.20; p=0.02)	**PEP vs TAU** (n=219) Mediator =sleep disturbance	-0.12 (-0.34 to 0.05)	-0.96 (-1.79 to -0.12; p=.03)	-1.07 (-1.92 to -0.23; p=0.01)

Note: PROCESS does not produce a p value for the indirect effect, owing to the assumptions of the percentile bootstrapping method that it uses to generate the CI. For both models, the dependent variable was depression at timepoint 4, and the covariates were baseline depression status, baseline depression score, diagnosis and study centre.

Abbreviations: PEP = Physical Exercise program, TAU = Treatment as usual.

Illness perception and depression as moderators of the effect of PEP intervention on valued life activities (RQ7)

As highlighted by the below table 11, both illness perception and depression did not show a significant moderation effect for the impact of PEP on the outcome of valued life activities at timepoint 4.

Table 11.

Results for potential moderators of the effect of PEP on valued life activities.

Model	**Co-efficient for moderation effect**	**95% CI; p-value**
PEP vs TAU (n=232) Moderator=illness perception	0.01	-0.01 to 0.03; p=0.27
PEP vs TAU (n= 232) Moderator=depression	-0.004	-0.06 to 0.05; p=0.89

Note: For both models, the dependent variable was valued life activities at timepoint 4, and the covariates were baseline valued life activities, baseline depression status, diagnosis and study centre.

Abbreviations: PEP = Physical Exercise program, TAU = Treatment as usual.

Sleep disturbance, pain, fatigue, and behavioural response as mediators of the effect of PEP intervention on valued life activities (RQ 8).

Sleep disturbance did not have a significant mediation effect on valued life activities score as shown by table 12, as the confidence intervals contained zero. Only a small proportion of the total effect was due to the indirect effect of sleep disturbance (0.01, CI -0.04 to 0.02) at timepoint 2, and also at timepoint 3 (indirect effect =-0.03, 95% CI -0.08 to 0.02). As shown by table 12, pain (-0.003, CI -0.03 to 0.03) accounted for only an extremely small proportion of the total effect when examining the effect on valued life activities at 56 weeks, and was not statistically significant. This was the same also for pain at timepoint 3 (indirect effect= -0.02, 95% CI -0.07 to 0.03). Fatigue was only a small proportion of the total effect for the change in valued life activities score at 56 weeks for PEP compared to TAU, with the indirect effect accounting for -0.03 of the total effect (CI -0.07 to 0.01). Fatigue at timepoint 3 accounted for a moderate proportion of the overall total effect, the indirect effect via fatigue was -0.08 (CI -0.16 to -0.03); this was a significant mediation effect. As highlighted in the table, behavioural response (-0.05, CI -0.11 – 0.01) at timepoint 2 as mediator accounted for a small, non-significant proportion of the overall total effect for the change in valued life activities score at 56 weeks. However, behavioural response at timepoint 3, showed a significant mediation and was a larger proportion of the total effect (in direct effect= -0.07, 95% CI -0.13 to -0.01).

Table 12.
Results for potential mediators of the effect of PEP on valued life activities.

Timepoint 2 (10 weeks)				Timepoint 3 (28 weeks)			
Model	**Indirect effect via Mediator (95% CI)**	**Direct effect not via Mediator (95% CI; p-value)**	**Total effect (95% CI; p-value)**	**Model**	**Indirect effect via Mediator (95% CI)**	**Direct effect not via Mediator (95% CI; p-value)**	**Total effect (95% CI; p-value)**
PEP vs TAU (n= 224) Mediator=sleep disturbance	-0.01 (-0.04 to 0.02)	-0.22 (-0.42 to -0.03; p=0.02)	-0.23 (-0.42 to -0.03; p=0.02)	**PEP vs TAU** (n=221) Mediator=sleep disturbance	-0.03 (-0.08 to 0.02)	-0.17(-0.36 to 0.02; p=0.08)	-0.20(-0.39 to -0.00; p=0.05).
PEP vs TAU (n=228) Mediator=pain	-0.003 (-0.03 to 0.03)	-0.23 (-0.42 to -0.04; p=0.02)	-0.23 (-0.42 to -0.04; p=0.02)	**PEP vs TAU** (n=220) Mediator=pain	-0.02 (-0.07 to 0.03)	-0.17 (-0.36 to 0.02; p=0.08)	-0.19 (-0.38 to 0.01; p=0.06)
PEP vs TAU (n=228) Mediator=fatigue	-0.03 (-0.07 to 0.01)	-0.20 (-0.39 to – 0.01; p=0.04)	-0.23 (-0.42 to -0.04; p=0.02)	**PEP vs TAU** (n=221) Mediator=fatigue	-0.08 (-0.16 to -0.03)	-0.11(-0.30 to 0.09; p=0.28)	-0.19 (-0.39 to 0.01; p=0.06)
PEP vs TAU (n=227) Mediator=behavioural response	-0.05 (-0.11 to 0.01)	-0.18 (-0.37 – 0.01; p=0.06)	-0.23 (-0.42 to -0.04; p=0.02)	**PEP vs TAU** (n=219) Mediator=Behavioural response	-0.07 (-0.13 to -0.01)	-0.14 (-0.33 to 0.05; p=0.16)	-0.21(-0.40 to -.01; p=0.04)

Note: PROCESS does not produce a p value for the indirect effect, owing to the assumptions of the percentile bootstrapping method that it uses to generate the CI. For both models, the dependent variable was valued life activities at timepoint 4, and the covariates were baseline valued life activities, baseline depression status, diagnosis and study centre. Abbreviations: PEP = Physical Exercise program, TAU = Treatment as usual.

Discussion

Moderation effects

None of the models suggested a significant moderation effect. The confidence intervals included zero, indicating non-significance, and most co-efficients were small. The exception to this was illness perception potentially moderating sleep disturbance in the CBA group. However, the effect was ambiguous and may only be operating at high levels of the moderator (at the 50th and 84th percentiles but not at the 16th percentile), suggesting that potentially only among participants with a higher illness perception score (increased perception of threat to illness) that there is a moderating effect; further research is warranted to clarify this. Overall, the results do not suggest that any of the baseline factors analysed here were having an appreciable moderating influence on the strength or direction of the effect of the interventions on outcomes.

Mediation effects

At timepoint 2 (10 weeks), the mediators only accounted for a very small to small proportion of the total effect on the outcomes at 56 weeks. The confidence intervals also contained zero which would indicate a non-significant effect. However, the additional analyses of mediators at timepoint 3 (28 weeks) showed a much larger indirect effect via fatigue on several outcomes, with confidence intervals that did not include zero. This was true for the outcome of MHQoL in both intervention groups, and for the outcomes of depression and valued life activities for the PEP group. These findings are consistent with previous research that suggested that quality of life was associated with fatigue and that fatigue was a potential modifying factor to improve

quality of life (Dean et al., 2018), although these findings were association rather than testing mediation. Findings from other inflammatory disease populations have also found fatigue to mediate psychological quality of life (Rodgers et al., 2021). Additionally, in a study that analysed data from three psychological intervention RCTs within a cancer population, it was found that improvement in fatigue mediated both depression and difficulties with activity (Müller et al., 2021), similar to current findings. Although not from the same population or intervention, it highlights that like the current findings, that fatigue as a mediator is on the causal pathway and that fatigue change due to an intervention has then influenced depression and engagement in activity. Furthermore, a review discussed that several studies have linked fatigue to depression in the IRD population (Sturgeon et al., 2016). A study, that studied a physical activity intervention, also found that higher fatigue was related to negative affect (Hegarty et al., 2015). Additionally, behavioural response at timepoint three also accounted for around a third of the total effect of PEP on valued life activities and indicated a significant mediation effect based upon confidence intervals. This was also consistent with findings discussed in a review that suggested that behaviour and how an individual responds to their illness, can then impact functioning in a rheumatoid arthritis population (Sturgeon et al., 2016). Furthermore, although in a differing clinical population, it was also found that in a study with those with chronic fatigue syndrome that behavioural response mediated ability to engage in activity following participation in a physical activity intervention (Chalder et al., 2015). The findings are therefore consistent with the current study. Furthermore, the authors suggested that physical activity based therapies would likely have a larger effect compared to other therapeutic interventions like CBT, which was then also confirmed by the current

findings in this study. The remaining mediators at timepoint three did not indicate significant mediation and the indirect effects were relatively small.

Additionally, the mediators having a larger impact at a later timepoint and after the intervention could also be expected based upon the results from the original study and other trials. Both fatigue impact and severity continued to improve following the intervention finishing, with scores decreasing further (Bachmair et al., 2022). Similarly, the RAFT trial which the CBA approach was adapted from, found that fatigue continued to improve over time and that fatigue had shown greater improvement at week 18 compared to 10. The authors suggested that this may have been due to the week 14 consolidation sessions (Hewlett et al.,2019). This, therefore, would suggest that benefits of the interventions were continuing to improve post-intervention. Additionally, it could be suggested that perhaps fatigue severity scores also needed to reduce to a clinically important difference before influencing the other outcomes which may be why there was significant mediation only at timepoint 3. Alternatively, as observed in the RAFT trial, it may be that there was a potential consolidation effect of the week-14 session.

Nonetheless, these findings therefore suggest that fatigue focused interventions that result in fatigue and behavioural response change at post-intervention then influence the outcomes of mental health-related quality of life, depression and engagement in valued life activities at 56-week follow-up.

Clinical Implications

As evidenced in the original LIFT study, these fatigue focussed interventions not only improved fatigue but also other secondary outcomes. The current findings highlight

the role and influence of fatigue and behavioural response in the changes in some of these outcome measures following intervention. These results therefore highlight that these mediators could be potential important treatment targets for improving areas of difficulty and that fatigue focussed interventions can influence other areas of difficulties through these mediators. These interventions should then be considered to not only improve fatigue but also other areas of individuals' lives because of these improvements.

Limitations

The study was limited by missing data. There was missing data across all of the outcomes, covariates, mediators and moderators, with the statistical package only able to analyse complete cases. As the study was exploratory, larger sample numbers would also be needed to draw full conclusions about reliable mediating and moderating effects.

It is also important to consider that part of this study occurred during the COVID-19 pandemic, with this clinical population being part of the shielding category. Research has found that those with IRD who were shielding had lower mental health quality of life, and also older people who were shielding showed increased depression, quality of life and were associated with anxiety (Cleaton et al., 2021; Di Gessa & Price, 2022; Lasseter et al., 2022). It could then be possible that any mediation or moderation effects may have also been influenced by this context and the impact it had on participants, although on the other hand these effects should have been similar across the three intervention groups. It may also be that other factors may have also influenced the changes in secondary outcomes that were not accounted for in the

models such as social isolation or loneliness which may have been a result of the lockdown context.

Strengths

Nonetheless, this study aimed to understand the underlying mechanisms of change for secondary outcome improvements following fatigue-focussed interventions in a randomised controlled trial context and highlighted that fatigue change post-intervention influenced these secondary outcomes. These findings therefore provide an important contribution to the understanding of the causal mechanisms of change for outcomes such as depression, which previously have been limited to association only studies within an IRD population. Additionally, the LIFT study itself had strengths in that it was pragmatic and embedded within rheumatology teams across UK. It was also delivered by multi-disciplinary team members which therefore enhances its applicability and it was also successfully delivered remotely.

Conclusions

This study was exploratory in nature but results suggested a role of fatigue at post-intervention, but not at earlier stages of an intervention, as a potential mediator of change in other outcomes at longer term follow-up. This was also true for behavioural response at post-intervention for the PEP group. This would suggest that variables at post-intervention influence change in outcomes at follow-up, although the influence may not be seen during the intervention itself. This work contributes to the understanding of what the causal mechanisms of these outcomes are and represents an important and novel step towards determining causal potential. Therefore, these

findings then would confirm that fatigue focussed interventions can modify other outcomes via their impact on fatigue and behaviour response in an IRD population.

MRP References

Bachmair, E.-M., Martin, K., Aucott, L., Dhaun, N., Dures, E., Emsley, R., Gray, S. R., Kidd, E., Kumar, V., Lovell, K., MacLennan, G., McNamee, P., Norrie, J., Paul, L., Packham, J., Ralston, S. H., Siebert, S., Wearden, A., Macfarlane, G., & Basu, N. (2022). Remotely delivered cognitive behavioural and personalised exercise interventions for fatigue severity and impact in inflammatory rheumatic diseases (LIFT): a multicentre, randomised, controlled, open-label, parallel-group trial. *The Lancet Rheumatology*, *4*(8), e534-e545. https://doi.org/https://doi.org/10.1016/S2665-9913(22)00156-4

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, *51*(6), 1173-1182. https://doi.org/10.1037/0022-3514.51.6.1173

Berner, C., Erlacher, L., Fenzl, K. H., & Dorner, T. E. (2018). A cross-sectional study on self-reported physical and mental health-related quality of life in rheumatoid arthritis and the role of illness perception. *Health and Quality of Life Outcomes*, *16*(1), 238. https://doi.org/10.1186/s12955-018-1064-y

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of psychosomatic research*, *52*(2), 69-77.

Broadbent, E., Petrie, K. J., Main, J., & Weinman, J. (2006). The Brief Illness Perception Questionnaire. *Journal of Psychosomatic Research*, *60*(6), 631-637. https://doi.org/https://doi.org/10.1016/j.jpsychores.2005.10.020

Cella, M., & Chalder, T. (2010). Measuring fatigue in clinical and community settings. *Journal of Psychosomatic Research*, *69*(1), 17-22. https://doi.org/https://doi.org/10.1016/j.jpsychores.2009.10.007

Chalder, T., Goldsmith, K. A., White, P. D., Sharpe, M., & Pickles, A. R. (2015). Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. *The Lancet Psychiatry*, *2*(2), 141-152. https://doi.org/10.1016/S2215-0366(14)00069-8

Cleaton, N., Raizada, S., Barkham, N., Venkatachalam, S., Sheeran, T. P., Adizie, T., Sapkota, H., Singh, B. M., & Bateman, J. (2021). The impact of COVID-19 on rheumatology patients in a large UK centre using an innovative data collection technique: prevalence and effect of social shielding. *Rheumatology international*, *41*(4), 707-714. https://doi.org/10.1007/s00296-021-04797-4

Cordingley, L., Prajapati, R., Plant, D., Maskell, D., Morgan, C., Ali, F. R., Morgan, A. W., Wilson, A. G., Isaacs, J. D., & Barton, A. (2014). Impact of psychological factors on subjective disease activity assessments in patients with severe rheumatoid arthritis. *Arthritis Care Res (Hoboken)*, *66*. https://doi.org/10.1002/acr.22249

Crowson, C. S., Matteson, E. L., Myasoedova, E., Michet, C. J., Ernste, F. C., Warrington, K. J., Davis III, J. M., Hunder, G. G., Therneau, T. M., & Gabriel, S. E. (2011). The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory

autoimmune rheumatic diseases. *Arthritis & Rheumatism*, *63*(3), 633-639. https://doi.org/https://doi.org/10.1002/art.30155

Dean, L. E., Macfarlane, G. J., & Jones, G. T. (2018). Five Potentially Modifiable Factors Predict Poor Quality of Life in Ankylosing Spondylitis: Results from the Scotland Registry for Ankylosing Spondylitis. *The Journal of Rheumatology*, *45*(1), 62-69. https://doi.org/10.3899/jrheum.160411

Di Gessa, G., & Price, D. (2022). The impact of shielding during the COVID-19 pandemic on mental health: evidence from the English Longitudinal Study of Ageing. *The British Journal of Psychiatry*, *221*(4), 637-643. https://doi.org/10.1192/bjp.2022.44

Fritz, M. S., & MacKinnon, D. P. (2007). Required Sample Size to Detect the Mediated Effect. *Psychological Science*, *18*(3), 233-239. https://doi.org/10.1111/j.1467-9280.2007.01882.x

Groarke, A., Curtis, R., Coughlan, R., & Gsel, A. (2004). The role of perceived and actual disease status in adjustment to rheumatoid arthritis. *Rheumatology (Oxford)*, *43*. https://doi.org/10.1093/rheumatology/keh262

Gwinnutt, J. M., Norton, S., Hyrich, K. L., Lunt, M., Barton, A., Cordingley, L., & Verstappen, S. M. M. (2021). Changes in the illness perceptions of patients with rheumatoid arthritis over the first year of methotrexate therapy. *Rheumatology (Oxford)*, *60*(5), 2355-2365. https://doi.org/10.1093/rheumatology/keaa615

Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). *Arthritis care & research*, *63*(S11), S240-S252.

Hayes, A. (2022). *The PROCESS macro for SPSS, SAS, and R*. Retrieved 04.01.2023 from http://www.processmacro.org/index.html

Hegarty, R. S. M., Conner, T. S., Stebbings, S., & Treharne, G. J. (2015). Feel the Fatigue and Be Active Anyway: Physical Activity on High-Fatigue Days Protects Adults With Arthritis From Decrements in Same-Day Positive Mood. *Arthritis Care & Research*, *67*(9), 1230-1236. https://doi.org/10.1002/acr.22582

Hewlett, S., Almeida, C., Ambler, N., Blair, P. S., Choy, E. H., Dures, E., Hammond, A., Hollingworth, W., Kadir, B., Kirwan, J. R., Plummer, Z., Rooke, C., Thorn, J., Turner, N., & Pollock, J. (2019). Reducing arthritis fatigue impact: two-year randomised controlled trial of cognitive behavioural approaches by rheumatology teams (RAFT). *Annals of the Rheumatic Diseases*, *78*(4), 465-472. https://doi.org/10.1136/annrheumdis-2018-214469

Hewlett, S., Ambler, N., Almeida, C., Blair, P. S., Choy, E., Dures, E., Hammond, A., Hollingworth, W., Kirwan, J., Plummer, Z., Rooke, C., Thorn, J., Tomkinson, K., & Pollock, J. (2015). Protocol for a randomised controlled trial for Reducing Arthritis Fatigue by clinical Teams (RAFT) using cognitive–behavioural approaches. *BMJ Open*, *5*(8), e009061. https://doi.org/10.1136/bmjopen-2015-009061

Irwin, M. R., Olmstead, R., Carrillo, C., Sadeghi, N., FitzGerald, J. D., Ranganath, V. K., & Nicassio, P. M. (2012). Sleep Loss Exacerbates Fatigue, Depression, and Pain in

Rheumatoid Arthritis. *Sleep*, *35*(4), 537-543. https://doi.org/10.5665/sleep.1742

Jenkins, C. D., Stanton, B.-A., Niemcryk, S. J., & Rose, R. M. (1988). A scale for the estimation of sleep problems in clinical research. *Journal of clinical epidemiology*, *41*(4), 313-321. https://doi.org/10.1016/0895-4356(88)90138-2

Katz, P. P., Radvanski, D. C., Allen, D., Buyske, S., Schiff, S., Nadkarni, A., Rosenblatt, L., Maclean, R., & Hassett, A. L. (2011). Development and validation of a short form of the valued life activities disability questionnaire for rheumatoid arthritis. *Arthritis Care Res (Hoboken)*, *63*(12), 1664-1671. https://doi.org/10.1002/acr.20617

Lasseter, G., Compston, P., Robin, C., Lambert, H., Hickman, M., Denford, S., Reynolds, R., Zhang, J., Cai, S., Zhang, T., Smith, L. E., Rubin, G. J., Yardley, L., Amlôt, R., & Oliver, I. (2022). Exploring the impact of shielding advice on the wellbeing of individuals identified as clinically extremely vulnerable amid the COVID-19 pandemic: a mixed-methods evaluation. *BMC public health*, *22*(1), 2145. https://doi.org/10.1186/s12889-022-14368-2

Lee, H., Cashin, A. G., Lamb, S. E., Hopewell, S., Vansteelandt, S., VanderWeele, T. J., MacKinnon, D. P., Mansell, G., Collins, G. S., Golub, R. M., McAuley, J. H., & group, A. G. (2021). A Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies: The AGReMA Statement. *JAMA*, *326*(11), 1045-1056. https://doi.org/10.1001/jama.2021.14075

Luyster, F. S., Chasens, E. R., Wasko, M. C., & Dunbar-Jacob, J. (2011). Sleep quality and functional disability in patients with rheumatoid arthritis. *J Clin Sleep Med*, *7*(1), 49-55.

Macfarlane, G. J. (n.d). *Lessening the Impact of Fatigue in inflammatory rheumatic diseases: a randomised Trial (LIFT)*. Retrieved 28/11/2022 from https://www.abdn.ac.uk/iahs/research/epidemiology/lift-1286.php#panel1731

Macfarlane, G. J., Rotariu, O., Jones, G. T., Pathan, E., & Dean, L. E. (2020). Determining factors related to poor quality of life in patients with axial spondyloarthritis: results from the British Society for Rheumatology Biologics Register (BSRBR-AS). *Annals of the Rheumatic Diseases*, *79*(2), 202-208. https://doi.org/10.1136/annrheumdis-2019-216143

Martin, K. R., Bachmair, E.-M., Aucott, L., Dures, E., Emsley, R., Gray, S. R., Hewlett, S., Kumar, V., Lovell, K., Macfarlane, G. J., MacLennan, G., McNamee, P., Norrie, J., Paul, L., Ralston, S., Siebert, S., Wearden, A., White, P. D., & Basu, N. (2019). Protocol for a multicentre randomised controlled parallel-group trial to compare the effectiveness of remotely delivered cognitive-behavioural and graded exercise interventions with usual care alone to lessen the impact of fatigue in inflammatory rheumatic diseases (LIFT). *BMJ Open*, *9*(1), e026793. https://doi.org/10.1136/bmjopen-2018-026793

Matcham, F., Scott, I. C., Rayner, L., Hotopf, M., Kingsley, G. H., Norton, S., Scott, D. L., & Steer, S. (2014). The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum*, *44*. https://doi.org/10.1016/j.semarthrit.2014.05.001

McCaffery, M., and Alexandra Beebe. (1994). *Pain: Clinical manual for nursing practice*. Mosby.

Müller, F., Wijayanto, F., Abrahams, H., Gielissen, M., Prinsen, H., Braamse, A., van Laarhoven, H. W. M., Groot, P., Heskes, T., & Knoop, H. (2021). Potential mechanisms of the fatigue-reducing effect of cognitive-behavioral therapy in cancer survivors: Three randomized controlled trials. *Psycho-Oncology*, *30*(9), 1476-1484. https://doi.org/https://doi.org/10.1002/pon.5710

Nicassio, P. M., Ormseth, S. R., Kay, M., Custodio, M., Irwin, M. R., Olmstead, R., & Weisman, M. H. (2012). The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis. *Pain*, *153*(1), 107-112. https://doi.org/https://doi.org/10.1016/j.pain.2011.09.024

Norton, S., Hughes, L. D., Chilcot, J., Sacker, A., van Os, S., Young, A., & Done, J. (2014). Negative and positive illness representations of rheumatoid arthritis: a latent profile analysis. *Journal of Behavioral Medicine*, *37*(3), 524-532. https://doi.org/10.1007/s10865-013-9506-9

Picariello, F., Chilcot, J., Chalder, T., Herdman, D., & Moss-Morris, R. (2023). The Cognitive and Behavioural Responses to Symptoms Questionnaire (CBRQ): Development, reliability and validity across several long-term conditions. *British Journal of Health Psychology*, 28, 619–638. https://doi.org/10.1111/bjhp.12644

Rodgers, S., Manjaly, Z.-M., Calabrese, P., Steinemann, N., Kaufmann, M., Salmen, A., Chan, A., Kesselring, J., Kamm, C. P., Kuhle, J., Zecca, C., Gobbi, C., von Wyl, V., & Ajdacic-Gross, V. (2021). The Effect of Depression on Health-Related Quality of Life Is Mediated by Fatigue in Persons with Multiple Sclerosis. *Brain sciences*, *11*(6), 751. https://www.mdpi.com/2076-3425/11/6/751

Skerrett, T. N., & Moss-Morris, R. (2006). Fatigue and social impairment in multiple sclerosis: The role of patients' cognitive and behavioral responses to their symptoms. *Journal of Psychosomatic Research*, *61*(5), 587-593. https://doi.org/https://doi.org/10.1016/j.jpsychores.2006.04.018

Sturgeon, J. A., Finan, P. H., & Zautra, A. J. (2016). Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. *Nat Rev Rheumatol*, *12*(9), 532-542. https://doi.org/10.1038/nrrheum.2016.112

Ware, J. E., Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. *Medical Care*, *34*(3). https://journals.lww.com/lww-medicalcare/fulltext/1996/03000/a_12_item_short_form_health_survey__construction.3.aspx

White, P. D., Goldsmith, K. A., Johnson, A. L., Potts, L., Walwyn, R., DeCesare, J. C., Baber, H. L., Burgess, M., Clark, L. V., Cox, D. L., Bavinton, J., Angus, B. J., Murphy, G., Murphy, M., O'Dowd, H., Wilks, D., McCrone, P., Chalder, T., & Sharpe, M. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *The Lancet*, *377*(9768), 823-836. https://doi.org/10.1016/S0140-6736(11)60096-2

Wolfe, F., & Michaud, K. (2009). Predicting depression in rheumatoid arthritis: The signal importance of pain extent and fatigue, and comorbidity. *Arthritis Care & Research*, *61*(5), 667-673. https://doi.org/https://doi.org/10.1002/art.24428

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361-370. https://doi.org/https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Appendices

Appendix 1.1 PRISMA guidelines

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	9
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	10
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	12
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	13
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	14-16
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	19
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	103
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	15-16
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	16
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	17-24
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	17-24
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	25

Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	28-43
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	20-24
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	16
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	16
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	16
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	25
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	19
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	19
Study characteristics	17	Cite each included study and present its characteristics.	20-24
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	26
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	28-43
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	28-43
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	28-33
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A

Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	26
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	44-45
	23b	Discuss any limitations of the evidence included in the review.	45
	23c	Discuss any limitations of the review processes used.	45
	23d	Discuss implications of the results for practice, policy, and future research.	44-45
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	14
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	14
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 1.2 Search strategy for each database

EMBASE search strategy

1 exp rheumatoid arthritis/

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3 1 or 2

4 exp fatigue/

5 fatigue$.tw.

6 (tired$ or weary or weariness or exhaustion or exhausted).tw.

7 ((astenia or asthenic) and syndrome).tw.

8 ((lack or loss or lost) adj3 (energy or vigo?r)).tw.

9 (apath$ or lassitude or weak$ or letharg$).tw.

10 (feel$ adj3 (drained or sleep$ or sluggish)).tw.

11 vitality.tw.

12 or/4-11

13 3 and 12

14 random$.ti,ab.

15 factorial$.ti,ab.

16 (crossover$ or cross over$ or cross-over$).ti,ab.

17 placebo$.ti,ab.

18 (doubl$ adj blind$).ti,ab.

19 (singl$ adj blind$).ti,ab.

20 assign$.ti,ab.

21 allocat$.ti,ab.

22 volunteer$.ti,ab.

23 crossover procedure.sh.

24 double blind procedure.sh.

25 randomized controlled trial.sh.

26 single blind procedure.sh.

27 or/14-26

28 exp animal/ or nonhuman/ or exp animal experiment/

29 exp human/

30 28 and 29

31 28 not 30

32 27 not 31

33 13 and 32

Medline

1. exp arthritis, rheumatoid/

2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. 1 or 2

4. exp Fatigue/

5. fatigue$.tw.

6. (tired$ or weary or weariness or exhaustion or exhausted).tw.

7. ((astenia or asthenic) and syndrome).tw.

8. ((lack or loss or lost) adj3 (energy or vigo?r)).tw.

9. (apath$ or lassitude or weak$ or letharg$).tw.

10. (feel$ adj3 (drained or sleep$ or sluggish)).tw.

11. vitality.tw.

12. or/4-11

13. randomized controlled trial.pt.

14. controlled clinical trial.pt.

15. randomized.ab.

16. placebo.ab.

17. drug therapy.fs.

18. randomly.ab.

19. trial.ab.

20. groups.ab.

21. or/13-20

22. (animals not (humans and animals)).sh.

23. 21 not 22

24. and/3,12,23

CINAHL search strategy

S75 S61 and S74

S74 S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73

S73 TI Allocat* random* or AB Allocat* random*

S72 (MH "Quantitative Studies")

S71 (MH "Placebos")

S70 TI Placebo* or AB Placebo*

S69 TI Random* allocat* or AB Random* allocat*

S68 (MH "Random Assignment")

S67 TI Randomi?ed control* trial* or AB Randomi?ed control* trial*

S66 AB “singl* blind*” or AB singl* mask* or AB doub* blind* or AB doubl* mask* or AB trebl* blind* or AB trebl* mask* or AB tripl* blind* or AB tripl* mask*

S65 TI singl* blind* or TI singl* mask* or TI doub* blind* or TI doubl* mask* or TI trebl* blind* or TI trebl* mask* or TI tripl* blind* or TI tripl* mask*

S64 TI clinical* trial* or AB clinical* trial*

S63 PT clinical trial

S62 (MH "Clinical Trials+")

S61 S42 and S60

S60 S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59

S59 ti vitality or ab vitality

S58 ab (feel* N2 drain*) or ab feel* N2 sleep* or ab feel* N2 sluggish

S57 ti feel* N2 drain* or ti feel* N2 sleep* or ti feel* N2 sluggish

S56 ab apath* or ab lassitude or ab weak* or ab letharg*

S55 ti apath* or ti lassitude or ti weak* or ti letharg*

S54 ab lack N2 vigour or abloss N2 vigour or ab lost N2 vigour

S53 ti lack N2 vigour or ti loss N2 vigour or ti lost N2 vigour

S52 ab lack N2 vigor or ab loss N2 vigor or ab lost N2 vigor

S51 ti lack N2 vigor or ti loss N2 vigor or ti lost N2 vigor

S50 ti lack N2 vigor or ti loss N2 vigor or ab lost N2 vigor

S49 ti lack N2 energy or ti loss N2 energy or ti lost N2 energy

S48 ab “astenia syndrome” or ab asthenic syndrome

S47 ti astenia syndrome or ti asthenic syndrome

S46 ab tired* or weary or weariness or exhaustion or exhausted

S45 ti tired* or weary or weariness or exhaustion or exhausted

S44 ti fatigue* or ab fatigue*

S43 (MH "Fatigue+")

S42 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41

S41 TI reumat* N2 nodule* or AB reumat* N2 nodule*

S40 TI reumat* N2 condition* or AB reumat* N2 condition*

S39 TI reumat* N2 diseas* or AB reumat* N2 diseas*

S38 TI reumat* N2 artrit* or AB reumat* N2 artrit*

S37 TI reumat* N2 arthrit* or AB reumat* N2 arthrit*

S36 TI revmarthrit* N2 nodule* or AB revmarthrit* N2 nodule*

S35 TI revmarthrit* N2 condition* or AB revmarthrit* N2 condition*

S34 TI revmarthrit* N2 diseas* or AB revmarthrit* N2 diseas*

S33 TI revmarthrit* N2 artrit* or AB revmarthrit* N2 artrit*

S32 TI revmarthrit* N2 arthrit* or AB revmarthrit* N2 arthrit*

S31 TI rheumat* N2 nodule* or AB rheumat* N2 nodule*

S30 TI rheumat* N2 condition* or AB rheumat* N2 condition*

S29 TI rheumat* N2 diseas* or AB rheumat* N2 diseas*

S28 TI rheumat* N2 artrit* or AB rheumat* N2 artrit*

S27 TI rheumat* N2 arthrit* or AB rheumat* N2 arthrit*

S26 TI revmatic N2 nodule* or AB revmatic N2 nodule*

S25 TI revmatic N2 condition* or AB revmatic N2 condition*

S24 TI revmatic N2 diseas* or AB revmatic N2 diseas*

S23 TI revmaticN2 artrit* or AB revmatic N2 artrit*

S22 TI revmatic N2 arthrit* or AB revmatic N2 arthrit*

S21 TI rheumatic N2 nodule* or AB rheumatic N2 nodule*

S20 TI rheumatic N2 condition* or AB rheumatic N2 condition*

S19 TI rheumatic N2 diseas* or AB rheumatic N2 diseas*

S18 TI rheumatic N2 artrit* or AB rheumatic N2 artrit*

S17 TI rheumatic N2 arthrit* or AB rheumatic N2 arthrit*

S16 TI revmatoid N2 nodule* or AB revmatoid N2 nodule*

S15 TI revmatoid N2 condition* or AB revmatoid N2 condition*

S14 TI revmatoid N2 diseas* or AB revmatoid N2 diseas*

S13 TI revmatoid N2 artrit* or AB revmatoid N2 artrit*

S12 TI revmatoid N2 arthrit* or AB revmatoid N2 arthrit*

S11 TI reumatoid N2 nodule* or AB reumatoid N2 nodule*

S10 TI reumatoid N2 condition* or AB reumatoid N2 condition*

S9 TI reumatoid N2 diseas* or AB reumatoid N2 diseas*

S8 TI reumatoid N2 artrit* or AB reumatoid N2 artrit*

S7 TI reumatoid N2 arthrit* or AB reumatoid N2 arthrit*

S6 TI rheumatoid N2 nodule* or AB rheumatoid N2 nodule*

S5 TI rheumatoid N2 condition* or AB rheumatoid N2 condition*

S4 TI rheumatoid N2 diseas* or AB rheumatoid N2 diseas*

S3 TI rheumatoid N2 artrit* or AB rheumatoid N2 artrit* *

S2 TI rheumatoid N2 arthrit* or AB rheumatoid N2 arthrit*

S1 (MH "Arthritis, Rheumatoid+")

Medline

Ovid MEDLINE(R) ALL <1946 to November 16, 2023>

1 exp Arthritis rheumatoid/ 126898

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw. 152176

3 1 or 2 193458

4 exp Fatigue/ 38228

5 fatigue$.tw. 126696

6 (tired$ or weary or weariness or exhaustion or exhausted).tw. 43159

7 ((astenia or asthenic) and syndrome).tw. 291

8 ((lack or loss or lost) adj3 (energy or vigo?r)).tw. 11491

9 (apath$ or lassitude or weak$ or letharg$).tw. 503136

10 (feel$ adj3 (drained or sleep$ or sluggish)).tw. 758

11 vitality.tw. 15662

12 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 694559

13 randomized controlled trial.pt. 603298

14 controlled clinical trial.pt. 95453

15 randomized.ab. 624705

16 placebo.ab. 243191

17 drug therapy.fs. 2640116

18 randomly.ab. 420953

19 trial.ab. 672863

20 groups.ab. 2597123

21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 5805731

22 (animals not (humans and animals)).sh. 5137080

23 21 not 22 5072602

24 3 and 12 and 23 1899

Note – then filtered by date .

AMED search strategy

1. exp arthritis, rheumatoid/

2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. 1 or 2

4. exp Fatigue/

5. fatigue$.tw.

6. (tired$ or weary or weariness or exhaustion or exhausted).tw.

7. ((astenia or asthenic) and syndrome).tw.

8. ((lack or loss or lost) adj3 (energy or vigo?r)).tw.

9. (apath$ or lassitude or weak$ or letharg$).tw.

10. (feel$ adj3 (drained or sleep$ or sluggish)).tw.

11. vitality.tw.

12. or/4-11

13. 3 and 12

PsycINFO search strategy

1. rheumatoid arthritis/

2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. 1 or 2

4. Fatigue/

5. fatigue$.tw.

6. (tired$ or weary or weariness or exhaustion or exhausted).tw.

7. ((astenia or asthenic) and syndrome).tw.

8. ((lack or loss or lost) adj3 (energy or vigo?r)).tw.

9. (apath$ or lassitude or weak$ or letharg$).tw.

10. (feel$ adj3 (drained or sleep$ or sluggish)).tw.

11. vitality.tw.

12. or/4-11

Web of Science search strategy

1: ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) NEAR/2 (arthrit* or artrit* or diseas* or condition* or nodule*)) (Topic) Date Run: Fri Nov 03 2023 11:24:39 GMT+0000 (Greenwich Mean Time) Results: 232760

2: (fatigue* or tired* or weary or weariness or exhaustion or exhausted or "astenia syndrome" or "asthenic syndrome" or apath* or lassitude or weak*) or ((lack or loss or lost) NEAR/2 (letharg* or energy or vigoor* or vigour*)) or ((Feel*) NEAR/2 (drained or sleep* or sluggish)) (Topic) Date Run: Fri Nov 03 2023 11:30:55 GMT+0000 (Greenwich Mean Time) Results: 1805006

or allocat* or prospective* or volunteer*or comparative or evaluation or "follow-up" or followup) (Topic) Date Run: Fri Nov 03 2023 11:31:46 GMT+0000 (Greenwich Mean Time) Results: 15802504

4: #3 AND #2 AND #1 Date Run: Fri Nov 03 2023 11:32:44 GMT+0000 (Greenwich Mean Time) Results: 3447

5: #3 AND #2 AND #1 Timespan: 2012-11-01 to 2023-11-03 Date Run: Fri Nov 03 2023 11:34:26 GMT+0000 (Greenwich Mean Time) Results: 1933

CENTRAL search strategy

#1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees	MeSH	7384
#2	((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/2 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab	Limits	18688
#3	(#1 OR #2)	Limits	19715
#4	MeSH descriptor: [Fatigue] explode all trees	MeSH	8625
#5	fatigue*:ti,ab	Limits	34742
#6	(tired* or weary or weariness or exhaustion or exhausted):ti,ab	Limits	5739
#7	((astenia or asthenic) and syndrome):ti,ab	Limits	46
#8	((lack or loss or lost) near/2 (energy or vigor)):ti,ab	Limits	441
#9	(apath* or lassitude or weak* or letharg*):ti,ab	Limits	19721
#10	(feel* near/2 (drained or sleep* or sluggish)):ti,ab	Limits	182
#11	vitality:ti,ab	Limits	3005
#12	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	Limits	61800
#13	(#3 AND #12)	Limits	1285

Appendix 1.3 – Systematic review, supplement secondary outcomes non-significant results.

S1 Depression Physical Activity

Author	Effect size	Confidence interval
Feldthusen et al., 2016	0.39	-0.10 to 0.87
Katz et al., 2018-I	-0.09	-0.60 to 0.43
Katz et al., 2018-II	0.14	-0.37 to 0.66
Li et al., 2020	-0.26	-0.69 to 0.18
Ward et al., 2018	-0.04	-0.83 to 0.74

S2 Pain Physical Activity

Author	Effect size	Confidence interval
Feldthusen et al., 2016	-0.17	-0.65 to 0.31
Katz et al., 2018-I	0.03	-0.49 to 0.54
Katz et al., 2018-II	-0.07	-0.59 to 0.45
Loeppenthin et al., 2022	0.00	-0.64 to 0.64
Pukšić et al., 2021	0.69	Not reported in paper, unable to calculate.
Ward et al., 2018	0.00	-0.78 to 0.78

S3 Pain Psychosocial interventions

Author	Effect size	Confidence interval
Ferwerda et al., 2017	-0.26	-0.65 to 0.13
Hewlett et al., 2019	0.10	-0.13 to 0.33
Zuidema et al., 2019	-0.21	-0.55 to 0.14

S4 Disability Psychosocial

Author	Effect size	Confidence interval
Hewlett et al., 2019	0.02	-0.21 to 0.25
Knittle et al., 2015	−0.02	−0.11 to 0.07

S5 Disease Activity Physical activity

Author	Effect size	Confidence interval

Feldthusen et al., 2016	-0.16	-0.64 to 0.32
Katz et al., 2018-I	0.05	-0.47 to 0.56
Katz et al., 2018-II	-0.04	-0.56 to 0.47
Pukšić et al., 2021	-0.23	-0.80 to 0.34
Ward et al., 2018	0.26	-0.54 to 1.03

S6 Disease Activity Psychosocial

Author	**Effect size**	**Confidence interval**
Ferwerda et al., 2017	-0.23	-0.61 to 0.16
Hewlett et al., 2019	0.02	-0.21 to 0.25
Knittle et al., 2015	0.40	–0.01 to 0.80
Pot-Vaucel et al., 2016	-0.33	-0.86 to 0.21
Yousefi et al., 2022- II MBSR group	-0.43	-1.06 to 0.22
Yousefi et al., 2022- II CBT group	-0.26	-0.90 to 0.38

Appendix 2.1 Research proposal – open science link

https://osf.io/6cwsx/?view_only=b60f6427ca2a409d9456c3a02ee86d4b

Appendix 2.2. Mediation reporting guidelines

Table 1. A Guideline for Reporting Mediation Analyses (AGReMA) Long-Form Checklist[a]

Section and topic	Item No.	Item description
Title and abstract		
Title	1	• Identify that the study uses mediation analyses
Abstract	2	• Provide a structured summary of the objectives, methods, results, and conclusions specific to mediation analyses
Introduction		
Background and rationale	3	• Describe the study background and theoretical rationale for investigating the mechanisms of interest • Include supporting evidence or theoretical rationale for why the intervention or exposure might have a causal relationship with the proposed mediators • Include supporting evidence or theoretical rationale for why the mediators might have a causal relationship with the outcomes
Objectives	4	• State the objectives of the study specific to the mechanisms of interest • The objectives should specify whether the study aims to test or estimate the mechanistic effects
Methods		
Study registration	5	• If applicable, provide references to any protocols or study registrations specific to mediation analyses and highlight any deviations from the planned protocol
Study design and source of data	6	• Specify the design of the original study that was used in mediation analyses and where the details can be accessed, supported by a reference • If applicable, describe study design features that are relevant to mediation analyses
Participants	7	• Describe the target population, eligibility criteria specific to mediation analyses, study locations, and study dates (start of participant enrollment and end of follow-up)
Sample size	8	• State whether a sample size calculation was conducted for mediation analyses • If so, explain how it was calculated
Effects of interest	9	• Specify the effects of interest
Assumed causal model	10	• Include a graphic representation of the assumed causal model including the exposure, mediator, outcome, and possible confounders
Causal assumptions	11	• Specify assumptions about the causal model
Measurement	12	• Clearly describe the interventions or exposures, mediators, outcomes, confounders, and moderators that were used in the analyses • Specify how and when they were measured, the measurement properties, and whether blinded assessment was used
Measurement levels	13	• If relevant, describe the levels at which the exposure, mediator, and outcome were measured
Statistical methods	14	• Describe the statistical methods used to estimate the causal relationships of interest • This description should specify analytic strategies used to reduce confounding, model building procedures, justification for the inclusion or exclusion of possible interaction terms, modeling assumptions, and methods used to handle missing data • Provide a reference to the statistical software and package used
Sensitivity analyses	15	• Describe any sensitivity analyses that were used to explore causal or statistical assumptions and the influence of missing data
Ethical approval	16	• Name the institutional research board or ethics committee that approved the study • Provide a description of participant informed consent or ethics committee waiver of informed consent
Results		
Participants	17	• Describe baseline characteristics of participants included in mediation analyses • Report the total sample size and number of participants lost during follow-up or with missing data
Outcomes and estimates	18	• Report point estimates and uncertainty estimates for the exposure-mediator and mediator-outcome relationships • If inference concerning the causal relationship of interest is considered feasible given the causal assumptions, report the point estimate and uncertainty estimate
Sensitivity parameters	19	• Report the results from any sensitivity analyses used to assess robustness of the causal or statistical assumptions and the influence of missing data
Discussion		
Limitations	20	• Discuss the limitations of the study including potential sources of bias
Interpretation	21	• Interpret the estimated effects considering the study's magnitude and uncertainty, plausibility of the causal assumptions, limitations, generalizability of the findings, and results from relevant studies
Implications	22	• Discuss the implications of the overall results for clinical practice, policy, and science
Other information		
Funding and role of sponsor	23	• List all sources of funding or sponsorship for mediation analyses and the role of the funders/sponsors in the conduct of the study, writing of the manuscript, and decision to submit the manuscript for publication
Conflicts of interest and financial disclosures	24	• State any conflicts of interest and financial disclosures for all authors
Data and code	25	• Authors are encouraged to provide a statement for sharing data and code for mediation analyses

[a] Designed for articles that report primary mediation analyses of randomized trials or observational studies or those that report secondary mediation analyses as the primary focus of an article. Republished with permission from the AGReMA group. This checklist is copyrighted by the AGReMA group under the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported (CC BY-NC-ND 3.0) license.

From Lee, H., Cashin, A. G., Lamb, S. E., Hopewell, S., Vansteelandt, S., VanderWeele, T. J., MacKinnon, D. P., Mansell, G., Collins, G. S., Golub, R. M., McAuley, J. H., & group, A. G. (2021). A Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies: The AGReMA Statement. JAMA, 326(11), 1045-1056. https://doi.org/10.1001/jama.2021.14075

Appendix 2.3. Measures collected during trial that were used for analysis.

Table A1. Measures analysed as part of the current study. Table is adapted from Martin et al., 2019. Protocol for a multicentre randomised controlled parallel-group trial to compare the effectiveness of remotely delivered cognitive-behavioural and graded exercise interventions with usual care alone to lessen the impact of fatigue in inflammatory rheumatic diseases (LIFT).

	Items	**assessment time point (weeks)**			
		0	10	28	56
Demographic data - Date of birth; gender; marital status; employment status; level of education.	**5**	**X**			
Primary Outcome Chalder Fatigue Scale (Likert scoring)	**11**	**X**	**X**	**X**	**X**
Secondary Outcome Hospital anxiety and depression scale (anxiety and depression)	**14**	**X**	**X**	**X**	**X**
Short Form-12	**12**	**X**	**X**	**X**	**X**
Pain numerical rating scale	**1**	**X**	**X**	**X**	**X**
Jenkin's sleep scale	**4**	**X**	**X**	**X**	**X**
Work Productivity and Activity Impairment Questionnaire	**6**	**X**	**X**	**X**	**X**
Valued Life Activities Scale (short 14 items)	**14**	**X**	**X**	**X**	**X**

Brief Illness Perception Questionnaire	**9**	**X**	**X**	**X**	**X**
Behavioural Response to Illness Questionnaire	**21**	**X**	**X**	**X**	**X**