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An abridged version of the Cochrane review of exercise therapy for chronic fatigue syndrome

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Abstract

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) is estimated to affect between 2 in 1000 and 2 in 100 adults depending on how diagnostic criteria are applied. Patients with CFS have long-lasting fatigue in addition to symptoms including muscle pain, concentration and sleep problems. These symptoms cause significant disability and distress to the people affected. This review is an update of a previous Cochrane review (2004) that showed that exercise therapy was a promising treatment for adults with CFS. The aim of this systematic review was to determine the effects of exercise therapy for patients with CFS.

We searched electronic databases, including SPORTDiscus, up to May 2014 using a comprehensive list of free-text terms for CFS and exercise. Randomised clinical trials from all health care settings with participants over 18 years with a primary diagnosis of CFS, able to attend an outpatient clinic for exercise therapy, were included.

We have included eight randomised clinical studies that reported data from 1518 participants. Seven studies used aerobic exercise such as walking, swimming, or cycling and one study used non-aerobic exercise. The exercise therapies lasted between 12 and 26 weeks. Meta-analysis was done when appropriate.

Exercise therapy was more effective at reducing fatigue than “passive” treatments or no treatment at end of treatment. Exercise therapy also had a positive effect on people’s daily physical functioning, sleep quality and self-rated overall health. Nearly twice as many patients reported improvement self-rated overall health after exercise therapy (40 per 100) compared to standard treatment (22 per 100). The evidence was too sparse and/or of too low quality to conclude if exercise therapy has an effect on pain, quality of life, anxiety or depression. Exercise therapy was not found to worsen

symptoms for people with CFS, while serious side effects were rare in all exercise and comparison groups.

Chronic fatigue syndrome, CFS, Myalgic encephalomyelitis, ME, exercise, exercise therapy, fatigue, recovery of function, adverse outcomes, systematic review

Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) is estimated to affect between 2 in 1000 and 2 in 100 adults depending on how diagnostic criteria are applied. Patients with CFS have long-lasting fatigue in addition to symptoms including muscle pain, concentration and sleep problems. These symptoms cause significant disability and distress to the people affected.

Exercise therapy is used as treatment for individuals with CFS and is recommended by treatment guidelines (1, 2). People with CFS should have the opportunity to make informed decisions about their care and treatment based on robust research evidence, and we therefore decided to update a previous Cochrane review from 2004 that showed that exercise therapy was a promising treatment for adults with CFS. The updated version was published earlier this year (3), and the current publication is an abridged version of this update. The aim of this systematic review was to determine the effects of exercise therapy (ET) for adults with CFS.

Materials and methods

Search methods for identification of studies

We searched The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR), the Cochrane Central Register of Controlled Trials (CENTRAL) and SPORTDiscus up to May 2014 using a comprehensive list of free-text terms for CFS and exercise. We located unpublished or ongoing trials through the World Health Organization (WHO) International Clinical Trials Registry Platform (to May 2014). We contacted the authors of included studies and screened reference lists to identify additional published or unpublished data.

Eligibility criteria

We included randomised controlled trials, cluster-randomised trials and randomised crossover trials. The participants had to be over 18 years with a primary diagnosis of CFS. Studies involving participants with co-morbid physical or common mental disorders were eligible only if the comorbidity did not provide an alternative explanation for fatigue. Studies with aerobic and

anaerobic interventions aimed at exercising big muscle groups, for example, walking, swimming, jogging and strength or stabilizing exercises were included. Comparators were passive control, psychological therapies, adaptive pacing therapy or pharmacological therapy. Primary outcomes were fatigue measured by any validated and adverse outcomes measured with any reporting system We also collected data for eight secondary outcomes; pain, physical functioning, quality of life, mood disorders, sleep, self-perceived changes in overall health, health service resource use and drop-outs.

Data collection and analysis

Two review authors independently performed study selection, risk of bias assessment and data extraction. Persistent disagreement was resolved by consulting a third review author. We used The Cochrane`s risk of bias tool (4). For each study, we extracted demographic and patient centered characteristics, details about the intervention and outcome data.

When deemed appropriate, we pooled the results of all available studies. Analysis was performed using Review Manager 5.3, and as we expected some degree of clinical heterogeneity, we used a random-effects model. We used mean difference (MD) and the corresponding 95% confidence interval (CI) to pool outcome data assessed by using the same rating scale, and standardized mean difference (SMD) to pool outcome data assessed on non-identical but similar scales. For dichotomous outcomes, we expressed the effect size in terms of risk ratio (RR) together with the corresponding 95% CI. Heterogeneity was assessed by calculating the I^2 and performing a Chi-square test. A p-value < 0.1 from the Chi -square test was used as an indicator of statistically significant heterogeneity.

We performed post hoc subgroups analyses to explore the impact of differences between studies (i.e. differences in treatment strategies, control conditions and diagnostic criteria. Post hoc sensitivity analysis were performed to explore the possible impact of our pooling strategy (e.g. the impact of using SMD vs MD). We also checked the robustness of the analyses by excluding outliers.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess grade the quality of the evidence (5).

Results

Our searches identified 908 unique records (Figure 1). We retrieved 50 records in full text of which eight randomised clinical trials were included (6-13). For detailed information on excluded studies see the full Cochrane review (3).

Figure 1. PRISMA flow diagram

Study and participant characteristics

The eight selected studies included 1518 participants in total with sample sizes ranging from 49 (8) to 641 participants (13). Two studies took place in primary care settings: one in the United Kingdom (12) and one in Australia (10). Two studies were performed in secondary care facilities: one in the United Kingdom (6) and one in New Zealand (8). One study recruited participants from a variety of sources but took place at a hospital in the USA (7). Finally, three studies were conducted at secondary or tertiary care settings in the United Kingdom (9, 11, 13). For detailed information see the full Cochrane review (3).

The total sample included more females than males (range 71% to 84%). Mean age varied between 33 and 45 years across studies, whereas median illness duration ranged between two and seven years. Three studies used the Centers for Disease Control and Prevention (CDC) 1994 criteria (14) as inclusion criteria (7, 8, 10), and five (6, 9, 11-13) used the Oxford criteria (15). Risk of bias varied across studies, but within each study, little variation was found in the risk of bias across our primary and secondary outcome measures, see Figure 2. For detailed information see the full Cochrane review (3).

Table 1 Study characteristics

Figure 2 Risk of Bias included studies

Intervention characteristics

The exercise therapy regimen lasted between 12 and 26 weeks. Seven studies used variations of aerobic exercise therapy such as walking, swimming, cycling or dancing at mixed levels in terms of intensity of the aerobic activity ranging from very low to quite rigorous (6, 8-13); the remaining study used anaerobic exercise (7). Scheduled therapist meetings could be conducted face-to-face or by telephone and varied from every second week to weekly; some sessions involved talking, and some exercise. Most of the included studies asked participants to exercise at home, most often between three and five times per week, with a target duration of 5 to 15 minutes per session using different means of incrementation (6, 8-13). Participants were asked to perform self-monitoring by using such tools as heart monitors, the Borg Scale or a diary including an exercise log to measure adherence to treatment, see Table 2. Control interventions included treatment as usual, relaxation plus flexibility and a waiting-list control group. For detailed information see the full Cochrane review (3).

Table 2 Intervention characteristics

The effect of exercise therapy

All included studies contributed data to the comparison of exercise therapy versus 'passive' control. Seven of eight studies (842 participant) contributed fatigue data for end of treatment (Figure 3a) and the pooled SMD estimate was -0.68 units (95% CI -1.02 to -0.35)(6, 8-13). These numbers are consistent with a modest to large improvement in fatigue symptoms (16), but due to considerable between-study heterogeneity we downgraded the evidence to moderate quality. The results were similar when we calculated mean differences (MD) according the fatigue scales originally used instead of using SMD. One study including 148 participants showed a reduction in fatigue score of 6.06 points (95% CI -6.95 to -5.17) on the Fatigue questionnaire ranging from 0 to 11 points (9). Three studies including 540 participants showed a reduction in fatigues score of 2.82 points (95% CI -4.07 to -1.57) on the 33 point Fatigue questionnaire (10, 12, 13). Another three studies involving 152 participants showed reduction of on 6.80 points (95% CI -10.31 to -3.28) using the 42 point Fatigue questionnaire (6, 8, 11).

One study (319 participants) monitored and reported serious adverse reactions in a systematic way (13). The main finding was that serious adverse reactions were rare in both groups, and there is currently no evidence for differences between the two groups; RR 0.99 (95% CI 0.14 to 6.97). As seen, the 95% confidence interval was very wide due to the low number of reported events (2 of 160 versus 2 of 159), and it was impossible to draw firm conclusions about possible group differences (13). With regard to other important outcomes, exercise seemed more beneficial than control when measuring physical functioning domain of SF-36 (MD 13.10, 95% CI 1.98 to 24.22; five studies, 725 participants, Fig 3b) (6, 8, 9, 12, 13), sleep quality according to Jenkins sleep scale (MD -1.49, 95% CI -2.95 to -0.02; two studies, 323 participants, Fig 3c) (9, 12), and self-perceived changes in overall health at end of treatment (RR 1.83, 95% CI 1.39 to 2.40; four studies, 489 participants, Fig 3d) (6, 8, 10, 12). For the remaining outcomes, the evidence base was too sparse to allow conclusions. A summary of findings table shows the results in natural numbers as well as the the quality of the evidence (Table 3).

Figure 3 Effects of exercise therapy versus treatment as usual on fatigue, physical functioning, sleep and overall health at end of treatment

Table 3 Exercise Therapy compared to treatment as usual Summary of Findings table (SoF)

Two trials compared the effectiveness of exercise therapy versus cognitive behavior therapy (CBT). Both studies measured differences in fatigue (7, 13) using a Fatigue questionnaire ranging from 0 to 33 points and Fatigue Severity Scale ranging from 1 to 7 points respectively, but only one trial reported results at end of treatment (13). This trial (298 participants) reported little or no difference

in fatigue at end of treatment; MD 0.20, (95% CI -1.49 to 1.89 on the Fatigue questionnaire ranging from 0 to 33 points) (13). The quality of the evidence was down rated to moderate, primarily due to a wide confidence interval. Serious adverse reactions were rare in both groups (RR 0.67, 95% CI 0.11 to 3.96) (13) and the quality of evidence was down rated to moderate due to few events. For the remaining outcomes we could not establish differences between exercise and CBT.

Discussion

Patients with CFS may generally benefit from and feel less fatigued following exercise therapy, and no evidence suggests that exercise therapy may worsen outcomes. A positive effect with respect to sleep, physical function and self-perceived general health has been observed, but no conclusions for the outcomes of pain, quality of life, anxiety, depression, drop-out rate and health service resources were possible. Further randomised trials with low risk of bias are needed to explore what type of exercise is most beneficial for people affected by CFS, i.e. type of activity, duration and intensity.

The strength of this review lies in its rigorous methods, which include thorough searching for evidence, systematic appraisal of study quality and systematic and well-defined data synthesis. Even though we tried to search as extensively as possible, we may have missed eligible trials, such as trials reported only in dissertations or in non-indexed journals. We had to make a cutoff regarding what kind of exercise should be included. We decided to exclude traditional Chinese exercise such as Tai Chi and Qigong, but to include pragmatic rehabilitation for which the type of exercise is described as walking, walking stairs, bicycling, dancing or jogging. The cutoff might be contentious, and discussion regarding what type of exercise should be included should be ongoing.

Meta-analysis of individual patient data (IPD) constitutes an alternative approach to meta-analysis of aggregate data. Analysis based on individual patient data in general will enable us to use a wider range of statistical and analytical approaches (17). In particular, by utilising IPD, it is possible to explore the relative importance of the various heterogeneity factors mentioned above more thoroughly, and to ensure that missing data and baseline differences are dealt with in standardised ways. With access to IPD, it is also possible to perform subgroup analyses that have not been previously reported. A project aimed at undertaking IPD analyses of the trials included in the present review has been initiated.

The results reported in this review correspond well with those of other systematic reviews (18-20) and with existing guidelines (1, 2). One meta-analysis of CBT and GET suggests that the two treatments are equally efficacious, especially for patients with co-morbid anxiety or depressive symptoms (21). The results are generally pointing in favour of exercise therapy, but in line with all clinical research, positive results does not imply that every individual patient will benefit. Positive

results mean that many patients are expected to benefit from treatment, some will not benefit and a few might even get worse. As with all other treatment, it is therefore essential that the health care provider communicates well and use clinical judgment in the patient encounter.

Conclusion

Encouraging evidence suggests that exercise therapy can contribute to the alleviation of some symptoms of CFS, especially fatigue. Exercise therapy seems to perform better than no intervention and similar to cognitive behavioural therapy.

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Table 1 Study demographics

Study ID	N	Gender	Duration of illness	Depression co-morbidity	Use of antidepressants (ADs)	Work and employment status
Fulcher 1997	66	49F/17M 65% female	2.7 years	20 (30%) possible cases of depression (HADS)	30 (45%) on full-dose AD (n = 20) or low-dose AD (n = 10)	26 (39%) working or studying at least part time
Jason 2007	114	95F/19M 83% female	> 5.0 years	44 (39%) with a current Axis I disorder (depression and anxiety most common)	Not stated	52 (46%) working or studying at least part time, 24% unemployed, 6% retired, 25% on disability
Moss-Morris 2005	49	34F/15M 69% female	3.1 years	14 (29%) possible or probable cases of depression (HADS)	Not stated	11 (22%) were unemployed and were unable to work because of disability
Powell 2001	148	116F/32M 78% female	4.3 years	58 (39%) possible or probable cases of depression (HADS)	27 (18%) used AD	50 (34%) were working, 64 (43%) were on disability
Wallman 2004	61	47F/14M 77% female	Not stated	Not stated	16 (26%) used AD	Not stated
Wearden 1998	136	97F/39M 71% female	2.3 years	46 (34%) with depressive disorder according to DSM-III-R criteria	Not stated	114 (84%) had recently changed occupation
Wearden 2010	296	230F/66M 78% female	7.0 years	53 (18%) had a depression diagnosis	160 (54%) were prescribed AD in the past 6 months	Not stated
White 2011	641	495F/146M 77% female	2.7 years	219 (34%) with any depressive disorder	260 (41%) used AD	Not stated

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Table 3 Exercise Therapy compared to treatment as usual

Results: what happens?	Treatment as usual	Exercise Therapy	Certainty of evidence
Symptoms of fatigue (SMD) Exercise therapy probably decreases fatigue symptoms		Standardised mean difference was 0.68 lower (95% CI -1.02 to -0.35)	⨁⨁⨁◯ Moderate[1]
Adverse events Exercise therapy probably makes no difference in patients that experience adverse events	13 per 1000	0 less per 1000 (from a decrease of 11 to an increase of 78)*	⨁⨁⨁◯ Moderate[2,3]
Quality of life We are uncertain of the effect of the intervention on this outcome as the certainty/quality of the evidence has been assessed as very low	We do not report results when the quality of the evidence is very low.		⨁◯◯◯ Very low[1,4]
Physical function Exercise therapy may increases physical function	Average score for physical function score ranged from 31.1 to 55.2 points on a scale form 0-100	Mean change was an increase of 13,1 points (from an increase of 2.0 points to 24.2) on a scale for 0-100*	⨁⨁◯◯ Low[1,5]
Depression We are uncertain of the effect of the intervention on this outcome as the certainty/quality of the evidence has been assessed as very low	We do not report results when the quality of the evidence is very low.		⨁◯◯◯ Very low[1,5,6]
Sleep quality (scale from 0 to 20) Exercise therapy may better quality of sleep	Average score for sleeps score range from 11.7 to 12.2 on a scale from 0 to 20	Mean change was a decrease of 1,5 points (from a decrease of 3.0 points to 0.0) on a scale for 0 to 20*	⨁⨁◯◯ Low[1,6]
Self-perceived changes in overall health Exercise therapy probably increases self-perceived overall health	218 per 1000	181 more per 1000 (from 85 to 305 more)*	⨁⨁⨁◯ Moderate[1]

*The numbers in brackets show the margin of error (95 % confidence interval). The confidence interval is a measure that shows the uncertainty of the result due to random errors.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
Standardized mean difference (SMD), above 0.5 can be interpreted as a moderate effect.
[1]Risk of bias (-1): All studies were at risk of performance bias, as they were unblinded.

[2]Risk of bias (0): This outcome is unlikely to have been affected by detection or performance bias.
[3]Imprecision (-1): low numbers of events and wide confidence intervals.
[4]Imprecision (-2): very low numbers of participants and wide confidence intervals, which encompass benefit and harm.
[5]Inconsistency (-1): variation in effect size and direction of effect across available studies.
[6]Imprecision (-1): Confidence interval fails to exclude negligible differences in favour of the intervention

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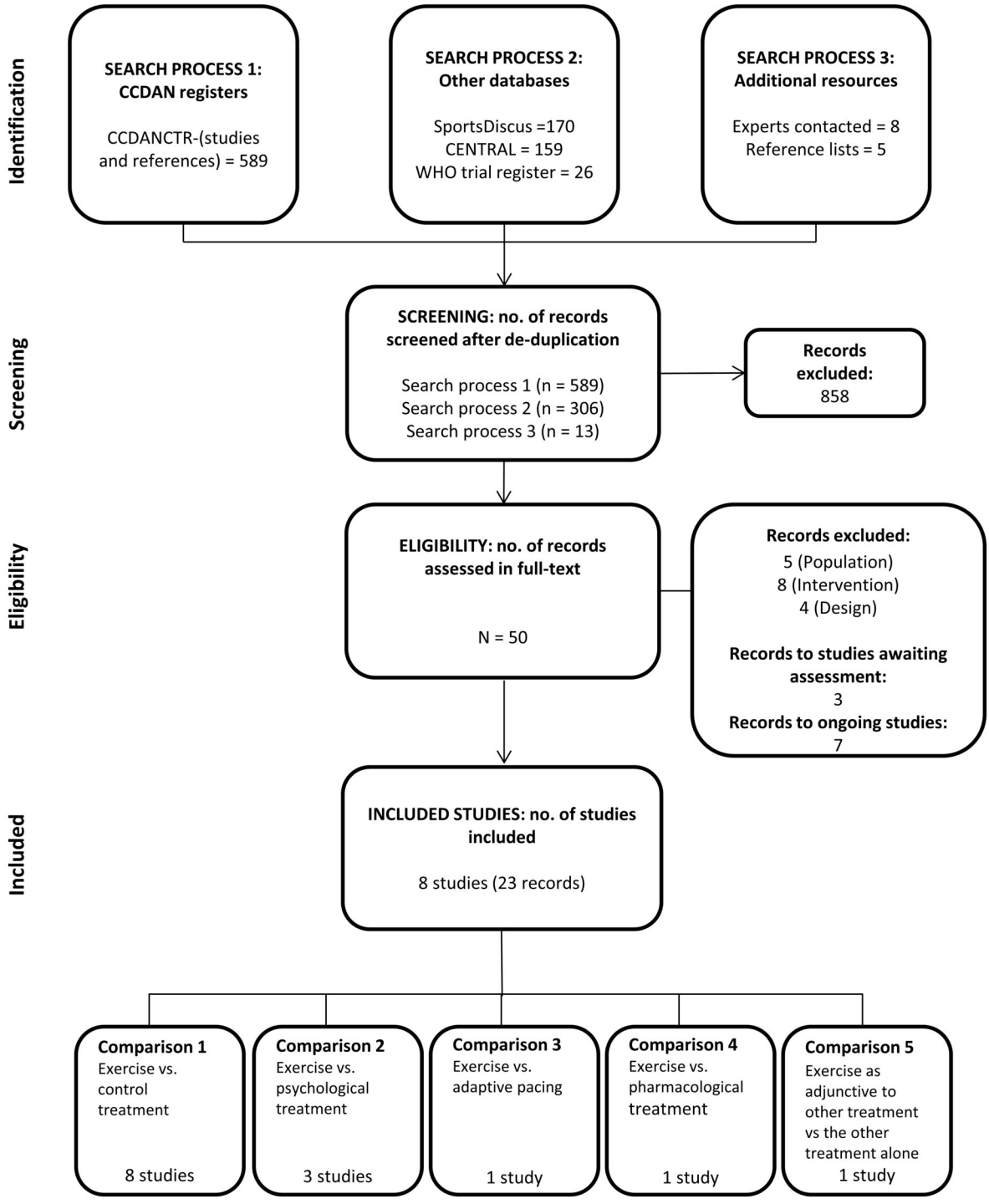

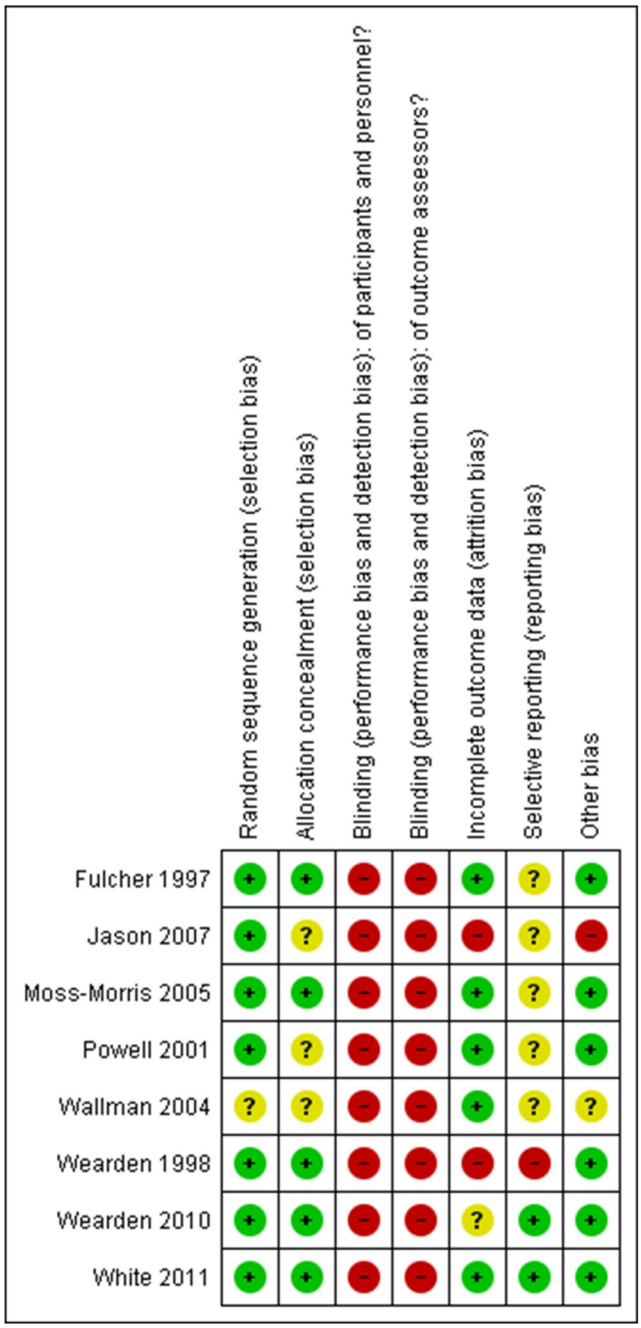

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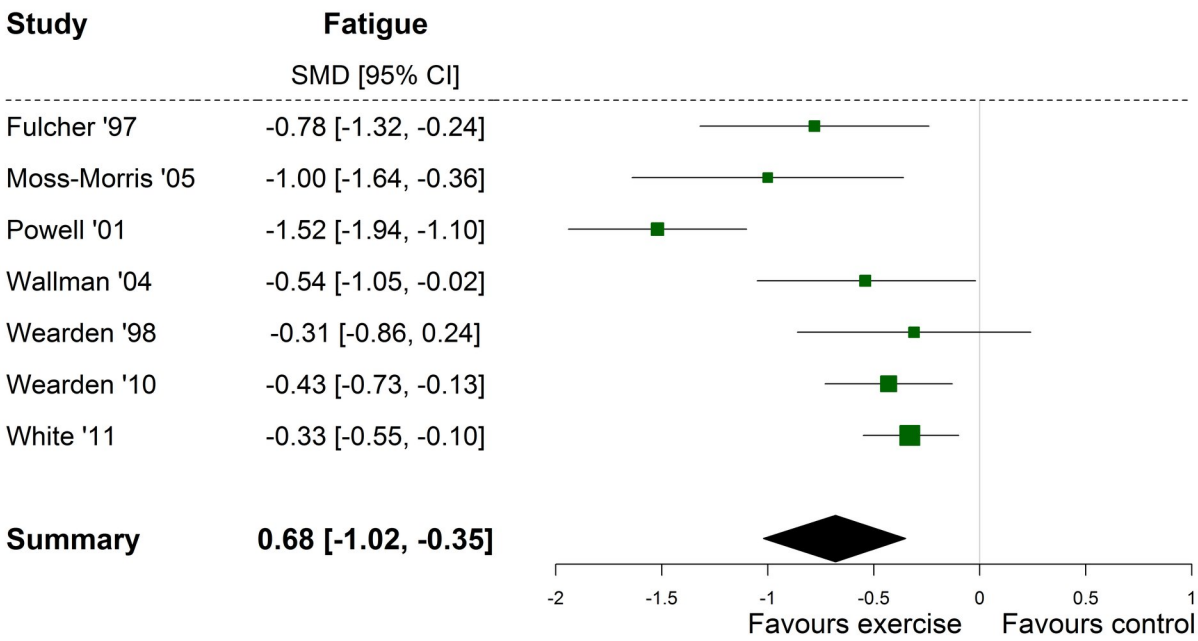

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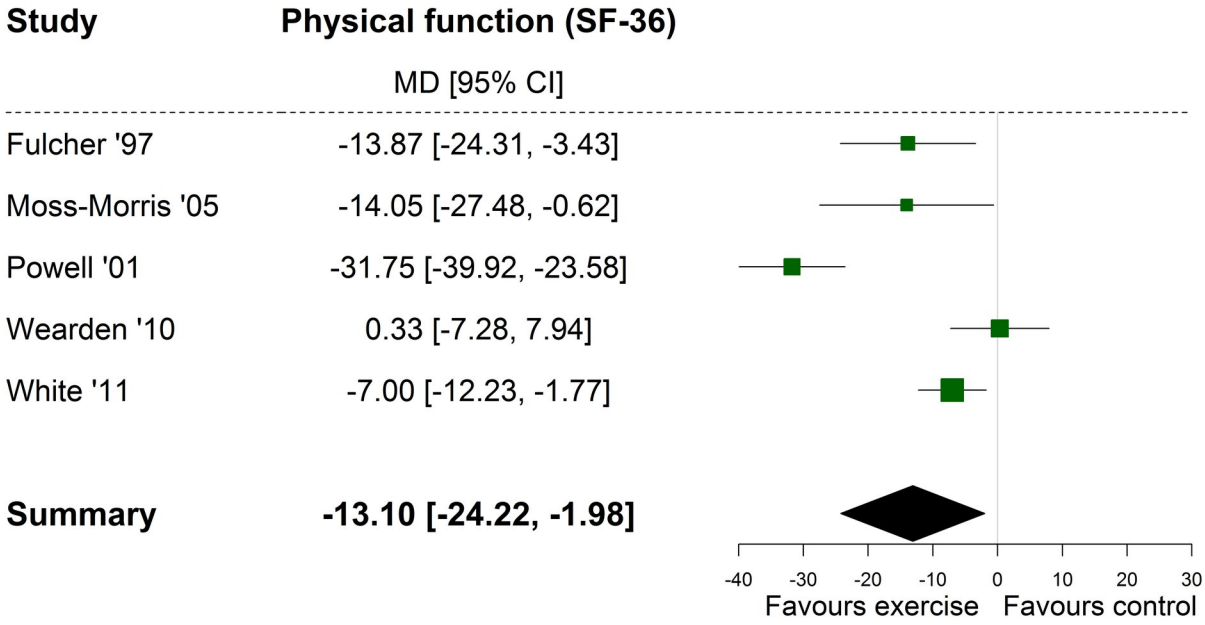

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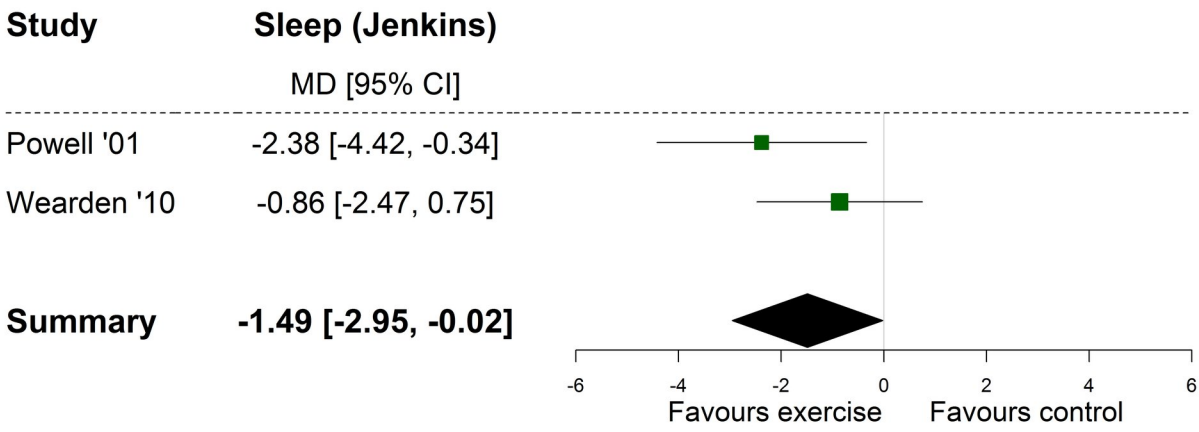

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