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ORIGINAL ARTICLE

Effect of Aerobic Exercise Training on Fatigue in Rheumatoid Arthritis: A Meta-Analysis

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Objective. **Rheumatoid arthritis (RA) fatigue is not being well-managed currently, and evidence of effective interventions is limited. Aerobic exercise may provide benefit to treat fatigue in RA. Therefore, the purpose of this meta-analysis is to analyze the effect of aerobic land-based exercise on fatigue in RA.**

Methods. **A literature search was conducted using PubMed, Cochrane Library, Embase, and trial registers to identify randomized controlled trials (RCTs) with a supervised land-based aerobic exercise program performed with an intensity between 50% and 90% of maximal heart rate, of at least 15 minutes' duration, performed at least 2 times a week, and lasting for a time period of at least 4 consecutive weeks. Risk of bias was assessed using the Cochrane tool. A meta-analysis of fatigue outcomes was performed by calculating the standardized mean difference (SMD) using a random-effects model.**

Results. **Five RCTs were included. None of the trials selected patients with RA for having fatigue. Risk of bias was low in 3 RCTs and unclear in 2. Land-based aerobic exercise programs had a positive effect on fatigue in RA compared to no exercise at 12 weeks, SMD −0.31 (95% confidence interval [95% CI] −0.55, −0.06). At 24 weeks, the effect of aerobic land-based exercise was smaller and not statistically significant: SMD −0.15 (95% CI −0.33, 0.02).**

Conclusion. **There is evidence with low risk of bias that an aerobic exercise program is effective in reducing fatigue among patients with RA, especially in the short term; however, effects are small. To substantiate the evidence, RCTs should be performed in patients with RA selected for having fatigue.**

INTRODUCTION

In rheumatoid arthritis (RA), fatigue is a frequent symptom, even among patients with low and moderate levels of disease activity (1,2). As much as 40% of the patients with RA may be severely fatigued, having fatigue levels similar to patients with chronic fatigue syndrome (CFS) (1). Indeed, fatigue in RA is a patient-relevant symptom; patients with RA express their fatigue as unpredictable, overwhelming, and different from normal tiredness (2), and it is often perceived as debilitating and restricting daily functioning (1,3–5). Potentially, fatigue in RA has a large impact on quality of life, and patients give high priority to reducing fatigue (6). RA fatigue is associated with multiple factors: disease-related factors (pain, joint damage, disability), cognitive and behavioral factors (anxiety, depression, illness beliefs, and stress), and personal factors (work/caring responsibilities, environment, health, and lost social support) (7).

However, RA fatigue is currently not being well-managed. Lack of knowledge about the causes of fatigue, as well as lack of knowledge of effective treatments, may contribute to fatigue being neglected during patient–physician contacts (2,8). Most rheumatologists pay attention to fatigue during the first consultation and less often during followup consultations (8). Clinicians may tend to assume that the patient will raise the issue. Having effective interventions for the treatment of fatigue in RA is of major importance, but evidence regarding effective interventions still is limited. Similar to CFS (9,10), in RA most evidence is available for the effectiveness of cognitive behavioral therapies (CBTs) and exercise (11–16).

The underlying mechanism of fatigue in RA is not known. Previous research supports that psychological factors, pain, and physical activity, but not the level of inflammation, are related to fatigue in RA (7,17,18).

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Significance & Innovations

- There is some evidence to suggest that several exercise forms provide benefit to treat fatigue in rheumatoid arthritis (RA). We performed the current meta-analysis to summarize the limited evidence and estimate the mean effect of aerobic land-based exercise programs on fatigue in RA.
- Published and notably also unpublished fatigue data were collected from randomized controlled trials of aerobic land-based exercise in RA. In total, 5 trials were included, of which only 1 originally reported fatigue in their manuscript. We requested and received unpublished fatigue data from the other 4 authors; hence, we were able to pool data from the 5 studies.
- This meta-analysis showed that aerobic land-based exercise training may be beneficial to treat fatigue in RA at 12 or 24 weeks, although the effect for both time points was small and only significant at 12 weeks of exercise training. The effect of exercise on fatigue was highest at 12 weeks, and this effect may become lower over time.

Physical functioning as well as activity level may play a role in maintaining fatigue levels in RA (19); a higher level of daily physical activity was associated with reduced levels of fatigue. It is well known from several randomized controlled trials (RCTs) in RA that short- and long-term exercise programs are beneficial to reduce pain and disability and that exercise can be performed safely (20). However, regarding fatigue the evidence is less clear. Systematic reviews indicate that there is evidence to suggest that several exercise forms provide benefit to treat fatigue in RA (15,16). As aerobic capacity is a very central concept of physical fitness/human performance, there is good reason to hypothesize that improving aerobic capacity may reduce fatigue. However, only 1 RCT has been performed on aerobic exercise in RA, with fatigue as the dedicated primary outcome measure (14). In that trial, fatigue decreased significantly for the exercise group compared to the control group (14). To summarize the limited evidence of the effect of an aerobic exercise program on fatigue and to get a better estimate of the mean effect, we performed the current meta-analysis. The purpose of this meta-analysis of RCTs was to analyze the short- (≤12 weeks) as well as the long-term (24 weeks) effect of land-based aerobic exercise programs on fatigue in RA, including published and unpublished fatigue data. In addition, the relation between the effect of the intervention and baseline fatigue and the relation between the effect of the intervention and disability were analyzed.

MATERIALS AND METHODS

Design. A literature search was conducted using the electronic databases PubMed, Cochrane Library, Embase, and 3 trial registers to identify RCTs comparing aerobic exercise versus no exercise in RA, regardless of whether fatigue outcomes were published. All authors were approached with a request to provide data on fatigue. Risk of bias of each RCT was assessed using the Cochrane Collaboration's tool for assessing risk of bias (21). Meta-analysis of fatigue outcomes was performed by calculating the standardized mean difference (SMD) using a random-effects model.

Inclusion criteria. RCTs were included if the following inclusion criteria were met: 1) inclusion of patients with RA according to the American College of Rheumatology/European League Against Rheumatism classification criteria (22) supervised land-based (cycling, running, or circuit training) aerobic exercise program, 3) the intervention was between 50% and 90% of maximal heart rate according to the American College of Sports Medicine guideline for improving aerobic capacity (23), 4) training sessions were at least 15 minutes at least 2 times a week, for at least 4 consecutive weeks (23), 5) the study was randomized, and 6) the control group did not perform exercise. Supervised land-based aerobic exercise was chosen as an inclusion criterion because this includes most established aerobic training methods that are easy to implement in different forms (cycling, walking, "aerobics"), and training intensity can be well regulated. Generally, supervised programs are more effective for inducing a significant improvement in aerobic capacity than home aerobic exercise (24,25). Fatigue was not among the inclusion criteria, because we also wanted to include studies in which fatigue data happened to be collected but were not reported.

Search strategy. A systematic search of PubMed, Embase, and the Cochrane Library database was performed in April 2014 for relevant RCTs from 1985 until April 2014, and the search strategies are shown in Table 1.

Further, the clinical trial registers at www.clinicaltrials.gov, www.trialregister.nl, and www.clinicaltrialsregister.eu were searched (Figure 1).

Selection. After screening of titles and abstracts by 2 of the authors (SAAR-vD and MF), the full text of the articles appearing to be relevant were read and inclusion/exclusion criteria were applied (SAAR-vD, supervised by JF). The first or last authors of all included studies were approached by e-mail to ask whether they had collected any fatigue questionnaires, such as the Bristol Rheumatoid Arthritis Fatigue (BRAF) multidimensional questionnaire, the Checklist Individual Strength, the Fatigue Severity Scale, the Functional Assessment of Chronic Illness Therapy–Fatigue, the Multidimensional Assessment of Fatigue (MAF), the Short Form 36 (SF-36) vitality subscale, or a visual analog scale (VAS), that were not reported in their published article.

Data extraction and study quality assessment. Data on fatigue measures were extracted for the intervention group and the control group at baseline and followup. Standard tables were used for data extraction by 1 of the authors (SAAR-vD, supervised by JF). Two authors (SAAR-vD and

Table 1. Search strategies in PubMed, Embase, and the Cochrane Library

Database	Search strategy
PubMed	("Arthritis, Rheumatoid"[Mesh] OR rheumatoid arthritis[all fields]) AND (("Exercise" [Mesh] OR "Exercise Therapy" [Mesh] OR exercise*[all fields] OR training[all fields] OR intervention [all fields] OR programs[all fields] OR program[all fields] OR programme [all fields] OR programmes [all fields] OR rehabilitation [Mesh] OR rehabilitation [subheading] OR rehabilitation [all fields] OR activity [all fields]) AND (aerobic* [all fields] OR dynamic [all fields])) AND (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])) OR "Meta-Analysis" [Publication Type] OR metaanalysis[tw] OR meta-analysis[tw] OR meta analysis[tw] OR systematic[sb])
Embase	"rheumatoid arthritis".ti,ab,kw. or rheumatoid arthritis.sh. and (exercise or "exercise therapy").sh. or exercise.af. or training.af. or intervention.af. or program*.af. or rehabilitation.af. or activity.af. and (aerobic or dynamic).af. Search strategy limited to randomized controlled trials
Cochrane	"rheumatoid arthritis" OR Arthritis, rheumatoid [Mesh] AND exercise [Mesh] OR exercise therapy [Mesh] OR exercise OR training OR intervention OR program OR programme OR rehabilitation OR activity AND aerobic OR dynamic. Search strategy limited to trials

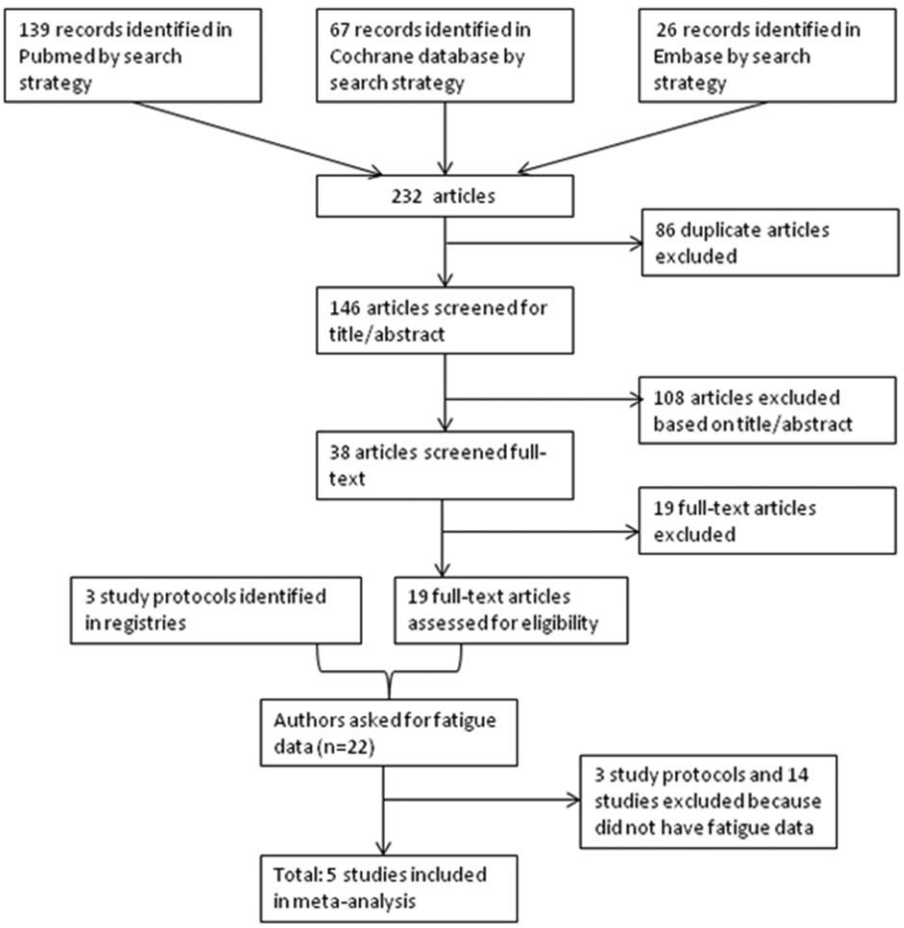

Figure 1. Flow chart search strategy.

Table 2. Cochrane Collaboration tool for assessing risk of bias*

Study	Selection bias: random sequence generation	Selection bias: allocation concealment	Performance bias: blinding of participants and personnel and outcome assessment	Attrition bias: incomplete outcome data	Reporting bias: selective reporting	Other bias: anything else, ideally prespecified	Total risk of bias
Van den Ende et al, 2000 (30)	:)	:)	:(	:)	:)	:)	Low
De Jong et al, 2003 (29)	:)	:)	:(	:)	:)	:)	Low
Neuberger et al, 2007 (14)	:)	:|	:(	:)	:)	:)	Unclear
Reid et al, 2011 (31)	:)	:)	:(	:)	:)	:)	Low
Stavropoulos-Kalinoglou et al, 2013 (28)	:|	:|	:(	:|	:)	:)	Unclear

JF) independently assessed the methodological quality of each study using the Cochrane Collaboration tool for assessing risk of bias (21). The risk of bias tool covers 9 items within 6 domains of bias: selection bias, performance/detection bias, attrition bias, reporting bias, and other bias (Table 2). There were 3 rating categories available for each item: 1) low risk of bias, which is unlikely to alter the results seriously, 2) unclear risk of bias, i.e., bias that raises some doubt about the results, and 3) high risk of bias, i.e., bias may alter the results seriously. All selected articles were scored by the 2 authors. Discordant judgments were resolved by discussion until consensus was reached.

Analysis. The effect of an exercise program on fatigue versus no exercise was assessed for each individual study by calculating the weighted SMD and 95% confidence interval (95% CI) of the experimental group versus the control group. Individual SMDs of all included studies were pooled using the inverse variance method (26). This was performed for both the short-term (≤12 weeks) and long-term (24 weeks) effects of exercise on fatigue. Heterogeneity of treatment effects among studies was statistically investigated using the I^2 statistic. The degree of heterogeneity was graded as low ($I^2 < 25\%$), moderate ($I^2 = 25$–75%), or high ($I^2 > 75\%$) (27). A random-effects model was used to pool the studies. Sensitivity analyses were performed regarding risk of bias (low versus other), fatigue data published (yes versus no), and length of supervised part of exercise program (≤12 weeks [short] versus 24 weeks [long]). Meta-regression analyses were performed to analyze the relation between baseline fatigue (standardized as percentage of maximum possible score) and the effect of the intervention (SMD), and to analyze whether there was a relation between the effects on disability (disability index of the Health Assessment Questionnaire) with the effects on fatigue (SMD). In these analyses the RCTs were weighted according to study size.

The meta-analyses were done using Review Manager 5, and the meta-regression was performed using SPSS 20.0.

RESULTS

Included studies. There were 232 articles identified by the search strategy, of which 86 were duplicates. After screening 146 unique articles on title/abstract, 38 titles were considered relevant for full-text reading (Figure 1). Nineteen studies of the 38 met the inclusion criteria and the other 19 studies were excluded. Reasons for exclusion were the study was not randomized (9 studies), duration of the intervention was <4 weeks (1 study), control group performed any form of aerobic exercise (home-based) (2 studies), intervention was a water-based exercise program (1 study) or strengthening exercise (1 study) or dance-based exercise (not at 50–90% of maximal heart rate) (1 study), the training intensity was not provided (2 studies), and the training was not supervised (2 studies).

Of the 19 included studies, only 1 study reported fatigue as a primary outcome measure (14). Primary outcomes of the other included studies were disease activity,

Table 3. Characteristics of included studies in meta-analysis*

	Intervention/ control, no.	Fatigue scale	Primary outcome	Baseline fatigue score, intervention/ control, mean ± SD	Exercise type	Adherence	No. per week	Intensity	Duration, no. minutes	Length, weeks	Control group
Van den Ende et al, 2000 (30)	34/29	VAS fatigue	Disease activity	5.3 ± 3.1/ 5.9 ± 3.2	Bicycle, muscle strength training	Mean ± SD no. of intensive exercise sessions was 16 ± 9	3	60% max HR	15	4	Usual care/ROM exercise
De Jong et al, 2003 (29)	149/149	SF-36 vitality	Radiographic damage of the large joints, disease activity	56.80 ± 17.16/ 55.46 ± 18.6	Warming-up, 20 min bicycle, 20 min circuit, 20 min sport and game, cooling down	No adherence over time, after 2 years 81% still participate in the exercise class	2	70–90% max HR	85	104	Usual care
Neuberger et al, 2007 (14)	67/73	MAF	Fatigue, pain, and depression	24.91 ± 10.25/ 21.88 ± 9.8	Warming up, low impact aerobics, strengthening and cooling down	83.3%	3	60–80% max HR	60	12	Baseline amounts exercise
Reid et al, 2011 (31)	17/17	MAF	Functional ability	17.46 ± 7.81/ 24.87 ± 9.55	Land-based: 10 min warming-up, 40 min circuit, 10 min cooling down	78%	2	Moderate to vigorous level, (moderate intensity: 5 or 6 on a 10-point scale, vigorous intensity: at a level of 7 or 8)	60	8	No intervention
Stavropoulos-Kalinoglou et al, 2013 (28)	18/17	MAF	Cardiorespiratory fitness and cardiovascular disease	22.82 ± 10.5/ 23.60 ± 11.3	10 min warming up, 30–40 main session consisting of walk on treadmill, cycle, row or hand ergometer, 5–10 min cooling down	88%, 76%	3	70% V_{O_2} max	50–60	24	Receiving verbal advice on exercise benefits and lifestyle changes

* VAS = visual analog scale; HR = heart rate; ROM = range of motion; SF-36 = Short Form 36 health survey; min = minutes; MAF = Multidimensional Assessment of Fatigue; V_{O_2} max = maximum oxygen consumption.

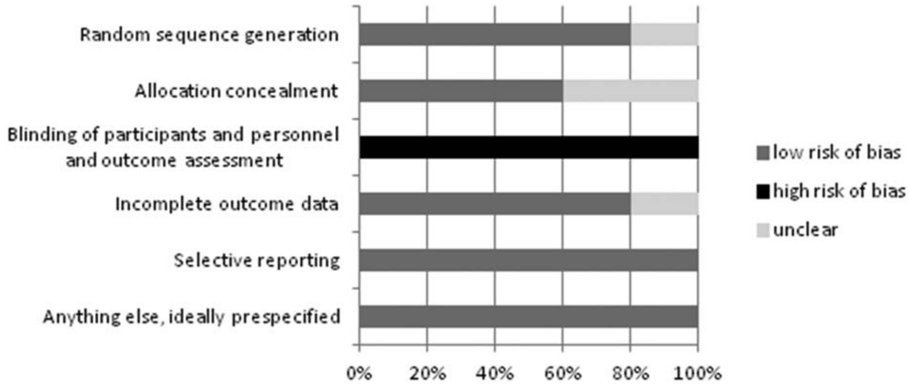

Figure 2. Percentage risk of bias per item of all included studies.

radiographic damage of the large joints, pain, depression, functional ability, cardiorespiratory fitness, and cardiovascular disease. Three studies were from the same research group (Neuberger) and with the same study population. Consequently, 16 authors were approached and responses were received from 13 authors. In 5 studies fatigue data had been collected and these data were all retrieved (Figure 1).

Also, the corresponding investigators of 3 study protocols found in the trial registers were approached for fatigue data (NCT00792675, NCT01553305, and NCT01966835). Only 1 study (NCT01553305) collected fatigue data, but this study was excluded because the control group performed a (self-administered) exercise program.

Characteristics of included studies. The characteristics of the included studies are shown in Table 3 (14,28–31). The smallest study included 34 patients (31), and the largest study (29) included 298 patients. The interventions included cycling, running, or circuit training for at least 15 consecutive minutes with a frequency of 2 or 3 times a week. The length of the supervised training programs differed between 4 weeks (30) and 104 weeks (29). However, all studies collected fatigue data at 24 weeks after baseline. In 3 studies the MAF was used as a fatigue scale, in 1 study the SF-36 health survey vitality subscale was used, and 1 study used a VAS fatigue scale (Table 3).

Adherence to the exercise program. The way adherence was reported differed highly between the included studies. In the study of van den Ende et al (30), the mean ± SD number of completed exercise sessions was 16 ± 9; 1 patient in the intervention group and 1 patient in the control group were lost to followup at 3 weeks of exercise. In the study by de Jong et al (29), 118 patients (81%) still participated in the exercise class after 2 years; no other data were reported. In the study by Neuberger et al (14), the median amount of exercise sessions followed in the class exercise group was 83%. The mean attendance rate for the study by Reid et al (31) at the 8-week gym group sessions was 78%. At 24 weeks, telephone interviews had been conducted and a large majority of participants (82%) responded that they did not continue with their exercise program, which was mainly attributed to a lack of access to suitable facilities and a lack of motivation (31). Mean attendance rate for the study by Stavropoulos-Kalinoglou et al (28) was 88% for the training group.

Study quality assessment. Blinding of participants and personnel and blinding of the outcome assessment was not present for the fatigue outcome in any included study, due to the nature of the intervention (exercise) and outcome (patient questionnaire). Therefore, a high risk of performance bias was not taken into account when summing up the domains into the overall risk of bias. Three studies had a low risk of bias according to the Cochrane Collaboration tool; 2 studies had an unclear risk of bias (Table 2). The percentage risk of bias per item for all included studies is shown in Figure 2.

Meta-analysis. The short-term effect of exercise on fatigue was calculated using the SMD of the intervention and control group at baseline compared to 4 weeks (30), 8 weeks (31), or 12 weeks (14,28). The long-term effect was calculated using the SMD in fatigue score at baseline compared to 24 weeks (24-week data available for all studies). De Jong et al (29) did not collect short-term fatigue data, and therefore their data were only included in the analysis of effects of 24 weeks of exercise.

The pooled analysis of the effect of the results at ≤12 weeks of exercise on fatigue revealed a larger reduction of fatigue in the intervention group compared to the control group, which was significant (SMD −0.31, 95% CI −0.55, −0.06, $P = 0.02$, $I^2 = 0\%$) (Figure 3A).

The pooled analysis of the effect of 24 weeks of exercise on fatigue also showed a larger reduction of fatigue in the intervention group compared to the control group; however, this was not significant (SMD −0.15, 95% CI −0.33, 0.02, $P = 0.09$, $I^2 = 2\%$) (Figure 3B). Heterogeneity according to the I^2 statistic was low for both the short- and long-term results.

Sensitivity analyses. When comparing the studies with a low risk of bias (30,31) with the other studies (14,28), the pooled analysis of the effect of short-term exercise on fatigue showed no effect in the low risk of bias group (SMD −0.15, 95% CI −0.57, 0.27, $P = 0.50$), but there was a larger and statistically significant effect of exercise on fatigue in the studies with an unclear risk of bias (14,28) (SMD −0.39, 95% CI −0.70, −0.09, $P = 0.01$).

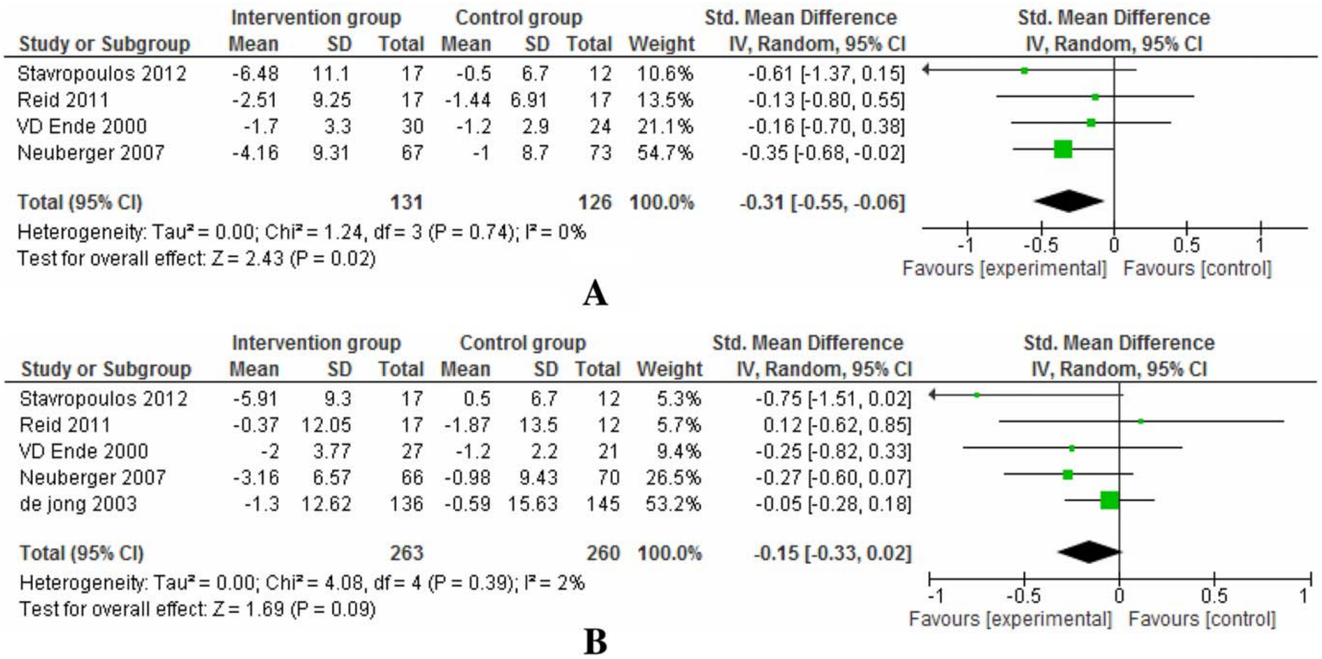

Figure 3. The difference in fatigue score between baseline and 8 or 12 weeks (short term) (**A**) and between baseline and 24 weeks (long term) (**B**). Forest plot of standardized mean difference, with 95% confidence interval (95% CI) for fatigue score. IV = inverse variance.

The pooled analysis comparing the study with fatigue as a reported primary outcome (14) with all studies that did not report fatigue outcomes in their published article showed a larger reduction of fatigue in the study by Neuberger et al (14) (SMD −0.35, 95% CI −0.68, −0.02, $P = 0.04$). However, there was no effect of exercise training on fatigue in the pooled other studies (SMD −0.25, 95% CI −0.62, 0.11, $P = 0.17$).

The only study in which an exercise program longer than 24 weeks was investigated is the study by de Jong et al (29), which was a 2-year supervised high-intensity group exercise program. The effect of the intervention group compared to the control group at 2 years was not significant ($P = 0.53$); the intervention group had a somewhat higher level of fatigue on the SF-36 vitality scale at 2 years of exercising (mean ± SD 0.77 ± 15.5) compared to baseline.

The pooled analysis comparing the studies with a short supervised part of the exercise program (≤12 weeks) (14,30,31) versus the studies with a longer supervised exercise program (24 weeks) (28,29) showed a somewhat larger reduction in fatigue (not significant) in the studies with a longer supervised program (SMD −0.30, 95% CI −0.95, 0.36, $P = 0.37$) than in studies with a shorter supervised program (SMD −0.21, 95% CI −0.48, 0.06, $P = 0.13$).

Meta-regression. In most studies the average baseline fatigue score was similar and ranged between 45% and 55% of the maximum score possible; in 1 study the level of fatigue at baseline was below 20%. There was no significant relation (see Supplementary Figure 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22561/abstract) between the level of baseline fatigue score and the effect of the intervention on fatigue ($\beta = -0.012$, $P = 0.396$, $R^2 = 0.25$).

The study with the lowest baseline fatigue score is the only study in which the benefit in the control group was larger than the benefit of the intervention group (a "reversed" effect). If this study is omitted in the meta-regression, the level of baseline fatigue also does not have a significant effect on the intervention effect ($P = 0.612$).

The meta-regression of the relation between the effect on fatigue with the effect on disability/functioning showed that larger effects on disability were associated with larger effects on fatigue ($\beta = 1.04$, $P = 0.027$, $R^2 = 0.947$).

DISCUSSION

This meta-analysis identified 5 RCTs in which the effect of a supervised land-based aerobic exercise program on fatigue in patients with RA was studied. Accordingly, this analysis showed by pooling the SMDs of included studies that aerobic exercise training may be beneficial to treat fatigue in RA. The effect of aerobic exercise on fatigue was highest and statistically significant at 12 weeks, while this effect diminished over time with no significant effect found at 24 weeks.

The 5 included trials were reasonably well performed and, accordingly, the overall risk of bias was judged as low. The main source of bias, common to all studies, was that the intervention could not be blinded for the patients while fatigue is being measured by patient questionnaire. This cannot be avoided, due to the nature of intervention and outcome. In the individual studies the effects of exercise on fatigue were not statistically significant, with 1 exception: showing the advantage of meta-analysis if studies are small. However, the effect sizes in the individual studies also were relatively small, usually with an SMD of less than −0.5. So far it can be concluded that in these RCTs, the effect of aerobic exercise for fatigue in RA was small at 12 and 24 weeks, with a low risk of bias. Unfortunately, in the several RCTs, different fatigue outcome measures were used. Three of the 5 included studies used the MAF as fatigue questionnaire (14,28,31) and 2 studies used a different fatigue outcome (29,30). This necessitated the use of the dimensionless SMD to enable comparison between studies. However, the use of different outcome measures did not cause a lot of heterogeneity. Unfortunately, of the 22 trials included, only 5 assessed fatigue outcomes (14,28–31), and fatigue was reported as the primary outcome measure in only 1 study. Notably, none of the trials selected patients with RA for having fatigue. This may have contributed to the relatively small effect sizes that were found; the effects of an intervention to reduce fatigue may be larger if patients are selected on fatigue levels as indication. While in meta-regression it was shown that in most studies fatigue was present at baseline, there was no indication that the effect depended on baseline level, presumably because the baseline level of fatigue was quite similar for most studies. Also, it could be that the different lengths of the exercise program and the degree of adherence contributed to the small effect size. It is conceivable that a number of participants may not have continued to exercise after the supervised training program was finished. Generally, supervised programs are more effective for inducing a significant improvement in aerobic capacity than home aerobic exercise (24,25). However, a recently performed RCT showed a significant effect of a home-based exercise program on fatigue (32). Three of the 5 included studies performed a supervised exercise program less than 24 weeks. In our sensitivity analysis, a larger reduction in fatigue, in the studies with a longer supervised exercise program, was found compared to studies with a shorter supervised part; however, it was not significant. Evidence from meta-analyses and RCTs showed that for CFS, CBT (10,11) and exercise (9) are effective treatments. Therefore, there is reason to consider CBT and exercise as treatment modalities for fatigue in RA as well. However, the factors contributing to fatigue are different in RA as compared to CFS, with the presence of chronic pain in RA as a predominant difference (18,33). Therefore, results in CFS cannot automatically be translated to RA. Regarding CBT to treat fatigue in patients with RA, several RCTs have shown that it is effective, although effect sizes are small (11–13). Regarding exercise, there is some evidence from 2 meta-analyses (15,16) to suggest that several exercise forms provide benefit to treat fatigue in RA. However, only 1 study on aerobic exercise was included in these meta-analyses. Although the evidence is not abundant and effects appear to be small, CBT and exercise appear to be promising interventions for the treatment of chronic severe fatigue in RA. This has also been suggested in patients with primary Sjögren's syndrome; fatigue might be reduced by targeting both physical activity and physical activity cognitions (34).

The current meta-analysis concentrates on land-based aerobic exercise and included all currently available evidence, including previously unpublished data in RA. Land-based exercise was chosen because this form of exercise is common, easy to implement in different forms (cycling, walking, "aerobics"), and the intensity can be well regulated. Other forms of exercise, such as strengthening exercises or a water-based or dance-based intervention program, could also have positive effects on fatigue in RA (15). If the most beneficial intensity of aerobic exercise to treat RA fatigue would be known, clinicians could provide this guidance to patients. If exercise has proven to be effective in a trial setting, physical exercise can be implemented by a guideline for the interdisciplinary treatment of fatigue in RA, and implementation through patient organizations. For acceptability and adherence it would be advantageous if patients could choose their favorite mode of exercise. Many patients do not want to take part in intensive exercise for a prolonged period of time; therefore a good solution could be to bring the patients to a certain level of aerobic conditioning by a short intensive phase of the exercise program and use patient-preferred modes of exercise for the maintenance phase. One efficient way to train aerobic capacity, for instance, is cycling; it can be implemented as "spinning" groups with or without peer-patients in the residential area of the patient and it can also be performed alone and/or at home. However, other exercise modalities can also be used, such as (Nordic) walking, exercise at home, as well as exercise at a regular sports center, exercise supervised by a therapist, or an individual exercise program.

In conclusion, the current meta-analysis provided evidence that there may be a positive effect of a supervised aerobic exercise program on fatigue in RA, but the effect was small and nonsignificant at the long term. However, patients in these studies were not selected for having fatigue, and therefore the effect may have been underestimated. For future research, we recommend performing a randomized study on the effects of exercise in patients with RA with fatigue as the main outcome, in patients selected on high fatigue levels. In the future, patients should be supported to continue the exercise program beyond the supervised part of the program, aiming to establish a better effect in the longer term. This could be performed by an internet-based individualized training, even in combination with group contact moments (35,36). In addition, the optimal dose and frequency of exercising to establish an effect on fatigue in patients with RA is yet unknown and should be studied. Further, it would be an advantage if a common fatigue outcome measure, such as the MAF, would be used in future trials to facilitate meta-analyses. Also, the BRAF questionnaire could be included as an RA-specific fatigue questionnaire, probably as a primary outcome measure (37).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rongen-van Dartel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Rongen-van Dartel, Repping-Wuts, Metsios, van den Hout, van den Ende, Neuberger, Reid, Fransen.

Analysis and interpretation of data. Rongen-van Dartel, Repping-Wuts, Bleijenberg, Metsios, van den Ende, Fransen.

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