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1 **Effects of Activity Pacing in patients with chronic conditions associated with fatigue**
2 **complaints: A meta-Analysis**

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1 In a relatively small sample this meta-analysis shows fatigue severity improved after activity
2 pacing interventions and provides a basis to integrate activity pacing in activity stimulation
3 programs for persons with chronic conditions.

- 4 • Activity pacing can feasibly be implemented within standard health care to manage
5 fatigue and physical activity behaviours in persons with chronic conditions.

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25 **Abstract**

1 A meta-analysis was conducted to (1) determine the effect of activity pacing interventions on
2 fatigue, physical functioning and physical activity among patients with chronic conditions
3 associated with fatigue complaints, and to (2) examine potential moderator effects of trial
4 characteristics (components of intervention and amount of patient-provider contact). Six
5 studies were included in the meta-analysis. Relevant content of the studies was extracted and
6 rated on methodological quality. Random-effects modelling was used to pool data across
7 studies. Medium (standardised mean difference = 0.50) and marginal (standardised mean
8 difference = 0.34) effects were found for fatigue at post-treatment and follow-up respectively.
9 Inconsequential effects were found for physical functioning and activity (standardised mean
10 difference = 0.08 to 0.30) at both assessment points. Subgroup analyses revealed components
11 of intervention and amount of patient-provider contact were not source of variance. Minimal
12 patient-provider contact had effect on fatigue comparable in magnitude to more intensive
13 contact. This meta-analysis of activity pacing in patients with fatigue complaints suggests that
14 activity pacing might have sustained beneficial effects on fatigue management, in particular on
15 fatigue reduction. The divergence in effects for all outcomes suggests that alternative ways
16 such as tailoring advice to individual's behaviour towards physical activity may be more
17 successful.

18 **Keyword:** Activity pacing, fatigue, physical functioning, physical activity, chronic conditions

19 **Introduction**

20 Promoting physical activity is essential to preserve the health, quality of life and physical
21 functioning of healthy individuals and those with chronic diseases [1-3]. Post-exertional fatigue
22 is a normal perceptual response in healthy humans but may be exacerbated in patients with
23 chronically fatiguing conditions such as chronic fatigue syndrome, cancer, fibromyalgia and
24 osteoarthritis [4,5,6]. Feelings of fatigue (subjective sensations of weariness) is a common
25 symptom in chronically fatiguing conditions [4,5,6]. Post-exertional fatigue may be a barrier
26 to physical activity and explain activity avoidance in patients with chronically fatiguing
27 conditions [6].

28 Fatigue may result in cycles of over-activity followed by periods of fatigue-induced inactivity
29 [7] and activity avoidance, negatively affecting patients' physical health and quality of life of
30 patients with chronically fatiguing conditions [6,8]. Fatigue management is therefore
31 paramount when programming physical activity for patients with conditions characterised by
32 heightened perceptions of fatigue or pain [9].

1 Activity pacing is a strategy to divide one's daily activities into smaller, more manageable,
2 portions, in a way that should not exacerbate their symptoms, which then allows gradual
3 progressive increases in physical activity [8,10,11]. The goals of activity pacing are to
4 disentangle the symptom experience from the activity experience, prevent over-exertion,
5 attenuate fluctuations in physical activity patterns and avert the detriment associated with
6 fatigue-induced inactivity [8]. While activity pacing is a highly endorsed clinical treatment
7 strategy in chronic pain [9], it remains poorly researched with very little literature in chronic
8 fatigue.

9 The results of the few studies on activity pacing effects in chronic fatiguing conditions have
10 been conflicting. While one study supported links between pacing and lower levels of fatigue
11 and higher physical functioning [12], a number of studies have found no association [13,14,15].
12 Consideration of these findings highlights uncertainty and confusion about the effect of activity
13 pacing on fatigue, physical functioning and activity in chronic fatigue.

14 The aims of the meta-analysis are thus: 1) To review literature on activity pacing interventions
15 and to determine the overall effect of activity pacing interventions on fatigue, physical
16 functioning and activity; both at post-treatment and follow-up, among patients with chronic
17 conditions associated with fatigue complaints; 2) To examine possible moderators such as
18 components of intervention arm, provider-patient contact frequency, the type of condition and
19 gender type of the sample.

20 **Methods**

21 This meta-analysis was completed in accordance with the Preferred Reporting Items for
22 Systematic Reviews and Meta-Analyses statement [16].

23 ***Inclusion criteria***

24 *Types of participants*

25 Studies were included if they were conducted in a participant group of adults (≥ 16 years), with
26 a chronic condition associated with fatigue complaints and fatigue was measured before and
27 after the intervention.

28 *Types of interventions*

29 Studies had to include a construct of activity pacing that measured patient behaviour, targeting
30 fatigue management, physical activity and/or physical functioning.

1 *Outcome measures*

2 Studies had to present statistical data allowing the calculation of effect sizes in the published
3 study or provided by the author(s) upon request, on at least one of the following outcomes;
4 fatigue, physical activity and/or physical functioning, measured at baseline (pre-treatment), at
5 post-treatment and/or at follow-up..

6 *Study Design*

7 Studies had to include a control condition, consisting of usual care, waiting list control, or
8 another type of intervention (e.g. relaxation).

9 Studies were included if they were randomized controlled trials published in peer review
10 journals in English. There were no restrictions with respect to the type of diagnostic criteria
11 used, setting, format and source of delivery of the intervention, as well as with respect to the
12 length of the intervention and assessment point(s).

13 *Search strategy*

14 Initially, electronic databases MEDLINE, PubMed, PEDro, CINAHL, Cochrane Database of
15 Clinical Trials, PsychINFO and Web of Science were searched for relevant articles up to July
16 2017. A comprehensive search strategy was used. Key words “activity pacing” and “fatigue”
17 were combined using an “and” statement. Key words related to physical activity (“exercise,”
18 “physical function,” “physical fitness,” “exercise therapy,” “activities of daily living,”
19 “therapeutic exercise,” “functional status,” and “rehabilitation”) were combined using an
20 “or” statement and then combined with the previous search using an “and” statement. The
21 searches were limited to “English language,” “humans,” and “all aged 16 and older.”
22 References and bibliographic lists of retrieved articles were also hand searched to find
23 additional studies.

24 *Study selection and Data Extraction*

25 Two reviewers independently scanned all the titles and abstracts and identified potentially
26 relevant articles to be retrieved using a custom-designed screening form. Where there was
27 uncertainty, full-text copies of papers were obtained. Studies were considered eligible if they
28 were randomized controlled trials; included patients with chronic conditions associated with
29 fatigue complaints and assessed fatigue before and after intervention; involved activity pacing
30 (activity pacing alone or in combination with psychosocial or exercise interventions [cognitive

1 behavioural therapy and/or graded exercise therapy]) program undertaken in a primary,
2 secondary, or tertiary setting; and comprised a control group that did not receive any form of
3 structured activity pacing but that could include usual or standard treatment.

4 Outcomes included the following: fatigue, physical functioning and physical activity, assessed
5 by recognized and validated measures.

6 Two reviewers independently selected trials to be included: disagreements were resolved by
7 consensus. Two reviewers independently extracted the data once the trials were formally
8 included in the review.

9 The following information was extracted from each selected study: 1) bibliographic
10 information (authors, year of publication, country and reference); 2) type of chronic condition
11 (chronic fatigue syndrome, fibromyalgia, other); 3) sample characteristics (sample size, gender,
12 age); 4) provider (psychologist/psychotherapist, exercise physiologist, physical therapist,
13 nurse, occupational therapist, other); 5) outcomes assessed (fatigue, physical activity, physical
14 functioning); 6) measures used to assess outcomes (type and name of measure); and 7)
15 assessment points (baseline, post-treatment — after the termination of the treatment, follow-up
16 —an additional measurement taken at a later point in time after the termination of the trial); 8)
17 type of care provided to the intervention group (activity pacing and/or graded exercise therapy
18 and/or cognitive behavioural therapy); 9) type of care provided to the control group (passive
19 control—waiting list control, treatment as usual, other; active control: relaxation/flexibility,
20 counselling, other); 10) length of intervention and number of patient–provider sessions. Tables
21 1 show the characteristics of the included studies.

22 [Table 1 near here]

23 *Quality and risk of bias assessment*

24 The methodological quality of the included trials was assessed using a 14-item modified
25 version of the Downs and Black checklist, [17]. The scale assesses characteristics of reporting,
26 internal and external validity of trials. Each item is scored 0 (not done and/or not reported) or
27 1 (done and/or reported). Total scores range from 0 to 14; higher scores indicate higher
28 methodological quality. The Cochrane Collaboration’s tool for assessing risk of bias [18] was
29 used to assess risk of bias in included studies. Risk of bias (high/low/uncertain) was classified
30 based on the following items from this scale: Selection bias —random sequence generation and
31 concealment of allocation; detection bias — blinding of participants and assessors; attrition

1 bias (incomplete outcome data) — information on attrition and inclusion of drop-outs in
2 analyses and selective reporting. Discrepancies in quality rating were resolved by consensus
3 between the two coders. Overall, inter-rater agreement on the items of the methodological
4 quality and risk of bias scales was satisfactory (Cohen's kappa = 0.68)

5 *Data Synthesis*

6 Effect sizes were the standardized mean difference [(mean a – mean b / pooled change standard
7 deviation)] with Hedge's *g* correction for small samples [19]. To calculate effect sizes for
8 selected outcomes, we extracted sample sizes and baseline, post-treatment and/or follow-up
9 means and standard deviations for the intervention and control groups. Authors of included
10 studies were contacted when necessary to retrieve missing data in published reports. When
11 reported in the original trials, we used data from intention-to-treat analyses. When several
12 measures were used for the same outcome (e.g. physical functioning), we chose the measure
13 most frequently used across the studies included. This was the case in one study [14], and in
14 this instance the Checklist Individual Strength measure was used for the effect of the
15 intervention on fatigue, as this was the tool most frequently used across the included studies.

16 **Data Analysis**

17 Analyses were conducted using the Review Manager (RevMan) Software Version 5.3 [20].
18 Main effects were calculated for each outcome (fatigue, physical activity and physical
19 functioning) at post treatment and at follow-up.

20 Main effects were weighted using the inverse variance method and aggregated using a random
21 effects model, in which the summary effect is an estimate of the mean of a distribution of effect
22 sizes [21]. Effect sizes were interpreted according to Cohen's guidelines (values of 0.20, 0.50
23 and 0.80 correspond to small, medium and large effect sizes) [22]. The confidence intervals
24 (CI) and corresponding *p*-values were considered as indicator of the significance of the effect.
25 We also inspected the standardized residuals (i.e. how much each study differs from the overall
26 effect) for outliers (>1.96).

27 We quantified between-study heterogeneity using I^2 statistic [23] that assesses the proportion
28 of observed dispersion that is due to real differences in the true effect sizes. The I^2 ranges from
29 0 to 100%, with values of 25%, 50% and 75% reflecting low, moderate and high heterogeneity
30 [23]. Whenever heterogeneity of effect sizes was observed ($I^2 \geq 50\%$), subgroup analyses were

1 conducted (where applicable) to examine whether effect sizes varied according to the potential
2 moderators.

3 Studies were grouped according to the following characteristics: i) activity pacing alone
4 intervention vs. activity pacing combined with cognitive behavioural therapy and/or graded
5 exercise therapy intervention; ii) minimal face-to-face individual/group patient(s)-provider
6 contact (≤ 3 sessions) vs. more contact (>10 sessions) and iii) fatigue-related condition vs. pain-
7 related condition. Between-groups Q statistic was used to compare the standardised mean effect
8 post-treatment between subgroups, when there were at least three studies in each subgroup.

9 **Results**

10 *Description of included studies*

11 A total of 79 potentially relevant articles were identified in the literature search and additional
12 hand searches. The abstracts of all the articles were scanned to identify studies meeting the
13 inclusion criteria. After the screening of abstracts 68 studies were excluded. Common reasons
14 for exclusion were nonrandomized designs ($n = 15$), inappropriate interventions ($n = 12$),
15 inappropriate sample groups ($n = 28$), and inappropriate outcome measures ($n = 9$). A total of
16 11 full-text articles were retrieved. Three articles [24-26] were not intervention studies and one
17 further study [27] did not include a control group and so were also excluded. Two articles
18 reported data from the same study [13,28] and were therefore grouped together for analysis.
19 Two authors of full articles were contacted to obtain additional data; however, only 1 provided
20 the necessary data for inclusion [29]. This resulted in 6 studies [12-15,29,30] eligible for
21 inclusion in the meta-analysis (table 1). The process of data screening is shown in figure 1.

22 [Figure 1 near here]

23 *Study characteristics*

24 Three studies were activity pacing only and three were activity pacing combined with graded
25 exercise therapy and/or cognitive behavioural therapy. The majority of the trials were
26 conducted in Europe (the United Kingdom, the Netherlands and Belgium) (3 studies, 50%).
27 The remaining studies were conducted in Australia (2 studies, 33%) and the United States of
28 America (1 study, 17%), in secondary–tertiary care settings (e.g. specialized clinics). Study
29 sample sizes varied widely from 32 to 319 patients (median, 54 patients), with a median
30 intervention duration of 10 weeks (range, 2 to 23 weeks) and individual or group sessions

1 varied from 1-16 face to face contacts (median, 7.5). Post-treatment assessment points varied
2 widely from 3 to 24 weeks and the follow-up assessment points was from 24 to 52 weeks.

3 At baseline, the intervention group and the control group in the included studies were similar
4 in terms of fatigue, physical functioning and physical activity ($p > 0.05$). Reported baseline
5 fatigue (mean and standard deviation or range) in the intervention groups and control groups
6 were comparable across the studies.

7 *Assessment of outcome and measures*

8 Fatigue was the outcome measured in six trials, and was assessed with the Chalder Fatigue
9 Scale [31] in two trials [15,30], the Checklist of Individual Strength [32] in one trial [12], while
10 both the Checklist of Individual Strength and the Chronic Fatigue Syndrome Symptom List
11 100 mm Visual Analogy Scale [32,33] were used in another trial [14]. Of the remaining trials,
12 one [13] used the Brief Fatigue Inventory [34] to assess fatigue and the other [29] used the
13 Somatic subscale of the Somatic and Psychological Health Report [35].

14 Physical functioning was reported in four studies, and the Short Form Health Survey-36
15 physical function subscale [36] was used in three studies [14,15,29]. The Impact of Rheumatic
16 Diseases on General Health and Lifestyle instrument [37] was used in the other study [12] to
17 assess physical functioning. Of the two trials that reported physical activity [29,30] the Older
18 Adult Exercise Status Inventory [38] was used in one trial [30], while the International Physical
19 Activity Questionnaire [39] was used in the other trial [29].

20 Three studies [14,13,30] had only post-treatment assessment points, while the remaining three
21 studies [12,15,29] had both post-treatment and follow-up assessment points.

22 *Participant characteristics*

23 In total, 563 participants with chronic conditions associated with fatigue were included in this
24 meta-analysis, with ages ranged from 16-74 years; approximately 82% were women. Patients
25 with chronic fatigue syndrome diagnosed according to the Oxford [40] or the Centres for
26 Disease Control and Prevention [41] criteria, were recruited in three trials. The essential
27 characteristics of chronic fatigue syndrome according to the Oxford and the Centres for Disease
28 Control and Prevention criteria are clinically evaluated, unexplained, persistent or relapsing
29 fatigue not alleviated by rest and a cluster of symptoms that include chronic fatigue, sore throat,
30 lymph node pain, post-exertional malaise, memory/concentration problems and unrefreshing
31 sleep. The remaining trials recruited either exclusively post cancer fatigue patients diagnosed

1 with the Somatic subscale of the Somatic and Psychological Health Report [35] of which
2 clinically-significant fatigue is an essential feature; or fibromyalgia patients diagnosed
3 according to the American College of Rheumatology criteria [42] with the essential
4 characteristics of unexplained, persistent widespread pain and symptoms of fatigue, cognitive
5 problems and waking unrefreshed; or hip or knee osteoarthritis patients as evidenced by
6 radiograph of osteoarthritis in that joint and a pain score of ≥ 4 out of the 5 items on the Western
7 Ontario and McMaster Universities Osteoarthritis Index pain subscale [43].

8 *Intervention characteristics*

9 In two studies [12,29], the intervention arm included activity pacing, cognitive behavioural
10 therapy and graded exercise therapy. The activity pacing intervention sought to encourage
11 patients to avoid exacerbations of their symptoms by planning daily and weekly schedules of
12 activities and rest breaks, and segmenting tasks into short time blocks. Cognitive behavioural
13 therapy was aimed at diminishing the daily perceived cognitive, behavioural, emotional, and
14 social consequences of illness and accompanying symptoms in order to optimize adherence to
15 treatments. The graded exercise therapy component consisted of aerobic activities adapted to
16 the individual's physical capacity assessed at baseline taking into account a gradual increase in
17 the duration and frequency of exercise sessions. The trials were delivered by clinical
18 psychologists and exercise physiologists. The number of sessions ranged from 11 to 16
19 sessions, weekly or fortnightly, lasting for 8-12 weeks.

20 In one trial, the intervention group received graded exercise therapy incorporating a pacing
21 construct, which consisted of individualized aerobic exercise based on baseline assessment and
22 taking into account a gradual increase in the duration and intensity to reduce fatigue and
23 increase activity [30]. Activity was gradually increased and rest was reduced, step by step as
24 tolerance developed. Patients were recommended not to exceed the levels of exercise agreed
25 upon beforehand by the therapist and patient, and to reduce their activity levels if symptoms
26 got worse. The number of sessions was 12, once a week, lasting for 12 weeks, consisting of 1
27 face-to-face and 6 telephone contacts.

28 Two studies [13,14] included tailored activity pacing programs delivered via an educational
29 module on activity pacing. The module outlined general principles of activity pacing as they
30 apply to one's condition and included the preplanning and prioritizing of activities, and
31 alternating active and rest periods before a symptom exacerbation. Patients were advised to
32 prevent over-activity. The focus was on a personalized report that summarized and visually

1 depicted each person's symptom-activity relationship based on their physical activity and
2 symptom data collected during a home monitoring period. Specific examples of where
3 symptoms seemed to affect activity were highlighted within and across the days from the home
4 monitoring period, and individual goals for pacing were formulated. The treatment also
5 included an educational support manual and a log book to monitor coping strategies. The
6 number of sessions ranged from 1 to 17 sessions, once or twice weekly, lasting for 3-10 weeks.

7 The trial conducted by Kos et al., [14] consisted of a stabilization phase and a grading phase.
8 The stabilization phase focused on coaching clients in how to perform activities of daily living
9 within the limits of their actual capacity. The activity duration advised within the program was
10 25%–50% below self-reported capacity, to account for any overestimations. Each activity
11 block was interspersed with breaks, with the length of the break equating to the duration of the
12 activity. Once clients were able to control their activities of daily living without excessive
13 feelings of fatigue, the grading phase was started during which activity level was increased
14 gradually. Participants conferred with a cognitive behavioural therapist to set relevant and
15 achievable personal physical activity goals, based on prioritized activities.

16 Adaptive pacing therapy was used in the trial by White et al., [15]. Therapeutic strategies
17 consisted of identifying links between activity and fatigue by the use of a daily diary. Patients
18 were encouraged to plan activities to avoid exacerbations, develop awareness of early warnings
19 of exacerbation, limit demands and stress, regularly plan rest and relaxation, and alternate
20 different types of activities, with advice not to undertake activities that required more than 70%
21 of participants' perceived energy envelopes. Increased activities were encouraged, if the
22 participant felt able, and as long as they did not exacerbate symptoms.

23 In summary, the theoretical models informing and guiding activity pacing intervention in the
24 included studies are operant theory and energy conservation [44,45]. The operant theory-based
25 interventions aimed to limit the extent to which activity is symptom-contingent (example,
26 reduce excessive resting when fatigue or pain are high) in order to achieve predetermined
27 activity goals [13,14,30]. The energy based interventions, on the other hand, sought to preserve
28 energy for completing valued activities while reducing overall symptoms [12,15,29]

29 *Quality of the studies and risk of bias*

30 The Cochrane Collaboration's tool for assessing risk of bias [18] was used to assess risk of bias
31 in included studies. Methodological quality of each study was then assessed using a modified
32 Downs and Black checklist, [17]. Table 2 shows the quality of the trials and risk of bias. The

1 trial by Sandler et al., [29] showed the highest quality and lowest risk of bias. The trial
2 conducted by Wallman et al., [30] showed the lowest quality and presented an uncertain risk
3 of bias on three criteria. The trials by van Koulil et al., [12] and Murphy et al., [13] presented
4 uncertain risk of bias on two and three criteria respectively. The trial by Murphy et al., [13]
5 presented a high risk of bias on selective reporting. In relation to attrition bias, most studies
6 presented adequate drop-out information and inclusion (intent to treat analysis). Two trials
7 [14,15] reported an adequate method of concealment, one presented high risk of bias [12] and
8 two studies did not report details on blinding of assessors [18,30].

9 [Table 2 near here]

10 *Synthesis of results*

11 Table 3 shows the overall results of the effect of activity pacing on fatigue, physical functioning
12 and physical activity at post-treatment and/or follow-up. The forest plots of the effects
13 comprising of the main effects are presented in figures 2, 3 and 4. Table 4 presents the results
14 of the subgroup analysis of effects on fatigue for the post-treatment assessment.

15 [Table 3 near here]

16 [Table 4 near here]

17 *Effects on fatigue*

18 Six studies [12-15,29,30] reported measures of fatigue at post-treatment (varying from 3 to 24
19 weeks). The pooled estimates showed moderate effect for fatigue at post-treatment
20 (standardised mean difference = 0.49; 95% CI [0.08 – 0.90]) but results were heterogeneous
21 between studies ($I^2 = 70$) (table 3).

22 Effects were larger when activity pacing was combined with graded exercise therapy or
23 cognitive behavioural therapy (standardised mean difference = 0.68; 95% CI [0.28 – 1.08])
24 compared with activity pacing alone (standardised mean difference = 0.27; 95% CI [-0.12 –
25 0.67]). The pooled estimate for the three studies which included minimal patient contact was
26 moderate (standardised mean difference = 0.49; 95% CI [0.14 – 0.85]) and homogeneous (I^2
27 = 0%) and was comparable in magnitude to the differences in interventions with more patient
28 contact which was also moderate (standardised mean difference = 0.51; 95% CI [0.14 – 0.86])
29 but more heterogeneous ($I^2 = 87\%$) (table 4).

1 Three studies [12,15,29] presented fatigue data at follow up (varying from 24 to 52 weeks after
2 baseline). The pooled estimates showed marginal effect for fatigue at follow-up (standardised
3 mean difference = 0.37; 95% CI [-0.10 – 0.77]), but results were heterogeneous between studies
4 ($I^2 = 71%$) (table 3) The forest plots of effect sizes comprising the main effects of activity
5 pacing on fatigue at both post-treatment and follow-up are illustrated in figure 2.

6 [Figure 2 near here]

7 *Effects on physical functioning*

8 Four studies [12,14,15,29] reported measures of physical functioning at post-treatment (3–24
9 weeks) and three studies [12,15,29] reported measures of physical functioning at follow-up
10 (24–52 weeks). Combined effect sizes were inconsequential at post-treatment (standardised
11 mean difference = 0.08; 95% CI [-0.36 – 0.51]) and at follow-up (standardised mean difference
12 = $d = -0.07$; 95% CI [-0.61 – 0.48]), but effects varied between studies at both assessment
13 points ($I^2 = 73%$ and $I^2 = 82%$ respectively) (table 3). The forest plots of effect sizes comprising
14 the main effects of activity pacing on physical functioning at both post-treatment and follow-
15 up are illustrated in figure 3.

16 [Figure 3 near here]

17 Due to the limited number of studies presenting data for physical functioning no further
18 potential moderator analyses were conducted.

19 *Effects on physical activity*

20 Post-treatment physical activity data (12 weeks) was available in only two studies [29,30].
21 Only one study [29] presented follow-up physical activity data (24 weeks). Overall main effect
22 for physical activity at post-treatment was not significant (standardised mean difference = 0.30;
23 95% CI [-0.08 – 0.68]), with evidence of homogeneity between studies ($I^2=0%$) (table 3). For
24 that reason, no further moderator analyses were conducted. The forest plots of effect sizes
25 comprising the main effects of activity pacing on physical activity at post-treatment are
26 illustrated in figure 4.

27 [Figure 4 near here]

28 *Sensitivity analyses*

29 Primary analyses were repeated with the exclusion of the trial by White et al. [15], which
30 presented a high risk of bias and poor methodological quality (table 2). Excluding this study

1 led to an increase in the magnitude of treatment effects for fatigue at post-treatment from
2 standardised mean difference = 0.50 to standardised mean difference = 0.67, and at follow-up
3 from standardised mean difference = 0.34 to standardised mean difference = 0.51. And also led
4 to an increase in the magnitude of treatment effects for physical functioning at post-treatment
5 from standardised mean difference = 0.08 to standardised mean difference = 0.23, and at
6 follow-up from standardised mean difference = -0.07 to standardised mean difference = -0.01
7 The exclusion of the trial conducted by Wallman et al., [30] because of high/uncertain risk of
8 bias in most categories and poor methodological quality, led to an increase in the overall point
9 estimate for fatigue at post-treatment (from standardised mean difference = 0.50 to standardised
10 mean difference = 0.52). Excluding both studies led to an increase in magnitude of treatment
11 effects for fatigue at post-treatment from standardised mean difference = 0.50 to standardised
12 mean difference = 0.75.

13 **Discussion**

14 To our knowledge, this is the first meta-analysis investigating the effectiveness of activity
15 pacing on fatigue severity, physical functioning and physical activity in patients with fatigue
16 complaints with or without a chronic condition. Six trials with baseline fatigue assessment and
17 post treatment and/or follow-up assessment point(s) were included. In addition, this meta-
18 analysis analysed the potential moderating effects of the following trial characteristics at post-
19 treatment: whether the intervention arm was activity pacing only or activity pacing with
20 behavioural and or exercise intervention and whether or not the intervention was a minimal
21 (direct face to face) contact intervention.

22 This meta-analysis shows that activity pacing interventions have beneficial effects on fatigue
23 at post-treatment (standardised mean difference = 0.50) and marginal effect at follow-up
24 (standardised mean difference = 0.34) in chronically fatiguing conditions. Treatment effects
25 varied widely between studies and subsequent subgroup comparisons revealed that components
26 of intervention arm and amount of face-to-face contact were not significant moderators of the
27 effect of the interventions on fatigue at post-treatment. The effect of minimal contact
28 interventions on fatigue (standardised mean difference = 0.49) was comparable in magnitude
29 to the effect of interventions of more intensive contact (standardised mean difference = 0.51).
30 The finding is somewhat similar to that of a recent meta-analysis on effects of behavioural and
31 psychological interventions that pointed at the beneficial effects of minimal contact
32 interventions on fatigue [46]. This makes a case for activity pacing as a plausible effective less

1 resource intensive activity stimulation program that could substitute for more resource
2 intensive programs such as cognitive-behavioural therapy and can be useful for patients
3 presenting difficulties in regularly attending health care facilities [47]. The lack of sustained
4 beneficial effect at follow-up may be accounted for by the limited number of studies providing
5 follow-up fatigue data. This highlights the need for future interventional studies on the long-
6 term effect of activity pacing on fatigue.

7 Furthermore, the overall effect sizes for intervention arms comprising of activity pacing
8 combined with cognitive behavioural therapy and/or graded exercise therapy on fatigue were
9 larger (effect size = 0.68) than intervention arms of activity pacing alone (effect size = 0.27).
10 It is however important to point out that of the studies included in our meta-analysis, only three
11 studies were activity pacing alone interventions, each of them with clearly distinct features.
12 One trial, was a tailored activity pacing intervention that focused on preplanning and
13 prioritizing of activities, and alternating active and rest periods before a symptom exacerbation
14 [13], another was an activity pacing trial that focussed on prioritizing of activities, and
15 alternating active and rest periods, and gradually increasing activities to prevent exacerbation
16 of symptom [14], and the last one was the adaptive pacing trial that restricted performance of
17 activities within limits of 70% of actual capacity [15]. The high heterogeneity found in this
18 subgroup and the limited number of trials is a limitation to this finding. This suggests that there
19 may differences in the effect of activity pacing interventions on fatigue across other particular
20 patient characteristics such as disease diagnosis, attitude towards physical activity, self-
21 efficacy and stage of behavioural change. Further exploratory studies on this is needed.

22 Regarding physical function, inconsequential main treatment effects of activity pacing were
23 found post-treatment (standardised mean difference = 0.08) and at follow-up (standardised
24 mean difference = -0.07). However, considerable variation in response was observed at both
25 assessment points. The small number studies included in this meta-analyses that reported
26 activity pacing effects on physical functioning limited further analyses of potential moderators
27 of the variance in activity pacing main effect. This points to the fact that there may be
28 differences in the effect of activity pacing interventions on physical functioning across other
29 particular patient and/or intervention characteristics. More research is clearly needed to analyse
30 the effects potential moderators.

31 Considering that activity pacing instruction directly relates to altering physical activity
32 patterns, it was interesting to find that only a handful of studies ($n = 2$) evaluated the effect of

1 activity pacing on physical activity in patients with high fatigue complaints. Although a small
2 non-significant main effect (standardised mean difference = 0.30) of activity pacing on physical
3 activity was found in this review, the responses were varied. The limited number of included
4 studies reporting on the effect of activity pacing on physical activity could account for the small
5 treatment effect found in this review is a limitation to this finding. Previous exploration into
6 the effects of activity pacing on physical activity has produced inconsistent findings. In some
7 studies, pacing was associated with lower levels of physical activity [12,13], while in other
8 studies pacing was related to high physical activity [24,25,44].

9 These inconsistencies may in part be explained by study design and interpretation of AP as
10 observed in this review. While some studies described activity pacing as managing energy
11 expenditure, aimed at staying within boundaries of physical limits by either focusing on
12 symptoms or by including rest [13,15,29], other studies included activity progression as an aim
13 of activity pacing [12,14,29]. This highlights the dearth of a standardized definition of activity
14 pacing and may reflect the ineffectiveness of activity pacing if not used to gradually increase
15 an individual's activity level [10].

16 Other features that could have moderated the findings are avoidance behaviour, naturalistic
17 pacing behaviour (level of activity pacing that persons implement in daily life without a
18 specifically instructed activity pacing program) and perceived difficulty in preventing over-
19 activity in daily life. With most of the studies aimed at preventing over-activity [13,15,29],
20 superior improvement may have been observed in persons with high natural engagement in
21 pacing and/or high perceived difficulty in preventing over-activity compared to persons with
22 avoidance behaviour, low natural engagement in pacing and/or low perceived difficulty in
23 preventing over-activity. Future studies exploring the impact of patients behaviour towards
24 physical activity is of utmost importance.

25 The discrepancy that was found in this meta-analysis between the effects found for fatigue and
26 for physical activity and physical functioning could indicate that the mere decrease of fatigue
27 does not necessary lead to improved outcomes in terms of physical activity and physical
28 functioning. This may point at the fact that alternative ways of promoting physical activity and
29 physical functioning, e.g. flexibility in physical activity goals in the form of tailoring advice to
30 individual's characteristics towards physical activity assessed at baseline and making use of
31 motivational interview may be more successful in changing this health behaviour and equally

1 managing fatigue. This provide further insight to help optimize tailored activity stimulation
2 programs.

3 *Limitations and recommendations for future research*

4 The limited number of eligible and included studies, coupled with the uneven distribution of
5 studies in subgroups limited the analyses of subgroups effect sizes of activity pacing on fatigue,
6 physical functioning and physical activity. Readers should therefore be cautious when
7 interpreting the pooled effect sizes. Emphasis should instead be placed on the distribution in
8 each category and the observed patterns in the data. Future studies should continue to explore
9 potential moderators that can account for differences between trial results. Among these are
10 patient and disease-related characteristics (e.g. illness duration, severity of disease, attitudes
11 towards pacing) and treatment features (e.g. pacing alone, pacing + graded activity).

12 Most of the categorization of intervention characteristics was based on the intervention
13 description provided in the articles. In many cases these descriptions were limited and the same
14 accounts for the description of the content of manuals that were used in different interventions.
15 Future studies should give a sufficiently detailed account of the content of the intervention/self-
16 help manual offered to patients. Although most of the outcomes were assessed using validated
17 measures, the way scores were calculated was not always clear. Future randomized controlled
18 trials should pay more attention to the way statistical data are presented, making an effort to
19 present effect sizes and raw data (means and standard deviations) for all outcomes and
20 assessment periods.

21 The number of studies included in this meta-analysis that presented follow-up assessment data
22 was limited and only available for a maximum period of 52 weeks. Hence, although activity
23 pacing had sustainable beneficial effects on fatigue management and small effects on physical
24 functioning after data synthesis, more research is needed to understand long-term effects. More
25 research on the impact of activity pacing on physical activity behaviour using subjective and
26 objective measures are needed.

27 There is the need to standardize activity pacing based on a clear theoretical concept and
28 consideration of the context in which the behaviour occurs. There is also a need for further
29 validity studies of measures of activity pacing to help streamline the construct. Additionally,
30 studies on the effect of natural pacing behaviour and perceive difficulty in preventing
31 overactivity on the effectiveness of pacing intervention are needed to help guide and refine
32 treatment efforts.

1 **Conclusion**

2 This meta-analysis of activity pacing in patients with chronic diseases associated with fatigue
3 complaints suggests that activity pacing might have sustained beneficial effects on fatigue
4 management, in particular on fatigue reduction for which small-to-moderate effects were
5 found. The finding that minimal contact interventions had similar effect compared to more
6 intensive contact intervention is important. This provides valuable insight that activity pacing
7 intervention can be feasibly implemented in standard health care and can be suitable for patients
8 who do not need more intensive forms of treatment.

9 More importantly, findings of the study demonstrate the need to further explore moderators
10 such as patient's behaviour towards physical activity assessed at baseline to help optimize the
11 tailoring of activity stimulation programs. All trials included in this meta-analysis had an initial
12 face-to-face patient-provider contact with patients, which may have led to increased motivation
13 of patients to engage in a behaviour change process. Notwithstanding the beneficial effects of
14 activity pacing reported in this meta-analysis and the valuable indications about targets and
15 format of future interventions, more research are needed to identify optimal features of activity
16 pacing.

17 **Declaration of Interest Statement**

18 The authors report no conflicts of interest

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22

23 **List of Figure Captions**

24 Figure. 1. Flow diagram of data screening.

25 Figure 2. Forest plot of the activity pacing effects on fatigue at (A) post-treatment and (B)
26 follow-up. The pooled SMD was .50 (95% CI [.14 – .86]) at post-treatment. The pooled SMD
27 was .34 (95% CI [-.01 – .77]) at follow-up.

28 Figure 3. Forest plot of the activity pacing effects on physical functioning at (C) post-
29 treatment and (D) follow-up. The pooled SMDs was .08 (95% CI [-.36 – .51]) at post-
30 treatment. The pooled SMD was -.07 (95% CI [-.61 – .48]) at follow-up.

31 Figure 4. Forest plot of the activity pacing effects on physical activity for post-treatment. The
32 pooled SMD was .30 (95% CI [-.08 – .68]) at post-treatment.

Table 1. Characteristics of Included studies

Study Intervention Led	Sample size (Male/Female) Age in years (Mean \pm SD) Condition Diagnosis	Intervention Condition (Control condition)	Structure of Session & Assessment (weeks)	Measure tool	Outcome
Van Koulil et al., [12] Cognitive Behavioural Therapist	84 (6/78) 41.7 \pm 10.9 Fibromyalgia	Pacing + CBT + GET (Waiting List)	16 group sessions/2x8 weeks + 1 booster session Post-treatment = 10 Follow-up = 24	CIS IRGL	Fatigue Physical function
Wallman et al., [30] Physiologist	61 (14/47) NA(16-74) Chronic Fatigue Syndrome	Pacing + GET (Relaxation/flexibility)	1 face to face session + 6 telephone calls/12 weeks Post-treatment = 12	Chalder Fatigue Questionnaire Older Adult Exercise Status Inventory	Fatigue Physical activity
Sandler et al., [29] Clinical psychologist Exercise physiologist	46 (3/43) 51.2 \pm 9.5 Post Cancer Fatigue	Pacing + CBT + GET (Education)	11-13 face to face sessions/12weeks Post-treatment = 12 Follow-up = 24	SOMA of SPHERE Short Form-36 IPAQ	Fatigue Physical function Physical activity
Kos et al., [14] Occupational Therapist	33 (0/33) 39.3 \pm 11.4 40.8 \pm 11.1 Chronic Fatigue Syndrome	Tailored Pacing (Relaxation)	3 face to face/1x3 weeks Post-treatment = 3	CIS & CFSSL Short Form Physical Function subscale	Fatigue Physical function
Murphy et al., [13] Occupational Therapist	32 (8/24) 61.9 \pm 7.9 Hip/Knee Osteoarthritis	Tailored Pacing (General Pacing)	2 face to face/1x2 weeks Post-treatment = 10	Brief Fatigue Inventory	Fatigue
White et al., [15] Occupational Therapist	319 (76/243) 38 \pm 12 Chronic Fatigue Syndrome	Adaptive Pacing + Specialist Medical Care (Specialist Medical Care)	14 face to face and telephone / 23 weeks Post-treatment = 24 Follow-up = 52	Chalder Fatigue Questionnaire Short Form Physical Function subscale	Fatigue Physical function

CBT: Cognitive Behavioural Therapy
GET: Graded Exercise Therapy

CIS: Checklist Individual Strength
IRGL: Impact of Rheumatic Diseases on General Health and Lifestyle Instrument

CFSSL: Chronic Fatigue Syndrome Symptom List

Table 2: Classification on methodological quality, risk of bias and moderators of included interventions.

Study ID	Methodological Quality Rating (0-14)	Random sequence generation	Allocation concealment	Blinding of participant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other: Dropout information
van Koulil et al., [12]	13	Low	High	Unclear	Unclear	Low	Low	Low
Wallman et al., [30]	11	Low	Unclear	Unclear	Unclear	Low	Low	Low
Sandler et al., [29]	13	Low	Low	Low	Low	Low	Low	Low
Kos et al., [14]	11	Low	Low	Unclear	Low	Low	Low	Low
Murphy et al., [13]	12	Unclear	Unclear	Unclear	Low	Low	High	Low
White et al., [15]	11	Low	Low	High	High	Low	Low	Low

Table 3: Pooled mean estimates for change in outcomes assessed at post-treatment and at follow-up.

Outcome	Assessment point	<i>k</i>	<i>n</i>	Standardised Mean Difference [95%CI]	<i>Z</i>	<i>p</i>	<i>I</i> ²
Fatigue	Post-treatment	6	563	0.50 [0.14, 0.86]	2.69	0.007	70%
	Follow-up	3	435	0.34 [-0.10, 0.77]	1.53	0.13	71%
Physical functioning	Post-treatment	4	470	0.08 [-0.36, 0.51]	0.35	0.73	73%
	Follow-up	3	435	-0.07 [-0.61, 0.48]	0.24	0.81	82%
Physical activity	Post-treatment	2	107	0.30 [-0.08, 0.68]	0.44	0.66	0%
	Follow-up	1	46	n/a	n/a	n/a	n/a

k = number of studies n/a = not applicable

Table 4: Subgroup analysis assessing the effect of study characteristics upon fatigue at post-treatment.

Moderator		Fatigue				
		k	SMD [95%CI]	Z	p ¹	I ²
Components of intervention arm	Pacing + GET + CBT	3	0.68 [-0.28, 1.08]	3.35 (p = 0.0008)	p = 0.16 I ² = 50.3%	I ² = 44% (p=0.17)
	Pacing only	3	0.27 [-0.12, 0.67]	1.35 (p = 0.18)		I ² = 45% (p=0.16)
Number of patient-provider contact	Minimal contact	3	0.49 [0.14, 0.85]	2.72 (p = 0.007)	p = 0.96 I ² = 0%	I ² = 0% (p=0.91)
	More contact	3	0.51 [-0.14, 1.17]	1.53 (p = 0.13)		I ² = 87% (p=0.0005)
Condition	Fatigue-related	4	0.28 [-0.01, 0.56]	1.90 (p = 0.06)	n/a	I ² = 36% (p=0.19)
	Pain-related	2	0.49 [0.49, 1.30]	4.36 (p < 0.0001)		I ² = 6% (p=0.30)

CBT = Cognitive Behavioural Therapy; GET = Graded Exercise Therapy; k = number of studies; p¹ = p-Values correspond to subgroup differences in effects; n/a = not enough interventions in the subgroup to allow for a comparison; SMD = Standardised Mean Difference

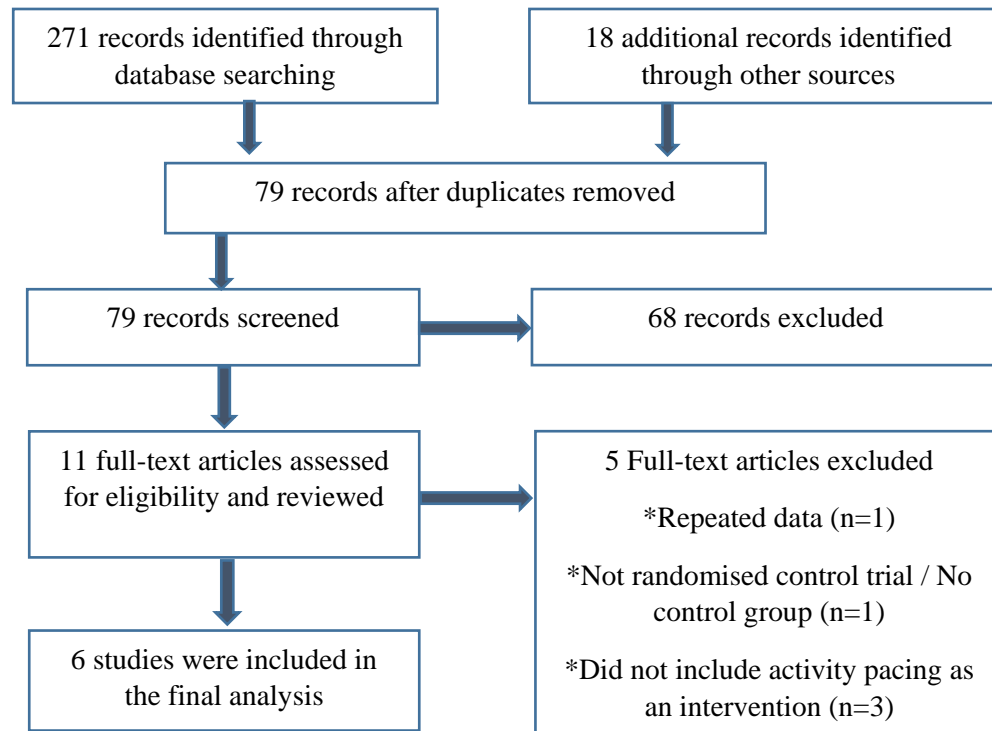
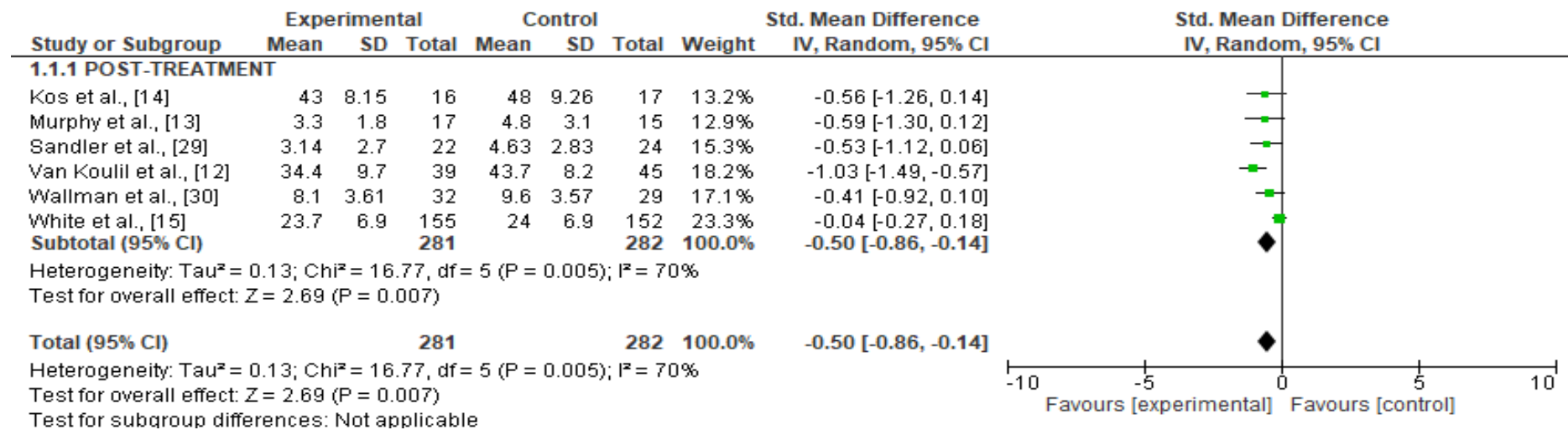


Figure 1 Flow diagram of data screening.

(A)



(B)

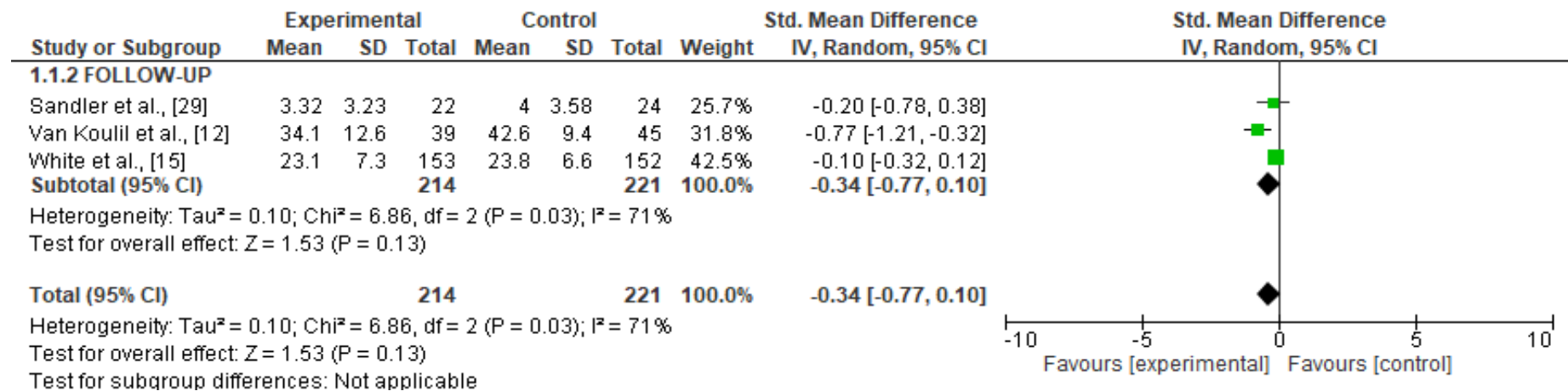
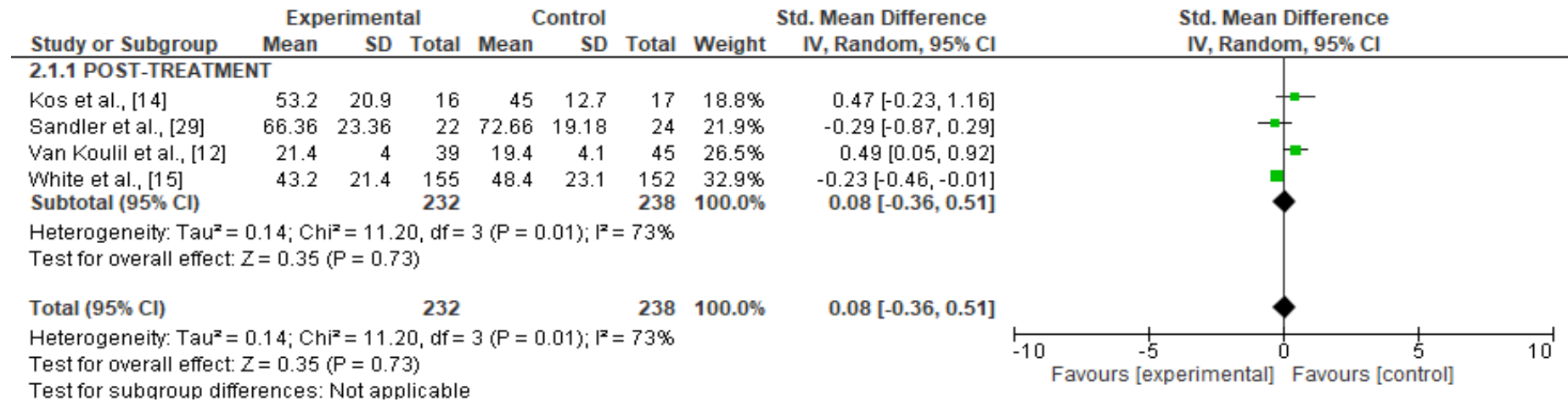


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(C)



(D)

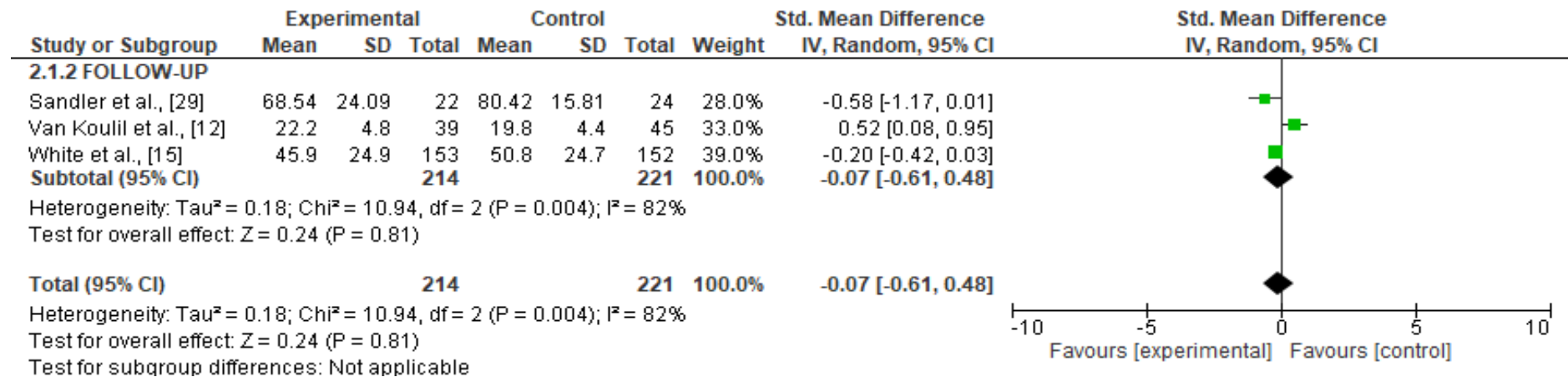


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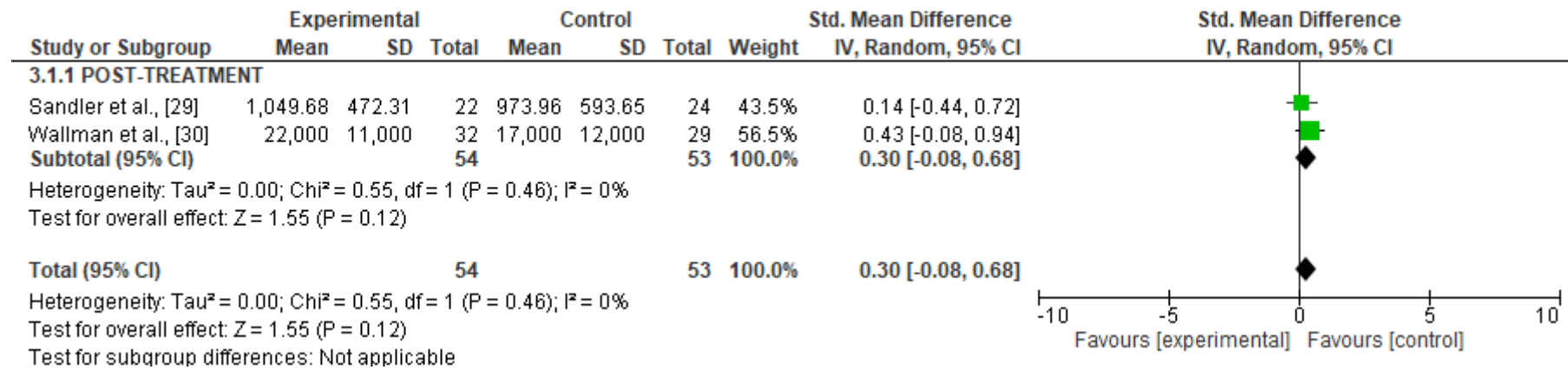


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