Taylor & Francis
Taylor & Francis Group

Fatigue: Biomedicine, Health & Behavior

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/rftg20

'Pacing' for management of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review and meta-analysis

Nilihan E.M. Sanal-Hayes, Marie Mclaughlin, Jacqueline L. Mair, Jane Ormerod, David Carless, Rachel Meach, Natalie Hilliard, Joanne Ingram, Nicholas F. Sculthorpe & Lawrence D. Hayes

To cite this article: Nilihan E.M. Sanal-Hayes, Marie Mclaughlin, Jacqueline L. Mair, Jane Ormerod, David Carless, Rachel Meach, Natalie Hilliard, Joanne Ingram, Nicholas F. Sculthorpe & Lawrence D. Hayes (29 Nov 2024): 'Pacing' for management of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review and meta-analysis, Fatigue: Biomedicine, Health & Behavior, DOI: 10.1080/21641846.2024.2433390

To link to this article: https://doi.org/10.1080/21641846.2024.2433390

Published online: 29 Nov 2024.

FATIGUE: BIOMEDICINE, HEALTH & BEHAVIOR
https://doi.org/10.1080/21641846.2024.2433390

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

'Pacing' for management of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review and meta-analysis

Nilihan E.M. Sanal-Hayes[1], Marie Mclaughlin[2], Jacqueline L. Mair[3,4], Jane Ormerod[5], David Carless[6], Rachel Meach[7], Natalie Hilliard[8], Joanne Ingram[9], Nicholas F. Sculthorpe[6] and Lawrence D. Hayes [10]

[1]School of Health and Society, University of Salford, Salford, UK; [2]Physical Activity for Health Research Centre, Institute for Sport, P.E. and Health Sciences, University of Edinburgh, Moray House School of Education and Sport, Edinburgh, UK; [3]Future Health Technologies, Singapore-ETH Centre, Campus for Research Excellence and Technological Enterprise (CREATE), Singapore; [4]Saw Swee Hock School of Public Health, National University of Singapore, Singapore; [5]Long COVID Scotland, Aberdeen, UK; [6]School of Health and Life Sciences, Sport and Physical Activity Research Institute, University of the West of Scotland, Glasgow, UK; [7]Department of Earth Sciences, University of Durham, Durham, UK; [8]Physios for ME, London, UK; [9]School of Education and Social Sciences, University of the West of Scotland, Glasgow, UK; [10]Lancaster Medical School, Lancaster University, Lancaster, UK

ABSTRACT

Background: Pacing typically comprises regulating activity to avoid post-exertional neuroimmune exhaustion, the worsening of symptoms after an activity. Yet, the efficacy of pacing to improve symptomology is unclear.

Objective: We aimed to undertake a PRISMA-accordant meta-analysis concerning the effect of pacing on ME/CFS patients' symptoms.

Data sources: Six electronic databases (PubMed, Scholar, ScienceDirect, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials [CENTRAL]) were searched; and websites MEPedia, Action for ME, and ME Action were also searched for grey literature.

Study selection: Studies ($k = 5$) selected from the 210 identified included randomised controlled trials (RCTs; $k = 2$), uncontrolled trials (UCTs; $k = 1$), intervention case series ($k = 1$), and sub-analysis of the PACE trial ($k = 1$), all of which had a pacing component, and an outcome measure reported pre- and post-pacing.

Study appraisal and methods: Three separate meta-analyses were conducted on changes in symptoms using standardised mean differences (SMDs) and random-effects models.

Results: The overall SMD showed pacing improved physical function ($k = 4$, SMD = 0.15 [95% CI = −0.39, 0.68], $p = 0.5951$). Pacing improved pain ($k = 4$, SMD = −0.11 [95% CI = −0.32, 0.10], $p = 0.3090$). Pacing improved fatigue ($k = 4$, SMD = −1.09 [95% CI = −2.38, 0.21], $p = 0.0998$).

ARTICLE HISTORY
Received 26 July 2024
Accepted 14 November 2024

KEYWORDS
Pacing; myalgic encephalomyelitis; chronic fatigue syndrome; physical function; pain, fatigue

CONTACT Lawrence D. Hayes l.hayes4@lancaster.ac.uk Lancaster Medical School, Health Innovation One, Faculty of Health & Medicine, Sir John Fisher Drive, Lancaster University, Lancaster, LA1 4AT, UK

Conclusions: Pacing exerted a trivial beneficial effect on physical function and pain. Fatigue was improved with a large effect, which did reach the $p < 0.05$ level. We cautiously conclude pacing likely exerts some beneficial effects on symptomology, particularly, fatigue, in people with ME/CFS. However, the level of empirical research is insufficient, and more high-quality RCTs are essential to support the NICE guidelines.

Abbreviations: Centers for Disease Control and Prevention (CDC); Chronic Pain Coping Inventory (CPCI); Cognitive behavioural therapy (CBT); Cochrane Central Register of Controlled Trials (CENTRAL); Graded exercise therapy (GET); Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); Physiotherapy Evidence Database (PEDro); Post-exertional neuroimmune exhaustion (PENE); Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA); Randomised control trial (RCT)

1. Introduction

1.1. Rationale

Myalgic Encephalomyelitis (ME) Chronic Fatigue Syndrome (CFS) and/or ME/CFS has been evident in the medical literature for decades and is thought to occur consequent to a viral infection [1]. ME/CFS is a debilitating condition characterised by severe fatigue, cognitive impairment, and a host of other symptoms, with no known cure or definitive treatment [2–6]. The condition has a prevalence of ~1%, equating to 670,000 people with ME/CFS living in the UK alone [7]. People with ME/CFS experience a severe and ongoing symptom load, and moreover half of the ME/CFS population are unemployed due to their condition [8]. To date, there is no pharmacological treatment or cure for ME/CFS, with symptom management being the primary therapeutic approach. There is a growing need for a standardised method of care for the management of symptoms associated with ME/CFS.

From a historical perspective, the 2007 NICE guidelines for people with ME/CFS advised that both cognitive behavioural therapy (CBT) and graded exercise therapy (GET) should be offered to people with ME/CFS [9]. As of the 2021 update, the NICE guidelines for people with ME/CFS do not advise CBT or GET, and the only recommended management strategy is 'pacing' [10]. Pacing, initially described by health psychologist Ellen Goudsmit in 1989, advises patients to: 'do as much as you can within your limits' [11–13]. It is an activity management strategy to help ME/CFS patients attempt to limit the number and severity of relapses while remaining as active as possible. In the years between changes to the NICE guidelines, the landmark PACE trial [14] was published in 2011. This large, randomised control trial (RCT; $n = 639$) compared pacing, GET, and CBT and reported GET and CBT as more effective than pacing for improving symptoms. Yet, this study has come under considerable criticism from patient groups and clinicians alike [15–18], with patients often arguing that GET not only fails to address the underlying biological nature of their conditions but can also lead to symptom exacerbation, resulting in long-term harm. Moreover, changes to the way the main outcomes were analysed were implemented, and this has led to criticism. This may partly explain why NICE revised its

guidance and only recommended pacing for symptom management people with ME/CFS [10]. There has been some controversy over the best treatment for people with ME/CFS in the literature and support groups, potentially amplified by the ambiguity of evidence for pacing efficacy and how pacing should be implemented. As such, before pacing can be advised, it is imperative literature concerning pacing is systematically reviewed and meta-analysed for efficacy. Despite a number of systematic reviews concerning pharmacological interventions or cognitive behavioural therapy in people with ME/CFS [15,19,20], to date, there are no systematic reviews concerning pacing efficacy. In fact, our recent scoping review [6] was the first to aggregate previous research concerning pacing for people with ME/CFS, with a focus on methodologies utilised.

A comprehensive review of pacing efficacy in ME/CFS is an essential tool to guide symptom management advice. Yet, despite the widespread use of pacing, the literature base is limited and includes clinical commentaries, case studies, case series, and a few RCTs. Encouragingly, our recent scoping review [6] identified 17 studies or patient surveys concerning pacing in people with ME/CFS. We noted several studies considered the same symptoms or patient outcomes, so there was scope to consider a tightly focussed research question to evaluate the efficacy of pacing in people with ME/CFS.

1.2. Objectives

Despite the potential of pacing to improve health outcomes in people with ME/CFS, there was no meta-analysis to provide a pooled analysis of published studies to date. Therefore, the aim of this investigation was to conduct a PRISMA-accordant meta-analysis of studies examining the effect of pacing on physical function, pain, and fatigue.

2. Methods

2.1. Eligibility criteria

Studies that met the following criteria were included in this review: (1) published as a full-text manuscript; (2) not a review; (3) participants with ME/CFS; (4) studies employed a pacing intervention or retrospective analysis of pacing or a case study of pacing (5) written in English language. Where a study reported the same variable twice (e.g. a pain visual analogue scale and a pain subsection of a questionnaire), we included the study only once to avoid double weighting The search strategy consisted of a combination of free-text and MeSH terms relating to ME/CFS and pacing, which were developed through an examination of published original literature and review articles. As an example, the search terms for PubMed were: 'ME/CFS' OR 'ME' OR 'CFS' OR 'chronic fatigue syndrome' OR 'PEM' OR 'post exertional malaise' OR 'pene' OR 'post-exertion neurogenic exhaust' AND 'pacing' OR 'adaptive pacing'. The search was performed within title/abstract.

2.2. Information sources

Six electronic databases [PubMed, Scholar, ScienceDirect, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL)] were searched to identify original research articles published from the earliest available date up until 16/11/2023.

Additional records were identified through reference lists of included studies. 'Grey literature' repositories including MEPedia, Action for ME, and ME Action were also searched with the same terms.

2.3. Study selection

Once each database search was completed and manuscripts were sourced, all studies were downloaded into a single reference list (Zotero, version 6.0.23) and duplicates were removed. Titles and abstracts were screened for eligibility by two reviewers independently and discrepancies were resolved through discussion between reviewers. Subsequently, full-text papers of potentially relevant studies were retrieved and assessed for eligibility by the same two reviewers independently. Any uncertainty by reviewers was discussed in consensus meetings and resolved by agreement. Descriptions were extracted with as much detail as was provided by the authors. Study quality was assessed using the Physiotherapy Evidence Database (PEDro) scale [21,22].

2.4. Data collection process

Data extracted from each study included; study sample size, intervention/control group descriptions, study design, analysis method, and outcome data. Data were extracted for pre- and post-pacing dependent variable values.

Where the SD for change between time points (i.e. pre- and post-training change) was not reported, it was calculated thusly:

$$SD_{change} = \sqrt{(SD_1^2 + SD_2^2 - (2 \cdot corr \cdot SD_1 \cdot SD_2))}$$

Whereby: corr: correlation coefficient, a value that describes the relationship between baseline and final measurements over time. The correlation coefficient used was 0.9 as a conservative estimate.

2.5. Data items

Analysis was carried out using the standardised mean difference (SMD), and interpreted as $\geq$0.2 = small effect, $\geq$ 0.5 = moderate effect, and $\geq$0.8 = large effect [23]. A random-effects model was fitted to the data. The amount of heterogeneity (i.e. τ^2), was estimated using the restricted maximum-likelihood estimator [24]. In addition to the estimate of τ^2, the *Q*-test for heterogeneity [25] and the I^2 statistic [26] are reported. An I^2 value of 25% may be interpreted as low, 50% as moderate and 75% as high between study heterogeneity. Due to the low *k*, tests for funnel plot asymmetry were considered inappropriate [27], so funnel plots were only visually inspected. The analysis was carried out using R (version 4.2.2) (R Core Team) [28] and the metafor package (version 3.8.1) [24]. Three random-effect meta-analyses (physical function, pain, fatigue) were conducted as each of these outcomes was reported the most in the literature. No subgroup analyses were performed due to the small sample size. Furthermore, methodological quality was assessed using the modified 0–10 PEDro scale [21].

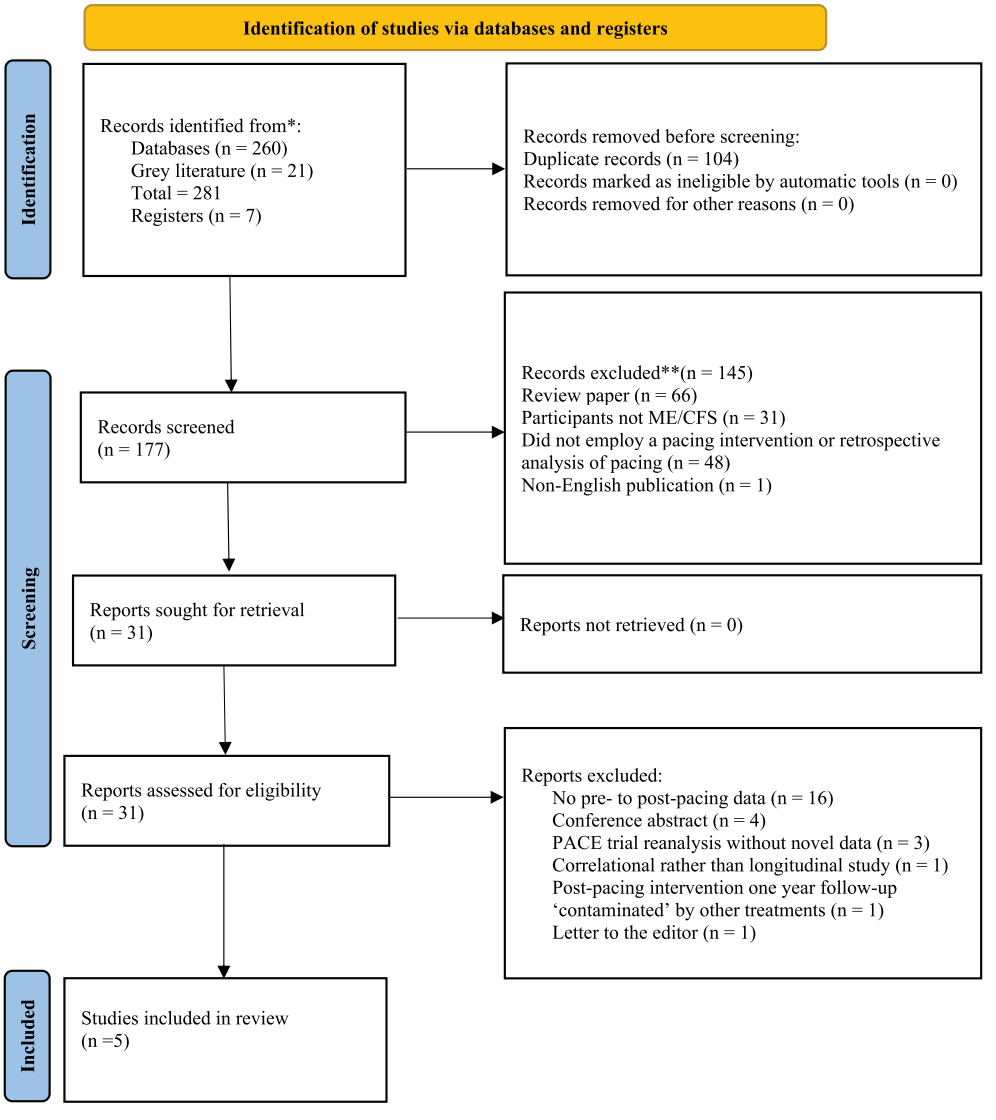

Figure 1. PRISMA flow diagram outlining exclusions of potential studies and final number of studies.

3. Results

3.1. Study selection

After the initial database search, 322 records were identified (see Figure 1). Once duplicates were removed, 210 titles and abstracts were screened for inclusion resulting in 31 studies being retrieved as full text and assessed for eligibility. Of those, 25 were excluded, and five articles remained and were used in the final quantitative synthesis. In one case, a paper [29] was a reanalysis of the PACE trial [14], but reported a different variable to the original study, and so we included this paper as it did not double-weight the SMD. Of these five articles, none reported all dependent variables of interest, thus why each meta-analysis and forest plots have $k < 5$.

Table 1. Description of included studies and data sets.

Ref.	Type of pacing and duration of intervention (if relevant)	Study design (RCT, observational cohort, etc.)	Participants (*n*, age, gender, ethnicity, time since diagnosis)	Comorbidities	Location	Recruitment setting and study setting	Outcome measures	PEDro Score
Antcliff et al. [31][a]	Six-week rehabilitation programme using the activity pacing framework (6 × 3.5 h sessions). Programme included understanding of graded exercise, relaxation and goal setting etc. Pacing was instructed in one session but not informed or standardised by any particular guide or framework.	Single-arm, repeated measures study, a non-randomised feasibility study	n = 6 Mean age 46 ± 12 years 100% female 80% white		UK	One National Health Service (NHS) pain service	Chalder fatigue scale 0–10 pain numerical pain rating scale. SF-12	5; fair
Bourke et al. [29]	PACE Trial reanalysis with activity pacing therapy. Duration of 52 weeks.	RCT with Specialist medical care (SMC) as comparator	*n* = 641 Mean age 39 years Mostly female 76% Around 90% Caucasian Time since diagnosis not reported.	Depressive disorder (34%)	UK	Patients from secondary-care specialist CFS clinic	0–4 muscle pain numerical rating scale from the international (CDC) criteria for CFS	6; good
Kos et al. [30]	Coached activity pacing self-management. Three individual therapy sessions of 60-90 min/wk for three consecutive weeks of 'activity pacing self-management'.	RCT with 'relaxation' as control	*n* = 33 (*n* = 16 in the experimental group, *n* = 17 in the control group) Mean age 41 ± 11 years All female Ethnicity and time since diagnosis not reported.	Not reported	Belgium	Waiting list for multidisciplinary rehabilitation and informed about the study through email University Hospital	Checklist individual strength SF-36	6; good

Nijs et al. [32]	Pacing self-management. Five different visits at 1-week intervals. Wore accelerometer for 24 h for a week.	Case series	$n = 7$ Mean age 43 ± 13 years All female Ethnicity not reported. Median illness duration of 96 ± 44 months	Not reported	Belgium	University-based chronic fatigue centre University Hospital	Checklist individual strength SF-36 Fatigue VAS Pain VAS	6; good
White et al. [14]	One year (52 weeks) of activity pacing therapy	RCT with specialist medical care (SMC) as comparator	$n = 641$ recruited, $n = 630$ analysed, $n = 607$ reported in results tables. $n = 159$ in pacing group, $n = 160$ in 'control' group Mean age 39 ± 12 years 76% women 94% white Duration of illness 32 (16–66) months	Co-morbid psychiatric condition (47%) Depressive disorder (33%)	UK	Outpatients attending six specialist chronic fatigue syndrome clinics	Chalder fatigue scale SF-36	6; good

SF-12 = 12-Item Short Form Health Survey questionnaire. SF-36 = 36-Item Short Form Health Survey questionnaire. UK = United Kingdom. VAS = Visual Analogue Scale.
[a]Antcliff et al. [31] data was sourced from the authors, and these data represent a ME/CFS subset of a larger cohort including chronic back pain and fibromyalgia.

Table 2. Diagnostic criteria used in included studies to define ME/CFS (if reported).

Study	Diagnostic criteria used
Antcliff et al. [31]	No diagnostic criteria included as this study included people with chronic low back pain, chronic widespread pain, fibromyalgia, and ME/CFS for ≥3 months'. Only the ME/CFS data were used in this meta-analysis.
Bourke et al. [29]	Oxford criteria (PACE trial sub-analysis).
Kos et al. [30]	Fukuda criteria.
Nijs et al. [32]	Fukuda criteria.
White et al. [14]	Oxford criteria (PACE trial).

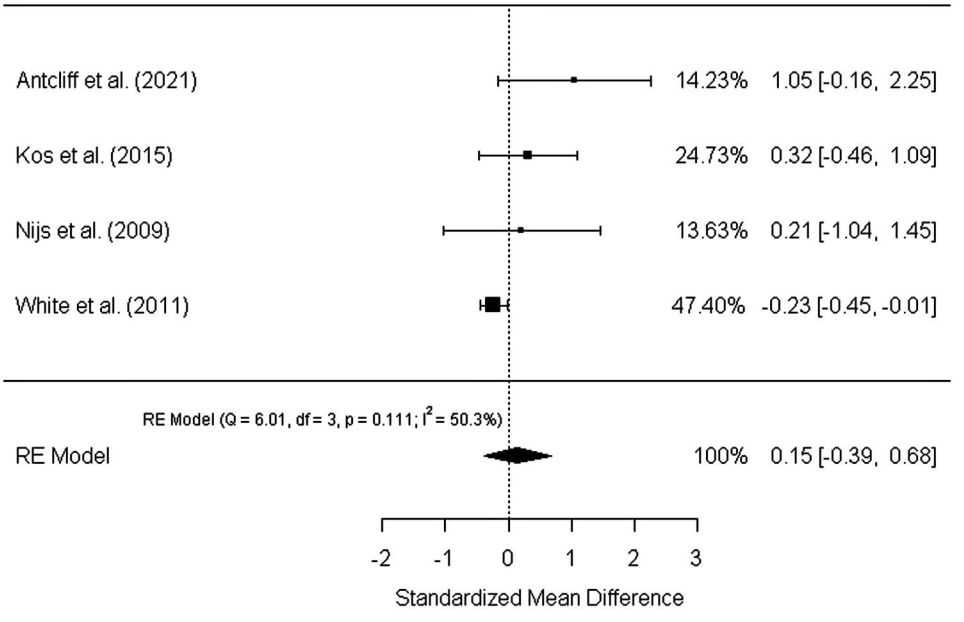

Figure 2. Summary of studies examining physical function following pacing. Note that symbol size of individual studies is representative of the weighting for the pooled standardised mean difference (SMD), which is also given as text as a percentage. Error bars represent 95% confidence intervals. A positive value (i.e. rightwards) represents a beneficial effect of pacing compared to control.

3.2. Study characteristics

Of the five studies included, two were randomised control trials (RCTs [14,30]), one was an uncontrolled trial [31], one was a case series [32], and one was a sub-analysis of the PACE trial reporting pain (not reported in the initial publication) [29] (Table 1). Diagnostic criteria for ME/CFS are summarised in Table 2.

3.3. Effect of pacing on physical function

A total of $k = 4$ studies were included in the physical function analysis. The observed SMDs ranged from −0.23 to 1.05 (for physical function, a higher value indicates a beneficial effect of pacing), with most estimates being positive (75%). The SMD was $\mu = 0.15$ (95% CI: −0.39, 0.68, $z = 0.5315$, $p = 0.5951$; Figure 2). According to the Q-test, the true

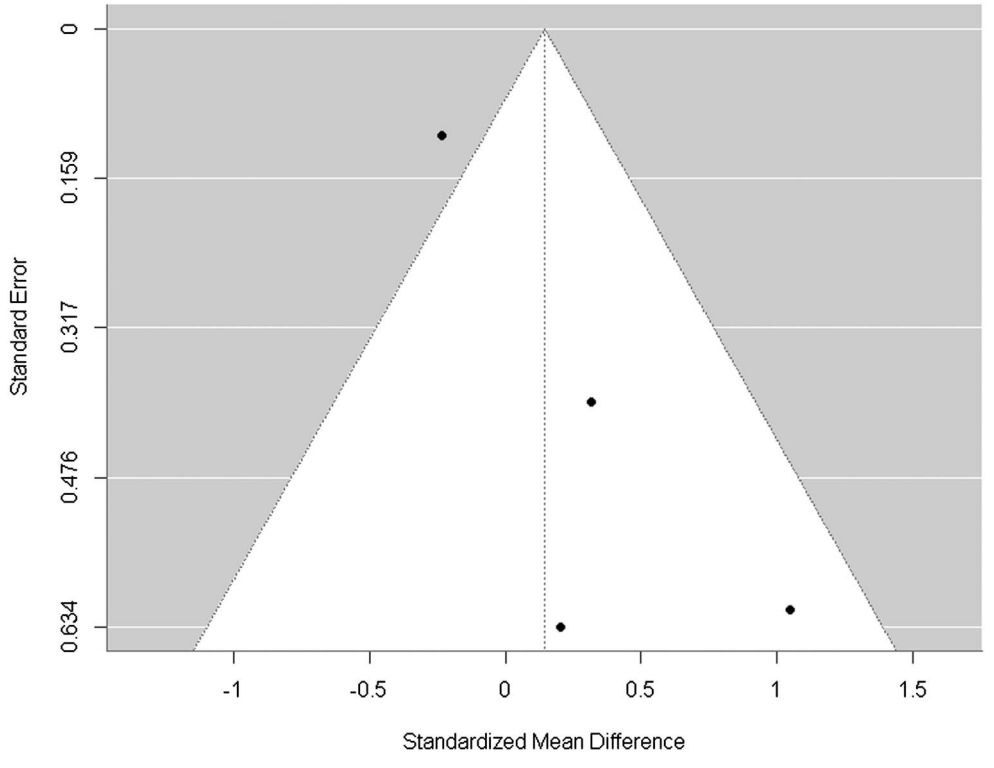

Figure 3. Funnel plot for evaluating the effect of pacing on physical function.

outcomes appeared to be heterogeneous ($Q(3) = 6.0134$, $p = 0.1110$, $\tau^2 = 0.1445$, $I^2 = 50\%$). A funnel plot of the estimates is shown in Figure 3.

3.4. Effect of pacing on pain

A total of $k = 4$ studies were included in the pain meta-analysis. The individual study SMDs ranged from −1.17 to 0.01 (for pain, a low value indicated a beneficial effect of pacing), with most estimates being negative (75%). The overall SMD was $\mu = -0.11$ (95% CI: −0.32, 0.10, $z = -1.0174$, $p = 0.3090$; Figure 4). The Q-test heterogeneity p value did not reach <0.05 ($Q(3) = 3.2246$, $p = 0.3583$, $\tau^2 = 0.000$, $I^2 = 0\%$). A funnel plot of the estimates is shown in Figure 5.

3.5. Effect of pacing on fatigue

A total of $k = 4$ studies were included in the fatigue meta-analysis. The observed SMDs ranged from −3.64 to −0.23 (for fatigue, a low value was preferential [i.e. less fatigued was better]), with all studies resulting in a lowering of fatigue with pacing. The pooled SMD was $\mu = -01.09$ (95% CI: −2.38, 0.21, $z = -1.6458$, $p = 0.0998$; Figure 6). According to the Q-test, the true outcomes appear to be heterogeneous ($Q(3) = 14.2895$, $p = 0.0025$, $\tau^2 = 1.4257$, $I^2 = 89\%$). A funnel plot of the estimates is shown in Figure 7.

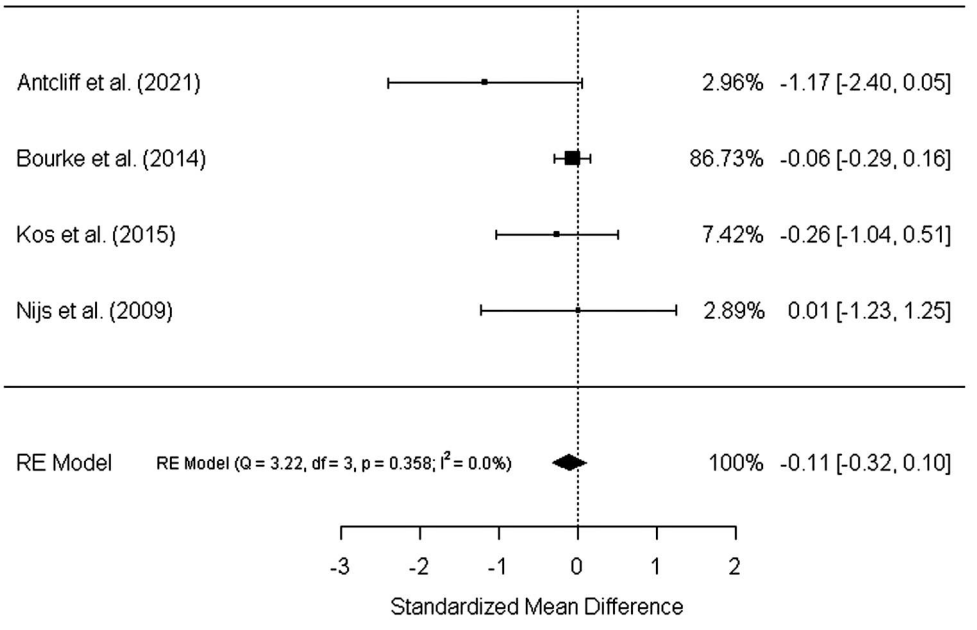

Figure 4. Summary of studies examining pain following pacing. Note that symbol size of individual studies is representative of the weighting for the pooled standardised mean difference (SMD), which is also given as text as a percentage. Error bars represent 95% confidence intervals. A negative value (i.e. leftwards) represents a beneficial effect of pacing compared to control (i.e. a reduction in pain).

4. Discussion

The main finding from this meta-analysis was that pacing exerted trivial effects in people with ME/CFS, but the magnitude and *p*-value varied with outcome measures. For example, pacing exerted a large beneficial effect on fatigue (−1.09, 95% CI: −2.38, 0.21) which did not reach statistical significance. However, pacing exerted a trivial effect on physical function (0.15, 95% CI: −0.39, 0.68) and pain (−0.11, 95% CI: −0.32, 0.10). Given that in most studies, pacing was no more harmless than control, and in some instances, was beneficial, we think it pragmatic that pacing should still be considered as a primary management strategy for people with ME/CFS. Given that pacing is currently the sole management strategy for people with ME/CFS (NICE guidelines [10]), this meta-analysis provides timely insight into the effect of pacing on health outcomes following the only suggested management strategy. However, there were several concerning observations. Study quality was generally 'good' according to the PEDRO ratings, but this rating does not consider statistical power, and the low *n* of many studies limits the strength of available evidence.

4.1. Effect of pacing on physical function

The pooled effect of pacing was trivial for physical function. Besides the original PACE trial [14], all other studies reported small to large improvements with pacing although none of the reported findings were statistically significant. However, it is worth noting that the PACE trial was the largest sample ($n = 159$ and $n = 160$ in the pacing and specialist medical care [SMC] control group respectively), and therefore these results weigh

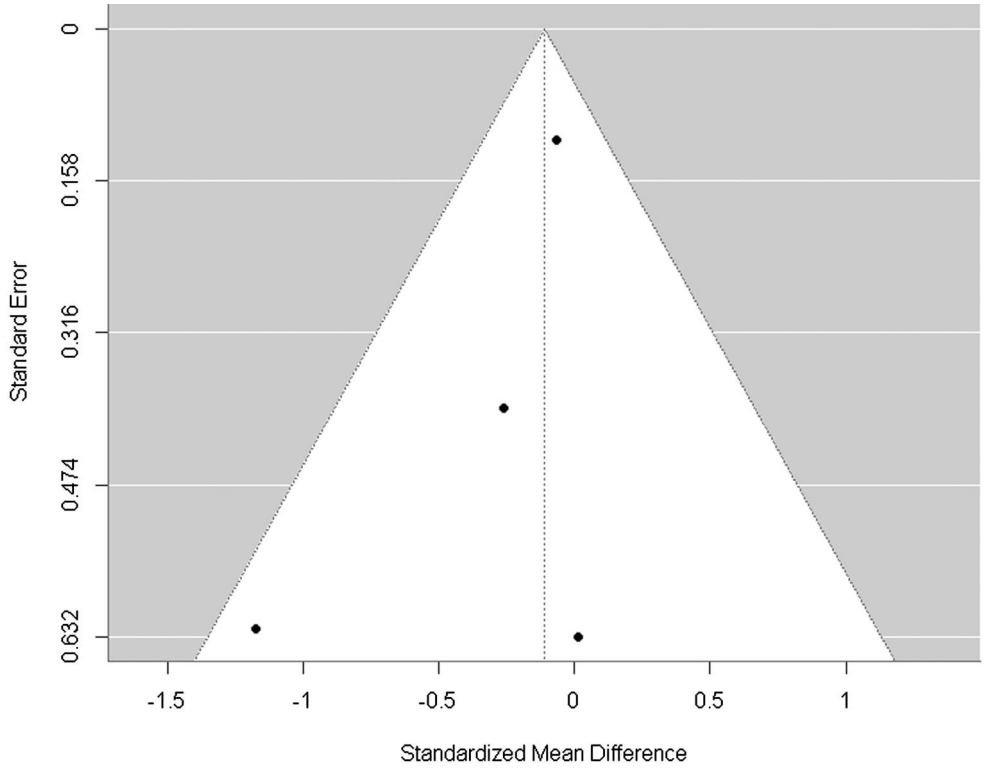

Figure 5. Funnel plot for evaluating the effect of pacing on pain.

heavily on the SMD (47% weighting). This was also the most robustly designed study compared to the other studies, which were either uncontrolled [31,32], or underpowered [30]. The study with the largest effect was a subset of participants in a single-arm feasibility study, and therefore this large change from baseline may overestimate the true effect without a control group comparison [31]. It is also clear from the forest plot (Figure 2) that the variance was large, with 95% confidence intervals crossing zero for three of the four studies. There is a pressing need for more high-quality RCTs considering how pacing influences physical function in people with ME/CFS, as even a small effect may have a meaningful effect of peoples' lives.

4.2. Effect of pacing on pain

The pooled effect of pacing was generally beneficial for pain. All other studies reported general improvements with pacing except Nijs and colleagues [32] whose study resulted in an SMD of 0.01. However, much like the results for physical function, a reanalysis of the PACE trial [29] was the largest sample ($n = 159$ and $n = 160$ in the pacing and specialist medical care [SMC] control group respectively), and therefore these results contributed 87% weighting to the pooled SMD. As Bourke et al. [29] observed no change to pain (SMD = −0.06) it is unsurprising the overall effect was trivial (−0.11) and did not reach statistical significance. Much like the physical function results above, the study with the

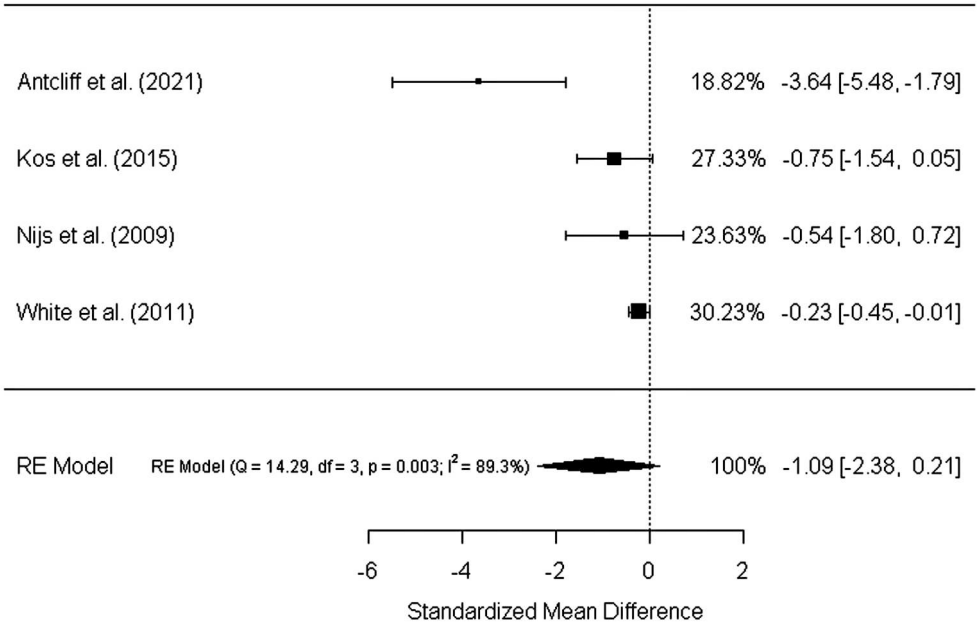

Figure 6. Summary of studies examining fatigue following pacing. Note that symbol size of individual studies is representative of the weighting for the pooled standardised mean difference (SMD), which is also given as text as a percentage. Error bars represent 95% confidence intervals. A negative value (i.e. leftwards) represents a beneficial effect of pacing compared to control (i.e. a reduction in fatigue).

largest effect was a subset of participants from a single-arm feasibility study and therefore the SMD may overestimate the true effect. Again, the variance was large, with 95% confidence intervals crossing zero for three of the four studies. The relatively small number of studies did hamper any interpretation of whether pacing influences pain in people with ME/CFS, and more high-quality RCTs concerning pain are yet again needed.

4.3. Effect of pacing on fatigue

The effects of pacing on fatigue are somewhat more convincing than concerning physical function or pain, as all studies reported small to very large statistically insignificant improvements with pacing and the pooled magnitude was large (−1.09) and not statistically significant. Encouragingly, the PACE trial [14] reported a positive effect of pacing compared to the control group for fatigue. This is encouraging because in the PACE trial, the control group was not a no-treatment group, and was provided with specialist medical care, which is beyond what many people with ME/CFS experience [33]. Despite this encouraging finding, more high-quality RCTs are yet again needed to confirm this preliminary observation.

4.4. Pacing interventions

Interventions were of varying durations, from 3-weeks consisting of 1 session/week pacing self-management [32], to 3 × 60-90-min sessions/week of 'activity pacing self-

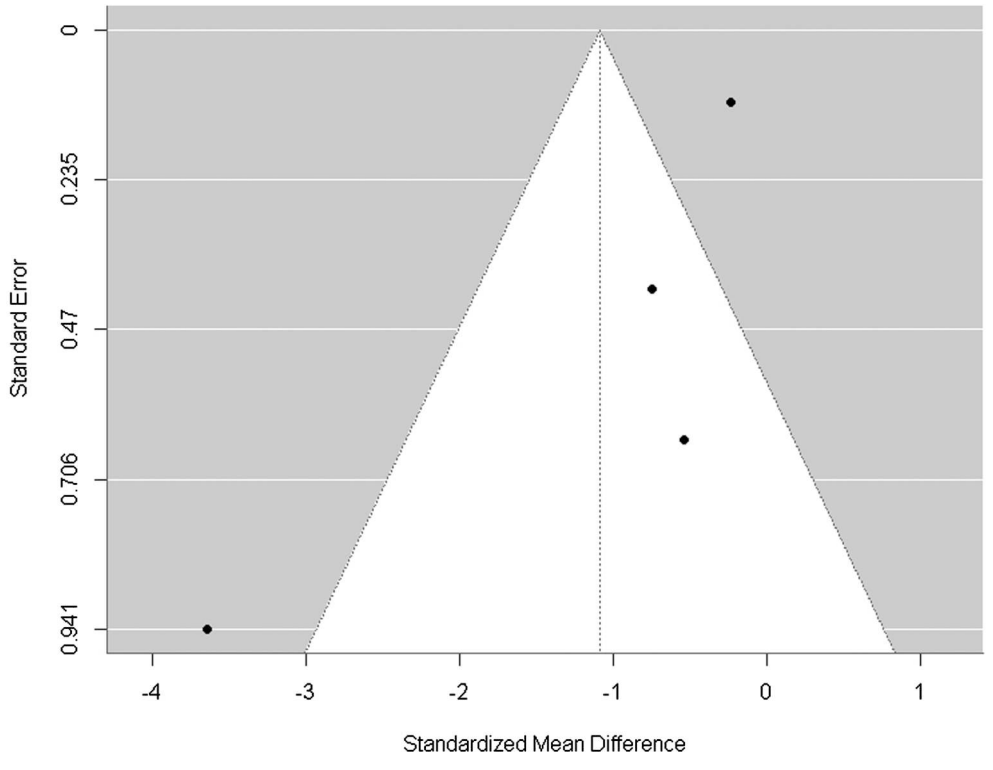

Figure 7. Funnel plot for evaluating the effect of pacing on fatigue.

management' [30], a 6-week rehabilitation programme using the activity pacing framework (6 × 3.5-hours sessions) [31], and 1-year of activity pacing therapy [14,29]. In addition to varying durations, interventions were also delivered in different ways across studies. However, all used approaches that required participants to implement strategies learned in educational sessions into practice in their day-to-day lives. While not all five intervention studies explicitly mentioned the 'Energy Envelope Theory' [34,35], which suggests that people with ME/CFS should not necessarily amplify or reduce their activity levels but rather engage in moderate activity and conserve energy, all these studies employed language resembling this theory, emphasising that participants should operate within 'limits', within their 'capacity', or similar phrasing. No contemporary studies using direct contemporaneous support (i.e. activity tracking and alerts for example) were evident.

4.5. Limitations

The major limitation of the present meta-analysis is the lack of studies, particularly high-quality and sufficiently powered RCTs. Not only would a larger sample of RCTs add weight to conclusions made herein, but it would also enable sub-analysis of different cohorts or approaches. As such, the current literature is some considerable way from such nuanced analysis. Consequently, our conclusions are conservative and preliminary, until a greater depth of literature is available concerning pacing in people with ME/CFS. Another

significant limitation of the research included in this meta-analysis is, with the exception of Antcliff et al. [31], most studies predate the widespread availability of mobile technology and, consequently, there is a lack evidence regarding technology-informed pacing. Given the proliferation of global smartphone usage [36], and the power of smartphones (and associated wearables) to track physical activity in the form of steps and/or heart rate [37–40], we find it perplexing that no pacing studies have been completed through digital health means. We expect this to change in the coming years, given the benefits of digital health interventions [41–45], which can remove barriers to research participation [46–48]. Indeed, the NICE guidelines speak to this necessity with specific mention of improved self-monitoring strategies, sleep strategies, and dietary strategies as research priorities [10], all of which can be measured using digital health approaches, in a scalable and labour-inexpensive way.

In this meta-analysis, we included pacing over any duration. The PACE trial [14] delivered pacing for 52 weeks, whilst Kos et al. [30] delivered only three weeks of pacing. It is impossible to know whether longer studies such as the PACE trial maybe experience a 'voltage drop' once participants have been in a study for a long time, or whether pacing requires a significant amount of time before it exerts a positive effect. If there were a larger number of studies within this meta-analysis, we could have interrogated this effect through meta-regression but due to the limited *k*, this was not possible. Moreover, we included studies which utilised any type of pacing. Pacing was implemented through educational sessions and, use of accelerometers and diaries, but generally, it was difficult to ascertain how this was completed. In fact, 100% of the studies were too vague in methodological description to replicate, which is a limitation of the existing research.

Whilst the literature assessment was comprehensive, it is possible that studies may have been missed from the analysis, but as six databases were searched, it is unlikely enough were missed to create a large change to SMDs. Furthermore, having two authors ensured agreement on inclusion and exclusion, which limited potential bias. To ensure a suitable *k* for meta-analysis, we included all studies which incorporated pacing, regardless of study design (i.e. RCT, single-arm, case series). Finally, the diagnostic criteria that studies employed to identify ME/CFS are described as having 'very serious limitations' by the 2021 NICE guidelines. Studies like Antcliff et al. [31], which lack specific diagnostic criteria, are particularly vulnerable to misclassification, increasing the risk of including individuals who do not actually meet the diagnostic threshold for ME/CFS but have fatigue caused by other underlying conditions. This misclassification bias can lead to overgeneralised conclusions regarding treatment effectiveness and the underlying mechanisms of the condition, ultimately weakening the quality and validity of the evidence. These issues underscore the urgent need for more precise and consistent diagnostic criteria in future research, ensuring that studies accurately capture ME/CFS patients and avoid including individuals with other conditions that may present similar symptoms.

5. Conclusion

There is insufficient evidence to conclude that pacing exerts a positive effect in people with ME/CFS for physical function, pain, and fatigue; although pacing may reduce

fatigue in ME/CFS patients. Therefore, further studies with greater sample sizes and quality are needed to validate these initial findings and determine the overall effectiveness of pacing in ME/CFS management. Given that we are 16 years after the earliest pacing study, and 13 years since the landmark PACE trial (at the time of writing), research has advanced at a slow rate. This is surprising seeing as pacing is the only NICE-recommended symptom management strategy, and more research funding is required to provide confidence in these recommendations.

Acknowledgements

Authors' contributions are given according to the CRediT taxonomy as follows: Conceptualisation, N. E.M.S-H., M.M., L.D.H, and N.F.S.; methodology, N.E.M.S-H., M.M., L.D.H., and N.F.S.; software, N.E.M.S-H., M.M., L.D.H., and N.F.S.B.; validation, N.E.M.S-H., M.M., L.D.H, and N.F.S.; formal analysis, N.E.M.S-H., M.M., L.D.H., and N.F.S.; investigation, N.E.M.S-H., M.M., L.D.H., and N.F.S.; resources, L.D.H., J.O., D.C., N.H., J.L.M., and N.F.S.; data curation, N.E.M.S.-H., M.M., L.D.H., and N.F.S.; writing – original draft preparation, N.E.M.S.-H., M.M., L.D.H., and N.F.S.; writing – review and editing, N.E.M.S-H., M.M., L.D.H., J.O., D.C., N.H., R.M., J.L.M., J.I., and N.F.S.; visualisation, N.E.M.S-H. and M.M., supervision, N.F.S; project administration, N.E.M.S-H., M.M., L.D.H., and N.F.S.; funding acquisition, L.D.H., J.O., D.C., N.H., J.L.M., J.I., and N.F.S. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by grants from the National Institute for Health and Care Research [grant number COV-LT2-0010] and the funder had no role in the conceptualisation, design, data collection, analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Notes on contributors

Nilihan E.M. Sanal-Hayes, a lecturer of psychology, writes on chronic fatiguing conditions. Her recent work has focussed on co-producing energy management (i.e. pacing) strategies for people with ME/CFS. She is also well-versed in digital interventions which incorporate measurements in both physiology and psychology.

Marie Mclaughlin, a lecturer of physiology, writes on both chronic fatiguing conditions and exercise oncology. Her recent works have incorporated cell culture, flow cytometry, and systematic review methodologies.

Jacqueline L. Mair, a senior scientist, writes on digital intervention design and evaluation. Her background is in physical activity and physiology.

Jane Ormerod, a retired nurse, is the PPI lead for this project and an advocate for people with long COVID (Long Covid Scotland).

David Carless, a reader of physical activity, conducts research that uses storied forms of communication to understand and represent human experience. Through a range of narrative, auto/ethnographic and arts-based methods, his work explores how mental health and identity are developed, threatened or recovered in sport and physical activity contexts.

Rachel Meach, a post doctoral researcher, conducts qualitative inquiry into health and the history of health. She has completed multiple enquiries concerning people with long covid.

Natalie Hilliard is a physiotherapist, specialising in treatment and management for people with ME, post-viral illnesses and long-covid. She has a body of work examining energy management (i.e. Pacing) for people with these illnesses.

Joanne Ingram, a senior lecturer of psychology, is a cognitive psychologist who has a body of work comparing pandemic-related variation in cognitive function to the patterns of cognitive decline frequently linked to ageing.

Nicholas F. Sculthorpe, a professor of clinical exercise physiology, has examined the role of physical activity and exercise as both a treatment and preventative measure in long-term conditions, including Multiple Sclerosis, Long COVID, and ageing. More recently, he has developed research interests in the role of mobile technology in health interventions (mHealth).

Lawrence D. Hayes, a lecturer of physiology, has a body of work examining chronic conditions such as long covid and ME/CFS. He has interests across multiple fields such as exercise physiology and mHealth.

ORCID

Lawrence D. Hayes http://orcid.org/0000-0002-6654-0072

References

[1] Hospital TMSOTRF. An outbreak of encephalomyelitis in the Royal Free Hospital Group, London, in 1955. Br Med J. 1957;2(5050):895. doi:10.1136/bmj.2.5050.895

[2] White P. Long COVID: don't consign ME/CFS to history. NATURE. 2020;587(7833):197. doi:10.1038/d41586-020-03136-0

[3] Barhorst EE, Boruch AE, Cook DB, et al. Pain-related post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia: a systematic review and three-level meta-analysis. Pain Med Malden Mass. 2022;23(6):1144–1157.

[4] Deumer U-S, Varesi A, Floris V, et al. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): an overview. J Clin Med. 2021;10(20):4786. doi:10.3390/jcm10204786

[5] Hayes LD, Sanal-Hayes NEM, Mclaughlin M, et al. People with long COVID and ME/CFS exhibit similarly impaired balance and physical capacity: a case-case-control study. Am J Med. 2023: S0002-9343(23)00465-5.

[6] Sanal-Hayes NEM, Mclaughlin M, Hayes LD, et al. A scoping review of 'pacing' for management of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): lessons learned for the long COVID pandemic. J Transl Med. 2023;21(1):720. doi:10.1186/s12967-023-04587-5

[7] Lim E-J, Ahn Y-C, Jang E-S, et al. Systematic review and meta-analysis of the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). J Transl Med. 2020;18(1):100. doi:10.1186/s12967-020-02269-0

[8] Collin SM, Crawley E, May MT, et al. The impact of CFS/ME on employment and productivity in the UK: a cross-sectional study based on the CFS/ME national outcomes database. BMC Health Serv Res. 2011;11(1):217. doi:10.1186/1472-6963-11-217

[9] Baker R, Shaw EJ. Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephalopathy): summary of NICE guidance. Br Med J. 2007;335 (7617):446–448. doi:10.1136/bmj.39302.509005.AE

[10] NICE. Overview | Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management | Guidance | NICE [Internet]. NICE; [cited 2022 Aug 22]. Available from: https://www.nice.org.uk/guidance/ng206.
[11] Goudsmit EM. The psychological aspects and management of chronic fatigue syndrome [Internet] [Thesis]. Brunel University, School of Social Sciences; 1996 [cited 2022 Jan 20]. Available from: http://bura.brunel.ac.uk/handle/2438/4283.
[12] Goudsmit EM, Howes S. Pacing to manage chronic fatigue syndrome.
[13] Goudsmit EM, Howes S. Pacing: a strategy to improve energy management in chronic fatigue syndrome. Health Psychol Update. 2008;17(1):46. doi:10.53841/bpshpu.2008.17.1.46
[14] White P, Goldsmith K, Johnson A, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768):823–836. doi:10.1016/S0140-6736(11)60096-2
[15] Vink M. PACE trial authors continue to ignore their own null effect. J Health Psychol. 2017;22(9):1134–1140. doi:10.1177/1359105317703785
[16] Petrie K, Weinman J. The PACE trial: it's time to broaden perceptions and move on. J Health Psychol. 2017;22(9):1198–1200. doi:10.1177/1359105317703789
[17] Stouten B. PACE-GATE: an alternative view on a study with a poor trial protocol. J Health Psychol. 2017;22(9):1192–1197. doi:10.1177/1359105317707531
[18] Agardy S. Chronic fatigue syndrome patients have no reason to accept the PACE trial results: response to Keith J Petrie and John Weinman. J Health Psychol. 2017;22(9):1206–1208. doi:10.1177/1359105317715476
[19] Kim D-Y, Lee J-S, Park S-Y, et al. Systematic review of randomized controlled trials for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). J Transl Med. 2020;18(1):7. doi:10.1186/s12967-019-02196-9
[20] Twisk FNM, Maes M. A review on cognitive behavorial therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. Neuro Endocrinol Lett. 2009;30(3):284–299.
[21] de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother. 2009;55(2):129–133. doi:10.1016/S0004-9514(09)70043-1
[22] Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83(8):713–721. doi:10.1093/ptj/83.8.713
[23] Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol [Internet]. 2013;4. doi:10.3389/fpsyg.2013.00863
[24] Author. Bias and efficiency of meta-analytic variance estimators in the random-effects model – Wolfgang Viechtbauer, 2005 [Internet]. [cited 2023 Sep 25]. Available from: https://journals.sagepub.com/doi/10.3102107699860300032 61.
[25] Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10(1):101–129. doi:10.2307/3001666
[26] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–1558. doi:10.1002/sim.1186
[27] Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Br Med J. 2011;343:d4002. doi:10.1136/bmj.d4002
[28] R Core Team. R: A language and environment for statistical computing. R foundation for statistical computing, Vienna, Austria. 2020. https://www.r-project.org/.
[29] Bourke JH, Johnson AL, Sharpe M, et al. Pain in chronic fatigue syndrome: response to rehabilitative treatments in the PACE trial. Psychol Med. 2014;44(7):1545–1552. doi:10.1017/S0033291713002201
[30] Kos D, van Eupen I, Meirte J, et al. Activity pacing self-management in chronic fatigue syndrome: a randomized controlled trial. Am J Occup Ther Off Publ Am Occup Ther Assoc. 2015;69(5):6905290020.

[31] Antcliff D, Keenan A-M, Keeley P, et al. Testing a newly developed activity pacing framework for chronic pain/fatigue: a feasibility study. BMJ Open. 2021;11(12):e045398. doi:10.1136/bmjopen-2020-045398
[32] Nijs J, van Eupen I, Vandecauter J, et al. Can pacing self-management alter physical behavior and symptom severity in chronic fatigue syndrome? A case series. J Rehabil Res Dev. 2009;46(7):985–996. doi:10.1682/JRRD.2009.01.0007
[33] Association ME. ME/CFS illness management survey results: '"No decisions about me without me." Part 1: Results and in-depth analysis of the 2012 ME association patient survey examining the acceptability, efficacy and safety of cognitive behavioural therapy, graded exercise therapy and pacing, as interventions used as management strategies for ME/CFS. 2015.
[34] Jason L, Muldowney K, Torres-Harding S. The energy envelope theory and myalgic encephalomyelitis/chronic fatigue syndrome. AAOHN J Off J Am Assoc Occup Health Nurses. 2008;56(5):189–195.
[35] Pesek JR, Jason LA, Taylor RR. An empirical investigation of the envelope theory. J Hum Behav Soc Environ. 2000;3(1):59–77. doi:10.1300/J137v03n01_04
[36] Silver L. Smartphone ownership is growing rapidly around the world, but not always equally [Internet]. Pew Res. Cent. Glob. Attitudes Proj. 2019 [cited 2022 Sep 22]. Available from: https://www.pewresearch.org/global/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/.
[37] Düking P, Giessing L, Frenkel MO, et al. Wrist-Worn wearables for monitoring heart rate and energy expenditure while sitting or performing light-to-vigorous physical activity: validation study. JMIR MHealth UHealth. 2020;8(5):e16716. doi:10.2196/16716
[38] Falter M, Budts W, Goetschalckx K, et al. Accuracy of apple watch measurements for heart rate and energy expenditure in patients with cardiovascular disease: cross-sectional study. JMIR MHealth UHealth. 2019;7(3):e11889. doi:10.2196/11889
[39] Mair JL, Hayes LD, Campbell AK, et al. A personalized smartphone-delivered just-in-time adaptive intervention (JitaBug) to increase physical activity in older adults: mixed methods feasibility study. JMIR Form Res. 2022;6(4):e34662. doi:10.2196/34662
[40] Fuller D, Colwell E, Low J, et al. Reliability and validity of commercially available wearable devices for measuring steps, energy expenditure, and heart rate: systematic review. JMIR MHealth UHealth. 2020;8(9):e18694. doi:10.2196/18694
[41] Burns SP, Terblanche M, Perea J, et al. Mhealth intervention applications for adults living with the effects of stroke: a scoping review. Arch Rehabil Res Clin Transl. 2021;3(1):100095.
[42] Ludwig K, Arthur R, Sculthorpe N, et al. Text messaging interventions for improvement in physical activity and sedentary behavior in youth. Systematic Review. JMIR MHealth UHealth. 2018;6(9):e10799. doi:10.2196/10799
[43] AhmedS A, van Luenen S, Aslam S, et al. A systematic review on the use of mHealth to increase physical activity in older people. Clin EHealth. 2020;3:31–39. doi:10.1016/j.ceh.2020.04.002
[44] Kononova A, Li L, Kamp K, et al. The Use of wearable activity trackers Among older adults: focus group study of tracker perceptions, motivators, and barriers in the maintenance stage of behavior change. JMIR MHealth UHealth. 2019;7(4):e9832. doi:10.2196/mhealth.9832
[45] Mair JL, Hayes LD, Campbell AK, et al. Should We Use activity tracker data from smartphones and wearables to understand population physical activity patterns? J Meas Phys Behav. 2022;1(aop):1–5.
[46] Morgan LL, Fahs PS, Klesh J. Barriers to research participation identified by rural people. J Agric Saf Health. 2005;11(4):407–414. doi:10.13031/2013.19719
[47] Spink A, Wagner I, Orrock P. Common reported barriers and facilitators for self-management in adults with chronic musculoskeletal pain: a systematic review of qualitative studies. Musculoskelet Sci Pract. 2021;56:102433. doi:10.1016/j.msksp.2021.102433
[48] Faithfull S, Brophy L, Pennell K, et al. Barriers and enablers to meaningful youth participation in mental health research: qualitative interviews with youth mental health researchers. J Ment Health Abingdon Engl. 2019;28(1):56–63. doi:10.1080/09638237.2018.1521926