

# **Effectiveness of Acceptance and Commitment Therapy for improving quality of life and mood in individuals with Multiple Sclerosis: A systematic review and meta-analysis**

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## Abstract

**Objective:** To review the evidence for the effectiveness of Acceptance and Commitment Therapy (ACT) intervention on quality of life and mood, for individuals with Multiple Sclerosis (MS).

**Method:** A systematic search was conducted of PsycINFO, CINAHL, Embase, MEDLINE, Web of Science, Scopus and ContextualScience.org up to 13/01/2022. Grey literature was also searched via ProQuest Dissertations and Theses, and PROSPERO. We included Randomised Controlled Trials (RCTs) published in English, that examined the effectiveness of ACT for people with a diagnosis of MS. We were interested in outcomes of Quality of Life (QoL), mood (e.g., anxiety, depression and stress), and ACT-targeted processes. Methodological quality was assessed using the Cochrane Risk of Bias Tool v2. Where available, the extracted data were entered into a meta-analysis to determine weighted effect size estimates for the outcomes of interest.

**Results:** Six studies (191 participants), out of 142 identified, met inclusion criteria. Meta-analyses indicated a statistically significant small effect on stress (SMD = -0.49 [95% CI of -0.89 – -0.08]), in favour of ACT. There were no statistically significant effects of ACT on anxiety (SMD = -0.41 [95% CI of -0.93 – 0.11]), depression (SMD = -0.92 [95% CI of -1.91 – 0.06]), or ACT-targeted processes (SMD = -0.18 [95% CI of -0.62 – 0.25]). There was a small, nonsignificant effect on QoL, in favour of control conditions (SMD=0.39 [95% CI of -0.08 – 0.85]). Methodological quality of the studies was variable; all but one study had at least one high risk of bias.

**Conclusions:** Findings suggest a small effect of ACT on reducing stress for people with MS, but not reducing anxiety or depression, or improving quality of life. Due to small sample sizes and few studies within this area, generalisability of findings is limited. Future trials should pay more attention to methodological rigour.

*Key words:* multiple sclerosis, acceptance and commitment therapy

# Effectiveness of Acceptance and Commitment Therapy for improving quality of life and mood in individuals with Multiple Sclerosis: A systematic review and meta-analysis

## 1. Introduction

Approximately 2.5 million people worldwide have a diagnosis of Multiple Sclerosis (MS) (MS Trust, 2020). The physical, cognitive, and psychological (e.g., anxiety, depression) problems caused by MS negatively impact the Quality of Life (QoL) of those living with the disease (Gil-González et al., 2020). This is further exacerbated by the uncertainty and life changes People with MS (pwMS) face, e.g., being unable to obtain an accurate prognosis or experiencing increased social isolation (Nielsen et al., 2018; Wilkinson & das Nair, 2013). Given the numerous factors impacting on QoL, it is understandable that pwMS experience significantly lower QoL in comparison to the general population (Amtmann et al., 2018), or even people with other neurological conditions (Hermann et al., 1996).

QoL is “an individual’s perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (WHO, 1995). Within MS research and clinical practice, there is increasing emphasis on QoL as a focus for treatment and a primary outcome to evaluate the effectiveness of interventions (Opara et al., 2010). Reduced QoL is associated with negative implications for psychiatric comorbidities within the MS population; most commonly dysfunction in mood, e.g., anxiety and depression (Hauer et al., 2020). Prevalence rates for depression and anxiety for pwMS vary from >20% for anxiety and depression *diagnoses* and >34% for *symptoms* (Hauer et al., 2020); Marrie et al., 2015;; Boeschoten et al., 2017).

### 1.1 Psychological interventions for pwMS

Within the MS population, psychological interventions are used to: treat depression and anxiety, aid coping with the diagnosis, support management of symptoms (e.g., pain and fatigue), and improve QoL (Thomas et al., 2006). A recent meta-analysis found psychological interventions had a significant effect on reducing depression and anxiety, and increasing QoL in pwMS [ $d = 0.271-0.398$ ], which was sustained at follow-up (>1-month post-intervention end) [ $d = 0.212-0.308$ ] (Sesel et al., 2018).

Whilst current service provision recommendations for pwMS do not specify the use of psychological interventions (National Institute for Health and Care Excellence [NICE], 2019), Cognitive Behavioural Therapy (CBT) is recommended for treating depression in neurological conditions more generally (NICE, 2009). A recent meta-analysis showed small to moderate effects of CBT on QoL and moderate effects on depression, in pwMS (Fiest et al., 2016). CBT is also reportedly effective at decreasing symptoms of anxiety and stress within the MS population (Graziano et al., 2014; Van Kessel et al., 2008). Indeed, CBT has consistently been found to have a modest benefit across several conditions on QoL (standardised mean difference

0.23; 95% confidence intervals 0.14–0.33) (Fordham et al., 2021). However, the effectiveness of CBT relative to other psychological interventions is more varied.

Sesel et al. (2018) found CBT to be less efficacious in comparison to other psychological interventions (e.g., progressive muscle relaxation and mindfulness) for anxiety, depression, fatigue, pain and QoL of pwMS. Sesel et al. (2018) suggested CBT is potentially unsuitable for the MS population due to the emphasis on learning strategies and completing certain homework tasks that can be challenging given cognitive impairment is common in MS. Further, CBT's focus on challenging negative thoughts has been criticised as invalidating, given these thoughts are likely to be realistic and logical within chronic, unpredictable conditions, such as MS (Meek et al., 2021). Therefore, there is an impetus to develop and evaluate other types of psychological therapies for pwMS.

## **1.2 Acceptance and Commitment Therapy**

Acceptance and Commitment Therapy (ACT) is a psychological intervention with a growing evidence base; since 1986 there have been 794 Randomised Control Trials (RCTs) of ACT in various health conditions (Hayes, 2021). ACT targets an individual's relationship to psychological events by increasing 'psychological flexibility', rather than seeking to change or challenge such events (Hayes et al., 2012). This is an important distinction between ACT and CBT. Whilst the focus of ACT is not on reduction of signs of distress, researchers have included symptom reduction outcomes within RCTs of ACT (Ost, 2014). It is also important to recognise some of these outcomes are often what is most concerning to individuals presenting to clinical services.

ACT has demonstrated efficacy for both psychological (anxiety and depression) and physical health (pain and substance use) outcomes (Gloster et al., 2020). Efficacy is sustained in comparison to control conditions (waitlist/treatment as usual/psychological placebo); however, findings are varied when ACT is compared to other established psychological interventions (e.g., CBT) (A-Tjak et al., 2014; Harrison et al., 2017; Ruiz, 2012).

## **1.3 ACT and MS**

Given thoughts and beliefs about symptoms often persisting or worsening are potentially 'accurate' in a chronic illness like MS, arguably ACT is a more appropriate psychological intervention for pwMS (Dennison et al., 2011). ACT has an emerging evidence base for use with pwMS, as acknowledged in British Psychological Society (BPS) guidance for psychological interventions for pwMS (BPS, 2021). A pilot study of a half-day ACT-workshop for 15 pwMS reported a large effect on reduction in depressive symptoms and improved QoL (Sheppard et al., 2010). Similarly, a pilot study of an ACT-based training programme for 37 pwMS also reported significant improvements for depression ( $g = 0.38$ ), stress ( $g = 0.33$ ), three ACT-targeted processes (defusion [ $g = -0.54$ ], values [ $g = -0.38$ ] and, acceptance [ $g = -0.39$ ]) and both physical and mental health components of QoL (Pakenham et al., 2018). Whilst these initial findings are encouraging, sample sizes are often small, therefore limiting

the representativeness of the treatment group and accuracy of the estimated effect sizes.

Regarding systematic reviews in this context, the effectiveness of ACT for chronic disease and long-term conditions has been shown for outcomes including QoL and reduction in distress (Graham et al., 2016). However, studies were found to be generally of low quality, with few RCTs and the majority had small sample sizes ( $M = 22.09$ ,  $SD = 12.57$ ). A systematic review of mindfulness (a focus of ACT) based interventions in pwMS showed significant effects on anxiety (0.36 – 0.39), depression (0.36 – 0.65), fatigue (0.38 – 0.41) and health-related QoL (0.28 – 0.86), which remained statistically significant at six-month follow-up (Simpson et al., 2014). However, only three studies were included in the review, highlighting the lack of research on interventions for pwMS.

#### **1.4 Purpose of this review**

Whilst there have been systematic reviews evaluating psychological interventions (including CBT, ACT psychotherapy and relaxation training) for pwMS (Fiest et al., 2016; Thomas et al., 2006), to date, there has not been a systematic review to evaluate the effectiveness of ACT-based psychological interventions in the MS population. Therefore, our aim was to synthesise the research to-date to (i) understand the effect of ACT on (a) QoL and mood, and (b) ACT-targeted processes, (ii) examine the quality of the evidence, and (iii) provide guidance for future research and offer clinical recommendations based on the extant evidence.

## **2. Method**

### **2.1 Protocol and registration**

The review protocol was prospectively registered on PROSPERO (CRD42021269541)<sup>1</sup> and at the University of Lincoln (project ID: 7106).

### **2.2 Eligibility Criteria**

Inclusion criteria:

1. Peer reviewed and grey literature, published in English
2. RCTs examining the effectiveness of ACT for pwMS
3. Adults ( $\geq 18$  years) with a clinically confirmed diagnosis of MS
4. All sub-types of MS
5. All types of ACT delivery modes (i.e., online, telephone, face-to-face), format (i.e., individual or in a group), length/number of sessions and facilitating clinician (e.g., psychologist, nurse, occupational therapist, etc.)
6. One or more measure of QoL and/or mood

Studies were excluded if:

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<sup>1</sup> This can be accessed at [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=269541](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=269541)

1. They were articles from conference papers and books
2. Outcome data from studies investigating a group of chronic disease or long-term neurological conditions did not have MS-related data available separately.
3. Outcome data from studies investigating “psychological interventions” did not have ACT-related data available separately.

We did not set a date restriction on studies.

### **2.3 Searching**

The following online databases were searched: PsycINFO, CINAHL, Embase, MEDLINE, Web of Science, and Scopus. Contextualscience.org list of RCTs in ACT was also searched using the keyword “multiple sclerosis”.

We accessed grey literature by searching ProQuest Dissertations and Theses, and PROSPERO, to help minimise this risk of publication bias within a review (Hopewell et al., 2007). Grey literature refers to documents not controlled by commercial publishing organisations, often representing research at its initial development (Adams et al., 2016; Pappas & Williams, 2011). If studies were identified through both grey literature and peer-reviewed publications, only the peer-reviewed publication was used.

We used the following search terms: multiple sclerosis, acceptance and commitment therapy, with truncations for a broader search of the literature. The search strategy was developed in consultation with the authors and a subject specialist librarian. See Appendix A for an example search strategy used in PsycINFO. Where appropriate, medical subject headings (MeSH) or subject descriptors (DE) were used for these terms and equivalent searches were conducted across all databases for consistency. QoL and mood were not included as search terms because these were not primary outcomes in some articles. Of the full-text articles screened, the reference lists were screened by title to identify any additional articles. The last search was conducted on 13/01/2022.

### **2.4 Study Selection**

The PRISMA flow diagram in Figure 1 outlines the searching and selection process. Studies from database searches were imported into RefWorks and duplicates removed. The first author (BT) applied the eligibility criteria to titles and abstracts. The remaining full-text articles were then reviewed against the eligibility criteria to obtain the selected papers for the review. Reasons for exclusion are summarised in Figure 1. Any uncertainties were resolved in consultation with one other author.

The primary outcomes of interest were QoL and mood. For the purpose of this review, ‘mood’ refers to key elements of psychological distress. Psychological distress can be conceptualised in terms of three related-but-distinct dimensions – depression, anxiety and stress (Lovibond & Lovibond, 1995). This approach to conceptualising and measuring distress is commonly applied, both in general

research on mood difficulties (Henry & Crawford, 2005; Sinclair et al., 2012) and specific investigations of ACT for pwMS (Pakenham et al., 2018). We were also interested in measures of the psychological processes in ACT, e.g., psychological flexibility.

## 2.5 Data Extraction

The first author (BT) extracted data from each eligible study and inputted into Microsoft Excel. A purpose-built form was used for data extraction, agreed between the authors (see Appendix B). Studies were assigned a number (1-6) for clarity within the results section.

## 2.6 Quality Appraisal

Methodological quality of the selected studies was assessed using the Cochrane Risk of Bias Tool version 2 (RoB2), which is recommended for use in reviews synthesising RCTs (Higgins et al., 2019). This tool assesses five main areas of bias: randomisation, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Risk of bias was judged as “low”, “some concerns”, or “high”, based on responses to signalling questions. The quality appraisal was conducted by two authors (BT and AB) independently. Any discrepancies in ratings were discussed and reviewed within the wider research team.

## 2.7 Data synthesis

Meta-analyses were conducted on the two outcomes of interest, QoL<sup>2</sup> and mood; we also conducted meta-analyses on ACT process measures. Data for these outcomes were continuous. Extracted means, standard deviations and sample sizes were entered into the Cochrane Review Manager software (RevMan), version 5.4 (The Cochrane Collaboration, 2020). We included Intention to Treat (ITT) analysis to limit attrition bias. Where studies had not given a mean, standard deviation or effect size, the median was taken as the mean value and interquartile ranges were used to estimate standard deviations using the following formula:  $SD=IQR/1.35$ . Where the mean and standard error were reported, standard deviations were calculated using the following formula:  $SD=SE \times \sqrt{N}$ .

We used a random effects model for each meta-analysis due to the variability between studies, e.g., variable outcome measures. The inverse variance method was used to calculate a weighted average and Standardised Mean Difference (SMD) was the summary statistic (Julian Higgins & Thomas, 2021). Forest plots were generated for comparisons and heterogeneity of studies was assessed using the  $I^2$  statistic. Variability between studies was anticipated due to clinical and methodological diversity; Julian Higgins & Thomas (2021) was used as a guide to

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<sup>2</sup> Where studies had reported physical health and mental health composites (MHC) for QoL, the MHC was included in the meta-analysis as this was deemed most appropriate to the aims of this review.

interpret the  $I^2$  statistic (i.e., 30-60% moderate, 50-90% substantial, 75-100% considerable heterogeneity).

Where a study used multiple measures of a single outcome of interest, the measure most used across studies was preferentially selected (as indicated in bold in Table 1); this maximised between-study homogeneity and cross-comparability for each outcome. Where studies had multiple data collection timepoints, those most similar across studies were selected. Any remaining timepoints were extracted and described narratively.

Further to overall pooled analyses, separate analyses were planned (for each outcome) to compare effects of ACT against active (e.g., alternative treatment) vs. passive (e.g., Treatment as Usual [TAU]) control conditions. Where this was not possible due to the limited number of studies (less than two), results were described narratively.

Sensitivity analyses were also conducted based on methodological quality of studies by removing the lowest scoring study on quality from the meta-analysis to examine the impact on the *SMD*. If there was no lowest scoring from the quality analysis, then sensitivity analysis was based on methodological similarity.

We intended to assess publication bias by funnel plot asymmetry analysis if there were at least 10 studies, as specified in the Cochrane Handbook (Page et al., 2021).

### **3. Results**

#### **3.1 Study Characteristics**

Initial searches retrieved 142 studies, 28 full-text articles were considered for inclusion, and six articles met inclusion criteria (with 191 participants in total). In addition, searches on PROSPERO identified nine “ongoing” articles; these were not included, and it was unclear when they were going to be completed. Table 1 outlines the relevant data extracted from each study.

Table 1 about here.

The eligible studies were published from 2012-2021 and conducted in Italy, Iran, the United Kingdom, and Sweden. Three studies examined QoL (1, 3, 6), four examined anxiety (1, 3, 5, 6), five examined depression (1, 3, 4, 5, 6) and two examined stress (1, 2). Four studies (1, 3, 5, 6) also included one or more ACT process measures. Three studies (3, 4, 6) compared ACT to Treatment as Usual (TAU), two studies (1, 5) compared ACT to Relaxation Training (RT) and one (2) did not specify the nature of the control. Table 2 shows the measures used for each primary outcome; subscales of these measures are noted in Table 1. Only one study reported on adverse events (3).

Table 2 about here.

Figure 1 about here.



The nature of the intervention was variable across studies. The number of sessions ranged from five to eight, with two studies including one-off “booster” sessions up to three months post-intervention completion. In addition, frequency of daily practice was difficult to control; Nordin & Rorsman (2012) reported a higher frequency of daily practice in the RT control group, potentially increasing consolidation of skills over the ACT intervention. Three studies used a group intervention format and two administered the intervention individually, either over the phone or face-to-face. Of those reporting who the facilitator was, two used a Trainee CP and two used qualified CPs.

**Table 1***Summary of the extracted data*

| Study number, author(s), date, location | Methods                | Participants   | Intervention  | QoL, mood-related or ACT-process outcomes  | Effect sizes <sup>c</sup> , summary and key findings  |
|---|------------------------|--|---|--|---|
| 1. Giovannetti et al. (2020), Italy     | Pilot single blind RCT | <b>Total:</b> <i>n</i> =39<br>ACT intervention: <i>n</i> =20<br>Control: <i>n</i> =19<br><b>Age (years)<sup>a</sup>:</b> <i>M</i> =45.7; <i>SD</i> =9.1; Range=NR<br><b>Gender<sup>a</sup>:</b> Women <i>n</i> =22 (59%)<br><b>Ethnicity/race:</b> NR<br><b>Type of MS<sup>a</sup>:</b> RR <i>n</i> =30 (81%); SP <i>n</i> =6 (16%); PP <i>n</i> =1 (3%) | <b>Mode of delivery:</b> group<br><b>Number, length, and frequency of sessions:</b> 7; 2.5hrs weekly sessions and 1 booster-session 5 weeks later,<br><b>Facilitator:</b> CP<br><b>Comparator:</b> 7 weekly 1 hour RT with a 1 hour booster session 5 weeks later.<br><b>Fidelity:</b> Assessed.<br><b>Adverse events:</b> NR | <b>Measures (with subscales)<sup>b</sup>:</b><br><b>QoL:</b> MSQoL-54 (physical health, mental health)<br><b>Mood:</b> HADS (anxiety, depression)<br>PSS (positive, negative)<br><b>ACT:</b> CompACT (OE, BA, VA)<br>MAAS<br>VLQ<br><b>AAQ-II</b><br>DDS<br><br><b>Timepoints:</b><br>Baseline (pre-randomisation)<br>Post-intervention: 7 weeks post-randomisation<br>Longer-term follow-up: 12 and 24 weeks post-randomisation | <b>MSQoL MHC.</b> <i>SMD</i> = 0.69 (CI 0.02, 1.35), favouring control.<br><b>HADS Anxiety.</b> <i>SMD</i> = -0.54 (CI -1.20, 0.11), favouring ACT.<br><b>HADS Depression.</b> <i>SMD</i> = -0.73 (CI -1.40, -0.06), favouring ACT.<br><b>PSS.</b> <i>SMD</i> = -0.43 (CI -1.08, 0.22), favouring ACT.<br><b>AAQ-II.</b> <i>SMD</i> = -0.30 (CI -0.95, 0.35), favouring ACT.<br><b>CompACT.</b> <i>SMD</i> = 0.46 (CI -0.20, 1.11), favouring control.<br><br>No statistically significant differences, at baseline, were found between ACT and RT apart from higher MSQoL-54 MHC in the ACT arm.<br>The majority of participants reported significant improvements at the three-month follow-up. |

**Table 1***Summary of the extracted data*

| Study number, author(s), date, location    | Methods                     | Participants   | Intervention  | QoL, mood-related or ACT-process outcomes   | Effect sizes <sup>c</sup> , summary and key findings   |
|--|-----------------------------|--|---|---|--|
| 2. Khalifeh-Soltani & Borhani (2019), Iran | Experimental pre- post-test | <b>Total:</b> $n=60$<br>ACT intervention: $n=30$<br>Control: $n=30$<br><b>Age (years):</b><br>ACT Intervention: $M=54.17$ ; $SD=11.02$ ; Range=49-58.<br>Control: $M=52.63$ ; $SD=10.18$ ; Range=48-58.<br><b>Gender:</b> NR<br><b>Ethnicity/race:</b> NR<br><b>Type of MS:</b> NR | <b>Mode of delivery:</b> NR<br><b>Number, length, and frequency of sessions:</b> NR<br><b>Facilitator:</b> NR<br><b>Comparator:</b> Control<br><b>Fidelity:</b> NR<br><b>Adverse Events:</b> NR | <b>Measures (with subscales):</b><br><b>Mood:</b> PSS (positive, negative)<br><br><b>Timepoints:</b><br>Baseline (immediately pre-intervention)<br>Post-intervention: Reported but timeframe not specified.<br>Longer-term follow-up: Reported but timeframe not specified. | <p>Differences between control and ACT intervention increased at each time-point, suggesting a “promising longitudinal trend” (p. 20). However, findings did not show ACT to be more efficacious than the control (RT) in showing significant improvements on all outcomes.</p> <p><b>PSS.</b> <math>SMD = -0.52</math> (CI -1.08, 0.22), favouring ACT.</p> <p>There was a positive effect of ACT on perceived stress in comparison to the control group. Scores in the control group decreased however this was not significant. Reported time limitations meant no follow-up examination was completed, despite reporting follow-up data.</p> |

**Table 1***Summary of the extracted data*

| Study number, author(s), date, location | Methods                          | Participants   | Intervention   | QoL, mood-related or ACT-process outcomes   | Effect sizes <sup>c</sup> , summary and key findings  |
|---|----------------------------------|--|--|---|---|
| 3. Meek et al. (2021), UK               | Feasibility RCT                  | <b>Total:</b> <i>n</i> =14<br>ACT intervention: <i>n</i> =7<br>Control: <i>n</i> =7<br><b>Age (years):</b><br>ACT Intervention: <i>M</i> =54.40; <i>SD</i> =6.58; Range=NR.<br>Control: <i>M</i> =51.60; <i>SD</i> =8.39; Range=NR.<br><b>Gender:</b> Women ACT intervention: <i>n</i> =5<br>Control: <i>n</i> =5<br><b>Ethnicity/race<sup>a</sup>:</b><br>White British <i>n</i> =14<br><b>Type of MS<sup>a</sup>:</b><br>SP <i>n</i> =14 | <b>Mode of delivery:</b><br>Telephone with 1 <sup>st</sup> session face-to-face; individual<br><b>Number, length, and frequency of sessions:</b><br>6; 30-minute weekly sessions<br><b>Facilitator:</b> Trainee CP<br><b>Comparator:</b> TAU<br><b>Fidelity:</b> Assessed<br><b>Adverse events:</b> None to report | <b>Measures (with subscales):</b><br><b>QoL:</b> EQ-5D-5L<br><b>Mood:</b> HADS (anxiety, depression)<br><b>ACT:</b> CompACT (OE, BA, VA)<br><b>Timepoints:</b><br>Baseline (pre-randomisation)<br>Post-intervention: 8 weeks post-randomisation<br>Longer-term follow-up: 12-weeks post-randomisation | <b>EQ-5D-5L.</b> <i>SMD</i> = 0.20 (CI -0.85, 1.25), favouring control.<br><b>HADS Anxiety.</b> <i>SMD</i> = -0.67 (CI -1.76, 0.42), favouring ACT.<br><b>HADS Depression.</b> <i>SMD</i> = -0.32 (CI -1.38, 0.73), favouring ACT.<br><b>CompACT.</b> <i>SMD</i> = 0.07 (CI -0.98, 1.12), favouring control.<br><br>No significant effect was found between or within groups. |
| 4. Mojtabaie & Khoshcheshm (2014), Iran | Quasi-experimental pre-post-test | <b>Total:</b> <i>n</i> =30<br>ACT intervention: <i>n</i> =15<br>Control: <i>n</i> =15<br><b>Age (years)<sup>a</sup>:</b><br><i>M</i> =NR; <i>SD</i> =NR; Range=20-45.<br><b>Gender:</b> NR<br><b>Ethnicity/race:</b> NR<br><b>Type of MS:</b> NR   | <b>Mode of delivery:</b><br>Face-to-face; group<br><b>Number, length, and frequency of sessions:</b><br>8; 45–60-minute workshops. Frequency: NR.<br>Frequency: NR<br><b>Facilitator:</b> NR   | <b>Measures (with subscales):</b><br><b>Mood:</b> BDI-II<br><br><b>Timepoints:</b><br>Baseline (immediately pre-intervention)<br>Post-intervention: timepoint not specified.  | <b>BDI-II.</b> <i>SMD</i> = -3.51 (CI -4.70, -2.32), favouring ACT.<br><br>The effect of ACT on depression was significant. Difference between depression scores post-intervention was also   |

**Table 1***Summary of the extracted data*

| Study number, author(s), date, location | Methods   | Participants  | Intervention  | QoL, mood-related or ACT-process outcomes   | Effect sizes <sup>c</sup> , summary and key findings   |
|---|-----------|---|---|---|--|
| 5. Nordin & Rorsman (2012), Sweden      | Pilot RCT | <b>Total:</b> <i>n</i> =21<br>ACT intervention: <i>n</i> =11<br>Control: <i>n</i> =10<br><b>Age (years):</b><br>ACT Intervention: <i>M</i> =43; <i>IQR</i> =36-45.<br>Control: <i>M</i> =48.5; <i>IQR</i> =38-55.<br><b>Gender*:</b> Women <i>n</i> =16<br><b>Ethnicity/race:</b> NR<br><b>Type of MS<sup>a</sup>:</b><br>SP <i>n</i> =5<br>RR <i>n</i> =16 | <b>Comparator:</b> No intervention<br><b>Fidelity:</b> Assessed.<br><b>Adverse events:</b> NR<br><b>Mode of delivery:</b> Face-to-face; group<br><b>Number, length, and frequency of sessions:</b> 4; weekly sessions. 1 booster session 3-months later<br><b>Facilitator:</b> CPs<br><b>Comparator:</b> RT; 3 face-to-face weekly group sessions and the 4 <sup>th</sup> session over the phone, individually. 1 booster session 3-months later.<br><b>Fidelity:</b> NR<br><b>Adverse events:</b> NR | Longer-term follow-up: NR.<br><b>Measures (with subscales):</b><br><b>Mood:</b> HADS (anxiety, depression)<br>BDI<br><b>ACT: AAQ-II</b><br><b>Timepoints:</b><br>Baseline (pre-randomisation)<br>Post-intervention: 14 weeks post-randomisation<br>Longer-term follow-up: 26-weeks post-randomisation | significant, in favour of ACT intervention.<br><b>HADS Depression.</b> <i>SMD</i> = -0.20 (CI -1.06, 0.66), favouring ACT.<br><b>HADS Anxiety.</b> <i>SMD</i> = 0.40 (CI -0.47, 1.27), favouring control.<br><b>AAQ-II.</b> <i>SMD</i> = 0.03 (CI -0.82, 0.89), favouring control.<br>Between group comparisons did not show ACT to be more efficacious over the control (RT) on any outcome. Within group comparisons showed ACT had a positive effect on AAQ-II; this was maintained at 3-month follow-up. Further, analysis also showed the control group experienced a larger decline in |

**Table 1***Summary of the extracted data*

| Study number, author(s), date, location | Methods   | Participants   | Intervention   | QoL, mood-related or ACT-process outcomes  | Effect sizes <sup>c</sup> , summary and key findings   |
|---|-----------|--|--|--|--|
| 6. Proctor et al. (2018), UK            | Pilot RCT | <p><b>Total:</b> <math>n=27</math><br/>           ACT intervention: <math>n=14</math><br/>           Control: <math>n=13</math><br/> <b>Age (years):</b><br/>           ACT Intervention <math>M=46</math>; <math>SD=12.4</math>, Range=NR.<br/>           Control: <math>M=45.8</math>; <math>SD=8.8</math>, Range=NR.<br/> <b>Gender:</b> Women ACT Intervention: <math>n=3</math>, Control: <math>n=0</math><br/> <b>Ethnicity/race:</b> NR<br/> <b>Type of MS:</b><br/>           ACT Intervention: RR <math>n=9</math>; PP <math>n=2</math>; SP <math>n=3</math><br/>           Control: RR <math>n=10</math>; PP <math>n=2</math>; SP <math>n=1</math></p> | <p><b>Mode of delivery:</b> Telephone; individual<br/> <b>Number, length, and frequency of sessions:</b> 8; weekly sessions.<br/>           Average length <math>M=14</math> mins; <math>SD=6</math><br/> <b>Facilitator:</b> Trainee CP<br/> <b>Comparator:</b> TAU<br/> <b>Fidelity:</b> NR<br/> <b>Adverse events:</b> NR</p> | <p><b>Measures (with subscales):</b><br/> <b>QoL:</b> EQ-5D-5L<br/> <b>Mood:</b> GAD-7<br/>           PHQ-9<br/> <b>ACT: AAQ-II</b><br/> <b>Timepoints:</b><br/>           Baseline (pre-randomisation)<br/>           Post-intervention: 12-weeks post-randomisation<br/>           Longer-term follow-up: NR</p> | <p>depressive symptoms compared to ACT.<br/> <b>EQ-5D-5L.</b> <math>SMD = 0.05</math> (-0.77, 0.86), favouring control.<br/> <b>GAD-7.</b> <math>SMD = -0.81</math> (CI -1.63, 0.02), favouring ACT.<br/> <b>PHQ-9.</b> <math>SMD = -0.17</math> (CI -0.95, 0.62), favouring ACT.<br/> <b>AAQ-II.</b> <math>SMD = -0.19</math> (CI -0.99, 0.62), favouring ACT.</p> <p>A large significant effect was found in favour of ACT, for GAD-7 at follow-up. Within the sample, there were higher levels of anxiety than depression, so it was hypothesized participants likely used the intervention to manage their primary presenting problem.</p> |

*Note.* NR = Not reported. AAQ-II; Acceptance and Action Questionnaire, BA; Behavioural Awareness, BDI-II; Beck's Depression Inventory, CompACT; Comprehensive Assessment of Acceptance and Commitment Therapy Processes, CP; Clinical Psychologist, DDS; Drexel

**Table 1***Summary of the extracted data*

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| Study number, author(s), date, location | Methods | Participants | Intervention | QoL, mood-related or ACT-process outcomes | Effect sizes <sup>c</sup> , summary and key findings |
|---|---------|--------------|--------------|---|--|
|---|---------|--------------|--------------|---|--|

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Defusion Scale, EQ-5D-5L; Euro Quality of Life measure, GAD-7; Generalised Anxiety Disorder-7 item, HADS; Hospital Anxiety and Depression Scale, MAAS; Mindful Awareness Attention Scale, MHC; Mental Health Composite, MSQoL-54; Multiple Sclerosis Quality of Life-54 item, OE; Openness to Experience, PHQ-9; Patient Health Questionnaire-9 item, PP; Primary Progressive, PSS; Perceived Stress Scale, RR; Relapsing Remitting, RT; Relaxation Training, SEIQoL-DW; Schedule for the Evaluation of Individual Quality of Life-Direct Weighting, SP; Secondary Progressive, TAU; Treatment as Usual, VA; Valued Action, VLQ; Valued Living Questionnaire.

<sup>a</sup>of total sample size.

<sup>b</sup>not included SEIQoL-DW as qualitative interview-based instrument.

<sup>c</sup>*SMD* not reported in paper but calculated in RevMan; all post-intervention.

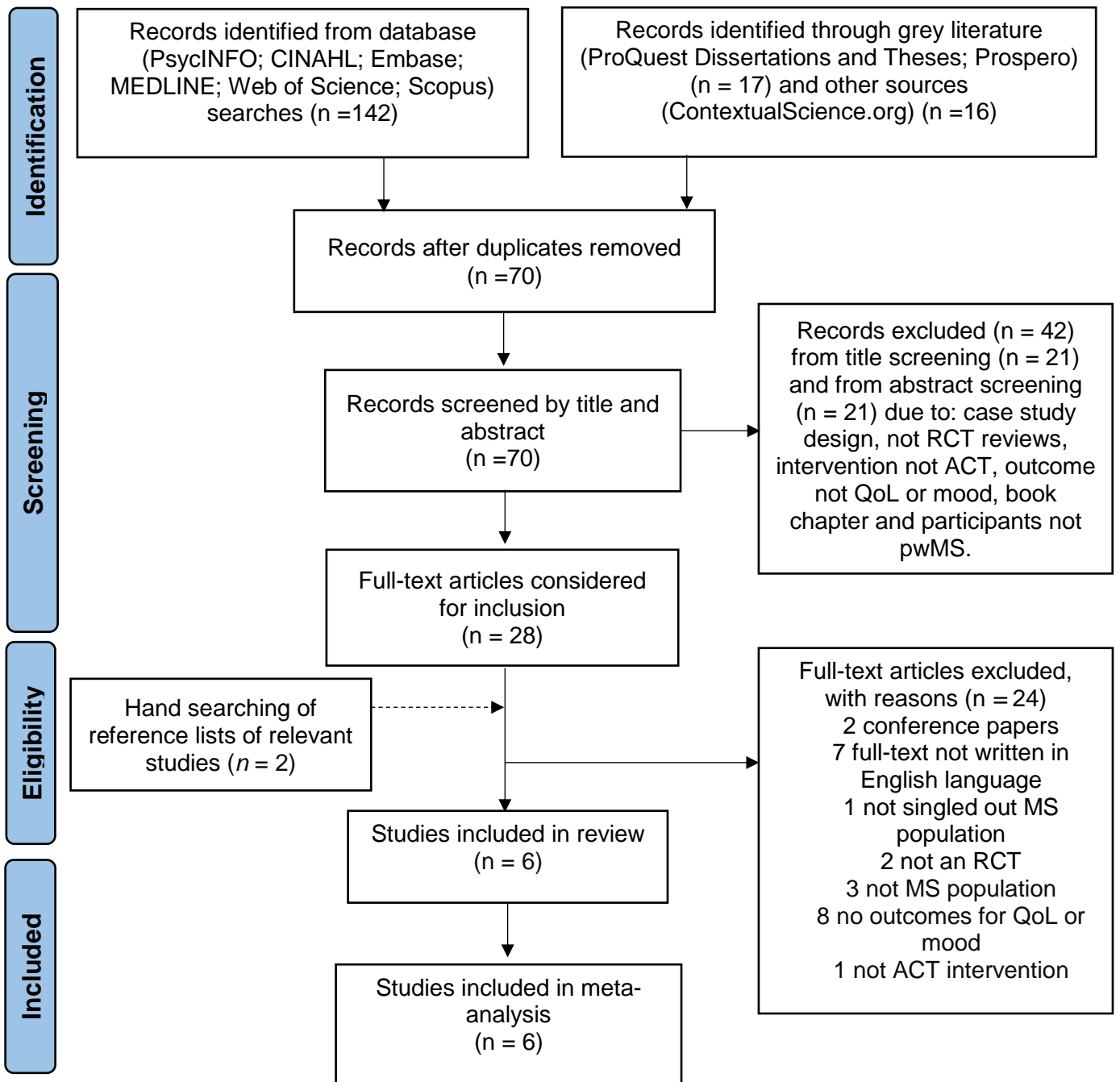
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**Table 2***Summary of measures used to assess primary outcomes of interest*

| Outcome of Interest    | Measure   |
|------------------------|---|
| Quality of Life        | Multiple Sclerosis Quality of Life-54 (MSQoL-54)<br>Euroqol Quality of Life measure (EQ-5D-5L)  |
| Mood                   | Anxiety<br>Hospital Anxiety and Depression Scale (HADS)<br>Generalised Anxiety Disorder measure (GAD-7)   |
|                        | Depression<br>Hospital Anxiety and Depression Scale (HADS)<br>Patient Health Questionnaire (PHQ-9)<br>Beck Depression Inventory (BDI/BDI-II)  |
|                        | Stress<br>Perceived Stress Scale (PSS)  |
| ACT-targeted processes | Comprehensive Assessment of ACT Processes (CompACT)<br>Mindful Awareness Attention Scale (MAAS)<br>Valued Living Questionnaire (VLQ)<br>Acceptance and Action Questionnaire (AAQ-II)<br>Drexel Defusion Scale (DDS) |



**Figure 1**  
*PRISMA Flow Diagram of Study Selection*



### 3.2 Quality Appraisal

For quality appraisal, the level of agreement between reviewers (BT and AB) was assessed and, before resolving any differences, overall linear weighted kappa = 0.877 ('almost perfect' agreement).

There was variability in the quality of studies, as detailed in Table 3 and summarised in Figure 2. Four of the six studies scored low risk of bias for randomisation because they used an independent researcher or computer-generated randomisation (1, 3, 5, 6). The remaining studies scored "some concerns" due to not outlining the randomisation process in detail.

Regarding deviations from the intended intervention, three studies (1, 2, 4) did not report whether the intervention was delivered in accordance with the intervention protocol, despite one of those publishing a protocol (1). The remaining three scored "low risk" as deviations from the trial protocol occurred and were reported (e.g., number of support-calls differed, or session homework completion was variable).

All studies were judged "low risk" for missing outcome data. Five studies reported outcome data for nearly (>95%) or all participants (1, 2, 3, 4, 5). The remaining study reported attrition, however had controlled for missing outcome data bias through intent-to-treat analyses (6).

Only one study (5) used blinding in scoring and analyses; all other studies either did not provide information on blinding or blinding did not occur, which introduces a risk that intervention knowledge could influence assessment outcome. Two studies (1, 3) were judged as low risk of bias for selection of the reported result as this occurred in accordance with a plan specified in a trial protocol. One study (6) had published a trial protocol however an analysis plan was not specified, which therefore met criteria for "some concerns". The remaining three studies were also judged as having "some concerns" due to no information found on conducting analyses in line with a pre-specified plan.

An overall risk of bias judgment was calculated by the RoB v2 algorithm (Higgins et al., 2019) and showed all except one study (5) to be "high" risk of bias.

**Table 3***Risk of Bias Judgements in Selected Studies*

| Study                                | Randomisation Process   | Deviations from Intended Interventions   | Missing Outcome Data   | Measurement of Outcome   | Selection of the Reported Result  |
|--------------------------------------|---|--|--|--|---|
| 1. Giovannetti et al. (2020)         | Low risk; "Randomization was provided by an independent randomization service at the Neuroepidemiology Unit, using computer-based stratified randomization" (p. 5). | Some concerns; Trial protocol <sup>a</sup> published but no information on whether deviations occurred.  | Low risk; Outcome data available for nearly all participants. "Two participants (ACT) withdrew before beginning the intervention due to unexpected work commitments" (p. 8). | High risk; Knowledge of intervention received likely to influence assessment of the outcome. | Low risk; Results were analysed in accordance with a published trial protocol, published before unblinded outcome data was available. |
| 2. Khalifeh-Soltani & Borhani (2019) | Some concerns; Unclear description provided. "experimental and control groups were matched using a simple random method" (p. 37).                                   | Some concerns; No information on availability of a trial protocol or adherence/deviations to a protocol.   | Low risk; Outcome data available for all participants.   | High risk; No information on blinding.   | Some concerns; No information on adherence/deviations from the analysis plan outlined in a trial protocol.                            |
| 3. Meek et al. (2021)                | Low risk; "randomisation was completed by the Lead Researcher using an online randomisation service and randomly sized  | Low risk; Deviations from the trial protocol <sup>b</sup> reported but are consistent with what would occur outside of the trial context. "30 support calls, four were rearranged" (p. 164). | Low risk; Outcome data available for nearly all participants. "all HADS, MSIS and EQ-5D-5L questionnaires completed (100%), and  | High risk; Knowledge of intervention received likely to influence assessment of the outcome. | Low risk; Results were analysed in accordance with a published trial protocol, published before unblinded                             |

**Table 3***Risk of Bias Judgements in Selected Studies*

| Study                            | Randomisation Process  | Deviations from Intended Interventions  | Missing Outcome Data  | Measurement of Outcome  | Selection of the Reported Result   |
|----------------------------------|--|---|---|---|--|
|                                  | permeated blocks to each arm (ratio: 1:1)" (p. 161).   | "the average length of time a participant took to complete the six-week intervention was 6.65 weeks (range = 5.29–8.14 weeks) (SD = 0.96 weeks)" (p. 164).                                      | 41 of 42 (98%) CompACT questionnaires completed (one pack returned unfilled). The MSSE was frequently completed incorrectly, due to an unclear layout, and 31 of 42 (74%) were interpretable" (p. 164). | "No blinding was used as participants were aware if they were receiving psychological therapy input, as this was not part of treatment as usual." (p. 161). | outcome data was available.  |
| 4.Mojtabie & Khoschcheshm (2014) | Some concerns; Unclear description provided. "participants were randomly distributed in control and experiment groups" (p. 871).                 | Some concerns; No information on availability of a trial protocol or adherence/deviations to a protocol.  | Low risk; Outcome data available for all participants.  | High risk; No information on blinding.  | Some concerns; No information on adherence/deviations from the analysis plan outlined in a trial protocol.               |
| 5.Nordin & Rosman (2012)         | Low risk; "Patients were randomly assigned by an independent co-worker to one of two treatment groups following pairwise matching based on EDSS, | Low risk; Deviations reported but are consistent with what would occur outside of the trial context. "One patient (RT group) had a MS relapse with complete recovery during treatment" (p. 89). | Low risk; Outcome data available for nearly all participants. "Discontinued intervention (withdrew at own request after first session) (n = 1)" (p. 88).  | Low risk; "Scoring and data analyses were conducted blindly" (p. 88).   | Some concerns; No information on adherence/deviations from the analysis plan outlined in a trial protocol <sup>c</sup> . |

**Table 3***Risk of Bias Judgements in Selected Studies*

| Study                   | Randomisation Process  | Deviations from Intended Interventions   | Missing Outcome Data  | Measurement of Outcome                 | Selection of the Reported Result  |
|-------------------------|--|--|---|--|---|
|                         | anxiety, and depression scores” (p. 88).   |  |   |  |   |
| 6.Proctor et al. (2018) | Low risk; “The randomisation sequence was computer-generated by one researcher (NM), concealed from other researchers, and entered into a standalone web-based system” (p. 5). | Low risk; Deviations from the trial protocol reported but are consistent with what would occur outside of the trial context. “three received the eight, scheduled support-calls, and completed the book within the expected seven weeks. Two received an extra phone-call, due to not completing chapters within the allotted time-period” (p. 8). | Low risk; Evidence the result was not biased by missing outcome data. “Overall, 9 of 27 (33%) participants dropped out of the study... RCT analysis used an intention-to-treat approach... This method provides unbiased estimates in the presence of missing data” (p. 8). | High risk; No information on blinding. | Some concerns; Analysis plan not specified on the published protocol; no information on adherence/deviations from an analysis plan. |

*Note.* Table shows risk of bias judgements using the Cochrane RoB Tool version 2.

<sup>a</sup>Protocols.io; doi: [dx.doi.org/10.17504/protocols.io.bcqjivun](https://doi.org/10.17504/protocols.io.bcqjivun)

<sup>b</sup>Clinicaltrials.gov; ID: NCT04239664

<sup>c</sup>trial protocol was available on request but unavailable in English.

<sup>d</sup>Clinicaltrials.gov; ID: NCT02596633

**Figure 2**  
*Risk of Bias Judgements; Output from RoB Tool v2*

|                                   | Randomisation process | Deviations from the intended intervention | Missing outcome Data | Measurement of the outcome | Selection of the reported result | Overall |
|-----------------------------------|-----------------------|---|----------------------|----------------------------|----------------------------------|---------|
| Giovannetti et al. (2020)         | +                     | !   | +                    | -                          | +                                | -       |
| Khalifeh-Soltani & Borhani (2019) | !                     | !   | +                    | -                          | !                                | -       |
| Meek et al. (2021)                | +                     | +   | +                    | -                          | +                                | -       |
| Mojtabie & Khoschcheshm (2014)    | !                     | !   | +                    | -                          | !                                | -       |
| Nordin & Rosman (2012)            | +                     | +   | +                    | +                          | !                                | !       |
| Proctor et al. (2018)             | +                     | +   | +                    | -                          | !                                | -       |

Note. Positive signs indicate “low risk” judgement, exclamation marks indicate “some concerns” judgement, and negative signs indicate “high risk judgements”

### 3.3 Meta-Analysis

All meta-analyses were conducted on outcomes post-intervention, which ranged from 7 weeks post-randomisation to 14 weeks post-randomisation.

#### 3.3.1 Quality of Life

Three studies (74 participants) measured QoL when comparing ACT against a control (1, 3, 6). Figure 3 shows the forest plot. A medium, nonsignificant effect on QoL, favouring the control group, was found ( $SMD = 0.39$  [95% CI of  $-0.08 - 0.85$ ]). Statistical heterogeneity was 0%.

Figure 3 about here.

Separate analyses on active vs. passive control conditions, by removing the active control (Relaxation Training [RT]) in study (1), showed no statistical heterogeneity ( $I^2 = 0\%$ ) and a nonsignificant small effect, favouring control ( $SMD = 0.10$  [95% CI of  $-0.54 - 0.75$ ]). For active control, a medium, significant effect on QoL was found, in favour of the RT control ( $SMD = 0.69$  [95% CI of  $0.02 - 1.35$ ]).

### 3.3.2 Mood

**Anxiety.** Four studies (97 participants) measured anxiety when comparing ACT against a control (1, 3, 5, 6). Figure 4 shows the forest plot for the meta-analysis. A medium, nonsignificant effect on anxiety was found, favouring ACT ( $SMD = -0.41$  [95% CI of  $-0.93 - 0.11$ ]). Statistical heterogeneity was moderate,  $I^2 = 35\%$ .

A large, significant effect on anxiety was found for the two studies using passive controls (3, 6), favouring ACT ( $SMD = -0.76$  [95% CI of  $-1.41 - -0.10$ ],  $p = 0.02$ ), with  $I^2 = 0\%$  heterogeneity. For the two studies using active controls of RT (1, 5), a nonsignificant small effect was found, favouring ACT ( $SMD = -0.12$  [95% CI of  $-1.04 - 0.80$ ]), with substantial heterogeneity ( $I^2 = 65\%$ ).

Figure 4 about here.

**Depression.** Five studies (127 participants) examined depression when comparing ACT against a control (1, 3, 4, 5, 6). Figure 5 shows the forest plot for the meta-analysis. A large, nonsignificant effect size was found, favouring ACT ( $SMD = -0.92$  [95% CI of  $-1.91 - 0.06$ ]). The  $I^2$  statistic showed substantial heterogeneity ( $I^2 = 84\%$ ). For the sensitivity analysis, one study (4) was removed on the basis of scoring lowest on the quality analysis and no overlap of the confidence intervals of the other studies. A medium, significant effect on depression was found, favouring ACT ( $SMD = -0.40$  [95% CI of  $-0.81 - -0.00$ ]).

Three studies used passive controls (3, 4, 6) and showed a large, nonsignificant effect on depression, favouring ACT ( $SMD = -1.30$  [95% CI of  $-3.25 - 0.66$ ]), with considerable heterogeneity ( $I^2 = 91\%$ ). For studies using active controls of RT (1, 5), a medium, significant effect on depression, in favour of ACT, was found ( $SMD = -0.53$  [95% CI of  $-1.06 - -0.00$ ],  $p = 0.05$ ), with no heterogeneity.

Figure 5 about here.

**Stress.** Two studies (97 participants) measured stress (1, 2); Figure 6 shows the forest plot. A medium, significant effect on stress was found, in favour of ACT ( $SMD = -0.49$  [95% CI of  $-0.89 - -0.08$ ]), with no heterogeneity.

One study (1) used an active control of RT. A moderate, nonsignificant effect, favouring ACT, was found ( $SMD = -0.43$  [95% CI of  $-1.08 - 0.22$ ]). The other (2) used a passive control. A moderate, significant effect was found, in favour of ACT ( $SMD = -0.52$  [ $-1.04 - -0.01$ ],  $p = 0.05$ ).

Figure 6 about here.

### 3.3.3 ACT-targeted Processes

The most frequent measure was the AAQ-II. This was used by three studies (1, 5, 6) (82 participants) and Figure 7 shows the forest plot for the meta-analysis. A

small, nonsignificant effect on AAQ-II scores was found, in favour of ACT ( $SMD = -0.18$  [95% CI of  $-0.62 - 0.25$ ]) with no heterogeneity.

Two studies used active controls of RT (1, 5) and showed a small, nonsignificant effect, favouring ACT ( $SMD = -0.18$  [95% CI of  $-0.70 - 0.34$ ]), with no heterogeneity. For passive control conditions of TAU (6), a small, nonsignificant effect, in favour of ACT, was found ( $SMD = -0.19$  [95% CI of  $-0.99 - 0.62$ ]).

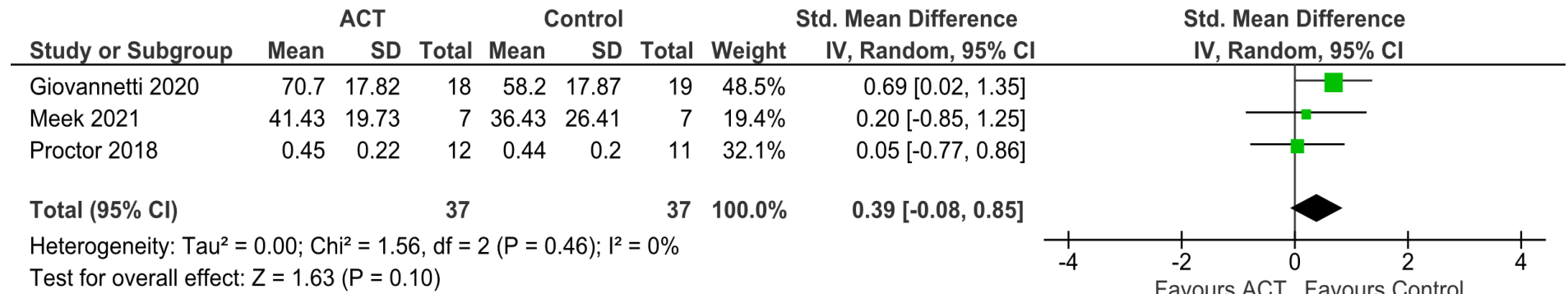
Regarding additional measures, two studies (1, 3) used the CompACT; with one (1) also measuring mindfulness, defusion and valued living. Both studies reported the ACT intervention was not more efficacious than the control in showing significant improvements on these outcomes.

Figure 7 about here.



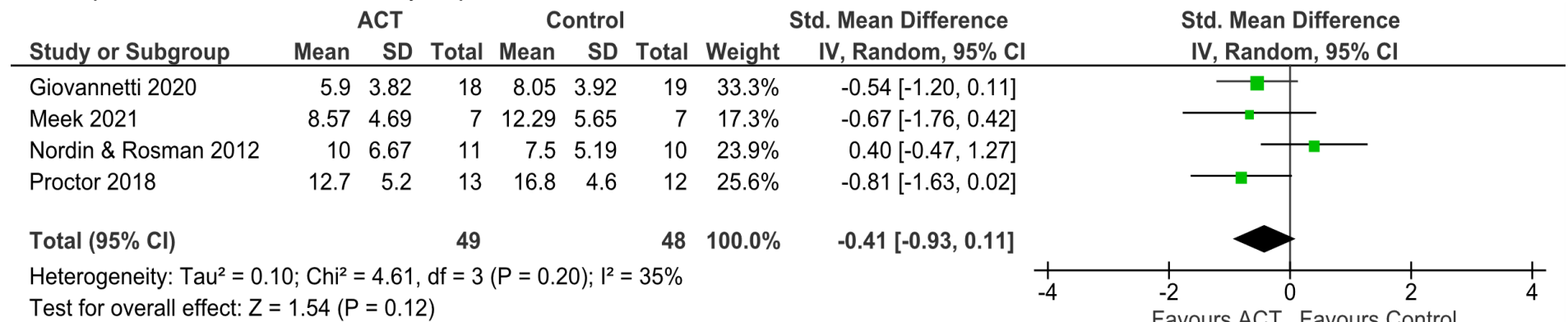
**Figure 3**

Forest plot for ACT vs Control; QoL at post-intervention



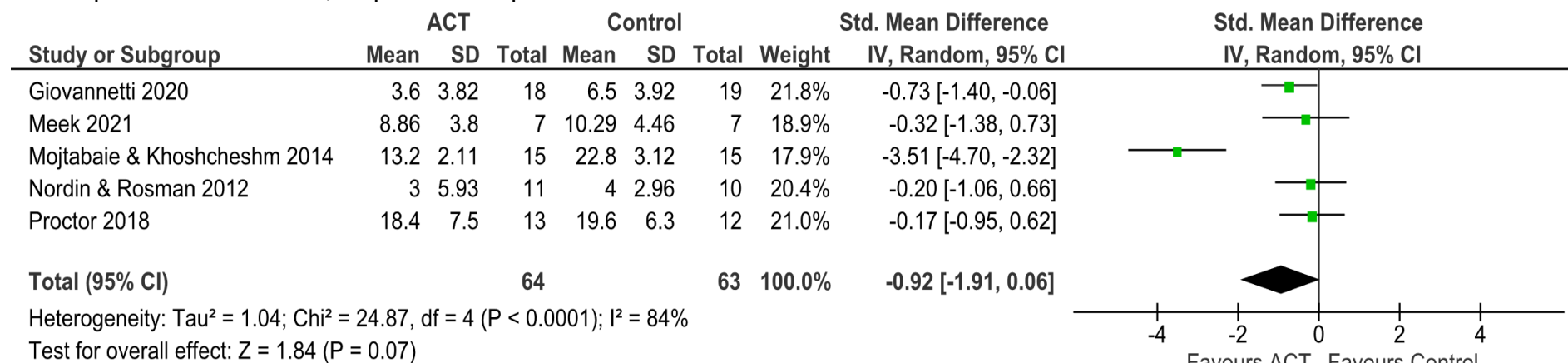
**Figure 4**

Forest plot ACT vs Control; Anxiety at post-intervention



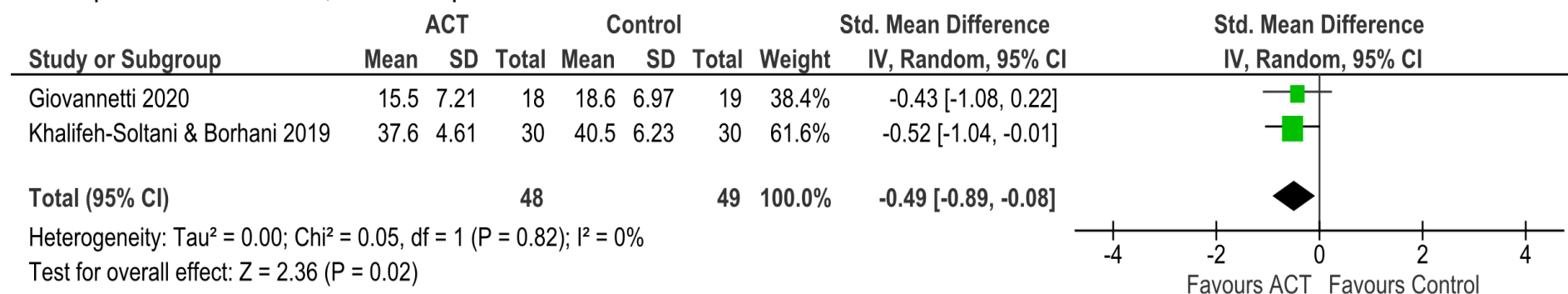
**Figure 5**

Forest plot ACT vs Control; Depression at post-intervention



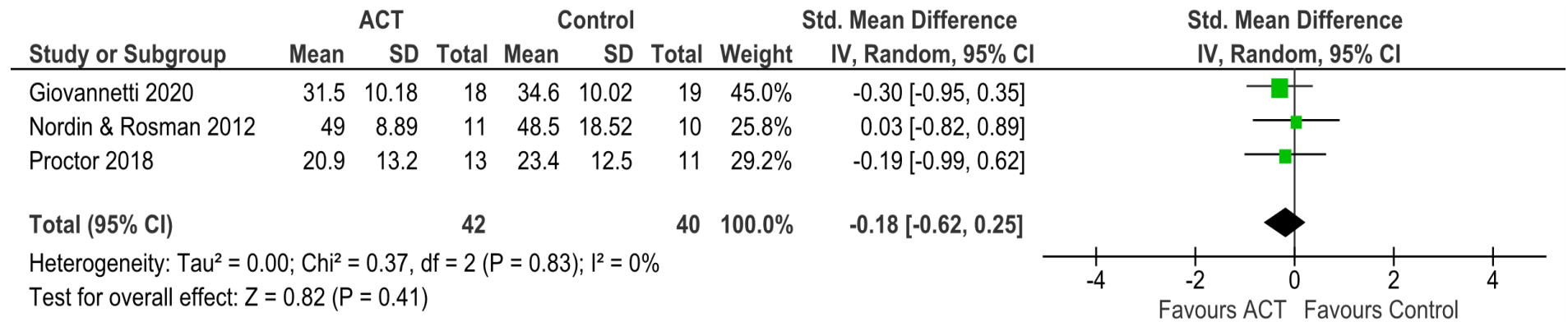
**Figure 6**

Forest plot ACT vs Control; Stress at post-intervention



**Figure 7**

Forest plot ACT vs Control; ACT processes at post-intervention



### **3.4 Longer-term follow-up timepoints**

Three studies (74 participants) included longer-term follow-up timepoints (1, 3, 5). Two studies (3, 5) measured 12-weeks and 26-weeks post-randomisation, respectively. One study included two longer-term follow-up points of 12 and 24-weeks post-randomisation (1).

Khalifeh-Soltani and Borhani (2019) reported means and SDs for a follow-up timepoint (timeframe was not specified) however noted “time limitations that did not allow for a follow-up examination on the study results” (p. 39). There was no reference to a follow-up assessment within their methods, therefore these results were not included in the review.

Where follow-up data were available, initial gains were sustained at each follow-up point following the ACT intervention for QoL, mood and ACT-targeted processes (1). Conversely, Meek et al. (2021) reported no significant effect on the outcomes of interest, which was also demonstrated at 12-week follow-up.

Nordin and Rorsman (2012) reported an effect on AAQ-II within the ACT arm, which was maintained at longer-term follow-up. Initially the effect on depressive symptoms favoured the control (RT) however this was not maintained at longer-term follow-up. The effect on anxiety favoured the control condition, which followed the same trend at follow-up; no effect was seen in the ACT intervention condition.

### **3.5 Publication bias**

This was not conducted as we had fewer than 10 studies.

## **4. Discussion**

This review examined the effectiveness of ACT for QoL and mood, and ACT-targeted measures, in pwMS. Six studies were eligible for the review and meta-analysis. There was no significant effect of ACT on most of the key outcomes of interest (anxiety, depression, quality of life, and ACT-targeted processes), particularly when compared to active controls (RT), except for the stress outcome, which showed a small significant difference favouring ACT. Overall, point estimates indicated effects in a small to moderate range, but there were wide confidence intervals reflecting a lack of robust evidence.

The meta-analysis did not find a significant positive effect of ACT on QoL, relative to control groups. In comparison to previous research (Pakenham et al., 2018; Sesel et al., 2018; Sheppard et al., 2010), this result was somewhat unexpected. The most frequent measure of QoL was the EQ-5D-5L, which includes mobility, usual activities, and pain/discomfort. Given the variable nature of MS, these factors may not change or can worsen for some pwMS, even in short timeframes, which may offer a potential explanation of our findings. In addition, Giovannetti et al. (2020) reported significantly higher ‘mental health component of QoL’ within the ACT

intervention group at baseline, suggesting a potential ceiling effect, which may also explain these findings.

With regards to anxiety and depression outcomes, our findings are largely not in keeping with previous research on psychological interventions, which has demonstrated positive effects of ACT on depression for pwMS (Pakenham et al., 2018; Sheppard et al., 2010). This is also the case when comparing our findings with the wider ACT literature (Gloster et al., 2020), which also showed ACT to be efficacious for anxiety and depression, in comparison to passive control conditions (i.e., waitlist and placebo) and TAU, but variable in comparison to active control conditions (e.g., CBT). One possible interpretation is that our inclusion of studies of lower methodological quality introduced potential bias. Specifically, we included one paper (Mojtabie & Khoshcheshm, 2014) that provided insufficient information around randomisation and intervention fidelity. Notably, when controlling for study quality by excluding this study from meta-analysis, our results were more aligned with previous research: demonstrating a medium significant effect of ACT on depression. More broadly, the sensitivity of our meta-analytic findings to the inclusion/exclusion of one small study ( $n = 30$ ) reflects the limited certainty with which we can estimate effects from available information. The few, small studies to date do not permit precise pooled estimates. Thus, while point estimates for anxiety and depression were in a direction favouring ACT, the confidence intervals around these estimates were wide and included zero.

Our findings related to the stress outcome was in line with previous studies (e.g., Pakenham et al., 2018), which indicated that there was a significant small positive effect of ACT, but the same caveats mentioned above related to study design apply.

Regarding the ACT-targeted process of psychological flexibility, as measured by the AAQ-II and CompACT, we did not find a significant difference between ACT and control conditions. Detecting a larger, significant effect was possibly limited due to the small sample size and number of studies including ACT process measures. Another possibility is that although some of these measures are frequently used in ACT studies, they may not be adequately tapping the ACT processes. Specifically, the process measure most used in reviewed studies (AAQ-II) has been shown to insufficiently represent the construct of psychological flexibility and be conflated with distress (lacking content and discriminant validity; Francis et al., 2016; Ong et al., 2020). Indeed, a recent review concluded that the AAQ-II should not be used as a measure of psychological flexibility in future research (Cherry et al., 2021). However, our results would suggest that there is little indication that the ACT interventions are operating through the proposed mechanism of change. Potentially, this means the intervention may be agnostic to these targeted processes or the measures are invalid, or potentially both. This has significant implications for the use of ACT in pwMS and the wider ACT research and practice.

#### **4.1 Strengths and limitations of included studies**

Overall, most studies indicated high risk of bias, so findings should be interpreted with caution. A large, contributing factor to this judgement was the measurement of the outcome. Only one study reported blinding participants (Nordin & Rosman, 2012). The challenge of blinding is consistent with conducting psychological intervention trials (das Nair et al., 2019) and can introduce response bias and expectations of a positive outcome from participants' perspective (Juul et al., 2021). Four studies completed baseline measures pre-randomisation; a strength that reduced potential risk of bias.

Across studies, there were small sample sizes with studies reporting a lack of power and a high attrition rate, limiting the confidence in the results (Meek et al., 2021). This issue which is commonly reported within psychological intervention studies on this population (Thomas et al., 2006). Only one study acknowledged potential adverse events, which is required when adhering to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Schulz et al., 2010). Further, only three studies assessed intervention fidelity, therefore, we do not know how ACT-compliant the interventions were. This may be linked to our finding of a lack of significant differences in the ACT process measures between intervention and control groups.

The inclusion of follow-up timepoints was variable. Of those that included longer-term follow-up timepoints, this enabled longer-term effects of the intervention to be examined. For example, Giovannetti et al. (2020) reported a "trend" of increasing difference between the ACT vs control group. Future studies would need to consider longer timescales to demonstrate whether efficacy is sustained.

#### **4.2 Strengths and limitations of the review**

Whilst the review was open to including grey literature (and thereby enhancing inclusiveness) all included studies were peer reviewed, introducing potential publication bias towards positive results (Dwan et al., 2008). This is not unexpected, as most RCTs tend to be published in peer-reviewed journals. Hand-searching of reference lists broadened the search strategy, which was developed and tested with a subject-specialist librarian.

We recognise that specifying outcomes of "QoL" and "mood" within the eligibility criteria somewhat limited the number of studies we could include. These, however, are common outcomes of interest for pwMS and clinicians when examining efficacy of psychological interventions, making direct comparisons more coherent. For pwMS, we acknowledge that there are additional outcomes of interest from psychological interventions and ACT research, such as pain and fatigue (Davoodi et al., 2019). Inclusion of these factors would broaden searches further and strengthen the applicability of findings for pwMS.

Only one author (BT) reviewed titles, abstracts and full texts for inclusion, but to reduce potential bias and increase reliability, a second author (AB) supported with uncertainty about inclusion and conducting the meta-analyses. Quality appraisal

analysis was completed by two authors (BT and AB). Despite a standardised tool being used, the subjective nature of the task introduces potential bias. This was minimised by using two independent raters consulting on the quality appraisal. Given the difficulties of blinding within psychological intervention trials, the review could be strengthened by applying the RoB v2 tool with adaptations, as suggested by (Munder & Barth, 2018).

Generalisability of findings is limited due to the small number of studies and the variability across the studies: number of participants varied ( $n = 14$  to 60), different comparators (TAU or RT) and outcome measures. The heterogeneity within the MS population (e.g., severity, duration of living with MS, MS type) should also be acknowledged when generalising findings. The limited number of studies and variable quality within the existing literature, is indicative of the state of the current evidence available, which needs to be addressed by further, fully-powered RCTs, that should include intervention fidelity assessments and outcomes covering adverse effects.

### **4.3 Implications**

Based on our review findings, there may be a use for providing ACT for pwMS to reduce stress, but there is little evidence to support the use of ACT if the objective is to improve QoL or reduce depression or anxiety. However, these findings are based on low-level primary evidence with methodological limitations. Therefore, future research should address these methodological limitations, including prioritising RCT designs, with longer-term follow-up points, including psychometrically-robust ACT process measures, and ensuring an appropriate randomisation method is used and reported. Whilst some studies have used RT as an active control, comparators should also include other psychological interventions, such as CBT, to explore direct comparisons. Crucially, fidelity assessments should be included to ensure credibility of the delivery of the ACT intervention. A cost-effectiveness analysis would also provide a more in-depth understanding of the effectiveness of ACT, particularly from a commissioner and service delivery perspective.

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### **Declaration of conflicting interests**

Bethany Thompson reports no conflicts of interest and completes this work as partial fulfilment of the requirements for a Doctorate in Clinical Psychology at the University of Nottingham and University of Lincoln.

Professor Roshan das Nair (RdN), Dr Nima Moghaddam and Dr Nikos Evangelou (NE) are active researchers in the fields of ACT and MS, and their studies have been included in the systematic literature review. NE has received lecture fees from Biogen and participated in paid advisory board for Biogen, Roche and Merck in

MS, and RdN has received funding to prepare and deliver lectures (speakers bureau) on cognitive rehabilitation and MS and mental health from Novartis, Merck, and Biogen.

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## **Appendices**

### **Appendix A.**

#### **Example search strategy in PsycINFO**

1. DE "Multiple Sclerosis"
2. Multiple sclerosis
3. S1 OR S2
4. DE "Acceptance and Commitment Therapy"
5. Acceptance and commitment\*
6. Acceptance based therap\*
7. Acceptance based behavio\*
8. S4 OR S5 OR S6 OR S7
9. S3 AND S8

**Appendix B.**  
**Data extraction form headings**

Study identification: Authors, title, date, country

Methodology: Design, recruitment, inclusion and exclusion criteria

Sample demographics: Total sample size, age, gender, race/ethnicity, type of MS, attrition

Intervention: Delivery mode, setting, number and length of sessions, administrator, comparison, compliance, fidelity assessment

Outcomes: Measures/subscales used, timepoints, adverse events

Results: Statistical methods used, number of missing participants, between group differences, effect sizes, post- intervention change from baseline

Key findings and additional comments