Psychological treatments for persistent depression: a systematic review and meta-analysis of quality-of-life and functioning outcomes

Authors: Susan McPherson[1] Hugo Senra[1,2]

[1] School of Health and Social Care, University of Essex, U.K. smcpher@essex.ac.uk

[2] Centre for Research in Neuropsychology and Cognitive and Behavioural Intervention (CINEICC), University of Coimbra, Portugal; hgsenra@fpce.uc.pt.

Corresponding Author: Professor Susan McPherson, School of Health and Social Care, University of Essex, Wivenhoe Park, Colchester, CO4 3SQ, United Kingdom

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

Abstract

To date it is unclear whether psychological therapies have potential to improve quality-of-life and functioning in patients with persistent depression. This meta-analysis examines the effect of psychological therapies for improving quality-of-life and functioning in patients with persistent forms of depression. Data sources include Medline and METAPSY, searched 07/2021. Eligible studies were randomised controlled trials where participants had Major Depressive Disorder on entry and met criteria for a persistent form of depression, for example chronic, treatment resistant or recurrent depression. Standardized mean differences (Hedge's *g*) were calculated in random-effects meta-analyses. Fourteen studies met inclusion criteria (N=1898). Psychological interventions were associated with improvements in patients' quality-of-life at the end-of-treatment: pooled *g*=0.24 (95% CI, 0.13-0.34); low to moderate levels of heterogeneity (I^2=0% [95% CI, 0%-41.2%]). Quality-of-life at follow-up: pooled *g*= 0.21 (95% CI, 0.10-0.32); low to high levels of heterogeneity considering the wide confidence intervals for I^2 (I^2=10.36% [95% CI, 0%-77.5%]). The psychological interventions were associated with improvements in patients' functioning at end-of-treatment: pooled *g*=0.35 (95% CI, 0.21-0.48); low to high levels of heterogeneity considering the wide confidence intervals for I^2 (I^2=0% [95% CI, 0%-81.7%]). Functioning at follow-up resulted in: pooled *g*=0.33 (95% CI, 0.15-0.51); low to high levels of heterogeneity considering the wide confidence intervals for I^2 (I^2=0% [95% CI, 0%-86.2%]). This meta-analysis highlights the potential benefits of psychological therapies for improving quality-of-life and functioning in patients with persistent depression, with strongest long-term effects for Mindfulness-Based Cognitive Therapy, Interpersonal Therapy in combination with anti-depression medication, and Long-Term Psychoanalytic Therapy.

Keywords: quality of life; functioning; persistent depression; psychological treatments; systematic review; meta-analysis

Psychological treatments for persistent depression: a systematic review and meta-analysis of quality-of-life and functioning outcomes

Typically, evidence-based guidelines for the treatment of adult depression find fewer efficacious treatments for persistent forms of depression than for acute or first-episode depression. This is likely to be in part because persistent forms of depression are more difficult to treat, are associated with greater comorbidity and have greater adverse impacts on psychological and physical functioning (Jobst et al., 2016) meaning many treatments found to be effective in acute depression do not work as well for this population. This leaves people experiencing persistent forms of depression with less choice of evidence-based treatments. This also means that people may be less likely to be offered psychological treatments because standard forms of psychological intervention are thought to be ineffective and therapeutic relationships considered too difficult to establish (Jobst et al., 2016).

Given that this leaves many people experiencing persistent depression at a disadvantage in relation to choice and availability of evidence-based treatments, it is important to consider carefully how we are assessing the effectiveness of treatments and whether current approaches to determining efficacy give the most helpful indication to patients and practitioners of what might help to relieve some of their suffering.

The World Health Organization ranked depression as the single largest contributor to global disability, having accounted for 7.5% of all years lived with disability (YLD). YLD is a parameter used by the World Health Organization to estimate years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability (World Health Organisation, 2017). Persistent forms of depression can contribute significantly to YLD due to their chronic disabling nature (Friedrich, 2017; Jia & Lubetkin, 2017). Previous randomized controlled trials (RCTs) have highlighted the potential benefits of psychological therapies for patients with depression (Cuijpers et al., 2018). In cases of persistent forms of

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

depression, previous RCTs of psychological interventions have sometimes included measures of health-related quality-of-life as secondary outcome measures. However, to the best of our knowledge no previous meta-analyses have yet examined the effect sizes associated with potential benefits of these interventions for patients' quality-of-life or functioning, which would be of paramount interest for clinical practice.

A previous meta-analysis of 44 trials of psychotherapy for depression reporting quality-of-life data included waitlist or placebo control studies of psychotherapy but excluded studies likely to fall into the category of persistent depression (Kolovos et al., 2016). Similarly, a meta-analysis of 153 trials of pharmacotherapy or psychological therapy examining quality-of-life and functioning outcomes excluded maintenance and continuation therapies (Kamenov et al., 2017). It is useful to look more closely at quality-of-life and functioning outcomes in persistent forms of depression because of the complexity and 'burden' in terms of high rates of suicide, low levels of social and physical functioning, severity, high health care costs and the relatively limited treatments for persistent depression demonstrating efficacy.

While in some contexts, persistent forms of depression are further classified, for example into treatment resistant depression (TRD), chronic depression and so on, international approaches have been moving towards combining these into a wider category of 'persistent depressive disorder' reflecting that there is significant overlap within these sub-classifications (McPherson, 2020). In terms of clinical practice, identifying a single individual as having either chronic depression or TRD is impractical in most clinical settings and can also risk stigmatising patients on account of their 'non-response' in the case of 'treatment-resistance' (Demyttenaere & Van Duppen, 2019). The current review follows the consensus in combining chronic forms of depression into a single category of persistent depression which follows the DSM 5 criteria for Persistent Depressive Disorder (F 34.1)

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

(American Psychiatric Association, 2013); although we focus on persistent forms of Major Depressive Disorder (MDD) rather than the milder variant of dysthymia (discussed further below).

Quality-of-life and functioning have sometimes been lumped together and sometimes differentiated. One example of differentiation is the defining of functioning as "performance in daily or social activities" versus quality-of-life as "satisfaction with these activities" (Kamenov et al., 2017). In this sense, quality-of-life might be regarded as a more subjective measure and functioning as a more objective measure. Nevertheless, conceptual clarity around the constructs of quality-of-life and functioning has been a longstanding difficulty (Moons et al., 2006). It is conceivable that these two types of outcome could be examined together to provide a more powerful analysis but this may in turn raise issues around the meaning and interpretation of quality-of-life and functioning as subjective versus objective indicators of patient recovery. In this review we have examined the constructs separately. This paper presents findings of a systematic review and meta-analyses of quality-of-life and functioning outcomes in psychological treatments for persistent forms of MDD. In prioritising construct validity (differentiating quality-of-life and functioning and focusing on psychological treatments only), the number of available studies will be significantly reduced but will reduce bias and heterogeneity and therefore provide some useful indications that might help improve patient choice and decision making for a group of patients currently disadvantaged in terms of choice and access.

Method

Design

The current systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews and meta-analyses (Moher et al., 2009). This systematic review is registered with the

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42021265571).

Search Strategy

Two authors conducted a systematic search of Medline as well as "METAPSY", a database of 411 RCTs of psychotherapies for depression maintained by the Vrije Universiteit Amsterdam (see https://evidencebasedpsychotherapies.shinyapps.io/metapsy).

The Medline search (run July 2021, updated April 2022) employed the full Medline search string developed by the METAPSY team (see Supplementary materials 1) with the following extension: AND (quality-of-life OR "quality-of-life" OR functioning) AND (resistan* OR "treatment resistant depression" OR refractor* OR non-respon* OR un-respon* OR TRD OR fail* OR inadequate OR difficult OR intractable OR chronic* OR persistent OR recurrent). The search was limited to RCTs with no time limit. All study titles in the METAPSY database were searched using Excel search function for the terms chronic, resistant, resistan, non-respons, TRD, refractory, recurrent, intractable or difficult.

Other sources were also searched including:

1. The 2017 NICE guideline draft update documentation for "further-line treatments" (Appendix J5) and "chronic depression" (Appendix J6) (National Institute for Health and Care Excellence, 2017);
2. Studies includes in recent systematic reviews of related topics (Cuijpers et al., 2010; Jobst et al., 2016; Spijker et al., 2013; Strawbridge et al., 2019); and
3. Searching of reference lists of articles addressing the topic.

We followed Cochrane guidelines for systematic reviews to select studies (Higgins et al., 2021). Two authors independently reviewed titles and abstracts and then the full-text articles to identify eligible studies. Results of both researchers were compared, and non-eligible studies and duplicates were excluded. The same researchers then read the abstracts of

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

the remaining article titles to determine whether they met the inclusion criteria. Abstracts providing sufficient detail for exclusion were removed, and the remaining full-text articles were retrieved to be fully analysed. Full-text articles were read to determine inclusion, and disagreements were resolved via consensus. See Figure 1 for PRISMA flowchart.

Study details were extracted and summarized (see Table 1).

Inclusion and Exclusion Criteria

Only RCTs were included in our review, as albeit not without critique, RCTs tend to be considered a more reliable and less biased analysis of treatments effect, in comparison with other research designs (Sullivan, 2011). RCTs were included that examined the efficacy of psychological interventions for chronic, treatment-resistant or recurrent depression. For the purpose of the review, participants had to have persistent MDD at entry into the randomised study according to DSM-5 (American Psychiatric Association, 2013), ICD-11 (World Health Organisation, 2018) or similar criteria. To be included, studies had to provide clear indication of a persistent form of MDD, for example a formal diagnosis of chronic or recurrent depression; or study entry criteria which required participants had a chronic course of depression (minimum 2 years) and/or treatment resistance (failed response to at least two treatments). Studies where participants had a dysthymic history were included but as above, participants had to have a diagnosis of MDD at study entry. In the most recent version of DSM, dysthymia was consolidated into the single diagnostic category of persistent depressive disorder (F34.1) along with long-term forms of MDD which are more severe. In previous versions of DSM, “dysthymia” fell into a separate category owing to it being a distinctly mild form of long-term depression and therefore distinct from MDD in terms of severity. Because in the current meta-analysis we wanted to avoid comparing psychotherapy for mild depression with psychotherapy for more severe forms of depression (MDD), studies were included only if the majority of participants (at least 80%) scored for MDD at entry to the

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

trial and were therefore experiencing an episode of MDD at the time treatment was initiated.. We included studies that recruited participants of any gender aged 18 or older.

As this systematic review is focussed on quality-of-life and functioning outcomes, eligible studies must have included a standardised and validated measure of quality-of-life and/or functioning. Although there is no universal definition for quality-of-life, as a general reference we were informed by the World Health Organization's definition: "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (World Health Organisation, 2012). This incorporates several dimensions generally assessed using subjective self-report tools covering perceptions of or satisfaction with physical health, psychological state, level of independence, social relationships and so on. Common measures were the Quality-of-life Enjoyment and Satisfaction Questionnaire (QLESQ); World Health Organization Quality-of-life Assessment (WHOQOL); EuroQol 5-dimensions (EQ-5D); and the Short-Form Survey (SF-12/36). Functioning in the context of outcome measurement is often used synonymously with quality-of-life by study authors and often covers similar domains but tends to be concerned with an assessment of social, physical, occupational or psychological functioning in an objective sense as opposed to the person's satisfaction or perception of it. Common measures were the Global Assessment Functioning Scale (GAF); and Range of Impaired Functioning Tool (Life-RIFT). Measures were only included which had reasonable psychometric properties and were well established and widely used. Some studies reported data from more than one quality-of-life or more than one functioning measure. In these cases we identified the most commonly used measures across the studies and used the most commonly available measure to improve consistency. For example, the GAF was the most commonly used functioning scale so if a study reported GAF data as well

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

as data from another functioning measure, we used the GAF data for the meta-analysis. See Table 1 for details of measures used in each study.

Studies must have included at least one psychological treatment arm. Psychological treatments are defined as treatments applying a psychological theory or theories as a core component of the treatment model. All forms of psychological therapy were eligible (face-to-face and remote therapies; group and individual therapies) as long as the treatment was clearly described, based on psychological theory(ies) and overseen or delivered by certified mental health practitioners (e.g. psychotherapist, psychiatrist, psychologist) and individual level data had been collected and reported. Psychological treatments could be delivered in combination with other treatments. All arms of the study involving a single psychological treatment or a combined treatment were included, as long as they had included a comparator. The comparators allowed were "no treatment", "waiting-list", "treatment as usual", "only anti-depressant medication", "psychological or pill placebo", or any type of active control as long as it did not include a formal psychotherapy or psychological treatment.

We excluded studies of children or adolescents (<18 years of age); and studies including patients with bipolar disorder or psychosis. Studies where patients had comorbid physical illness or other mental health diagnosis were included as long as they met the criteria for persistent depression. All study settings were considered for this review.

Data Extraction

Both authors independently extracted data from articles. The following data were extracted: country in which the study was conducted; year of publication; sample size at baseline, end-of-treatment, and follow-up; percentage of female participants; participants' mean age; study setting; number and percentage of individuals who dropped out, or were lost during the treatment and during the follow-up; number of treatment sessions; treatment duration (in weeks); follow-up duration (in weeks); psychological treatment; control /

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

comparator condition; quality-of-life measure, functioning measure (see Table 1). Baseline, end-of-treatment and follow-up mean, standard deviation and sample size for each quality-of-life and functioning measure were extracted for meta-analysis.

Study Quality

Study quality was independently assessed by both authors for all RCT studies included in this review, using the revised Cochrane risk-of-bias tool for randomized trials (Sterne et al., 2019; RoB2). The Cochrane tool was designed to address several sources of bias including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The tool allowed us to appraise whether the risk of bias for each source of bias is low, high or with some concerns. Ratings were conducted specifically in relation to the outcomes of interest: quality-of-life and functioning.

Statistical Analysis

We used the standardized mean difference (SMD) Hedge's *g* as the effect size because all RCTs included in our meta-analyses assessed differences in outcomes for all patients, using standardized questionnaires. The focus of the meta-analyses was primarily on computing effect sizes for end-of-treatment quality-of-life and functioning outcomes (psychological treatment vs control group), to investigate the effectiveness of psychological treatment for improving patients' quality-of-life and functioning. Secondarily, we have run additional meta-analyses to compute effect sizes for follow-up data on quality-of-life and functioning outcomes (also psychological treatment vs control group). In one of the included studies there were three arms with two different psychological treatments included: Cognitive Behavioural Analysis System of Psychotherapy (CBASP), and Brief Supportive Psychotherapy (BSP) (Kocsis et al., 2009). The CBASP arm was chosen for the meta-analysis examining end-of-treatment functioning outcomes while the BSP arm was included in the meta-analysis conducted as part of our sensitivity analysis.

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

As the follow-up time points differed across studies we used the last available follow-up time point reported in each study. Between-study heterogeneity was measured by computing Cochran's *Q*, I^2, and *H*. Confidence intervals (95%) for I^2 and for *H* were calculated (Higgins & Thompson, 2002). I^2 is commonly interpreted according to thresholds: low heterogeneity (0%-40%); moderate heterogeneity (30%-60%); substantial heterogeneity (50%-90%); high heterogeneity (75%-100%) (Higgins et al., 2021). I^2 should be interpreted with caution as it can be biased when a meta-analysis has few studies (von Hippel, 2015), so *H* is needed to confirm heterogeneity as it does not depend on the number of studies included in the meta-analysis (Higgins & Thompson, 2002). An *H* value of 1 suggests homogeneity and *H* values higher than 1 the presence of heterogeneity (Higgins & Thompson, 2002).

Given the potential for high rates of heterogeneity (Higgins & Thompson, 2002), a random-effects model was used, in which pooled estimated of effect sizes (Hedges' *g*) for quality-of-life and functioning were computed separately with weight estimated via restricted maximum likelihood. Four separate meta-analyses were undertaken to compute effect sizes for: end-of-treatment quality-of-life outcomes; follow-up quality-of-life outcomes; end-of-treatment functioning outcomes; and follow-up functioning outcomes. Meta-analysis, meta-regression, sensitivity analysis and publication bias analysis were undertaken using Comprehensive Meta-analysis Software (Version 3.3) and RStudio software (metafor package).

Meta-regression and Sensitivity Analysis

Meta-regression analysis using a mixed-effect model was conducted to investigate potential factors explaining variance and heterogeneity in our meta-analysis, including number of treatment sessions, and drop-out rate (all covariates were inserted as continuous variables). As meta-regression should not be considered in meta-analysis with fewer than 10 studies (Higgins et al., 2021), we only investigated the effect of covariates for the pool of

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

studies included in the meta-analysis for end-of-treatment quality-of-life outcomes. Sensitivity analysis was undertaken to compute effect sizes for: fixed-effect models; the same meta-analysis without studies with high risk of bias; the same meta-analysis without the study with the smallest sample size; and the meta-analysis of end-of-treatment functioning outcomes when considering the BSP arm from the Kocsis 2009 study (Kocsis et al., 2009).

In this meta-analysis our pool of studies included different types of comparators. Six studies compared the psychological therapy with treatment as usual (TAU) (Cladder-Micus et al., 2018; Fonagy et al., 2015; Morriss et al., 2016; Nakagawa et al., 2017; Souza et al., 2016; Valenstein et al., 2016). In these studies, TAU is described as a condition in which patients can receive any of the following interventions (without specifying): supportive therapy, psychological consultation, psychiatric nurse support, anti-depressant medication (ADM), psychoeducation. There were also two other studies with one of the above comparators although not defined as TAU in these studies: psychoeducation (Chiesa et al., 2015); supportive therapy (Schramm et al., 2017). In four studies, the comparator was ADM (de Mello et al., 2001; Kocsis et al., 2009; Schramm et al., 2008; N. Wiles et al., 2014). The remaining two studies had a waiting list control which did not entail any form of intervention (Harley et al., 2008; Röhricht et al., 2013). Considering the number of trials examined in our meta-analysis and the corresponding comparators included in each trial, we have run three separate sensitivity analyses: studies comparing the psychological therapy with TAU (N=6); studies comparing the therapy with TAU or supportive therapy or psychoeducation (N=8); and the above 8 studies plus those with an ADM control group (N=10). We carried out these sensitivity analyses for end-of-treatment and follow-up timepoints in the quality-of-life meta-analysis. For functioning outcomes we ran only one sensitivity analysis on the larger category (TAU, supportive therapy, psychoeducation or ADM control groups; N=6). This was to avoid an analysis with less than five trials included.

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

Publication Bias

Publication bias was inspected by checking funnel plot asymmetry, and testing for statistical significance with both Egger's regression, and Begg & Mazumdar test, only for meta-analyses including ten or more studies (Higgins et al., 2021). The trim & fill method was also computed as part of the sensitivity analysis to inspect publication bias for meta-analysis examining end-of-treatment and follow-up quality-of-life and functioning outcomes, following previous recommendations (Mavridis & Salanti, 2014).

Results

Study Selection and Characteristics

The study selection process is described in the PRISMA flowchart (Figure 1). We identified 765 articles from the databases and other sources, of which 683 were excluded on the basis of title and abstract review, including exclusion of duplicate articles, leaving 82 articles for full-text revision. After checking the full-texts, we excluded 63 for not meeting eligibility criteria, with a final list of 19 articles to be reviewed representing 14 studies. The main reasons for not meeting the eligibility criteria were: non-RCT studies; studies where participants did not meet criteria for a persistent form of depression or did not have MDD at study entry; studies not providing necessary quality-of-life or functioning outcome data (means, standard deviations and corresponding sample sizes) to enable inclusion in the meta-analysis.

Table 1 summarises the main characteristics of the 14 RCTs included (Chiesa et al., 2015; Cladder-Micus et al., 2018; de Mello et al., 2001; Fonagy et al., 2015; Harley et al., 2008; Hirshberg, 2008; Hollinghurst et al., 2014; Morriss et al., 2016; Nakagawa et al., 2017; Röhricht et al., 2013; Schramm et al., 2008, 2017, 2019; Souza et al., 2016; Valenstein et al., 2016; N. Wiles et al., 2013, 2014; N. J. Wiles et al., 2008, 2016) and refers to studies by first

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

author and year (Total N=1898). See Supplementary Materials 2 for full list of included studies. All studies examined the effect of psychological interventions on middle-aged adults, with the most frequent mean age ranging from 40 to 50 years old. In eleven trials, the sample was mainly composed of females (>50%). Among included RCTs, four were from the UK (N=697 [36.7%)]; three were from the U.S. (N=758 [39.9%)]; two from Germany (N=168); two from Brazil (N=58); and one each from Italy (N=43), Netherlands (N=96), and Japan (N=78). The majority of studies (N=13) were conducted at outpatient mental health settings.

A range of psychological therapies were assessed in the 14 RCTs. Mindfulness Based Cognitive Therapy (MBCT; n=2) is a group therapy including elements of cognitive behavioural therapy along with meditation based skills training. Cognitive Behavioural Therapy (CBT; n=2) is an individual therapy combining principles of cognitive and behavioural psychology; although sometimes delivered remotely or by computer, both studies in the present review involved traditional individual face-to-face CBT. Cognitive Behavioural Analysis System of Psychotherapy (CBASP; n=2) is an individual cognitive behavioural therapy including an interpersonal problem-solving algorithm similar to interpersonal therapy but more structured. Dialectical Behaviour Therapy (DBT; n=1) is a group therapy combining CBT and MBCT along with interpersonal effectiveness skills training. Interpersonal Therapy (IPT; n=3) is an individual therapy focusing on the relationship between the depressive episode and current interpersonal problems. Long-Term Psychoanalytic Psychotherapy (LTPP; n=1) was an individual once weekly psychodynamic psychotherapy over 18 months. Body psychotherapy (BPT; n=1) was in this case a group therapy using body techniques to address psychological distress such as movement strategies, grounding, motor expression of unmet needs and so on. Brief Supportive Psychotherapy (BSP; n=1) "emphasizes the nonspecific or "common" factors assumed to be important ingredients across psychotherapies including reflective listening, empathy, evoking affect,

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

therapeutic optimism, and acknowledgment of patients' assets" (Kocsis et al., 2009). Mutual Peer Support (MPS; n=1) varies in content but in this case involved peer-to-peer telephone support facilitated by professionals; participating peers were trained in expressive-supportive approaches and psychoeducation. The Specialist Depression Service (SDS; n=1) was a collaborative care programme involving CBT combined with pharmacological treatment delivered by a mental health specialist. All psychological treatments followed a manual or treatment guidelines but a minority of studies formally assessed treatments for adherence to the manual (Cladder-Micus et al., 2018; Fonagy et al., 2015; Kocsis et al., 2009; Nakagawa et al., 2017; Schramm et al., 2008). Drop-out rates across studies ranged from 0% to 40%.

Risk of Bias within Studies

The risk of bias assessments are presented in Supplementary Materials 3. Two studies (Cladder-Micus et al., 2018; de Mello et al., 2001) were rated as having high risk of bias. These were both as a result of high risk in the "missing outcome" domain of the RoB2 assessment tool. The source of bias for that domain was identified in both studies for the drop-out rates which were noticeably higher in the IPT group than the control group. Given attending weekly IPT sessions would require a higher level of functioning than the control groups which required less frequent, shorter or less intense sessions, these very different drop-out rates could potentially relate to the outcome of interest. Most other studies were rated as having "some concerns" overall, which were largely owing to concerns in the "missing outcomes" domain and/or the "measurement of outcome" domain. "Missing outcomes" concerns tended to relate to drop-out rates above 5% but where there was no reason to suggest differential drop-out rates by group. In relation to the "Measurement of outcome" domain, the RoB2 manual indicates that there is a risk of bias when "outcome assessors [are] aware of the intervention received by study participants" and where this knowledge *could* influence their rating. Normally "outcome assessors" are part of the

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

research team and this bias can be reduced by blinding research team assessors. However, the RoB2 manual also states that "for participant-reported outcomes, the outcome assessor is the study participant". This means that where the outcome of interest is a self-report tool, we must consider the outcome assessor to be the participant who (in most cases) knows which study group they are in (since it is difficult to disguise from participants that they are in the psychological therapy arm of the trial). All of the quality-of-life measures included were self-report and so where it was clear that the participants would know which trial arm they were in it was necessary to rate this domain as "some concerns".

Synthesis of Results

Overall in this meta-analysis, psychological interventions were associated with improvements in patients' quality-of-life at the end-of-treatment (N=11), with a pooled SMD (Hedges *g*) of 0.24 (95% CI, 0.13-0.34; Figure 2) and low to moderate levels of heterogeneity (Q=5.92, p=0.82; I^2=0% [95% CI, 0%-41.2%]; H=1 [95% CI, 1-1.70]). Analysis of quality-of-life at follow-up (N=9) resulted in a pooled SMD (Hedges *g*) of 0.21 (95% CI, 0.10-0.32; Figure 3) and low to high levels of heterogeneity considering the wide confidence intervals for I^2 and for H (Q=7.76, p=0.46; I^2=10.36% [95% CI, 0%-77.5%]; H=1.12 [95% CI, 1-4.45]).The pooled effect sizes showed a slight decreasing tendency from the end-of-treatment point to the follow-up point (0.237 and 0.210 respectively). However, within this pooled effect, individual therapies show varied trends. CBT shows both small and medium effects which are maintained at follow-up while MPS and CBASP show small effects which deteriorate at follow-up. BPT, LTPP, MBCT, SDS and IPT alone all show medium effect sizes at end-of-treatment. LTPP maintains medium effects at follow-up while effects for SDS and MBCT increase slightly at follow-up. IPT in combination with ADM has a large effect (0.651) which gets larger at follow-up (0.773).

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

The psychological interventions were also associated with improvements in patients' functioning at end-of-treatment (N=7), with a pool SMD (Hedges *g*) of 0.35 (95% CI, 0.21-0.48; Figure 4) and low to high levels of heterogeneity considering the wide confidence intervals for I^2 and for *H* (Q=4.57, *p*=0.6; I^2=0% [95% CI, 0%-81.7%]; *H*=1 [95% CI, 1-5.47]). Analysis of functioning at follow-up (N=5) resulted in a pooled SMD (Hedges *g*) of 0.33 (95% CI, 0.15-0.51; Figure 5) and low to high levels of heterogeneity considering the wide confidence intervals for I^2 and for *H* (Q=3.02, *p*=0.55; I^2=0% [95% CI, 0%-86.2%]; *H*=1 [95% CI, 1-7.26]). Our analysis of functioning outcomes therefore suggests a tendency for a similar effect at follow-up in comparison to end-of-treatment (0.34 to 0.33). Again this masks different trends for different therapies. Three different CBASP trials have both small, medium and large effects at end-of-treatment but the two which report follow-up data show a slight decrease in effect size at follow-up. LTPP has a medium effect size at end-of-treatment which is maintained at follow-up. DBT has a small effect and no follow-up data while SDS has a medium effect at end-of-treatment which decreases at follow-up.

Meta-Regression and Sensitivity Analysis

Meta-regression by number of treatment sessions, and drop-out rates did not significantly affect the overall result of the meta-analysis for end-of-treatment quality-of-life outcomes (Table 2). Sensitivity analysis (see Supplementary Materials 4) shows similar effect sizes and confidence intervals for all analyses run for end-of-treatment quality-of-life outcomes, in comparison to the main analysis. The analysis of quality-of-life outcomes at follow-up when only studies with TAU as comparator were included shows a considerably lower effect size with a confidence interval crossing the line of null effect and a non-significant p-value, in comparison to the main analysis. However, the effect sizes and corresponding confidence intervals got closer to the values found in the main analysis when studies with other comparators were added (supportive therapy and ADM). The sensitivity

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

analysis for the remaining conditions (fixed-effects, high risk of bias, etc) shows similar effect sizes both for quality-of-life and for functioning outcomes.

Risk of Bias across Studies (Publication Bias)

No asymmetry was detected in the funnel plots; P-values from Egger's regression and the Begg & Mazumdar test were non-significant ($p>0.05$), suggesting no evidence of risk of publication bias (see Supplementary Materials 5 and 6). Sensitivity analysis using the trim and fill method also did not suggest risk of publication bias (see Supplementary Materials 7-10).

Discussion

To the best of our knowledge this is the first meta-analysis examining the effect of psychological treatments for persistent depression on quality-of-life or functioning outcomes. In general the results suggest that some psychological therapies might have a beneficial effect on patients' quality-of-life or functioning. The pooled effect size at end-of-treatment and follow-up for quality-of-life outcomes is relatively modest in comparison with previous meta-analyses examining mental health outcomes in relation to psychological therapies for chronic depression (Cuijpers et al., 2010, 2018) suggesting a slight decreasing effect in the follow-up period. Given that our analysis focuses on people who experience persistent forms of depression, the long-term effects are arguably more relevant than end-of-treatment effects in terms of informing patient choice, although the set of studies with long-term follow-up data is unfortunately smaller because of lack of reporting of long-term follow-up data. Studies of MBCT, LTPP and IPT in combination with ADM have the highest effect sizes for quality-of-life and/or functioning at follow-up (all greater than 0.5); while the evidence for CBASP is contradictory.

To date no national guidelines prioritise quality-of-life or functioning outcomes as the basis of treatment recommendations. In terms of recommendations for persistent forms of

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

depression, the latest draft UK national guideline recommends BA alone; or CBT, IPT or Short-Term Psychodynamic Psychotherapy (STPP) alone or in combination with pharmacological treatments and does not mention CBASP (National Institute for Health and Care Excellence, 2021). The American Psychological Association depression guideline recommends IPT, CBT or LTPP for long-term depression in adults and specifically recommends against CBASP (American Psychological Association, 2019). These recommendations are primarily based on evidence from symptom-based reviews although the latest draft NICE guideline has examined some quality-of-life or functioning outcomes for some studies. Should future guideline approaches include quality-of-life and functioning outcomes more systematically then it may be conceivable that patient choice could be improved by including all of these treatments, with the addition of MBCT, and with a more personalised and choice-based approach to determining which treatment might best fit the individual.

While the pooled effect sizes are small to medium, some of the individual effect sizes found in the present meta-analysis are generally of greater magnitude than those found in previous meta-analyses of quality-of-life outcomes for acute depression. Those previous reviews excluded maintenance and continuation treatments and found small and moderate effect sizes only (Kamenov et al., 2017; Kolovos et al., 2016). The medium and large effect sizes in the present review are promising given that psychological interventions have tended to be considered difficult to achieve effects with persistent depression and given the assumption that therapeutic relationships are difficult to achieve with intransient depression (Jobst et al., 2016). However the variability in effect sizes and the overall pooled effects which are small to moderate indicate that there is much more to learn about how to personalise depression care such that we can understand in more detail the likelihood of an individual benefitting from a particular psychological treatment. Taking these findings into

account in treatment recommendations could enable a greater choice of treatments for patients and could enhance personalisation of care for a group of patients for whom there are relatively few evidence based treatments normally recommended and/or available.

A recent international survey shows that service users value several non-symptom outcomes, many of which are reflected in quality-of-life or functioning outcome measures (Chevance et al., 2020). These aspects of treatment effects are particularly relevant to psychological therapy given that effect sizes on symptom outcomes can be similar among different forms of psychological treatments. It is inevitably difficult for patients to be involved in personalised decision making in the absence of clear information about the effectiveness of treatments in terms of the outcomes they value and thus reviews which prioritise those outcomes could help patients make informed decisions.

Having said this, it is important to acknowledge that quality-of-life and functioning measures, even when differentiated from each other, may not fully reflect the outcomes patients are concerned with. There is a large degree of variation in the style and content of different quality-of-life measures meaning that even our focussed approach may not be adequate to inform clear guidelines, patient decision making and personalised care. To inform clinician and patient decision making even better it may also be necessary to take into account findings concerning therapy alliance, therapist experience and patient preference which, combined, may have greater impacts on outcomes than therapy 'brand' (Flückiger et al., 2018; Wampold, 2015). Furthermore, research on patient experience and improved collecting of data on harms and adverse effects in psychological therapies can provide more context on why some individuals might benefit more or less in different ways from different psychological therapies (McPherson et al., 2020). We would suggest that guidelines which aim to improve patient choice and personalised care would need to take all of these different forms of evidence into account and hence expand the range of psychological therapies

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

recommended for persistent forms of depression, offering these significantly disadvantaged patients much greater choice.

Main Limitations

As noted, there are some limitations of having focused on psychological treatments only. However, this allowed us to prioritise construct validity, reflected in low to null between-study heterogeneity at end-of-treatment and follow-up compared to I^2=0.68 found in a previous review which included pharmacotherapy and psychological treatments and lumped quality-of-life and functioning outcomes together (Kamenov et al., 2017). Prioritising construct validity was undertaken with a view to creating an analysis that could inform real clinical practice with patients with persistent depression who would prefer to choose between psychological treatments and whose treatment goals may be specific to their own life satisfaction or functioning. Additional limitations of the approach include the impacts of completer versus intention-to-treat analyses; inflation of effects from non-blinding in psychological therapies; and large variations in duration of follow-up. Further, the number of trials reporting data on quality-of-life and functioning outcomes in relation to the effect of psychological therapies for persistent depression is limited which prevent us drawing stronger conclusions. Of note is that there were several eligible studies which collected quality-of-life or functioning data but did not report the data at all or in a way that was amenable to meta-analysis. Clearly the findings of this review should be interpreted with caution; but this also raises questions about risk of bias assessments for traditional meta-analyses of symptom outcomes in that unreported outcomes could be unreported because they do not show a positive effect – this form of bias would currently go undetected in a meta-analysis of symptom outcomes. Nevertheless, this systematic review indicates that where data are reported, it is possible to look at the effects on quality-of-life and functioning of treatments for persistent forms of depression and to provide some indications concerning a range of

Accepted version. Published version accessed via: https://doi.org/10.1037/pst0000448

psychological treatments which may be beneficial for some patients over the long-term in relation to quality-of-life outcomes.

Conclusions

The present review focused on quality-of-life and functioning outcomes in psychological treatments for persistent depression. Although findings must be treated with caution, there is some preliminary indication that a wider range of psychological therapies could potentially be considered as evidence-based options than those indicated by systematic reviews of symptom outcomes. Specifically, the current review suggests that MBCT, IPT in combination with ADM and LTPP could potentially be considered for treatment recommendations while CBASP requires more research to help understand contradictory findings. Including these treatments as evidence-based options could enable a greater choice of treatments for a patient group that is relatively disadvantaged in terms of choice and access to available evidence based treatments.

References

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

American Psychological Association. (2019). *Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts*. https://www.apa.org/depression-guideline/guideline.pdf

Chevance, A., Ravaud, P., Tomlinson, A., Le Berre, C., Teufer, B., Touboul, S., Fried, E. I., Gartlehner, G., Cipriani, A., & Tran, V. T. (2020). Identifying outcomes for depression that matter to patients, informal caregivers, and health-care professionals: qualitative content analysis of a large international online survey. *The Lancet Psychiatry*, *7*(8), 692–702. https://doi.org/10.1016/S2215-0366(20)30191-7

Chiesa, A., Castagner, V., Andrisano, C., Serretti, A., Mandelli, L., Porcelli, S., & Giommi, F. (2015). Mindfulness-based cognitive therapy vs. psycho-education for patients with major depression who did not achieve remission following antidepressant treatment. *Psychiatry Research*, *226*(2–3), 474–483. https://doi.org/10.1016/j.psychres.2015.02.003

Cladder-Micus, M. B., Speckens, A. E. M., Vrijsen, J. N., T. Donders, A. R., Becker, E. S., & Spijker, J. (2018). Mindfulness-based cognitive therapy for patients with chronic, treatment-resistant depression: A pragmatic randomized controlled trial. *Depression and Anxiety*, *35*(10), 914–924. https://doi.org/10.1002/da.22788

Cuijpers, P., Karyotaki, E., Reijnders, M., & Huibers, M. J. H. (2018). Who benefits from psychotherapies for adult depression? A meta-analytic update of the evidence. *Cognitive Behaviour Therapy*, *47*(2), 91–106. https://doi.org/10.1080/16506073.2017.1420098

Cuijpers, P., van Straten, A., Schuurmans, J., van Oppen, P., Hollon, S. D., & Andersson, G. (2010). Psychotherapy for chronic major depression and dysthymia: A meta-analysis. *Clinical Psychology Review*, *30*(1), 51–62. https://doi.org/10.1016/j.cpr.2009.09.003

de Mello, M. F., Myczcowisk, L. M., & Menezes, P. R. (2001). A randomized controlled trial comparing moclobemide and moclobemide plus interpersonal psychotherapy in the treatment of dysthymic disorder. *The Journal of Psychotherapy Practice and Research*, *10*(2), 117–123. http://www.ncbi.nlm.nih.gov/pubmed/11264335

Demyttenaere, K., & Van Duppen, Z. (2019). The Impact of (the Concept of) Treatment-Resistant Depression: An Opinion Review. *International Journal of Neuropsychopharmacology*, *22*(2), 85–92. https://doi.org/10.1093/ijnp/pyy052

Flückiger, C., Del Re, A. C., Wampold, B. E., & Horvath, A. O. (2018). The alliance in adult psychotherapy: A meta-analytic synthesis. *Psychotherapy*, *55*(4), 316–340. https://doi.org/10.1037/pst0000172

Fonagy, P., Rost, F., Carlyle, J., McPherson, S., Thomas, R., Pasco Fearon, R. M., Goldberg, D., & Taylor, D. (2015). Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the Tavistock Adult Depression Study (TADS). *World Psychiatry*, *14*(3), 312–321. https://doi.org/10.1002/wps.20267

Friedrich, M. J. (2017). Depression Is the Leading Cause of Disability Around the World. *JAMA*, *317*(15), 1517. https://doi.org/10.1001/jama.2017.3826

Harley, R., Sprich, S., Safren, S., Jacobo, M., & Fava, M. (2008). Adaptation of Dialectical Behavior Therapy Skills Training Group for Treatment-Resistant Depression. *Journal of Nervous & Mental Disease*, *196*(2), 136–143. https://doi.org/10.1097/NMD.0b013e318162aa3f

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (Eds.). (2021). *Cochrane Handbook for Systematic Reviews of Interventions* (Version 6.). Wiley.

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, *21*(11), 1539–1558. https://doi.org/10.1002/sim.1186

Hirshberg, D. (2008). "It was bad or it was good:" Alaska Natives in Past Boarding Schools. *Journal of American Indian Education*, *47*(3), 5–30. https://doi.org/https://www.jstor.org/stable/24398766

Hollinghurst, S., Carroll, F. E., Abel, A., Campbell, J., Garland, A., Jerrom, B., Kessler, D., Kuyken, W., Morrison, J., Ridgway, N., Thomas, L., Turner, K., Williams, C., Peters, T. J., Lewis, G., & Wiles, N. (2014). Cost-effectiveness of cognitive–behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: economic evaluation of the CoBalT Trial. *British Journal of Psychiatry*, *204*(1), 69–76. https://doi.org/10.1192/bjp.bp.112.125286

Jia, H., & Lubetkin, E. I. (2017). Incremental decreases in quality-adjusted life years (QALY) associated with higher levels of depressive symptoms for U.S. Adults aged 65 years and older. *Health and Quality of Life Outcomes*, *15*(1), 9. https://doi.org/10.1186/s12955-016-0582-8

Jobst, A., Brakemeier, E.-L., Buchheim, A., Caspar, F., Cuijpers, P., Ebmeier, K. P., Falkai, P., Jan van der Gaag, R., Gaebel, W., Herpertz, S., Kurimay, T., Sabaß, L., Schnell, K., Schramm, E., Torrent, C., Wasserman, D., Wiersma, J., & Padberg, F. (2016). European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe. *European Psychiatry*, *33*, 18–36. https://doi.org/https://doi.org/10.1016/j.eurpsy.2015.12.003

Kamenov, K., Twomey, C., Cabello, M., Prina, A. M., & Ayuso-Mateos, J. L. (2017). The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis. *Psychological Medicine*, *47*(3), 414–425. https://doi.org/10.1017/S0033291716002774

Kocsis, J. H., Gelenberg, A. J., Rothbaum, B. O., Klein, D. N., Trivedi, M. H., Manber, R., Keller, M. B., Leon, A. C., Wisniewski, S. R., Arnow, B. A., Markowitz, J. C., Thase, M. E., & REVAMP Investigators. (2009). Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP Trial. *Archives of General Psychiatry*, *66*(11), 1178–1188. https://doi.org/10.1001/archgenpsychiatry.2009.144

Kolovos, S., Kleiboer, A., & Cuijpers, P. (2016). Effect of psychotherapy for depression on quality of life: meta-analysis. *British Journal of Psychiatry*, *209*(6), 460–468. https://doi.org/10.1192/bjp.bp.115.175059

Mavridis, D., & Salanti, G. (2014). How to assess publication bias: funnel plot, trim-and-fill method and selection models. *Evidence Based Mental Health*, *17*(1), 30–30.

https://doi.org/10.1136/eb-2013-101699

McPherson, S. (2020). A NICE game of Minecraft: philosophical flaws underpinning UK depression guideline nosology. *Medical Humanities*, *46*(3), 162–165. https://doi.org/10.1136/medhum-2019-011658

McPherson, S., Wicks, C., & Tercelli, I. (2020). Patient experiences of psychological therapy for depression: a qualitative metasynthesis. *BMC Psychiatry*, *20*(1), 313. https://doi.org/10.1186/s12888-020-02682-1

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Moons, P., Budts, W., & De Geest, S. (2006). Critique on the conceptualisation of quality of life: A review and evaluation of different conceptual approaches. *International Journal of Nursing Studies*, *43*(7), 891–901. https://doi.org/10.1016/j.ijnurstu.2006.03.015

Morriss, R., Garland, A., Nixon, N., Guo, B., James, M., Kaylor-Hughes, C., Moore, R., Ramana, R., Sampson, C., Sweeney, T., & Dalgleish, T. (2016). Efficacy and cost-effectiveness of a specialist depression service versus usual specialist mental health care to manage persistent depression: a randomised controlled trial. *The Lancet Psychiatry*, *3*(9), 821–831. https://doi.org/10.1016/S2215-0366(16)30143-2

Nakagawa, A., Mitsuda, D., Sado, M., Abe, T., Fujisawa, D., Kikuchi, T., Iwashita, S., Mimura, M., & Ono, Y. (2017). Effectiveness of Supplementary Cognitive-Behavioral Therapy for Pharmacotherapy-Resistant Depression. *The Journal of Clinical Psychiatry*, *78*(8), 1126–1135. https://doi.org/10.4088/JCP.15m10511

National Institute for Health and Care Excellence. (2017). *Depression in adults: treatment and management (update)*. https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0725/documents

National Institute for Health and Care Excellence. (2021). *Depression in adults: treatment and management (update). Draft guidance consultation (November 2021)*. https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0725/documents

Röhricht, F., Papadopoulos, N., & Priebe, S. (2013). An exploratory randomized controlled trial of body psychotherapy for patients with chronic depression. *Journal of Affective Disorders*, *151*(1), 85–91. https://doi.org/10.1016/j.jad.2013.05.056

Schramm, E., Kriston, L., Elsaesser, M., Fangmeier, T., Meister, R., Bausch, P., Zobel, I., Bailer, J., Wambach, K., Backenstrass, M., Klein, J. P., Schoepf, D., Schnell, K., Gumz, A., Löwe, B., Walter, H., Wolf, M., Domschke, K., Berger, M., … Härter, M. (2019). Two-Year Follow-Up after Treatment with the Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy for Early-Onset Chronic Depression. *Psychotherapy and Psychosomatics*, *88*(3), 154–164. https://doi.org/10.1159/000500189

Schramm, E., Kriston, L., Zobel, I., Bailer, J., Wambach, K., Backenstrass, M., Klein, J. P., Schoepf, D., Schnell, K., Gumz, A., Bausch, P., Fangmeier, T., Meister, R., Berger, M., Hautzinger, M., & Härter, M. (2017). Effect of Disorder-Specific vs Nonspecific Psychotherapy for Chronic Depression. *JAMA Psychiatry*, *74*(3), 233. https://doi.org/10.1001/jamapsychiatry.2016.3880

Schramm, E., Schneider, D., Zobel, I., van Calker, D., Dykierek, P., Kech, S., Härter, M., & Berger, M. (2008). Efficacy of Interpersonal Psychotherapy plus pharmacotherapy in chronically depressed inpatients. *Journal of Affective Disorders*, *109*(1–2), 65–73. https://doi.org/10.1016/j.jad.2007.10.013

Souza, L. H., Salum, G. A., Mosqueiro, B. P., Caldieraro, M. A., Guerra, T. A., & Fleck, M. P. (2016). Interpersonal psychotherapy as add-on for treatment-resistant depression: A pragmatic randomized controlled trial. *Journal of Affective Disorders*, *193*, 373–380. https://doi.org/10.1016/j.jad.2016.01.004

Spijker, J., van Straten, A., Bockting, C. L. H., Meeuwissen, J. A. C., & van Balkom, A. J. L. M. (2013). Psychotherapy, Antidepressants, and Their Combination for Chronic Major Depressive Disorder: A Systematic Review. *The Canadian Journal of Psychiatry*, *58*(7), 386–392. https://doi.org/10.1177/070674371305800703

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., … Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*, l4898. https://doi.org/10.1136/bmj.l4898

Strawbridge, R., Carter, B., Marwood, L., Bandelow, B., Tsapekos, D., Nikolova, V. L., Taylor, R., Mantingh, T., de Angel, V., Patrick, F., Cleare, A. J., & Young, A. H. (2019). Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis. *British Journal of Psychiatry*, *214*(1), 42–51. https://doi.org/10.1192/bjp.2018.233

Sullivan, G. M. (2011). Getting Off the "Gold Standard": Randomized Controlled Trials and Education Research. *Journal of Graduate Medical Education*, *3*(3), 285–289. https://doi.org/10.4300/JGME-D-11-00147.1

Valenstein, M., Pfeiffer, P. N., Brandfon, S., Walters, H., Ganoczy, D., Kim, H. M., Cohen, J. L., Benn-Burton, W., Carroll, E., Henry, J., Garcia, E., Risk, B., Kales, H. C., Piette, J. D., & Heisler, M. (2016). Augmenting Ongoing Depression Care With a Mutual Peer Support Intervention Versus Self-Help Materials Alone: A Randomized Trial. *Psychiatric Services*, *67*(2), 236–239. https://doi.org/10.1176/appi.ps.201400454

von Hippel, P. T. (2015). The heterogeneity statistic I2 can be biased in small meta-analyses. *BMC Medical Research Methodology*, *15*(1), 35. https://doi.org/10.1186/s12874-015-0024-z

Wampold, B. E. (2015). How important are the common factors in psychotherapy? An update. *World Psychiatry : Official Journal of the World Psychiatric Association (WPA)*, *14*(3), 270–277. https://doi.org/10.1002/wps.20238

Wiles, N. J., Hollinghurst, S., Mason, V., Musa, M., Burt, V., Hyde, J., Jerrom, B., Lewis, G., & Kessler, D. (2008). A Randomized Controlled Trial of Cognitive Behavioural Therapy as an Adjunct to Pharmacotherapy in Primary Care Based Patients with Treatment Resistant Depression: A Pilot Study. *Behavioural and Cognitive Psychotherapy*, *36*(1), 21–33. https://doi.org/10.1017/S135246580700389X

Wiles, N. J., Thomas, L., Turner, N., Garfield, K., Kounali, D., Campbell, J., Kessler, D., Kuyken, W., Lewis, G., Morrison, J., Williams, C., Peters, T. J., & Hollinghurst, S. (2016). Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBalT randomised controlled trial. *The Lancet Psychiatry*, *3*(2), 137–144. https://doi.org/10.1016/S2215-0366(15)00495-2

Wiles, N., Thomas, L., Abel, A., Barnes, M., Carroll, F., Ridgway, N., Sherlock, S., Turner, N., Button, K., Odondi, L., Metcalfe, C., Owen-Smith, A., Campbell, J., Garland, A., Hollinghurst, S., Jerrom, B., Kessler, D., Kuyken, W., Morrison, J., … Lewis, G. (2014). Clinical effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: the CoBalT randomised controlled trial. *Health Technology Assessment*, *18*(31). https://doi.org/10.3310/hta18310

Wiles, N., Thomas, L., Abel, A., Ridgway, N., Turner, N., Campbell, J., Garland, A., Hollinghurst, S., Jerrom, B., Kessler, D., Kuyken, W., Morrison, J., Turner, K., Williams, C., Peters, T., & Lewis, G. (2013). Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant

depression: results of the CoBalT randomised controlled trial. *The Lancet*, *381*(9864), 375–384. https://doi.org/10.1016/S0140-6736(12)61552-9

World Health Organisation. (2012). *WHOQOL User Manual*. https://www.who.int/publications/i/item/WHO-HIS-HSI-Rev.2012.03

World Health Organisation. (2017). *Depression and Other Common Mental Disorders Global Health Estimates*. https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf

World Health Organisation. (2018). Chapter VIII: Diseases of the nervous system (Others disorders of the nervous system) (ICD-11). In *International Statistical Classification of Diseases and Related Health Problems*. WHO. https://icd.who.int/browse11/l-m/en

Table 1

Study characteristics

Reference	Country	Setting	Mean age (SD)	% Female	Intervention(s): end-of-treatment N	Control Condition: end-of-treatment N	End-of-treatment (weeks)	Drop-out rate (%)	Follow-up (weeks)	QOL measure	Functioning measures
Chiesa 2015	Italy	University Institute of Psychiatry	T:50.9 (11.5) C: 46.7 (10.9)	72	MBCT: 23	EDUC: 20	8	0	26	PGWBI	None
Cladder-Micus 2018	Netherlands	Several mental health services	T: 46.8 (9.5) C: 47.3 (10.9)	62	MBCT: 44	TAU: 52	8	16	24	WHOQOL-BREF	None
Mello 2001	Brazil	Public Hospital	20 to 60 years old*	80	IPT+ADM: 11	ADM: 13	24	31	48	Q-LES-Q	GAF
Fonagy 2015	U.K.	Adult mental health service	T: 42.7 (10.4) C: 46.1 (9.9)	66.5	LTPP: 57	TAU: 54	60	14	104	Q-LES-Q	GAF
Harley 2008	U.S.	Psychiatric outpatient services	41.8**	75	DBT: 10	Wait-list: 9	16	0	None	None	LIFERIFT
Kocsis 2009	U.S.	Eight academic centres	T: 45.9 (11.8) C: 43.2 (13.4)	55	CBASP+ADM: 168 BSP+ADM: 175	ADM: 80	12	13.8	None	None	LIFE-RIFT
Morriss 2016	U.K.	Outpatient mental health services	T: 47 (11.6) C: 46 (11.3)	61	SDS: 78	TAU: 66	52	39.6	78	EQ-5D-3L	GAF
Nakagawa 2017	Japan	University Hospital; Psychiatric hospital	T: 39.5 (9.2) C: 41.7 (10.7)	36	CBT: 39	TAU: 39	16	2.5	12	SF36	None
Rohricht 2013	U.K.	Community mental	T: 46.9 (11.7) C: 48.5 (9.1)	41	BPT: 11	Wait-list: 12	10	21.4	10	MANSA	None

		health services									
Schramm 2017/2019 (a)	Germany	Outpatient mental health services	T: 44.6 (12) C: 45.2 (11.6)	66	CBASP: 121	SP: 110	48	13.8	104	SF12	GAF
Schramm 2008	Germany	Inpatient mental health services	T: 40 (10.8) C: 45.9 (9.4)	66.7	IPT+ADM: 18	ADM+CM: 19	5	9.5	52	None	GAF
Souza 2016	Brazil	Outpatient mental health services	T: 49.2 (12.5) C: 49.3 (12.3)	85	IPT+TAU: 16	TAU: 18	19	5	None	WHOQOL -BREF	None
Valenstein 2015	U.S.	Outpatient mental health services	54.9 (10.9)**	19	MPS: 120	TAU: 206	26	11	52	Q-LES-Q	None
Wiles 2008/2013/ 2014/2016/ Hollinghurst 2014	U.K.	Outpatient mental health services	T: 49.2 (11.9) C: 50 (11.5)	72	CBT+ADM: 206	ADM: 213	18	5.1	52	SF12	None

Notes. Schramm, 2019 is the 2-year follow-up of the RCT Schramm, 2017; T: Treatment group; C: Control group; * mean age not available; ADM: Anti-depressant medication; ** only overall mean age available; BPT: Body Psychotherapy; BSP: Brief Supportive Psychotherapy; CBASP: Cognitive behavioural analysis system of psychotherapy; CBT: Cognitive-Behavioural Therapy; CM: Clinical Management; DBT: Dialectic-Behavioural Therapy; EDUC: Psychoeducation; EQ-5D: EuroQol Quality of Life Index – 5 dimensions; GAF: Global Assessment Functioning Scale; IPT: Interpersonal Psychotherapy; Life-RIFT: Range of Impaired Functioning Tool; LTPP: Long-Term Psychoanalytic Psychotherapy; MANSA: Manchester Short Assessment of Quality of Life; MBCT: Mindfulness-based cognitive therapy; MPS: Mutual Peer Support; PGWBI: Psychological General Well-Being Index; QOL: Quality of Life; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; SDS: Specialist depression service comprising collaborative care involving combined psychological (CBT) and pharmacological treatment delivered by a mental health specialist; SP: supportive psychotherapy; SF-12/36: Short-Form Survey; TAU: Treatment as Usual; WHOQOL-BREF: World Health Organization Quality of Life Scale.

Table 2

Meta Regression

	β (95% CI)	SE	P-value
Intercept	0.222 (-0.296, 0.740)	0.264	0.401
Number of treatment sessions	-0.003 (-0.021, 0.015)	0.009	0.753
Drop-out rates	0.875 (-2.039, 3.790)	1.487	0.556

Note. Model $F_{2,8} = 0.347$; $R^2 = 0$; *P-value* = 0.840; $I^2 = 0\%$; $H^2 = 1$

Figure 1
PRISMA flowchart

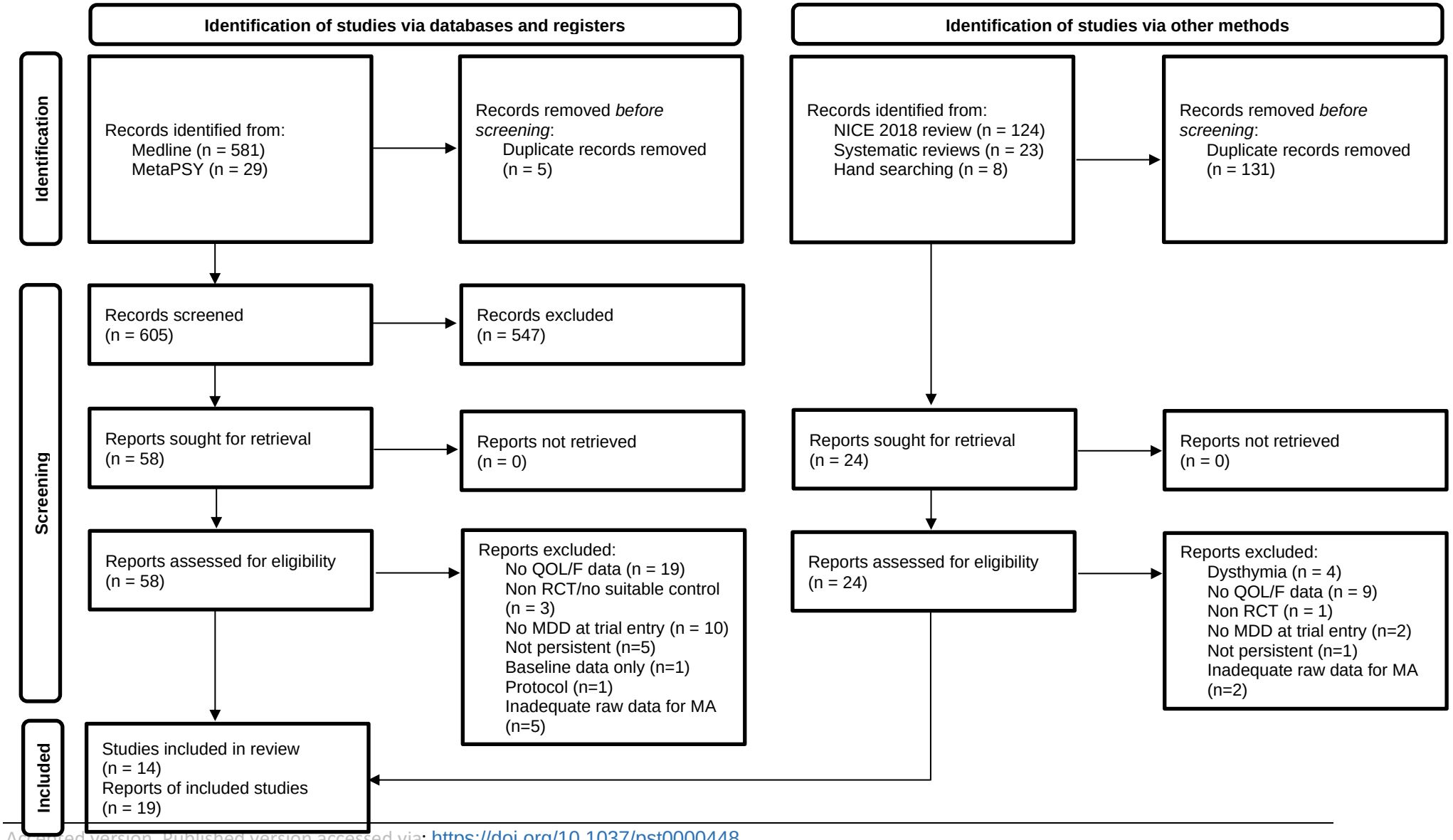

Figure 2

End of treatment forest plot: Quality of life

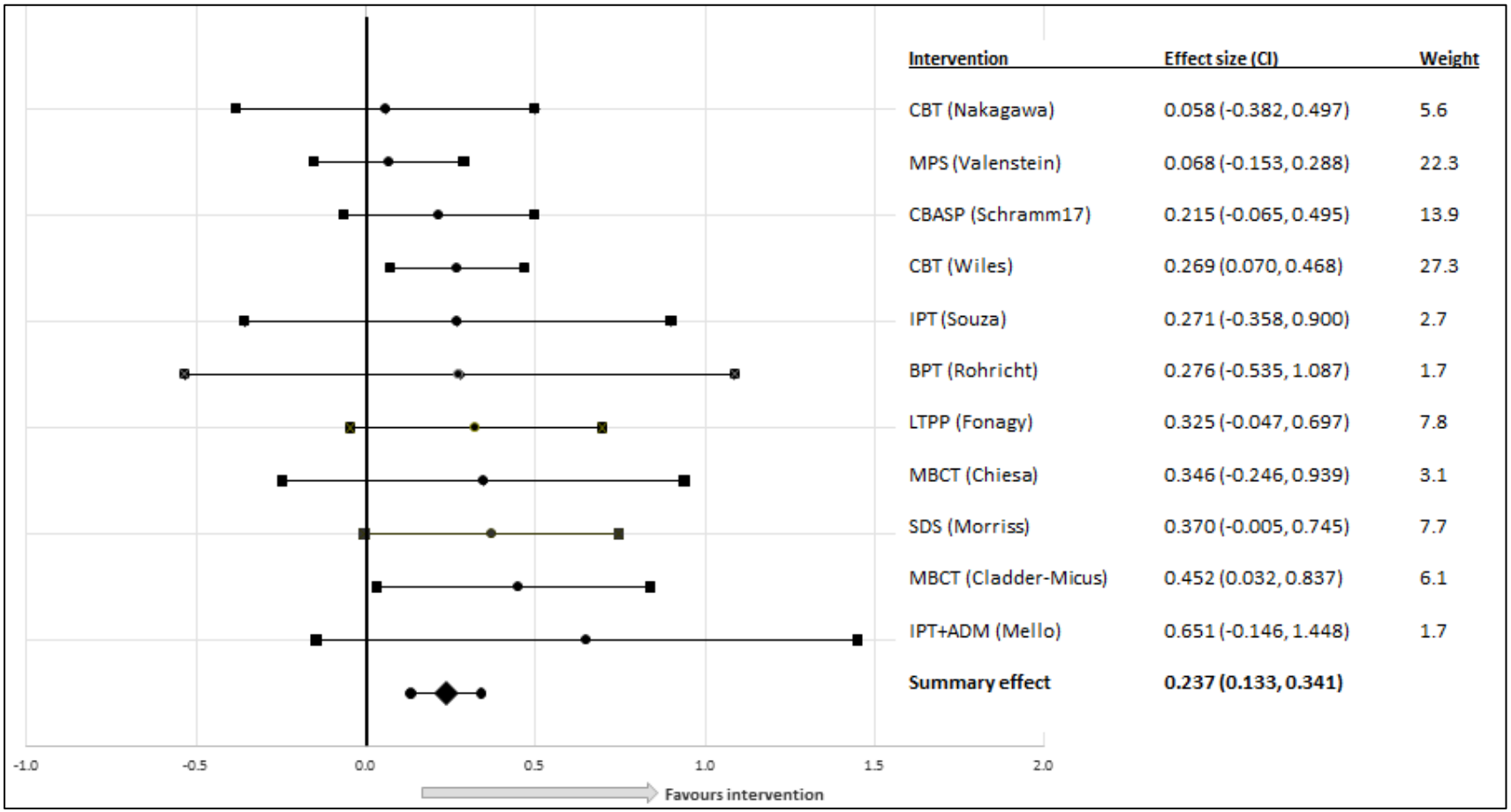

Figure 3

Follow-up forest plot: Quality of life

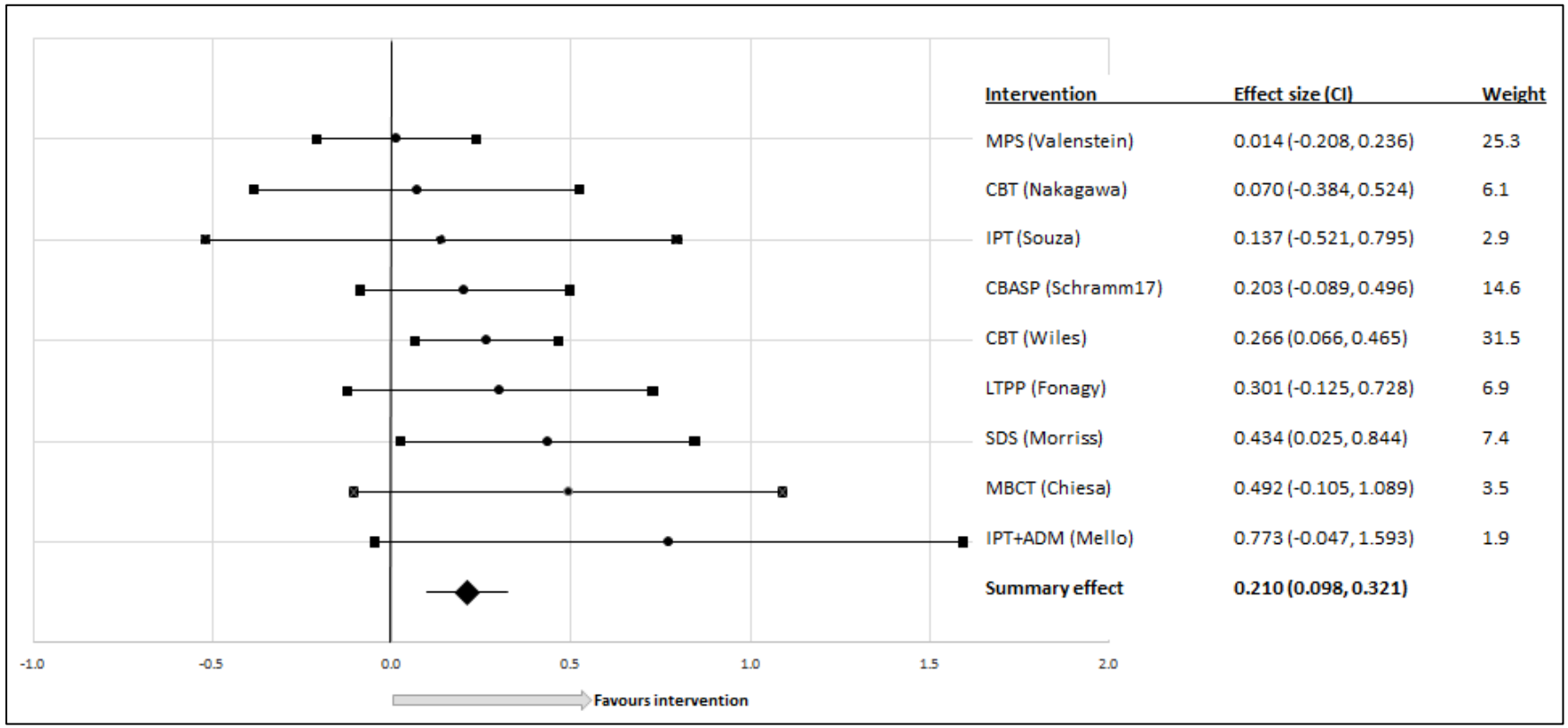

Figure 4

End of treatment forest plot: Functioning

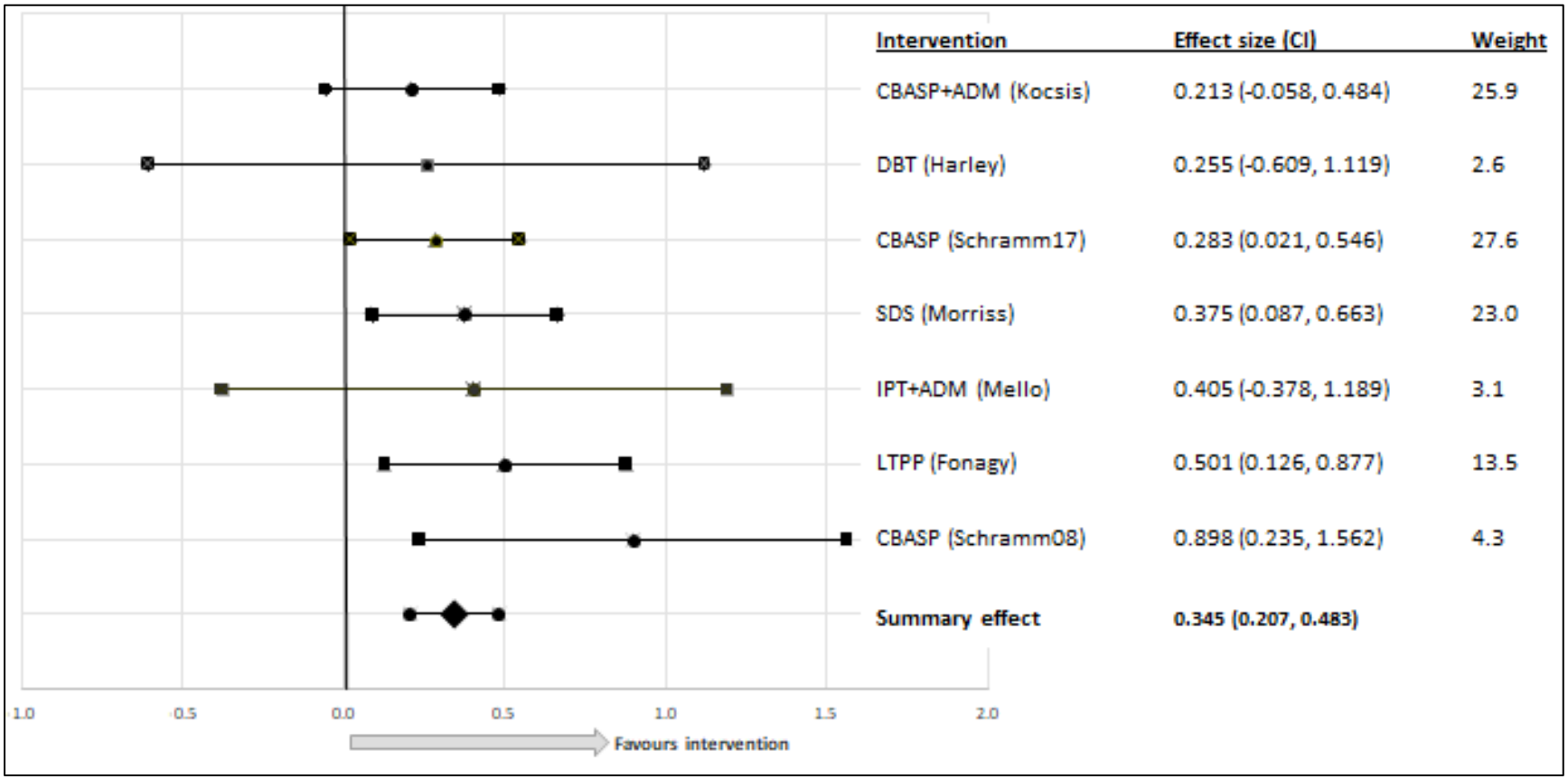

Figure 5

Follow-up forest plot: Functioning