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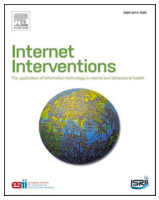

The effect of internet-delivered cognitive behavioral therapy for depression and anxiety on quality of life: A meta-analysis of randomized controlled trials

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ABSTRACT

Although numerous studies have examined the effects of internet-delivered cognitive behavioral therapy (iCBT) for depression and anxiety on quality of life, no meta-analysis has yet been conducted to integrate the results of these studies. We conducted systematic searches in PubMed, Cochrane, and PsycInfo, which included terms for treatment type, modality of delivery, condition, and main outcome. We included studies that met the following inclusion criteria: (a) randomized controlled trials, (b) patients allocated to some form of the control condition, (c) patients receiving some type of treatment of anxiety and/or depression involving Internet-delivered Cognitive Behavioral Therapy, (d) use of a validated outcome measure assessing the level of quality of life, (e) conducted with adult participants diagnosed with anxiety disorder and/or unipolar depression, (f) papers written in English. We analyzed 40 randomized controlled trials with a total of 4289 participants that met inclusion criteria. The pooled between-group effect size for the quality of life overall score was small ($g = 0.35$, 95 % CI: 0.26–0.44, $p = .0001$), favoring iCBT over the control conditions. Regarding the distinct quality of life domains measured by the World Health Organization Quality of Life Assessment, a statistically significant difference between iCBT and control conditions was found only for the physical health domain ($g = 0.56$, 95 % CI: 0.06–1.07, $p = .029$), in favor of iCBT. In both cases, heterogeneity was moderate. While the effect on the quality of life is small (the overall quality of life score) to moderate (the physical health domain score), we conclude that iCBT for depression and anxiety may be a promising approach for improving the quality of life of patients.

1. Introduction

Depression and anxiety are among the most common mental health problems in the world (Whiteford et al., 2015). These disorders are large contributors to the global non-fatal disease burden (James et al., 2018; Whiteford et al., 2015), and are related to massive direct and indirect economic costs (Kessler and Greenberg, 2000; Wang et al., 2003). Moreover, both depression and anxiety are associated with lowered quality of life for individuals living with the conditions (Mendlowicz and Stein, 2000; Papakostas et al., 2004). Despite the large personal and societal costs of depression and anxiety, treatment rates for both disorders in most countries are low (Wang et al., 2007). Also in high-income countries treatment is often provided many years after the onset of the condition (Wang et al., 2005). Therefore, it is important to implement clinically efficacious and cost-effective interventions targeting depression and anxiety. Fortunately, numerous studies have shown that the aforementioned mental disorders can be effectively treated with cognitive behavior therapy (CBT) (Cuijpers et al., 2013; Öst, 2008). However, there are several access barriers to conventional, face-to-face CBT, such as limited accessibility, high cost, and perceived stigma (Gunter and Whittal, 2010; Mohr et al., 2010). Internet-delivered cognitive behavior therapy (iCBT) has been proposed as a potential solution to increase accessibility and reduce the cost of CBT for psychiatric disorders (Andersson, 2016).

ICBT can be delivered with or without the therapist guidance and usually includes the same components as face-to-face CBT. The

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difference is that psychoeducational materials, instructions, homework assignments and the guidance are provided online (Andersson et al., 2017; Hedman et al., 2012). There is strong evidence for the clinical efficacy of iCBT for depression and anxiety disorders (Andersson et al., 2019). What is more, research suggests that iCBT targeting both mental health problems can be cost-effective (Donker et al., 2015) and have enduring effects (Andersson et al., 2018). Whereas in most trials iCBT is compared with waitlist control groups, results of a meta-analysis conducted by Carlbring et al. (2018) suggest that iCBT and face-to-face CBT can be equally effective in treating depression and several anxiety disorders, such as social anxiety disorder, panic disorder, spider phobia, and snake phobia. To sum up, based on the results of recent meta-analytic reviews we can conclude that iCBT is effective in reducing symptoms of depression and anxiety (Andersson et al., 2019). However, there is no separate meta-analysis specifically focused on the effect of iCBT for depression and anxiety on another important indicator of treatment efficacy—quality of life.

Quality of life refers to "subjective well-being, life satisfaction, perceptions of social relationships, physical health, economic status, and functioning in daily activities and work" (Hofmann et al., 2014, p. 375). Both depression and anxiety are associated with substantial impairments in quality of life (Mendlowicz and Stein, 2000; Papakostas et al., 2004). Results of a general population survey conducted in Finland indicated that depressive and anxiety disorders accounted for, respectively, 55 % and 30 % of the quality-adjusted life-years loss identified in the study (Saarni et al., 2007). A meta-analysis conducted by Hofmann et al. (2014) showed that CBT for anxiety disorders is effective in improving quality of life and that the modality of delivery was a moderator, with face-to-face individual and group CBT leading to better outcomes than iCBT. However, the aforementioned meta-analysis included studies published up until February 2013, and the number of studies investigating the effects of iCBT has increased rapidly in the past few years (Andersson et al., 2019). A more recent meta-analysis, that encompasses studies published till October 2016, confirmed that CBT for depression was associated with improvements in quality of life. The same study showed that the modality of delivery was not an important moderator. Nevertheless, the studies included in this meta-analysis were labeled as an individual, group, or computer-based CBT, and that the last category differed significantly from iCBT (Hofmann et al., 2017). For example, one of the four studies marked as computer-based examined the efficacy of treatment as usual combined with an interactive instructional program on CD-ROM (Levin et al., 2011). The meta-analytic statistics were not presented for iCBT separately (Hofmann et al., 2017). Therefore, there is a need for a separate meta-analysis synthesizing the effects of iCBT for depression and/or anxiety on quality of life.

Both of the previous meta-analyses (Hofmann et al., 2014, 2017) examined only pre-post effects. The aim of this meta-analysis of randomized controlled trials (RCTs) was to investigate the effect of iCBT for depression and anxiety on quality of life. Initially, we aimed to examine (a) the overall within-group and (b) the overall between-group effects of iCBT for anxiety and depression on quality of life, and to verify (c) the role of potential moderators of the intervention effect (treatment target, duration of the treatment, presence/lack of human support, study quality, type of control group). However, when considering the concerns raised by Cuijpers et al. (2017) we decided not to include pre-post effects in our review. Cuijpers et al. (2017, p. 367) argued that "insofar as possible pre-post SMDs (standardized mean differences) should be avoided because they can contribute to biased outcomes and do not give reliable information about treatment effects". One reason why pre-post SMDs should be avoided is that the baseline and post-test scores are not independent of each other, and the correlation between them is usually not reported. What is even more important with regard to pre-post SMD, is that "it only calculates the change within one group. That means that the pre-post SMD is uncontrolled and it is impossible to disentangle which proportion of the SMD is caused by the intervention and which by natural recovery and other processes" (Cuijpers et al., 2017, p. 365). This becomes particularly problematic when considering depression and other disorders that involve substantial natural or spontaneous change (Cuijpers et al., 2017). Because the between-group SMDs control for such factors, they are a much better choice. Therefore, in our meta-analysis, we focused on the overall between-group effect of iCBT for anxiety and depression on quality of life and potential moderators of this effect.

2. Methods

2.1. Protocol

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A protocol of meta-analysis was prospectively registered using the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42020180558).

2.2. Eligibility criteria

Following the PRISMA guidelines (Moher et al., 2009) we describe inclusion criteria in terms of Participants, Interventions, Comparators, and Outcomes (PICOs), along with criteria for the publication language. We included studies that met the following inclusion criteria:

(a) Randomized controlled trials;
(b) Patients allocated to some form of the control condition (e.g. waitlist, active control group, treatment as usual);
(c) Patients receiving some type of treatment of anxiety and/or depression involving Internet-delivered Cognitive Behavioral Therapy (iCBT);
(d) Use of a validated outcome measure assessing the level of quality of life (e.g. Quality of Life Inventory, EQ-5D; the quality of life does not have to be the primary outcome in the study);
(e) Conducted with adult participants (at or above the age of 18 years) diagnosed with anxiety disorder and/or unipolar depression (disorders confirmed through diagnostic interview or the elevated level of symptoms as indicated by self-report measures);
(f) Papers written in English.

We excluded studies not meeting inclusion criteria, but also pilot studies, feasibility studies, secondary analyses, studies in which the intervention was computerized and not available online, studies on blended treatments, and studies using quality of life measures that assess the quality of life specifically in individuals with certain health problems (e.g. Quality of Life in Epilepsy Inventory, Schröder et al., 2014; Functional Assessment of Cancer Therapy—General, Murphy et al., 2020).

2.3. Search strategy

A search was conducted by two independent assessors (N.M. and A. G.) in May 18, 2020, using three databases: PubMed, Cochrane, and PsycInfo. We compiled search strings of terms for treatment type (e.g. CBT, iCBT, cognitive-behavioral/cognitive-behavioural therapy), modality of delivery (e.g. internet delivered, online, eHealth), condition (e.g. depression, generalized anxiety, social phobia) and main outcome (quality of life). There were no restrictions with regard to the publication date. Our complete electronic search strategy on Cochrane is provided in Appendix A. Moreover, we manually searched for further relevant papers via reference lists of several meta-analyses and systematic reviews related to the topic.

2.4. Study selection and data extraction

We selected studies for inclusion in two steps. In the first step, two

assessors (N.M. and A.G.) screened the titles and abstracts of all papers independently and retained studies that were potentially related to the topic of interest. In the second step, both assessors independently examined full texts of papers to assess their eligibility for inclusion. If two papers reported data from the same trial, the paper providing the most complete data was selected. In the case of a study investigating more than one type of iCBT (e.g. self-help and guided) versus a control group, the different variants of iCBT were included as separate comparisons against the control condition. If the iCBT group was compared with multiple control groups, the most passive control group was chosen as the comparison condition (e.g. waitlist group instead of an attention control group). Any discrepancies between the assessors were resolved through discussion, where necessary with senior researchers (A.M. and G.A.). Both in step 1 and in step 2 we achieved high inter-rater agreement ($\kappa = 1.0$ and $\kappa = 0.91$, respectively). Extracted information included: title, authors, year of publication, the country where the study took place, participants' demographics (sex, age, sample size), treatment target (anxiety and/or unipolar depression), outcome measure, characteristics of the iCBT, duration of the treatment, type of control condition, information for the assessment of the risk of bias, and information for moderation analyses. When relevant data were not reported in the published paper, we contacted the corresponding authors.

2.5. Quality assessment

We evaluated the quality of the included studies using the Cochrane Collaboration's tool (RoB 2) for randomized trials (Sterne et al., 2019). The tool is structured into five bias domains: (a) bias arising from the randomization process, (b) bias due to deviations from intended interventions, (c) bias due to missing outcome data, (d) bias in the measurement of the outcome, and (e) bias in the selection of the reported result. Within each domain, two independent assessors (A.G. and A.M.) answered few signaling questions and, as a result, rated the studies as "low risk of bias", "some concerns", or "high risk of bias". These domain-level judgments led to an overall risk-of-bias judgment for each study.

2.6. Data analysis

Data were analyzed using Comprehensive Meta-Analysis (CMA) version 3. We calculated Hedges' *g* by transforming means, sample sizes, and standard deviations. The primary statistical analysis was a meta-analysis of between-group effects with quality of life as the outcome, using the post-treatment means and standard deviations. Because the number of effect sizes was small, we decided not to examine the between-group effects at longer term follow-up. We followed the cutoffs suggested by Cohen (1998), according to which effect sizes of 0.20 are believed to be small, while effect sizes of 0.50 are medium, and effect sizes of 0.80 are large. In the case of both intention-to-treat and per-protocol data being published, we used the former category in the meta-analysis. In order to avoid the potential risk of unit-of-analysis problem for multi-arm trials, that may arise when we include the same group of participants (e.g. control group) twice in the same meta-analysis, we choose to divide the 'shared' group into two or more to obtain independent comparators in line with recommendations of Higgins et al. (2019). We expected considerable heterogeneity between studies. Therefore, we conducted all pooled analyses using the random effects model, which allows the true effect size could vary from study to study (Borenstein et al., 2010).

We investigated several potential moderators of the effect sizes, such as treatment target (anxiety and/or unipolar depression) and presence/lack of human support. Considering the type of control condition as a potential moderator, we followed the suggestions of Mohr et al. (2009) who divided control conditions into three classes: (a) conditions where the investigator defines and manages the treatment, (b) conditions where the treatment is not determined by the investigator or provided by the study, and (c) no-treatment control conditions. Therefore, in our meta-analysis we labeled control conditions as: active control group, treatment as usual, and waitlist. Duration of treatment was also examined as a potential moderator. Following Păsărelu et al. (2017) we decided to create two categories—short treatments (with <6 modules) and long treatments (consisting of 6 and more modules). Regarding the last potential moderator, study quality, we labeled studies either as high quality (studies that meet at least three quality criteria) or low quality (studies that meet less than three quality criteria). Because all possible moderators that we examined were categorical, we conducted subgroup analyses to test for them. The subgroup analyses were performed according to the mixed-effect model. In this model, the random-effects model is used within subgroups, whereas a fixed-effect model is used across subgroups (Borenstein et al., 2010).

To calculate the heterogeneity of the effect sizes, we used the I^2 statistic. Following Higgins et al. (2003) we assigned adjectives of low, moderate, and high to I^2 values of 25 %, 50 %, and 75 %, respectively. Additionally, we reported Cochran's *Q* statistics. Publication bias was assessed by inspecting the funnel plot, using Egger's test of the intercept, and using the trim and fill method proposed by Duval and Tweedie (2000) implemented in CMA version 3. We also conducted sensitivity analyses to verify whether study quality was related to outcome, by excluding studies rated as "high risk of bias" or "some concerns".

3. Results

3.1. Study selection and characteristics

The literature search resulted in a total of 1581 records. After the deletion of duplicates, 1159 papers were examined using their titles and abstracts. Of these, 116 records were found potentially relevant and assessed for eligibility. A total of 39 papers met all inclusion criteria. One paper described two independent studies, both meeting the inclusion criteria (Furmark et al., 2009). Therefore, a total of 40 RCTs were included in this meta-analysis. Fig. 1 displays the paper inclusion process. Selected characteristics of the studies that were included can be seen in Table 1.

In total, post-treatment data from 2556 participants in iCBT and 1733 participants in the control conditions were available for analysis. All the studies included were published between 2003 and 2019. They were carried out in Australia, Canada, Germany, Ireland, the Netherlands, Romania, South Korea, Sweden, Switzerland, and the USA. In terms of treatment target, patients received iCBT for anxiety disorders in 22 studies, for depression in 14 studies, and for both conditions in 4 studies. When it comes to the control conditions, most of the included studies compared iCBT with waitlist ($k = 21$). Other studies compared it with treatment as usual ($k = 3$), or active control groups, in the form of an online discussion forum/group ($k = 6$)(Andersson et al., 2005; Andersson et al., 2012; Boettcher et al., 2014; Carlbring et al., 2011; Hedman et al., 2011a, 2011b; Johansson et al., 2012), face-to-face individual CBT ($k = 1$) (Carlbring et al., 2005), face-to-face group CBT ($k = 3$) (Andersson et al., 2013; Hedman et al., 2011b; Kiropoulos et al., 2008), applied relaxation ($k = 2$) (Carlbring et al., 2003; Furmark et al., 2009), attention control group ($k = 1$) (Nordgren et al., 2014), mobile interpersonal psychotherapy ($k = 1$) (Dagöö et al., 2014), information-only control group ($k = 1$) (Richards et al., 2006), or e-mail support from a clinician ($k = 1$) (Silfvernagel et al., 2018). The 40 studies included 47 comparisons between some type of iCBT and a control group—seven studies included two comparisons. Number of modules in the interventions ranged from 3 to 15. One study that did not report this number was excluded from the moderator analysis (Tulbure et al., 2018). Most of the iCBT interventions included human support ($k = 37$), while the remaining ones were self-guided ($k = 10$).

As for the quality of life measures, the Quality of Life Inventory (QOLI; Frisch et al., 1992) and the World Health Organization Quality of Life Assessment (WHOQOL-BREF; the WHOQOL Group, 1998), were most frequently used measures. The latter was the only quality of life

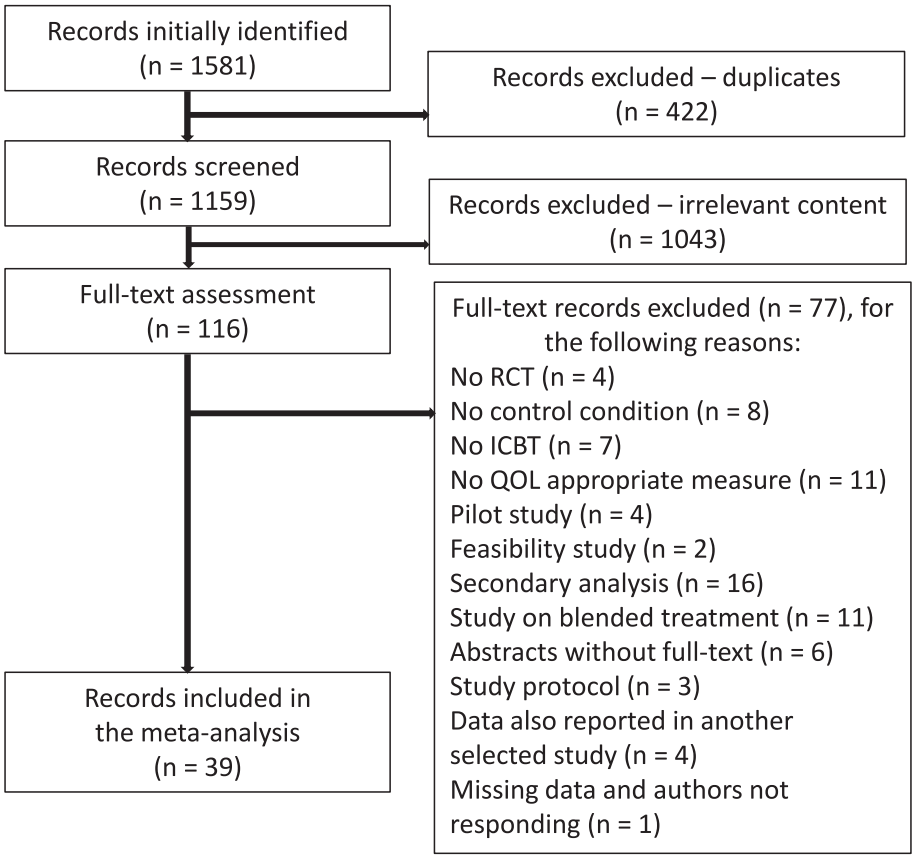

Fig. 1. Flow diagram of study selection process.

measure for which, in most studies, only separate domain means were reported (Jones et al., 2016; Kiropoulos et al., 2008; Loughnan et al., 2019; Pugh et al., 2016; Richards et al., 2006). These domains were: physical health, psychological, social relationships, and environment. WHOQOL-BREF also includes an overall quality-of-life score, which is based on two additional items. Other quality of life measures used in the trials were EuroHis-QOL (Schmidt et al., 2006), EuroQol (EQ-5D; EuroQol-Group, 1990), Short-Form Health Surveys (SF-12 and SF-36; Jenkinson et al., 1997; Ware and Sherbourne, 1992), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993).

3.2. Assessment of quality

Figs. 2 and 3 present the quality of the included studies ($k = 40$). No analyzed research indicated doubts about the reported outcome measurement ($k = 0$). Single studies concerned assessors according to meeting two criteria: deviations from the intended interventions ($k = 1$) and missing outcome data ($k = 1$). For a few studies ($k = 6$) there were some concerns about the randomization process. The biggest issue was the selection of the reported result ($k = 17$) related to the lack of information about the study protocol. Twenty studies met all quality criteria. Two independent reviewers (A.G. and A.M.) assessed research quality according to the Risk of Bias framework (RoB 2, Sterne et al., 2019). Overall assessor's judgment of the study resulted from answering a total of 22 questions in five domains. The inter-rater agreement was 57.50 % ($\kappa = 0.36$; 95 % CI [0.13, 0.60]). Disagreements were discussed till a consensus was reached. No studies were assessed as 'high risk' of bias.

3.3. Pooled post-treatment effects on the quality of life

3.3.1. Post-treatment effect on the quality of life for overall quality of life measures

In 35 RCTs that reported quality of life overall score (42 comparisons, $N = 4001$), iCBT was compared to control conditions at post-treatment. As shown in Fig. 4, the pooled between-group effect size for the quality of life was $g = 0.35$ (95 % CI: 0.26–0.44, $p = .0001$), favoring iCBT over control conditions. Heterogeneity was moderate in the results ($Q(41) = 71.50$, $p = .0001$, $I^2 = 42.66$).

3.3.2. Post-treatment effect on the quality of life for distinct quality of life domains

The World Health Organization Quality of Life Assessment (WHO-QOL-BREF; the WHOQOL Group, 1998) was the only measure for which in most studies authors provided data for distinct quality of life domains (5 RCTs, 6 comparisons, $N = 288$). The heterogeneity among effect sizes was statistically significant ($Q(23) = 49.60$, $p = .001$, $I^2 = 53.63$). A statistically significant difference between iCBT and control conditions was found for the physical health domain ($g = 0.56$, 95 % CI: 0.06–1.07, $p = .029$), in favor of iCBT (see Fig. 5). The pooled between-group effect sizes were $g = 0.359$ (95 % CI: −0.04–0.76, $p = .078$) for the psychological domain, $g = 0.24$ (95 % CI: −0.09–0.58, $p = .158$) for the social relationships domain, and $g = 0.25$ (95 % CI: −0.02– 0.52, $p = .074$) for the environment domain, suggesting no differences between the iCBT and control conditions (see Figs. 6, 7, and 8).

3.4. Moderator analyses

In order to explore possible moderators, subgroup analyses were used in categories such as treatment target (anxiety, depression, or both), presence or lack of human support, type of control condition

Table 1
Selected characteristics of the included studies.

Study name	Total *N*	Treatment target	% F	Age (*M*) [range]	Country	Modules (weeks)	ICBT type	Control condition	Quality of life measures
Andersson et al. (2005)	85	Depression	74	NR [NR]	Sweden	5 (8–10)	Guided iCBT	AC	QOLI
Andersson et al. (2012)	204	Anxiety	61.5	NR [NR]	Sweden	9 (9)	Guided iCBT	AC	QOLI
Andersson et al. (2013)	69	Depression	78.3	42.3 [NR]	Sweden	7 (9)	Guided iCBT	AC	QOLI
Berger et al. (2011)	76	Depression	69.7	38.8 [20–78]	Switzerland	10 (10)	1. Guided iCBT 2. Self–help iCBT	WL	WHOQOL–BREF
Boeschoten et al. (2017)	171	Depression	80.1	48.90 [NR]	Netherlands	5 (5–10)	Guided iCBT	WL	EQ–5D
Boettcher et al. (2014)	91	Anxiety	71.4	NR [NR]	Sweden	8 (8)	Self–help iCBT	AC	QOLI
Boettcher et al. (2018)	209	Anxiety	77	35.40 [NR]	Sweden	9 (6)	1. Self–help iCBT parallel treatment 2. Self–help iCBT sequential treatment	WL	QOLI
Carlbring et al. (2003)	22	Anxiety	68	37.9 [NR]	Sweden	6 (NR)	guided iCBT	AC	QOLI
Carlbring et al. (2005)	49	Anxiety	71	35.0 [NR]	Sweden	10 (10)	Self–help iCBT	AC	QOLI
Carlbring et al. (2006)	60	Anxiety	60	36.7 [NR]	Sweden	10 (10)	Guided iCBT	WL	QOLI
Carlbring et al. (2007)	57	Anxiety	65	NR [19–52]	Sweden	9 (9)	Guided iCBT	WL	QOLI
Carlbring et al. (2011)	54	Anxiety	76	38.8 [22–63]	Sweden	6–10 (10)	Guided iCBT	AC	QOLI
Carlbring et al. (2013)	80	Depression	82.5	44.4 [NR]	Sweden	7 (8)	Guided iCBT	WL	QOLI
Dagöö et al. (2014)	52	Anxiety	51.9	36.81 [20–65]	Sweden	9 (9)	Guided iCBT	AC	QOLI
Dahlin et al. (2016)	85	Anxiety	83.5	39.48 [NR]	Sweden	7 (7–9)	Guided iCBT	WL	QOLI
Dear et al. (2015)	70	Anxiety	60.5	NR [60–81]	Australia	5 (8)	Guided iCBT	WL	EQ–5D
Enrique et al. (2019)	188	Depression	73	39.86 [NR]	Ireland	8 (8)	Guided iCBT	WL	EQ–5D
Farrer et al. (2012)	118	Depression	NR	NR [NR]	Australia	6 (6)	1. Guided iCBT 2. Self–help iCBT	WL	EUROHIS–QOL
Furmark et al. (2009) Study 1	80	Anxiety	67.7	NR [19–69]	Sweden	9 (9)	guided iCBT	WL	QOLI
Furmark et al. (2009) Study 2	58	Anxiety	68	NR [20–63]	Sweden	9 (9)	Guided iCBT	AC	QOLI
Ham et al. (2019)	42	Anxiety & depression	85.7	NR [20–65]	South Korea	5 (10)	Self–help iCBT	WL	SF–36
Hange et al. (2017)	77	Depression	67.5	35.8 [NR]	Sweden	7 (12)	Guided iCBT	TAU	EQ–5D
Hedman et al. (2011a)	81	Anxiety	74	NR [25–69]	Sweden	12 (12)	Guided iCBT	AC	QOLI
Hedman et al. (2011b)	126	Anxiety	35.7	NR [18–64]	Sweden	15 (15)	Guided iCBT	AC	QOLI
Johansson et al. (2012)	121	Depression	71.1	44.7 [20–75]	Sweden	8–10 (10)	1. Guided iCBT standardized treatment 2. Guided iCBT tailored treatment	AC	QOLI
Jones et al. (2016)	46	Anxiety	86.7	NR [60–80]	Australia	7 (7–10)	Guided iCBT	WL	WHOQOL–BREF
Kiropoulos et al. (2008)	86	Anxiety	72.1	38.96 [20–64]	Australia	6 (12)	Guided iCBT	AC	WHOQOL–BREF
Loughnan et al. (2019)	77	Anxiety & depression	100	31.61 [NR]	Australia	3 (4)	Self–help iCBT	TAU	WHOQOL–BREF
McCall et al. (2018)	65	Anxiety	72	21.86 [NR]	Canada	7 (112–168)	Self–help iCBT	WL	Q–LES–Q–SF
Moritz et al. (2012)	210	Depression	78.5	NR [NR]	Germany	10 (8)	Self–help iCBT	WL	WHOQOL–BREF
Nordgren et al. (2014)	100	Anxiety	63	35.4 [NR]	Sweden	7–10 (10)	Guided iCBT	AC	QOLI
Paxling et al. (2011)	89	Anxiety	79.8	39.3 [NR]	Sweden	8 (8)	Guided iCBT	WL	QOLI
Pugh et al. (2016)	47	Depression	100	NR [NR]	Canada	7 (7–10)	Guided iCBT	WL	WHOQOL–BREF
Richards et al. (2006)	32	Anxiety	31.2	36.59 [NR]	Australia	6 (8)	1. Guided iCBT 2. Guided iCBT + stress management	AC	WHOQOL–BREF
Rollman et al. (2018)	704	Anxiety & depression	79.8	42.7 [NR]	United States	8 (8–16)	1. Guided iCBT 2. Guided iCBT + support group	TAU	SF–12 MCS
Silfvernagel et al. (2018)	66	Anxiety & depression	75.8	66.1 [60–77]	Sweden	6–8 (8)	Guided iCBT	AC	QOLI
Titov et al. (2015)	52	Depression	72.7	NR [61–76]	Australia	5 (8)	Guided iCBT	WL	EQ–5D
Tulbure et al. (2018)	79	Depression	82.3	32.05 [NR]	Romania	9 (NR)	1. Guided iCBT 2. Guided religious iCBT	WL	QOLI

(*continued on next page*)

Table 1 (*continued*)

Study name	Total *N*	Treatment target	% F	Age (*M*) [range]	Country	Modules (weeks)	ICBT type	Control condition	Quality of life measures
Vernmark et al. (2010)	58	Depression	68.2	36.82 [19–69]	Sweden	7 (8)	Guided iCBT	WL	QOLI
Warmerdam et al. (2008)	253	Depression	71.1	45 [NR]	Netherlands	5–8 (5–8)	1. Guided iCBT 2. PST	WL	EQ–5D

Notes: Total *N* = sample size of all conditions included in the analyses, % F = percentage of female participants in total sample, Age = age in total sample, *M* = mean, NR = not reported, ICBT = Internet–delivered Cognitive Behavioral Therapy, PST = Problem Solving Therapy AC = active control, WL = waitlist, TAU = treatment as usual, QOLI = Quality of Life Inventory, WHOQOL–BREF = World Health Organization Quality of Life Assessment, EQ–5D = EuroQol, EUROHIS–QOL = EUROHIS–QOL (full name), SF–12 = Short-Form Health Survey (12 items), SF–36 = Short-Form Health Survey (36 items), Q–LES–Q–SF = Quality of Life Enjoyment and Satisfaction Questionnaire.

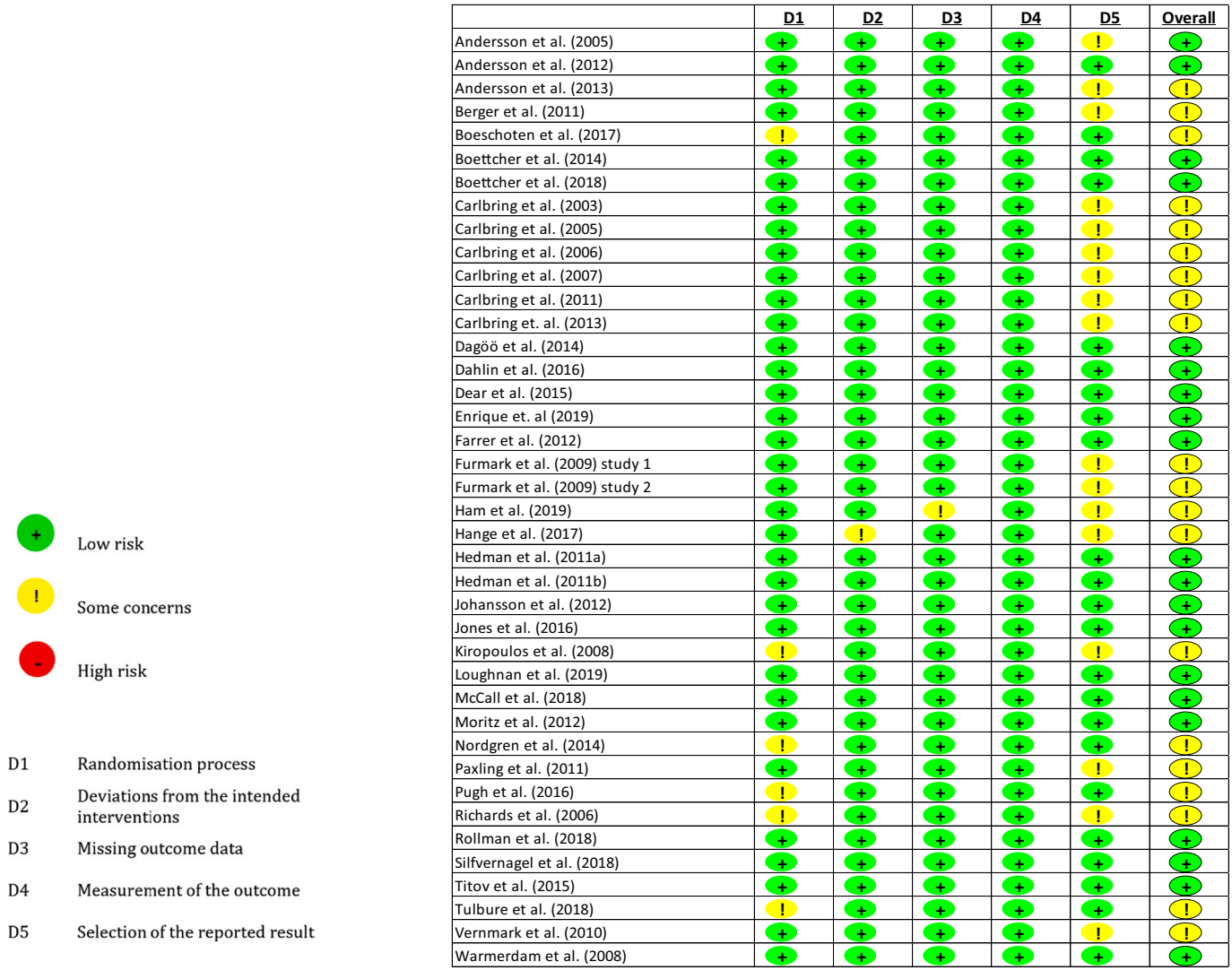

Fig. 2. Risk of bias assessment of included RCTs.

(waitlist, active control group, or treatment as usual), duration of treatment (short or long). Because all studies included in the meta-analysis meet at least three quality criteria and were labeled as high quality, we did not perform subgroup analysis with study quality as a potential moderator.

3.4.1. *Moderator analyses for overall quality of life measures*

With regard to the overall quality of life measures, all of the investigated moderators, namely treatment target ($Q_{bet} = 0.79$, $df = 2$, $p = .675$), presence or lack of human support ($Q_{bet} = 0.01$, $df = 1$, $p = .919$), type of control condition ($Q_{bet} = 2.41$, $df = 2$, $p = .300$), and duration of treatment ($Q_{bet} = 0.17$, $df = 1$, $p = .675$), proved to be non-significant (see Table 2). As seen in Table 2 the effect was not statistically significant in the group of RCTs targeting both anxiety and depression ($g = 0.25$, 95 % CI: −0.02–0.53, $p = .074$), but was statistically significant in the other two groups, targeting only anxiety ($g = 0.39$, 95 % CI: 0.25–0.52, $p = .0001$), or only depression ($g = 0.34$, 95 % CI: 0.20–0.48, $p = .0001$). However, this does not suggest that the effect size was significantly smaller in this group, because the between-group difference was not significant ($Q_{bet} = 0.79$, $df = 2$, $p = .675$). The effect was

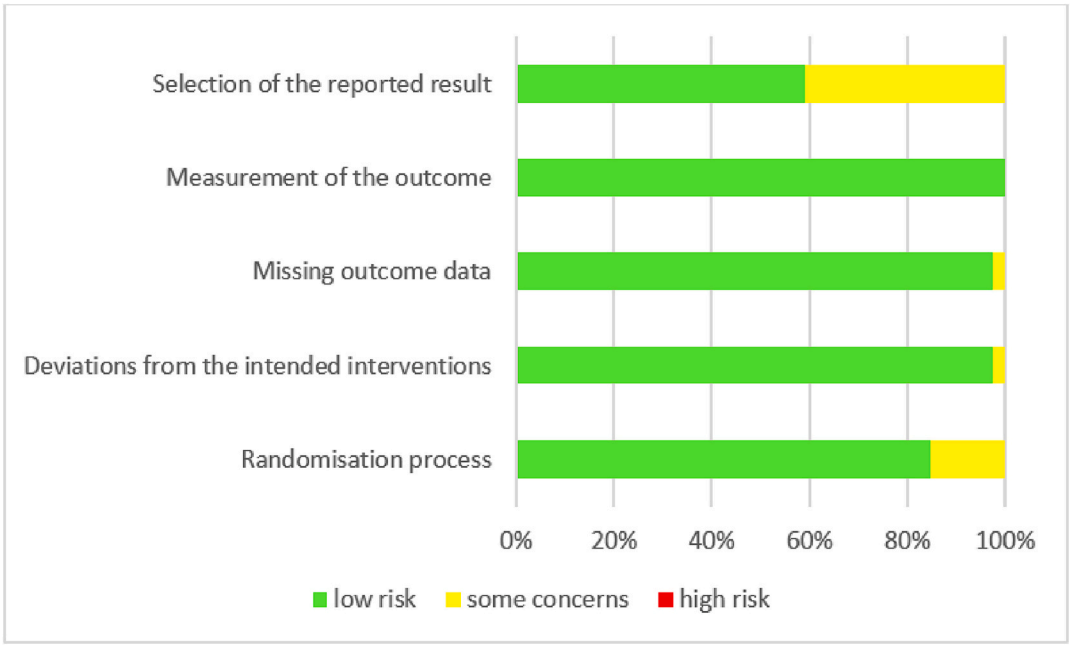

Fig. 3. Risk of bias assessment of included RCTs presented as percentages.

Study name	Comparison	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Andersson et al. (2005)	iCBT vs active control	0,321	0,219	0,048	-0,108	0,750	1,467	0,142
Andersson et al. (2012)	iCBT vs active control	0,282	0,140	0,020	0,007	0,557	2,011	0,044
Andersson et al. (2013)	iCBT vs active control	0,406	0,241	0,058	-0,066	0,878	1,686	0,092
Berger et al. (2011)	iCBT guided vs waitlist	0,984	0,353	0,125	0,291	1,676	2,784	0,005
Berger et al. (2011) (2)	iCBT self-help vs waitlist	0,556	0,341	0,116	-0,112	1,224	1,632	0,103
Boeschoten et al. (2017)	iCBT vs waitlist	-0,199	0,153	0,023	-0,498	0,100	-1,304	0,192
Boettcher et al. (2014)	iCBT vs active control	0,395	0,210	0,044	-0,016	0,807	1,883	0,060
Boettcher et al. (2018)	iCBT parallel vs waitlist	0,324	0,207	0,043	-0,081	0,729	1,568	0,117
Boettcher et al. (2018) (2)	iCBTsequential vs waitlist	0,153	0,208	0,043	-0,254	0,561	0,738	0,460
Carlbring et al. (2003)	iCBT vs active control	-0,295	0,413	0,170	-1,104	0,514	-0,715	0,474
Carlbring et al. (2005)	iCBT vs active control	0,204	0,282	0,079	-0,349	0,756	0,722	0,470
Carlbring et al. (2006)	iCBT vs waitlist	0,432	0,258	0,067	-0,074	0,937	1,675	0,094
Carlbring et al. (2007)	iCBT vs waitlist	0,384	0,264	0,070	-0,133	0,901	1,454	0,146
Carlbring et al. (2011)	iCBT vs active control	0,684	0,276	0,076	0,143	1,225	2,477	0,013
Carlbring et. al. (2013)	iCBT vs waitlist	0,018	0,221	0,049	-0,416	0,452	0,080	0,936
Dagöö et al. (2014)	iCBT vs active control	0,366	0,276	0,076	-0,175	0,906	1,326	0,185
Dahlin et al. (2016)	iCBT vs waitlist	0,123	0,215	0,046	-0,298	0,545	0,573	0,567
Dear et al. (2015)	iCBT vs waitlist	0,645	0,243	0,059	0,169	1,122	2,656	0,008
Enrique et. al (2019)	iCBT vs waitlist	0,249	0,146	0,021	-0,037	0,535	1,707	0,088
Farrer et al. (2012)	iCBT guided vs waitlist	0,477	0,279	0,078	-0,070	1,023	1,710	0,087
Farrer et al. (2012) (2)	iCBT self-help vs waitlist	0,772	0,297	0,088	0,190	1,354	2,599	0,009
Furmark et al. (2009) study 1	iCBT vs waitlist	0,468	0,225	0,050	0,028	0,909	2,087	0,037
Furmark et al. (2009) study 2	iCBT vs active control	-0,234	0,260	0,068	-0,744	0,275	-0,900	0,368
Ham et al. (2019)	iCBT vs waitlist	0,523	0,308	0,095	-0,081	1,127	1,698	0,090
Hange et al. (2017)	iCBT vs TAU	-0,064	0,230	0,053	-0,515	0,387	-0,280	0,780
Hedman et al. (2011a)	iCBT vs active control	0,724	0,227	0,052	0,279	1,170	3,185	0,001
Hedman et al. (2011b)	iCBT vs active control	0,301	0,178	0,032	-0,048	0,650	1,691	0,091
Johansson et al. (2012)	iCBT standardized vs active control	0,302	0,267	0,072	-0,223	0,826	1,128	0,259
Johansson et al. (2012) (2)	iCBT tailored vs active control	0,247	0,268	0,072	-0,279	0,772	0,920	0,357
McCall et al. (2018)	iCBT vs waitlist	0,145	0,246	0,061	-0,337	0,628	0,591	0,555
Moritz et al. (2012)	iCBT vs waitlist	0,389	0,139	0,019	0,117	0,662	2,805	0,005
Nordgren et al. (2014)	iCBT vs active control	1,370	0,221	0,049	0,937	1,803	6,205	0,000
Paxling et al. (2011)	iCBT vs waitlist	0,508	0,214	0,046	0,090	0,927	2,379	0,017
Rollman et al. (2018)	iCBT vs TAU	0,190	0,153	0,023	-0,109	0,489	1,245	0,213
Rollman et al. (2018) (2)	iCBT+ support group vs TAU	0,209	0,151	0,023	-0,087	0,506	1,382	0,167
Silfvernagel et al. (2018)	iCBT vs active control	0,216	0,244	0,060	-0,262	0,694	0,886	0,376
Titov et al. (2015)	iCBT vs waitlist	0,717	0,282	0,080	0,163	1,270	2,538	0,011
Tulbure et al. (2018)	iCBT vs waitlist	0,829	0,332	0,110	0,179	1,479	2,498	0,012
Tulbure et al. (2018) (2)	iCBTreligious vs waitlist	0,756	0,363	0,132	0,043	1,468	2,079	0,038
Vernmark et al. (2010)	iCBT vs waitlist	0,489	0,263	0,069	-0,027	1,004	1,859	0,063
Warmerdam et al. (2008)	iCBT vs waitlist	0,295	0,184	0,034	-0,067	0,656	1,597	0,110
Warmerdam et al. (2008) (2)	iCBT(PST) vs waitlist	0,295	0,186	0,035	-0,070	0,659	1,585	0,113
		0,352	0,046	0,002	0,262	0,443	7,634	0,000

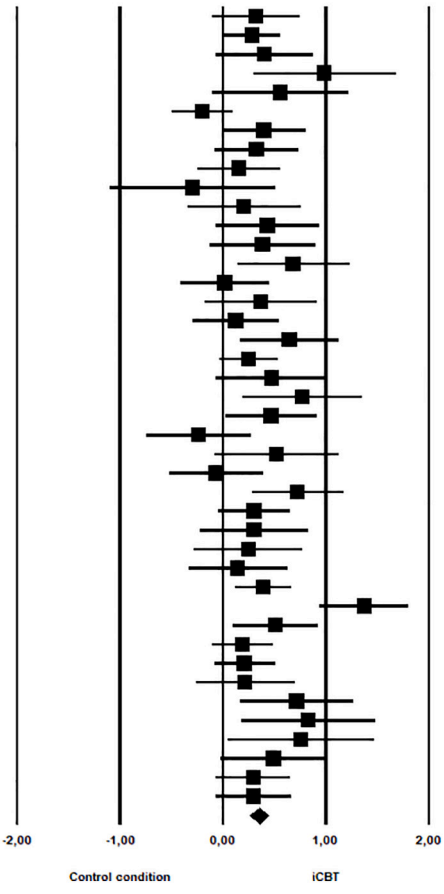

Fig. 4. Forest plot overall quality of life measures.

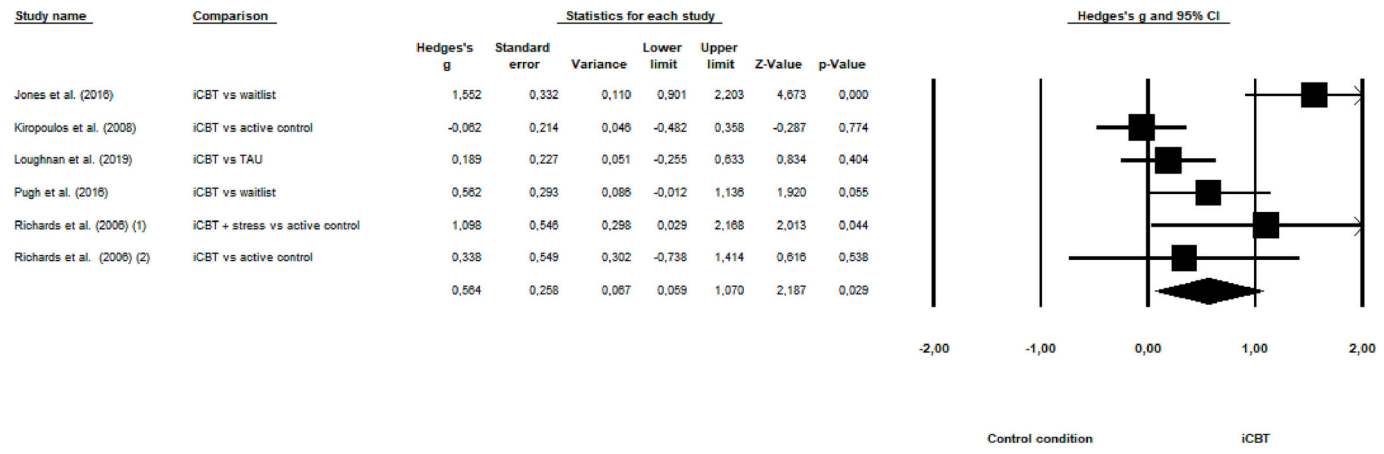

Fig. 5. Forest plot physical health domain of quality of life.

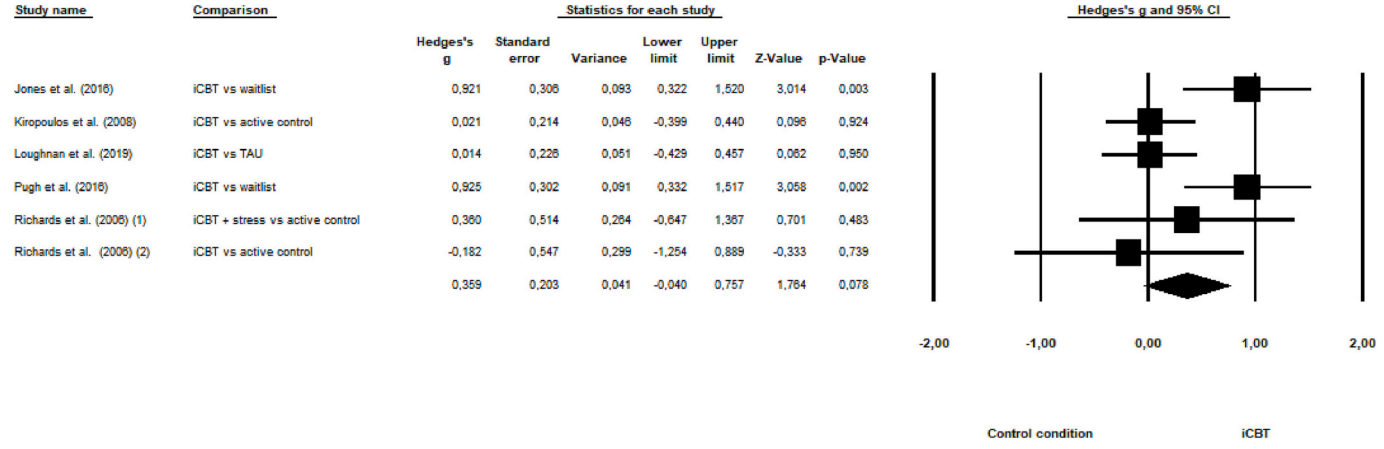

Fig. 6. Forest plot psychological domain of quality of life.

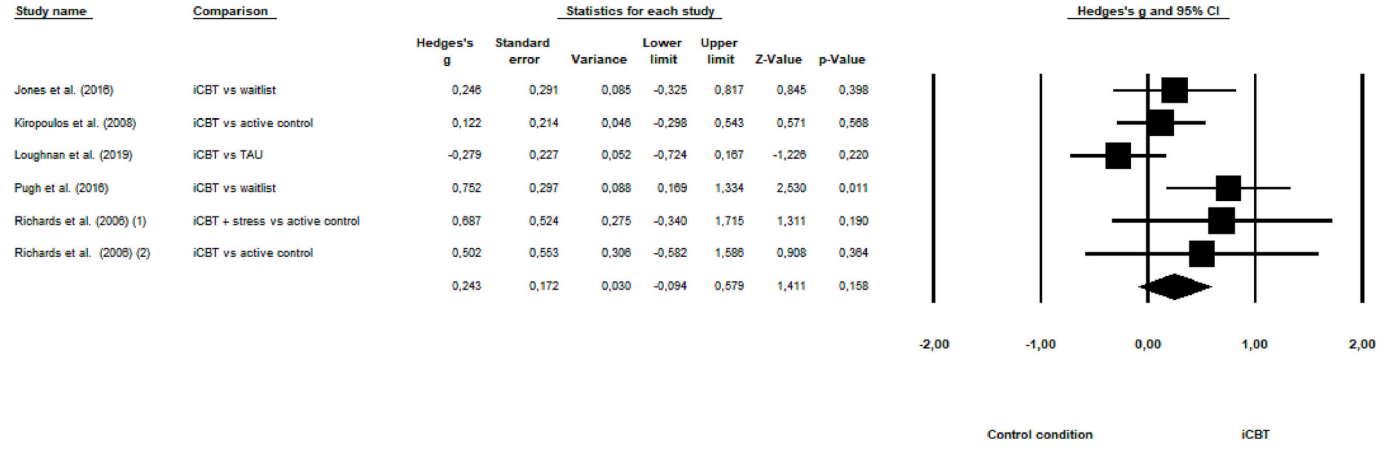

Fig. 7. Forest plot social relationships domain of quality of life.

also not statistically significant for the group of RCTs comparing iCBT with TAU ($g = 0.13$, 95 % CI: −0.16–0.42, $p = .368$), and statistically significant in groups comparing iCBT with an active control group ($g = 0.38$, 95 % CI: 0.23–0.59, $p = .0001$), and a waitlist control ($g = 0.37$, 95 % CI: 0.25–0.49, $p = .0001$). In this case between-group difference was also not statistically significant ($Q_{bet} = 2.41$, $df = 2$, $p = .300$), suggesting that the effect size was not related to the type of control condition in the RCT.

3.4.2. *Moderator analyses for distinct quality of life domains*

Initially, we planned to conduct moderator analyses for the distinct quality of life domains measured by WHOQOL-BREF (the WHOQOL Group, 1998). However, for all of the pre-specified moderators, half or more categories contained fewer than four comparisons, which may be considered too small to allow for subgroup analysis (Fu et al., 2011): treatment target (anxiety: $k = 4$, depression: $k = 1$, both anxiety and depression: $k = 1$), human support (presence of human support: $k = 5$,

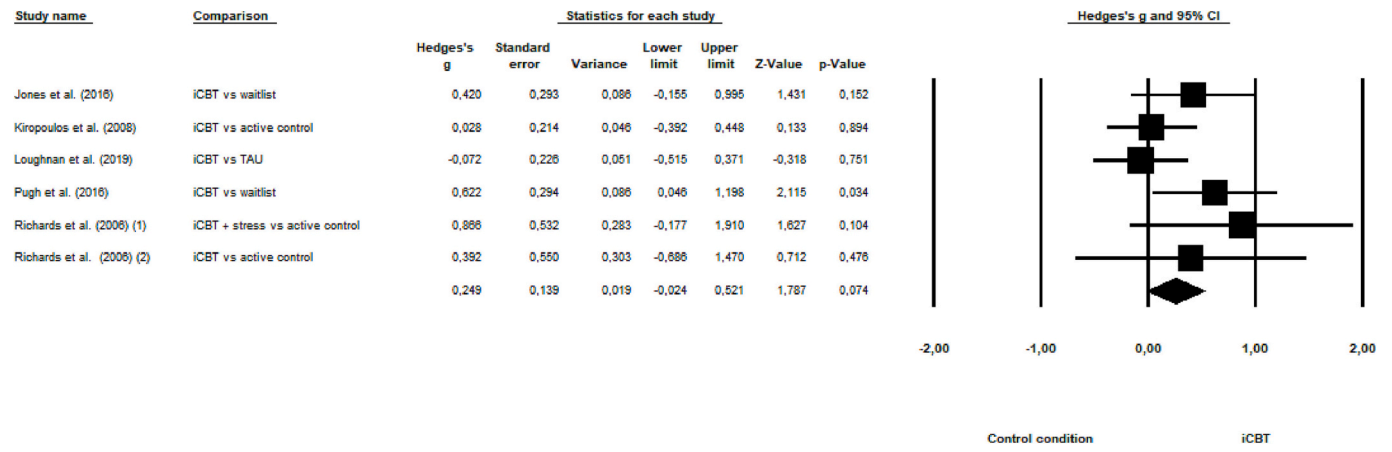

Fig. 8. Forest plot environment domain of quality of life.

Table 2
Moderator analysis—overall quality of life measures.

Moderator	N	g	95 % Cl	Q_{bet}	p
Treatment target					
Anxiety	19	0.387	0.251–0.524	0.787	.675
Depression	19	0.343	0.205–0.481		
Anxiety and depression	4	0.251	−0.024–0.526		
Human support					
Presence of human support	33	0.350	0.248–0.453	0.010	.919
Lack of human support	9	0.362	0.161–0.563		
Type of control condition					
Waitlist	24	0.370	0.249–0.491		
Active control group	15	0.384	0.230–0.538	2.408	.300
Treatment as usual	3	0.134	−0.157–0.425		
Duration of treatment					
Short (<6 modules)	7	0.385	0.154–0.616	0.175	.675
Long (≥6 modules)	33	0.331	0.231–0.432		

Notes: N = number of comparisons; CI = confidence intervals.

lack of human support: $k = 1$), type of control condition (waitlist: $k = 2$, active control group: $k = 3$, treatment as usual: $k = 1$), and duration of treatment (short: $k = 1$, long: $k = 5$). Therefore, we did not conduct the subgroup analysis for the distinct quality of life domains.

3.5. Sensitivity analyses

We conducted sensitivity analyses by excluding studies rated as "high risk of bias" ($k = 0$) or "some concerns" ($k = 20$) (see Fig. 2). Sensitivity analysis for RCTs that reported quality of life overall score (18 RCTs, 23 comparisons) showed that the pooled between-group effect size was $g = 0.32$ (95 % CI: 0.24–0.40, $p = .0001$), favoring iCBT over control conditions (see Fig. 9). Tests of heterogeneity demonstrated that the heterogeneity might not be important ($Q(22) = 13.83$, $p = .907$, $I^2 = 0.000$).

Regarding RCTs assessing the distinct quality of life domains (2 RCTs, 2 comparisons), the heterogeneity among effect sizes was high ($Q(7) = 29.10$, $p = .0001$, $I^2 = 75.948$). Due to high variation in results, we decided not to perform analyses for the distinct quality of life domains (Higgins et al., 2019).

3.6. Publication bias

We examined the funnel plot and conducted Egger's test to assess publication bias with regard to the overall quality of life measures. The studies were not distributed symmetrically (Egger's intercept: 1.659, 95 % CI [0.167–3.15], $t = 2.24$, $p = .03$) suggesting the possibility of a publication bias (see Fig. 10). In the next step, we used the trim and fill method (Duval and Tweedie, 2000) and determined that to make the plot symmetrical 11 studies need to fall to the left of the mean. After adjusting for publication bias by imputing these eleven hypothetical, missing studies, the estimate of the mean effect size comparing iCBT to control condition on quality of life dropped to $g = 0.242$, 95 % CI: 0.14–0.34.

According to Sterne et al. (2011) it is not recommended to use tests for funnel plot asymmetry when the number of studies included in the meta-analysis is <10 as statistical power is usually too low to distinguish chance from real asymmetry. Therefore, we did not assess publication bias for distinct quality of life domains measured by WHOQOL-BREF (the WHOQOL Group, 1998; $k = 6$).

4. Discussion

The goal of our meta-analysis of randomized controlled trials (RCTs) was to investigate the effect of iCBT for depression and anxiety on quality of life. We were mainly interested in (a) the overall between-group effect of iCBT for anxiety and depression on quality of life, and (b) the role of potential moderators of the intervention effect. We included 35 RCTs with 42 comparisons for the quality of life overall score and 5 RCTs with 6 comparisons for distinct quality of life domains measured by the World Health Organization Quality of Life Assessment (WHOQOL-BREF; the WHOQOL Group, 1998). Overall, study quality was moderate, with half of the studies rated "low risk", and the other half "some concerns".

We found a small and statistically significant effect size of the iCBT for depression and anxiety for the quality of life overall score in comparison to the control conditions. We also found a medium effect size for the physical health domain of quality of life. The effect sizes for the other domains (psychological domain, social relationships domain, and environment domain) were not statistically significant, suggesting no difference between the iCBT and control conditions. These results are partially in line with the previous meta-analysis on the effect of CBT for anxiety disorders on quality of life. Taking into account only within-group effects, Hofmann et al. (2014) showed that improvements were greater for physical and psychological domains than for environmental and social domains. In both our and the aforementioned meta-analysis the sample for this sub-analysis was relatively small, and we agree with Hofmann et al. (2014) that we need to be cautious when generalizing the findings.

For the overall quality of life score, all of the investigated moderators were not significant, including treatment target, presence or lack of human support, type of control condition, and duration of treatment. It

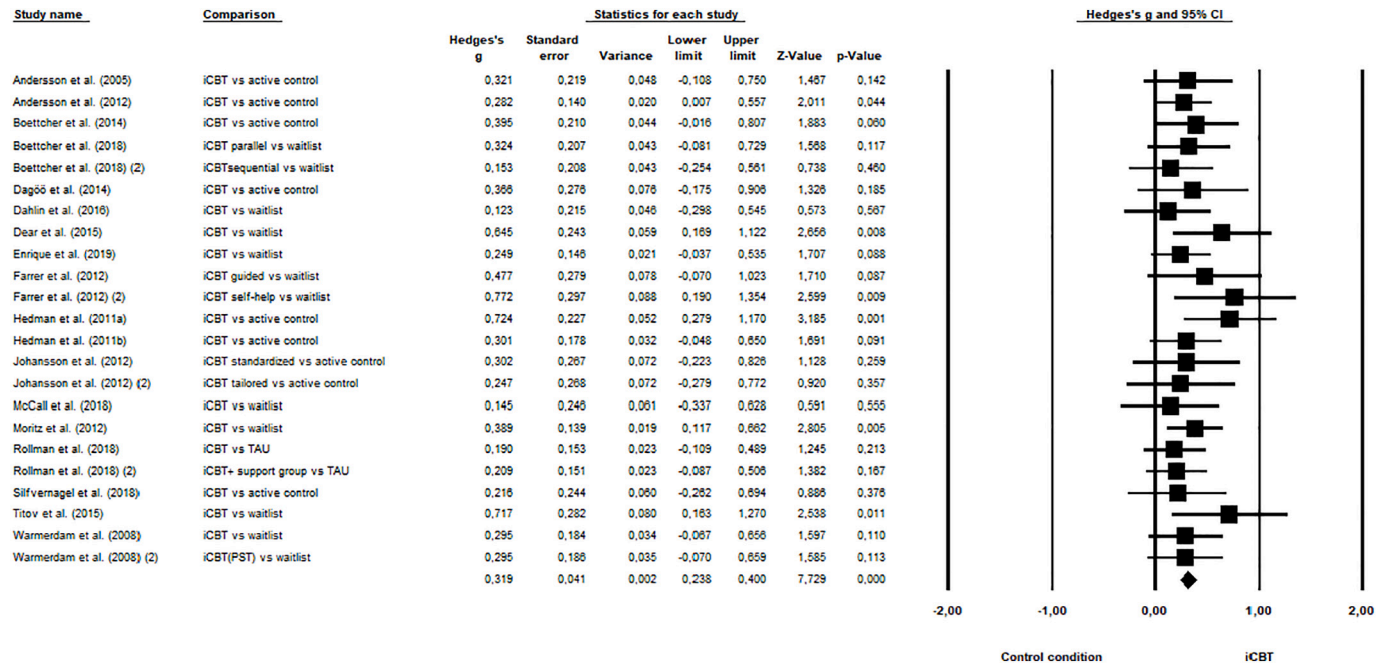

Fig. 9. Sensitivity analyses—forest plot overall quality of life measures.

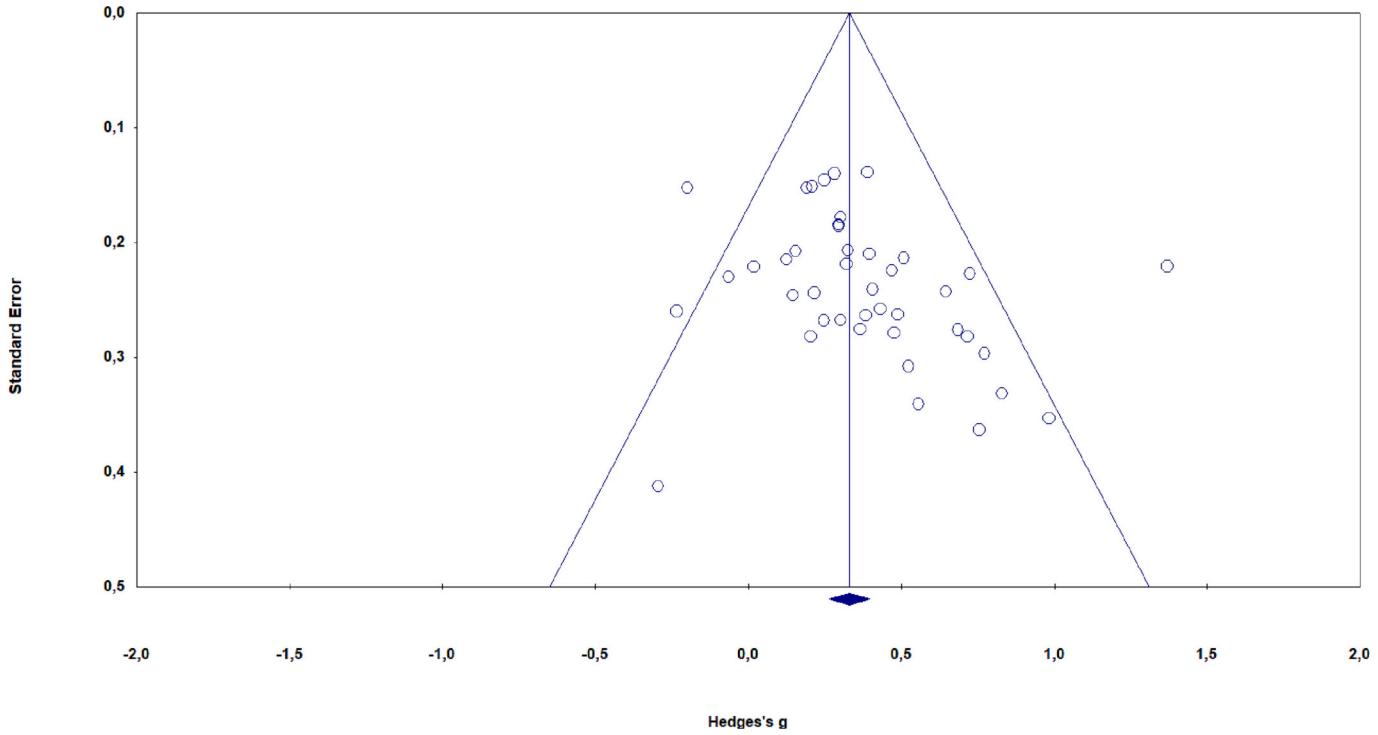

Fig. 10. Funnel plot overall quality of life measures.

is possible that other unidentified moderators may contribute to the heterogeneity of the observed effect sizes. For the distinct quality of life domains, the number of comparisons was considered to be too small to allow subgroup analyses.

4.1. Strengths and limitations

To our knowledge, this is the first meta-analysis examining the efficacy of iCBT focusing on the effects on quality of life. Previous meta-analyses have taken a broader scope and investigated the effects of the two most common treatments for depression (SSRI and CBT) on quality of life (Hofmann et al., 2017), or the effect of CBT for anxiety disorders on quality of life (Hofmann et al., 2014). Further, previous meta-analyses have examined only pre-post effects, while our meta-analysis focused on the overall between-group effects of iCBT.

The findings reported have to be considered in light of several limitations. First, the findings are limited to short-term effects only. Second, studies were mainly conducted in Western high-income countries.

Therefore, we cannot generalize to other cultural contexts. Third, we compared iCBT against control conditions including waitlist, active control group, and treatment as usual. The active control conditions were very diverse and included face-to-face individual CBT, group CBT, discussion forums, applied relaxation, mobile interpersonal psychotherapy, attention control, and e-mail support. What is more, treatment as usual is highly variable in different settings and countries, and is often not clearly described or measures (Yorganci et al., 2020). In our meta-analysis, we followed the suggestions of Mohr et al. (2009) who presented a framework for the selection and design of control conditions. However, different meta-analyses in the field of Internet-based interventions use different control conditions, and the same intervention can be classified in different ways in different meta-analyses. Therefore, we believe that there is a need for a better classification of control conditions created specifically for the context of Internet-based interventions, that would facilitate the compilation and comparisons between conditions in trials. Furthermore, in our meta-analysis, when comparing the iCBT group with multiple control groups, the most passive control group was selected as the comparison condition. This approach not only limits the opportunity to obtain a more comprehensive understanding of the effect of iCBT compared to active control groups but also hinders the moderator analysis due to the limited number of comparisons. Another limitation is related to the duration of treatment as a potential moderator. When examining it, we decided to create two categories based on the number of modules: short treatments (with fewer than 6 modules) and long treatments (with 6 or more modules), which do not cover the actual length of treatment as reported in Table 1 in terms of weeks. Considering the quality assessment of the included studies, the observed level of interrater agreement might generate uncertainties. We computed the free-marginal kappa ratio, which yielded a value of 0.36. According to Fleiss (1981), kappa values below 0.40 suggest a poor interrater agreement. Nevertheless, as demonstrated by Hartling et al. (2009), interrater agreement indicators tend to deteriorate as the number of questions increases. In our analysis the assessors responded to a total of 22 queries.

Moreover, all RCTs included in our meta-analysis used only self-report measures for quality of life. However, Costanza et al. (2008) argued that subjective indicators of quality of life are valid, and that many objective indicators merely assess the opportunities that individuals have to improve quality of life rather than the actual perceived quality of life. Our meta-analysis was also challenged by different measures used to measure the quality of life. Most of the RCTs reported the overall quality of life score. Nonetheless, in the case of the RCTs using the WHOQOL-BREF, most authors provided data for distinct quality of life domains. Although we initially planned to calculate one pooled between-group effect size, we had to conduct sub-analyses for the different WHOQOL-BREF subscales. Because the sample for this sub-analysis was relatively small, caution should be exercised interpreting the findings. Moreover, in our meta-analysis, we included trials conducted with adult participants diagnosed with anxiety disorder and/or unipolar depression. Therefore, caution should be exercised when generalizing these findings to other age groups, as well as subclinical and general populations. Another limitation is related to splitting the control group in order to avoid the potential risk of a unit-of-analysis problem, because this method overcomes the problem only partially. On the other hand, Higgins et al. (2019) posited that this approach has a potential advantage as it enables performing approximate investigations of heterogeneity.

4.2. Future research

The promising results this meta-analysis suggest a need to systematically continue to investigate the effects of iCBT for various disorders on measures of quality of life. In our meta-analysis, we only included studies conducted with adult participants. Future meta-analyses could examine other target populations, such as children, adolescents, and older adults. Because the findings of this meta-analysis were limited to short-term effects, future studies should report long-term effects to determine if outcomes are maintained over time in a consistent manner in order to facilitate comparisons (e.g. at one-year follow-up). The heterogeneity in our meta-analysis, both for the overall quality of life score and distinct quality of life domains, was moderate. However, for the overall quality of life score, all of the investigated moderators were non-significant. This may suggest that other, unidentified moderators might contribute to heterogeneity. In our meta-analysis, we included studies that used diagnostic interviews or self-reported measures to determine the presence of anxiety disorder and/or unipolar depression. One potential moderator to consider is whether a disorder was established with a diagnostic interview or operationalized as a high score on a self-report measure. It is also possible that individual patient meta-analyses may be a more sensitive approach to investigate possible reasons of heterogeneity.

5. Conclusions

In conclusion this meta-analysis suggests that iCBT for depression and anxiety may be a promising approach for improving the quality of life of patients. The effect sizes are however small to moderate and further research is needed.

Ethics approval and consent to participate

Not applicable.

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Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.invent.2023.100654.

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