COMPARISON OF REMOTE CBT VS IN-PERSON CBT

REMOTE VERSUS IN-PERSON COGNITIVE BEHAVIOR THERAPY FOR PSYCHIATRIC AND SOMATIC DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

By SARA ZANDIEH, MA

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2022) Hamilton, Ontario (Health Research Methodology)

TITLE: Remote vs in-person cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis of randomized controlled trials

AUTHOR: Sara Zandieh

SUPERVISOR: Dr. Jason Walter Busse

NUMBER OF PAGES: xiv, 61

Lay Abstract

Cognitive behavior therapy (CBT) is an evidence-based form of psychotherapy that targets irrational beliefs and dysfunctional behavior patterns. CBT has been shown effective for several psychiatric and chronic somatic conditions; however, cost and availability of local therapists are important barriers to access. Remote CBT has been proposed as more cost-effective and scalable than in-person CBT, but the relative effectiveness of in-person vs. remote CBT is uncertain. In our review of studies comparing the effectiveness of in-person CBT to remote CBT, we found high certainty evidence they are equally effective across a range of conditions.

Abstract

Background: It has been demonstrated that remote cognitive behavior therapy (CBT) is more effective than usual care; however, the comparative effectiveness of remote versus in-person CBT is uncertain. The objective of this thesis is to conduct a systematic review and meta-analysis to address this issue.

Methods: MEDLINE, EMBASE, PsycINFO, CINAHL, Web of Science were searched from

inception to May 11, 2022, for randomised control trials that: (1) enrolled adults (≥18 years) presenting with any psychiatric or somatic disorder, and (2) randomized them to guided remote CBT or in-person CBT. We used a random effects model for pooling the effects on primary outcomes across trials, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to assess the certainty of evidence, and the Instrument to Assess the Credibility of Effect Modification Analyses (ICEMAN) to rate the credibility of subgroup effects.

Results: We identified a total of 32 randomized control trials with 2,962 patients that were eligible for review. There were ten studies focused on the treatment of anxiety and related disorders, six on depressive symptoms, three on chronic pain, four on body image/eating disorder, four on insomnia, three on chronic tinnitus, one on alcohol use disorder, and one on insomnia comorbid with depression. High certainty evidence from 32 studies revealed no difference in the overall pooled estimate between remote CBT and in-person CBT (standardized mean difference = -0.07, 95% CI: -0.19 to 0.06).

Conclusion: High certainty evidence shows there is no difference in effectiveness between in-person and remote CBT.

Acknowledgment

First and foremost, I would like to express my sincere appreciation to my supervisor, Dr. Jason Busse, for his outstanding knowledge, immense support, and understanding he provided to me throughout my Master's at McMaster University. Thank you for your inspiring mentorship. I extend my deepest gratitude to Dr. Randi McCabe and Dr. Behnam Sadeghirad for their insightful comments and the valuable knowledge they shared with me during the course of this project. I also would like to thank my external examiner, Dr. Peter Bieling, for his time and assistance to enhance my thesis.

I acknowledge and sincerely thank Dr. Li Wang and Dr. Maryam Abdollahzadeh for their guidance and help. Also, I thank my friends and supporters at McMaster University: Rachel Couban, Dr. Vahid Ashoorion, Fatima Sheikh, and Jane Jomy for their encouragement and helpful comments.

Last but not certainly least, I am grateful and humbled to my parents for encouraging me to pursue my dreams, as well as to my beloved spouse, Amin, for his enormous understanding and support.

Table of Contents

List of Figures and Tables

List of Abbreviations and Symbols

ACT= Acceptance Commitment Therapy

CBT= Cognitive Behavior Therapy

CI= Confidence Interval

GRADE= Grading of Recommendation, Assessment, Development and Evaluation

ICBT= Internet-delivered Cognitive Behavior Therapy

ICEMAN= Instrument for assessing the Credibility of Effect Modification Analyses

IQR= Interquartile Range

ITT= Intention-to-Treat

LOCF= Last Observation Carried Forward

MBCT= Mindfulness-based Cognitive Therapy

OCD= Obsessive-Compulsive Disorder

OSF= Open Science Framework

PP= Per Protocol

PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

PTSD= Post traumatic Stress Disorder

RCT= Randomized Controlled Trials

SMD= Standardized Mean Difference

TAU= Treatment as Usual

WHO= World Health Organization

Declaration of Academic Achievement

I, Sara Zandieh, declare that my thesis is my research work. I am the sole author of this thesis document and was involved in all stages of the research project under the supervision of Dr. Jason W. Busse, Dr. Randi E. McCabe, and Dr. Behnam Sadeghirad contributed to the editing and review of my thesis and were members of my thesis committee. Dr. Peter J. Bieling acted as the external reviewer. To the best of my knowledge, this thesis does not infringe upon any existing copyrights.

1.0 BACKGROUND

1.1 Mental Health and Cognitive Behavioral Therapy

Mental disorders are a major cause of disability, and the World Health Organization (WHO) has estimated that one in five people in post-conflict settings will experience depression, anxiety disorder, post-traumatic stress disorder, bipolar disorder, or schizophrenia (1). One in every two Canadians will experience a mental illness by the age of 40, and the annual economic burden of mental illness in Canada is >$50 billion (2). Access to treatment is an important barrier to care, particularly for individuals who live in remote areas or in areas without sufficient clinical resources, (3) and there is increasing interest in remote healthcare (4).

Cognitive Behavior Therapy (CBT) is a form of psychotherapy that focuses on the identification and modification of dysfunctional thought and behavior patterns (5). CBT has been found effective for chronic pain, anxiety, depression, and other mental illnesses, (6) (7) (8) (9) and in 2019 the WHO advised that access to CBT was essential for evidence-based mental healthcare (4). E-health technology can facilitate remote delivery of CBT, but it remains uncertain whether this form of delivery is similarly effective as in-person treatment.

1.2 Remote CBT

E-health is a term used for leveraging information technologies to prevent and manage the disease and includes Telehealth, Internet-based interventions, computer-based

interventions, etc. The use of E-Health interventions to manage chronic disorders is expanding along with the use and development of digital technology (10). In 2022, the Agency for Healthcare Research and Quality (AHRQ) reviewed 351 studies and found that telehealth has experienced an unprecedented rise as a result of the COVID-19 pandemic (11).

Remote CBT is now available in various modalities, including interactive voice response, through applications, and via telephone, and among them, Internet-delivered CBT treatment (iCBT) is more well-established. iCBT entails psychotherapy based on CBT principles that is delivered by a remote provider via the Internet. It can be guided, where the patient interacts with a healthcare professional, or unguided, where the patient receives no assistance from a healthcare provider (3).

The most recent systematic review of in-person vs. iCBT reviewed the literature up to February 2017 and found that iCBT may be similarly effective to in-person CBT but suggested there may be important differences based on the clinical condition being targeted. They also found moderate unexplained heterogeneity in their pooled estimate of effect and did not assess the overall certainty of evidence (12). A 2019 Health Technology Assessment by Health Quality Ontario found that iCBT was more effective than waitlist control for mild to moderate depression and social anxiety disorder, and may be effective for anxiety and panic disorder, but concluded the relative effectiveness of iCBT vs. in-person delivery was uncertain (3).

1.3 Structure of remote CBT

Remote CBT is guided by therapists who provide feedback to patients, with scheduling similar to face-to-face treatment, and can be delivered either through live chat or asynchronously (e.g., through email on a secure platform). A systematic review found that iCBT and in-person CBT showed no significant differences in rates of adherence (81% and 84%, respectively) (13). Remote CBT materials typically contain text, graphics, and audiovisual information. Homework is assigned after each session, which typically occurs on a weekly basis (14). The specific intervention is tailored to the patient's health condition (15). For instance, for the management of chronic pain, cognitive strategies include identifying pain-provoking cues in everyday life, modifying maladaptive pain-related cognitions, attention diverting strategies, and behavioral strategies such as relaxation skills, activity pacing, and promoting physical activity (16).

1.4 Objective

We conducted a systematic review and meta-analysis to explore the effectiveness of remote vs in-person CBT that addresses the limitations of the prior review.

2.0 METHODS

2.1 Standardized reporting and protocol registration

We registered our protocol (Open Science Framework identifier: 10.17605/OSF.IO/7ASRC), adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, and followed GRADE guidance for communicating our findings (17).

2.2 Information sources and searches

A medical librarian (RJC) developed database specific search strategies without language restrictions and searched MEDLINE, EMBASE, PsychInfo, and CINAHL from inception to May 11, 2022 **(Appendix A)**. We searched reference lists of all eligible articles and relevant systematic reviews to identify additional studies

2.3 Eligibility criteria

We included interventional studies that randomized adult patients (≥18 years of age), with a clinical condition, to remote or in-person CBT. We excluded studies that administered CBT without therapist guidance, and virtual reality treatments in which a therapist accompanies the patient. Several studies have found that remote CBT with therapist guidance is more effective than self-guided CBT (15, 18-20) therefore, it was possible to take different results if we include unguided interventions. We excluded trials administering psychotherapy other than CBT (e.g., Acceptance Commitment Therapy, Mindfulness-based cognitive therapy) or studies that administered CBT in addition to

another intervention (e.g., motivational interviewing). All interventions were reviewed by a clinical expert (RM), blinded to the trial results, to confirm eligibility

2.4 Selection and data extraction

Pairs of trained reviewers (SZ, BI, HC, AP) screened titles and abstracts of identified citations and full texts of all potentially eligible studies. We used online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; http://systematic-review.net) to facilitate literature screening. Disagreements were resolved by discussion to reach consensus or by involvement of an adjudicator (RM) if needed.

2.5 Data extraction

Using standardized, pilot-tested forms, each eligible trial underwent duplicate data abstraction by pairs of trained reviewers (SZ, MA, BI, HC, AP). Reviewers addressed discrepancies through discussion or adjudication by a third reviewer if needed. When outcome data were available at multiple time-points, we used data from the longest follow-up time. We collected information on study characteristics (e.g., first author, year of publication), patient characteristics (e.g., country of residence, sex, age, comorbid psychological conditions, prescribed psychotropic medication, educational level), treatment and comparison details (e.g., number of sessions, duration of treatment, the formats of remote and in-person therapies, clinicians' background, length of follow-up, patients recruitment methods) and results of the primary outcome for each trial. All of the primary outcomes reported in the studies were continuous and we used a hierarchy to select

the primary outcome: first, if the trial declared primary outcome, in either the paper or associated protocol or clinical trials registry. If it was not clear, we consider the outcome the author of trial used to calculate sample size and if it was not helpful, the first patient-important outcome that they reported in their results section was considered as the primary outcome. Moreover, we captured the type of analyses trials used and if they reported multiple types of analyses such as intention-to-treat and per-protocol, we preferred intention-to-treat analysis for the review because this analysis compares the treatment groups based on every patient's initial allocation following randomization and to prevent any bias in trials, this approach is advised (21) **(Appendix B)**. Reviewers resolved disagreements through consensus or with the help of a third reviewer. For trials that randomized patients to more than two arms, we only extracted data relating to the comparison of interest for our review (i.e., in-person vs. remote CBT).

2.6 Risk of bias

Three pairs of independent reviewers used a modified Cochrane risk of bias instrument (22, 23) to assess risk of bias in each trial, in duplicate, for the following domains: random sequence generation, allocation concealment, blinding of patients, healthcare providers, data collectors, and outcome assessors, missing outcome data (>10% missing data was considered at high risk of bias), and selective outcome reporting. We assessed this last domain by comparing the reported results with those proposed in their pre-specified protocols if it was available, otherwise by comparing the reported results with those proposed in the study methods. Response options for each item were “definitely or probably

yes" (combined as at low risk of bias) and "definitely or probably no" (combined as at high risk of bias).

2.7 Data synthesis

We generated standardized mean difference and standard error for each included trial and then pooled them across trials to derive the pooled standardized mean difference and the associated 95% confidence interval (95%CI) (24). We used the DerSimonian-Laird method and random-effects models for all meta-analyses, which are conservative as they consider both within- and between-study variability (25). We used Cohen's categories for classifying average effect sizes: 0.20 = small, 0.50 = medium, 0.80 = large (26). We used Stata version 17.0 (StataCorp LP., College Station, TX, USA) for all analyses, and set our level of statistical significance at $p \leq 0.05$.

2.8 Subgroup analysis and meta-regression

We used visual inspection of forest plots, the I^2 statistic, to examine heterogeneity among effect estimates of included studies (24) and constructed a Galbraith plot to assess heterogeneity and get information about the study-specific effect sizes, their precisions, and detecting potential outliers (27). We tested the following a priori hypotheses to explore between-study variability: (1) clinical condition, (2) whether in-person CBT was provided individually or in group therapy, and (3) risk of bias on a component-by-component basis. We conducted one post-hoc subgroup analysis to explore the impact of individual vs. group in-person CBT on treatment effects.

All clinical conditions from eligible trials were provided to a psychologist (RM), blinded to results, for grouping various clinical conditions into similar categories, e.g., we put studies focused on the treatment of PTSD, trait anxiety, panic disorder, social anxiety disorder, and OCD in the anxiety and related disorders category. We conducted subgroup analysis only if there were two or more studies in each subgroup. We used meta-regression to explore the association between treatment effect and length of follow-up and the proportion of loss to follow-up if there were at least 10 studies available for analysis (28). We assessed the credibility of subgroup effects using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) when we observed a statistically significant test of interaction ($p \leq 0.05$) (29).

2.9 Certainty of evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of the evidence for pooled estimates. In this approach, randomized trials begin as high certainty but may be rated down to moderate, low, or very low based on limitations in risk of bias, indirectness, imprecision, inconsistency, or publication bias (30). We considered the pooled effect estimate to be precise if the associated 95%CI excluded a small effect (i.e., 0.2) (26). We did not rate down the quality of evidence for risk of bias if the subgroup analysis showed no association of treatment effect with risk of bias (24). Blinding of patients and therapists is not possible in trials of psychotherapy; (31) however, based on a meta-epidemiological study of 1,153 trials that found no systematic differences in treatment effects between blinded and unblinded trials (32), we did not rate down for risk of bias if blinding was the only criterion

that was unmet. If there were at least 10 studies for meta-analysis, we evaluated small-study effects with contour-enhanced funnel plots and Egger's test (33).

3.0 RESULTS

3.1 Study selection

Of 9157 citations, 30 English language trials (34-65) and individual trials published in Mandarin (55) and Persian (65) that enrolled 2962 patients, were eligible for the review (Figure 1). One trial (44) randomized patients to CBT delivered in-person at their home, in-person at a therapist's office, or remotely. We combined data from both in-person CBT arms. Another trial (64) assigned participants to three arms: 12-sessions of in-person CBT, 6-sessions of in-person CBT, and 6-sessions of remote CBT. We only included data from the two arms with the same number of sessions.

3.2 Study Characteristics

The 32 eligible trials enrolled a median of 79 patients (interquartile range [IQR] 52 to 116), and 64% of participants (1894 of 2962) were female with an average age of 40.48. Studies were conducted in Sweden (n=10), Australia (n=7), the United States of America (n=4), the Netherlands (n=2), and China (n=2), as well as individual trials in Spain, Germany, Finland, France, England, and Iran. Trials enrolled patients presenting with anxiety-related disorders (n=10), depression and mood disorders (n=6), insomnia (n=4), body image/eating disorders (n=4), chronic pain (n=3), chronic tinnitus (n=3), insomnia with depression (n=1), and alcohol use disorder (n=1). The number of treatment sessions ranged from 5 to 21, and the median length of follow-up was 180 days (IQR 104 to 341). 17 out of 32 studies have published protocols to assess selective reporting (Table 1).

Fifteen studies (46.9%) randomized patients to in-person group therapy whereas 17 (53%) provided in-person individual CBT. Types of remote CBT included interactive voice response technology (34), computerized CBT (39, 51, 56, 59, 64), Telehealth cognitive processing therapy (44), videoconference (58), and iCBT (35, 37, 38, 40-43, 45-55, 60-63, 65-67). One study (3%) was funded by industry (57), 25 by not-for-profit organizations (34, 35, 37-42, 44-47, 49, 50, 52-56, 59-63, 68), and six studies did not report a source of funding (36, 43, 48, 58, 64, 65).

Figure 1. PRISMA flow diagram of study selection

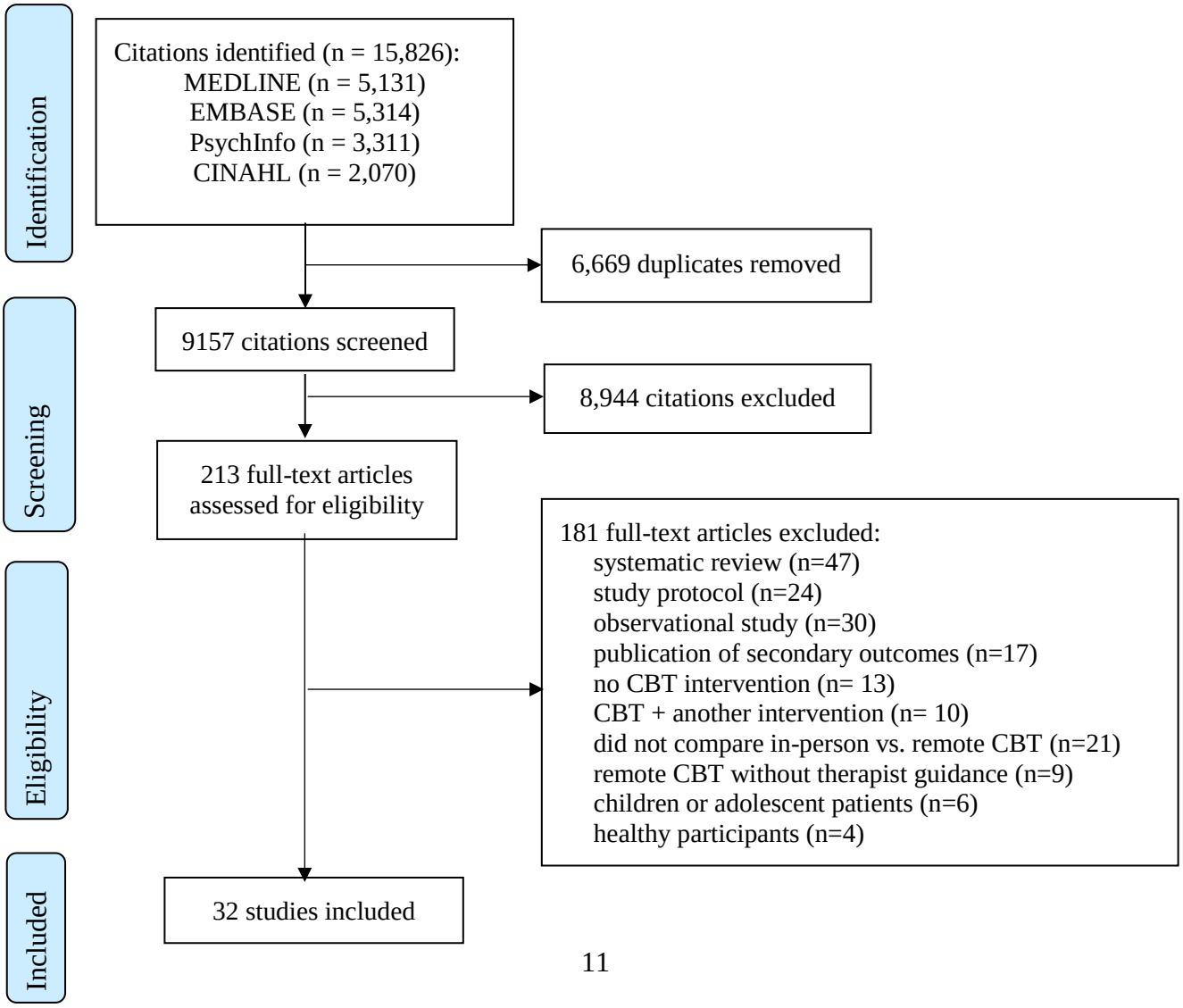


Table1. Study Characteristics

Study	No. of participants	Mean age	% Female	Country of Residence	Clinical Condition	Primary outcome measure	No. of Sessions	Length follow-up (days)	Link of pre-specified protocol
Heapy, 2017 (34)	125	58	21	USA	Chronic Back Pain	average pain intensity measured by the Numeric Rating Scale	10	270	https://clinicaltrials.gov/ct2/show/NCT01025752
Anderson, 2013 (35)	69	42	78	Sweden	Depression	depression severity score measured by the Montgomery Åsberg Depression Rating	7	1,095	no protocol
Andrews, 2011 (36)	37	32	41	Australia	Social phobia	social phobia score measured by the Social Interaction Anxiety Scale	6	56	https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12609000212257
Axelsson, 2020 (37)	204	39	70	Sweden	Health Anxiety	health anxiety score measured by Health Anxiety Inventory	12	365	no protocol
Bergström, 2010 (38)	104	34	61	Sweden	Panic disorder	panic disorder severity measured by Panic Disorder Severity Scale	10	180	https://www.clinicaltrials.gov/ct2/show/NCT00845260
Bessell, 2012 (39)	56	46	61	England	Appearance concern	appearance concern measured by Derriford Appearance Scale-24	8	180	no protocol
Blom, 2015 (40)	48	54	48	Sweden	Insomnia	Insomnia severity measured by Insomnia Severity Index	8	180	no protocol
Milgrom, 2021 (41)	78	32	100	Australia	Postnatal Depression	severity of depression measured by Beck Depression Inventory II	6	147	https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12613000881730
Ying, 2022(42)	220	42	53	China	Depression	depressive symptoms measured by Center for Epidemiological Studies Depression Scale	5	180	www.chictr.org.cn/historyversionpub.aspx?regno=ChiCTR2100049671

Kaldo, 2008(43)	51	46	43	Sweden	Distress Associated with Tinnitus	tinnitus distress measured by Tinnitus Reaction Questionnaire	7	365	no protocol
Peterson, 2022 (44)	120	41	12	USA	Posttraumatic Stress Disorder	PTSD symptom severity measured by PTSD Checklist for DSM-5 (PCL-5)	12	180	https://clinicaltrials.gov/ct2/show/NCT02290847
Lundstrom, 2022 (45)	80	33	65	Sweden	Obsessive-Compulsive Disorder	OCD severity measured by Yale-Brown Obsessive Compulsive Scale	10	365	https://pubmed.ncbi.nlm.nih.gov/30185575/
Carlbring, 2005 (46)	49	35	71	Sweden	Panic disorder	physiological sensations experienced by anxiety measured by Body Sensations Questionnaire	7	365	no protocol
Conrad, 2015 (47)	84	51	42	Germany	chronic tinnitus	tinnitus distress measured by Tinnitus Handicap Inventory	18	365	https://clinicaltrials.gov/ct2/show/NCT01205906
de Boer, 2014 (48)	72	52	64	Netherland	non-specific chronic pain	pain catastrophizing measured by Pain catastrophizing scale	8	60	no protocol
Gollings, 2006 (49)	40	22	100	Australia	body dissatisfaction and disordered eating	body shape concern measured by Body Shape Questionnaire	8	60	no protocol
Hedman, 2011 (50)	126	35	36	Sweden	Social anxiety disorder	social phobia measured by Clinical administered Liebowitz Social Anxiety Scale	15	180	https://clinicaltrials.gov/ct2/show/NCT00564967
Jarnefelt, 2020 (51)	53	43	74	Finland	Insomnia	severity of insomnia measured by Insomnia Severity Index	10	180	https://clinicaltrials.gov/ct2/show/NCT02523079
Jasper, 2014 (52)	84	51	42	Sweden	Chronic tinnitus	tinnitus distress measured by Tinnitus Handicap Inventory	18	180	https://clinicaltrials.gov/ct2/show/NCT01205906
Johansson, 2021 (53)	301	50	38	Sweden	Alcohol use disorder	number of standard drinks consumed measured by time-line follow-back (TLFB) method	8	180	https://www.clinicaltrials.go

									v/ct2/show/NCT02671019
Kiropoulos, 2008 (54)	86	39	72	Australia	Panic Disorder	panic severity measured by Panic disorder severity scale	12	84	no protocol
Ye, 2016 (55)	53	46	81	China	Insomnia	sleep onset latency	8	56	no protocol
Leterme, 2020 (56)	80	37	65	France	Adjustment disorder with anxiety	trait anxiety measured by State-Trait Anxiety Inventory	5	180	https://clinicaltrials.gov/ct2/show/NCT02621775
Lancee, 2016 (57)	60	39.85	80	Netherland	Insomnia	insomnia severity measured by Insomnia Severity Index	6	180	https://clinicaltrials.gov/ct2/show/NCT01955850
Stubbings, 2013 (58)	26	30	58	Australia	Mood and Anxiety Disorders	depression, anxiety and stress measured by Depression Anxiety and Stress Scale	12	42	https://www.australianclinicaltrials.gov.au/anzctr/trial/ACTRN12609000819224
Thase, 2018 (59)	154	46	66	USA	Depression	depression severity measured by Hamilton Rating Scale for Depression	21	180	no protocol
Wagner, 2014 (60)	62	38	65	Switzerland	Depression	depression severity measured by Beck Depression Inventory II	7	90	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12611000563965
Paxton, 2007 (61)	79	26	100	Australia	Boding Image and Eating Disorder	body dissatisfaction measured by Body Shape Questionnaire	8	180	no protocol
Vallejo, 2015 (62)	40	52	100	Spain	Fibromyalgia	global impact fibromyalgia measured by Fibromyalgia Impact Questionnaire	10	365	no protocol
Zerwas, 2017 (63)	196	28	98	USA	Bulimia Nervosa	abstinence from binge eating and purging measured by Eating Disorders Examination Interview	16	365	https://clinicaltrials.gov/ct2/show/NCT00877786
Kenardy, 2003 (64)	95	37	76	Australia	Panic Disorder	panic-anxiety composite score	6	180	no protocol

Azimi, 2019 (65)	30	NR	67	Iran	Insomnia and comorbid Depression	Gross memory impairment measured by Rivermead Behavioural Memory Test	6	30	no protocol

DSM V= Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; NR = not reported; PTSD = Post-traumatic Stress Disorder; OCD = Obsessive Compulsive Disorder; USA= United States of America

3.3 Risk of Bias

All eligible studies were at high risk of bias for unblinding of patients and healthcare providers, and only five studies blinded outcome assessors (38, 45, 50, 59, 63). Two studies (44, 51) were at high risk of bias for randomization sequence generation, nine (28%) were at high risk of bias for allocation concealment, (44, 49, 51, 55, 57, 59, 60, 64, 65) and most (23 of 32; 71%) were at high risk of bias for missing outcome data. We found evidence of selective outcome reporting in two studies (6%) (35, 36) **(Appendix C).**

3.4 In-Person vs. Remote CBT for Primary Outcomes

High certainty evidence from 32 trials (2,962 patients) showed little to no difference in primary outcomes among trials between in-person and remote CBT (SMD = -0.07, 95% CI -0.19 to 0.06) (**Figure 2, Table 2**). We found no evidence of credible subgroup effect for clinical conditions, risk of bias, and individual vs group in-person therapy, and the results of meta-regression show that length of follow-up time is not associated with the effect size and can not explain heterogeneity (p= 0.39) **(Appendix E to Appendix M).** We conducted a sensitivity analysis, excluding one potential outlier which was a trial with 1095 days of follow-up. We found no statistically significant association again **(Appendix N)**.

Figure 2. Forest plot of Primary outcome among patients that received in-person vs. remote CBT in 32 randomized clinical trials

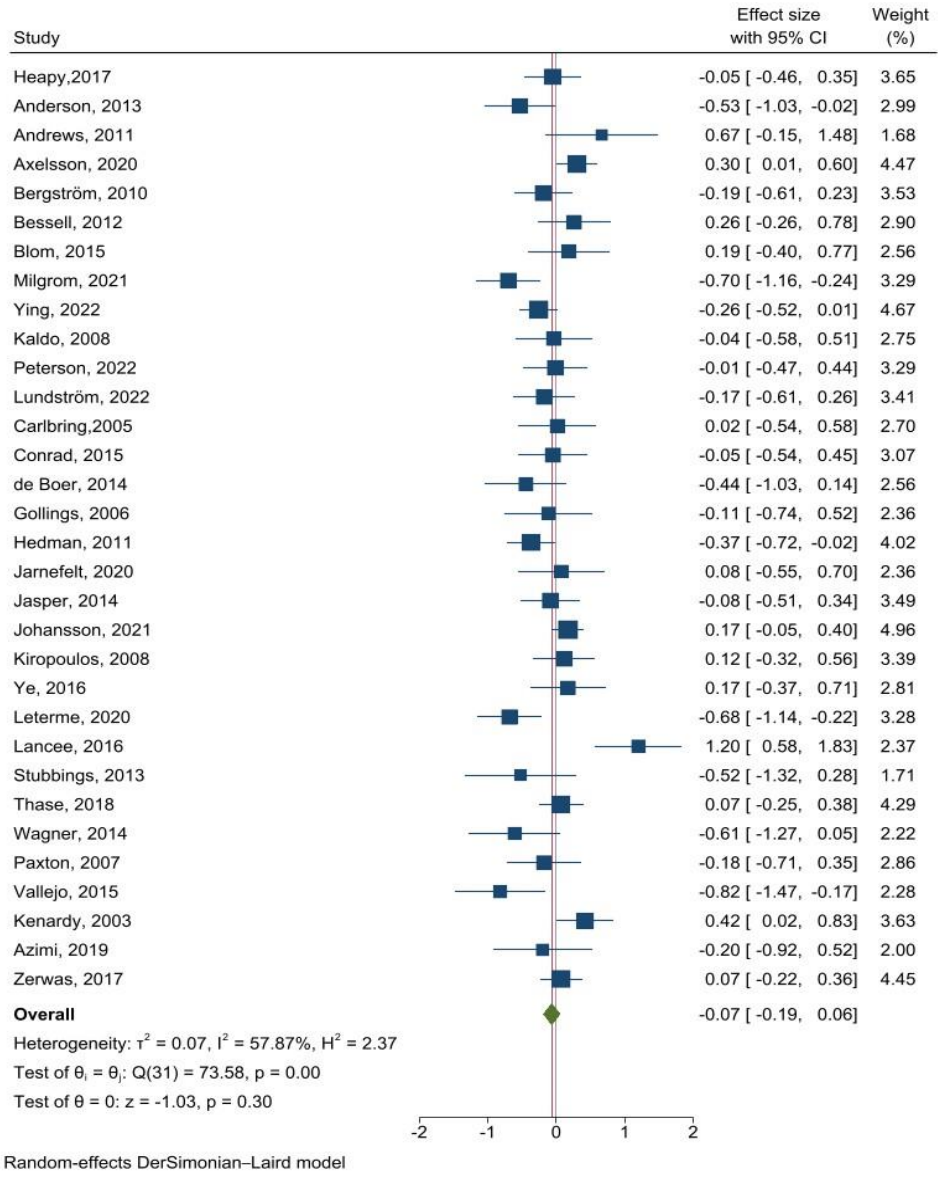


Table 2. GRADE Evidence Profile of In-Person vs Remote CBT for Patients with Psychological and Somatic Complaints Included in Randomized Clinical Trials

Outcome	No. of trials	No. of participants	Length of follow-up Median (IQR)	Risk of bias	Inconsistency	Indirectness	Imprecision	Small-study effects	SMD (95%CI)	Certainty of evidence
The primary outcome of each trial	32	2,962	180 days (104 to 341)	No serious risk of bias[1]	No serious inconsistency[2] (I^2 = 58%)	No serious Indirectness	No serious Imprecision[3]	Undetected[4] Egger's test (p=0.37)	-0.07 (-0.19 to 0.06)	High

95% CI = 95% confidence interval; SMD = Standardised Mean Difference

1. We did not rate down for risk of bias as subgroup analysis showed no significant difference in trials at low versus the high risk of bias on a component-by-component basis.
2. The Galbraight plot shows that most of the studies are mostly scattered on the right side of the plot and there is no substantial heterogeneity because of almost all of the studies except one lie in the 95% CIs area. In addition, this plot shows we have one outlier as it is located too far away from the 95% Cis region **(Appendix Q)**.
3. Although the estimate of precision includes no effect, we did not rate down for imprecision because the 95%CI did not include small effects (SMD ≥0.2).

4. The contoured-enhanced funnel plot shows that trials are distributed symmetrically around the pooled effect size and visual inspection of the plot does not indicate the small study effect and we can see small studies in non-significant areas on both sides of pooled effect. Therefore, there is no sign of publication bias **(Appendix P)**. We conducted Egger's test which measures the relationship between the intervention effect and its standard error. Under the null hypothesis of there being no small study effect, the p-value was 0.37.

4.0 DISCUSSION

4.1 Main Findings

High certainty evidence shows no difference in effectiveness whether CBT is delivered in-person or remotely with therapist guidance, across a range of clinical conditions. This finding was unaffected by the length of follow-up or whether in-person CBT was provided individually or through group sessions.

4.2 Relation to other studies

Our finding is in line with the previous meta-analyses that compared in-person CBT with remote CBT (3, 12, 19, 69-71). However, previous studies all had some limitations. For example, except one of them, they did not assess the certainty of evidence by GRADE nor investigate subgroup effects to address heterogeneity.

Carlbring et al. in 2018 included 20 RCTs that compared iCBT to face-to-face CBT and they reported their results probably were inconclusive, recommending more rigorous RCTs are needed to make a firm conclusion. Moreover, they limited their search to only one database and did not include non-English studies, as a result, they missed a couple of eligible trials to include in the review (39, 47, 48, 55, 58, 60, 64). On the other hand, they included the following trials that were not eligible based on our experts' suggestions: 1) a virtual reality treatment in which a therapist accompanies the patient (72), 2) a self-help intervention with no professional support for the participants (73), 3) a trial investigating Acceptance Commitment Therapy which is different from CBT (74), 4) a trial that

compared internet-delivered self-help with one-session exposure treatment in patients with spider phobia (75), 5) a trial that compared internet-delivered self-help with one-session exposure treatment in patients with snake phobia (76), and 6) a couple therapy intervention that was described as "traditional sexual counseling" which is not comparable to standard individual/group delivered CBT(77).

One of the reviews in 2019 (19) only focused on chronic health conditions but several eligible trials targeting chronic pain patients and patients with tinnitus were left out of the review (34, 47, 48). This review also included a study (78) comparing face-to-face group Mindfulness-Based Cognitive Therapy (MBCT) and eMBCT with treatment as usual (TAU).

Another review conducted by Health Quality Ontario in 2019 revealed that guided iCBT when compared with individual or group face-to-face therapy did not significantly improve panic disorder symptoms with very low quality of evidence and social anxiety disorder with low quality of evidence (3). However, this review was limited to the treatment of depression and anxiety disorders and they were uncertain about their conclusion. Additionally, many trials comparing remote and in-person CBT were not included in their review.

4.3 Strength and Limitations

Strengths of our review include a comprehensive search for eligible randomized trials in any language that identified 19 studies not included in the most recent prior review. We used the GRADE approach to appraise the certainty of evidence, pre-defined subgroup analyses to explore sources of heterogeneity, and assessed the credibility of all potential subgroup effects. Further, inclusion of trials conducted in 11 countries supports the generalizability of our findings; however, low- and middle-income countries were poorly represented. The novelty of our review is including all types of modalities of remote CBT, while the last reviews focused on one type of modality (e.g. iCBT). We had an Independent assessment of CBT interventions with the assistance of our adjudicator (RM) to make sure we include the right treatment.

Our review has some limitations. Studies eligible for our review included diverse patients presenting with a wide range of clinical conditions; however, there are many conditions that are candidates for CBT that were not represented or informed by only a single trial (e.g., alcohol use disorder). We found no evidence for credible subgroup effects based on clinical conditions, but it remains possible that some conditions may respond more favorably to in-person or remote delivery of CBT. Our pooled estimate of effect was associated with moderate unexplained heterogeneity. We did not rate down evidence quality because the magnitude and direction of effects was largely consistent across trials, and a substantial proportion of between-study variability was contributed by one trial (57) that only contributed 2% of the weight to our pooled estimate. None of the trials eligible

for our review explored stepped-care (i.e., remote CBT is offered first, and then non-responders are provided with in-person CBT), and our findings do not extend to this type of care. In addition, patients enrolled in trials eligible for review consented to being randomized to either in-person or remote CBT and likely do not include individuals who have strong preferences for one method of delivery over the other.

4.4 Implications

CBT is an effective therapy for numerous mental illnesses and somatic complaints (6) (7) (8) (9); however, there are resource requirements for in-person therapy. Our review provides high certainty evidence that remote delivery of CBT with therapist guidance is no less effective than in-person delivery. Remote delivery of CBT enables clinicians to manage more patients with fewer resources than in-person therapy. Furthermore, there are less demands on patients' time as travel for face-to-face sessions is unnecessary (15). Remote CBT is also more cost-effective than in-person delivery. (79, 80) One randomized trial found therapists spent an average of 120 minutes per week on in-person CBT versus 11 minutes per week on internet-based internet iCBT, with savings ranging from $6190 to $6593 per treated participant (45). In addition, remote CBT may be associated with increased attendance rates, difference in attendance sessions between remote and in-person CBT was significant; $t(371) = -1.94$, $p = .053$, $d = .10$ (81). Our findings suggest that remote CBT is an effective alternative to in-person delivery and could facilitate greater access for patients; however, both resource availability and patient preference should be considered.

4.5 Conclusion

In this systematic review of randomized controlled trials, high certainty evidence shows that, across a range of psychological and somatic conditions, there is little to no difference in effectiveness between in-person and remotely delivered CBT.

5.0 REFERENCES

1. Charlson F, van Ommeren M, Flaxman A, Cornett J, Whiteford H, Saxena S. New WHO prevalence estimates of mental disorders in conflict settings: a systematic review and meta-analysis. The Lancet. 2019;394(10194):240-8.

2. Ahmad S, Briante C, Khan M, Smetanin P, Stiff D. The life and economic impact of major mental illnesses in Canada. Ottawa, Ontario: Canadian Electronic Library; 2015.

3. Internet-Delivered Cognitive Behavioural Therapy for Major Depression and Anxiety Disorders : A Health Technology Assessment. Toronto, ON, CA: Health Quality Ontario; 2019.

4. Organization WH. WHO highlights urgent need to transform mental health and mental health care 2022 [updated 17 June 2022 Available from: https://www.who.int/news/item/17-06-2022-who-highlights-urgent-need-to-transform-mental-health-and-mental-health-care.

5. Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JAJ, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials. Depression and Anxiety. 2018;35(6):502-14.

6. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14(1):S1.

7. Liu J, Gill NS, Teodorczuk A, Li Z-j, Sun J. The efficacy of cognitive behavioural therapy in somatoform disorders and medically unexplained physical symptoms: A meta-analysis of randomized controlled trials. Journal of Affective Disorders. 2019;245:98-112.

8. Williams ACdC, Eccleston C, Morley S, Williams ACdC. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2012;2019(9):CD007407-CD.

9. Busse JW, Montori VM, Krasnik C, Patelis-Siotis I, Guyatt GH. Psychological Intervention for Premenstrual Syndrome: A Meta-Analysis of Randomized Controlled Trials. Psychotherapy and Psychosomatics. 2009;78(1):6-15.

10. Catwell L, Sheikh A. Evaluating eHealth Interventions: The Need for Continuous Systemic Evaluation. PLOS Medicine. 2009;6(8):e1000126.

11. Effective Health Care Program AfHRaQ, Rockville, MD. Use of Telehealth During the COVID-19 Era 2022. Available from: https://effectivehealthcare.ahrq.gov/products/virtual-health-covid/draft-comment.

12. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf EJCbt. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. 2018;47(1):1-18.

13. van Ballegooijen W, Cuijpers P, van Straten A, Karyotaki E, Andersson G, Smit JH, et al. Adherence to Internet-Based and Face-to-Face Cognitive Behavioural Therapy for Depression: A Meta-Analysis. PLOS ONE. 2014;9(7):e100674.

14. Andersson G. Internet-Delivered Psychological Treatments. Annu Rev Clin Psychol. 2016;12(1):157-79.

15. Andersson G, Titov N, Dear BF, Rozental A, Carlbring P. Internet-delivered psychological treatments: from innovation to implementation. World Psychiatry. 2019;18(1):20-8.

16. Ferwerda M, van Beugen S, van Middendorp H, Spillekom-van Koulil S, Donders ART, Visser H, et al. A tailored-guided internet-based cognitive-behavioral intervention for patients with rheumatoid arthritis as an adjunct to standard rheumatological care: results of a randomized controlled trial. PAIN. 2017;158(5):868-78.

17. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. Journal of Clinical Epidemiology. 2020;119:126-35.

18. Karyotaki E, Efthimiou O, Miguel C, Bermpohl FMg, Furukawa TA, Cuijpers P, et al. Internet-Based Cognitive Behavioral Therapy for Depression: A Systematic Review and Individual Patient Data Network Meta-analysis. JAMA Psychiatry. 2021;78(4):361-71.

19. Mehta S, Peynenburg VA, Hadjistavropoulos HD. Internet-delivered cognitive behaviour therapy for chronic health conditions: a systematic review and meta-analysis. Journal of Behavioral Medicine. 2019;42(2):169-87.

20. Gandy M, Pang STY, Scott AJ, Heriseanu AI, Bisby MA, Dudeney J, et al. Internet-delivered cognitive and behavioural based interventions for adults with chronic pain: a systematic review and meta-analysis of randomized controlled trials. PAIN. 2022.

21. Shah PB. Intention-to-treat and per-protocol analysis. Canadian Medical Association Journal. 2011;183(6):696-.

22. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

23. Akl EA, Sun X, Busse JW, Johnston BC, Briel M, Mulla S, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. Journal of Clinical Epidemiology. 2012;65(3):262-7.

24. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.

25. Murad MH, Montori VM, Ioannidis JPA, Prasad K, Cook DJ, Guyatt G. Fixed-Effects and Random-Effects Models. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice, 3rd ed. New York, NY: McGraw-Hill Education; 2015.

26. Cohen J. Statistical power analysis for the behavioral sciences (Revised ed.). Hillsdale, NJ: Lawrence Earlbaum Associates. Inc; 1988.

27. Anzures-Cabrera J, Higgins JPT. Graphical displays for meta-analysis: An overview with suggestions for practice. Research Synthesis Methods. 2010;1(1):66-80.

28. Baker WL, Michael White C, Cappelleri JC, Kluger J, Coleman CI. Understanding heterogeneity in meta-analysis: the role of meta-regression. Int J Clin Pract. 2009;63(10):1426-34.

29. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. Canadian Medical Association Journal. 2020;192(32):E901-E6.

30. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

31. Juul S, Gluud C, Simonsen S, Frandsen FW, Kirsch I, Jakobsen JC. Blinding in randomised clinical trials of psychological interventions: a retrospective study of published trial reports. BMJ Evidence-Based Medicine. 2021;26(3):109-.

32. Moustgaard H, Clayton GL, Jones HE, Boutron I, Jørgensen L, Laursen DRT, et al. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. BMJ. 2020;368:l6802.

33. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002.

34. Heapy AA, Higgins DM, Goulet JL, LaChappelle KM, Driscoll MA, Czlapinski RA, et al. Interactive Voice Response–Based Self-management for Chronic Back Pain: The COPES Noninferiority Randomized Trial. JAMA Internal Medicine. 2017;177(6):765-73.

35. Andersson G, Hesser H, Veilord A, Svedling L, Andersson F, Sleman O, et al. Randomised controlled non-inferiority trial with 3-year follow-up of internet-delivered versus face-to-face group cognitive behavioural therapy for depression. Journal of Affective Disorders. 2013;151(3):986-94.

36. Andrews G, Davies M, Titov N. Effectiveness randomized controlled trial of face to face versus Internet cognitive behaviour therapy for social phobia. Australian & New Zealand Journal of Psychiatry. 2011;45(4):337-40.

37. Axelsson E, Andersson E, Ljotsson B, Bjorkander D, Hedman-Lagerlof M, Hedman-Lagerlof E. Effect of Internet vs Face-to-Face Cognitive Behavior Therapy for Health Anxiety: A Randomized Noninferiority Clinical Trial. JAMA Psychiatry. 2020;77(9):915-24.

38. Bergstrom J, Andersson G, Ljotsson B, Ruck C, Andreewitch S, Karlsson A, et al. Internet-versus group-administered cognitive behaviour therapy for panic disorder in a psychiatric setting: a randomised trial. BMC Psychiatry. 2010;10:54.

39. Bessell A, Brough V, Clarke A, Harcourt D, Moss T, Rumsey N. Evaluation of the effectiveness of Face IT, a computer-based psychosocial intervention for disfigurement-related distress. Psychology, Health & Medicine. 2012;17(5):565-77.

40. Blom K, Tarkian Tillgren H, Wiklund T, Danlycke E, Forssen M, Soderstrom A, et al. Internet-vs. group-delivered cognitive behavior therapy for insomnia: A randomized controlled non-inferiority trial. Behaviour Research & Therapy. 2015;70:47-55.

41. Milgrom J, Danaher BG, Seeley JR, Holt CJ, Holt C, Ericksen J, et al. Internet and Face-to-face Cognitive Behavioral Therapy for Postnatal Depression Compared With Treatment as Usual: Randomized Controlled Trial of MumMoodBooster. Journal of Medical Internet Research. 2021;23(12):e17185.

42. Ying Y, Ji Y, Kong F, Wang M, Chen Q, Wang L, et al. Efficacy of an internet-based cognitive behavioral therapy for subthreshold depression among Chinese adults: a randomized controlled trial. Psychological medicine. 2022:1-11.

43. Kaldo V, Levin S, Widarsson J, Buhrman M, Larsen H-C, Andersson G. Internet versus group cognitive-behavioral treatment of distress associated with tinnitus: A randomized controlled trial. Behavior Therapy. 2008;39(4):348-59.

44. Peterson AL, Mintz J, Moring JC, Straud CL, Young-McCaughan S, McGeary CA, et al. In-office, in-home, and telehealth cognitive processing therapy for posttraumatic stress disorder in veterans: A randomized clinical trial. BMC Psychiatry Vol 22 2022, ArtID 41. 2022;22.

45. Lundström L, Flygare O, Andersson E, Enander J, Bottai M, Ivanov VZ, et al. Effect of Internet-Based vs Face-to-Face Cognitive Behavioral Therapy for Adults With Obsessive-Compulsive Disorder: A Randomized Clinical Trial. JAMA Network Open. 2022;5(3):e221967-e.

46. Carlbring P, Nilsson-Ihrfelt E, Waara J, Kollenstam C, Buhrman M, Kaldo V, et al. Treatment of panic disorder: live therapy vs. self-help via the Internet. Behaviour Research & Therapy. 2005;43(10):1321-33.

47. Conrad I, Kleinstauber M, Jasper K, Hiller W, Andersson G, Weise C. The changeability and predictive value of dysfunctional cognitions in cognitive behavior therapy for chronic tinnitus. International Journal of Behavioral Medicine. 2015;22(2):239-50.

48. de Boer M, Versteegen G, Vermeulen K, Sanderman R, Struys M. A randomized controlled trial of an internet-based cognitive-behavioural intervention for non-specific chronic pain: An effectiveness and cost-effectiveness study. European Journal of Pain. 2014;18(10):1440-51.

49. Gollings E, Paxton S. Comparison of Internet and face-to-face delivery of a group body image and disordered eating intervention for women: a pilot study. Eating Disorders. 2006;14(1):1-15.

50. Hedman E, Andersson G, Ljotsson B, Andersson E, Ruck C, Mortberg E, et al. Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: a randomized controlled non-inferiority trial. PLoS ONE [Electronic Resource]. 2011;6(3):e18001.

51. Jarnefelt H, Harma M, Sallinen M, Paajanen T, Virkkala J, Martimo KP, et al. Cognitive behavioural therapy for insomnia among shift workers: Analyses of an RCT study up to 24 months post-treatment. Journal of Sleep Research Conference: 25th Congress of the European Sleep Research Society, ESRS. 2020;29(SUPPL 1).

52. Jasper K, Weise C, Conrad I, Andersson G, Hiller W, Kleinstauber M. Internet-based guided self-help versus group cognitive behavioral therapy for chronic tinnitus: a randomized controlled trial. Psychotherapy & Psychosomatics. 2014;83(4):234-46.

53. Johansson M, Sinadinovic K, Gajecki M, Lindner P, Berman AH, Hermansson U, et al. Internet-based therapy versus face-to-face therapy for alcohol use disorder, a randomized controlled non-inferiority trial. Addiction. 2021;116(5):1088-100.

54. Kiropoulos LA, Klein B, Austin DW, Gilson K, Pier C, Mitchell J, et al. Is internet-based CBT for panic disorder and agoraphobia as effective as face-to-face CBT? Journal of Anxiety Disorders. 2008;22(8):1273-84.

55. Ye YY, Liu J, Li XJ, Liu YZ, Lang Y, Lin L, et al. The efficacy of internet-based cognitive behavioral therapy for insomnia. [Chinese]. Medical Journal of Chinese People's Liberation Army. 2016;41(4):307-11.

56. Leterme AC, Behal H, Demarty AL, Barasino O, Rougegrez L, Labreuche J, et al. A blended cognitive behavioral intervention for patients with adjustment disorder with anxiety: A randomized controlled trial. Internet Interventions. 2020;21:100329.

57. Lancee J, van Straten A, Morina N, Kaldo V, Kamphuis JH. Guided Online or Face-to-Face Cognitive Behavioral Treatment for Insomnia: A Randomized Wait-List Controlled Trial. Sleep. 2016;39(1):183-91.

58. Stubbings DR, Rees CS, Roberts LD, Kane RT. Comparing in-person to videoconference-based cognitive behavioral therapy for mood and anxiety disorders: Randomized controlled trial. Journal of Medical Internet Research. 2013;15(11):169-84.

59. Thase ME, Wright JH, Eells TD, Barrett MS, Wisniewski SR, Balasubramani G, et al. Improving the efficiency of psychotherapy for depression: Computer-assisted versus standard CBT. The American Journal of Psychiatry. 2018;175(3):242-50.

60. Wagner B, Horn AB, Maercker A. Internet-based versus face-to-face cognitive-behavioral intervention for depression: a randomized controlled non-inferiority trial. Journal of Affective Disorders. 2014;152-154:113-21.

61. Paxton SJ, McLean SA, Gollings EK, Faulkner C, Wertheim EH. Comparison of face-to-face and internet interventions for body image and eating problems in adult women: an RCT. International Journal of Eating Disorders. 2007;40(8):692-704.

62. Vallejo MA, Ortega J, Rivera J, Comeche MI, Vallejo-Slocker L. Internet versus face-to-face group cognitive-behavioral therapy for fibromyalgia: A randomized control trial. Journal of Psychiatric Research. 2015;68:106-13.

63. Zerwas SC, Watson HJ, Hofmeier SM, Levine MD, Hamer RM, Crosby RD, et al. CBT4BN: A randomized controlled trial of online chat and face-to-face group therapy for bulimia nervosa. Psychotherapy and Psychosomatics. 2016;86(1):47-53.

64. Kenardy JA, Dow MG, Johnston DW, Newman MG, Thomson A, Taylor C. A Comparison of Delivery Methods of Cognitive-Behavioral Therapy for Panic Disorder: An International Multicenter Trial. Journal of Consulting and Clinical Psychology. 2003;71(6):1068-75.

65. Azimi M, Moradi A, Hasani J. Effectiveness of cognitive behavioral therapy for insomnia (traditional and Internet-based) on everyday memory of people with insomnia and comorbid depression. Advances in Cognitive Science. 2019;20(4):20-34.

66. Anderson P, Jacobs CH, Lindner GK, Edwards S, Zimand E, Hodges L, et al. Cognitive behavior therapy for fear of flying: sustainability of treatment gains after September 11. Behavior Therapy. 2006;37(1):91-7.

67. Jasper K, Weise C, Conrad I, Andersson G, Hiller W, Kleinstauber M. The working alliance in a randomized controlled trial comparing Internet-based self-help and

face-to-face cognitive behavior therapy for chronic tinnitus. Internet Interventions. 2014;1(2):49-57.

68. Jarnefelt H, Harma M, Martimo KP, Paajanen T, Paunio T, Sallinen M, et al. Non-pharmacological interventions of insomnia among shift workers: An RCT trial in occupational health setting. Sleep Medicine. 2017;40(Supplement 1):e147.

69. Dedert E, McDuffie JR, Swinkels C, Shaw R, Fulton J, Allen KD, et al. Computerized Cognitive Behavioral Therapy for Adults with Depressive or Anxiety Disorders. 2013.

70. Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman EJWp. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. 2014;13(3):288-95.

71. Adelman CB, Panza KE, Bartley CA, Bontempo A, Bloch MH. A meta-analysis of computerized cognitive-behavioral therapy for the treatment of DSM-5 anxiety disorders. The Journal of Clinical Psychiatry. 2014;75(7):11699.

72. Botella C, Gallego M, Garcia-Palacios A, Guillen V, Banos R, Quero S, et al. An Internet-based self-help treatment for fear of public speaking: A controlled trial. Cyberpsychology, Behavior, and Social Networking. 2010;13(4):407-21.

73. Spek V, NyklÍČEk I, Smits N, Cuijpers PIM, Riper H, Keyzer J, et al. Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: a randomized controlled clinical trial. Psychological Medicine. 2007;37(12):1797-806.

74. Lappalainen P, Granlund A, Siltanen S, Ahonen S, Vitikainen M, Tolvanen A, et al. ACT Internet-based vs face-to-face? A randomized controlled trial of two ways to deliver Acceptance and Commitment Therapy for depressive symptoms: An 18-month follow-up. Behaviour Research and Therapy. 2014;61:43-54.

75. Andersson G, Waara J, Jonsson U, Malmaeus F, Carlbring P, Öst LG. Internet-Based Self-Help Versus One-Session Exposure in the Treatment of Spider Phobia: A Randomized Controlled Trial. Cognitive Behaviour Therapy. 2009;38(2):114-20.

76. Andersson G, Waara J, Jonsson U, Malmaeus F, Carlbring P, Öst L-G. Internet-Based Exposure Treatment Versus One-Session Exposure Treatment of Snake Phobia: A Randomized Controlled Trial. Cognitive Behaviour Therapy. 2013;42(4):284-91.

77. Schover LR, Canada AL, Yuan Y, Sui D, Neese L, Jenkins R, et al. A randomized trial of internet-based versus traditional sexual counseling for couples after localized prostate cancer treatment. Cancer. 2012;118(2):500-9.

78. Compen F, Bisseling E, Schellekens M, Donders R, Carlson L, Lee Mvd, et al. Face-to-Face and Internet-Based Mindfulness-Based Cognitive Therapy Compared With Treatment as Usual in Reducing Psychological Distress in Patients With Cancer: A Multicenter Randomized Controlled Trial. Journal of Clinical Oncology. 2018;36(23):2413-21.

79. Hedman E, El Alaoui S, Lindefors N, Andersson E, Ruck C, Ghaderi A, et al. Clinical effectiveness and cost-effectiveness of Internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-year follow-up of a randomized trial. Behaviour Research & Therapy. 2014;59:20-9.

80. Nordgren LB, Hedman E, Etienne J, Bodin J, Kadowaki Å, Eriksson S, et al. Effectiveness and cost-effectiveness of individually tailored Internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: A randomized controlled trial. Behaviour Research and Therapy. 2014;59:1-11.

81. Milosevic I, Cameron DH, Milanovic M, McCabe RE, Rowa K. Face-to-face versus Video Teleconference Group Cognitive Behavioural Therapy for Anxiety and Related Disorders: A Preliminary Comparison. The Canadian Journal of Psychiatry. 2022;67(5):391-402.

6.0 APPENDICES

6.1 Appendix A: summary of the search and strategy for remote CBT vs in-person CBT

	Total
MEDLINE	5131
EMBASE	5314
PsycInfo	3311
CINAHL	2070
Subtotal	15826
-dupes	6,669
Total	9157

May 11, 2022

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

---

1 Internet-Based Intervention/ (943)
2 Internet/ (79173)
3 (internet or computer or computerized).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (936793)
4 (virtual or online).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (255171)
5 or/1-4 (1125862)
6 exp Cognitive Behavioral Therapy/ (34142)
7 ((cognitive or behavio?r*) adj3 therapy).mp,jw. (78403)
8 Psychotherapy/ (56580)
9 Psychotherapy, Group/ (14385)
10 ((psychological or psychotherap*) adj3 (treatment or intervention)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol

supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (14412)
11 or/6-10 (152406)
12 5 and 11 (9037)
13 randomized controlled trial.pt. (568831)
14 controlled clinical trial.pt. (94874)
15 randomi?ed.ab. (671298)
16 placebo.ab. (228333)
17 drug therapy.fs. (2491521)
18 randomly.ab. (382381)
19 trial.ab. (600273)
20 groups.ab. (2351679)
21 or/13-20 (5372718)
22 exp animals/ not humans.sh. (5007370)
23 21 not 22 (4678361)
24 5 and 11 and 23 (5131)
25 limit 24 to ed=20210927-20220511 (410)

EMBASE (OVID)

Database: Embase <1974 to 2022 May 10>
Search Strategy:
---
1 internet/ or web-based intervention/ (118628)
2 (internet or computer or computerized).mp. (1839130)
3 (virtual or online).mp. (357828)
4 or/1-3 (2114211)
5 exp cognitive behavioral therapy/ (20315)
6 ((cognitive or behavio?r*) adj3 therapy).mp,jw. (116976)
7 psychotherapy/ (91342)
8 ((psychological or psychotherap*) adj3 (treatment or intervention)).mp. (21012)
9 or/5-8 (203912)
10 4 and 9 (13780)
11 randomized controlled trial/ (707876)
12 Controlled clinical study/ (465554)
13 random$.ti,ab. (1786058)
14 randomization/ (93759)
15 intermethod comparison/ (282803)
16 placebo.ti,ab. (340403)
17 (compare or compared or comparison).ti. (563886)
18 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2492444)
19 (open adj label).ti,ab. (96663)

20 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (256119)
21 double blind procedure/ (194713)
22 parallel group$1.ti,ab. (29310)
23 (crossover or cross over).ti,ab. (116153)
24 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (378924)
25 (assigned or allocated).ti,ab. (446449)
26 (controlled adj7 (study or design or trial)).ti,ab. (406746)
27 (volunteer or volunteers).ti,ab. (267325)
28 human experiment/ (574420)
29 trial.ti. (357813)
30 or/11-29 (5755405)
31 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8972)
32 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (308888)
33 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (19749)
34 (Systematic review not (trial or study)).ti. (208892)
35 (nonrandom$ not random$).ti,ab. (17756)
36 "Random field$".ti,ab. (2700)
37 (random cluster adj3 sampl$).ti,ab. (1438)
38 (review.ab. and review.pt.) not trial.ti. (991175)
39 "we searched".ab. and (review.ti. or review.pt.) (41762)
40 "update review".ab. (122)
41 (databases adj4 searched).ab. (50518)
42 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1150286)
43 Animal experiment/ not (human experiment/ or human/) (2413831)
44 or/31-43 (3958536)
45 30 not 44 (5097203)
46 10 and 45 (5314)
47 limit 46 to dc=20210925-20220511 (491)

PsycInfo (OVID)
Database: APA PsycInfo <1806 to May Week 1 2022>

Search Strategy:
---
1 internet/ (30330)
2 online therapy/ (3629)

3 (internet or computer or computerized).mp. (221044)
4 (virtual or online).mp. (136957)
5 or/1-4 (313914)
6 exp cognitive behavior therapy/ (24761)
7 ((cognitive or behavio?r*) adj3 therapy).mp,jw. (93862)
8 psychotherapy/ (56475)
9 ((psychological or psychotherap*) adj3 (treatment or intervention)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (22036)
10 or/6-9 (159655)
11 5 and 10 (8121)
12 limit 11 to "therapy (best balance of sensitivity and specificity)" (2193)
13 (double-blind or random: assigned or control).tw. (525035)
14 exp clinical trials/ (13203)
15 (controlled adj3 trial*).mp. (59088)
16 (clinical adj2 trial*).mp. (51264)
17 (randomi?ed adj7 trial*).mp. (70174)
18 or/13-17 (592961)
19 11 and 18 (3311)
20 12 or 19 (3311)
21 limit 20 to up=20210925-20220511 (175)

CINAHL (EBSCO)

Wednesday, May 11, 2022 4:12:48 PM

#	Query	Results
S28	S27 Limiters - Published Date: 20210901-20220531	149
S27	S10 AND S26	2,070
S26	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	953,339
S25	AB (CLUSTER W3 RCT)	452
S24	MH (CROSSOVER DESIGN) OR MH (COMPARATIVE STUDIES)	452,680
S23	AB (CONTROL W5 GROUP)	133,317
S22	PT (randomized controlled trial)	141,292
S21	MH (placebos)	13,314

S20	MH (sample size) AND AB (assigned OR allocated OR control)	4,337
S19	TI (trial)	164,009
S18	AB (random*)	372,462
S17	TI (randomised OR randomized)	127,215
S16	MH cluster sample	4,971
S15	MH pretest-posttest design	49,145
S14	MH random assignment	73,530
S13	MH single-blind studies	15,573
S12	MH double-blind studies	52,803
S11	MH randomized controlled trials	127,977
S10	S4 AND S9	4,774
S9	S5 OR S6 OR S7 OR S8	61,872
S8	TX ((psychological or psychotherap*) N3 (treatment or intervention))	12,739
S7	(MH "Psychotherapy") OR (MH "Psychotherapy, Group")	28,206
S6	TX ((cognitive or behavio?r*) N3 therapy)	28,630
S5	(MH "Cognitive Therapy")	20,464
S4	S1 OR S2 OR S3	349,817
S3	TX virtual or online	129,157
S2	TX internet or computer or computerized	253,767
S1	(MH "Internet") OR (MH "Internet-Based Intervention")	53,874

6.2 Appendix B: Table 3.Type of analyses for eligible studies

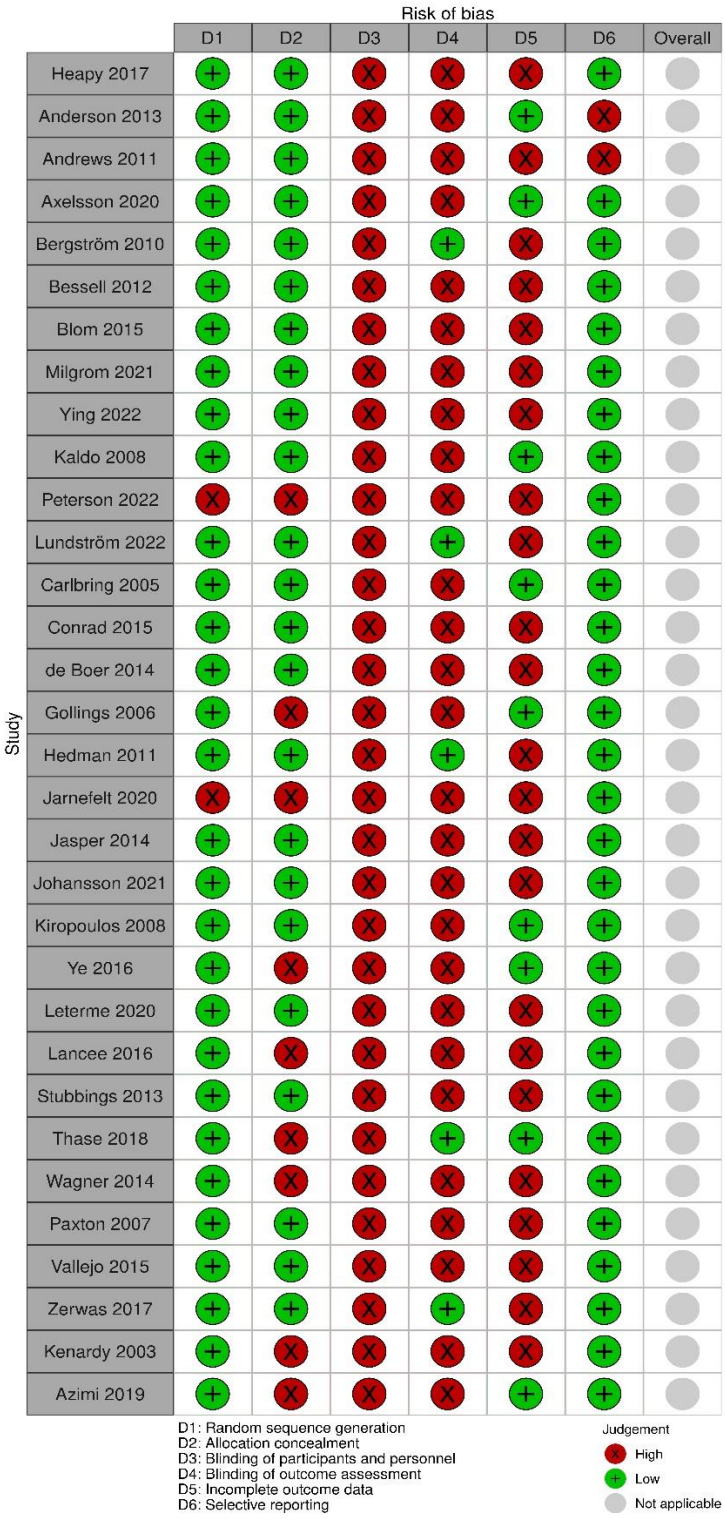
Study	Type of analysis				Type of imputation (Comments)
	1) Intention-to-treat (ITT) with complete data	2) Intention-to-treat (ITT) with imputed data	3) per-protocol (PP) analyses without imputation	4) per-protocol (PP) analyses with imputation	
Heapy 2017	*			*	NA
Anderson 2013		*		*	Maximum likelihood estimation
Andrews 2011		*			Who did not complete the post-treatment questionnaires were replicated as their post-treatment scores.
Axelsson 2020		*		*	Multiple imputations by chained equations (20 samples).
Bergström 2010		*			Account for missing data we used a mixed effects models approach
Bessell 2012		*			NR
Blom 2015		*	*		Linear regression formula was used to impute missing Internet values (ISI) from telephone values
Milgrom 2021		*			NR
Ying 2022		*			least-squares means (LS means)
Kaldo 2008					(last observation carried forward;LOCF).
Peterson 2022	*				NA
Lundstrom 2022		*			NR
Carlbring		*			Carrying forward data

2005					
Conrad 2014	*	*		*	The procedure produced five data sets using the monotone multiple imputation algorithm
de Boer 2014	*	*			'baseline observation carried forward' (BOCF)
Gollings 2006	*				NA
Hedman 2011	*	*			missing values were replaced with "no change" (carrying forward last observation)
Jarnefelt 2020		*			carry forward last observation
Jasper 2014		*			monotone multiple imputation algorithm
Johansson 2021		*	*		The imputations were performed using predictive mean matching and fully conditional specification (10 maximum iterations), with the constraint that baseline variables were predictors-only.
Kiropoulos 2008	*				NA
Ye 2016	NR	NR	NR	NR	NR
Leterme 2020		*	*	*	Multiple imputation, using missing at random assumption, using a regression-switching approach (chained equation with m = 20 imputations) with a predictive mean matching method for continuous variables and logistic regression (binary, ordinal, or polynomial) for qualitative variables
Lancee 2016	*	*			Multiple imputation using missing at random assumption
Stubbings 2013			*		NA
Thase 2018		*			A multiple imputation method was used. Five complete data sets were generated using the Markov Chain Monte Carlo method with a single chain to create five different imputations of missing data. The results from the 5 complete data sets were then combined and averages were calculated to estimate the missing scores in the analyses of continuous measures
Wagner 2014	*				Missing data adressed by carrying forward the first available data (i.e., baseline observation)
Paxton 2007	*	*			NR
Vallejo 2015		*			NR

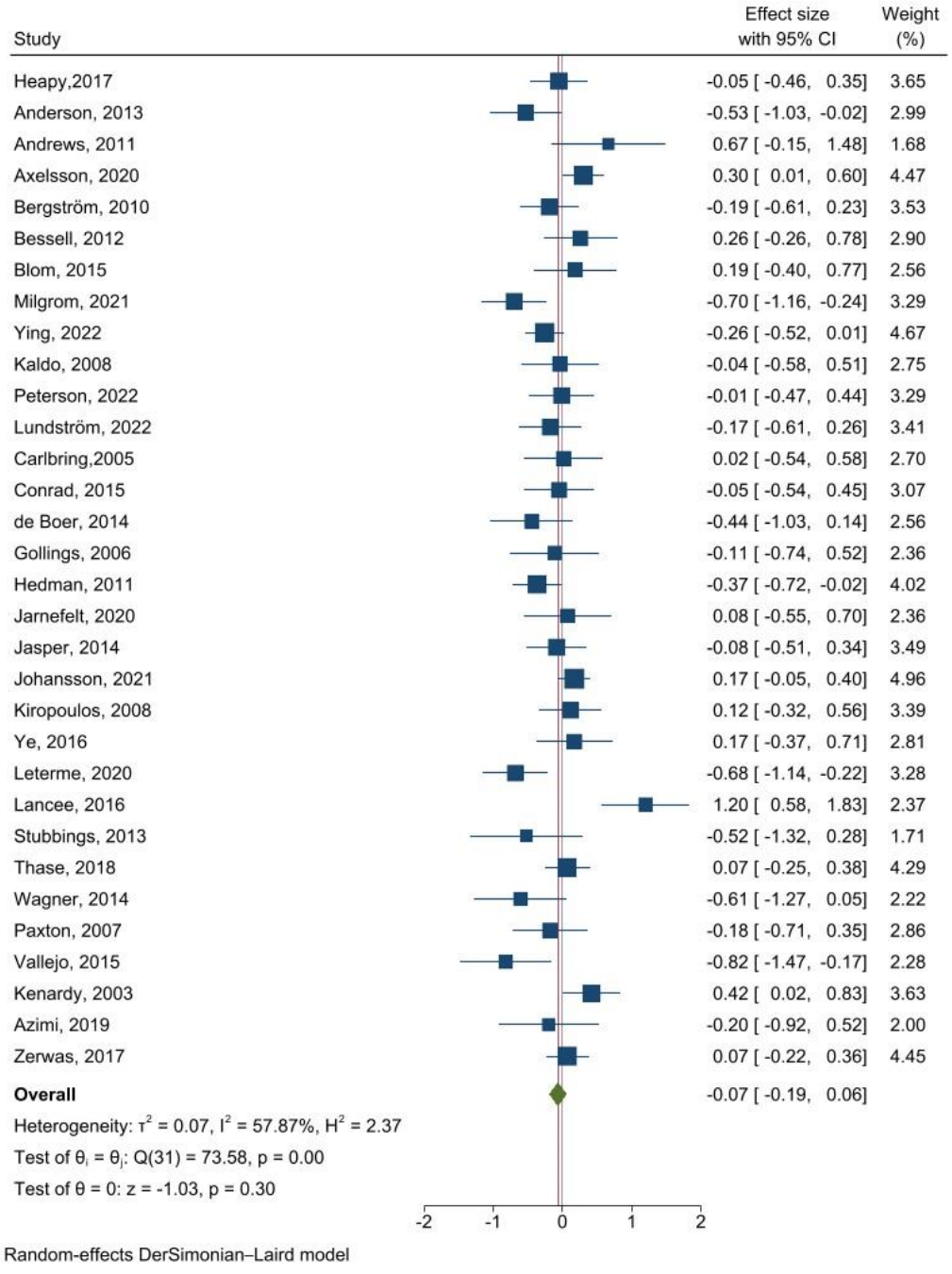
Zerwas 2017	*	*			Multiple imputation by chained equations (MI) and maximum likelihood estimation with the expectation maximization imputation
Kenardy 2003	*		*		All cases with available pretreatment data were carried forward.
Azimi 2019	NR	NR	NR	NR	NR

NR= not reported NA= Not Applicable

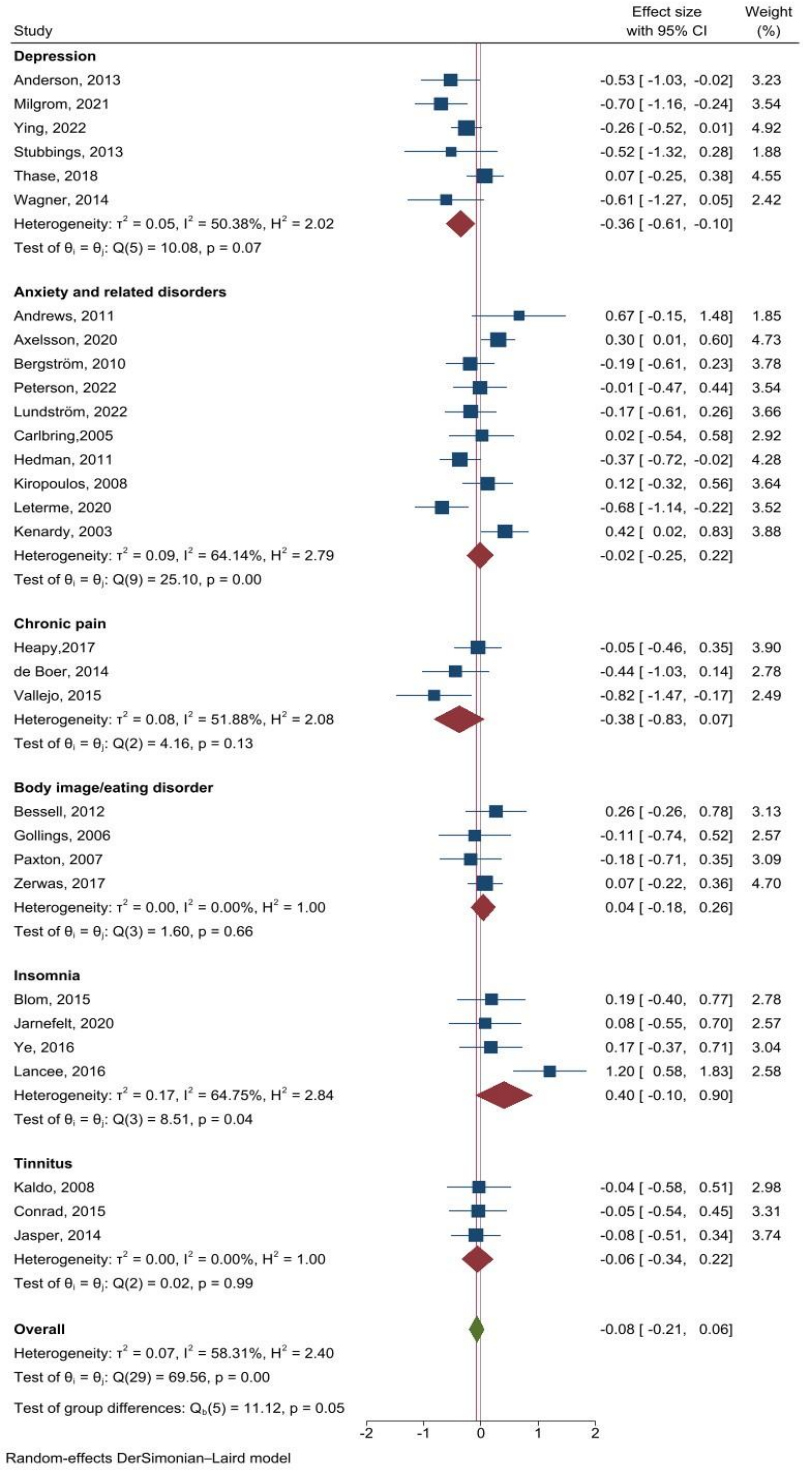
6.3 Appendix C: Risk of Bias Diagram



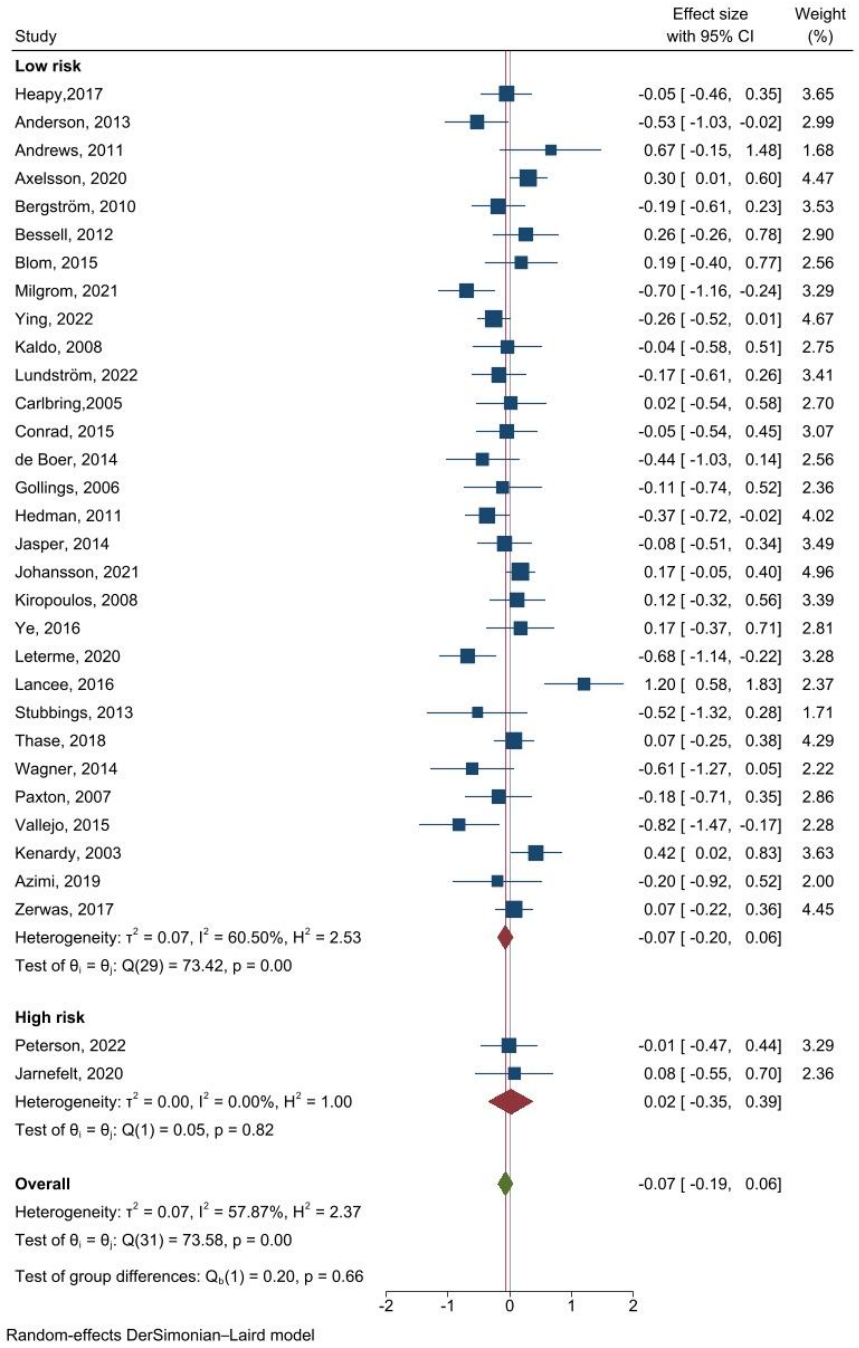
6.4 Appendix D: Forest plot for overall effect



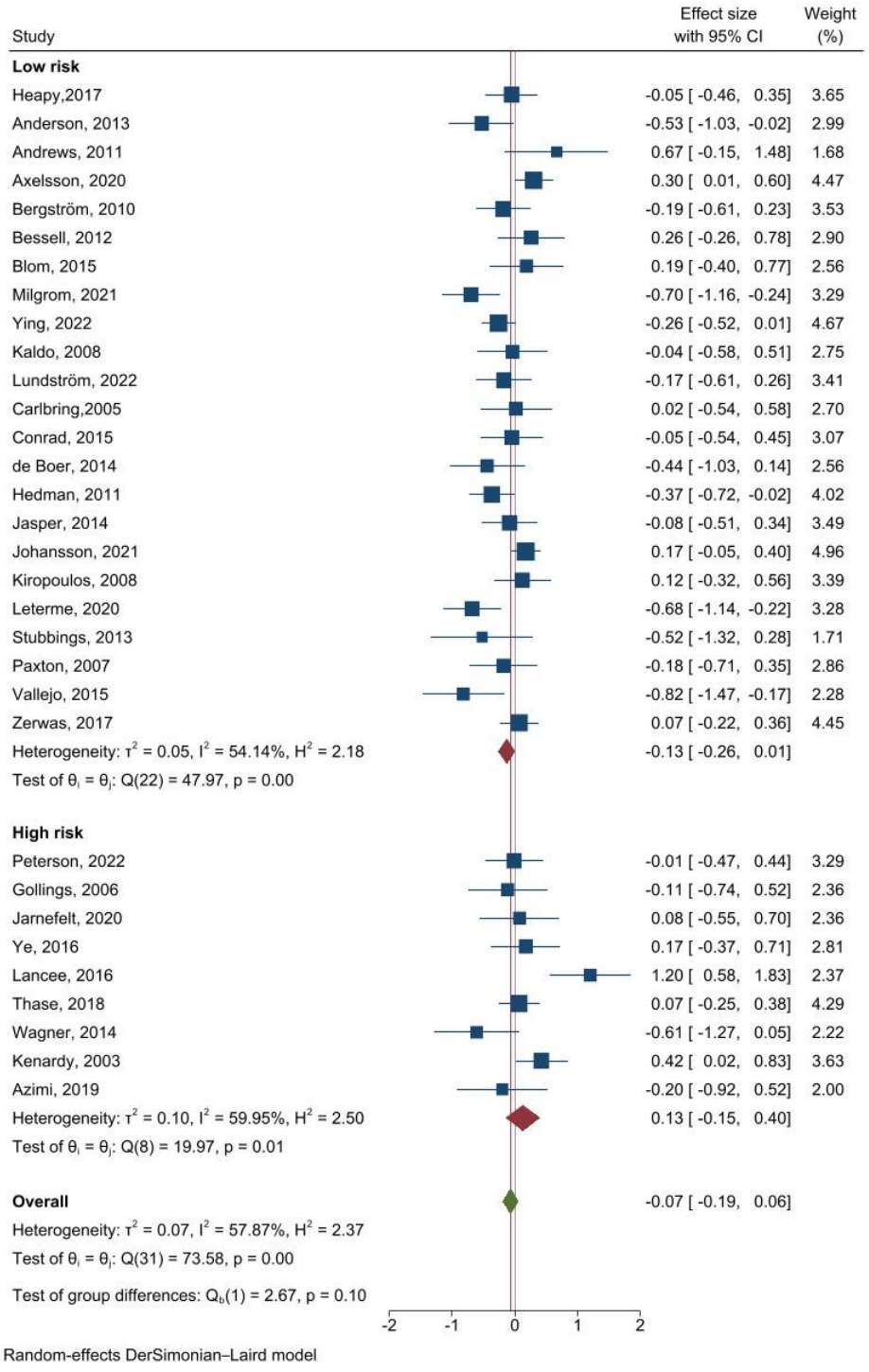
6.5 Appendix E: Forest plot for subgroup clinical conditions



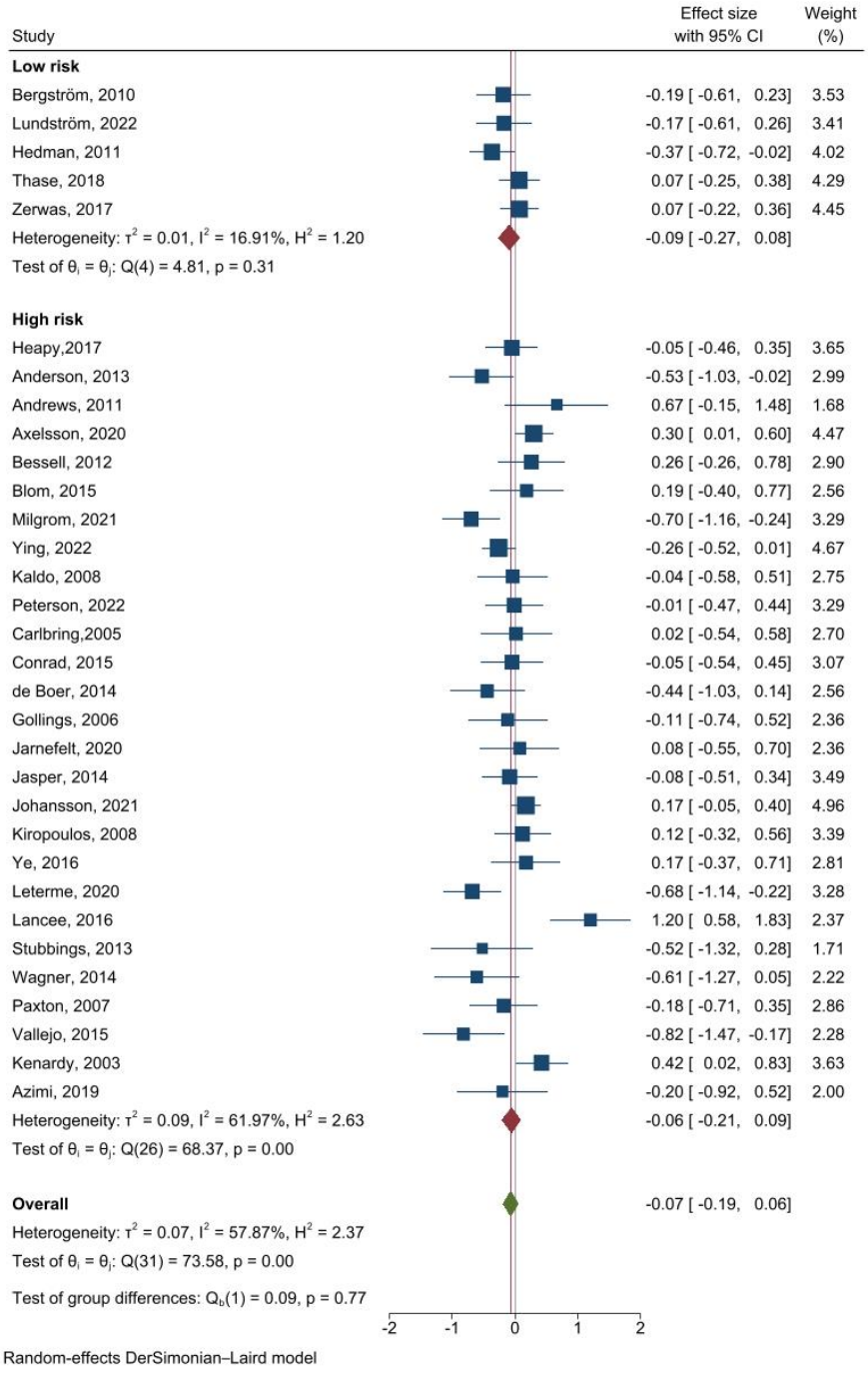
6.6 Appendix F: Subgroup for Random sequence generation



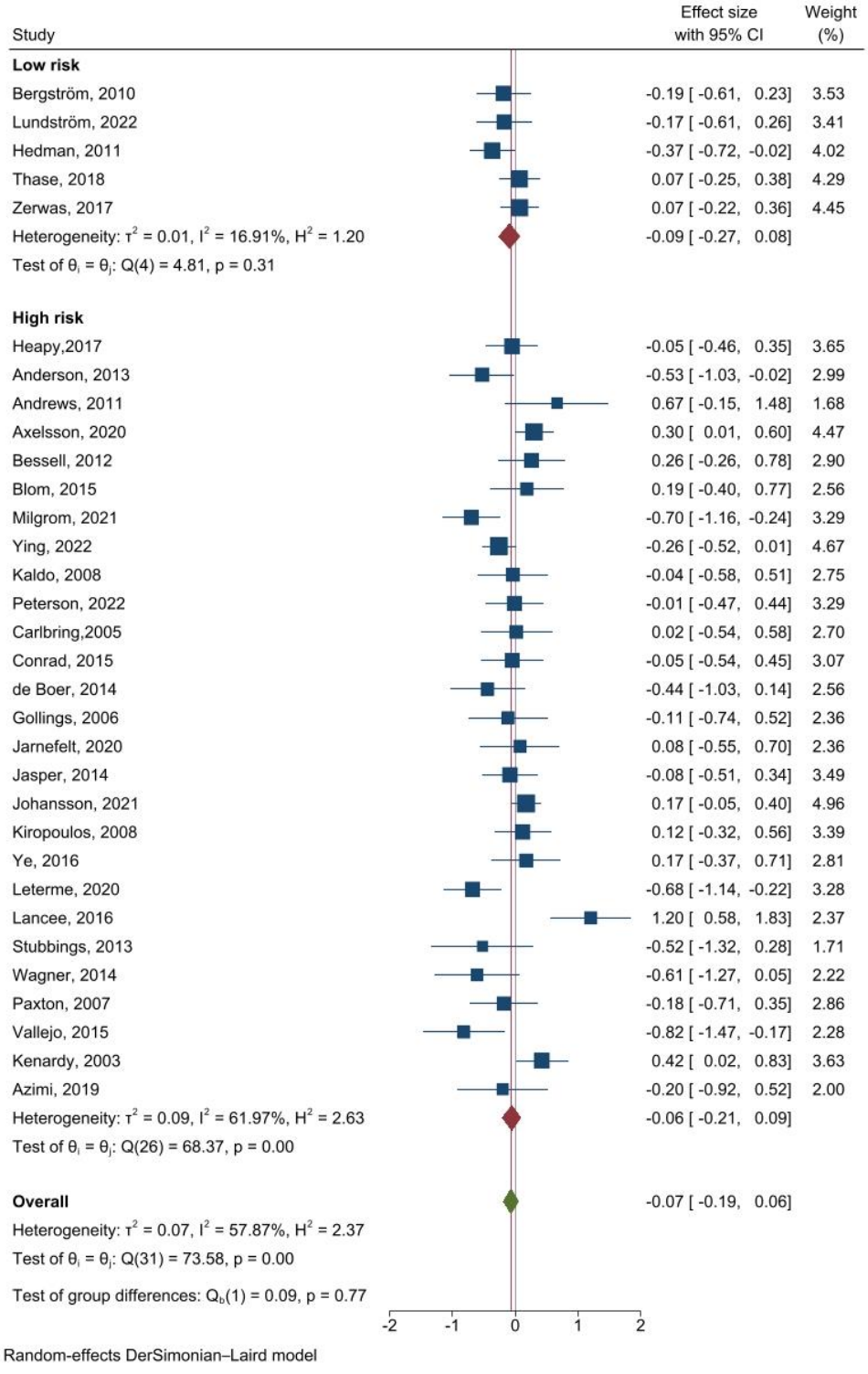
6.7 Appendix G: Subgroup for Allocation concealment



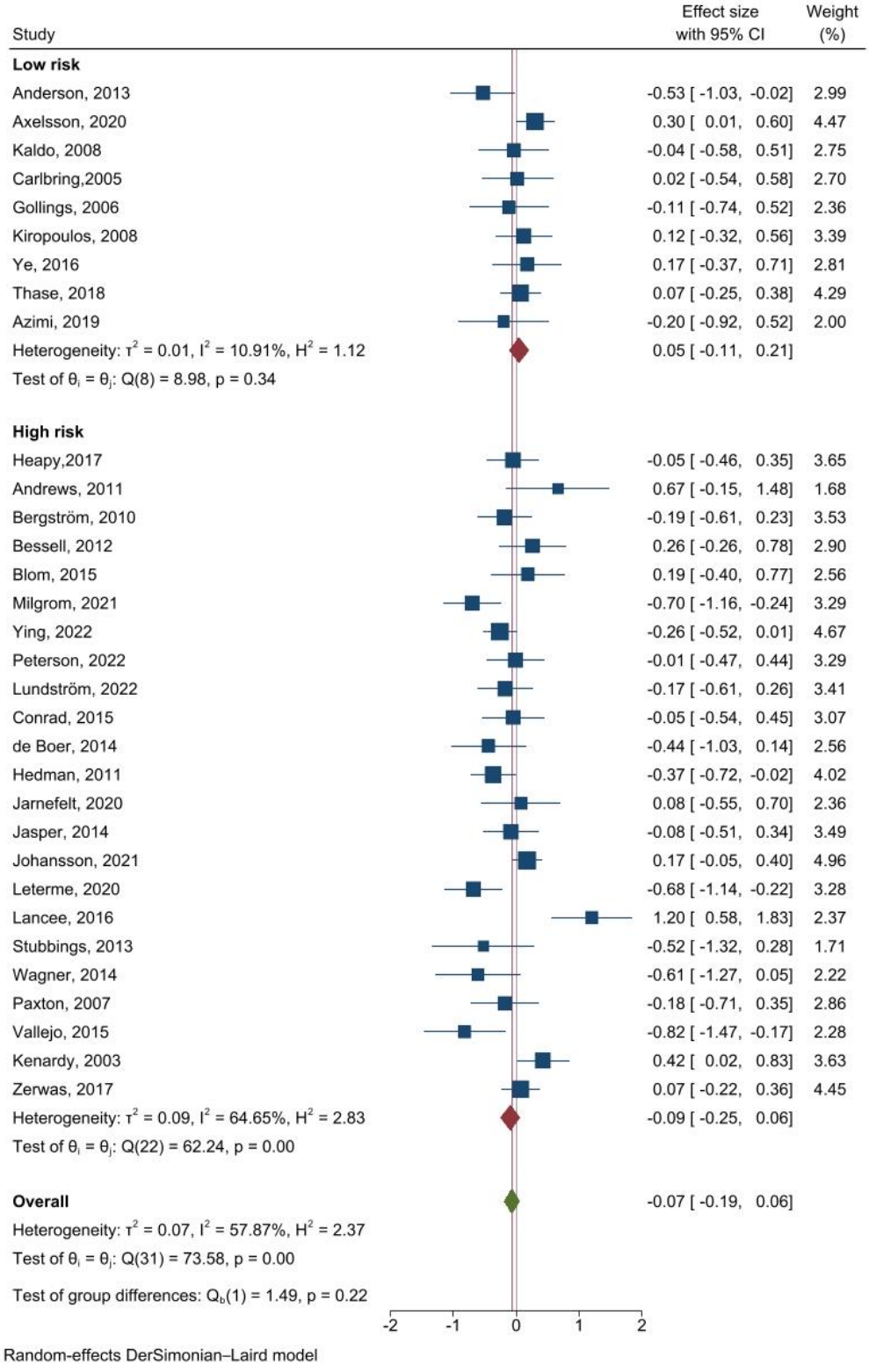
6.8 Appendix H: Subgroup for Blinding of data collectors



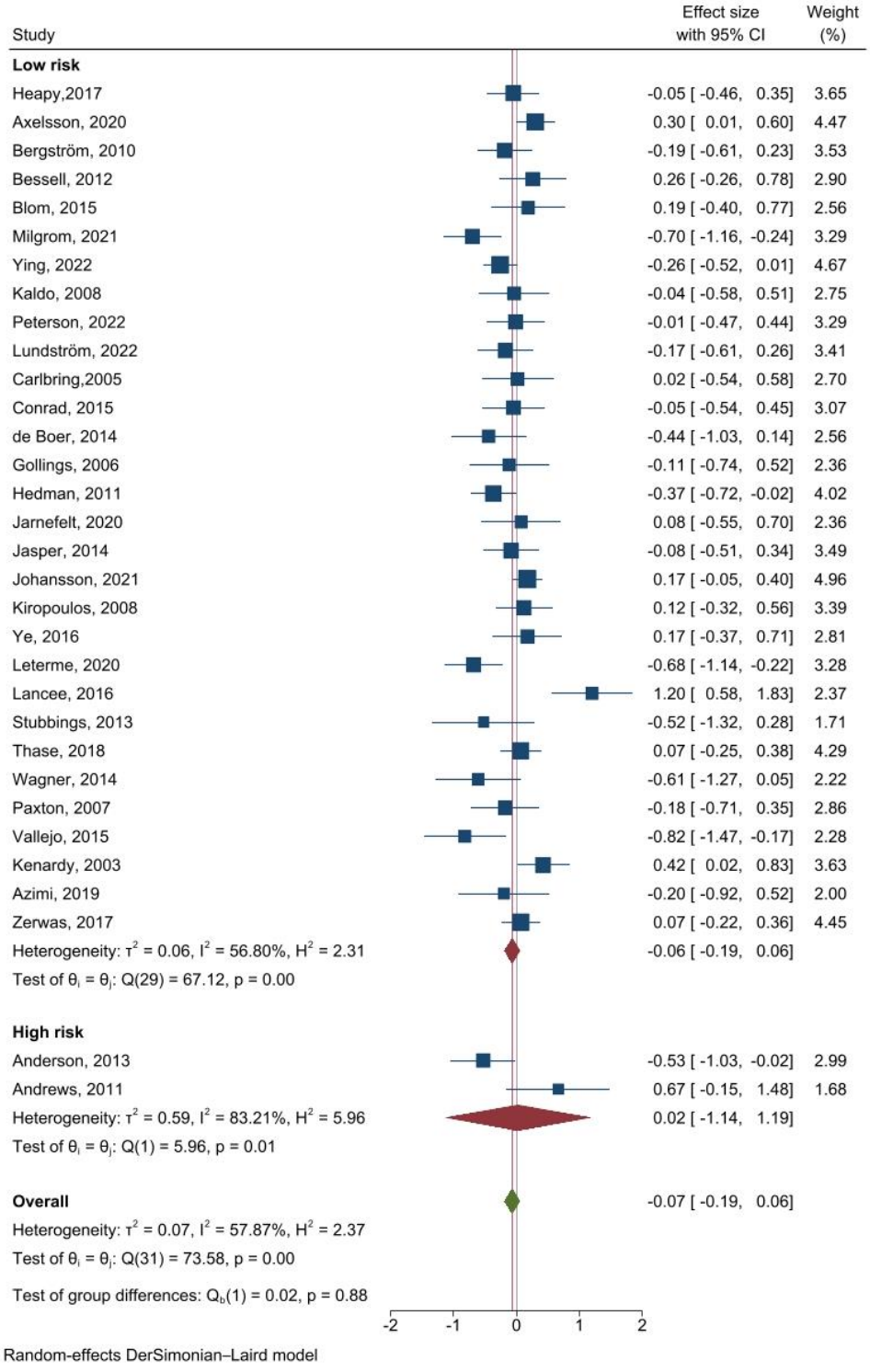
6.9 Appendix I: Subgroup for Blinding of outcome assessors



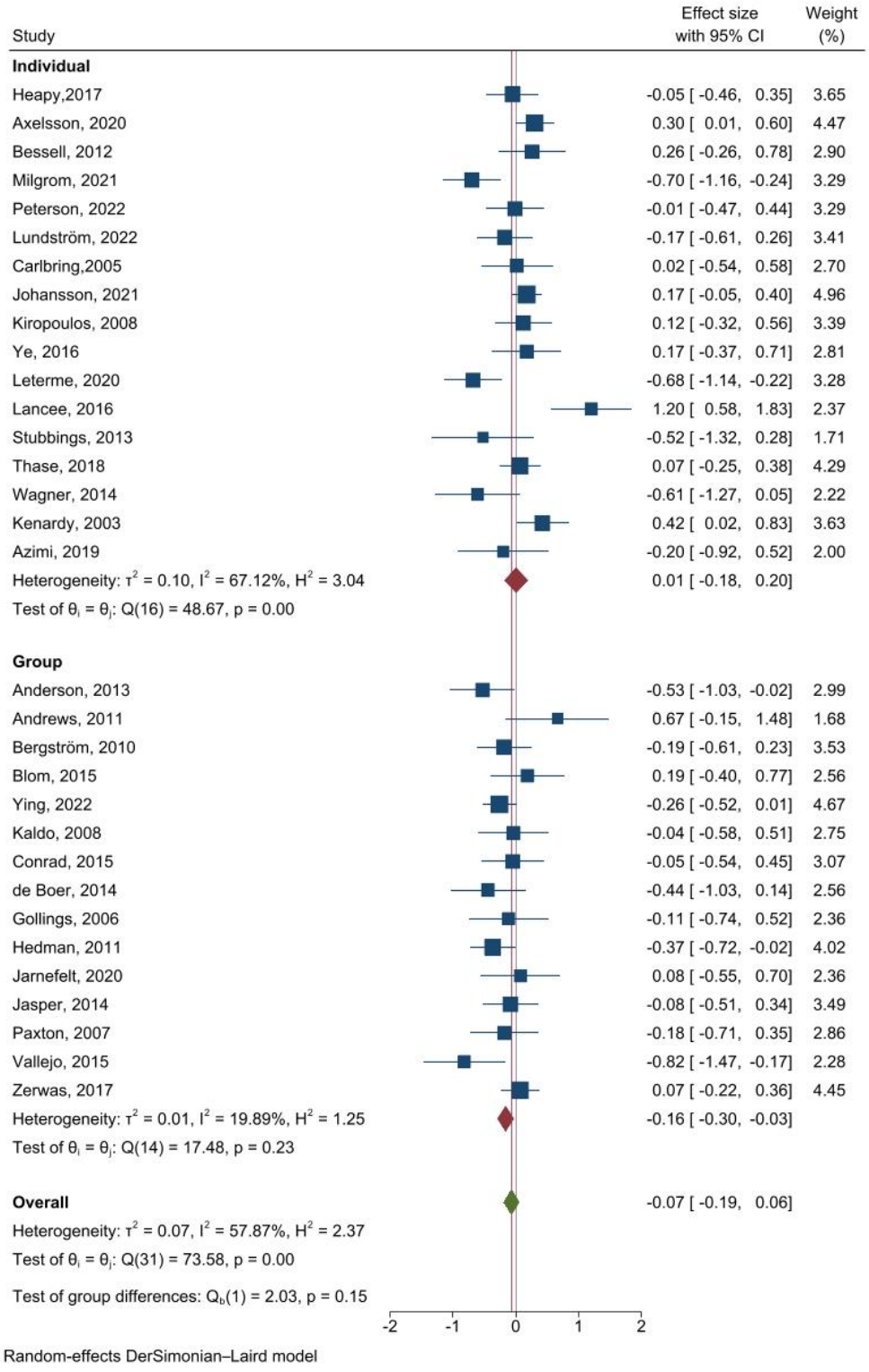
6.10 Appendix J: Subgroup for missing outcome data



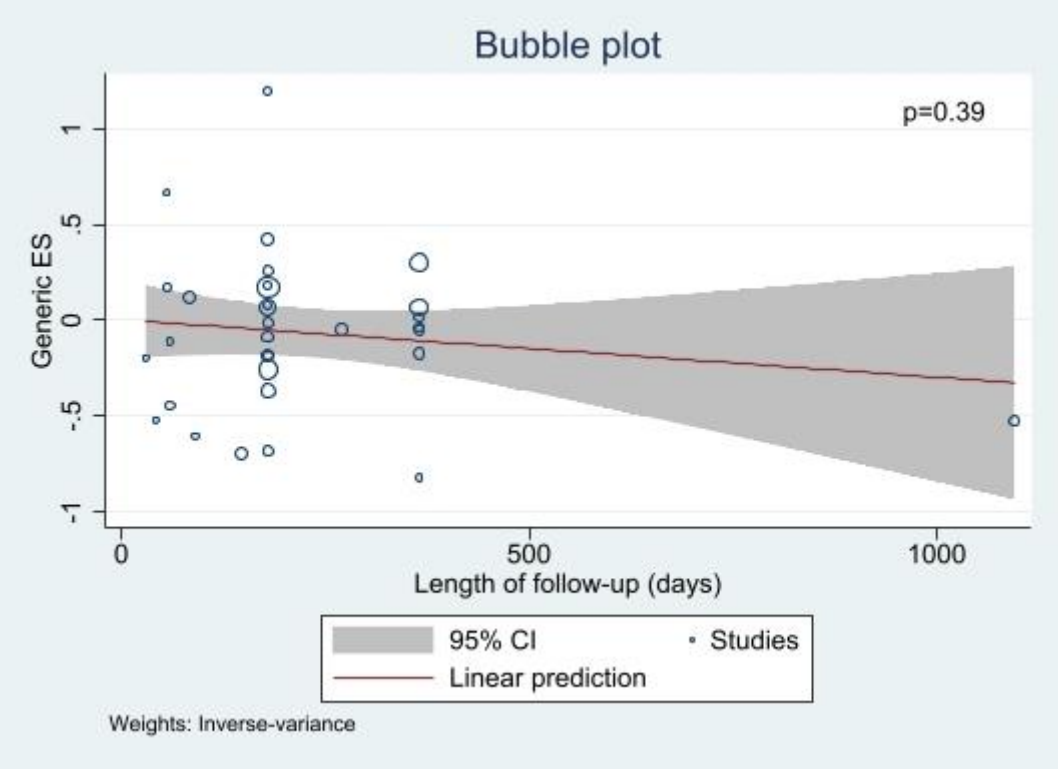
6.11 Appendix K: Subgroup for selective reporting



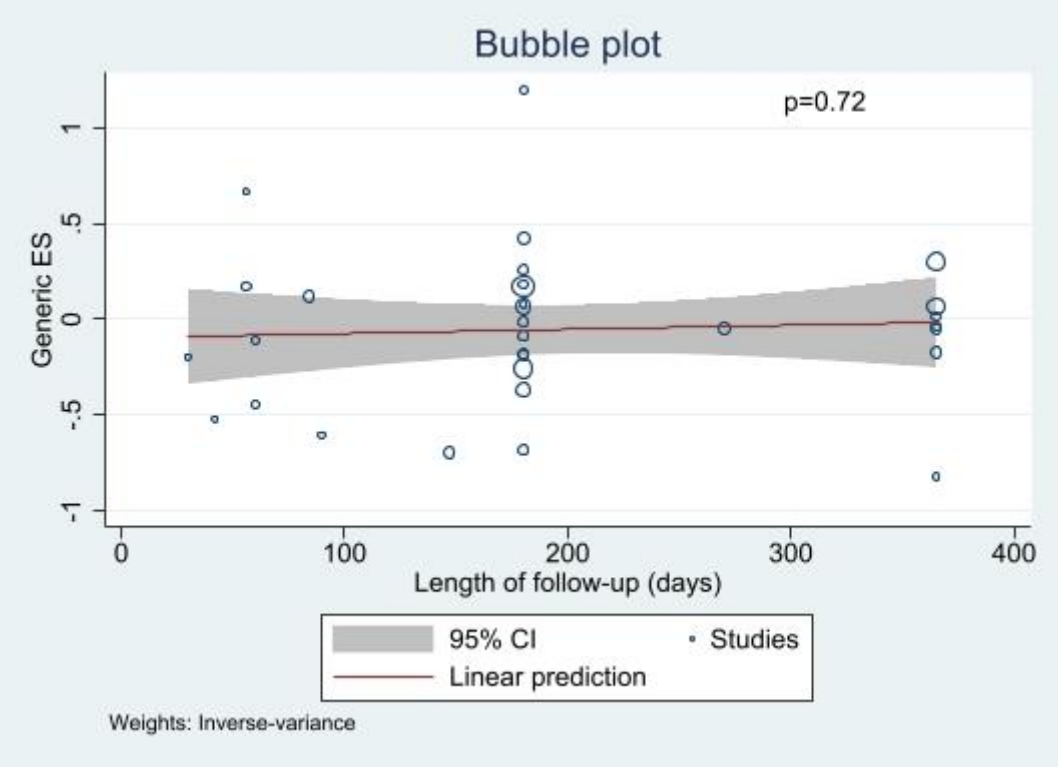
6.12 Appendix L: Subgroup for individual therapy vs group therapy



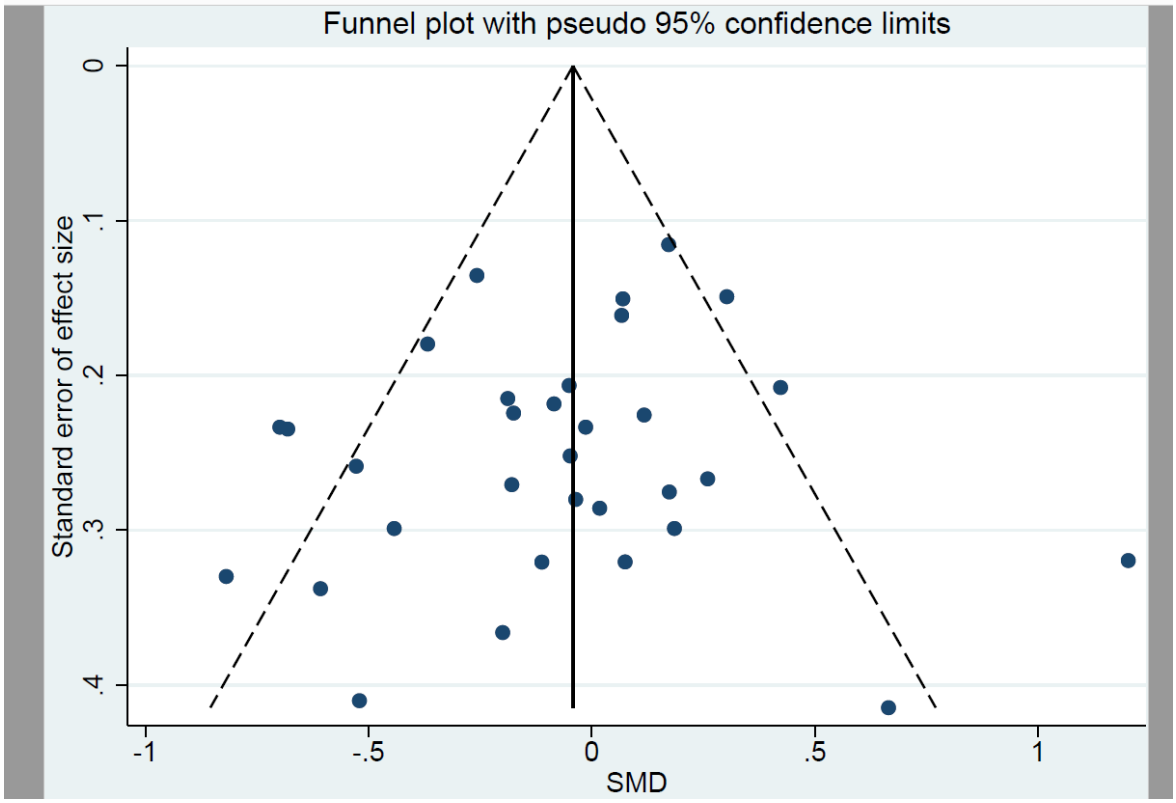
6.13 Appendix M: Meta-regression for loss to follow-up



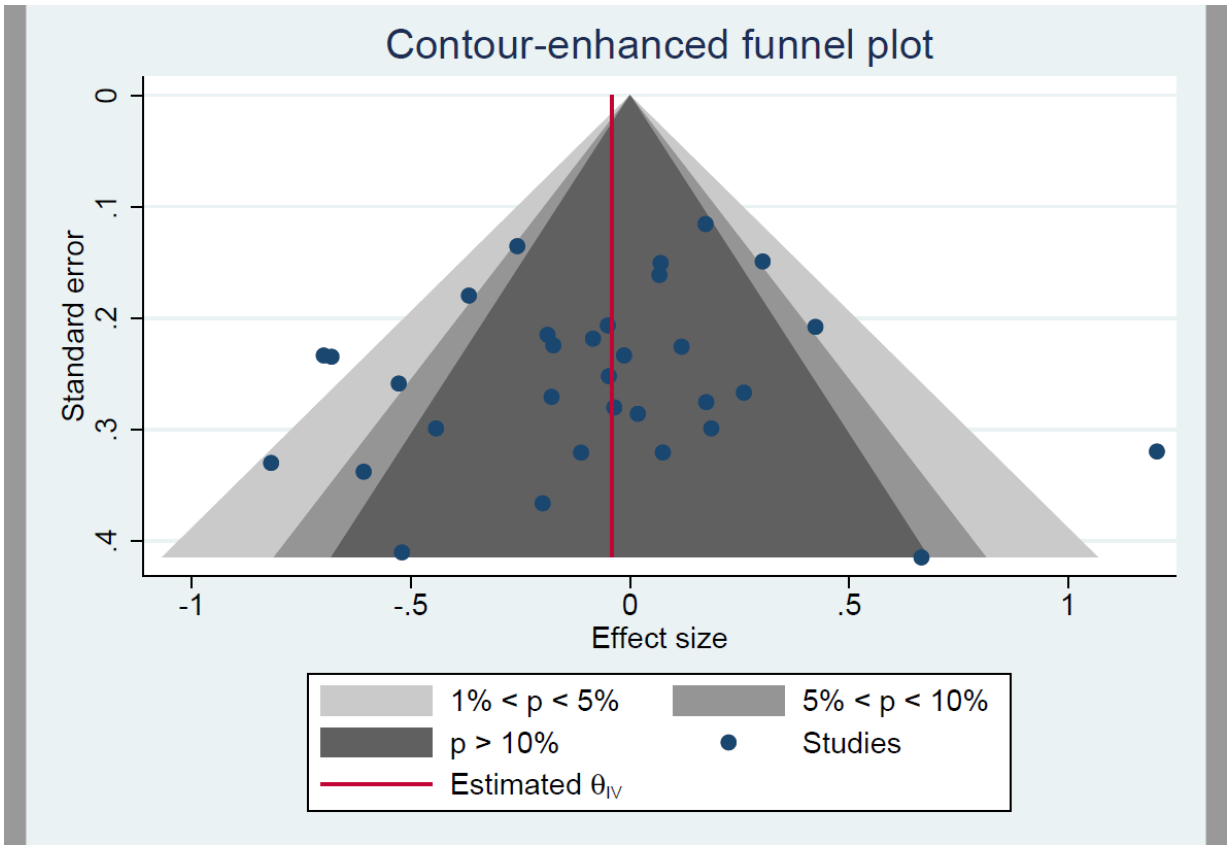
6.14 Appendix N: Meta-regression for loss to follow-up without outlier



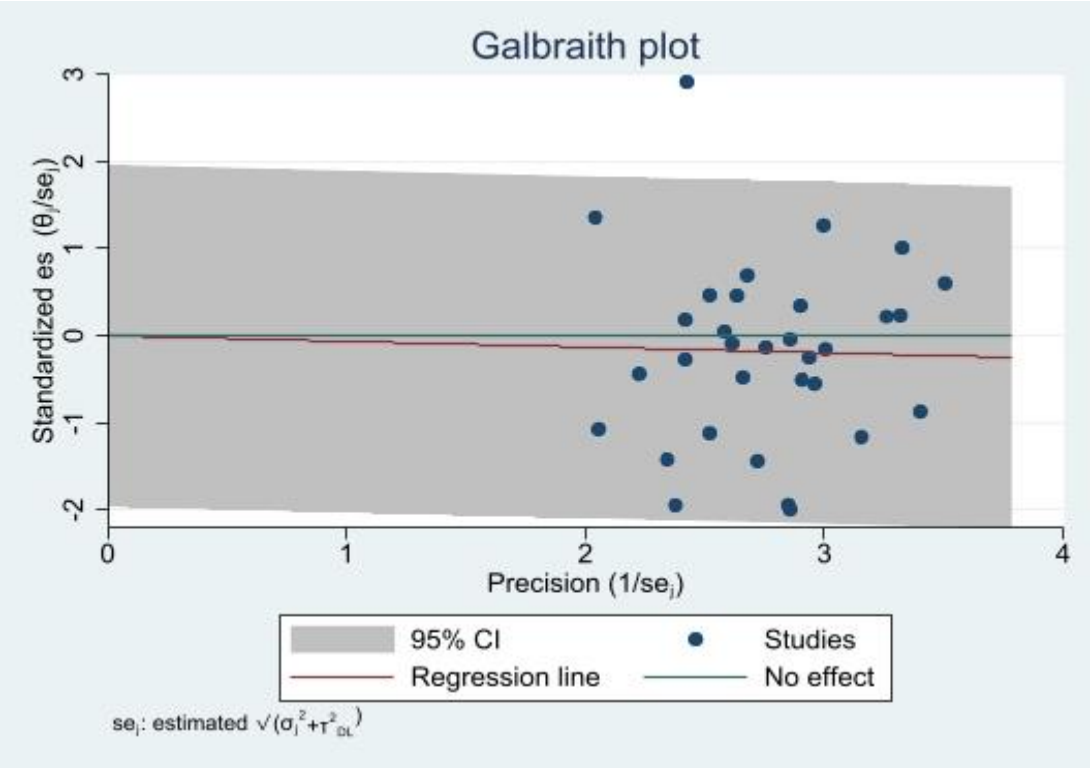
6.15 Appendix O: Funnel plot



6.16 Appendix P: Contoured funnel plot



6.17 Appendix Q: Galbraight plot



6.18 Appendix R: ICEMAN Table

ICEMAN Evaluation for health conditions subgroup

Outcome	Patient's important primary outcome
Subgroup analysis	Type of health conditions
1: Is the analysis of effect modification based on comparison within rather than between trials?	Completely between
2: For within trial comparisons, is the effect modification similar from trial to trial?	Not applicable
3: For between-trial comparisons, is the number of trials large?	Rather small or unclear
4: Was the direction of effect modification correctly hypothesized a priori?	Probably no or unclear
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?	Chance a likely explanation or unclear
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?	Probably no or unclear
7: Did the authors use a random effects model?	Definitely yes
8: If the effect modifier is a Continuous variable, were arbitrary cut points avoided?	Not applicable
Overall credibility	Low