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Review

Effects and moderators of coping skills training on symptoms of depression and anxiety in patients with cancer: Aggregate data and individual patient data meta-analyses

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HIGHLIGHTS

- The average effect of CST on symptoms of anxiety and depression in cancer patients are statistically significant but small
- Younger patients and patients who received chemotherapy benefit more from CST
- CST effects are larger when delivered face-to-face, led by a psychologist and targeted to patients with psychological distress

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ABSTRACT

Purpose: This study evaluated the effects of coping skills training (CST) on symptoms of depression and anxiety in cancer patients, and investigated moderators of the effects.
Methods: Overall effects and intervention-related moderators were studied in meta-analyses of pooled aggregate data from 38 randomized controlled trials (RCTs). Patient-related moderators were examined using linear mixed-effect models with interaction tests on pooled individual patient data (n = 1953) from 15 of the RCTs.
Results: CST had a statistically significant but small effect on depression (g = −0.31,95% confidence interval (CI) = −0.40;-0.22) and anxiety (g = −0.32,95%CI = -0.41;-0.24) symptoms. Effects on depression symptoms were significantly larger for interventions delivered face-to-face (p = .003), led by a psychologist (p = .02) and targeted to patients with psychological distress (p = .002). Significantly larger reductions in anxiety symptoms were found in younger patients ($p_{interaction}$ < 0.025), with the largest reductions in patients < 50 years (β = −0.31,95%CI = -0.44;-0.18) and no significant effects in patients ≥70 years. Effects of CST on depression (β = −0.16,95%CI = -0.25;-0.07) and anxiety (β = −0.24,95%CI = -0.33;-0.14) symptoms were significant in patients who received chemotherapy but not in patients who did not ($p_{interaction}$ < 0.05).
Conclusions: CST significantly reduced symptoms of depression and anxiety in cancer patients, and particularly when delivered face-to-face, provided by a psychologist, targeted to patients with psychological distress, and given to patients who were younger and received chemotherapy.

1. Introduction

A substantial proportion of patients with cancer experience symptoms of depression and anxiety (these symptoms will be referred to as depression and anxiety throughout the manuscript for clarity). Previous studies found that 7–31% of patients suffer from depression and 8–19% of patients experience anxiety, with proportions varying by the type of cancer and assessment method (Krebber et al., 2014; Mitchell et al., 2011; Zhu et al., 2017). Evidence suggests that, next to fatigue (Barsevick et al., 2013) and pain (van den Beuken-van Everdingen, Hochstenback, Joosten, Tjan-Heijnen, & Janssen, 2016), depression and anxiety are among the most common symptoms that affect cancer patients' health-related quality of life (Cleeland et al., 2000; Dauchy, Dolbeault, & Reich, 2013; Hutter et al., 2013; Jacobsen & Jim, 2008; Nikbakhsh, Moudi, Abbasian, & Khafri, 2014; Pirl, 2004) and treatment adherence (Arrieta et al., 2013; Barber et al., 2015). It is therefore important to adequately address depression and anxiety in clinical cancer care.

Various psychosocial interventions are available to manage depression and anxiety, which can be subdivided into psycho-education, supportive interventions with a focus on acknowledgement of problems and expression of emotions, coping skills training (CST), (psycho-dynamic) psychotherapy and spiritual or existential therapy (Cunningham A.J. 1995). Although each of these types of interventions can be used to treat or ameliorate depression and anxiety in cancer patients, the focus here will be on the evidence on the efficacy of CST, as this is the most prevalent form of therapy (Kalter et al., 2018). CST, which encompasses interventions like cognitive behavioural therapy (CBT) or problem solving therapy, aims to enhance the patient's ability to cope with the sequela of cancer and its treatment. In these interventions, patients learn new cognitive-behavioural skills such as relaxation, mental imagery, thought and affect management, and activity planning (Jacobsen & Jim, 2008; Kalter et al., 2018). Results from previous meta-analyses have shown that CST reduces depression (medium effect size of 0.34–0.38) and anxiety (medium effect size of 0.31–0.42) in patients with cancer (Ballesio et al., 2017; Matthews, Grunfeld, & Turner, 2016; Sheard & Maguire, 1999). However, there is a substantial heterogeneity in effects across the different studies that may be explained by specific patient- and intervention-related characteristics. Previous meta-analyses and randomized controlled trials (RCTs) reported larger benefits of CST in men versus women, married versus single patients, patients with breast cancer versus other types of cancer, patients with metastatic versus local or loco-regional disease, patients who received chemotherapy versus other types of treatment, interventions led by a mental health professional versus nurses or other health care professionals, and in studies that specifically selected patients with higher distress levels (Andersson & Cuijpers, 2009; Faller et al., 2013; Spek et al., 2007; van der Meulen et al., 2015; Willems, Mesters, Lechner, Kanera, & Bolman, 2017; Williams & Dale, 2006). Information on these moderators of intervention effects is essential to better target specific patient groups to maximize benefits of CST.

Meta-analyses in which aggregate (summary) data (AD) from a large number of studies are pooled, allow investigations of differences in effects across characteristics of the intervention (Lyman & Kuderer, 2005). However, AD meta-analyses do not allow testing interactions between the intervention and potential moderator variables at the individual patient level. Rather, AD meta-analyses use measures of central tendency (e.g., means such as with age, or proportions such as with sex) (Riley, Lambert, & Abo-Zaid, 2010). As a consequence, moderator effects of patient characteristics evaluated in AD meta-analyses may be confounded by other trial characteristics, also referred to as ecological bias (Berlin, Santanna, Schmid, Szczech, & Feldman, 2002; Riley et al., 2010), and should therefore be interpreted with caution.

Ecological bias can be reduced by using individual patient data (IPD) in a meta-analysis (Berlin et al., 2002; Stewart & Tierney, 2002; Tierney et al., 2015). However, the collection of IPD is labour intensive and time consuming and depends on the ability and willingness of investigators of eligible studies to share their data. This makes it difficult

to include all available RCTs, which may introduce retrieval bias in estimating the overall intervention effects (Riley et al., 2010).

In previous analyses on IPD collected in the **P**redicting **O**ptimaL **C**ancer **R**ehab**I**litation and **S**upportive care (POLARIS) study (Buffart et al., 2013), we found small but statistically significant effects of psychosocial interventions (including CST) on quality of life (β = 0.12, 95% confidence interval (CI) = 0.07; 0.17), emotional function (β = 0.12, 95%CI = 0.07; 0.18) and social function (β = 0.10, 95%CI = 0.05; 0.15) (Kalter et al., 2018). Additionally, moderator effects on one or more of these outcomes were found for age, marital status, treatment with chemotherapy, baseline emotional function, type of psychosocial intervention, and interventions targeting patients with distress (Kalter et al., 2018).

In the present paper, we combine AD and IPD meta-analyses to reduce retrieval and ecological bias, in the investigations of the effects of CST on depression and anxiety in patients with cancer, and to identify patient-related moderators (i.e., demographic, clinical, and psychosocial characteristics) and intervention-related moderators of those effects.

2. Methods

The conduct and reporting of the AD and IPD meta-analyses are based on the Preferred reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009) and PRISMA-IPD statement (Stewart & Tierney, 2002). The IPD were collected as part of the POLARIS study. The study protocol was registered in PROSPERO International prospective register of systematic reviews, in February 2013 (CRD42013003805) (Buffart et al., 2013).

2.1. Identification and inclusion of studies

A literature search was conducted in April 2019 to identify studies that could be used to examine the overall effect of CST on depression and anxiety, and the potential moderator effects of intervention-level characteristics via AD meta-analyses. In contrast to the original broader literature search for POLARIS conducted in 2012 (Kalter et al., 2018), the current literature search specifically focussed on CST and on depression and anxiety as outcomes. Relevant published studies were identified via systematic searches in five electronic databases (PubMed, EMBASE, PsycINFO, CINAHL and CENTRAL), and reference checking of systematic reviews and meta-analyses. Search terms included depression, anxiety, cancer, and psychosocial interventions. The full search terms can be found in Appendix 1. Articles were included when the study 1) was a RCT; 2) included a usual care, wait-list or attention control group; 3) included adult patients with cancer (excluding survivors of childhood cancer); 4) measured depression and/or anxiety as one of the outcomes using a validated multi-item questionnaire; and 5) evaluated the effects of coping skills training, as defined by Cunningham (Cunningham A.J. 1995), the goal being to help patients acquire new coping skills. Studies focussing on psychoeducation, support, psychodynamic psychotherapy, and spiritual or existential therapy were excluded from the present analyses (Cunningham A.J. 1995; Kalter et al., 2018).

To investigate demographic, clinical and personal (patient-level) moderators of the effect of CST, we used IPD from the POLARIS study of which detailed descriptions of the design and procedures have been published previously (Buffart et al., 2013; Buffart et al., 2017; Kalter et al., 2018; Kalter, Sweegers, Verdonck-de Leeuw, Brug, & Buffart, 2019). Briefly, IPD from 22 of 61 eligible RCTs focussing on psychosocial interventions were included in the POLARIS database (Kalter et al., 2018), of which 14 RCTs evaluated the effects of CST on

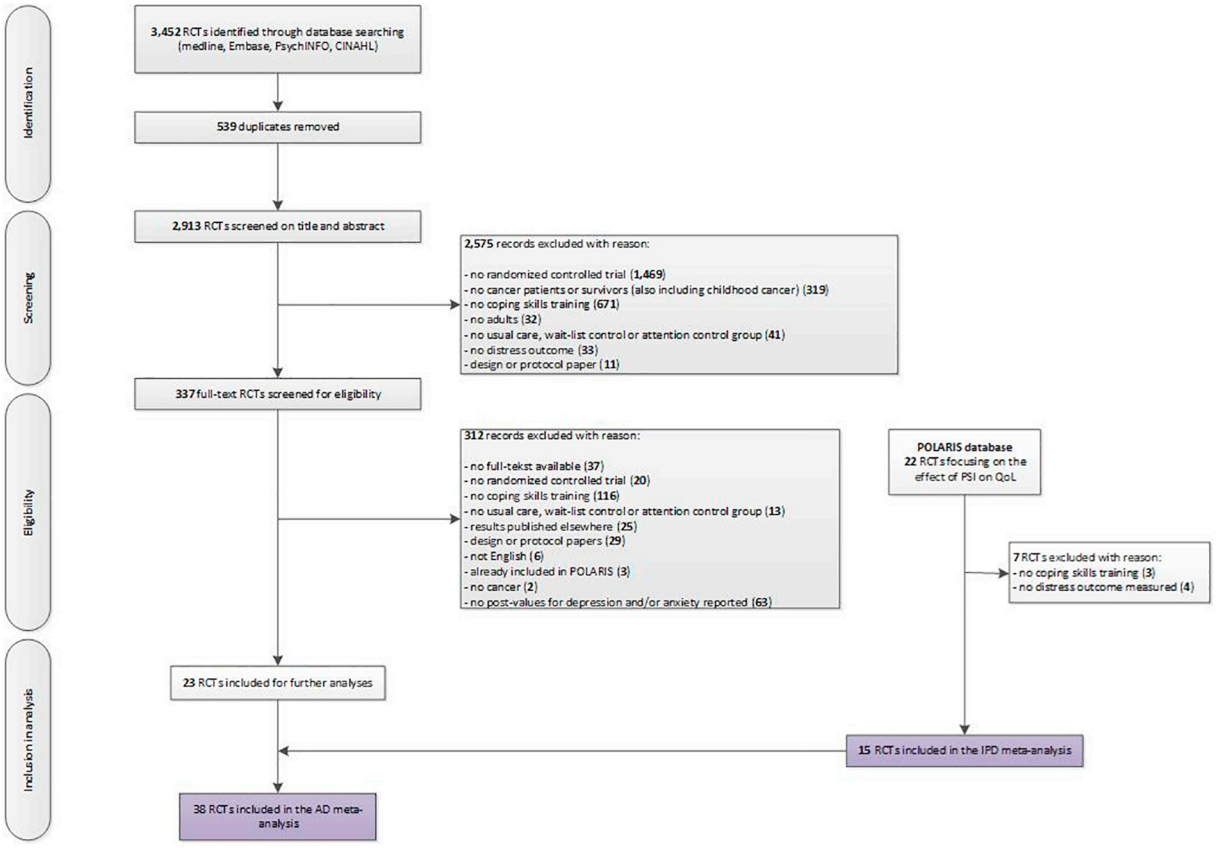

Fig. 1. Flowchart of inclusion randomized controlled trials (RCTs) in the POLARIS study and additionally identified RCTs in the more recent literature search.

depression and anxiety (Armes, Chalder, Addington-Hall, Richardson, & Hotopf, 2007; Arving et al., 2007; Braamse et al., 2016; Duijts, Oldenburg, van Beurden, & Aaronson, 2012; Ferguson et al., 2012; Gellaitry, Peters, Bloomfield, & Horne, 2010; Gielissen, Verhagen, Witjes, & Bleijenberg, 2006; Goedendorp et al., 2010; Graves, Carter, Anderson, & Winett, 2003; Heiney et al., 2003; Johansson et al., 2008; Mann et al., 2012; Savard, Simard, Ivers, & Morin, 2005; van den Berg, Gielissen, Custers, van der Graaf, & Ottevanger, 2015), and one additional RCT assessed the effects on depression only (Northouse et al., 2013). Detailed information on the selection of studies can be found in the flowchart (Fig. 1). Detailed information on reasons for not sharing IPD is presented in our previous publication (Kalter et al., 2018).

2.2. Outcome variables

Depression and anxiety were assessed with validated, multi-item patient-reported outcome measures (PROMs). We used baseline or pre-intervention and the first post-intervention assessments to evaluate the short-term intervention effects of CST on depression and anxiety. As some studies used multiple questionnaires to assess depression and/or anxiety, we selected the most-frequently used symptom-specific questionnaires over generic questionnaires or other symptom-specific questionnaires for analyses. The Center for Epidemiologic Studies Depression Scale (CES-D) was chosen over the Profile of Mood States (POMS) depression subscale in one study (Ferguson et al., 2012), and in three studies the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) was used instead of the Patient Health Questionnaire (Braamse et al., 2016), the Symptom Checklist (van den Berg et al., 2015) and the Beck Depression Inventory (Savard et al., 2005). For anxiety, the State-Trait Anxiety Inventory (STAI) was chosen over the Symptom Checklist (Goedendorp et al., 2010) and the POMS anxiety subscale (Ferguson et al., 2012) in two studies and the HADS-A over the Symptom Checklist (van den Berg et al., 2015). In one study (Braamse et al., 2016), both HADS-A and STAI were included, and the data from the HADS-A was selected as this was the most frequently used PROM.

2.3. Possible moderators

Potential intervention-related moderators (to be used in the AD meta-analyses) were identified from previously conducted meta-analyses (Andersson & Cuijpers, 2009; Faller et al., 2013; Kalter et al., 2018; Schneider et al., 2010; Spek et al., 2007). They included timing and method of intervention delivery, intervention strategy, intervention duration, intervention focus, health-care professional leading the intervention and whether the intervention targeted patients with elevated levels of depression or anxiety. The timing of intervention delivery was categorized as during treatment or after cancer treatment according to the Physical Activity and Cancer Control framework (Courneya & Friedenreich, 2007). The method of delivery was dichotomised into face-to-face intervention or other (telephone/web−/video-based). As cognitive behavioural therapy was the most frequently used CST, we dichotomised intervention strategy into cognitive behavioural therapy versus other (e.g., problem solving therapy, stress management training, expressive writing). Intervention duration was dichotomised into ≤ 12 weeks versus > 12 weeks. Intervention focus was dichotomised into psychological distress (anxiety/depression) versus other outcomes (e.g., fatigue, insomnia, quality of life). The health care professional leading the intervention was categorized as psychologist, nurse, or other. Further, studies were dichotomised into those that specifically targeted patients with high levels of depression and/or anxiety before the start of the intervention and those that did not.

Potential demographic, clinical and personal moderators that we studied in the IPD meta-analyses were identified from previous publications on the moderator effects of CST or other psychosocial interventions (Badger et al., 2013; Faller et al., 2013; Guo et al., 2013; Heron-Speirs, Baken, & Harvey, 2012; Heron-Speirs, Harvey, & Baken, 2013). Potential demographic moderators included baseline age, sex, marital status, education level, and baseline values of depression or anxiety, and were categorized in line with our previous publications (Buffart et al., 2017; Kalter et al., 2018). We dichotomised marital status into single versus married or living with partner, and education level into low-medium (elementary, primary, or secondary school, lower or secondary vocational education) or high (higher vocational, college, or university education). Baseline values for depression and anxiety were assessed as moderators by using the pooled z-score. Potential clinical moderators included type of cancer, the presence of distant metastases at baseline, and type of cancer treatment. Type of cancer was categorized into breast, male genitourinary, gastrointestinal, hematological, gynecological, respiratory tract, and other types. The presence of distant metastasis and type of treatment (i.e. surgery, chemotherapy, radiotherapy, SCT and hormone therapy) were dichotomized. As hormone therapy for breast cancer may continue for several years after treatment, women on hormone therapy only (who completed other primary cancer treatments) were considered as being after treatment.(Kalter et al., 2018) Men receiving androgen deprivation therapy for prostate cancer were considered as being during treatment.(Kalter et al., 2018).

2.4. Quality assessment

Two independent researchers rated the quality of the included studies from published papers using the Cochrane 'risk of bias' assessment tool (J. P. Higgins et al., 2011). The quality rating of the studies with IPD has been described previously (Kalter et al., 2018). The quality was graded as high (+), low (−) or unclear (?) on the following aspects: random sequence generation (high quality if a random assignment was used), allocation concealment (high quality in case of central, computerized allocation or use of sequentially numbered sealed envelopes), incomplete outcome (high quality if intention-to-treat analyses were performed, and less than 10% of the outcome data were missing or adequate imputation techniques were used), and incomplete reporting (high quality if the outcome was reported such that the data could be entered in the AD meta-analysis). Other potential sources of bias that were rated were adherence (high quality if $\geq$80% of intervention sessions were attended) and contamination (high quality in case of no or limited adoption ($< 20\%$) of the intervention in the control group). Items related to blinding were omitted because blinding of patients and personnel is difficult in case of CST. Also, the rating of blinding of outcome assessors was excluded because anxiety and distress were assessed with PROMs.

2.5. Statistical analysis

Descriptive statistics (mean, standard deviation (SD), numbers and proportions) were used to describe the patient-, and intervention-related characteristics.

2.5.1. Aggregate data (AD) meta-analysis

Effect sizes for all individual studies included in the AD meta-analyses were calculated by subtracting the published average post-intervention values of symptoms of depression and anxiety of the intervention group from the values of the control group, and dividing the result by the pooled SD of the intervention and control group (Cuijpers, 2016). When average scores or SD were not reported, we investigated whether other statistics could be used to calculate effects sizes (i.e., average scores and 95% CI, between-group differences and *p*-values). Studies were considered outliers if the 95% CI of the effect did not overlap with the 95% CI of the pooled effect (Cuijpers, 2016). We performed all AD meta-analyses with and without outliers. The heterogeneity was high when outlies were included, also in the subgroups (generally $I^2 > 75\%$ for depression and $I^2 > 60\%$ for anxiety). We

therefore presented the results of AD meta-analyses without outliers, reducing the heterogeneity. All individual effect sizes were pooled in a random effects model using Hedges g, thereby adjusting for studies with small sample sizes (Hedges & Olkin, 1985). Using Cohen's convention, effects of 0.2–0.49 were considered small, 0.50–0.79 as moderate and at or above 0.8 as large (Cohen, 2013). The I^2 statistic was reported as an indicator of heterogeneity, with an I^2 of 25% representing low, 50% representing moderate and 75% representing high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003).

Analyses of the overall effect and differences in effects between subgroups across intervention-related moderators were conducted using Comprehensive Meta-Analysis software (V.2.2.064). Differences between subgroups were considered statistically significant when $p \leq .05$.

2.5.2. Individual patient data (IPD) meta-analysis

To allow pooling of the different PROMs in the IPD meta-analysis, individual scores were recoded into z-scores by subtracting the mean score at baseline from the individual score, then dividing the result by the mean standard deviation per outcome measure at baseline. Subsequently, the pooled z-scores were used for further analyses.

A one-step IPD meta-analysis was conducted to study whether patient-level characteristics moderated the effects of CST on depression and anxiety. Linear mixed model analyses with a two-level structure (1: patient; 2: study) were used to take into account the clustering of patients within studies by using a random intercept on study level. To limit regression to the mean, the post-intervention value (z-scores) of the outcome was regressed onto the intervention and adjusted for the baseline value (z-scores). Moderators of intervention effects were

Table 1
Description of characteristics of the studies included in the individual patient data (IPD) and aggregate data (AD) meta-analyses (38 studies, $n = 5246$).

Study (first author, year)	Country	Study sample (n)	Mean Age (yr)	Sex (% male)	Type of cancer	PROM depression	PROM anxiety	Quality assessment					
								RSG	AC	IO	IR	Adh	Con
Studies included in IPD meta-analysis only													
Armes et al., 2007	UK	60	59	40	Mixed	HADS-D	HADS-A	+	+	+	+	−	?
Arving et al., 2007	SWE	179	55	0	Breast	HADS-D	HADS-A	+	?	+	+	?	?
Braamse et al., 2016	NL	95	54	68	Hematologic	HADS-D	HADS-A	+	+	+	+	−	+
Duijts et al., 2012	NL	212	48	0	Breast	HADS-D	HADS-A	+	+	+	+	−	?
Ferguson et al., 2012	USA	40	50	0	Breast	CES-D	STAI-S	+	+	+	+	?	?
Gellaitry et al., 2010	UK	93	58	0	Breast	POMS	POMS	+	?	−	−	?	?
Gielissen et al., 2006	NL	112	45	51	Mixed	BDI	STAI-S	?	+	+	+	?	?
Goedendorp et al., 2010	NL	163	56	36	Mixed	POMS	POMS	+	+	+	−	?	?
Graves et al., 2003	USA	32	56	0	Breast	POMS	POMS	?	?	−	−	?	?
Heiney et al., 2003	USA	66	50	0	Breast	POMS	POMS	+	?	−	+	+	?
Johansson et al., 2008	SWE	260	64	43	Mixed	HADS-D	HADS-A	+	+	?	+	?	?
Mann et al., 2012	UK	96	54	0	Breast	WHQ	WHQ	+	+	+	+	+	?
Northouse et al., 2013	USA	484	60	39	Mixed	CES-D	−	+	+	+	+	+	+
Savard et al., 2005	CAN	57	54	0	Breast	HADS-D	HADS-A	+	?	+	+	+	?
van den Berg et al., 2015	NL	150	51	0	Breast	HADS-D	HADS-A	+	+	+	+	+	?
Additional studies identified for AD meta-analysis													
Aguado Loi et al., 2012	USA	220	57	20	Mixed	CES-D	STAI-S	+	+	+	+	0	?
Aguado Loi et al., 2017	USA	219	55	29	Mixed	CES-D	STAI-S	+	+	+	+	0	?
Badger et al., 2007	USA	75	54	0	Breast	CES-D	Combination[a]	?	?	?	+	+	?
Desautels et al., 2018	CAN	62	57	0	Breast	HADS-D	−	+	+	+	+	?	?
Dirksen & Epstein, 2008	USA	81	58	0	Breast	CES-D	STAI-S	+	+	?	+	?	?
do Carmo et al., 2017	Brazil	63	53	65	Mixed	HADS-D	HADS-A	+	+	+	+	+	−
Downe-Wamboldt et al., 2007	USA	175	62	40	Mixed	CES-D	−	+	+	−	+	0	?
Garssen et al., 2013	NL	85	53	0	Breast	POMS	STAI-S	−	?	+	+	?	?
Gonzalez-Fernandez et al., 2018	Spain	52	52	8	Mixed	HADS-D	HADS-A	?	?	−	+	?	?
Kangas et al., 2013	AUS	35	55	80	Head/neck	BDI	STAI-S	?	?	+	+	?	?
Kurtz et al., 2005	USA	237	55	47	Mixed	CES-D	−	?	?	−	+	?	?
Manne et al., 2017	USA	234	55	0	Gynecologic	BDI	−	?	?	+	+	?	?
Napoles et al., 2015	USA	151	51	0	Breast	GSD	GSD	+	+	+	+	+	?
Ream et al., 2015	UK	44	53	39	Mixed	HADS-D	HADS-A	+	?	−	+	?	?
Ren et al., 2019	CHN	392	47	0	Breast	HAMD	HAMA	+	+	+	+	?	?
Steel et al., 2016	USA	261	61	73	Mixed	CES-D	−	+	+	?	+	0	?
Stefanopoulou et al., 2015	UK	68	69	100	Prostate	HADS-D	HADS-A	+	+	+	+	?	?
Stoerkel et al., 2018	USA	100	?	0	Breast	PROMIS-D	PROMIS-A	+	+	−	+	+	?
Strong et al., 2008	UK	200	57	29	Mixed	SCL-20	SCL-10	+	+	+	+	?	?
van de Wal et al., 2017	NL	88	59	47	Mixed	HADS-D	HADS-A	+	+	+	+	−	?
Van der Meulen et al., 2012	NL	205	60	70	Head/neck	CES-D	−	?	+	+	+	−	+
Wells-Di Gregorio et al., 2019	USA	28	57	18	Mixed	−	STAI	+	+	+	+	−	?
Wu et al., 2016	CHN	72	51	25	Thyroid	SDS	SAS	?	?	−	+	0	?

Notes. The number of patients was reported at baseline. The number of patients included in the analyses might therefore differ as i.e. not all patients completed the questionnaire.

Abbreviations: AD-MA = Aggregate Data Meta-analysis; AUS = Australia; BDI: Beck Depression Index; CAN = Canada; CES-D: Center for Epidemiologic Studies – Depression Scale; CHN = China; DASS21 = Depression, Anxiety and Stress Scale, 21-item version, Anxiety (−A), or Depression (−D) subscale; GSD = General Symptoms of Distress; HADS: Hospital Anxiety and Depression Scale; HAMA = Hamilton anxiety scale; HAMD = Hamilton depression rating scale; IPD-MA = Individual Patient Data Meta-analysis; NL = The Netherlands; POMS: Profile of Mood States; PROM = Patient-reported Outcome Measure; PROMIS = Patient-Reported Outcome Measurement Information System-57, Anxiety (−A) or Depression (−D) subscale; SAS: Self-rating Anxiety Scale; SCL: Short Checklist – originally contains 90 questions, but here we also found shorter lists; SDS: Self-rating Depression Scale; STAI: State-Trait Anxiety Index; SWE = Sweden; UK = United Kingdom; USA = United States of America; WHQ: Women's Health Questionnaire.

Quality assessment: + = high quality; − = low quality;? = unclear quality; 0 = not applicable; RSG = random sequence generation; AC = allocation concealment; IO = incomplete outcome; IR = incomplete reporting; Adh = adherence; Con = contamination.

[a] Combination of four items from the Positive and Negative Affect Schedule, one item from the Short Form-12, and three items from the Index of Clinical Stress.

Table 2
Intervention characteristics of the studies included in the individual patient data (IPD) and aggregate data (AD) meta-analyses (38 studies, n = 5246).

Study (first author, year)	Targeted intervention	Intervention focus	Timing (during/ after treatment)	Intervention strategy	Intervention duration, mean	Method of delivery	Leading profession
Studies also included in IPD meta-analysis							
Armes et al., 2007	No	Fatigue	During	CBT	9–12 weeks	Web	Nurse
Arving et al., 2007	No	Psychological distress	During	Problem-solving therapy	17 weeks	F2f	Psychologist
Braamse et al., 2016	No	Psychological distress	After (stepped care initiated 6 weeks after SCT)	Problem-solving therapy	5 weeks	Tel	Psychologist
Duijts et al., 2012	No	Menopausal symptoms	After (4 months – 5 years post treatment)	CBT	6 weeks	F2f	Psychologist
Ferguson et al., 2012	No	Cognitive change	After (≥ 18 months post-treatment)	CBT	4 weeks	F2f	Psychologist
Gellaitry et al., 2010	No	Emotional support	After (< 12 months post diagnosis, after radiotherapy)	Expressive writing intervention	< 1 week	Tel	None
Gielissen et al., 2006	No	Fatigue, functional impairment	After (mean (SD): 4.9 (3.7) years)	CBT	26 weeks	F2f	Psychologist
Goedendorp et al., 2010	No	Fatigue	During	CBT	30 weeks	F2f	Psychologist
Graves et al., 2003	No	Quality of life	After (< 5 years post diagnosis, mean 2.5 years)	Social cognitive therapy	8 weeks	F2f	Psychologist
Heiney et al., 2003	No	Symptom management, social support	After (mean (SD) =151.3 (53.5) days after diagnosis)	Coping skills intervention	6 weeks	Tel	Other
Johansson et al., 2008	No	Quality of life, psychological distress	During	CBT	16 weeks	F2f	Psychologist
Mann et al., 2012	No	Hot flushes	After (mean (SD): 37.1 (43.0) months post diagnosis)	CBT	6 weeks	F2f	Psychologist
Northouse et al., 2013	No	Psychological distress	During/ after	Dyadic therapy	10 weeks	F2f	Nurse
Savard et al., 2005	No	Insomnia	After (mean (SD): 2.8 (4.2) year post treatment)	CBT	8 weeks	F2f	Psychologist
van den Berg et al., 2015	No	Psychological distress	After (2–4 months post-treatment)	CBT	16 weeks	Web	None
Additional studies identified for AD meta-analysis							
Aguado Loi et al., 2012	No	Psychological distress	During	Stress management training	During 4 cycles chemotherapy	Web	None
Aguado Loi et al., 2017	No	Psychological distress	During	Stress management training	During 4 cycles chemotherapy	Web	None
Badger et al., 2007	No	Psychological distress	During	Communication skills training	6 weeks	Tel	Nurse
Desautels et al., 2018	Yes	Psychological distress	After (mean (SD): 14.3 (4.0) months post-diagnosis)	CBT	8 weeks	F2f	Psychologist
Dirksen & Epstein, 2008	No	Fatigue, psychological distress	After (> 3 months post-treatment, mean (SD) months: 65.0 (85.9) for intervention and 51.3 (58.4) for control)	CBT	6 weeks	F2f+	Nurse
do Carmo et al., 2017	No	Psychological distress	During	CBT	5 weeks	F2f	Psychologist
Downe-Wamboldt et al., 2007	No	Psychological distress	During	Problem-solving therapy	13 weeks	Tel	Nurse
Garssen et al., 2013	No	Psychological distress	During/after	Stress management training	Unknown	F2f	Psychologist
Gonzalez-Fernandez et al., 2018	Yes	Psychological distress	After (not further specified)	Behavioural activation; Acceptance and commitment therapy	12 weeks	F2f	Psychologist
Kangas et al., 2013	Yes	Psychological distress	During	CBT	6 weeks	F2f	Other
Kurtz et al., 2005	No	Psychological distress	During	CBT	20 weeks	F2f	Nurse
Manne et al., 2017	No	Psychological distress	During	CBT	7 weeks	F2f	Other
Napoles et al., 2015	No	Quality of life	During/after	Social cognitive therapy	8 weeks	F2f	Other
Ream et al., 2015	No	Fatigue	During	Motivational interviewing	Unknown	Tel	Other
Ren et al., 2019	Yes	Psychological distress	After (1 week to 1 year post mastectomy)	CBT	12 weeks	F2f	Psychologist
Steel et al., 2016	No	Cancer-related symptoms	During	CBT	Unknown	Web	Other
Stefanopoulou et al., 2015	No	Hot flushes	After (mean (SD) months since diagnosis: 24.8 (20.7) for intervention and 29.6 (35.5) for control)	CBT	4 weeks	Tel	Psychologist
Stoerkel et al., 2018	No	Psychological distress	Before and after	Stress management	4 weeks	Audio-file	Other
Strong et al., 2008	Yes	Psychological distress	During/after	Problem-solving therapy	13 weeks	F2f	Nurse
van de Wal et al., 2017	No	Fear of recurrence	After (mean (SD) years: 1.9 (1.5) for intervention and 2.1 (1.4) for control)	CBT	11 weeks	F2f+	Psychologist
Van der Meulen et al., 2012	No	Psychological distress	During	CBT	52 weeks	F2f	Nurse

(*continued on next page*)

Table 2 (*continued*)

Study (first author, year)	Targeted intervention	Intervention focus	Timing (during/ after treatment)	Intervention strategy	Intervention duration, mean	Method of delivery	Leading profession
Wells-Di Gregorio et al., 2019	Yes	Sleep difficulties	During	CBT with elements of ACT	6 weeks	F2f+	Other
Wu et al., 2016	No	Quality of life, mental health	During	Supportive-expressive group therapy	52 weeks	F2f	Nurse

Notes. Abbreviations: ACT = acceptance and commitment therapy; AD = Aggregate data; CBT = Cognitive behavior therapy; F2f = Face-to-face; F2f + =Face-to-face in combination with telephone or web-based consults or videos; IPD = Individual Patient Data; Tel = Telephone consults; Web = Web-based consults.

examined by subsequently adding each moderator and its interaction term with the intervention into the regression model. The likelihood ratio test was used to determine whether adding the interaction term significantly improved the fit of the model. To reduce ecological bias for patient-level interactions, within-trial interaction was separated from between-trial interaction by centering the individual value of the covariate around the mean study value of that covariate (Helgeson, Lepore, & Eton, 2006). Significance level of the interaction terms was set at $p \leq .05$. If adding the interaction term significantly improved the statistical model, strata were built starting with the most significant moderator for both depression and anxiety.

Regression coefficients (β) and 95% CI are reported, which represent the between group difference in z-scores of depression or anxiety, and correspond to a Cohen's d effect size (Cohen, 2013). Statistical analyses were performed using SPSS 22.0 and R Studio.

2.5.3. Representativeness of the IPD sample and publication bias

To examine whether the studies included in the IPD meta-analyses were a representative sample of all eligible studies, we compared the pooled effects of RCTs with IPD versus those not included using the published data.

We also investigated publication bias for all eligible studies by inspecting the funnel plot and calculating the effect size with a correction for possible publication bias using Duval and Tweedie's procedure (Duval & Tweedie, 2000). This procedure trims (removes) studies in case of asymmetry in the funnel plot, estimates the true 'center' of the funnel and replaces (fills) the omitted studies around the center. A statistically significant dispersion between the true effect size and the calculated effect size after correcting for possible missing studies or an asymmetry in the funnel plot, calculated using Egger's test, could suggest publication bias. A $p \leq .05$ was applied as the criterion for statistical significance.

3. Results

3.1. Characteristics of studies and patients

The literature search identified 3452 references, of which 23 new RCTs (C. X. Aguado Loi et al., 2017; Claudia X. Aguado Loi et al., 2012; Badger, Segrin, Dorros, Meek, & Lopez, 2007; Butow et al., 2017; Desautels, Savard, Ivers, Savard, & Caplette-Gingras, 2018; Dirksen & Epstein, 2008; do Carmo, Paiva, de Oliveira, Nascimento, & Paiva, 2017; Downe-Wamboldt et al., 2007; Garssen et al., 2013; Gonzalez-Fernandez, Fernandez-Rodriguez, Paz-Caballero, & Perez-Alvarez, 2018; Greer et al., 2012; Kangas, Milross, Taylor, & Bryant, 2013; Kurtz, Kurtz, Given, & Given, 2005; Manne et al., 2017; Napoles et al., 2015; Ream, Gargaro, Barsevick, & Richardson, 2015; Ren et al., 2019; Steel et al., 2016; Stefanopoulou, Yousaf, Grunfeld, & Hunter, 2015; Stoerkel et al., 2018; Strong et al., 2008; van de Wal, Thewes, Gielissen, Speckens, & Prins, 2017; Van der Meulen et al., 2012; Wells-Di Gregorio et al., 2019; Wu et al., 2016) were added to the 15 RCTs available in the POLARIS database (Fig. 1). This resulted in 37 RCTs evaluating the effects of CST on depression and 31 on anxiety (Table 1). Sample sizes of the included studies ranged from 28 to 484 (Table 1). Of the 38 included RCTs, 17 (45%) were conducted during cancer treatment, 16 (42%) after cancer treatment, 4 (11%) included patients either during or after cancer treatment, and 1 (2%) before and after surgery (Table 2). In total, 25 (66%) RCTs examined interventions with face-to-face sessions, 21 (55%) RCTs examined interventions that included CBT as intervention strategy, 26 (68%) RCTs evaluated interventions with a duration ≤12 weeks, and 17 (45%) RCTs examined interventions that were led by a psychologist (Table 2). We identified 6 (16%) RCTs that selected patients based on high levels of distress.

In total, 28 (74%) of the included RCTs reported random sequence generation, 25 (66%) RCTs reported adequate allocation concealment, 25 (66%) had adequate completeness of outcome data, 35 (92%) had

Table 3
Demographic and clinical characteristics, and baseline depression and anxiety of patients included in the individual patient (IPD) meta-analysis.

Variable	Control (n = 878)	Intervention (n = 1075)
Demographic		
Age, mean (SD) years	54.7 (11.2)	55.8 (11.3)
Age categories, n (%)		
< 50 years	291 (33.1)	312 (29.0)
50–70 years	493 (56.2)	615 (57.2)
≥ 70 years	92 (10.5)	147 (13.7)
Unknown	2 (0.2)	1 (0.1)
Gender, n (%)		
Male	188 (21.4)	232 (21.6)
Female	690 (78.4)	843 (78.4)
Marital status, n (%)		
Single/living alone	192 (21.9)	226 (21.0)
Married/living together	581 (66.2)	747 (69.5)
Unknown	105 (12.0)	102 (9.5)
Educational level, n (%)		
Low/medium	384 (43.7)	429 (39.9)
High	230 (26.2)	310 (28.8)
Unknown	264 (30.1)	336 (31.3)
Clinical		
Type of cancer, n (%)		
Breast	595 (67.8)	705 (65.6)
Genitourinary	93 (10.6)	113 (10.5)
Gynecological	12 (1.4)	10 (0.9)
Gastrointestinal	63 (7.2)	108 (10.0)
Lung	51 (5.8)	96 (8.9)
Hematological	56 (6.4)	37 (3.4)
Other	8 (0.9)	6 (0.6)
Distant metastasis at baseline, n (%)[a]		
No	763 (86.9)	947 (88.1)
Yes	50 (5.7)	66 (6.1)
Unknown	65 (7.4)	62 (5.8)
Surgery, n (%)[b]		
No	120 (13.7)	184 (17.1)
Yes	708 (80.6)	866 (80.6)
Unknown	50 (5.7)	25 (2.3)
Chemotherapy, n (%)		
No	273 (31.1)	350 (32.6)
Yes	603 (68.7)	722 (67.2)
Unknown	2 (0.2)	3 (0.3)
Radiotherapy, n (%)		
No	356 (40.5)	480 (44.7)
Yes	499 (56.9)	573 (53.3)
Unknown	23 (2.6)	22 (2.0)
Hormone therapy		
Patients with breast cancer (n = 1300), n (%)		
No	215 (36.1)	314 (44.5)
Yes	327 (55.0)	341 (48.4)
Unknown	53 (8.9)	50 (7.1)
Patients with prostate cancer (n = 156), n (%)		
No	36 (52.2)	49 (56.3)
Yes	33 (47.8)	37 (42.6)
Unknown	…	1 (1.1)
SCT, n (%)[c]		
Allogenic SCT	…	…
Autologous SCT	48 (100.0)	24 (100.0)

Variable	Control (n = 878)		Intervention (n = 1075)	
	Pre mean (SD)	Post mean (SD)	Pre mean (SD)	Post mean (SD)
Depression[d]				
HADS depression subscale, range 0–21 (k = 7)	4.1 (3.5)	3.6 (3.2)	4.2 (3.6)	3.4 (3.3)
CES-D total score, range (k = 2)	36.8 (12.1)	34.7 (13.0)	37.5 (9.8)	36.5 (9.8)
POMS depression subscale, range 0–60 (k = 3)	6.4 (10.5)	6.9 (10.2)	7.3 (8.6)	6.3 (7.0)
BDI total score, range 0–63 (k = 1)	8.1 (4.2)	8.7 (5.1)	11.3 (6.5)	6.4 (7.1)
WHQ depression subscale, range 0–1 (k = 1)	0.49 (0.33)	0.45 (0.31)	0.35 (0.34)	0.22 (0.24)
SCL-90 depression subscale, range 0–72 (k = 1)	21.4 (5.3)	20.4 (4.2)	21.3 (6.0)	20.3 (5.3)
Anxiety[d]				

(*continued on next page*)

Table 3 (*continued*)

Variable	Control (n = 878)		Intervention (n = 1075)	
	Pre mean (SD)	Post mean (SD)	Pre mean (SD)	Post mean (SD)
HADS anxiety subscale, range 0–21 (k = 7)	6.3 (4.4)	5.5 (4.1)	6.2 (4.2)	4.7 (3.9)
STAI state subscale, range 20–80 (k = 2)	39.3 (9.2)	40.8 (11.0)	42.7 (9.6)	37.1 (10.7)
POMS anxiety subscale, range 0–36 (k = 3)	6.3 (6.3)	6.6 (6.7)	8.3 (6.5)	7.7 (6.4)
WHQ anxiety subscale, range 0–1 (k = 1)	0.45 (0.30)	0.41 (0.33)	0.34 (0.25)	0.23 (0.27)
SCL-90 anxiety subscale, range 0–40 (k = 1)	13.5 (4.2)	12.2 (3.3)	13.5 (3.8)	12.0 (2.9)

BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies – Depression scale; HADS = Hospital Anxiety and Depression Scale; k = number of trials; n = number of patients; POMS = Profile of Mood States; SCL-90 = Symptom Checklist; SCT = stem cell transplantation; SD = standard deviation; STAI = State Trait Anxiety Index; WHQ = Women's Health Questionnaire;

[a] Proportion of patients of solid tumors (n = 1881).

[b] Proportion of patients without SCT (n = 1881).

[c] Proportion of patients with SCT (n = 72).

[d] Higher scores represents higher level of depression and anxiety.

complete outcome reporting, 9 (24%) described adequate intervention adherence, and 3 (8%) provided information on contamination (Table 1).

IPD was available for 15 RCTs (Armes et al., 2007; Arving et al., 2007; Braamse et al., 2016; Duijts et al., 2012; Ferguson et al., 2012; Gellaitry et al., 2010; Gielissen et al., 2006; Goedendorp et al., 2010; Graves et al., 2003; Heiney et al., 2003; Johansson et al., 2008; Mann et al., 2012; Northouse et al., 2013; Savard et al., 2005; van den Berg et al., 2015) including 1953 patients with cancer, of whom 1075 were randomly allocated to the intervention and 878 to the control group. The mean (SD) age of patients was 55.3 (11.3) years, 78.5% were female, 68.0% were married and/or lived with a partner, 27.6% were highly educated, 66.6% were diagnosed with breast cancer, and 5.9% had distant metastatic disease at baseline (Table 3).

3.2. Effect of CST on depression and anxiety and intervention-related moderators using AD meta-analyses

After removing outliers (3 RCTs for depression (Badger et al., 2007; Desautels et al., 2018; Manne et al., 2017), 4 RCTs for anxiety (Badger et al., 2007; Garssen et al., 2013; Kangas et al., 2013; Wells-Di Gregorio et al., 2019), CST resulted in a statistically significant reduction in depression (g = −0.31, 95%CI = -0.40; −0.22) and anxiety (g = −0.32, 95%CI = -0.41; −0.24) compared to the control group overall (Table 4). The intervention effects on depression were significantly larger for interventions that were delivered face-to-face compared to those delivered via other methods (p = .003), for interventions led by a psychologist (p = .02), and for studies that specifically targeted patients with high levels of psychological distress (p = .002, Table 4). Intervention effects on anxiety seemed larger for interventions delivered following treatment (p = .06), that were delivered face-to-face (p = .10), and those targeting patients with high levels of psychological distress (p = .06), but this was not statistically significant (Table 4). Intervention effects on depression and anxiety did not differ significantly across subgroups for intervention strategy, duration, and focus (Table 4).

3.3. Patient-level moderators evaluated with IPD meta-analyses

Age significantly moderated intervention effects on anxiety (p = .02), with statistically significant effects of CST in patients aged < 50 years (β = −0.31, 95%CI = -0.44; −0.18), and 50–70 years (β = −0.11, 95%CI = -0.21; −0.00), while the effect in patients older than 70 years was not statistically significant (β = −0.02, 95%CI = -0.29; 0.24) (Table 5). For reference, the overall intervention effect on anxiety based on IPD is −0.17 (95%CI = −0.25; −0.10, Table 5).

Receiving chemotherapy significantly moderated the effect of CST on depression (p = .03) and anxiety (p = .05): Reductions in depression (β = −0.16, 95%CI = -0.25; −0.07) and anxiety (β = −0.24, 95%CI = -0.33; −0.14) were statistically significant in patients who received chemotherapy, but not in patients who did not receive chemotherapy. No other demographic and clinical variables significantly moderated the CST effect on depression and anxiety.

3.4. Representativeness of the IPD sample and publication bias

Pooled effects of studies with IPD on depression (p = .06) and anxiety (p = .47) seemed somewhat smaller than the effects of studies without IPD, but differences were not statistically significant (Table 4). Consequently, we found no evidence that the sample of studies with IPD was not a representative sample of published studies. The average effect sizes, however, indicate a slightly underestimation the overall effect.

The Duvall and Tweedie's trim and fill procedure suggested that 9 trials were missing for depression and 7 trials for anxiety, resulting in an adjusted effect size of −0.21 (95%CI = −0.31; −0.11) for depression and of −0.23 (95%CI = −0.33; −0.13) for anxiety after adjusting for possible publication bias (Table 2). The Egger's test was statistically significant for depression (p = .04), but not for anxiety (p = .20), indicating a presence of publication bias for depression.

4. Discussion

These AD and IPD meta-analyses showed that CST is effective in reducing depression and anxiety in patients with cancer during and after treatment, however, with small overall effects. The findings are in line with results from previous meta-analyses (Cuijpers, van Straten, Andersson, & van Oppen, 2008; Kalter et al., 2018; Sheard & Maguire, 1999). Additionally, our meta-analyses found that the effect of CST was moderated by age and chemotherapy treatment, and by method of intervention delivery, leading profession, and whether it was specifically targeted to patients with high levels of psychological distress. These findings have important implications to further improve CST interventions and to target interventions specifically to patients that benefit most, thereby optimizing benefits.

The finding that CST is modestly helpful in reducing depression and anxiety in patients with cancer, regardless of the timing of intervention delivery in the cancer trajectory, is congruent with our previous findings for quality of life (Kalter et al., 2018). However, this may be related to the broader categories that we used for the analyses, or to other factors that may have a larger influence than timing, such as whether the intervention was specifically targeted to patients with distress or not, or the specific cognitions and behaviors that were targeted by the intervention. In contrast to previous studies that found no significant differences in effects between face-to-face interventions and internet-based interventions in reducing anxiety (Kiropoulos et al., 2008) and fatigue (Carlbring, Andersson, Cuijpers, Riper, & Hedman-Lagerlof, 2018), we found larger effects of face-to-face interventions on depression and we found a similar

Table 4
Effect of CST on depression and anxiety, stratified per potential intervention-level moderator subgroups, based on AD meta-analyses (38 studies, n = 5246).

	Depression				Anxiety			
	N	g (95%CI)	I^2 (95%CI)	Egger's test (p)	N	g (95%CI)	I^2 (95%CI)	Egger's test (p)
Comparison								
Overall[a]	39	−0.58 (−0.79; −0.36)	91 (89–92)		33	−0.42 (−0.53; −0.30)	57 (32–70)	
Overall without outliers	36	−0.31 (−0.40; −0.22)	40 (1–59)		29	−0.32 (−0.41; −0.24)	19 (0–48)	
Overall adjusted for missing studies		−0.21 (−0.31; −0.11)		0.04		−0.23 (−0.33; −0.13)		0.20
	N	g (95%CI)	I^2 (95%CI)	Between-group difference (p)	N	g (95%CI)	I^2 (95%CI)	Between-group difference (p)
Timing				0.82				0.06
During	14	−0.34 (−0.49; −0.19)	41 (0–67)		9	−0.22 (−0.36; −0.09)	0 (0–54)	
Post	17	−0.36 (−0.50; −0.23)	35 (0–63)		17	−0.40 (−0.52; −0.28)	25 (0–58)	
Method of delivery				0.003				0.10
Face-to-face	25	−0.39 (−0.50; −0.28)	46 (2–65)		21	−0.37 (−0.48; −0.26)	26 (0–56)	
Other	11	−0.14 (−0.26; −0.02)	0 (0–51)		8	−0.23 (−0.36; −0.09)	0 (0–56)	
Intervention strategy				0.15				0.45
CBT	17	−0.38 (−0.50; −0.25)	34 (0–62)		15	−0.35 (−0.47; −0.24)	18 (0–56)	
Other	19	−0.25 (−0.36; −0.14)	36 (0–62)		14	−0.29 (−0.41; −0.17)	19 (0–57)	
Intervention duration				0.46				0.93
≤12 weeks	22	−0.32 (−0.44; −0.19)	44 (0–65)		20	−0.33 (−0.44; −0.21)	31 (0–59)	
> 12 weeks	11	−0.26 (−0.36; −0.15)	0 (0–51)		8	−0.32 (−0.45; −0.19)	0 (0–56)	
Intervention focus				0.84				0.31
Distress	20	−0.31 (−0.43; −0.19)	55 (15–71)		14	−0.36 (−0.49; −0.23)	38 (0–66)	
Other	16	−0.30 (−0.41; −0.18)	7 (0–49)		15	−0.27 (−0.39; −0.16)	0 (0–46)	
Leading profession CST				0.02				0.24
Psychologist	17	−0.44 (−0.59; −0.28)	52 (3–71)		16	−0.37 (−0.51; −0.24)	38 (0–65)	
Nurse	9	−0.26 (−0.37; −0.14)	4 (0–56)		5	−0.36 (−0.54; −0.17)	0 (0–64)	
Other	10	−0.15 (−0.28; −0.03)	0 (0–53)		8	−0.22 (−0.35; −0.10)	0 (0–56)	
Targeted study				0.002				0.06
Yes	5	−0.60 (−0.81; −0.40)	19 (0–70)		4	−0.62 (−0.98; −0.27)	67 (0–87)	
No	31	−0.25 (−0.33; −0.17)	21 (0–49)		25	−0.27 (−0.36; −0.19)	0 (0–39)	
Included in POLARIS				0.06				0.47
Yes	16	−0.21 (−0.31; −0.12)	0 (0–45)		15	−0.29 (−0.40; −0.18)	0 (0–46)	
No	20	−0.38 (−0.51; −0.24)	55 (16–72)		14	−0.36 (−0.51; −0.21)	47 (0–70)	

g: Hedges' g; I^2: indicator of heterogeneity (%); N: number of study arms included.
[a] The study of Arving et al. (2007) and the study of Gonzalez-Fernandez et al., 2018 included 3 study arms resulting in the comparison of two intervention arms with a control group.

Table 5
Effects of CST on depression and anxiety, stratified by potential patient-level moderator subgroups, based on IPD meta-analyses (15 studies).

Effects of CST	Depression β (95% CI)	χ2 [df], p-value	Anxiety β (95% CI)	χ2 [df], p-value
	−0.12 (−0.19; −0.05)*		−0.17 (−0.25; −0.10)*	
Age, years		2.37 [1], 0.12		5.14 [1], 0.02*
Age categories				
< 50 years	…		−0.31 (−0.44; −0.18)*	
50–70 years	…		−0.11 (−0.21; −0.00)*	
≥70 years	…		−0.02 (−0.29; 0.24)	
Gender		1.50 [1], 0.22		0.79 [1], 0.37
Marital status		0.35 [1], 0.55		0.69 [1], 0.41
Education level		0.29 [1], 0.59		0.03 [1], 0.86
Type of cancer		2.49 [6], 0.87		5.08 [6], 0.53
Distant metastasis at baseline		0.18 [1], 0.67		1.79 [1], 0.18
Baseline value of outcome[a]		1.84 [1], 0.18		0.99 [1], 0.32
Surgery		0.46 [1], 0.50		1.98 [1], 0.16
Chemotherapy		4.50 [1], 0.03*		3.85 [1], 0.05*
No	−0.05 (−0.17; 0.07)		−0.08 (−0.21; 0.05)	
Yes	−0.16 (−0.25; −0.07)*		−0.24 (−0.33; −0.14)*	
Radiotherapy		0.09 [1], 0.76		0.44 [1], 0.50
Hormone Breast		0.10 [1], 0.75		0.02 [1], 0.89
Hormone Prostate		0.96 [1], 0.33		2.58 [1], 0.11

Regression coefficients (β), 95% confidence intervals (CI), and Chi-square test with corresponding degrees of freedom and *p*-values are presented.
* $p < .05$.
[a] Baseline depression as moderator for outcome depression, baseline anxiety as moderator for outcome anxiety.

trend for anxiety. Particularly interventions led by a psychologist showed the largest benefits on depression. This indicates that, for optimal effectiveness of the intervention, it is important that the intervention is delivered by psychologists, and preferably face-to-face. Finally, we found that only a minority of RCTs specifically selected patients with depression or anxiety at study entry, but those that did showed substantially larger effects. This is in line with findings from previous reviews of studies targeting patients with higher levels of depression or anxiety at baseline (van der Meulen et al., 2015; Williams & Dale, 2006), that showed significantly larger reductions in depression and anxiety. It clearly highlights that, to optimize effectiveness and cost-effectiveness of CST, it is important to target patients that need it the most. However, our results did not support the moderator effect of baseline depression or anxiety, which may be explained by the low levels of depression or anxiety in the studies with IPD, as they were not targeted specifically to patients with high levels of distress.

Our results did not yield any evidence that other intervention characteristics such as intervention strategy (cognitive behavior therapy versus other strategies like problem-solving therapy and stress management training), or intervention focus (psychological distress versus other outcomes like fatigue and insomnia) moderated the effects of CST on depression and anxiety. For some analyses on potential moderators, we needed to make broad categories for statistical power, but the categories may have been too heterogeneous. Therefore, to gain additional insight into which intervention characteristics are more or less important for reducing depression and anxiety among patients with cancer, future studies need to align study characteristics (e.g., distress measure and eligibility criteria) or to directly compare different intervention characteristics while keeping others similar.

With respect to patient-related moderators, in line with our previous publication on quality of life (Kalter et al., 2018), the analyses on IPD showed that younger patients had larger benefit from CST. This may be explained by higher supportive care needs (and thus more room for improvement) in younger patients compared to older patients (Kalter et al., 2018; Linden, Vodermaier, MacKenzie, & Greig, 2012; O'Hea et al., 2016; Schuurhuizen, Braamse, Konings, Verheul, & Dekker, 2019; Simning, Conwell, Mohile, & van Wijngaarden, 2014). On the other hand, older patients with cancer-related depression or anxiety may have less or other specific or (supportive) care needs compared to younger patients that are not, or only partly, met by CST (Kalter et al., 2018). Further research is needed to identify the specific supportive care needs of the older cancer patient population experiencing depression and anxiety.

We did not observe any moderating effects of sex in our study. This is in line with our IPD meta-analyses focusing on quality of life (Kalter et al., 2018). Overall, findings of previous descriptive studies have been mixed. Some studies report that depression (Albert, 2015; Hong & Tian, 2014) and anxiety (Linden et al., 2012) are generally more prevalent in women than in men, and therefore, women could benefit more from these interventions. However, another study among patients with various cancer types found that men more often experience anxiety than women (Hong & Tian, 2014).

In line with our previous meta-analysis on quality of life, our study found a moderator effect of chemotherapy, where patients who received chemotherapy experienced larger reductions in depression and anxiety after CST compared to those who did not. This may be related to higher levels of depression and anxiety associated with chemotherapy (Kyranou et al., 2014; Yang et al., 2016). As hormone therapy has also been associated with increased levels of depression and anxiety (Sharpley, Christie, & Bitsika, 2014), larger effects of CST were also expected in patients who received hormone therapy as part of their treatment compared to those who did not. This, however, did not prove to be the case in our study. The lack of moderator effects of other treatment types may result from our dichotomisation of each treatment into whether patients received treatment or not, which does not take into account the intensity of treatment. Due to the differences in data collected and provided by the original studies, we were unable to specify types of surgery (e.g., mastectomy or lumpectomy), or types of chemotherapy, radiotherapy or hormone therapy in further detail. Since the cancer diagnosis and its treatment are closely related, the effect of treatment types should be examined within more homogenous groups of patients.

5. Strengths and limitations

A strength of this study is that AD and IPD meta-analyses were combined which provided us the unique opportunity to use the advantages of both approaches. The strength of the AD meta-analysis is the ability to include a larger number of RCTs compared with an IPD meta-analysis, which provided a larger database to test differences in intervention characteristics at the study level. In addition, the strength of the IPD-meta-analysis is the ability to test demographic, clinical, and psychosocial characteristics as effect moderators at the patient level

using a large sample, and to conduct stratified analyses with sufficient power. However, although we maximised power for each analyses by combining both types of meta-analyses, some study-level moderators may still have been underpowered due to small subgroups, or loss of information by forming subgroups.

A limitation of IPD meta-analysis is the need to obtain the original data for an RCT to be included in the analysis. This may result in retrieval bias, since IPD can often only be obtained from a subset of studies. However, there was no significant difference in effects between studies with and without IPD, indicating our IPD sample was representative of the studies identified in the AD meta-analysis. Nevertheless, overall, there seemed to be a publication bias for depression; studies with larger effects on depression appeared more likely to be published, which may have resulted in an overestimation of the effect of CST on depression. Other possible biases that may have been present in the RCTs under investigation could be related to the absence of information on adherence to the intervention and potential contamination of the control group. Finally, our investigation was limited to the short-term intervention effects of CST as very few RCTs examined longer term effects. Research into long-term effects of CSI for depression and anxiety is therefore warranted.

In conclusion, CST significantly reduces symptoms of depression and anxiety during and after cancer treatment; however, the overall effects are small, and possibly of limited clinical relevance. CST effects were significantly larger in patients who were younger, and received chemotherapy as part of their cancer treatment, as well as in studies in which the intervention was delivered face to face and by a psychologist. Significant and clinically meaningful benefits can be obtained by targeting patients with high levels of psychological distress. Further research is needed to unravel differences in effects between different intervention-characteristics in more detail.

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Contributors

Buffart, Brug, Verdonck-de Leeuw are members of the steering committee of POLARIS. Courneya, Newton, Jacobsen and Aaronson are members of the international advisory board. These authors contributed to the concept and the design of the study. Buffart, Kalter, Schreurs, and Abrahams were involved with data collection, data analyses, and drafting the manuscript.

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Declaration of Competing Interest

None declared.

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None.

Appendix A. Search terms used in pubmed search

#1 neoplasms

"neoplasms"[Mesh] OR metastas*[tiab] OR neoplas* [tiab] OR tumor*[tiab] OR cancer*[tiab] OR.

tumor[tiab] OR tumora*[tiab] OR tumorb*[tiab] OR tumorc*[tiab] OR tumord*[tiab] OR tumore*[tiab] OR tumorf*[tiab] OR tumorg*[tiab] OR tumorh*[tiab] OR tumori*[tiab] OR tumork*[tiab] OR tumorl*[tiab] OR tumorm*[tiab] OR tumorn*[tiab] OR tumoro*[tiab] OR tumorp*[tiab] OR tumorr*[tiab] OR tumors*[tiab] OR tumort*[tiab] OR tumoru*[tiab] OR tumorv*[tiab] OR tumorw*[tiab] OR tumorx*[tiab] OR tumory*[tiab] OR tumorz*[tiab] OR tumor'*[tiab] OR tumor1[tiab].

#2 psychosocial therapy

"Social Support"[Mesh] OR "Behavior Therapy"[Mesh] OR "cognitive therapy"[Mesh] OR "Mind-body therapies"[Mesh] OR "relaxation therapy"[Mesh] OR "counseling"[Mesh] OR "biofeedback, psychology"[Mesh] OR "guideline adherence"[Mesh] OR "patient compliance"[Mesh] OR "patient education as topic"[Mesh] OR "Health promotion"[Mesh] OR "Health education"[Mesh] OR "health behavior"[Mesh] OR "Reinforcement (Psychology)"[Mesh] OR "social support"[tiab] OR "Behavior therapy"[tiab] OR "cognitive therapy"[tiab] OR "Mind-body therapies"[tiab] OR counselor* [tiab] OR "psychology biofeedback"[tiab] OR "guideline adherence"[tiab] OR "patient compliance"[tiab] OR "patient education as topic"[tiab] OR "Health promotion"[tiab] OR "Health education"[tiab] OR "health behavior"[tiab] OR "Reinforcement (Psychology)"[tiab] OR alternative therap*[tiab] OR "Psychophysiology"[tiab] OR "behavior training"[tiab] OR "behavior treatment"[tiab] OR "desensitization"[tiab] OR "CBT"[tiab] OR cognitive behavior therap*[tiab] OR cognitive behavior treatment*[tiab] OR cognitive behavioural therap*[tiab] OR cognitive behavioural treatment*[tiab] OR cognitive behavior therap*[tiab] OR cognitive behavior treatment*[tiab] OR cognitive behavioural therap*[tiab] OR cognitive behavioural treatment*[tiab] OR "anthroposophy"[tiab] OR "complementary medicine"[tiab] OR complementary therap*[tiab] OR mind-body relation*[tiab] OR mind-body therap*[tiab] OR mind body techniq*[tiab] OR mind body therap*[tiab] OR "naturopathy orthomolecular medicine"[tiab] OR polarity thera*[tiab] OR reflexotherap*[tiab] OR spiritual therap*[tiab] OR "mind-body and relaxation techniques"[tiab] relaxation therap*[tiab] OR client centered therap*[tiab] OR nondirective therap*[tiab] OR "biofeedback (psychology)"[tiab] OR psychoneuroimmunolog*[tiab] OR psychophysiologic respons*[tiab] OR "patient adherence"[tiab] OR "treatment compliance"[tiab] OR health behav*[tiab] OR health promoting behav*[tiab] OR health related behav*[tiab] OR "conditioning"[tiab] OR "differential reinforcement"[tiab] OR "knowledge of results (psychology)" [tiab].

#3 Outcome measures

depressive OR anxiety OR distress.

#4 Randomized controlled trials

"randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized controlled trials"[mh] OR "random allocation" [mh] OR "double-blind method" [mh] OR "single-blind method" [mh] OR "clinical trial" [pt] OR "clinical trials" [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies [pt] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]).

(RCT Filter kort: "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[sh] OR "randomly"[tiab] OR "trial"[tiab] OR "groups"[tiab])

#5 Adult (not child)

(("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR

adolescen*[tiab] OR child*[tiab] OR schoolchild*[tiab] OR infant*[tiab] OR girl*[tiab] OR boy*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab] OR youth*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR puber*[tiab]) NOT ("Adult"[Mesh] OR adult*[tiab] OR man[tiab] OR men[tiab] OR woman[tiab] OR women[tiab]))

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