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REVIEW ARTICLE

Impact of non-pharmacological interventions on quality of life, anxiety, and depression scores in patients with colorectal cancer: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Purpose Different non-pharmacological interventions have been considered and applied to patients with colorectal cancer to improve their quality of life and distress symptoms; however, there is little evidence comparing the effectiveness of these strategies. This review aimed at assessing the effect of non-pharmacological interventions on quality of life, anxiety, and depression scores among patients with colorectal cancer.

Methods A systematic search for articles published until August 1, 2020, in the English language was performed in Medline, EMBASE, Web of Science, and the Cochrane Library; the reference lists of eligible articles were scanned for other potentially eligible publications. A meta-analysis was performed using random-effects models to estimate pooled effect sizes.

Results Twenty studies were included, representing a total of 3438 patients with colorectal cancer. Non-pharmacological interventions were associated with a significant reduction in anxiety (standardized mean difference [SMD] = − 0.157; 95% confidence interval [CI], − 0.312–[− 0.002]) and depression (SMD = − 0.207; 95% CI, − 0.390–[− 0.024]) scores during 5–8 months of follow-up. Subgroup analyses revealed that interventions delivered face-to-face improved patients' quality of life during 1–4 months of follow-up. Moreover, interventions delivered face-to-face but without a behavioral component were associated with improved anxiety scores, whereas interventions with a behavioral component improved the depression scores during 5–8 months of follow-up.

Conclusions Non-pharmacological interventions were associated with reduced anxiety and depression scores, whereas interventions delivered face-to-face were associated with improved quality of life scores in patients with colorectal cancer. Given the few studies and patients included in this meta-analysis, these conclusions should be interpreted with caution.

Keywords Colorectal cancer · Non-pharmacological Intervention · Quality of life · Anxiety · Depression · Meta-analysis

Introduction

Colorectal cancer (CRC) is the third most common cancer type among both sexes worldwide, with approximately 1.8 million new cases and approximately 900,000 deaths in 2018 [1]. The incidence and mortality rates of CRC continue to increase in many low- and middle-income countries, in contrast to developed countries, where mortality rates tend to decrease, likely due to increased access to CRC screening and treatment, and a lower prevalence of associated risk factors [1, 2].

Recovery from CRC includes management of side effects of treatment as well as the introduction and maintenance of healthy lifestyle choices [2]. Studies have shown that CRC survivors are affected by the psychosocial consequences of their disease: 13–38% of patients present with distress [3–5], which can persist for years after treatment completion; in fact, CRC can affect mental health at any stage of the patient's journey. Depression, anxiety, and fear of recurrence alongside reduced levels of social support affect patients with CRC and

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reduce their quality of life (QoL) [6–9]. QoL is reported to be an accurate prognostic factor of CRC outcomes and has been increasingly recognized in clinical trials to be on par with traditional end points, such as tumor response and survival [10].

Previous literature reviews have shown that psychoeducation [11, 12], exercise [13, 14], and yoga [15, 16] can improve the QoL of patients with cancer. Other non-pharmacological interventions, including psychological, social, and physical activities (excluding complementary and alternative therapies or medicines) [17], have been examined in previous studies involving CRC survivors. In this systematic review, we aimed to summarize the evidence on the impact of these non-pharmacological interventions on the QoL- and mental health–related outcomes in CRC survivors.

A previous review conducted by Otto et al. [18] showed the association of physical activity with QoL and mortality rate in patients with CRC; however, only three studies accounted for QoL as an outcome. Two separate systematic reviews [19, 20] have examined similar associations; however, these studies did not include a quantitative synthesis due to the high levels of heterogeneity between the included studies. A recent Cochrane review performed by McGettigan et al. included a meta-analysis that showed that physical activity may improve health-related QoL in patients with cancer (six studies). However, there was no evidence of the effect of physical activity on anxiety or depression [21]. Finally, Son et al. performed a meta-analysis of findings from eight randomized trials that evaluated the impact of psychosocial interventions on health-related QoL in patients with CRC [22]; however, outcomes, such as anxiety and depression scores, were not evaluated. Furthermore, the impact of exercise or other behavioral interventions was not examined in this review.

Currently, there is no meta-analysis on non-pharmacological interventions for patients with CRC yet. Quantified evidence is needed to compare the effectiveness of various strategies. This systematic review and meta-analysis aimed to assess the impact of non-pharmacological therapies on psychosocial outcomes in CRC survivors, including QoL, anxiety, and depression scores.

Methods

The study protocol was prospectively registered with PROSPERO (registration number: CRD42020206053). This study was developed and reported according to the updated PRISMA guidelines [23].

Literature search

The literature search was limited to articles published in the English language and indexed in health-related databases, including Medline (PubMed), EMBASE, the Cochrane Library, and Web of Science. The search included articles that were published until August 1, 2020.

Our literature search involved the following keywords: colorectal neoplasms, colorectal cancer, colorectal tumor, non-pharmacological therapy, cognitive therapy, behavio* therapy, and physical exercise*. In addition, the reference lists of eligible studies were checked for other potentially relevant publications.

The search terms used in PubMed were as follows: ([“Colorectal Neoplasms” [Mesh]] OR [Colorectal Neoplasm] OR [Neoplasm, Colorectal] OR [Colorectal Carcinoma] OR [Carcinoma, Colorectal] OR [Carcinomas, Colorectal] OR [Colorectal Carcinomas] OR [Colorectal Cancer] OR [Cancer, Colorectal] OR [Cancers, Colorectal] OR [Colorectal Cancers] OR [Colorectal Tumors] OR [Colorectal Tumor] OR [Tumor, Colorectal] OR [Tumors, Colorectal] OR [Neoplasms, Colorectal]) AND ([non-pharmacological therapy] OR [psychological therapy] OR [Psychotherapy] OR [Cognitive Therapy] OR [behavio* therapy] OR [Homeopathy] OR [Hypnosis] OR [physical exercises]). In addition, PubMed’s randomized controlled trial (RCT) filter was applied to the results of this search.

Selection criteria

Two authors (Meng and Wang) screened the shortlisted titles and abstracts for eligibility; disagreements were resolved by consensus. The same authors performed the full-text review of eligible articles.

Studies were eligible for inclusion if they met the following criteria: (1) participants were CRC survivors of any age; (2) interventions were non-pharmacological therapies, defined as any treatment without a proven or supposed pharmacological activity, including physical exercise and psychotherapy, delivered by trained personnel, such as nurses, therapists, or exercise instructors; (3) the primary outcome was the QoL score, and secondary outcomes were anxiety and depression scores, measured with standardized instruments; (4) the study design was an RCT, as this study type is associated with a low risk of bias, high internal validity, and the capacity to provide the strongest evidence of intervention effects.

Studies were excluded if they met any of the following criteria: (1) participants were patients with cancer types other than CRC, or patients who only showed psychological distress along with CRC; (2) interventions were delivered by a non-professional; (3) outcomes were not assessed with standardized instruments; and (4) the follow-up period was < 1 month.

Data extraction and quality assessment

Data were extracted from eligible studies independently by two authors (Meng and Wang), using data extraction forms

developed specifically for this review; any discrepancies were resolved by a third reviewer.

Information on the following variables was extracted from the articles: article title, first author name, publication year, study design, sample size, participant characteristics (age, sex, income, and marital status), location of cancer, disease stage, need for stoma creation, adjuvant therapy, intervention characteristics (timing, provider, description, and duration), outcome measurement tools, outcome estimates (overall scores, mean differences, standard deviations, and 95% confidence interval [CI] or standard error of the mean values), and follow-up duration.

For quality assessment of the included studies, we used the Cochrane Handbook for Systematic Reviews of Interventions, version 6.0 (Revman version 5.4, The Nordic Cochrane Centre, Copenhagen). Seven components associated with the risk of bias were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias [24, 25]. Disagreements were resolved by discussion between two reviewers.

Statistical analysis

Narrative synthesis was conducted for all studies. Statistical analyses were performed using Stata 16.0 (Stata Corp., College Station, TX, USA). In this review, we compared the impact of a non-pharmacological intervention vs. that of a control condition on patient outcomes, including QoL, anxiety, and depression scores. Outcome scores with the corresponding standard deviations (SDs) were measured with suitable instruments.

For continuous variables, pooled effects were summarized as Hedge's g standardized mean differences (SMDs), as different scales were used in different studies. We calculated SMDs using mean scores and SDs. When SDs were not reported in the original articles, they were calculated from the provided data, using the standard error of the mean, 95% CI, or the p- or t-value. As the duration of follow-up and assessment time points differed between studies, we considered the clinically relevant follow-up duration (1–4 months and 5–8 months).

Heterogeneity was assessed using I^2 ($I^2 > 50\%$ means high heterogeneity), representing the proportion of the total variation across studies attributed to heterogeneity. If I^2 was > 75%, we performed sensitivity analysis to assess the risk of bias for the overall effect. Visual inspection of forest plots was performed to assess heterogeneity. A random-effects model was used to estimate pooled effects when significant heterogeneity was found between studies; subgroup and sensitivity analyses were performed to explore the possible sources of heterogeneity. We conducted subgroup analyses according to the type of intervention administered: (1) intervention delivered face-to-face vs. that delivered otherwise; and (2) intervention with a behavioral component vs. that with an educational component. We defined a behavioral intervention as that inducing a change in behavior and in which patients' practices were significantly quantified and assessed, and an educational intervention was defined as delivery of information that inculcated knowledge and guided patients' behaviors and perspectives.

Publication bias was assessed using a visual inspection of funnel plots and the Egger's regression asymmetry test. These effects were assumed to be present for p values < 0.05.

Results

The literature search yielded 5138 items; after excluding duplicates, the titles and abstracts of 4933 records were screened for eligibility. After removing unsuitable articles, most of which did not report the relevant outcomes, we examined the full text of 158 articles. Finally, a total of 20 RCTs met the eligibility criteria of the present study and were included in the quantitative synthesis (Fig. 1). We included one study that evaluated patients with CRC and patients with anal cancer [26] because the proportion of patients with anal cancer was negligible in the study's population (2.1% [n = 1]) in the intervention group and 2.6% [n = 1] in the control group).

Quality assessment

Table 1 shows findings from the risk of bias assessment of the included RCTs. Overall, 7 (35%) [27–33], 9 (45%) [26, 34–41], and 4 (20%) [42–45] studies had a low, medium, and high risk of bias, respectively. Notably, in most studies, the nature of the intervention (e.g., home visit or physical exercise) precluded participant or personnel blinding.

Study characteristics

Table 1 shows the summary of the study characteristics (20 studies, including a total of 3438 patients). Participants' mean age ranged from 53.6 to 68.8 years in the intervention groups and from 53.0 to 68.3 years in the control groups. Studies were conducted in China [27, 35, 36, 39–41] (6/20, 30%), the USA [30, 34, 37, 38, 45] (5/20, 25%), and Australia [31, 32, 42] (3/20, 15%); the remaining six studies were performed in the UK [33], Korea [28], Sweden [26], Denmark [43], Canada [44], and Germany [29]. In total, 55% (11/20) and 85% (17/20) of the studies were published during 2015–2020 and 2010–2020, respectively.

Non-pharmacological interventions were mostly delivered after surgery (19/20). In general, interventions were delivered on a weekly basis using various strategies (i.e., interview, exercise, writing, or telephone-based education). Most studies

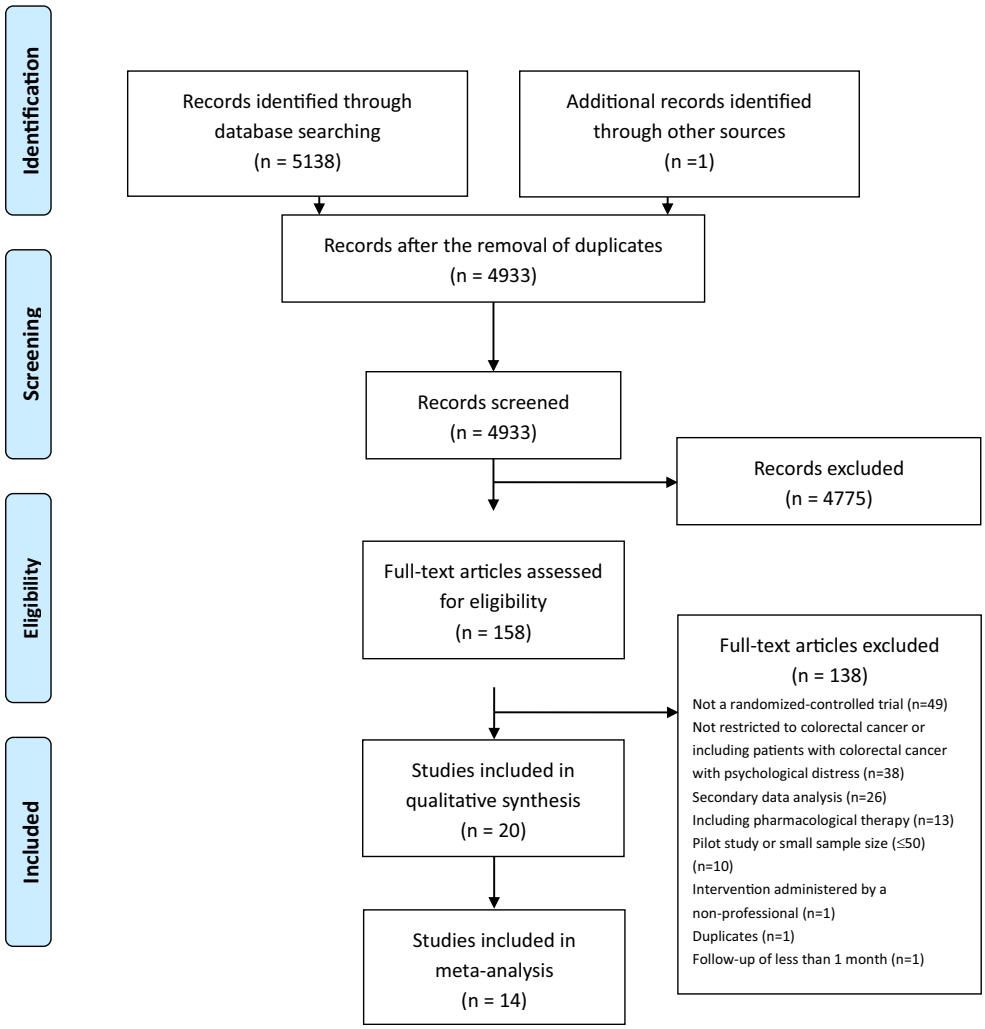

Fig. 1 PRISMA flow diagram capturing systematic review study selection

(15/20) included control groups that received the usual standard of care, a needs assessment only, or that were wait-listing for interventions. Other control conditions were relative to the specific interventions.

The QoL score was reported as the endpoint in 19 studies, where it was mainly measured using the European Organization for Research and Treatment of Cancer QoL Questionnaire [46] and the Functional Assessment of Cancer Therapy-Colorectal [47]. Psychological outcomes, including anxiety or (and) depression scores, were reported as end points in 14 studies; they were commonly assessed with the Hospital Anxiety and Depression Scale [48] and the Brief Symptom Inventory scores [49]. The reasons for the exclusion of some trials are provided in Online Resource 1.

Quality of life outcomes

QoL was assessed in 19 (95%) studies that included 3362 patients. Eight (42.11%) trials reported statistically significant improvements in overall QoL or its sub-score in the intervention groups than in the control group. Among six trials at low risk of bias, two (33.33%) reported statistically significant improvements [27, 31]; three (50%) of these trials involved face-to-face interventions [27–29], and five (83.33%) of these trials involved interventions with a behavioral component [27–32].

A total of 11 trials reported QoL scores during 1–4 months of follow-up, which could be combined in a meta-analysis; of these, six trials involved face-to-face interventions, and seven trials involved interventions with a behavioral component. Among these 11 trials, non-pharmacological interventions were associated with a statistically significant and clinically meaningful improvement in the QoL scores during 1–4 months of follow-up; however, there was significant heterogeneity between these studies (SMD, 0.368; 95% CI, 0.070–0.665; I^2 = 85.9%; Fig. 2a). There was no association between non-pharmacological interventions and QoL scores among 11 trials that involved a follow-up period of 5–8 months (SMD, 0.108; 95% CI, − 0.023–0.240; I^2 = 29.9%).

Table 1 Summary of the characteristics of the included randomized controlled trials

Study	Mean age (intervention/control)	Gender (% male)	Income (% ≥ USD 50 thousand/year)	Marital status (% married/cohabiting)	Location of cancer	Stages of disease	Need of stoma (%)	Adjuvant therapy
Mandy, 2020, Hong Kong, China	66.6/64.9	62.5			Colon 60% Rectal 40%	Stages I–IV	12.5	Chemotherapy 60% Radiotherapy 19%
Ramirez, 2020, USA	56.35/55.76	46.2	15.3	61.5		Stages I–IV		
Yang, 2020, Taiwan, China	59.97/63.62	47.1	41.2	69.1		Stages I–IV		
Kim, 2019, Korea	55.7/56.8	49.3	46.5% > USD 3000/month	77.5	Colon 64.8% Rectal 35.2%	Stages II–III		Chemotherapy
Li, 2019, China	60.06/58.47	63.4				Stages II–III		Chemotherapy
Cramer, 2016, Germany	68.70/68.26	61.1		79.6	Colon 44.4% Rectal 53.7%	Stages I–III	44.4	Chemotherapy 44.4% Radiotherapy 19.8%
DuHamel, 2016, USA	56.73/54.27	0	69.1	57.1	Rectosigmoid and anal 30.4% Rectal 69.6%	Stages I–III	Permanent 14.3	Chemotherapy 44.4% Radiotherapy 19.8%
Jefford, 2016, Australia	62.1/63.1	51.6		70	Colon 55.8% Rectal 35.0% Overlapping 10.1%	Stages I–III		Chemotherapy 70.0% Radiotherapy 51.6%
Ohlsson, 2016, Sweden	66.1/65.9	62.8		62.8	Colon 59.3% Rectal 38.4% Anal 2.3%	Stage I–IV		Chemotherapy 39.5% Radiotherapy 26.7%
Lepore, 2015, USA	54.44/55.80	50.8		65.8	Colon 56.0% Rectal 44.0%	Stages I–III		Chemotherapy 75.6% Radiotherapy 39.4%
Hawkes, 2014, Australia	66.3	54	27% > USD 65000/year	77	Colon 67% Rectal 33%	Stages I–III		Chemotherapy 23.7% Radiotherapy 0.5%
Pinto, 2013, USA	55.6/59.5	43.5	56.5% > USD 60000/year	71.7	Colon 56.5% Rectal 43.5%	Stages I–III		Chemotherapy 82.6% Radiotherapy 43.5%
Young, 2013, Australia	68.6/67.0	55.5		76.2	Colon 66.8% Rectal 33.3%	Stages I–IV	37.7	
Lee, 2010, Hong Kong, China	58.9/60.5	66.3		89.6			28.9	69.86
Ross, 2005, Denmark	68.8/68.1	48.6		60.2		Stages I–IV	33.3	Chemotherapy 14.1% Radiotherapy 6.0%

Table 1 (continued)

Courneya, 2003, Canada	61.13/59.92	58	61.5% > USD 40000/year	76.3	Colon 76.1% Rectal 23.9%	Stages I–IV		Chemotherapy 65.2% Radiotherapy 20.7%
Zhang, 2014, China	53.6/53.0	64.45		94.75	Colon 48.65% Rectal 51.45%	Stages II–III		Chemotherapy
O'Connor, 2014, UK	63.12/68.29	64.5		71	Rectal 100%			Chemotherapy Radiotherapy
Mayer, 2018, USA	59.34/57.84	68.5			Colon 100%	Stages I–III	4.2	Chemotherapy 47.9%
Cheung, 2003, Hong Kong, China	60.1/56.4	67.8		78			100	Chemotherapy Radiotherapy

Study	Timing	Intervention		Control	Follow-up	Primary outcome	Secondary outcome	Risk of bias
Mandy, 2020, Hong Kong, China	Pre and post	Physical activity, PA (n = 56)	*Behavioral* Patients did 30 min of moderate-to-vigorous physical activity (MVPA) 5 days a week in the first 6 months and progressing toward the target of 60 min of MVPA 5 days a week over the next 6 months. *Face-to-face* Patients received individual face-to-face motivational interviews.	Usual care (n = 56)	6 months 12 months 18 months 24 months	SF-12, FACT-C	HADS	Low
Ramirez, 2020, USA	Post	Patient Navigator LIVESTRONG Cancer Navigation Services, PN-LCNS n = 35	*Educational* Patients were presented with the PN-LCNS program: promote usage of PN-LCNS services for 3 months; help to address and overcome barriers to using the PN-LCNS program; orient participants to the availability of community resources, such as social work and psychosocial service referrals, child/elder care, transportation, and financial services available at local community clinics; and assist with accessing and planning future medical appointments for treatment follow-up.	Patient navigation only n = 35	3 months 9 months 21 months	FACT-C		Some concern
Yang, 2020, Taiwan, China	Post	Occupational therapy n = 34	*Educational/face-to face* Patients were given consultations using the technique of motivational interviewing based on a CRC education handbook at three time points. While the first consultation that lasted 30 min was conducted at bedside during discharge preparation, the second and third consultations that took 15–20 min each.	Was given a CRC education handbook (the same handbook) only during discharge preparation n = 34	1 month 3 months	WHO-QOL-BREF		Some concern

Table 1 (continued)

Kim, 2019, Korea	Post	Home-based exercise *n* = 37	Behavioral Patients increased the level of PA to 18 metabolic equivalent of task (MET) hours per week during the first 6 weeks, the level of PA was increased to 27 MET-hours per week depending on individual health conditions. *Educational* Patients were provided with two types of exercise DVDs, including both the moderate- and vigorous-intensity version, which comprised 30 min of resistance training using major and core muscles to be performed at home every day. *Face-to-face* Patients met with exercise trainers once each week at the clinic as a group for the first 3 weeks and again at the sixth week.	Usual activities or exercises *n* = 34	3 months	FACT-C	Low
Li, 2019, China	Pre	Incremental Patient Care Program *n* = 149	*Educational* Patient health education: Over the first 2 weeks, patients were provided with general health education materials, including information about nutrition, physical activity, and mental health care; detailed instruction was given once every 2 months for 6 months. Telephone counseling; regular examination; care activities. *Behavioral* Physical exercise: Over the first 3 months, patients participated in low-intensity physical exercises: relaxation (30 min five times a week), body awareness and restorative exercise (90 min once a week) and massage (30 min twice a week). Over the subsequent 3 months, patients participated in high-intensity physical exercise for 90 min followed by 30 min of relaxation exercise three times a week.	Usual care *n* = 149	6 months	EORTC QLQ-C30	HADS	Some concern
Cramer, 2016, Germany	Post	Yoga *n* = 27	*Behavioral/face-to-face* Patients were given weekly 90-min classes of traditional hatha yoga over a period of 10 weeks, and the patients should concentrate on their body with inner involvement during classes while adopting a non-competitive attitude.	Wait list *n* = 27	1 week 10 weeks 22 weeks	FACT-C	HADS	Low
	Post		*Educational/face-to-face*	Assessment only *n* = 37	4 months 8 months	EORTC QLQ-C30	BSI	Some concern

Table 1 (continued)

DuHamel, 2016, USA		Cancer survivorship intervention-sexual health *n* = 33	Patients were given four 1-h individual sessions: (a) an overview of sexual health and an evaluation of the patient's sexual health, (b) discussion of strategies to improve sexual functioning and overall well-being, (c) education on effective communication methods for the patient to use with their partner, and (d) providing additional resources such as educational booklets or relevant referrals. Each session included homework assignments as well as booster calls between sessions to promote adherence and to help participants implement strategies learned during sessions.					
Jefford, 2016, Australia	Post	Survivor Care *n* = 106	*Educational* Patients were given information package: DVD, booklet, question prompt list; a tailored Survivorship Care Plan: cancer diagnosis, treatments, health promotional advice, supportive care, and psychosocial elements, as well as recommendations for follow-up; and received telephone follow-up. *Face-to-face* Patients were given nurse-led, face-to-face end-of-treatment session, approximately 60 min.	Usual care *n* = 110	2 months 6 months		EORTC QLQ CR-29	High
Ohlsson, 2016, Sweden	Post	Psycho-Educational Program *n* = 47	*Educational/face-to-face* Patients attended seven meetings (once a week, each 60 min) with informational lectures on the following topics: colorectal cancer, music and relaxation; the operating theatre; the importance of physical activities; the meaning of food, crisis, and crisis intervention; and patients' organizations; a 60-min discussion and reflection with peers.	Usual care *n* = 39	1 month 6 months 12 months	SF-36		Some concern
Lepore, 2015, USA	Post	Expressive writing *n* = 101	*Behavioral* Patients were instructed to write for 15 min twice a week for 2 weeks about their deepest thoughts and feelings concerning their cancer, also other highly upsetting experiences.	Write for 15 min twice a week for 2 weeks about current daily activities (day 1), how they manage time (day 2), current leisure activities and ways of relaxing (day 3), and current eating habits (day 4).	1 month	EORTC QLQ-C30	CES-D	Low

Table 1 (continued)

				n = 92				
Hawkes, 2014, Australia	Post	Multiple health behavior change intervention *n* = 205	*Educational* Patients were given 11 telephone-delivered health coaching sessions: the cancer experience, colorectal cancer-related symptoms, and specific acceptance and commitment therapy (ACT) processes in relation to lifestyle behaviors; a participant handbook: educational information on health behaviors and core ACT processes; the quarterly study newsletter sent to usual care participants. *Behavioral* Patients were given regular motivational postcards: behavior change and participant retention; a pedometer: physical activity.	Usual care *n* = 205	6 months 12 months	FACT-C	BSI-18	Low
Pinto, 2013, USA	Post	Physical activity, PA *n* = 20	*Educational* Patients received in person instructions on how to exercise at a moderate intensity level, how to monitor heart rate, and how to warm up before exercise and cool down after exercise. *Behavioral* Patients were given home logs to monitor PA participation and a pedometer to wear during walks for exercise; during the first few weeks of the intervention, participants were encouraged to exercise for at least 10 min on at least 2 days/week, and the goals were gradually increased over the 12 weeks to 30 min/day on at least 5 days/week.	Received weekly calls over 12 weeks during which the symptom questionnaire was administered to monitor problems such as headaches, also received CRC survivorship tip sheets *n* = 26	3 months 6 months 12 months	FACT-C, SF-36 PF		Some concern
Young, 2013, Australia	During or post	CONNECT intervention *n* = 387	*Educational* Patients received five scheduled, structured telephone calls on days 3 and 10 and then at 1, 3, and 6 months after hospital discharge, based on the findings of a clinical audit of postoperative needs of patients with colorectal cancer. Each call includes 22 standardized screening questions about common physical, psychosocial, information, supportive care, and rehabilitation/follow-up needs.	Usual care *n* = 369	1 month 3 months 6 months	FACT-C		Low
Lee, 2010, Hong Kong, China	Post	Body-Mind-Spirit intervention *n* = 84	*Educational/behavioral/face-to-face* Each group of patients consisted of 10 to 12 members and met weekly for 5 weeks; each meeting lasted 3 h: in-depth sharing, emotional expression,	Assessment only *n* = 82	1 month 4 months 8 months 12 months	SF-36	CECS	Some concern

Table 1 (continued)

			meditation, and physical exercise support and helping others.					
Ross, 2005, Denmark	Post	Home visit *n* = 125	*Educationa/face-to-face* Patients received home visits (five times during the first 2–3 months and visits were repeated approximately 4, 7, 11, 16, and 24 months after discharge, totalling 10 visits in all) which were aimed at providing emotional and informational support and encouraging the patients to make use of their own social network to cope with the disease: possible symptoms indicative of a relapse were discussed at each visit, but apart from that, the patients chose the topics of discussion and the setting of the visits.	Assessment only *n* = 124	3 months 6 months 12 months 24 months	EORTC QLQ-C30	HADS	High
Courneya, 2003, Canada	Post	Home-based exercise *n* = 69	*Behavioral* Patients were given a home-based, personalized exercise program that took into account their baseline fitness test results, exercise history, performance status, adjuvant therapy and personal preferences, the goal was to have participants exercising at least 3–5 times per week, for 20–30 min.	Usual care *n* = 33	4 months	FACT-C	STAI, CES-D	High
Zhang, 2014, China	Post	Self-efficacy-enhancing intervention *n* = 76	*Educational* Patients received four health-coaching sessions which were conducted via telephone during the patients' chemotherapy for a 6-month period. These sessions aimed to strengthen participants' self-efficacy in symptom management and were guided by a protocol. Each session included a discussion of symptom distress, chemotherapy adherence, and self-management strategies; the nurse provided encouragement and reinforcement to the participants' efforts and successes, and empowered them through support; the duration of each phone call varied from 20 to 40 min.	Standard care *n* = 76	3 months 6 months	FACT-G	HADS	Some concern
O'Connor, 2014, UK	Post	Information pack *n* = 43	*Educational* At patients' first meeting with the Stoma Care Nurse Specialists, patients received a series of leaflets from the new information pack depending on their condition, treatment plan, and the information that they wished to receive;	Usual care, and were offered the generic colorectal cancer and stoma information leaflets *n* = 33	6 months		HADS	Low

Table 1 (continued)

			the tailored information pack consists of a series of fourteen leaflets on various aspects of disease and treatment of RC.					
Mayer, 2018, USA	Post	SurvivorCHESS program *n* = 144	*Educational* Patients were given all materials provided to the control group, plus smartphones with the SurvivorCHESS application, along with voice and data services for the study period; SurvivorCHESS is a smartphone CHESS application that included core services of skill building (promoting competence), support services (promoting relatedness), and information services and tools (promoting autonomy). After 6 months, a certified personal trainer was made available for users to ask questions about physical activity.	Received the National Cancer Institute's Facing Forward: Life after Cancer Treatment booklet, the National Coalition for Cancer Survivorship's Cancer Survival Toolbox, and a pedometer *n* = 140	3 months 6 months 9 months	FACT-C	NCCN distress tool	High
Cheung, 2003, Hong Kong, China	Post	Progressive Muscle Relaxation Training, PMRT *n* = 29	*Educational* The sequences of PMRT were recorded on an audio cassette tape and given to patients: two teaching sessions, which included one briefing and one training session during the postoperative period, were given to subjects before the intervention. *Behavioral* Patients were given a 20-min period, required subjects to tense and relax different muscle groups in combination with deep breathing, 10 major muscle groups.	Usual care *n* = 30	1 week 5 weeks 10 weeks	WHO–QOL	STAI	Some concern

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; *HADS*, Hospital Anxiety and Depression Scale; *SF*, Short Form Health Survey; *FACT-C*, Functional Assessment of Cancer Therapy-Colorectal; *WHO-QOL*, World Health Organization Quality of Life scale; *BSI*, Brief Symptom Inventory; *CES-D*, Center for Epidemiologic Studies Depression scale; *CECS*, Courtauld Emotional Control Scale; *STAI*, State-Trait Anxiety Inventory

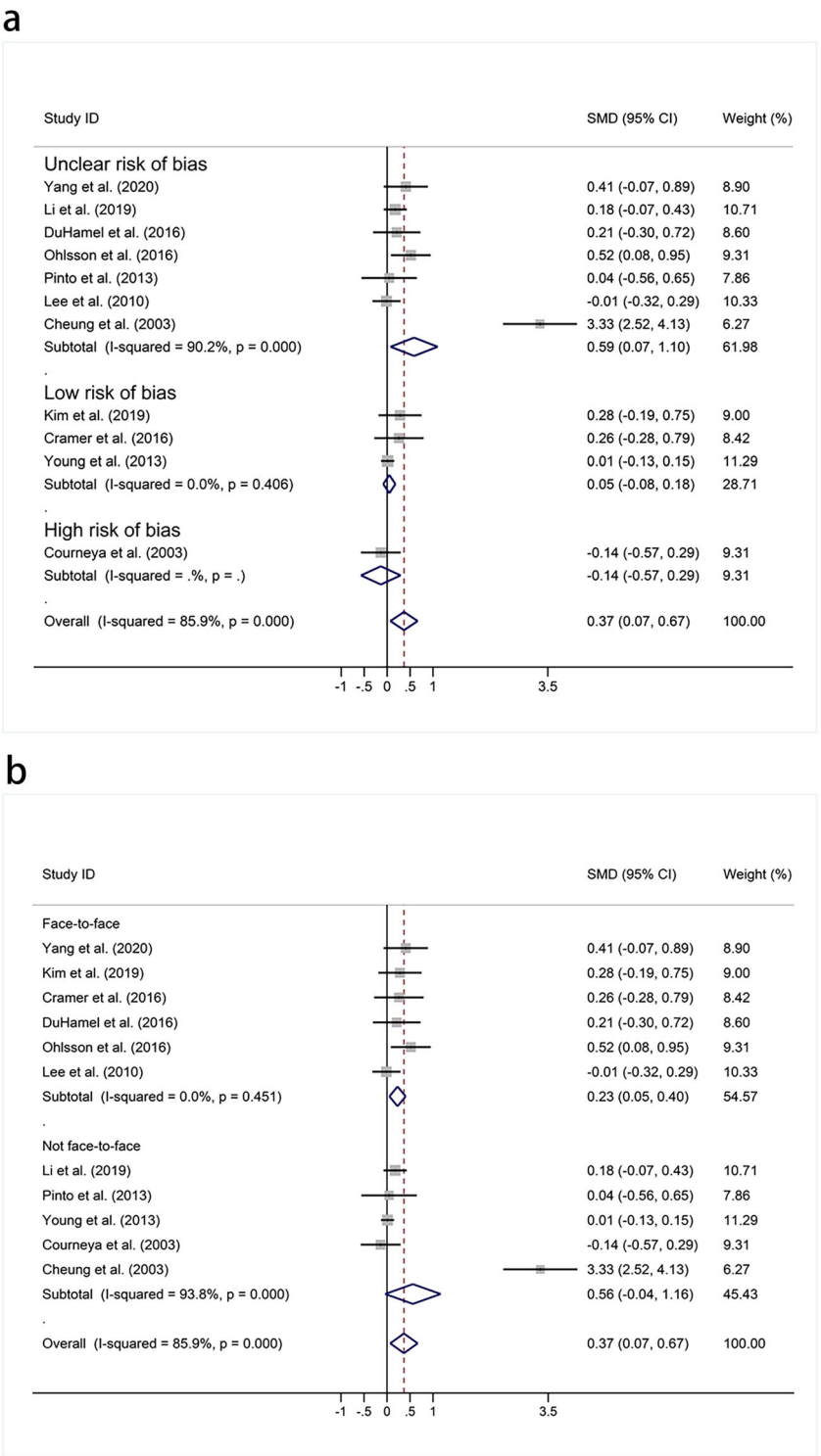

Fig. 2 **a** Impact of non-pharmacological interventions on quality of life during 1–4 months of follow-up. **b** Impact of non-pharmacological interventions (face-to-face vs. not face-to-face) on quality of life during 1–4 months of follow-up. SMD, standardized mean difference; CI, confidence interval

In sensitivity analyses restricted to trials at low risk of bias, non-pharmacological interventions were not associated with improved QoL scores during 1–4 months of follow-up (SMD, 0.048; 95% CI, − 0.084–0.180; 3 trials; I^2 = 0.0%; Fig. 2a).

Furthermore, in trials that involved 1–4 months of follow-up (6 trials), face-to-face delivered interventions were associated with attenuated improvement in the QoL scores (SMD, 0.228; 95% CI, 0.052–0.404; I^2 = 0.0%; Fig. 2b); this association was not detected in studies that involved a 5–8-month follow-up period (Online Resource 2). There was no association between the behavioral component of interventions and changes in QoL in either follow-up category of studies (Online Resource 2). Evidence of publication bias was detected by the Egger

test (p = .075) and by the visual examination of an asymmetrical funnel plot (Fig. 3).

Anxiety-related outcomes

There were 13 trials involving 2148 patients that assessed the impact of non-pharmacological interventions on anxiety scores. Five (38.46%) trials reported statistically significant reductions in specific anxiety scores or overall distress scores [29, 33, 39–41]. Of four trials at low risk of bias, two reported statistically significant reductions in anxiety scores [29, 33].

Effect estimates from seven trials involving 862 participants, followed up for 1–4 months, were pooled in a meta-analysis of anxiety-related outcomes. Of these, one [37] and four [36, 37, 39, 41] trials were assessed at a low and at unclear risk of bias, respectively; two trials were assessed at a high risk of bias [36, 38]. Non-pharmacological interventions were not associated with changes in anxiety scores during 1–4 months of follow-up (SMD, − 0.402; 95% CI, − 0. 913–0.109; I^2 = 91.9%). However, in studies involving 5–8 months of follow-up (five trials, 644 patients), non-pharmacological interventions were associated with a significant reduction in anxiety scores (SMD, − 0.157; 95% CI, − 0.312–[− 0.002]; I^2 = 0.0%; Fig. 4a).

Among the studies involving 14 months of follow-up, only one trial was at low risk of bias [29]; this trial reported an association between a non-pharmacological intervention and a decreased anxiety score (SMD, − 0.642; 95% CI, − 1.190–[− 0.094]).

Subgroup analyses revealed that intervention type or content did not affect anxiety scores during 1–4 months of follow-up (Online Resource 2). However, in studies with 5–8 months of follow-up, a non-pharmacological intervention was delivered face-to-face (SMD, − 0.237; 95% CI, −0. 435–[− 0.039]; I^2 = 0.0%; Fig. 4b), and an intervention without a behavioral component (SMD, − 0.288; 95% CI, − 0.548–[− 0.028]; I^2 = 0.0%; Fig. 4c) was associated with decreased anxiety scores.

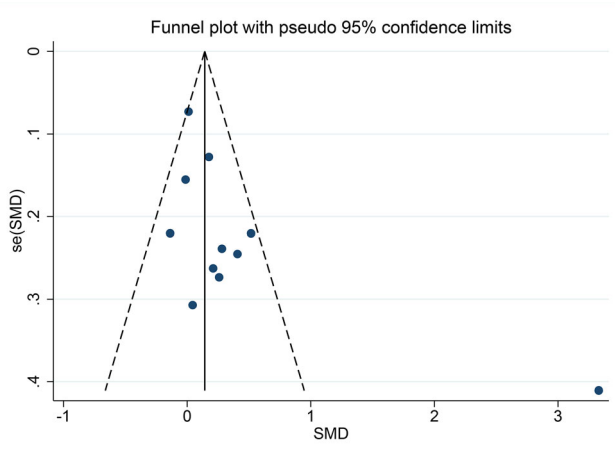

Fig. 3 Funnel plot of the meta-analysis of quality of life. SMD, standardized mean difference

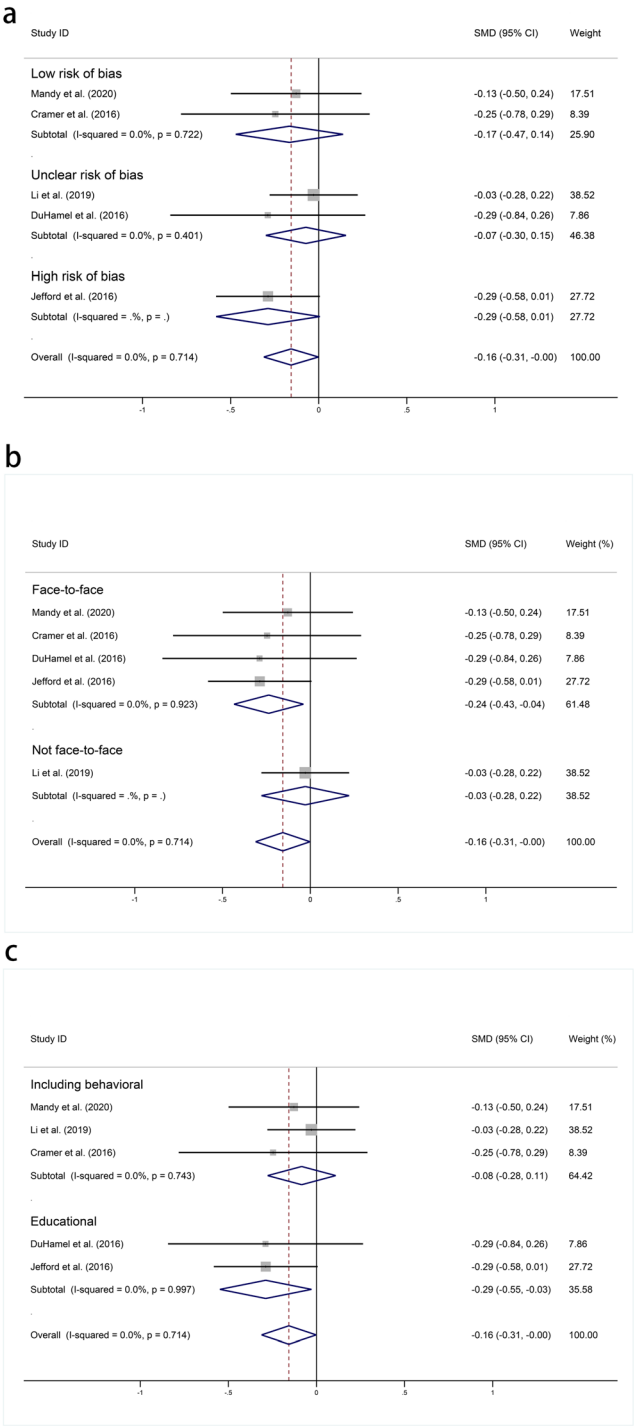

Fig. 4 **a** Impact of non-pharmacological interventions on anxiety during 5–8 months of follow-up. **b** Impact of non-pharmacological interventions (face-to-face vs. not face-to-face) on anxiety during 5–8 months of follow-up. **c** Impact of non-pharmacological interventions (behavioral vs. educational) on anxiety during 5–8 months of follow-up. SMD, standardized mean difference; CI, confidence interval

Depression-related outcomes

Twelve trials that involved 2066 patients assessed depression scores. Three trials reported a statistically significant reduction in depression component scores or overall distress scores [29, 36, 40]. Of five trials at low risk of bias, one reported statistically significant reductions in the symptom burden [29].

Estimates reported in five trials involving 619 participants and a 1–4-month follow-up period were pooled in a meta-analysis of depression outcomes, showing no association between non-pharmacological interventions and reduced depression scores (SMD, − 0.061; 95% CI, − 0.293–0.170; I^2 = 45.3%). In studies involving 5–8 months of follow-up (four trials, 465 patients), non-pharmacological interventions were associated with a reduction in depression scores (SMD, − 0.207; 95% CI, − 0.390–[− 0.024]; I^2 = 0.0%; Fig. 5a).

Subgroup analyses revealed no impact of intervention type or content on depression scores during 1–4 months of follow-up (Online Resource 2). During 5–8 months of follow-up, interventions delivered face-to-face did not affect depression scores (Online Resource 2); however, interventions that included a behavioral component were associated with a decrease in depression scores (SMD, − 0.245; 95% CI, − 0.439–0.051; I^2 = 0.0%; Fig. 5b) during the same period.

The influence of patients' sociodemographic data on outcomes

Collected pre-intervention characteristics were not complete among trials. We presented meta-regression by these characteristics for outcomes with ≥ 10 analyzable trials [50] and performed subgroup analysis for other outcomes with > 1 analyzable trial in each subgroup. Most of the effects showed no impact on outcomes. In trials that involved 5–8 months of follow-up, mean age < 60 years was associated with attenuated improvement in the QoL scores (SMD, 0.220; 95% CI, 0.006–0.433; I^2 = 0.0%; 3 trials). In studies with 5–8 months of follow-up, mean age > 60 years (SMD, − 0.229; 95% CI, − 0.441–[− 0.017]; I^2 = 0.0%; 3 trials) was associated with decreased anxiety scores.

Discussion

In this systematic review and meta-analysis, non-pharmacological interventions were associated with significant improvements in the QoL scores assessed during 1–4 months of follow-up and a significant reduction in anxiety and depression scores during 5–8 months of follow-up. However, due to methodological heterogeneity among the included RCTs, sensitivity analyses were restricted to trials with a low risk of bias; no association between non-pharmacological interventions and QoL scores was detected in these analyses. Nevertheless, subgroup analyses revealed that intervention type, specifically, an intervention delivered face-to-face, was associated with improved QoL scores during 1–4 months of follow-up; similarly, face-to-face interventions improved anxiety scores during the same follow-up period. Moreover, interventions that included a behavioral component were associated with improved depression scores during 5–8 months of follow-up. In the narrative synthesis, evidence of associations between non-pharmacological interventions and measures of QoL, anxiety, and depression was mixed; in fact, 25–42% of studies showed improvements in the related measures. Such conclusions indicate that non-pharmacological interventions may help in reducing the incident rate of distress, improving QoL, and reducing medical costs, which could be considered in establishing clinical norms.

Positive results were also found in sociodemographic data, that is, mean age < 60 years was associated with improvement in the QoL scores and mean age > 60 years was associated with decreased anxiety scores in 5–8 months of follow-up. Considering that the relevant effect sizes were small and based on small sample sizes; thus, these findings should be interpreted with caution. In addition, we can learn from funnel plots in Fig. 2 that Cheung et al. showed significant improvement in the QoL scores during 1–4 months of follow-up, which may be explained by the patient's overall need for stoma. The study showed that stoma patients had been more prevalently troubled by frequent or irregular bowel than non-stoma patients [51]; therefore, they may benefit more from Progressive Muscle Relaxation Training.

This study assessed the impact of non-pharmacological therapies on the QoL- and mental health–related scores; we included 13 trials that were not included in the 2018 systematic review and meta-analysis [22] and seven trials published since the publication of the 2017 systematic review [52]. In addition, this study evaluated the risk of bias in each trial and presented pooled estimates of three important outcomes based on a systematic review of the literature.

The present synthesis of the evidence regarding the association between non-pharmacological interventions and QoL and mental health scores in patients with CRC should be interpreted with caution due to between-study heterogeneity and other methodological limitations. High-quality studies on non-pharmacological interventions using standardized protocols and innovative methods are required to improve the representation of clinical conditions. Although this meta-analysis included patients with CRC with any disease stage, excluding only patients with clinically recognized distress for the sake of homogeneity, some of the included trials recruited participants with disease stages I–III, which may have introduced selection bias. It should be noted that the effects of non-pharmacological interventions may be more difficult to demonstrate among patients with CRC with a lower disease stage, as these patients tend to report lower QoL impairment or

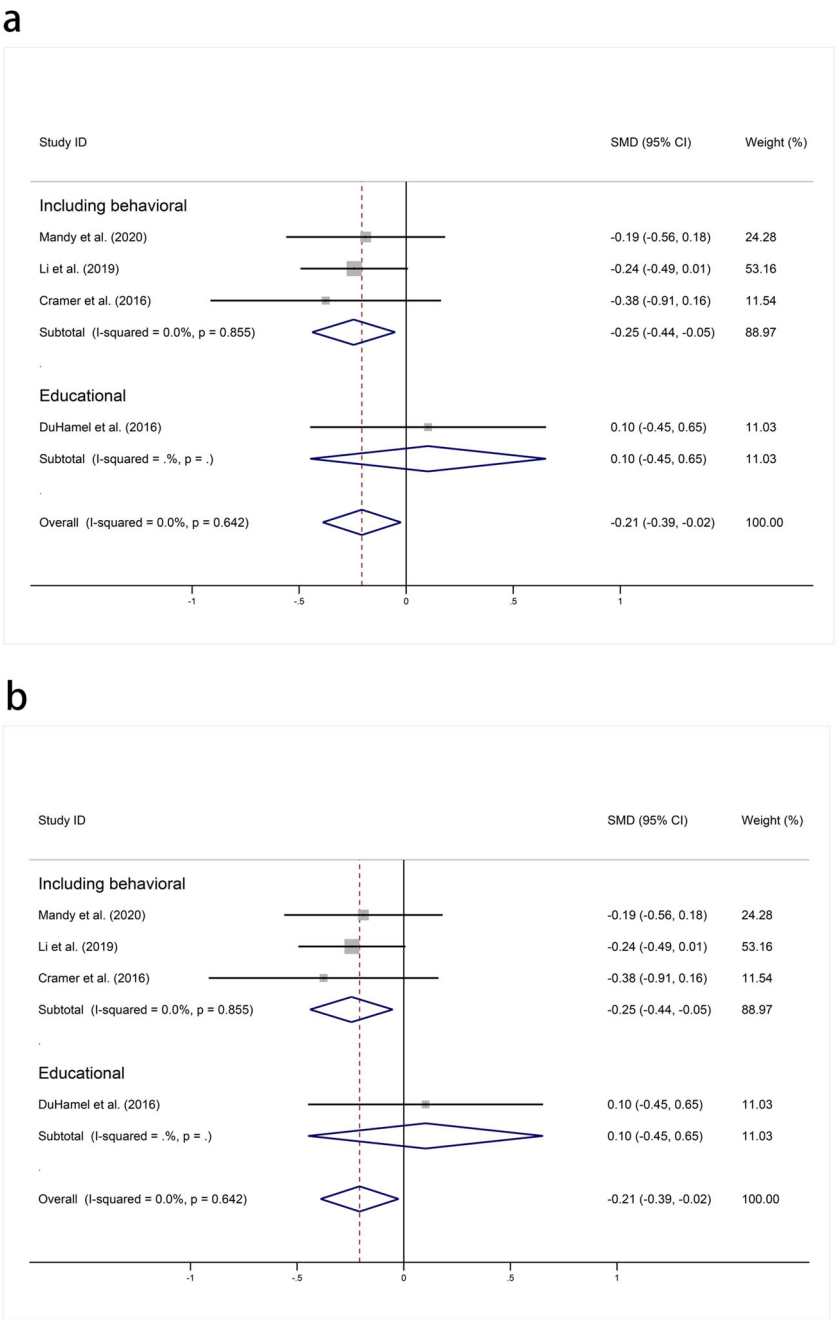

Fig. 5 **a** Impact of non-pharmacological interventions on depression during 5–8 months of follow-up. **b** Impact of non-pharmacological interventions (behavioral vs. educational) on depression during 5–8 months of follow-up. SMD, standardized mean difference; CI, confidence interval

distress levels than those with more advanced disease. Future meta-analyses should account for these differences between patient groups to prevent ceiling effects.

In addition, this review involved a broad literature search to identify RCTs that conformed with our definition of a non-pharmacological intervention; consequently, eligible studies included a wide spectrum of intervention delivery models, ranging from philosophical through spiritual to physical models. Although all interventions met our prespecified definition of a non-pharmacological intervention, their diversity likely increased the rate of heterogeneity in our meta-analysis. Therefore, a random-effects model was used in the meta-analysis to account for each study's contribution to the pooled effect.

Given the variety of intervention delivery models used in the included RCTs, there is a need to establish optimal models of intervention for patients with CRC. Consistent with the findings reported by Son et al. [22], this study showed that interventions delivered face-to-face are associated with a short-term QoL improvement, suggesting that personalized interventions should be prioritized when resources permit them. Moreover, in this study, anxiety and depression scores

among CRC survivors decreased during 5–8 months of follow-up, suggesting mid-, but not short-term, effects of these interventions. This effect may be accounted for by the time needed for patients to understand the information they are given and to adapt to the new exercise habits. However, the relevant effect sizes were small and based on small sample sizes; thus, these findings should be interpreted with caution. Future trials involving large samples are required to assess the impact of non-pharmacological interventions on the QoL- and mental health–related outcomes among CRC survivors over time.

This review has several limitations. First, given that our definition of a "non-pharmacological" intervention was a general one, our literature search may have missed some studies. Second, the results of subgroup analyses should be interpreted with caution, as these statistical tests may have been underpowered, and might have been influenced by pre-intervention characteristics, such as mean age and the need for stoma. Some intervention types in one class might not be comparable. Third, the assessment of bias is subjective, and blinding is sometimes not feasible (especially when educational or behavioral interventions or severely ill participants are involved); both factors may have affected the validity of the study. Fourth, in the included RCTs, primary and secondary outcomes were assessed with various tools and were based on different definitions of QoL, anxiety, and depression. Therefore, only the overall QoL score was extracted for meta-analysis, whereas the other distress outcomes were excluded. Given these limitations, the results of this systematic review and meta-analysis should be interpreted with caution.

In conclusion, in this meta-analysis, non-pharmacological interventions were associated with a reduction in anxiety and depression scores, whereas face-to-face delivery of an intervention was associated with improved QoL scores among patients with CRC. Moreover, interventions delivered face-to-face but without a behavioral component were associated with improved anxiety scores, whereas interventions with a behavioral component improved depression scores.

Future studies should identify the effective components of non-pharmacological interventions and evaluate whether concomitant positive effects are observed on QoL, anxiety, and depression scores.

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Availability of data and material Datasets supporting the conclusions of this article are included in the manuscript and in its supplementary files.

Code availability Not applicable.

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Declarations

Ethics approval Not applicable.

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