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REVIEW

Efficacy of complementary and integrative medicine on health-related quality of life in cancer patients: a systematic review and meta-analysis

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Abstract: Complementary and integrative medicine (CIM) has been used for improving health-related quality of life (HRQOL) in patients with cancer. The objective of this review is to evaluate the effects of CIMs on the HRQOL of cancer patients. We identified randomized controlled trials (RCTs) involving patients with cancer at any stage by retrieving electronic databases from the inception to February 14, 2018 (Systematic Review Registration: PROSPERO CRD42018091609). The main outcomes were HRQOL scores and related domains such as physical well-being scores. The standardized mean difference was used for the analysis and heterogeneity was assessed with the I^2 statistic. A Bayesian framework was used to estimate the ranking order of efficacy in HRQOL change. Finally, 34 RCTs with 3,010 patients were included. As a whole, the results showed clearly superior efficacy of CIM in improving HRQOL. For different domains of HRQOL, different CIM interventions may play different roles. The ranking order of efficacy in change HRQOL was qigong plus mindfulness, Chinese herbal medicine, multimodal complementary medicine, qigong, nutritional supplement, mindfulness, acupuncture, yoga, and massage, and it was different among different domains. There was no evidence of publication bias. In conclusion, CIM may improve the HRQOL of cancer patients. More studies, especially focusing on male cancer patients, are needed to increase the confidence level of our findings.

Keywords: complementary medicine, alternative medicine, integrative medicine, health-related quality of life, randomized controlled trials

Introduction

Data from GLOBOCAN 2012, produced by the International Agency for Research on Cancer, indicated that an estimated 14.1 million new cancer cases and 8.2 million cancer deaths occurred in 2012 worldwide.[1] This trend has not been curbed by the progress of medical research.

Because low health-related quality of life (HRQOL), especially resulting from inadequate treatment (eg, chemotherapy), may deteriorate cancer patients' condition and even increase mortality,[2] the HRQOL is a central consideration for many physicians in their decision-making process in catering to different treatment options.[3,4] Identifying the efficacy of long-term treatment strategies in improving low HRQOL in patients with cancer is of paramount importance.

Complementary and integrative medicine (CIM), according to the National Center for Complementary and Integrative Health, refers to the non-mainstream therapies which can be used along with conventional treatment. In general, it

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encompasses many diverse therapies including natural products (such as herbs and botanicals), mind and body practices (such as acupuncture, massage and mediation), and other complementary health approaches.[5] With more interest in CIM and a growing body of evidence supporting the use of CIM among patients with cancer, more medical clinics and cancer centers are trying to address public interest and demand by providing CIM services.[6–8] Unfortunately, many integrative practices remain under study, with insufficient evidence to be definitively recommended. The best CIM method for cancer patients has not yet been established. Therefore, in the present systematic review, we examined the randomized clinical trial (RCT) evidence to compare the relative efficacy of different CIM interventions, hoping to provide significant information for patients, health-care practitioners, and policy makers on the course of tumor treatment prescription to treat low HRQOL in patients with cancer.

Materials and methods

We followed the PRISMA guidelines for this systematic review and meta-analysis.[9] A previously established protocol registered with PROSPERO (CRD42018091609) was conducted and associations of each CIM with HRQOL were compared using a direct meta-analysis and Bayesian network meta-analysis. Good research practices on indirect treatment comparisons, as emphasized in the International Society for Pharmacoeconomics and Outcomes Research Task Force, were rigorously followed[10,11] and quality of evidence was appraised by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[12]

Search strategy and selection criteria

We searched PubMed, MEDLINE, Embase, Web of Science, Cochrane Central, and Clinical Trial registries (http://www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu) from inception to February 14, 2018. We also manually screened published systematic reviews and presentations from major conference proceedings such as the American Society of Clinical Oncology for additional studies. The references of the final included articles were also reviewed. The search was conducted by two investigators (MFZ and WFL) independently.

The search terms were "CIM", "complementary and integrative medicine", "complementary and alternative therapies", "complementary medicine", "alternative medicine", "integrative medicine", "HRQOL", "quality of life", "health related quality of life", "life quality", "neoplasia", "tumor", "cancer", "malignant neoplasm", "oncology", "onco*", and "integrative oncology".

To be eligible, RCTs comparing CIM-based intervention with a control group receiving no intervention for psychological functioning and HRQOL in patients with cancer were included. In addition, selected evaluation tools for overall HRQOL were those HRQOL questionnaires which were most widely used in clinical research, including the Functional Assessment of Cancer Therapy (FACT),[13] Functional Assessment of Chronic Illness Therapy (FACIT),[14] MD Anderson Symptom Inventory (MDASI),[15] 36-item Short Form Health Survey 36 (SF-36),[16] and European Organisation for Research and Treatment of Cancer (EORTC).[17]

We excluded observational studies, trials with unclear effective CIM treatments (eg, music therapy and aromatherapy), and studies conducted in special populations (eg, patients with mental illness or care), to avoid excessive heterogeneity.

Data abstraction and quality assessment

Data from the included studies were extracted by two authors (YRZ and HW) independently on to a standardized form including the name of study, first author, study design, and blinding; patient characteristics; and the frequency, duration, and schedule of the primary intervention. The primary outcome was the HRQOL score changes between baseline and after treatment, which were measured in terms of several multidimensional generic questionnaires consisting of multiple domains such as physical well-being, social well-being, emotional well-being, sleep quality, and fatigue. All data were abstracted using study-reported modified intention-to-treat analysis. Data abstraction discrepancies were resolved by consensus in consultation with a third reviewer (ZHZ). The risk of bias of an individual study was assessed in the context of the primary outcome using the Cochrane Risk of Bias assessment tool.[18]

Quality of evidence

We assessed the quality of evidence of estimates derived from network meta-analysis using the GRADE methodology.[12,19] For direct comparisons in this system, RCTs start at high quality and may be downgraded to levels of moderate, low, and very low quality owing to heterogeneity, risk of bias, indirectness, imprecision, and/or publication bias. For the indirect estimates, it starts at

the lowest rating of the two pairwise estimates that contribute as first-order loops, but may be further downgraded in consideration of imprecision or intransitivity (heterogeneity such as different clinical or methodological characteristics). The higher rating of the direct or indirect estimates would be applied to the network meta-analysis if their ratings were similar.

Statistical analysis

The DerSimonian and Laird random-effects model was used for direct meta-analysis to estimate pooled standardized mean differences (SMDs) and 95% CI incorporating within- and between-study heterogeneity.[20] The I^2 statistic was calculated to assess study heterogeneity.[21] The Hartung–Knapp method was used to address possible type I errors in post-hoc sensitivity analyses.[22] Funnel-plot symmetry and Egger's regression test were used to assess the publication bias, with the test value $P<0.05$ indicating publication bias.[23]

For the indirect meta-analysis, we performed a random-effects network meta-analysis in ADDIS version 1.14.1. Network meta-analysis models in ADDIS are implemented in the Bayesian framework and estimated using Markov chain Monte Carlo (MCMC) methods.[24] This approach is recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit technical support documents on evidence synthesis.[25] Since this network meta-analysis is an indirect comparison based on the comparison of placebo/conventional care without CIM and multiple CIMs, statistical analysis is performed directly under the consistency model without the need to carry out consistent tests. Statistical significance was assessed using 95% CI, with CI spanning 1 indicating $P>0.05$, suggesting no statistical significance. Then, a network diagram was drawn and finally a rank-order graph of each CIM was constructed.

Results

Characteristics of the included studies

In total, 574 unique studies were found using the search strategy, most of which were duplicate records or not reporting RCTs. Thus, 149 full-text articles were fully reviewed according to the inclusion and exclusion criteria, resulting in a final sample of 34 studies (Figure 1). All studies are two-arm trials, in which one arm is a CIM intervention, including yoga (eight trials), nutritional supplement (NS) (six trials), Chinese herbal medicine (CH) (four trials), acupuncture (four trials), multimodal complementary medicine (MCM) (three trials), qigong (three trials), mindfulness (MM) (three trials), massage (two trials), or qigong plus MM (one trial), while the other arm is placebo or usual care without CIM treatment.

The characteristics of patients included in the RCTs enrolled in this review are summarized in Table 1. Overall, these 34 trials were reported between 2006 and 2017 and included 3,010 participants (the range of size of trials was 13 to 275 participants). The primary outcome (HRQOL score changes) was reported in all studies. Among the trials, 16 trials were from the USA, five trials from Germany, four trials from China, four trials from Australia, two trials from Japan, and two trials from the UK; and South Korea, Malaysia, Turkey, and Italy each had one trial. The age of patients ranged from 44.7 to 70.3 years (median 56 years) across all studies, and 92% were female. Breast cancer (20 studies) was the most studied cancer among the enrolled studies, followed by various cancers (seven studies), colorectal cancer (three studies), prostate cancer (one study), lung cancer (one study), hepatic carcinoma (one study), and ovarian cancer (one study). The mean HRQOL score of patients at the baseline of CIM treatment was 82.5 (range 20.7–152.1), while it was 80.4 (range 16.6–143.2) in the control group. However, after treatment, the mean HRQOL score of patients in the CIM group was 87 (range 24.4–145.2), while it was 81.8 (range 20–131.4) in the control group.

Quality assessment and risk of bias of the included trials

Using Cochrane's Risk of Bias assessment tool, the result indicated that 11 studies were scored as high quality. Most studies scored high risk are ascribed to the bias on blinding of personnel, since blinding of personnel was not applicable during the exercise interventions. Furthermore, several studies were judged as unclear risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. The results are shown in Figure 2.

Direct meta-analysis of the included studies

After extracting the data of the included studies, available direct comparisons and network of trials were compiled and are shown in Figure 3. All agents were associated with HRQOL and CIMs compared with placebo/usual care without CIMs. In post-hoc sensitivity analysis using the

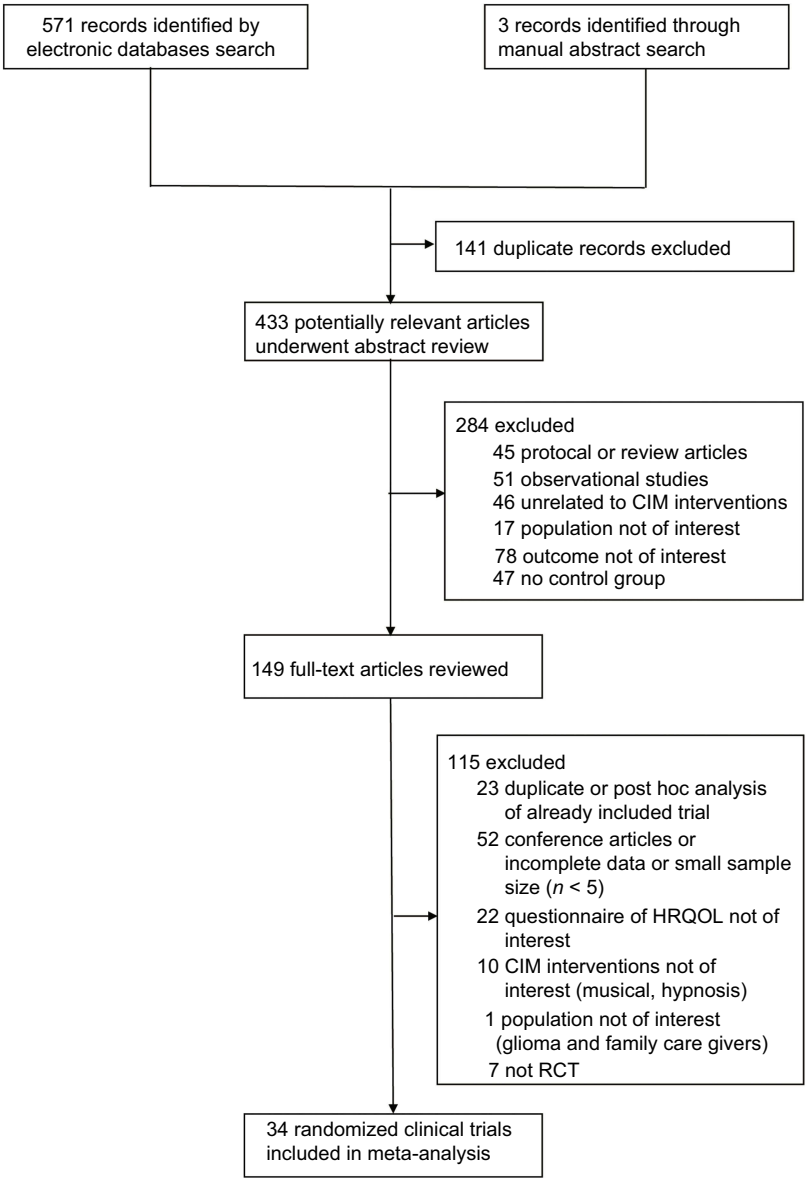

Figure 1 Flowchart of the study identification and selection process.
Abbreviations: CIM, complementary and integrative medicine; HRQOL, health-related quality of life; RCT, randomized clinical trial.

Hartung–Knapp method, all results were consistent. The results indicated that, taking usual care without CIM treatment as a comparator, all the CIM treatments reported the effects on HRQOL and emotional well-being. Most enrolled studies compared yoga and NS with control on all the treatment efficacy evaluation dimensions, such as HRQOL and emotional well-being. Furthermore, for the change in HRQOL from endpoint to baseline, we used direct meta-analysis and the results showed that all the subgroups of different CIM treatments did not show obvious heterogeneity. Therefore, a fixed-effect model was employed to test the effects. The test for total effect showed clearly superior efficacy of CIM treatments in improving HRQOL (mean difference 3.99 [2.32, 5.67]), although subgroup analysis demonstrated that only CH (mean difference 6.03 [0.15, 11.92]) and qigong + MM (mean difference 12.66 [8.75, 16.57]) was significantly favored over usual care (Figure 4). On the other hand, for the multiple domains related to HRQOL, the overall effect for total CIM treatments may improve emotional (SMD 0.18 [0.05, 0.31]) and physical well-being (SMD 0.22 [0.06, 0.37]), with moderate heterogeneity (Table 2). Yoga seems to aggravate sleep quality (SMD −0.81 [−1.18, −0.08]), which is contrary to the traditional conception that yoga may reduce sleep problems.[60]

Table 1 Characteristics of the included randomized clinical trials comparing CIM interventions vs control

CIM type	Study	Year	Country	Period	Age (years): mean (SD)	Female: n (%)	mITT/completers				Specific method[a]	Cancer	Outcomes of interest reported					
							Intervention		Control				HRQOL	Fatigue	Emotional	Physical	Social	Sleep
Yoga	Cramer et al[26]	2014	Germany	Sept 2012–Dec 2013	I: 68.70 (9.13); C: 67.81 (10.37)	21 (38.9)	27	27	27	27	90 min/t, 1 weekly	Colorectal	√	√	√	√	√	√
	Harder et al[27]	2015	UK	Apr 2011–May 2013	I: 54.6 (10.9); C: 55.8 (11.6)	92 (100)	46	31	46	33	N/A, ≥1 weekly	Breast	√		√	√	√	
	Siedentopf et al[28]	2013	Germany	Jun 2008–Nov 2009	I: 55.82 (10.72); C: 58.41 (9.91)	93 (100)	49	30	44	23	N/A, 2 weekly	Breast	√					
	Littman et al[29]	2012	USA	May 2007–Apr 2008	I: 60.6 (7.1); C: 58.2 (8.8)	63 (100)	32	27	31	27	N/A, 5 weekly	Breast	√	√	√	√	√	
	Chandwani et al[30]	2010	USA	N/A	I: 51.39 (7.97); C: 54.02 (9.96)	61 (100)	30	27	31	29	120 min/t, 1 weekly	Breast	√		√	√	√	
	Moadel et al[31]	2007	USA	2001–2005	I: 55.11 (10.07); C: 54.23 (9.81)	128 (100)	108	84	56	44	1.5 h/t, 1 weekly	Breast	√	√	√	√	√	
	Pruthi et al[32]	2012	USA	Nov 2010–Aug 2011	I: 58 (6.8); C: 55 (8.3)	30 (100%	15	11	15	10	60 min/t, 8 weekly	Breast	√					
	Ben-Josef et al[33]	2017	USA	Oct 2014–Jan 2016	I: 66.2 (5.3); C: 68.2 (7.3)	68 (100)	35	22	33	28	75 min/t, 2 weekly	Prostate	√					

(*Continued*)

Table 1 (Continued).

CIM type	Study	Year	Country	Period	Age (years): mean (SD)	Female: n (%)	mITT/completers				Specific method[a]	Cancer	Outcomes of interest reported					
							Intervention		Control				HRQOL	Fatigue	Emotional	Physical	Social	Sleep
Nutritional supplement	Lesser et al[34]	2013	USA	Sept 2004–Mar 2009	I: 52 (13.5); C: 50 (11)	236 (100)	122	78	114	61	CoQ10+ vitamin E: 300 mg/300 IU, 3/d, po	Breast	√	√				√
	Lustberg et al[35]	2017	USA	Nov 2011–Oct 2013	I: 61.2 (6.6); C: 57.8 (9.1)	44 (100)	22	17	22	15	EPA + DHA; 4.3 g/day, po	Breast	√		√	√	√	
	Noguchi et al[36]	2014	Japan	Feb 2012–May 2012	I: 50.5 (14.0); C: 51.2 (10.9)	45 (100)	15	11	15	13	Biorinck granule (Chlorella granules); 4 sticks/d, po	Breast	√		√		√	
	Norman et al[37]	2006	Germany	Nov 2008–Nov 2009	I: 65.10 (12.55); C: 61.6 (13.82)	11 (35.5)	16	16	15	15	Creatine monohydrate: 20 g/d (first week); 5 g/d (maintainence phase), po	Colorectal	√	√	√	√	√	
	Can et al[38]	2009	Turkey	Oct 2005–Dec 2006	54.32 (12.77)[e]	13 (35)	20	17	20	20	Kefir: 250 mL ×2/d, po	Colorectal	√		√	√	√	
	Cruciani et al[39]	2009	USA	N/A	I: 66.5 (12.8); C: 70.3 (12.9)	16 (55)	17	10	12	7	L-carnitine: 0.5 g/d (initial 2 days), 1 g/d (second 2 days), 2 g/d (maintainence phase), po	Various	√	√	√	√	√	

(*Continued*)

Table 1 (Continued).

CIM type	Study	Year	Country	Period	Age (years): mean (SD)	Female: n (%)	mITT/completers				Specific method[a]	Cancer	Outcomes of interest reported					
							Intervention		Control				HRQOL	Fatigue	Emotional	Physical	Social	Sleep
Chinese herbal medicine	Han et al[40]	2016	China	Sep 2011–Mar 2014	I: 59.19 (9.44); C: 59.63 (10.06)	42 (40.6)	53	52	53	47	Herb compound decoction: 200 mL ×2/day, po	Lung	√					
	Marx et al[41]	2017	Australia	Mar 2014–Feb 2015	I: 57 (14); C: 59 (11)	32 (63)	24	15	27	19	Ginger capsule: 300 mg ×4/d, po	Various	√					
	Tian et al[42]	2010	China	Sep 2005–May 2008	I: 51.44 (10.5); C: 52.37 (10.81)	16 (16.5)	49	49	48	48	Ganji decoction: 1 dose/d, po + ailitong (a Chinese medical pad-shaped plaster preparation): 2/d for 10 days, externally applied	Hepatic	√		√			
	Jeong et al[43]	2010	Korea	May 2009–Oct 2009	I: 49.4 (10.8); C: 53.4 (8.0)	25 (62.5)	20	18	20	18	Bojungikki-tang: 2.5 g ×3/d, po	Various	√	√				

(*Continued*)

Table 1 (Continued).

CIM type	Study	Year	Country	Period	Age (years): mean (SD)	Female: n (%)	mITT/completers				Specific method[a]	Cancer	Outcomes of interest reported					
							Interve-ntion		Control				HRQOL	Fatigue	Emotio-nal	Physical	Social	Sleep
Acupunct-ure	Johnston et al[44]	2011	USA	N/A	I: 55 (6.4); C: 53 (7.2)	NS	6	6	7	6	50 min, 8 weekly	Breast	√	√				
	Smith et al[45]	2013	Australia	Apr 2010–Feb 2011	I: 55 (8.8); C: 58 (7.5)	30 (100)	10	9	10	10	A total of 5 needles, sti-mulated manually and retained for 20 min, 2 weekly (initial), 1 weekly (final 3 weeks)	Breast	√	√				
	Zick et al[46]	2016	USA	Mar 2011–Oct 2014	I: 59.7 (9.4); C: 61.0 (10.0)	288 (100)	98	71	96	83	A total of 5 needles, sti-mulated manually and retained for 30 min, daily	Breast	√		√	√	√	√
	Deng et al[47]	2013	USA	Aug 2004–Apr 2009	I: 54 (8.9); C: 53 (10.4)	80 (82)	49	34	52	40	A total of 14 needles, sti-mulated manually and retained for 20 min, 1 weekly	Various	√					
Multimodal comple-mentary medicine	Spahn et al[48]	2013	Germany	N/A	I: 58.1 (8.5); C: 55.3 (11.4)	64 (100)	32	30	32	25	6 h/t, daily [b]	Breast	√	√	√	√	√	
	Domnick et al[49]	2017	Germany	2009–2010	I: 60 (10); C: 60.8 (10)	67 (67)	50	50	50	50	35–40 min/t, 1–4 weekly [c]	Various	√				√	
	Witt et al[50]	2015	Italy	Apr 2011–Mar 2012	I: 56.3 (10.9); C: 56 (11)	275 (100)	136	1-14	139	1-13	N/A[d]	Breast	√	√	√	√	√	√

(*Continued*)

Table 1 (Continued).

CIM type	Study	Year	Country	Period	Age (years): mean (SD)	Female: n (%)	mITT/completers				Specific method[a]	Cancer	Outcomes of interest reported					
							Interve-ntion		Control				HRQOL	Fatigue	Emotio-nal	Physical	Social	Sleep
Qigong	Chen et al[51]	2013	China	2005–2007	I: 45.3 (6.3); C: 44.7 (9.7)	96 (100)	49	49	47	46	40 min/t, 5 weekly	Breast	√	√				√
	Liu et al[52]	2017	Hong Ko-ng	2012–2013	I: 50.9 (7.0); C: 51.3 (7.3)	158 (100)	79	45	79	60	>40 min/t, daily	Breast	√					
	Loh et al[53]	2014	Malaysia	2010–2011	N/A	132 (100)	66	32	66	32	30 min/t, 2 weekly	Breast	√		√	√	√	
Mindfulne-ss	Blaes et al[54]	2016	USA	2012–2013	I: 55 (10); C: 57 (10)	38 (90.5)	28	24	14	11	2.5 h/t, 8 weekly	Various	√	√				√
	Milbury et al[55]	2013	USA	Oct 2007–2012	I: 53.0 (6.6); C: 54.1 (8.6)	42 (100)	18	18	24	23	60 min/t, 2 weekly	Breast	√	√	√	√		√
	Reich et al[56]	2017	USA	Feb 2009–Sept 2013	56.6 [f]	51 (100)	24	15	27	19	15–45 min/t, daily	Breast	√	√	√			√
Massage	Sharp et al[57]	2010	UK	Jun 2002–Feb 2005	I: 57.7 (10.12); C: 59.36 (10.23)	123 (100)	61	61	62	62	1 h/t, 1 weekly	Breast	√		√	√	√	
	Judson et al[58]	2011	USA	2006–2009	I: 58.8 (13); C: 63 (9)	45 (100)	22	22	23	23	30 min/t, 1 weekly	Ovarian	√					
Qigong + mindful-ness	Oh et al[59]	2012	Australia	Oct 2007–May 2008	I: 64.6 (12.3); C: 61.1 (11.0)	38 (47)	37	23	44	31	90 min, 2 weekly [e]	Various	√					

Notes: [a]Duration of practicing CIM each time, how often CIM practiced. [b]Nutrition counseling, relaxation exercises, physical exercises, stress reduction, basics of cognitive restructuring, and hydrotherapy. [c]Conversations and dialogue with physicians, foot reflexology introduction, relaxation techniques, nutrition counseling, informative session, art therapeutic painting, physiotherapy, yoga, psycho-oncology, healing massage introduction, single sessions of foot reflexology and healing massage. [d]Infusions with ingredients (eg, high-dose vitamin C), acupuncture, hyperthermia, movement therapy (eg, qigong), enzyme therapy, mistletoe therapy, Chinese herbal medicine. [e]Qigong and mindfulness. [f]Total study population.

Abbreviations: CIM, complementary and integrative medicine; HRQOL, health-related quality of life; mITT, modified intention to treat (last-observation-carried-forward analysis); I, intervention group; C, control group; N/A, no detailed information; t, time; d, day; CoQ10, coenzyme Q10; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Figure 2 Quality assessment of the trials included in the analysis: review authors' judgments about each risk of bias item for all included studies (**A**), and for each included study (**B**).

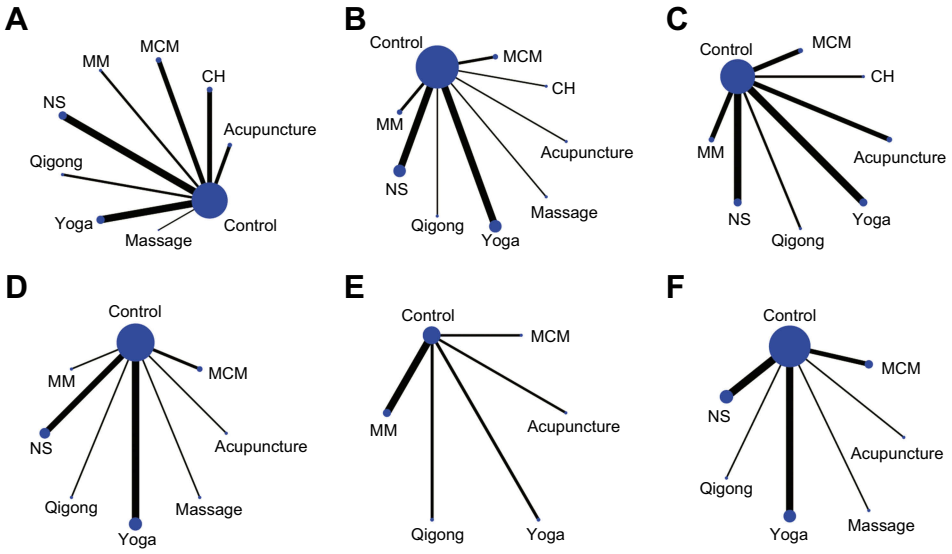

Figure 3 Network of included studies with the available direct comparisons for all outcomes. (**A**) Health-related quality of life (HRQOL); (**B**) emotional well-being; (**C**) fatigue; (**D**) physical well-being; (**E**) sleep quality; (**F**) social well-being. The size of the nodes and the thickness of the edges indicate the number of included studies.
Abbreviations: CH, Chinese herbal medicine; MCM, multimodal complementary medicine; MM, mindfulness; NS, nutritional supplement.

Network meta-analysis of the included studies

To further demonstrate the relative effect of each intervention on the HRQOL, network meta-analysis was applied and the ranking probability for each treatment was estimated. Graphical results are shown in Figure 5. The overall ranks were interpreted by the surface under the cumulative ranking (SUCRA) technique.[61] For HRQOL,

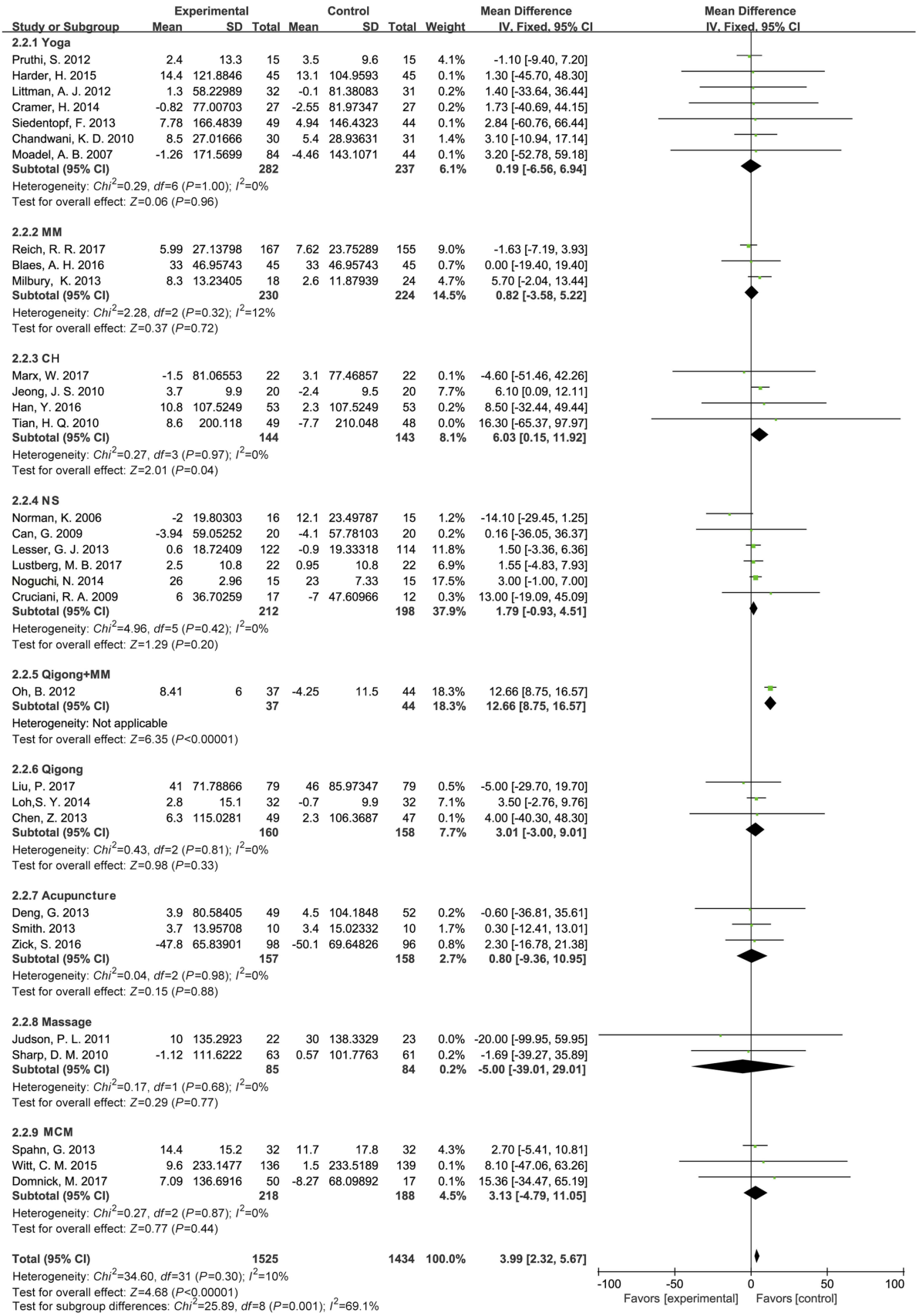

Figure 4 Direct meta-analysis of the change in health-related quality of life from endpoint to baseline.
Abbreviations: CH, Chinese herbal medicine; MCM, multimodal complementary medicine; MM, mindfulness; NS, nutritional supplement.

Table 2 Summary of direct meta-analysis for different domains of quality of life

CIM treatments	Fatigue scores			Emotional scores			Physical scores			Social scores			Sleep scores		
	No. of studies	SMD (95% CI)	I^2	No. of studies	SMD (95% CI)	I^2	No. of studies	SMD (95% CI)	I^2	No. of studies	SMD (95% CI)	I^2	No. of studies	SMD (95% CI)	I^2
Yoga	3[26,28–31]	0.17 (−0.09, 0.43)	0%	5[26,30–33]	0.24 (−0.06, 0.54)	53%	5[26,27–29,33]	0.4 (0.02, 0.78)	70.4%*	5[26,30–33]	0.14 (−0.08, 0.34)	0%	1[26]	−0.81 (−1.18, −0.08)	0%*
Mindfulness	3[54–56]	0.13 (−0.44, 0.70)	75%	2[55,56]	0.09 (−0.36, 0.54)	54%	1[56]	−0.11 (−0.72, 0.50)	0%	—	—	—	3[54–56]	−0.38 (−1.24, 0.53)	89%
Chinese herbal medicine	1[43]	0.43 (−0.20, 1.05)	0%	1[40]	0.27 (−0.13, 0.67)	0%	—	—	—	—	—	—	—	—	—
Nutritional supplement	3[34,36,39]	0.09 (−0.61, 0.79)	77%	5[35–39]	0.21 (−0.29, 0.71)	62%	4[35–38]	0.07 (−0.33, 0.47)	31%	5[35–39]	0.11 (−0.19, 0.41)	0%	—	—	—
Qigong	1[53]	0.17 (−0.23, 0.57)	0%	1[53]	0.13 (−0.36, 0.62)	0%	—	—	—	1[52]	−0.47 (−0.97, 0.02)	0%	1[51]	0.17 (−0.23, 0.57)	0%
Qigong + mindfulness	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Acupuncture	1[44]	−0.07 (−0.94, 0.81)	0%	1[44]	0.3 (0.02, 0.59)	0%*	1[47]	0.17 (−0.12, 0.45)	0%	1[47]	0.08 (−0.22, 0.34)	0%	1[45]	−0.23 (−0.52, 0.05)	0%
Massage	—	—	—	1[57]	0.18 (−0.18, 0.53)	0%	—	—	—	1[57]	0.03 (−0.32, 0.38)	0%	—	—	—
Multimodal complementary medicine	2[48,50]	0.08 (−0.34, 0.50)	61%	2[48,50]	0.08 (−0.13, 0.3)	0%	2[48,50]	0.18 (−0.03, 0.4)	0%	3[48,49,50]	0.01 (−0.19, 0.21)	0%	1[50]	0.14 (−0.1, 0.37)	0%
Total CIM	14	0.13 (−0.03, 0.29)	46.80%	18	0.18 (0.05, 0.31)	36.7%*	13	0.22 (0.06, 0.37)	37.8%*	16	0.05 (−0.08, 0.15)	0%	7	−0.17 (−0.48, 0.13)	78%

Note: *Statistically significant results.

Abbreviations: CIM, complementary and integrative medicine; SMD, standard mean difference.

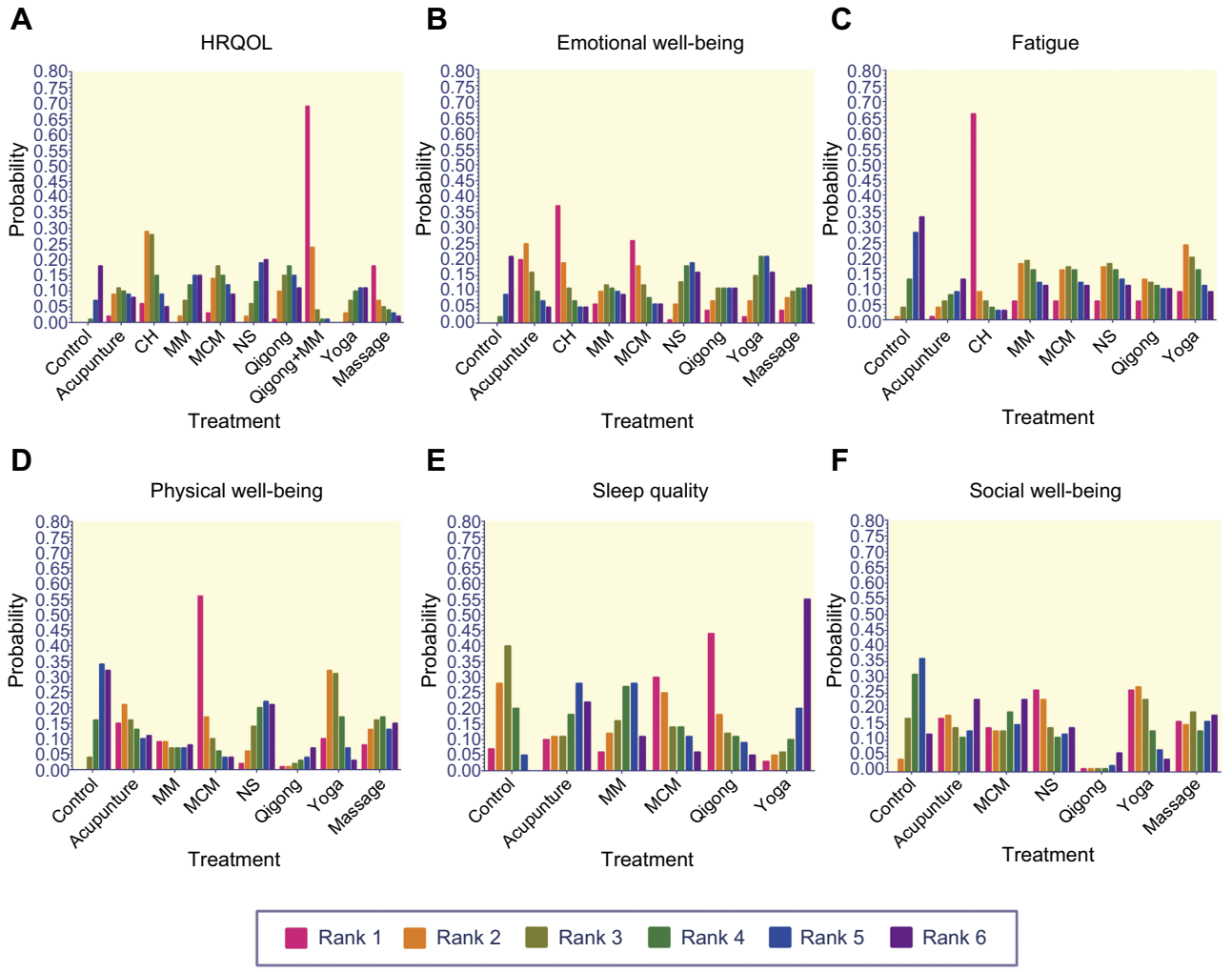

Figure 5 Ranking probability for each treatment on health-related quality of life. Rank 1 is best and rank 6 is worst.
Abbreviations: CH, Chinese herbal medicine; MCM, multimodal complementary medicine; MM, mindfulness; NS, nutritional supplement.

qigong + MM (SUCRA: 0.985) was shown to be the most efficacious treatment, followed by CH (SUCRA: 0.865), MCM (SUCRA: 0.65), qigong (SUCRA: 0.64), NS (SUCRA: 0.59), MM (SUCRA: 0.50), acupuncture (SUCRA: 0.44), yoga (SUCRA: 0.405), massage (SUCRA: 0.365), and control (SUCRA: 0.26), which means that all the treatments are more effective than control (Figure 5A). For emotional well-being, the ranking probability was CH > yoga > acupuncture > MCM > NS > MM > massage > qigong > control (Figure 5B). For fatigue, the ranking probability was CH > yoga > control > MM > NS > MCM > qigong > acupuncture (Figure 5C). For physical well-being, the ranking probability was yoga > MCM > control > NS > acupuncture > massage > MM > qigong (Figure 5D). For sleep quality, the ranking probability was control > yoga > qigong > MM > MCM > acupuncture (Figure 5E). For social well-being, the ranking probability was control > yoga > NS > MCM > massage > acupuncture > qigong (Figure 5F).

Publication bias and network coherence

There was no evidence of publication bias, either qualitatively based on funnel-plot asymmetry (Figure 6) or quantitatively based on Begg's regression test (Figure 7) (P>0.05 for all comparisons), although the number of studies included in each comparison was small. Evaluation of the Monte Carlo error suggested adequacy of convergence, which suggested good model fit.

Quality of evidence

The GRADE evidence profiles are shown in Table 3. The GRADE level of meta-analysis combining direct and indirect evidence was moderate for overall CIM interventions. Regarding each CIM intervention, the GRADE

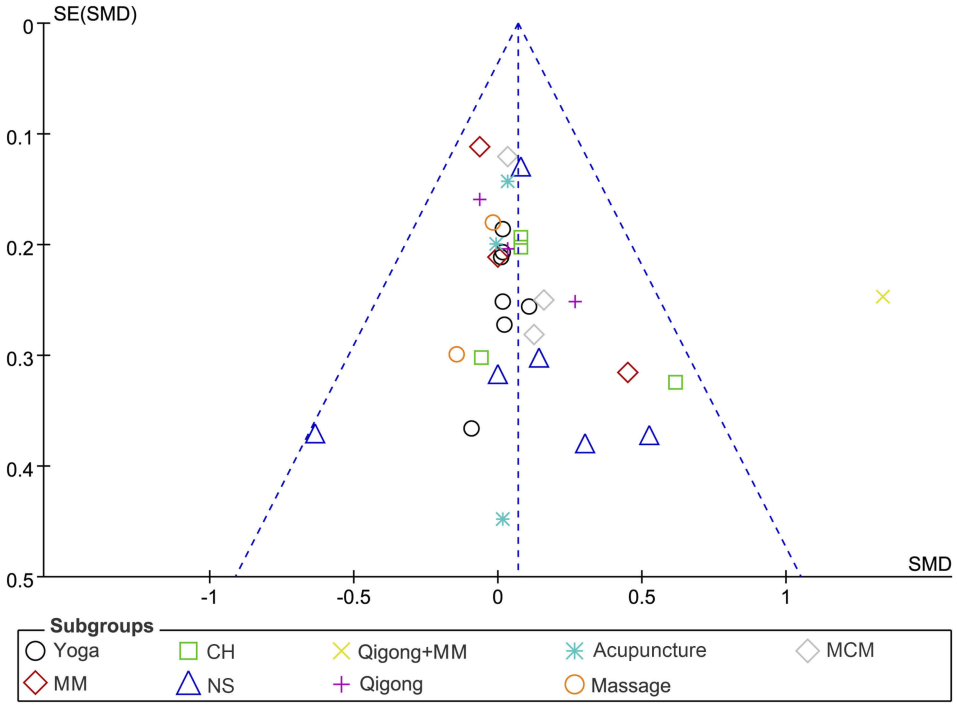

Figure 6 Funnel plot of publication bias. The dashed line represents the expected distribution of studies on the graph in the absence of publication bias.
Abbreviations: CH, Chinese herbal medicine; MCM, multimodal complementary medicine; MM, mindfulness; NS, nutritional supplement; SMD, standardized mean difference.

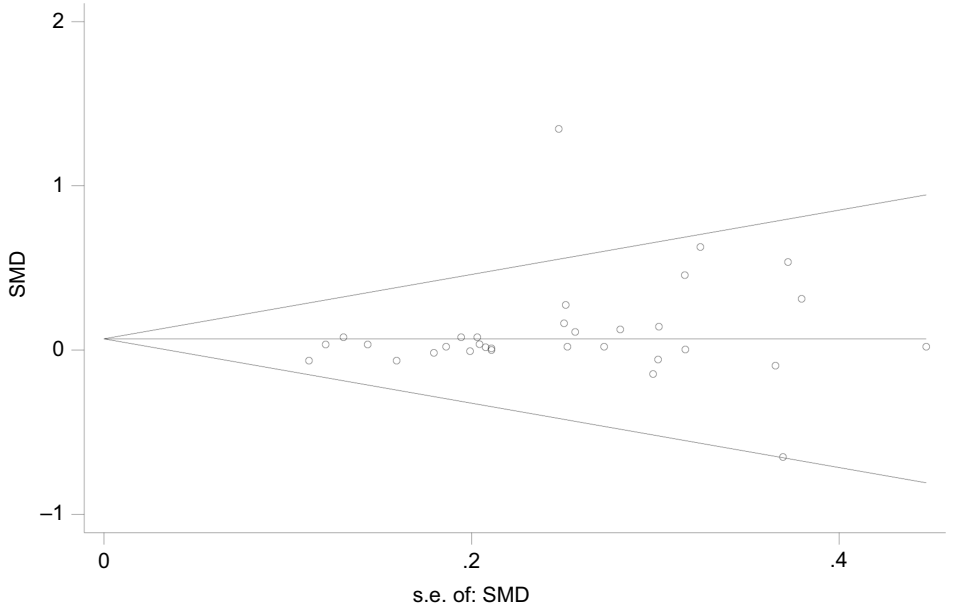

Figure 7 Begg's funnel plot with pseudo-95% confidence limits: publication bias of complementary and integrative medicine interventions vs control.
Abbreviation: SMD, standardized mean difference.

quality of evidence was moderate for NS, yoga, and CH, while it was low for the remaining treatments.

Discussion

As a major global health problem, cancer is a terrible disease in which complications from conventional treatments may reduce the HRQOL, which in turn affects the prognosis of patients. Therefore, more and more clinicians take HRQOL into consideration when establishing a therapeutic regimen to gain an optimal response. In the present meta-analysis, we combined direct and indirect evidence from 34 RCTs in 3,010 patients with tumor to

Table 3 Overall GRADE quality of evidence from network meta-analysis

CIM	HRQOL changes from baseline
NS	Moderate
Yoga	Moderate
CH	Moderate
Acupuncture	Low
Massage	Low
MM	Low
Qigong	Low
Qigong + MM	Low
MCM	Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; CIM, complementary and integrative medicine; HRQOL, health-related quality of life; NS, Nutritional supplement; CH, Chinese herbal medicine; MM, mindfulness; MCM, multimodal complementary medicine.

demonstrate the potential advantage of different CIM treatments on the HRQOL. The results tended to provide moderate-quality or low-quality evidence for moderate beneficial effects of CIM interventions on the HRQOL of cancer patients. As a whole, the change in HRQOL scores was statistically significant between CIM treatment (mean range from 82.5 to 87.0) and control (mean range from 80.4 to 81.8) groups. Direct meta-analysis for total effect also showed the clearly superior efficacy of CIM treatments, although subgroup analysis demonstrated that only CH and qigong + MM were significantly favored more than usual care.

In this study, yoga was the most studied intervention, with eight trials included in the analysis, followed by NS, CH, and acupuncture. When we searched PubMed briefly with random words we found that the most papers had been published on NS, followed by acupuncture, CH, and yoga, which indicated that studies on acupuncture and CH may focus more on the unambiguous diseases rather than functional discomfort such as HRQOL. However, it may also be due to the complexity of acupuncture and CH, for which it is difficult to make a blank control, an essential requirement for RCTs.[62–64] Therefore, more RCTs on acupuncture and CH are needed to explore their effects on HRQOL of cancer patients, since they have been elaborately studied in the fields of specific diseases such as cancers. Nearly half of the included studies were conducted in the USA, which may be related to its highly developed medical research. This may influence the conclusions of our study and the multiplicity of study locations serves to increase the level of confidence in our findings.

In 2012, about 14.1 million new cases of cancer were diagnosed worldwide, with the most common types being lung (13%), breast (12%), and colorectal cancer (10%).[65] In our analysis, breast cancer was the most studied cancer and most of the participators (92%) were female, with only one study focusing on the most widespread cancer, ie, lung cancer. Only 8% of the enrolled participants were male, which may reduce the credibility of our conclusions and make it difficult to recommend such CIM interventions among male cancer patients. Therefore, more high-quality RCTs, in greater detail and focusing on various cancers among both female and male patients, are needed and will prove valuable.

Although tests showed the clearly superior efficacy of CIM treatments in improving HRQOL, yoga seems to aggravate sleep quality (SMD −0.81 [−1.18, −0.08]). However, there was only one study reporting the sleep scores after treatment with yoga, so more research is needed to clarify the effects of yoga on sleep quality with more certainty.

Traditional Chinese medicine (TCM) has been long practiced and is becoming ever more widely recognized as providing curative and/or healing treatments for a number of diseases and physiological conditions.[66] CH, acupuncture, and moxibustion are among the most popular types of TCM. CH showed a significantly superior relative effect on HRQOL, emotional well-being, and fatigue. CH is complicated and variable since it often employs combined prescriptions of multiple herbs for disease treatment.[64] Such complexity and variability are based on an empirical set of principles that is referred to as monarch, minister, assistant, and guide.[67] Therefore, only a small number of RCTs on CH have been conducted, most of which are of poor methodological quality owing to difficulties in the design and implementation of placebo-blinded trials.[68] Modernization of CH, such as pharmacological studies including chemistry-focused, target-directed, and systems-biology-based studies, may promote its development. Acupuncture, however, in this analysis, did not show superiority in improving HRQOL. In accord with previous studies,[69] yoga was found to play an important role in both emotional and physical well-being.

Although all included studies were RCTs without obvious risks of bias, limitations are present and should be accounted for when interpreting the study's findings. First, only 34 RCTs were included in the present study according to the selected criteria and no more than eight trials were conducted for each CIM intervention. The

small sample size limited statistical power and study generalizability, meaning that the actual effects of CIMs may be small, although they showed superior relative effects from the existing data. Individual patient data and more detailed subgroups would have enabled us to provide more detailed insights. So, larger and more diverse samples are needed to calculate the best intervention for the exact tumor type and even the exact domains, such as emotional well-being or sleep quality, to remove the potentially confounding influence of such differences. On the other hand, other psychosocial support services such as music and art therapy or psychological counseling may also make sense, although they are excluded from the present study. The HRQOL of tumor patients is often complex and difficult to resolve, and a consistently effective CIM treatment is still lacking, making it important to examine this in future research. Second, although we have tried to figure out which intervention may be best for HRQOL by ranking the probability for each treatment using ADDIS, there is still a lack of clinical trials comparing the different efficacy of different CIMs. In addition, research focusing more on male cancer patients may make the recommended CIMs more convincing for all cancer patients. More tools which are commonly used in integrative oncology research, such as Measure Yourself Concerns and Well-being (MYCaW)[70] and the Edmonton Symptom Assessment Scale (ESAS),[71] may be used in future research.

Conclusion

This systematic review provides a comprehensive overview of the relationship between different CIM interventions and the HRQOL of tumor patients. The results demonstrated clearly superior efficacy of CIM treatments in improving HRQOL, and different CIM interventions may play different roles in HRQOL such as emotional and physical well-being. More studies, especially focusing on male cancer patients, are needed to increase the confidence levels of our findings.

Data sharing

Data are available from the corresponding authors at cbb8202@126.com (BBC) or changquanling@smmu.edu.cn (CQL).

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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