

Review

# Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors—a meta-analysis

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## Abstract

**Objective:** To evaluate the effect of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life (HRQoL) outcomes in breast cancer patients and survivors.

**Methods:** A meta-analysis was carried out to quantify the effects of behavioral and exercise interventions on fatigue, depression, anxiety, body-image, stress and HRQoL. Summary effect sizes and standard errors were calculated. The presence of publication bias was explored and sensitivity analyses were performed to identify possible sources of heterogeneity.

**Results:** In total, 56 studies were included. Statistically significant results were found for the effect of behavioral techniques on fatigue (ES  $-0.158$ ; 95% CI  $-0.233$  to  $-0.082$ ,  $p < 0.001$ ), depression (ES  $-0.336$ ; 95% CI  $-0.482$  to  $-0.190$ ,  $p < 0.001$ ), anxiety (ES  $-0.346$ ; 95% CI  $-0.538$  to  $-0.154$ ,  $p < 0.001$ ) and stress (ES  $-0.159$ ; 95% CI  $-0.310$  to  $-0.009$ ,  $p = 0.038$ ). For the effect of physical exercise interventions, statistically significant results were found on fatigue (ES  $-0.315$ ; 95% CI  $-0.532$  to  $-0.098$ ,  $p = 0.004$ ), depression (ES  $-0.262$ ; 95% CI  $-0.476$  to  $-0.049$ ,  $p = 0.016$ ), body-image (ES  $0.280$ ; 95% CI  $0.077$  to  $0.482$ ,  $p = 0.007$ ) and HRQoL (ES  $0.298$ ; 95% CI  $0.117$  to  $0.479$ ,  $p = 0.001$ ).

**Conclusions:** The results indicate that behavioral techniques and physical exercise improve psychosocial functioning and HRQoL in breast cancer patients and survivors. Future research is needed on the effect of physical exercise on stress and the effect of the combined intervention in breast cancer patients.

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**Keywords:** breast cancer; behavioral techniques; physical exercise; oncology; meta-analysis

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## Introduction

Breast cancer is the most prevalent cancer in women worldwide, responsible for 23% of all cancer cases. In 2002, there were 1.15 million new cases of breast cancer and approximately 4.4 million women, diagnosed with the disease in the previous 5 years, were still alive [1]. Early detection and improved diagnosis and treatment have resulted in increased survival rates [2]. Many women who survive breast cancer experience a range of disease and treatment-related problems that are often persistent in nature, including vasomotor symptoms, decreased psychosocial functioning and reduced health-related quality of life (HRQoL) [3,4]. Over the past several decades, a variety of behavioral techniques, such as cognitive behavioral

therapy and stress management techniques, and physical exercise interventions for problems related to breast cancer treatment have been developed, many of which have been evaluated in the context of randomized controlled trials.

Previously, Tatrow *et al.* [4] published a meta-analysis of clinical trials of behavioral techniques in breast cancer, and Markes *et al.* [5] and McNeely *et al.* [6] have done so for trials of physical exercise programs. The focus of the Tatrow *et al.* review was restricted to trials that focused on psychological distress and pain as outcomes. The two overviews of physical exercise trials focused on interventions, carried out during adjuvant breast cancer treatment. Both meta-analyses included studies up to 2006. Since then, several studies have been published.

The current meta-analysis included randomized controlled trials up to March 2009, has a large sample size, and is more comprehensive than previously published meta-analyses in terms of both outcome measures and interventions. Specifically, it includes the two most prevalent, non-pharmacologic approaches to enhance psychosocial functioning and HRQoL of women with breast cancer.

## Material and methods

### Search strategy

The electronic databases of The Cochrane Library, Pubmed, EMBASE, CINAHL, Psycinfo and SportDiscus were searched until March 2009, with no language restrictions. The search terms used were related to breast cancer (MeSH terms breast cancer, breast neoplasm), behavioral techniques (MeSH terms behavior therapy, cognitive therapy, mind–body and relaxation techniques, counseling, social support, hypnosis, biofeedback) [4] and physical exercise (MeSH terms exercise, physical exercise, aerobic exercises, physical activity, motor activity), in combination with the outcome measures fatigue, depression, anxiety, body-image (self concept, body image, self esteem, self perception) stress and HRQoL, all MeSH terms. References cited in published original and review papers were examined until no further studies were found.

Eligible for inclusion were randomized controlled trials that addressed the effect of behavioral techniques or physical exercise on any of the previously noted outcome measures. Publications without sufficient quantitative data to calculate the effect size and corresponding standard error were excluded. Items of the PRISMA statement on reporting meta-analyses were checked, where applicable [7].

### Data extraction

Two reviewers (one blinded for authors, publication year, journal name and acknowledgements) extracted a range of data from each publication, including: (1) general information (e.g. geographic area of the study); (2) characteristics of the study (e.g. follow-up time); (3) characteristics of the patient population (e.g. breast cancer stage); (4) characteristics of the intervention (e.g. type, frequency and duration) and (5) outcome measures. Differences between studies on these factors were employed in sensitivity analyses. Quantitative data were extracted to calculate effect sizes. Data on effect size that could not be obtained directly were recalculated, where possible.

### Statistical analysis

Standardized mean differences (SMD) with 95% confidence intervals were calculated for each study. SMD is the difference in means divided by the pooled standard deviation. In case of a small number of patients, SMD was calculated as Hedges' *g* with adjustment for small sample bias [8]. A negative SMD usually implies a positive effect of the intervention, e.g. a lower fatigue score means less fatigued. Using Cohen's rules of thumb, small, moderate and large effect sizes are generally defined as 0.2, 0.5 and 0.8, respectively [9]. Summary effect sizes and corresponding standard errors for each outcome measure were pooled with standard meta-analytic procedures using the Stata statistical software package [10]. In case of homogeneity between studies, fixed effects analyses were used. Heterogeneity was investigated by evaluating whether confidence intervals around the individual effect sizes of pooled studies overlapped sufficiently, using the Cochran's *Q* ( $p < 0.10$ ) [11]. If heterogeneity was observed, the summary effect sizes were pooled with random effects analyses using the DerSimonian and Laird method [8]. Previous to the overall pooling, intra-study effects were calculated when an outcome was assessed with several measures and/or at several points in time in any given study, or if two studies used the same study sample. For example, in the study of Savard *et al.* [12], depression was measured with the Hospital Anxiety and Depression Scale, the Beck Depression Inventory and the Hamilton Depression Rating Scale. The three effect sizes and standard errors from these measurements were combined with intrastudy pooling before the summary effect size and standard error for depression was calculated. Data were pooled if at least two studies on a specific outcome measure were available.

As studies with significant results are more likely to be published than studies without significant results, publication bias was explored with the use of Egger's unweighted regression asymmetry test [13]. This test employs a graphical plot of estimates of effect versus some measure of their precision for each of the primary studies. The plot is known as a funnel plot because studies of smaller size will have a wider distribution of results than studies of larger size, due to a higher degree of random variation. If the possibility of publication is greater for larger and more positive studies, the smaller negative studies may not appear in the literature. This may lead to asymmetry in the funnel [14]. Any evidence of selection bias would suggest that studies with negative or inconclusive results remained hidden and unpublished and consequently were not included in the overall pooling.

Finally, to explore possible reasons for observed heterogeneity, in case of random effects analyses,

sensitivity analyses were performed whereby studies with corresponding characteristics are pooled. The following study characteristics were included in these analyses: geographic area of the study, follow-up time, stage of breast cancer (i.e. stage 0–IIIA defined as non-metastatic breast cancer versus stage IV defined as metastatic breast cancer), timing of intervention (i.e. during (D) or after (A) breast cancer treatment), individual (I) or group (G) intervention, and frequency and duration of the intervention.

## Results

### Study characteristics

The literature search initially identified 171 articles, 115 of which were excluded after initial review for the following reasons: not a randomized controlled trial ( $n = 66$ ), insufficient quantitative data ( $n = 38$ ), outcomes of interest not assessed ( $n = 10$ ) or interventions of interest not tested ( $n = 1$ ).

The study characteristics of the remaining 56 studies are presented in Table 1(a) and (b). Thirty-nine articles examined the effect of behavioral techniques (Table 1(a)) [3,12,15–51] and 14 articles addressed the effect of physical exercise on psychosocial and HRQoL outcomes (Table 1(b)) [52–65]. Three studies investigated the effect of both behavioral techniques and physical exercise [66–68].

Of the 42 studies that evaluated the effect of behavioral techniques, 27 were performed in North-America, 6 in Europe, 5 in Asia, 3 in Oceania and 1 in South-America. The patient samples of 33 studies consisted of non-metastatic breast cancer patients, whereas 4 studies reported on metastatic patients and 5 studies on a mix of non-metastatic and metastatic patients. The behavioral techniques took place during breast cancer treatment in 30 studies and after treatment in 12 studies. In 19 studies, the intervention involved interventions at the individual level, in 20 studies a group intervention, and in 3 studies both individual and group interventions (Table 1(a)).

Of the 17 studies that investigated the effect of physical exercise, 12 were performed in North-America, 3 in Europe, 1 in Asia and 1 in Oceania. Only one study included metastatic breast cancer patients. In 8 studies, the physical exercise intervention took place during breast cancer treatment and in 9 studies after treatment. Eight studies involved individual interventions, 6 studies group interventions, and 3 studies both individual and group interventions (Table 1(b)).

### Effectiveness of behavioral techniques

Fourteen studies investigated the effect of behavioral techniques on fatigue in breast cancer patients [12,18,20,21,26,27,29,30,32,42,45–47,68]

A summary effect size of  $-0.158$  was found (95% CI  $-0.233$  to  $-0.082$ ,  $p < 0.001$ ), which indicates a positive effect of the intervention on fatigue. Twenty-three studies investigated the effect of these behavioral techniques on depression. A summary effect size of  $-0.336$  was obtained (95% CI  $-0.482$  to  $-0.190$ ,  $p < 0.001$ ) [12,18,19,21,25–27,29,30,32,34–36,38–40,43,45–47,49,51,66]. Twenty-three studies explored the effect of behavioral techniques on anxiety. Pooling resulted in a summary effect size of  $-0.346$  (95% CI  $-0.538$  to  $-0.154$ ,  $p < 0.001$ ) [12,17,19,21,25–30,32,34–36,38,40,42,43,45–47,51,66]. Three studies evaluated the effect on body-image (ES =  $0.827$ , 95% CI  $-0.004$  to  $1.658$ ,  $p = 0.051$ ) [27,33,35] and 16 studies assessed the effect of behavioral techniques on stress (ES =  $-0.159$ , 95% CI  $-0.310$  to  $-0.009$ ,  $p = 0.038$ ). [15,17–19,22–24,37,42–44,46,49–51,68]. Results of 27 studies on the effect of behavioral techniques on HRQoL of breast cancer patients were pooled. [3,12,15,16,20,22,23,25,26,28,31]–[33,37,39–42,44–50,67,68]. Meta-analytic procedures revealed a summary effect size of  $0.045$  (95% CI  $-0.044$  to  $0.135$ ,  $p = 0.322$ ), which indicates a minor, but non-significant, increase in HRQoL when applying behavioral techniques. Two studies were combined because the same patient population was used [45,46]. The results were obtained with random effects analyses for the outcome measures quality of life, depression, anxiety, body-image and stress and with fixed effects analyses for the outcome measure fatigue (Figure 1 and Table 2).

### Effectiveness of physical exercise interventions

The effect of physical exercise on fatigue was investigated in 11 studies. A summary effect size of  $-0.315$  was found (95% CI  $-0.532$  to  $-0.098$ ,  $p = 0.004$ ), which indicates a positive effect of this intervention on fatigue [53–60,62,63,68]. Six studies investigated depression (ES =  $-0.262$ , 95% CI  $-0.476$  to  $-0.049$ ,  $p = 0.016$ ) [55–57,60,62,66], four studies evaluated anxiety (ES =  $-1.133$ , 95% CI  $-2.423$  to  $0.156$ ,  $p = 0.085$ ) [55,56,58,66] and seven studies examined the effect of physical exercise on body-image (ES =  $0.280$ , 95% CI  $0.077$  to  $0.482$ ,  $p = 0.007$ ) [54–57,62–64]. Thirteen studies examined the effect of physical exercise on HRQoL [52–58,60,61,64,65,67,68]. A summary effect size of  $0.298$  was found (95% CI  $0.117$  to  $0.479$ ,  $p = 0.001$ ) (Figure 2). Contrary to behavioral techniques, physical exercise has a positive and significant effect on HRQoL. As only one study examined the effect of physical exercise on stress, a summary effect size could not be calculated [68]. Two studies were combined because the same patient population was used [55,56]. All the results were obtained with random effects analyses (Figure 2 and Table 2).

Table 1. Characteristics of the included studies that investigated the effect of (a) behavioural techniques interventions (b) physical exercise interventions

Author [ref]	Year	Country	FU (wks)	N	Stage <sup>a</sup>	Intervention	b	c	Wks	Sessions	Outcome measure	Questionnaires
(a)												
Allen [15]	2002	USA	17, 35	164	I-III/A	Problem solving training	D	I	12	6	QoL, stress	CARES, IES, MHI-5
Antoni [17]	2006	USA	26, 52	199	0-III	Stress management	D	G	10	10	Anx <sup>4</sup> , stress	IES, HRS-A, ABS
Antoni [16]	2006	USA	26, 52	199	0-III	Stress management	D	G	10	10	QoL <sup>1</sup>	SIP, PSOM, ABS
Badger [18]	2005	USA	6, 10	48	I-III	Telephone counseling	D	I	6	6	Fat <sup>2</sup> , dep <sup>3</sup> , stress	CES-D, MFI, ICS
Badger [66]	2007	USA	6, 10	96	I-III	Telephone counseling	D	I	6	6	Dep <sup>3</sup> , anx <sup>4</sup>	CES-D
Banerjee [19]	2007	India	6	68	II-III	Integrated yoga	D	G	6	6	Dep <sup>3</sup> , anx <sup>4</sup> , stress	HADS, PSS
Bordeleau [20]	2003	Canada	17, 35, 52	235	IV	Therapist-led support	D	G	1	52	QoL, fat <sup>2</sup>	EORTC QLQ-C30
Bridge [21]	1988	UK	6	154	I-II	Relaxation and imagery	D	I	6	6	Fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup>	POMS
Chan [22]	2006	Hong Kong	17, 35	76	0-III	Body-mind, social support, self-help	D	G	5, 8	5, 8	QoL, stress	GHQ, PSS
Cho [67]	2006	South Korea	10	55	I-II	Psychology-based education	A	G	10	10	QoL <sup>1</sup>	QoL
Coleman [23]	2005	USA	13, 22, 35, 56	106	0-III	Telephone support and education	D	I	56	56	QoL, stress	SES
Cruess [24]	2000	USA	10	34	I-II	Cognitive behavioural stress therapy	D	G	10	10	Stress	POMS
Culos-Reed [25]	2006	Canada	7	38	0-III	Yoga program	A	G	7	7	QoL, dep <sup>3</sup> , anx <sup>4</sup>	EORTC QLQ-C30, POMS
Dirksen [26]	2008	USA	10	81	I-III	Insomnia intervention	A	I	10	6	QoL, fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup>	FACT-B, CES-D, POMS, STAI
Edelman [27]	1999	Australia	8, 13, 26	124	IV	Cognitive behavioural therapy, relaxation	D	G	21	12	Fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup> , body <sup>5</sup>	POMS, CSEI
Edmonds [28]	1999	Canada	17, 35, 61	66	IV	Group therapy	D	G	35	35	QoL, anx <sup>4</sup>	FLIC, MAC
Fillion [68]	2008	Canada	4, 13	87	0-III	Psycho-education and physical exercise	A	G	8	5	QoL, fat <sup>2</sup> , stress	SF-12, MFI, POMS
Fukui [29]	2000	Japan	6, 26	50	I-III	Psychosocial therapy	A	G	6	6	Fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup>	POMS, MAC, HADS
Ganz [3]	2000	USA	17	76	I-II	Comprehensive menopausal assessment	A	I	17	4	QoL <sup>1</sup>	SF-36
Gaston-Johansson [30]	2000	USA	2 d, 1 w	128	II-IV	Comprehensive coping strategy	D	I	22	3	Fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup>	STAI, BDI, VAS-F
Gustafson [31]	2001	USA	9, 22	246	I-II	Comprehensive health enhancement	D	I	22	3	QoL <sup>1</sup>	FACT-B
Heiney [32]	2003	USA	6, 17	68	I-II	Therapeutic groups by telephone	D	G	6	6	QoL, fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup>	QoL-BC, POMS
Helgeson [33]	1999	USA	9/10, 34	312	I-III	Education, peer discussion group	A	G	21	11	QoL, body <sup>5</sup>	SF-36, CARES, RSE
Hidderley [34]	2004	UK	9	31	I-II	Autogenic training	A	G	8-10	8-10	Dep <sup>3</sup> , anx <sup>4</sup>	HADS
Kalaitzi [35]	2007	Greece	13	40	0	Combined psychosexual	A	G	12	6	Dep <sup>3</sup> , anx <sup>4</sup> , body <sup>5</sup>	CES-D, STAI
Kissane [36]	2003	Australia	26, 52	303	I-II	Cognitive G therapy	D	G	20	23	Dep <sup>3</sup> , anx <sup>4</sup>	HADS, MAC
Lev [37]	2001	USA	17, 35	56	I-II	Nurse self-efficacy	D	I	21	5	QoL, stress	FACT-B, SDS
Marchioro [39]	1996	Italy	4, 13, 26, 39	36	0-III	Psychological therapy	D	I	39	57	QoL, dep <sup>3</sup>	FLIC, BDI
McArdle [40]	1996	UK	13, 26, 52	272	0-IV	Support from nurse and voluntary org.	D	I	26	8	QoL, dep <sup>3</sup> , anx <sup>4</sup>	GHQ, HADS
Meneses [41]	2007	USA	13, 26	256	0-II	Breast cancer education	A	I	26	8	QoL <sup>1</sup>	QoL-BC
Moadel [42]	2007	USA	13	128	I-IV	Yoga	D	G	12	12	QoL, fat <sup>2</sup> , anx <sup>4</sup> , stress	FACT-G, FACT-F, DMI
Nunes [43]	2007	Brazil	3, 5	34	I-II	Relaxation and guided imagery	D	I	3.5	24	Dep <sup>3</sup> , anx <sup>4</sup> , stress	ISSI, STAI, BAI, BDI
Samarel [44]	1997	USA	8, 16	181	I-II	Support group with coaching	D	G	8	8	QoL, stress	SDS, POMS-LASA, IFS-CA
Sandgren [45]	2003	USA	22	222	I-III	Health education, emotional expression	D	I	18	6	QoL, fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup>	FACT-B, POMS
Sandgren [46]	2007	USA	26, 56	218	I-III	Health education, emotional expression	D	I	18	6	QoL, fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup> , stress	FACT-G, POMS, PSS

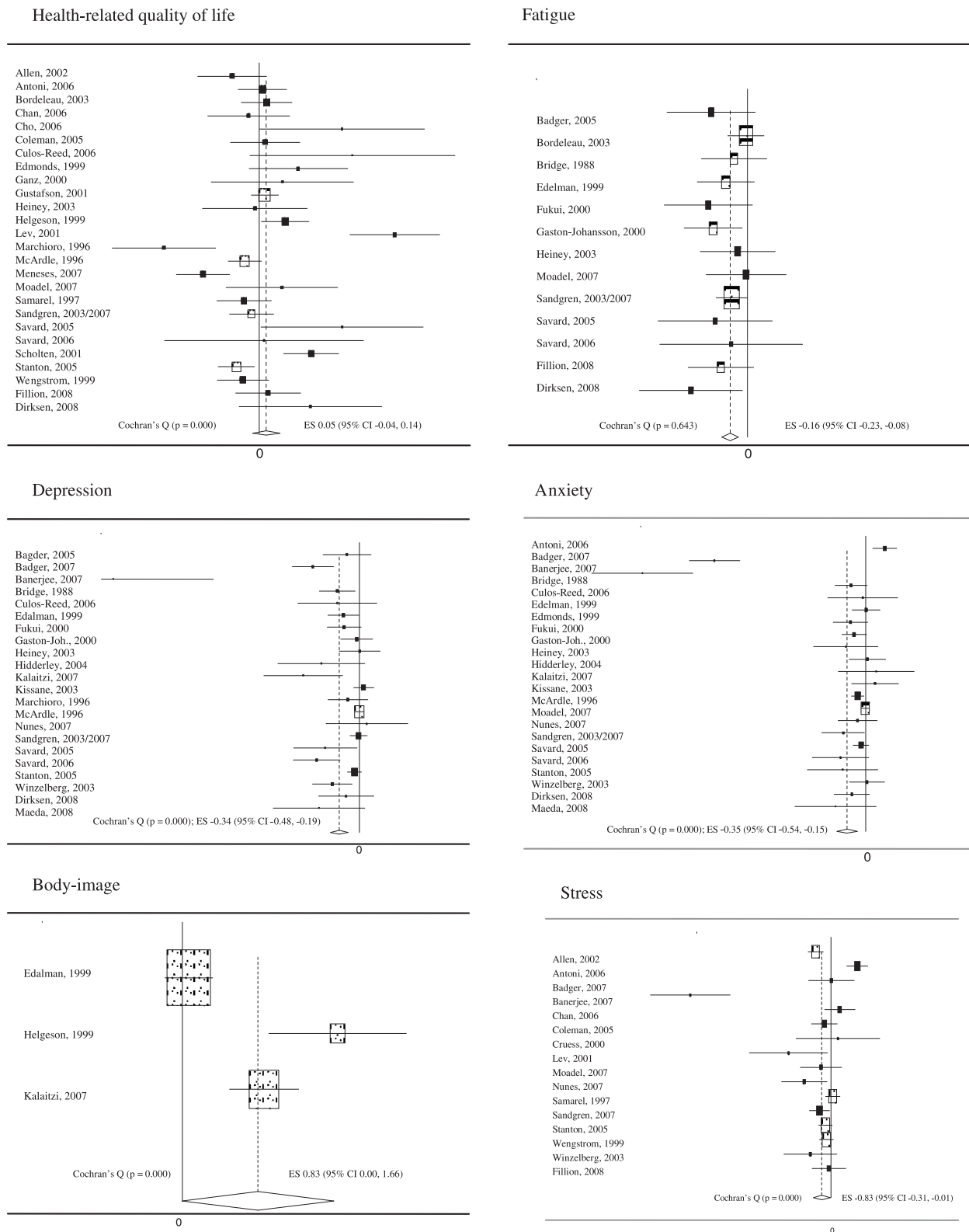
Savard [47]	2005	Canada	8	57	I-III	Insomnia treatment	A	G	8	8	QoL <sup>1</sup> , fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup>	QLQ-C30+3, HADS, MFI
Savard [12]	2006	Canada	8	45	IV	Cognitive therapy for depression	D	I	17	11	QoL <sup>1</sup> , fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup>	QLQ-C30, HADS, BDI, HDRS, MFI
Scholten [48]	2001	Australia	1, 13, 26	84	I-II, IV	Psychosocial counseling	D	I			QoL <sup>1</sup>	VAS
Stanton [49]	2005	USA	26, 52	558	I-II	Psycho educational counseling	A	I	2	2	QoL <sup>1</sup> , dep <sup>3</sup> , stress	SF-36, CES-D, IES
Wengstrom [50]	1999	Sweden	3, 5, 7, 18	134	0-IV	Nurse-care	D	I	18	7	QoL <sup>1</sup> , stress	CARES-sf, IES
Winzelberg [51]	2003	USA	12	72	0-III	Web-based support	D	I	12	12	Dep <sup>2</sup> , anx <sup>1</sup> , stress	CES-D, PCL-C, STAI, PSS, mini-MAC
Maeda [38]	2008	Japan	13, 26	28	I-III	Psycho educational counseling	D	I	13	3	Dep <sup>2</sup> , anx <sup>4</sup>	HADS
(b)												
Badger [66]	2007	USA	6, 10	96	I-III	Self-management exercise protocol	D	I	4	6	Dep <sup>3</sup> , anx <sup>4</sup>	CES-D
Basen-Engquist [52]	2006	USA	26	60	0-IV	Lifestyle physical activity	A	G	1	24	QoL <sup>1</sup>	SF-36
Campbell [53]	2005	UK	12	22	0-II	Supervised exercise program	D	G	2	12	QoL <sup>1</sup> , fat <sup>2</sup>	FACT-B, PFS
Cho [67]	2006	South Korea	10	55	I-II	Comprehensive G rehabilitation	A	G	5	10	QoL <sup>1</sup>	QoL
Courneya [54]	2003	Canada	15	53	I-IIIa	Exercise training	A	I	3	15	QoL <sup>1</sup> , fat <sup>2</sup> , body <sup>5</sup>	FACT-B, RSE, FS
Courneya [55]	2007	Canada	17	242	I-IIIa	Aerobic, resistance exercise training	D	I	3	17	QoL <sup>1</sup> , fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup> , body <sup>5</sup>	FACT-An, CES-D, RSE, SAI
Courneya [56]	2007	Canada	26	242	I-IIIa	Aerobic, resistance exercise training	D	I	3	17	QoL <sup>1</sup> , fat <sup>2</sup> , dep <sup>3</sup> , anx <sup>4</sup> , body <sup>5</sup>	FACT-An, CES-D, RSE, SAI
Daley [57]	2007	UK	8, 24	108	0-III	Aerobic exercise	A	I	3	8	QoL <sup>1</sup> , fat <sup>2</sup> , dep <sup>3</sup> , body <sup>5</sup>	FACT-B, PFS, BDI, PSPP
Fillion [68]	2008	Canada	4, 13	87	0-III	Physical exercise and psycho-education	A	G	1	4	QoL <sup>1</sup> , fat <sup>2</sup> , stress	SF-12, MFI, POMS
Milne [58]	2008	Australia	6, 12	58	I-IIa	Aerobic, resistance exercise training	A	I	3	12	QoL <sup>1</sup> , fat <sup>2</sup> , anx <sup>4</sup>	FACT-B, SCFS, SPAS-7
Mock [59]	2005	USA	6, 17-26	119	I-II	Walking exercise	D	I	5,5	14	Fat <sup>2</sup>	PFS
Mutrie [60]	2007	Scotland	12, 26	203	0-III	Supervised G exercise	D	G	3	12	QoL <sup>1</sup> , fat <sup>2</sup> , dep <sup>3</sup>	FACT-B, FACT-F, BDI
Ohira [61]	2006	USA	26	86	0-III	Weight training	A	I	2	26	QoL <sup>1</sup>	CARES
Pinto [62]	2003	USA	12	24	0-II	Aerobic exercise	A	I	4	26	Fat <sup>2</sup> , dep <sup>3</sup> , body <sup>5</sup>	POMS, BES
Pinto [63]	2005	USA	12, 26, 39	86	0-II	Home-based exercise	A	I	3,5	12	Fat <sup>2</sup> , body <sup>5</sup>	LAS-F, BES
Sandel [64]	2005	USA	13, 26	35	0-III	Dance/movement	D	G	1,5	12	QoL <sup>1</sup> , body <sup>5</sup>	FACT-B, SF-36, BIS
Segal [65]	2001	Canada	26	123	I-II	Self-directed, supervised exercise	D	I	5	26	QoL <sup>1</sup>	SF-36

Quality of life<sup>1</sup>, fatigue<sup>2</sup>, depression<sup>3</sup>, anxiety<sup>4</sup>, body-image<sup>5</sup>, ABS = Affects balance scale, BAI = Beck anxiety inventory, BDI = Beck depression inventory, CARES = Cancer rehabilitation evaluation system, CES-D = Center for epidemiologic studies-depression scale, CEI = Coopersmith self-esteem inventory, DMI = Distressed mood index, EORTC QLQ-C30 = European organisation for research and treatment of cancer quality of life questionnaire, FACT-B = The functional assessment of cancer therapy—breast cancer, FACT-F = The functional assessment of cancer therapy—fatigue, FACT-G = The functional assessment of cancer therapy—general, FLIC = Functional living index for cancer, GHQ = General health questionnaires, HADS = Hospital anxiety and depression scale, HDRS = Hamilton depression rating scale, HRSA = Hamilton rating scale for anxiety, ICS = Index of clinical stress, IES = Impact of events scale, IFS-CA = Inventory of functional status—cancer, ISSL = Inventory of stress symptoms Ipp for adults, MAC = Mental adjustment to cancer, MFI = Multidimensional fatigue inventory, MH-5 = Mental health inventory, mini-MAC = Mini-mental adjustment to cancer scale, PCL-C = Posttraumatic stress disorder checklist, POMS = Profile of mood states, POMS-LASA = Profile of mood states - linear analog self assessment, PSOM = Positive states of mind, PSS = Perceived stress scale, QoL-BC = quality of life questionnaire—breast cancer, RSE = Rosenberg analogue scale—fatigue, BDI = The beck depression inventory-II, BES = Body esteem scale, BIS = Body image scale, CARES = Cancer rehabilitation evaluation system, CES-D = Center for epidemiologic studies-depression scale, FACT-An = The functional assessment of cancer therapy—anemia scale, FACT-B = The functional assessment of cancer therapy - breast cancer, FACT-F = The functional assessment of cancer therapy—fatigue, FS = Fatigue scale, LAS-F = Linear analog scale for fatigue, PFS = The revised piper fatigue scale, POMS = Profile of mood states, PSPP = The physical self-perception profile, RSE = Rosenberg self-esteem scale, SAI = Spielberger state anxiety inventory, SCFS = Schwartz cancer fatigue scale, SF-36 = Medical outcomes study—short form, SPAS-7 = Social physique anxiety scale.

<sup>a</sup>Stage 0-IIIa defined as non-metastatic BC, stage IV defined as metastatic BC.

<sup>b</sup>D = intervention during BC treatment, A = intervention after BC treatment.

<sup>c</sup>I = individual, G = group.



**Figure 1.** Summary effect sizes and corresponding confidence intervals for the effect of behavioral techniques on the outcome measures health-related quality of life, fatigue, depression, anxiety, body-image and stress

**Publication bias**

For the articles on behavioral techniques, publication bias was detected for the outcome measure depression ( $p = 0.001$ ) and anxiety ( $p = 0.045$ ) (Figure 3(a)). No publication bias was observed

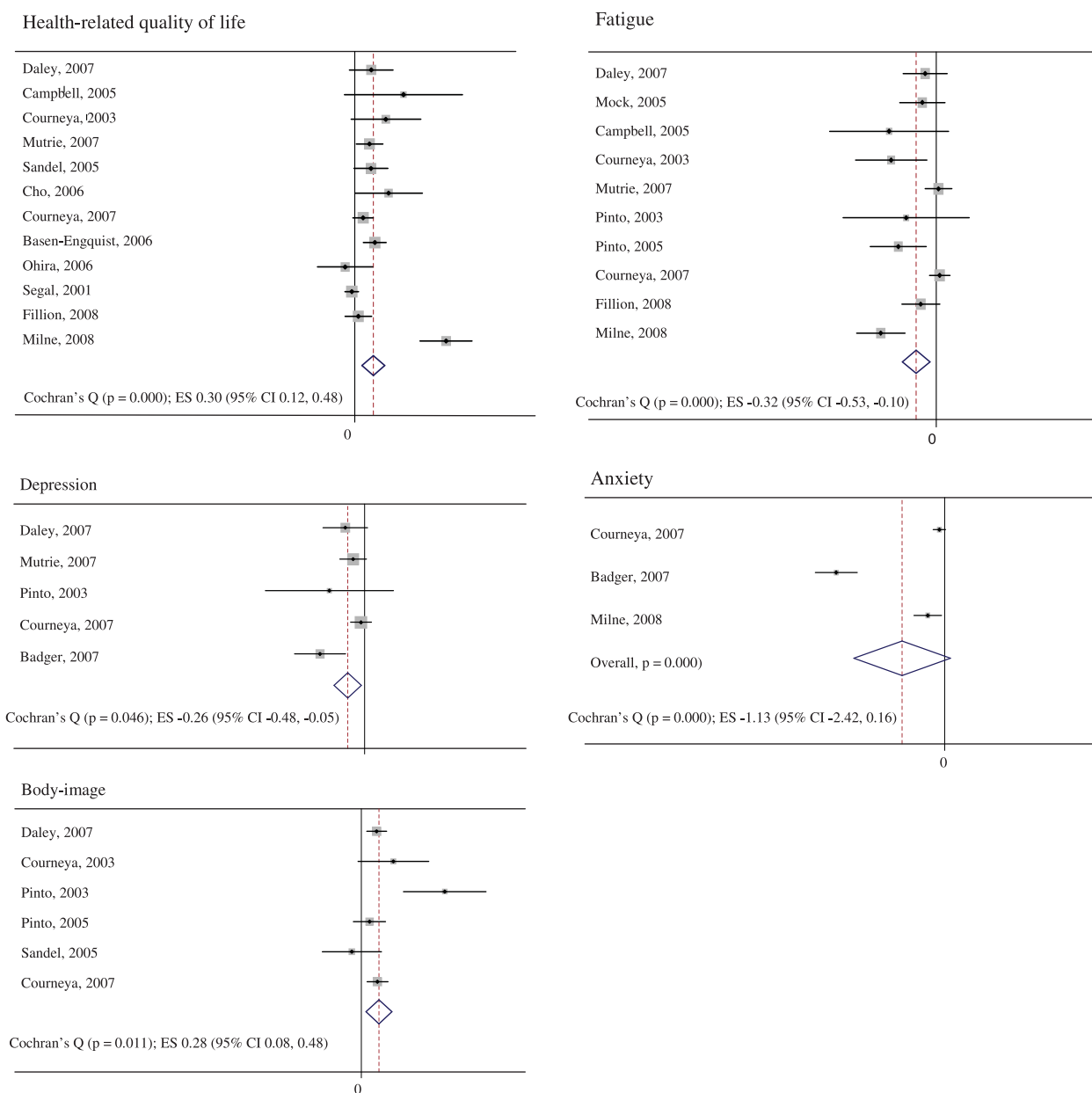
for the outcome measures fatigue ( $p = 0.061$ ), body-image ( $p = 0.247$ ), stress ( $p = 0.222$ ) or HRQoL ( $p = 0.123$ ).

With regard to physical exercise, publication bias was found for two outcome measures, fatigue ( $p = 0.009$ ) and HRQoL ( $p = 0.034$ ) (Figure 3(b)).

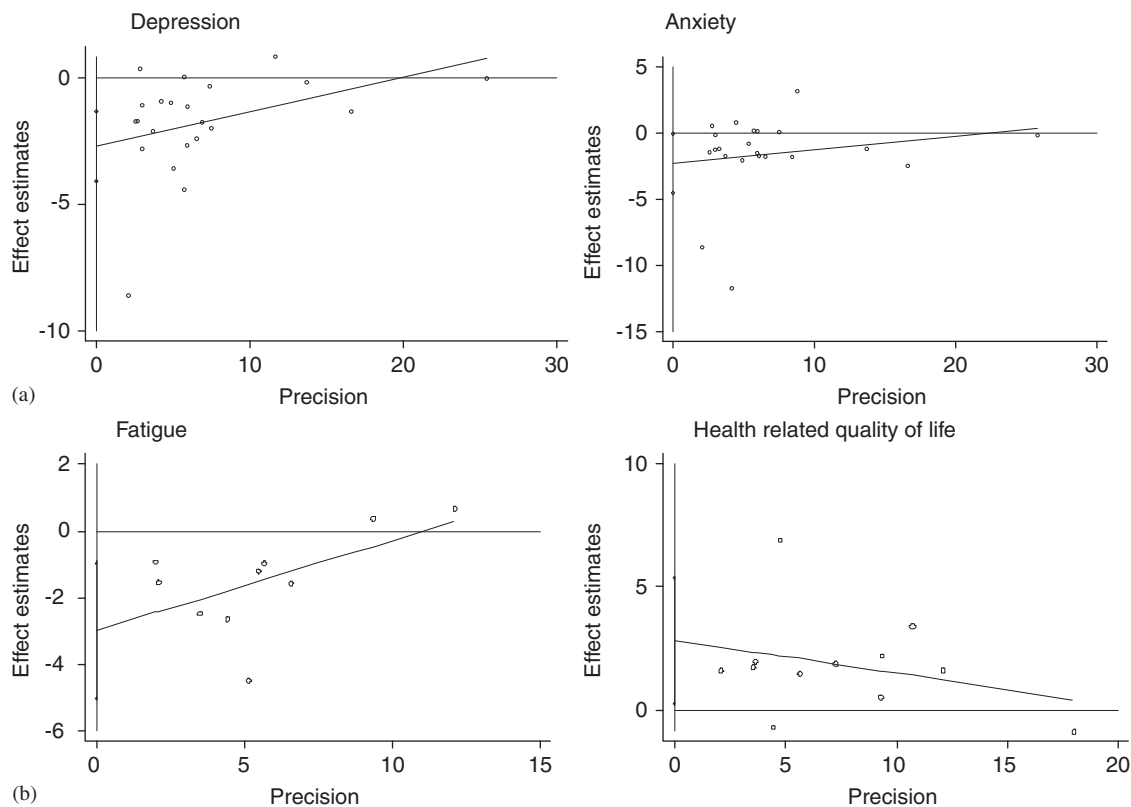
**Table 2.** Estimates and significance of effects per intervention

Outcome measure	Estimate of effect (95% CI)	F or R <sup>a</sup>	Significance of effect	Publ. bias
<i>Behavioural techniques</i>				
Quality of life	0.045 (-0.044 to 0.135)	Random	Z = 0.99, p = 0.322	P = 0.123
Fatigue	-0.158 (-0.233 to -0.082)	Fixed	Z = 4.10, p = 0.000	P = 0.061
Depression	-0.336 (-0.482 to -0.190)	Random	Z = 4.35, p = 0.000	P = 0.001
Anxiety	-0.346 (-0.538 to -0.154)	Random	Z = 3.41, p = 0.001	P = 0.045
Stress	-0.159 (-0.310 to -0.009)	Random	Z = 2.08, p = 0.038	P = 0.222
Body-image	0.827 (-0.004 to 1.658)	Random	Z = 1.95, p = 0.051	P = 0.247
<i>Physical exercise</i>				
Quality of life	0.298 (0.117 to 0.479)	Random	Z = 3.23, p = 0.001	P = 0.034
Fatigue	-0.315 (-0.532 to -0.098)	Random	Z = 2.85, p = 0.004	P = 0.009
Depression	-0.262 (-0.476 to -0.049)	Random	Z = 2.41, p = 0.016	P = 0.126
Anxiety	-1.133 (-2.423 to 0.156)	Random	Z = 1.72, p = 0.085	P = 0.334
Body-image	0.280 (0.077 to 0.482)	Random	Z = 2.70, p = 0.007	P = 0.080

<sup>a</sup>F = fixed; R = Random



**Figure 2.** Summary effect sizes and corresponding confidence intervals for the effect of physical exercise interventions on the outcome measures health-related quality of life, fatigue, depression, anxiety and body-image



**Figure 3.** (a) Behavioral techniques: publication bias plots for the outcome measure depression and anxiety. (b) Physical exercise: publication bias plots for the outcome measures quality of life and fatigue

For the outcome measures depression ( $p = 0.126$ ), anxiety ( $p = 0.334$ ) and body-image ( $p = 0.800$ ), no publication bias was detected.

### Sensitivity analyses

For the behavioral techniques studies, the calculation of Cochran's  $Q$  resulted in the identification of heterogeneity in all outcome measures, except fatigue ( $p = 0.643$ ) (Figure 1). Sources of heterogeneity, based on the extracted qualitative data could not be identified by means of meta-regression analysis.

With regard to physical exercise, calculation of the statistic  $I^2$  and Cochran's  $Q$  resulted in the identification of heterogeneity in all outcome measures (Figure 2). Sources of heterogeneity that could be identified by means of meta-regression analysis for the outcome measure HRQoL were follow-up time and whether the intervention consisted of individual or group sessions. A source of heterogeneity for the outcome measure fatigue was the timing of the intervention (i.e. during or after breast cancer treatment). For the outcome measure depression, follow-up time, exercise frequency and the duration of the intervention were identified sources of heterogeneity. Sources of heterogeneity that could be identified for the outcome measure anxiety were the exercise frequency and the duration of the intervention. For the outcome measure body-image, exercise

frequency and the duration of the intervention were sources of heterogeneity.

## Discussion

### General findings

This meta-analysis provides a comprehensive summary of studies exploring the effectiveness of a range of behavioral techniques and physical exercise interventions, during and after treatment, on long-term sequelae such as fatigue, depression, anxiety, body-image, stress and HRQoL in breast cancer patients and survivors.

Statistically significant, but modest, results were found for the effect of behavioral techniques on fatigue and stress, with stronger effects found on depression and anxiety. No significant effects were observed for body-image or HRQoL.

For physical exercise interventions, statistically significant and moderate effects were observed for fatigue, depression, body-image and HRQoL. The effect on anxiety was in the expected direction, but was not statistically significant. Only one study assessed the effect of physical exercise on stress, and thus a summary effect size could not be calculated.

### Comparison with previous meta-analyses

The results of this meta-analysis are rather consistent with previously published meta-analyses. Tatrow



*et al.* [4] reported a statistically significant effect of behavioral techniques on distress, but not on pain. In the meta-analysis by Markes *et al.* [5], an improvement in fatigue was found, but the effect was not statistically significant. McNeely *et al.* [6] concluded that physical exercise is an effective intervention in improving quality of life and fatigue in breast cancer patients and survivors. However, these findings were based on a relatively small number of trials (three and six studies, respectively).

The current meta-analysis included randomized controlled trials up to March 2009, has a larger sample size and is more comprehensive, than the previously published meta-analyses in terms of both outcome measures and interventions. Also, the inclusion of only randomized controlled trials contributed to high internal validity. The results of this meta-analysis are important for breast cancer patients who may experience long-term sequelae from their treatment, such as decreased psychosocial functioning and reduced HRQoL. The overview of behavioral and physical interventions may be helpful to clinicians and patients alike in addressing a broad range of symptoms and functional limitations associated with breast cancer and its treatment.

### Limitations

Notwithstanding these strengths, several limitations of the current study should also be noted. First, heterogeneity existed in the pooling of almost all outcome measures, except for the effect of physical exercise on fatigue. As a consequence, random effect analyses were used, resulting in wider confidence intervals and relatively more weight being given to smaller studies [8]. Second, we could not identify any significant sources of heterogeneity of outcomes in the randomized controlled trials of behavioral techniques. A potential explanation for this is the variation in type of intervention, beyond the difference between individual and group sessions, frequency and duration of the intervention. As the exploration of every feature of an intervention is not feasible, we focused on a few key characteristics of interventions that clearly differed between studies. With regard to the behavioral interventions, other characteristics than the ones we included could be the cause of heterogeneity. Further research should be conducted to clarify this matter. Third, publication bias was found in the randomized controlled trials of behavioral techniques, for the outcome measure depression and anxiety, and in the randomized controlled trials of physical exercise for the outcome measures fatigue and HRQoL. As a result, studies with minor or negative results could be missed. Finally, an effect on psychosocial functioning or HRQoL is frequently preceded or accompanied by a change in behavior. For

example, one has to comply with a training program or with specific exercise advice in order to achieve the desired outcome (e.g., reduction in fatigue, improvement in body image or enhanced quality of life). Very few studies provided complete information on the intermediate outcome of behavior change to allow this to be incorporated in this meta-analysis.

### Interpretation of findings

The results obtained from this meta-analysis are relevant for researchers and practitioners alike. They highlight areas in which future research is needed. For example, no studies were found exploring the effect of behavioral techniques or physical exercise on vasomotor symptoms and sexual dysfunction in breast cancer patients. Further work is needed to better understand and treat these long-term consequences. For practitioners, results of this meta-analysis can be used to better inform patients of the psychosocial effects of breast cancer and its treatment, and to develop strategies for minimizing or ameliorating those adverse effects.

The results indicate that a range of behavioral techniques, including behavioral therapy, cognitive therapy, education, relaxation, counseling and/or social support can be used by breast cancer patients to effectively reduce fatigue, depression, anxiety and stress. A few examples of key elements, within these interventions, that are hypothesized to improve psychosocial functioning and reduce symptoms include recognition, being taken seriously, and normalization of problems and symptoms. They may lead to feelings of relief, and offer alternative strategies to deal with stress and psychosocial problems [69]. Further, physical exercise may increase muscle strength, endurance, improve blood pressure and cholesterol levels [70] and influence the central dopaminergic, noradrenergic and serotonergic systems [71]. The results of the current meta-analysis suggest that these physiological effects may influence the outcome measures of interest, i.e. resulting in reduced fatigue and depression, improved body-image and improvement in overall HRQoL.

No significant effects of behavioral techniques were observed on body-image and HRQoL, and of physical exercise interventions on anxiety. For the latter, a potential explanation is the limited number of studies focusing on anxiety that were included in the pooling. An intervention combining both behavioral techniques and physical exercise may yield stronger effects, as evidenced by the studies of Cho *et al.* [67] and Fillion *et al.* [68]. The former study found a statistically significant effect on HRQoL, while the latter study reported a significant effect on fatigue, emotional distress and physical quality of life.

It should be noted that heterogeneity existed in most of the meta-analytic poolings. Consequently, sensitivity analyses were applied to detect potential sources of heterogeneity. The variables identified can be used or considered in the development of interventions for breast cancer patients and survivors with psychosocial and health-related problems. However, it is quite difficult to identify the most optimal exercise program or behavioral technique based on the data of this meta-analysis. Further research is needed that provides head-to-head comparisons of different interventions (elements) to support practitioners in clinical decision-making.

## Conclusion

Behavioral techniques are effective in improving fatigue, depression, anxiety and stress in breast cancer patients and survivors. Physical exercise is an effective intervention to improve fatigue, depression, body-image and HRQoL. Future research is needed on the effect of physical exercise on stress. In addition, the combined effect of these interventions deserves further study.

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## Conflict of interest

The authors declare that they have no competing interests. The submitted material has not been published and is not under consideration for publication elsewhere. A related randomized controlled trial has passed Ethical Committee Review.

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