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Yoga in addition to standard care for patients with haematological malignancies (Review)

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[Intervention Review]

Yoga in addition to standard care for patients with haematological malignancies

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ABSTRACT

Background

Haematological malignancies are malignant neoplasms of the myeloid or lymphatic cell lines including leukaemia, lymphoma and myeloma. In order to manage physical and psychological aspects of the disease and its treatment, complementary therapies like yoga are coming increasingly into focus. However, the effectiveness of yoga practice for people suffering from haematological malignancies remains unclear.

Objectives

To assess the effects of yoga practice in addition to standard cancer treatment for people with haematological malignancies.

Search methods

Our search strategy included the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950 to 4th February 2014), databases of ongoing trials (controlled-trials.com; clinicaltrials.gov), conference proceedings of the American Society of Clinical Oncology, the American Society of Hematology, the European Haematology Association, the European Congress for Integrative Medicine, and Global Advances in Health and Medicine. We handsearched references of these studies from identified trials and relevant review articles. Two review authors independently screened the search results.

Selection criteria

We included randomised controlled trials (RCTs) of yoga in addition to standard care for haematological malignancies compared with standard care only. We did not restrict this to any specific style of yoga.

Data collection and analysis

Two review authors independently extracted data for eligible studies and assessed the risk of bias according to predefined criteria. We evaluated distress, fatigue, anxiety, depression and quality of sleep. Further outcomes we planned to assess were health-related quality of life (HRQoL), overall survival (OS) and adverse events (AE), but data on these were not available.

Main results

Our search strategies led to 149 potentially relevant references, but only a single small study met our inclusion criteria. The included study was published as a full text article and investigated the feasibility and effect of Tibetan Yoga additional to standard care (N = 20; 1 person dropped out before attending any classes and no data were collected) compared to standard care only (N = 19). The study included people with all stages of Hodgkin and non-Hodgkin's lymphoma, with and without current cancer treatment. The mean age was 51 years.

We judged the overall risk of bias as high as we found a high risk for performance, detection and attrition bias. Additionally, potential outcome reporting bias could not be completely ruled out. Following the recommendations of GRADE, we judged the overall quality of the body of evidence for all predefined outcomes as 'very low', due to the methodical limitations and the very small sample size.

The influence of yoga on HRQoL and OS was not reported. There is no evidence that yoga in addition to standard care compared with standard care only can improve distress in people with haematological malignancies (mean difference (MD) -0.30, 95% confidence interval (CI) -5.55 to 4.95; P = 0.91). Similarly, there is no evidence of a difference between either group for fatigue (MD 0.00, 95% CI -0.94 to 0.94; P = 1.00), anxiety (MD 0.30, 95% CI -5.01 to 5.61; P = 0.91) or depression (MD -0.70, 95% CI -3.21 to 1.81; P = 0.58).

There is very low quality evidence that yoga improves the overall quality of sleep (MD -2.30, 95% CI -3.78 to -0.82; P = 0.002). The yoga groups' total score for the *Pittsburgh Sleep Quality Index* (PSQI) was 5.8 (± 2.3 SD) and better than the total score (8.1 (± 2.4 SD)) of the control group. A PSQI total score of 0 to 5 indicates good sleep whereas PSQI total score 6 to 21 points towards significant sleep disturbances. The occurrence of AEs was not reported.

Authors' conclusions

The currently available data provide little information about the effectiveness of yoga interventions for people suffering from haematological malignancies. The finding that yoga may be beneficial for the patients' quality of sleep is based on a very small body of evidence. Therefore, the role of yoga as an additional therapy for haematological malignancies remains unclear. Further high-quality randomised controlled trials with larger numbers of participants are needed to make a definitive statement.

PLAIN LANGUAGE SUMMARY

Yoga in addition to standard care for people with blood or lymph node cancer

Background

Blood and lymph node cancers are referred to as haematological malignancies. These are types of cancer that affect the blood, bone marrow and other parts of the lymphatic system. The most common ones are lymphomas, leukaemias and myelomas. Depending on the kind of cancer and how far it has spread, there are a lot of different options to manage the disease. Usually chemotherapy, radiotherapy or a combination of both is used to treat the disease. If the cancer is widespread, a transplantation of the patients' own bone marrow cells combined with an aggressive chemotherapy can be a treatment option.

People with cancer most commonly experience high emotional distress, anxiety, fatigue, depression and sleeping problems. These symptoms can persist, even when the treatment has ended. In search of ways to manage and cope with such conditions, more and more patients are turning to complementary and alternative therapies.

Yoga

Yoga, originating in a thousand year old Indian tradition, is becoming more and more popular. There are hundreds of different styles of yoga, but in the Western world, yoga training mostly consists of three main elements: physical postures, breathing exercises and meditation. An increasing number of cancer patients use yoga as an additional way to improve their well-being. However, a systematic evaluation about the effects of yoga in the management of haematological malignancies is still missing.

Objectives

We reviewed the evidence about the effects of yoga on people with haematological malignancies. We also considered overall survival, distress, fatigue, depression, anxiety, sleep quality and adverse events as important outcomes. We compared people suffering from haematological malignancies treated with yoga and standard cancer care with those treated with standard cancer care only.

Findings

We included a single trial with 39 participants in the review (20 in the yoga group and 19 in the control group). The trial looked at a seven-week Tibetan Yoga program in a group of people with Hodgkin and non-Hodgkin's lymphoma. The average age was 51 years. The trial involved patients who were currently receiving anti-cancer therapy as well as patients who were not receiving active therapy. The trial found insufficient data to make a judgement about the efficacy of yoga on distress, fatigue, depression and anxiety compared with patients not practicing yoga. Yoga can improve the patients' quality of sleep. The trial gave no information about health-related quality of life, overall survival or adverse events.

On the basis of the GRADE criteria, we judged the overall quality of evidence for yoga concerning the outcomes distress, fatigue, anxiety, depression and quality of sleep as 'very low'.

Conclusion

There are not enough data to say how effective yoga is in the management of haematological malignancies. Therefore, the role of yoga for haematological malignancies remains unclear. Further large, high-quality randomised controlled trials are needed.

The evidence is up-to-date as of 4 February 2014.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Yoga in addition to standard care versus standard care only for haematological malignancies

Yoga in addition to standard care versus standard care only for haematological malignancies

Patient or population: patients with haematological malignancies

Intervention: yoga in addition to standard

Comparison: standard care only

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of patients (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Yoga in addition to standard care versus standard care only				
Health-related quality of life	See comment	See comment	Not estimable		See comment	The study provided no data with regard to this outcome.
Distress Scale from: 0 to 75. Higher scores indicate a more severe impact of distress	The mean score of distress in the control groups was **10**	The mean score of distress in the intervention groups was **0.3 lower** (5.55 lower to 4.95 higher)	**MD -0.30** (95% CI -5.55 to 4.95)	39 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
Fatigue Scale from: 0 to 10. Higher scores indicate a higher level of fatigue	The mean level of fatigue in the control groups was **3**	The mean level of fatigue in the intervention groups was **0 higher** (0.94 lower to 0.94 higher)	**MD 0.00** (95% CI -0.94 to 0.94)	39 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
Anxiety Scale from: 20 to 80. Higher scores indicate higher levels of state anxiety	The mean state anxiety in the control groups was **34**	The mean state anxiety in the intervention groups was **0.3 higher** (5.01 lower to 5.61 higher)	**MD 0.30** (95% CI -5.01 to 5.61)	39 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	

Depression Scale from: 0 to 60. Higher scores indicate more depressive symptoms	The mean level of depression in the control groups was **10**	The mean level of depression in the intervention groups was **0.7 lower** (3.21 lower to 1.81 higher)	**MD -0.70** (95% CI -3.21 to 1.81)	39 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
Quality of sleep Scale from: 0 to 21. Higher scores indicate a lower quality of sleep	The mean quality of sleep in the control groups was **8**	The mean quality of sleep in the intervention groups was **2.3 lower** (3.78 to 0.82 lower)	**MD -2.30** (95% CI -3.78 to -0.82)	39 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
Adverse events	See comment	See comment	Not estimable	39 (1 study)	See comment	The study provided no data with regard to this outcome.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Serious imprecision due to very small sample size; therefore, we downgraded two points.
[2] Study participants and personnel administering the intervention were not blinded; also risk of attrition and detection bias and possible outcome reporting bias.

BACKGROUND

Description of the condition

Haematological malignancies are malignant neoplasms of the myeloid or lymphatic cell lines and include lymphomas, leukaemia, myeloma, myelodysplastic syndromes and myeloproliferative diseases. Haematological malignancies can affect bone marrow, blood cells, lymph nodes and other parts of the lymphatic system.

In the United States of America there were 149,990 new cases of leukaemia, lymphoma and myeloma expected in 2013. This constitutes about 9% of all new diagnosed cancer cases in the USA. The combined age-adjusted incidence rates for leukaemia (12.8), lymphoma (22.5) and myeloma (5.9) including all various subcategories add up to 41.2 new cases of haematological malignancies per 100,000 men and women per year (Facts 2013; Howlader 2013). Due to the different types, subtypes and the initial stage of the haematological neoplastic disease, the clinical course varies widely. Accordingly, therapy can range from "watchful waiting" to radiotherapy and intensive systematic chemotherapy, including bone marrow transplantation.

Various alternative or additional treatment options are available for people suffering from haematological malignancies, such as immunotherapy or newer classes of drugs such as tyrosine kinase or histone deacetylase inhibitors. Additionally, supportive and palliative care is also available in order to manage psychosocial and physical aspects of the disease and its treatments (Facts 2013; NCCN 2012). Like cancer patients in general, people with haematological malignancies often have to deal with severe side effects of their cancer treatment, substantially affecting their health-related quality of life (HRQoL) as well as evoking psychological distress and anxiety (Luebbert 2001; Mitchell 2011). In order to manage the effects of their illness, many cancer patients use complementary and alternative medicine (CAM) in addition to standard care. This can include yoga, which is one of the most commonly used complementary therapies (Barnes 2008; Mao 2007; Saydah 2006).

Description of the intervention

Yoga is a mind-body exercise with its origin in Indian philosophy rooting in an over 4000 year-old tradition (Innes 2005). The word *yoga* comes from the Sanskrit word "*yuj*", meaning yoke or union, describing the union between mind, body and spirit. It was originally designed as a method of discipline and attitudes to help people reach spiritual enlightenment through the eight limbs of yoga practice. These eight limbs contain ethical principles for living (*yamas* and *niyamas*), physical postures (*asanas*), breathing practices to regulate the breath and balance life energy (*pranayama*), meditative practices (*pratyahara*, *dharana*, and *dyana*) and spiritual enlightenment (*samadhi*) (Bower 2005; Collins 1998; NCCAM 2012). In Western civilisation yoga is considered as a form of CAM (Alexander 2008). The National Center for Complementary and Alternative Medicine defines CAM as "a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms" (NCCAM 2012).

Although there are many different styles of yoga, in Western civilisation the focus of yoga practice is on the physical postures and breathing practices not necessarily connected to religious beliefs or a strong spiritual way of life (Collins 1998). In recent publications, yoga has shown positive effects on a variety of specific health conditions including persistent pain (Wren 2011), asthma (Bidwell 2012), cardiovascular disease (Raub 2002), irritable bowel syndrome (Kuttner 2006), metabolic syndrome (Innes 2005), diabetes (Pandey 2011), psychiatric disorders such as depression and anxiety (Cabral 2011), and cancer (Banerjee 2007; Bower 2012; Culos-Reed 2006).

Cancer patients often have to deal with severe side effects and psychological distress during their cancer treatment, substantially affecting their HRQoL. Among the most common symptoms of cancer and its treatment are pain, depression and fatigue, which may even persist after the treatment has ended (Lin 2011). In the past decade, chemotherapy and several new drugs have helped to increase the rates of blood cancer cure and remission. Therefore, the HRQoL and the absence of side effects during and after the therapy have become more and more important (Howlader 2013). Yoga practice, solely used in addition to standard cancer therapy, is considered to have positive effects on the HRQoL and cancer-related side effects (Woodyard 2011). Most studies investigating these effects have focused on breast cancer. The findings, that yoga practice is feasible for cancer patients and shows positive effects on anxiety, emotional functioning, cancer-related distress and cancer-related symptoms like fatigue, seem promising for an implementation in the management of haematological malignancies (Banasik 2011; Bower 2005; Culos-Reed 2006; Danhauer 2009; Moadel 2007; Raghavendra 2007; Rao 2009; Vadiraja 2009).

How the intervention might work

Even though the mechanisms of how yoga affects the body are not entirely understood, there are different studies supporting the theory that yoga benefits physical and mental health via down-regulation of the hypothalamic pituitary adrenal axis and the sympathetic nervous system activity (Ross 2010). It is assumed that yoga practice reduces the allostatic load (the 'wear and tear on the body') in stress response systems and restores optimal homeostasis by increasing the activity of the inhibitory neurotransmitter gamma amino-butyric acid (GABA) and the parasympathetic nervous system (Streeter 2012). In Western culture, yoga is mostly associated with *asana*, the physical practice of yoga. It is regarded as a gentle form of physical activity or exercise (Hagins 2007). Physical exercise in people with haematological malignancies has shown beneficial effects on various outcomes like fitness and quality of life (Coleman 2008; Courneya 2009; Mello 2003; Moyer-Mileur 2009; Persoon 2013; Thorsen 2005).

Why it is important to do this review

Yoga practice has shown considerable therapeutic potential for the complementary treatment of people with solid cancers without having severe adverse effects. However, there is only little information on yoga and its effects in people with haematological malignancies. Therefore, it is important to perform this review in order to systematically collect and appraise the available evidence and determine the effects of yoga on haematological malignancies. To our knowledge, there has been no previous comprehensive systematic review of yoga interventions for people suffering from haematological malignancies.

OBJECTIVES

To assess the effects of yoga practice in addition to standard cancer treatment for people with haematological malignancies.

METHODS

Criteria for considering studies for this review

Types of studies

We prepared the review according to the Cochrane protocol (Felbel 2012). We only considered randomised controlled trials (RCTs). We included both full-text and abstract publications if sufficient information was available on study design, characteristics of participants, interventions and outcomes.

Types of participants

We included trials on people with confirmed diagnosis of haematological malignancies. We did not apply age, gender or ethnicity restrictions. We considered all subtypes and stages of haematological malignancies, including newly diagnosed patients and those with relapsed or drug resistant disease. If trials had consisted of mixed populations with different conditions or types of cancers, we would have used data from the haematological malignancy subgroups. If subgroup data for these participants had not been available (after contacting the authors of the trial), we would have excluded the trial if less than 80% of participants had haematological malignancies. However, in the trial included in this review, only people with lymphoma were randomised.

Types of interventions

We included RCTs investigating the effects of yoga in addition to standard care compared with standard care only. We included any form of yoga (i.e. Ashtanga, Bikram, Iyengar, Kundalini, Therapeutic, Tibetan and Power yoga, as well as every other form of yoga). We only included studies using yoga as the main intervention. We only considered studies with a minimum duration of four weeks and a frequency of at least an hour of yoga practice per week.

Anticancer treatment such as chemotherapy, radiotherapy or monoclonal antibodies should have been given according to the underlying disease. Supportive care given either as necessary or following a fixed schedule was allowed. It must have been intended for participants in both groups to receive identical care.

Types of outcome measures

Primary outcomes

We planned to evaluate HRQoL as primary efficacy endpoint, but no data were available. The HRQoL had to be measured with reliable and valid instruments like the Functional Assessment of Cancer Therapy-General (FACT-G) (King 2014), the Short Form Health Survey (SF-36) (Ware 1992) or disease specific questionnaires like the EORTC-QLQ-MY24 for people with myeloma (Osborne 2012).

Secondary outcomes

We analysed the following as secondary outcomes.

- Distress.
- Fatigue.
- Anxiety.
- Depression.
- Quality of sleep.

We planned to analyse the following as secondary outcomes, but no data were available.

- Overall survival (OS). We defined OS as the time interval from random treatment assignment onto a study to death from any cause or to the last follow-up.
- Adverse events (AE) if strictly yoga-related or classified as Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher (CTCAE 2009).

Search methods for identification of studies

Electronic searches

We adapted the search strategies as suggested in chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We did not apply any language restriction to reduce possible language bias.

We searched the following databases and sources:

- Databases of medical literature:
  - Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 1), search strategy see Appendix 1;
  - Ovid MEDLINE (1950 to 4th February 2014), search strategy see Appendix 2.
- Conference proceedings of annual meetings of the following societies, if not included in CENTRAL:
  - American Society of Hematology (ASH) (2005 to 2013);
  - American Society of Clinical Oncology (ASCO) (2005 to 2013);
  - European Haematology Association (EHA) (2005 to 2013);
  - European Congress for Integrative Medicine (ECIM) (2011 to 2013);
  - Global Advances in Health and Medicine (2011 to 2014).
- Electronic search in databases of ongoing trials:
  - Meta-register of controlled trials: http://www.controlled-trials.com/mrct/ ;
  - Meta-register of controlled trials: http://clinicaltrials.gov/ .

Searching other resources

We handsearched references of all identified trials, relevant review articles and current treatment guidelines for further literature.

Data collection and analysis

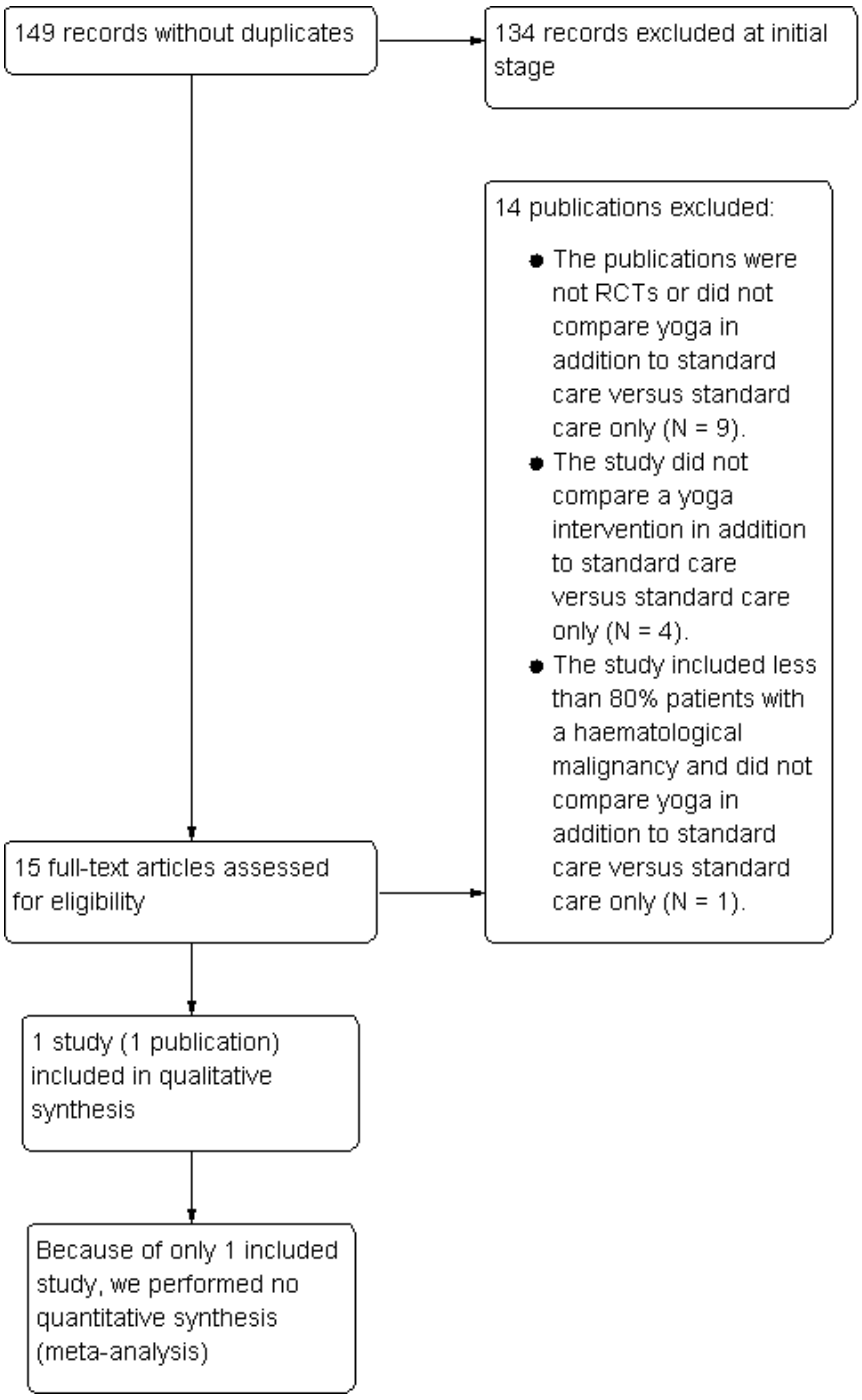
Selection of studies

As proposed in chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), two review authors (SF, NS) independently screened the results of the search strategies for eligibility for this review by reading the abstracts. In the case of disagreement we obtained the full text publication. If no consensus had been reached, we would have asked a third review author to give us her or his opinion, but this procedure was not necessary.

We documented the study selection process in a flow chart as recommended in the PRISMA statement (Moher 2009) showing the

total numbers of retrieved references and the numbers of included and excluded studies (see Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (SF, NS) independently extracted the data according to the guidelines described in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If it were required, we would have contacted authors of individual studies for additional information. We used a standardised data extraction form containing the following items:

- General information: author, title, source, publication date, country, language, duplicate publications.
- 'Risk of bias' assessment: sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.

- Study characteristics: trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analyses, statistical methods, power calculation, treatment cross-overs, compliance with assigned treatment, length of follow-up, time point of randomisation.
- Participant characteristics: underlying disease, stage of disease, histological subtype, additional diagnoses, age, gender, ethnicity, number of participants recruited/allocated/evaluated, participants lost to follow-up, type of treatment (multi-agent chemotherapy, intensity of regimen, number of cycles), additional radiotherapy.
- Interventions: type, duration and intensity of the yoga intervention, standard care, duration of follow-up.
- Outcomes: HRQoL, OS, distress, fatigue, anxiety, depression, quality of sleep, and AEs.

We used both full text versions and abstracts including additional information (for example slides) of eligible studies to retrieve the data. We would have extracted trials reported in more than one publication on one form only. If these sources had not provided sufficient information, we had planned to contact the authors for additional details, however, this was not necessary.

Assessment of risk of bias in included studies

To assess the risk of bias, we used a validity assessment form containing the items as suggested in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

- Sequence generation.
- Allocation concealment.
- Blinding (patients, personnel, outcome assessors).
- Incomplete outcome data.
- Selective outcome reporting.
- Other sources of bias.

For every criterion, we made a judgement using one of three categories.

1. 'Low risk': if the criterion was adequately fulfilled in the study, i.e. the study was at a low risk of bias for the given criterion.
2. 'High risk': if the criterion was not fulfilled in the study, i.e. the study was at high risk of bias for the given criterion.
3. 'Unclear': if the study report did not provide sufficient information to allow for a judgement of 'Yes' or 'No' or if the risk of bias was unknown for one of the criteria listed above.

Measures of treatment effect

We calculated continuous outcomes as mean differences. For binary outcomes we would have calculated risk ratios (RR) with 95% confidence intervals (CI). For time-to-event outcomes, we would have extracted hazard ratios (HR) from published data according to Parmar and Tierney (Parmar 1998; Tierney 2007). If we had been in the position to include more than one trial in this review, we would have assessed the heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. The I^2 statistic would have been used to quantify possible heterogeneity (Higgins 2011c).

Dealing with missing data

As suggested in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d), there are many potential sources of missing data which had to be taken into account: at study level, at outcome level and at summary data level. If we had considered important data as missing, we would have contacted the original investigators to request missing data. If data were still missing, we would have made explicit our assumptions for any methods used; for example, that the data were assumed to be missing at random or that missing values were assumed to have a particular value, such as a poor outcome. We would have imputed missing data for participants who were lost to follow-up after randomisation (dichotomous data) assuming poor outcome (worst case scenario) for missing individuals. We would have performed sensitivity analysis to assess how robust results were to reasonable changes in the assumptions that were made. We would have addressed the potential impact of missing data on the findings of the review in the discussion.

Assessment of heterogeneity

As our analysis contained only one study, we did not conduct a meta-analysis. Had a meta-analysis been possible, we would have assessed heterogeneity of treatment effects between trials by using a Chi^2 test with a significance level at $P < 0.1$ as described in chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). In that case, we would have used the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 50\%$ substantial heterogeneity and $I^2 > 75\%$ considerable heterogeneity). We would have explored potential causes of heterogeneity by sensitivity and subgroup analyses wherever possible.

Assessment of reporting biases

In a meta-analysis with at least 10 trials we would have explored potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test as proposed in chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). We would have considered a P value of less than 0.1 significant for this test. On the basis of a single trial included, we did not perform these steps.

Data synthesis

If we had found more than a single trial meeting the inclusion criteria and had we considered the data sufficiently similar to be combined, we would have pooled results by conducting meta-analyses using the random-effects model, while we would have used the fixed-effect model as a sensitivity analysis. If there had been more trials but they were clinically too heterogeneous to combine (e.g. various types of diseases), we would have performed meta-analyses by subgroups only without calculating an overall estimate. If different tools were used to evaluate HRQoL fatigue, anxiety, depression or quality of sleep, we would have calculated standardised mean differences to determine effect sizes. We performed analyses according to the recommendations in chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c) and used the Cochrane statistical package Review Manager 5 for analysis (RevMan 2011).

We created a 'Summary of findings' table on relative and absolute risks in each group with the help of GRADEpro software. We

summarised the evidence of HRQoL, distress, fatigue, anxiety, depression, quality of sleep and adverse effects in this Summary of findings for the main comparison.

Subgroup analysis and investigation of heterogeneity

Due to the fact that we were only able to include a single trial, it was not possible to explore heterogeneity for different subgroups. If we had found more trials suitable for inclusion into this review, we would have taken the following parameters into consideration for subgroup analyses, as these parameters are known to cause heterogeneity.

- Age (< 18 years, 18 to 40 years, 41 to 60 years, > 60 years).
- Entity of underlying disease (indolent non-Hodgkin's lymphoma, aggressive non-Hodgkin's lymphoma, acute leukaemia, chronic myeloid leukaemia, multiple myeloma, chronic lymphocytic leukaemia, Hodgkin lymphoma).
- Therapy of underlying disease (first-line, relapse therapy).
- Type/duration/intensity of yoga intervention.

Sensitivity analysis

If we had performed a meta-analysis, we would have based sensitivity analysis on:

- quality components with regard to low and high risk of bias;
- fixed-effect modelling.

RESULTS

Description of studies

Only one RCT was found eligible for inclusion in this review.

Results of the search

The search strategy was run on 30th May 2012 and again on 4th February 2014. Our literature search resulted in 149 possibly relevant references through electronic database searches and handsearching. Of these, 134 were excluded at the initial stage of screening because they were duplicates or did not fulfill our predefined inclusion criteria. The remaining 15 publications were retrieved as full-text publications or abstract publications for detailed evaluation. Finally, one full-text publication (one trial) with 39 participants was formally included in this systematic review. The overall number of references screened, identified, selected, excluded and included is documented according to PRISMA in the flow diagram (Figure 1).

Included studies

Only one trial with a total of 39 participants fulfilled our inclusion criteria (Cohen 2004). We extracted data from the full text publication of this trial. The recruitment period was not reported. The trial was published first as a full text publication in April 2004. Characteristics of the included trial are summarised in the Characteristics of included studies table.

Design

The included trial was a two-armed RCT using a wait-list control design. The trial was primarily designed to assess the feasibility of a Tibetan Yoga intervention in people with lymphoma. In both the intervention group and the control group, there were participants currently receiving chemotherapy as well as participants currently not receiving treatment during the trial.

Sample sizes

The included trial randomised 39 participants.

Setting

The study was conducted at The University of Texas, M. D. Anderson Cancer Center in the United States of America.

Participants

To be included into the trial the participants had to be 18 years or older and be able to read and speak English. Only people with a confirmed diagnosis of lymphoma who were either receiving chemotherapy or had received it within the past 12 months were included. The current or received chemotherapy had to be either a regimen with combined cyclophosphamide, doxorubicin, vincristine and prednisone or regimens with the same drug classes to control for the more severe side effects. The average participant age in both the Tibetan Yoga and the control group was 51 years. The majority of participants, 63.2% (N = 24), had a diagnosis of non-Hodgkin's lymphoma, while 36.8% (N = 14) had Hodgkin lymphoma. Four participants (21.1%) in each group received current cancer treatment while 15 participants per group (78.9%) were not receiving current cancer treatment. The distribution across the disease stages was not statistically significantly different (Tibetan Yoga group: Stage I, 22%; Stage II, 39%; Stage III, 17%; Stage IV, 22%. Control group: Stage I, 22%; Stage II, 33%; Stage III, 12%; Stage IV, 33% according to Ann Arbor Criteria).

Interventions

Cohen 2004 compared the effects of a seven weekly Tibetan Yoga intervention in addition to standard care with a control group receiving standard care only. The Tibetan Yoga intervention was held once per week. The average duration of the individual sessions was not reported. Every session was supervised by an experienced Tibetan Yoga instructor. The participants received printed materials covering a new area of the program after each class and were encouraged to continue practicing at home at least once a day. In case of a missed yoga session, the opportunity to make up for this by attending another session was offered. After the last session the participants received an audiotape guiding them through all learned techniques. Outcomes of the intervention were measured at baseline and one week, one month and three months after the last yoga session. With the exception of the follow-up assessments, the control group had no contact with the research personnel but were offered to attend the Tibetan Yoga program after the last follow-up. To what extent this opportunity was used is not reported.

Outcomes

The included trial was designed as a feasibility study and did not prespecify a primary outcome. The trial evaluated distress, fatigue, anxiety, depression and quality of sleep as outcomes. Adverse events were not reported.

The author reported to have used mixed-model regression analyses to assess the impact of the Tibetan Yoga intervention relative to the control group. They regressed follow-up assessments on group, time to follow-up assessment, the corresponding baseline measure and participant characteristics used in the minimisation-

adaptive assignment procedure. The author stated that there were no statistically significant group-by-time interactions for any outcome. Therefore, they reported all outcomes as average intervention effects across all follow-up time points and adjusted for co-variables.

Funding

The trial was supported in part by a grant from the Bruce S. Gelb Foundation.

Conflict of interest

No potential conflict of interest of the authors was mentioned.

Excluded studies

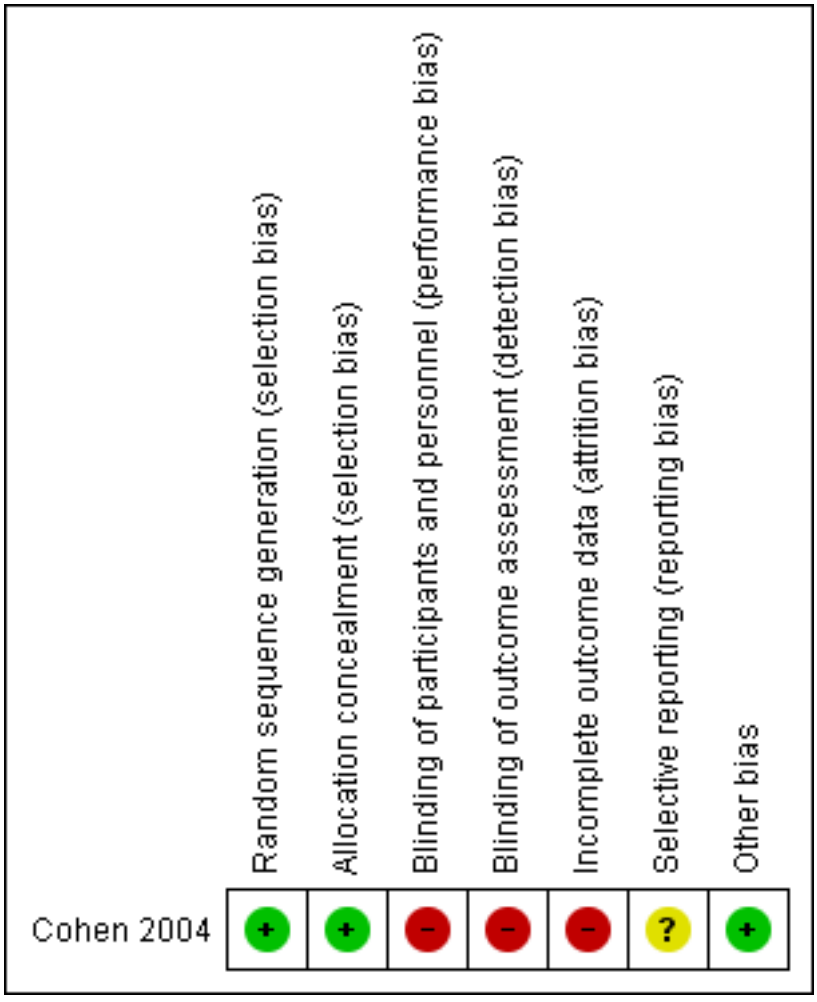
We identified 14 additional publications as potentially relevant for this review. However, after obtaining the full text articles, we excluded the publications for the following reasons: 13 publications were not reporting on RCTs or did not compare yoga interventions with standard care only (Adamsen 2006; Buffart 2012; Feng 2004; Fonteyn 2005; Habermann 2009; Jarden 2013; Kelly 2009; Kvillemo 2011; Phipps 2012; Shvarts 2013; Silva 2011; van Haren 2013; Williams 2006) and one trial included less than 80% participants with haematological malignancies and focused only on breathing techniques (Dhruva 2012). For more details see the Characteristics of excluded studies table.

Risk of bias in included studies

Overall we judged the risk of bias of the included trial as high.

For detailed information see the 'Risk of bias' table for the included trial and for an overview of the results, please see Figure 2.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The study was reported as randomised through the use of minimisation. Potential study participants had to fill out a set of questionnaires. Subsequently, they were assigned either to the intervention or the control group based on the initial questionnaires. According to the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011b) minimisation used for a random sequence generation even implemented without a random element is considered to be equivalent to being random. Therefore, we judged the risk for allocation sequence bias as 'low'. The allocation process is reported to be concealed from all investigators because relevant information for the allocation process was entered into a computer program. The group assignment was

performed consecutively by the computer program. Therefore, we judged the risk of selection bias as 'low'.

Blinding

In the included trial neither participants nor personnel such as the yoga instructor were blinded. This was to be expected since the nature of the intervention makes blinding extremely difficult. Outcome assessors were also not reported to be blinded. Consequently, we judged the risk for performance bias as 'high'.

Incomplete outcome data

The included trial was published as a full text article. One participant of the intervention group dropped out of the study before attending any yoga session. The reason for the dropout was not reported. Reasoning that this dropout equalised the group size of both intervention and control group, the study authors decided to collect no follow-up data for this participant. Although no other dropouts were reported, only 30 out of 38 participants who completed the intervention according to protocol also completed at least one follow-up. Therefore, we judged the risk for attrition bias as 'high'.

Selective reporting

There was no study protocol for the included trial in http://www.controlled-trials.com/mrct/ available.

The study authors planned their trial as a feasibility study and hypothesised that yoga had an effect on multiple outcomes.Therefore, they prespecified no primary outcome. All preplanned secondary outcomes as mentioned in the full text article are reported. However, the article mentions some unspecified administered measures assessing some proposed mediators of the benefits of yoga program which were not reported in the publication. For those reasons the risk for reporting bias was judged as 'unclear'.

Other potential sources of bias

The study appeared to be free of other sources of bias and was, therefore, judged as having a 'low' risk. However, it is important to note that there were some differences in the baseline values between the yoga and control groups.

Effects of interventions

See: **Summary of findings for the main comparison** Yoga in addition to standard care versus standard care only for haematological malignancies

The only trial eligible for inclusion in this review used a traditional taught form of Tibetan Yoga in a weekly session format (Cohen 2004). The trial compared a Tibetan Yoga intervention in addition to standard care with standard care only.

The purpose of the trial was to assess whether yoga was feasible for people suffering from lymphoma and the negative effects of its treatment. Furthermore, Cohen et al. tried to investigate the effects of the Tibetan Yoga intervention on distress, fatigue, anxiety, depression and quality of sleep. Outcomes were measured at baseline and one week, one month and three months after the last yoga session. Even though 39 participants were included into the trial and only one person dropped out, outcome data were only available for 30 participants (16 in the yoga group and 14 in the control group). The P values and 95% confidence intervals are presented in relation to the group comparisons for the follow-up data. The follow-up adjustment scores represent least-square means that were adjusted for the baseline value of the outcome measure and the information used for minimisation (state anxiety, age, gender, treatment status and type of cancer, e.g. Hodgkin or non-Hodgkin's lymphoma).

Primary outcomes

Health-related Quality of Life (HRQoL)

This outcome was not evaluated in the included trial.

Secondary outcomes

Distress

The included trial used the*Impact of Events Scale (IES)* to assess the participants' subjective level of stress. The IES is a validated and well established questionnaire designed to measure a person's cognitive responses to stressful events (Sundin 2002; Sundin 2003) and has been used in various cancer populations (Bleiker 2000; Brown 2003; Chen 2005; Kangas 2002). The IES is a 15-item self reported scale that provides separate scores for the two subscales *Intrusive thoughts* and *Avoidance* plus a total score. The score for the total scale ranges from 0 to 75 with scores greater than 25 suggesting a moderate to severe impact of distress (Horowitz 1979).

Cohen et al. found no statistically significant differences between the two groups. The yoga group showed no statistically significant improvement in comparison to the control group. The yoga groups' mean total score was 10.2 (± 8.2 standard deviation (SD)). The wait-list control group showed a mean total score of 10.5 (± 8.5 SD) (mean difference (MD) -0.30, 95% confidence interval (CI) -5.55 to 4.95; P = 0.91). These scores represent the average effects across all follow-up time points (Cohen 2004).

Fatigue

The *Brief Fatigue Inventory* (BFI) is an established and validated questionnaire to assess fatigue severity in clinical settings. It is often used in cancer populations and has shown satisfactory psychometric properties in this concern (Catania 2013; Mendoza 1999; Mystakidou 2008; Radbruch 2003). The BFI contains nine items providing a total score ranging from 0 to 10. The usual fatigue severity is defined as none (0 points), mild (1 to 3 points), moderate (4 to 7 points) and severe (8 to 10 points) (Chang 2007).

There were no statistically significant differences between the yoga and control groups. Both groups showed an identical mean total score of 3.1 (± 1.5 SD) representing the average intervention effect across all follow-up time points (MD 0.00, 95% CI -0.94 to 0.94; P = 1.00) (Cohen 2004).

Anxiety

In order to evaluate anxiety, Cohen et al. used the validated *Spielberger State Trait Anxiety Inventory* (STAI). The STAI is often used for the assessment of anxiety in cancer populations and distinguishes state and trait anxiety in two separate scales (Heim 1993; Klein 2011; Stark 2002). Each scale contains 20 separate questions for assessing either state or trait anxiety. Cohen et al. reported to have only used the inventory for state anxiety to assess the participants' current level of anxiety. Each of the two scales ranges from 20 to 80 with higher scores indicating greater anxiety

(Spielberger 1970). Scores from 39 to 55 and higher are suggested as cut-off points to detect clinically significant symptoms in the state anxiety scale. However, up to now no validated cut-off scores exist for cancer patients (Julian 2011).

In the trial, the two study groups showed no statistically significant differences. The yoga group showed a mean total score of 34.1 (± 8.4 SD) and the wait-list control group a mean total score of 33.8 (± 8.5 SD) (MD 0.30, 95% CI -5.01 to 5.61; P = 0.91). These scores represent the average effects across all follow-up time points (Cohen 2004).

Depression

To measure depression, the *Centers for Epidemiologic Studies-Depression* (CES-D), was used by Cohen et al. It is a validated questionnaire, commonly used to evaluate depression in cancer patients and has presented satisfactory psychometric properties for breast cancer patients (Hann 1999).The questionnaire contains 20-items and is focused on the affective components of depression. The score ranges from 0 to 60 with higher scores indicating greater depressive symptoms (Radloff 1977). A score of 16 or greater hints at a risk of clinical depression.

There were no statistically significant differences between the yoga and control groups. The yoga group showed a mean total score of 9.0 (± 4.2 SD) and the control group a mean total score of 9.7 (± 3.8 SD) (MD -0.70, 95% CI -3.21 to 1.81; P = 0.58). These scores represent the average intervention effect across all follow-up time points (Cohen 2004).

Quality of sleep

Cohen et al. used the validated *Pittsburgh Sleep Quality Index* (PSQI) to measure quality of sleep. The PSQI is a self-rated questionnaire containing 19 items. In psychometric evaluations the PSQI was found to be a reliable and valid instrument for the assessment of sleep quality in cancer patients (Beck 2004; Carpenter 1998; Kotronoulas 2011). It assesses the quality of sleep and sleep disturbances over one month in seven subscales (*Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Use of sleeping medications* and*Daytime dysfunction*) providing a total score from 0 to 21. Total PSQI scores greater than 5 were found to provide a good measure to divide poor sleepers (PSQI total score 6 to 21) from good sleepers (PSQI total score 0 to 5) and hint at significant sleep disturbances (Buysse 1989).

In the included trial, yoga practise led to a significantly better quality of sleep in comparison to standard care only. The yoga group's mean total score representing the average intervention effect across all follow-up time points was 5.8 (± 2.3 SD). The mean total score of the control group was 8.1 (± 2.4 SD) (MD -2.30, 95% CI -3.78 to -0.82; P = 0.002). The yoga practitioners showed statistically significant better results for the PSQI total score, as well as for the four subscales S*ubjective sleep quality, Sleep latency, Sleep duration* and*Use of sleeping medications.* The yoga arm showed no statistically significant differences for the subscales *Sleep efficiency, Sleep disturbances* and*Daytime dysfunction (* Cohen 2004).

Subscale results

For the results of the seven subscales of the PSQI please see Table 1.

Overall survival (OS)

The included trial was primarily designed as a feasibility study and did not provide any information about the participants' overall survival. Therefore, no conclusion can be drawn as to whether or not a yoga intervention could favourably influence the overall survival of people with lymphoma.

Adverse events

The included trial did not report any adverse events. Since yoga interventions are known for their relative lack of serious adverse events, especially when they are focused on visualisation, breathing and mindfulness instead of on demanding physical postures, it is likely that no major adverse advents related to the intervention occurred during the trial. However, it cannot be ruled out that minor yoga-related adverse events may have occurred but were not reported.

DISCUSSION

Summary of main results

The following findings emerge from this systematic review, evaluating the role of yoga in addition to standard care compared with standard care only for the management of haematological malignancies. The single trial that met our inclusion criteria evaluated the feasibility, psychological adjustment and sleep quality in a group of 39 patients with Hodgkin and non-Hodgkin's lymphoma treated by a Tibetan Yoga intervention.

- Trials that investigate the effects of yoga interventions for people with haematological malignancies or include people with haematological malignancies are still very rare, despite the increasing scientific interest about yoga.
- Yoga interventions seem to be feasible for people suffering from haematological malignancies, especially when they are primarily focused on meditation and breathing techniques instead of demanding physical postures.
- There is no evidence for differences between yoga in addition to standard care and standard care only for the endpoints distress, fatigue, anxiety or depression.
- There is some evidence that yoga interventions in addition to standard care may improve the quality of sleep up to a three month follow-up.
- There are no data for HRQoL, OS and AEs.

Overall completeness and applicability of evidence

This systematic review included only a single study. The included study is an RCT using minimisation for randomisation. The study enrolled only a total of 39 patients suffering from lymphoma. Other haematological malignancies were not considered. The trial included participants undergoing treatment or having completed treatment within the previous 12 months. The chosen style of yoga was Tibetan Yoga, a gentle form of yoga less commonly used in the Western civilisation. The trial was conducted in the United States of America. Even though we did not apply language limitations for our search, we were only able to include one paper published in the English language. Therefore, we might have missed some non-translated trials from India or the Asian region, where the practice of yoga is more common than in Western countries.

In terms of applicability, the majority of participants were female (63.2%). The mean participant age was 51 years. Ethnicity or further socio-demographic information was not provided. In order to enable future comparison between trials investigating haematological malignancies and yoga, a detailed description of the study population would be useful. The included trial measured the effect of Tibetan Yoga at the end of the intervention with follow-up of three months. Thus, how sustainable the observed improvement in sleep quality is remains unclear.

The included study used only self report questionnaires to assess outcomes. While this may reduce the risk of bias through an unblinded outcome assessor, it may be susceptible to response bias. Furthermore, because of the present lack of understanding about the mechanisms of how yoga interventions might work, it is not possible to estimate if the benefits can be attributed directly to the Tibetan Yoga intervention program or to some nonspecific associated elements such as received care and attention. Due to the small sample size which reduces the validity of findings by itself, we did not perform a subgroup analysis. Therefore, we are not able to predict whether the observed improvement of sleep quality might affect all participants or just a small subgroup to a larger extent.

Quality of the evidence

Results of this systematic review should be interpreted with caution owing to the risk of bias. The quality of the one trial included was at high risk of bias and the number of 39 patients included into this trial was very small. The trial was at a high risk of performance bias because of lack of blinding of the participants and the personnel administering the intervention. This is a common problem in trials investigating yoga and comparable interventions, since blinding for participants and instructors demands a great amount of effort. Additionally, the trial was at a high risk of detection bias because of unblinded outcome assessors. The trial reported only outcomes for 30 out of 38 participants who completed the study and was, therefore, at a high risk of attrition bias.

In consideration of the high risk of bias of the included trial and the very small number of participants included (N = 39) we judged the overall quality of evidence as 'very low'. For further details please see the Summary of findings for the main comparison and Figure 2.

Potential biases in the review process

The primary limitation of this systematic review is the very small number of eligible randomised controlled trials that met our inclusion criteria. Although we performed an extensive search of the literature with no language restrictions, it is possible that we might have missed Asian or Indian RCTs that were unpublished, ongoing or published as dissertation only. Therefore, publication bias and language bias cannot be excluded.

Agreements and disagreements with other studies or reviews

To our knowledge this is the first comprehensive systematic review focusing on yoga interventions for people with haematologic malignancies. There are several recent systematic reviews evaluating the effectiveness of yoga for people with solid cancers (Boehm 2012; Buffart 2012; Cramer 2012; Lin 2011; Zhang 2012). For the most part, these reviews focused on breast cancer. All these reviews evaluated yoga as a feasible intervention for cancer patients that is not associated with serious adverse events.

Lin 2011 reported that yoga group interventions for cancer patients compared to wait-list control groups or supportive therapy groups showed statistically significantly greater improvements in psychological health, including anxiety, depression, distress and stress, but only a small positive effect on HRQoL. The meta-analysis found no statistically significant improvements in overall effects for physical health. A positive effect of yoga on fatigue was not observed. Comparable results regarding fatigue were found by Boehm 2012. Investigating the effect of yoga on fatigue, they included multiple diseases such as cancer, multiple sclerosis, chronic pancreatitis, fibromyalgia, asthma and healthy populations into their meta-analysis and observed only a small positive effect on fatigue that was even smaller in cancer populations. Summarising 12 RCTs with breast cancer patients and one with patients with lymphoma (Cohen 2004) in a meta analysis, Buffart 2012 found yoga to be a feasible intervention for cancer patients and survivors. They observed a small effect on functional well-being and moderate to large effects for psychosocial outcomes in patients with breast cancer. The effects of yoga on physical function and sleep in breast cancer patients were only small and not statistically significant. Zhang 2012 found a mild HRQoL-improvement for women with breast cancer and observed only a slight improvement for psychologic function outcomes, such as anxiety, depression, distress and sleep, which were not statistically significant. Cramer 2012 investigated the effects of yoga on HRQoL and psychological health in breast cancer patients and survivors. They found evidence for a moderate short-term effect on global HRQoL along with small short-term effects on the functional, social and spiritual quality of life. However, the observed short-term effects on HRQoL could not be clearly attributed to the yoga intervention rather than bias. Owing to its positive risk profile, they concluded that yoga can be recommended as an intervention to improve psychological health during breast cancer treatment, but evidence for longer-term effects of yoga was still missing. Most of the authors criticised the fact that the majority of the included RCTs were of lower quality and generally contained only small numbers of participants.

AUTHORS' CONCLUSIONS

Implications for practice

No reliable conclusions can be drawn at present regarding the efficacy of yoga as a treatment for haematological malignancies. A lack of relevant quantitative research was identified. There is some evidence that yoga interventions in addition to standard care may improve the quality of sleep in people with lymphoma. However, this finding must be interpreted cautiously since these data originated only from a single small study.

Implications for research

More high-quality trials with larger numbers of participants are needed to evaluate potential favourable or unfavourable effects of yoga for people suffering from haematological malignancies. To achieve this goal, multicentre studies in different countries should be considered. Studies should emphasise good methodical quality, longer follow-up periods and include patient relevant outcomes such as adverse events, quality of life and overall survival.

Yoga can be considered as a many-faceted intervention consisting of different elements like physical postures, meditation and breathing techniques. These elements may influence patients and

outcomes in different ways. Since the effects and mechanisms of yoga interventions are not fully scientifically understood, researchers would be well advised to agree on a standardised set of well validated instruments for outcome assessment. In order to enable better conclusions and make future trials more comparable, a detailed description of intervention procedures and yoga postures in forthcoming studies is recommended. In regard to the many different styles of yoga it could be useful to either concentrate on the most popular styles of yoga or to focus on particular aspects of the interventions such as physical postures.

Due to the nature of a yoga intervention, blinding of participants is problematic. Sham procedures may be an option to enable a better differentiation between the effects of the yoga intervention and the influence of given attention to the participants. Even if this is not possible, the blinding of outcome assessors is crucial to reduce detection bias. This is noteworthy since the trial included in this review did not report blinding of outcome assessors.

Available safety data for yoga practiced by cancer patients suggest that yoga is not associated with serious adverse events if it is practiced cautiously and supervised by qualified yoga instructors. However, even if no adverse events were observed, most studies fail to report the presence or absence of them. Therefore, future studies should place more value on the reporting of adverse events and the reasons for withdrawals and study dropouts.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cohen 2004

Methods	Study design: RCT. Number of randomised participants: 39. Date of study start: not reported. Date of study end: not reported. Length of intervention: 7 weeks. Duration of units of yoga intervention: not reported. Randomisation • Assignment of participants either to intervention group or the wait-list control group after completing a baseline questionnaire. • Group assignment was conducted sequentially using minimisation. Recruitment period • The recruitment period was not reported. Median follow-up time • Follow-up assessments were conducted 1 week, 1 month, and 3 months after the last session.
Participants	Eligibility criteria • People with lymphoma who were either receiving chemotherapy or had received it within the past 12 months. • Participants had to be receiving either a regimen with combined cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or regimens with the same drug classes. • At least 18 years of age. • Able to read and speak English. Exclusion criteria • Major psychiatric illness. Patients (N = 39) • Tibetan Yoga group (N = 20); (N = 1 dropped out of the study before attending any classes, therefore, no follow-up data were collected). • Control group (N = 19). • Time from initial cancer diagnosis: not reported. • Ethnicity: not reported. • Education level and employment status: not reported. • Comorbidities: not reported. Mean age • In both intervention and control groups mean participant age was 51 years. Gender

Cohen 2004 *(Continued)*

- In both intervention and control groups 12 (63.2%) participants were female and 7 (36.8%) participants were male.

Stage of disease (Ann Arbor Criteria)

Intervention group:

7 participants had Hodgkin lymphoma, 15 participants were not actively receiving treatment for their cancer, 4 participants were actively receiving chemotherapy.

- Stage I: 22%
- Stage II: 39%
- Stage III: 17%
- Stage IV: 22%

Control group:

7 participants had Hodgkin lymphoma, 15 participants were not actively receiving treatment for their cancer, 4 participants were actively receiving chemotherapy.

- Stage I: 22%
- Stage II: 33%
- Stage III: 12%
- StageIV: 33%

Country

- The study was carried out at the M. D. Anderson Cancer Center, University of Texas, United States of America.

Interventions	Tibetan Yoga group • Format: group-session and individual training. • Duration of intervention: yoga sessions over 7 weeks. • Frequency of intervention: 1 session per week plus individual training. • Duration of yoga session: not reported. • Tibetan Yoga was used as an intervention, taught in its traditional format, including a number of components such as breathing, visualisation and mindfulness. • The exercises were not demanding physically, being composed of simple motions done with specific breathing patterns and supposed to be easy to perform by individuals undergoing cancer treatment. • Start of the first yoga session approximately 1 to 3 weeks after the baseline assessment. • Yoga program was divided into four aspects: 1) controlled breathing and visualisation; 2) mindfulness; 3) postures from the *Tsa lung* and 4) a preliminary set of postures from the *Trul khor.* • Participants who missed a class were encouraged to attend a class at another time. • Participants also were provided with printed materials after each class that covered a new area of the program. • Participants were encouraged to practice techniques at home. • After the last class, participants were given an audiotape that walked them through all of the techniques. They were encouraged to practice the techniques at least once per day. • Adherance: 1 person dropped out of the intervention group before attending any session and was not included in the data analysis. All other participants completed at least one yoga session, 6 (32%) attended all 7 sessions, 5 (26%) attended 5 to 6 sessions, 6 (32%) attended 2 to 3 sessions, 2 (10%) attended only 1 session. Control group • Waiting list. • No intervention was provided. • No contact with research personnel except during follow-up assessment.

Cohen 2004 *(Continued)*

	• Participants were offered the opportunity to take part in the Tibetan Yoga program after 3 month follow-up assessment.
Outcomes	Primary outcome: • Primary outcome measure was not prespecified. • Quote: "because it is hypothesised that yoga has an effect on multiple outcomes and because, to some extent, this was a feasibility study, a primary outcome measure was not prespecified". Secondary outcomes: • Feasibility • Anxiety, assessed by the Speilberger State Anxiety Inventory [STAI] • Depression assessed by the Centers for Epidemiologic Studies-Depression [CES-D] • Fatigue assessed by the Brief Fatigue Inventory [BFI] • Distress assessed by the Impact of Events Scale [IES] • Quality of sleep assessed by Pittsburgh Sleep Quality Index [PSQI] The occurrence of adverse events was not reported. Outcomes were measured at baseline and 1 week, 1 month and 3 months after the last yoga session.
Notes	The study was supported in part by a grant from the Bruce S. Gelb Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients were assigned to either the Tibetan Yoga group or the wait-list control group once they had completed the baseline questionnaires. Group assignment was conducted sequentially using minimisation, a form of adaptive assignment (...)” Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote: “The allocation process was concealed from all investigators because all the relevant information was entered into a computer program and group assignment was determined by the program.” Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel such as the Tibetan Yoga instructor were unblinded, as common in this kind of intervention. Comment: Not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessors is not reported. Comment: Not done
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: ”One patient in the Tibetan Yoga group dropped out of the study before attending any classes, making the number of patients in that group 19; therefore, we did not collect any follow-up data for this patient”. Quote: "16 of 19 patients (84%) in the Tibetan Yoga group completed at least one follow-up“. "14 of 19 patients (74%) in the control group completed at least one follow-up."

Cohen 2004 *(Continued)*

		Comment: Only one participant is reported as a dropout before the end of the trial but follow-up data are only given for 30 out of 38 participants who completed the trial. Additionally, the reasoning for the dropout is not reported.
Selective reporting (reporting bias)	Unclear risk	Quote: "Other measures assessing some proposed mediators of the benefits of the yoga program were administered but are not reported here". Comment: Selective reporting of outcomes is unlikely but cannot be excluded.
Other bias	Low risk	The study was supported in part by a grant from Bruce S. Gelb Foundation Comment: The study appears to be free of other sources of bias.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adamsen 2006	This study was excluded as it was not an RCT and used a multidimensional exercise intervention instead of yoga as the main intervention.
Buffart 2012	This publication was excluded as it was not an RCT.
Dhruva 2012	This study was excluded because less than 80% of the included participants had a haematological malignancy and the study focused only on *pranayama* (breathing techniques).
Feng 2004	This study was excluded as it was not an RCT.
Fonteyn 2005	This study was excluded as it was not an RCT and used mindfulness meditation instead of yoga as the main intervention.
Habermann 2009	This study was excluded as it was not an RCT and did not compare a yoga intervention in addition to standard care with standard care only.
Jarden 2013	This study was excluded as it focused on aerobic progression and did not compare a yoga intervention in addition to standard care with standard care only.
Kelly 2009	This study was excluded as it was not an RCT and did not compare a yoga intervention in addition to standard care with standard care only.
Kvillemo 2011	This study was excluded as it was not an RCT and used a mindfulness stress-reduction training program instead of yoga as the main intervention.
Phipps 2012	This study was excluded as it did not compare a yoga intervention in addition to standard care with standard care only.
Shvarts 2013	This study was excluded as it did not compare a yoga intervention in addition to standard care with standard care only.
Silva 2011	This publication was excluded as it was not an RCT and did not compare a yoga intervention in addition to standard care with standard care only.
van Haren 2013	This publication was excluded as it was not an RCT and did not compare a yoga intervention in addition to standard care with standard care only.

Study	Reason for exclusion
Williams 2006	This study was excluded as it was not an RCT and did not compare a yoga intervention in addition to standard care with standard care only.

DATA AND ANALYSES

Comparison 1. Yoga in addition to standard care versus standard care only

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Distress	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-5.55, 4.95]
2 Fatigue	1	39	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.94, 0.94]
3 Anxiety	1	39	Mean Difference (IV, Fixed, 95% CI)	0.30 [-5.01, 5.61]
4 Depression	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-3.21, 1.81]
5 Quality of sleep	1	39	Mean Difference (IV, Fixed, 95% CI)	-2.3 [-3.78, -0.82]

Analysis 1.1. Comparison 1 Yoga in addition to standard care versus standard care only, Outcome 1 Distress.

Study or subgroup	Yoga		Standard care only		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Cohen 2004	20	10.2 (8.2)	19	10.5 (8.5)		100%	-0.3[-5.55,4.95]
Total ***	**20**		**19**			**100%**	**-0.3[-5.55,4.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.11(P=0.91)							

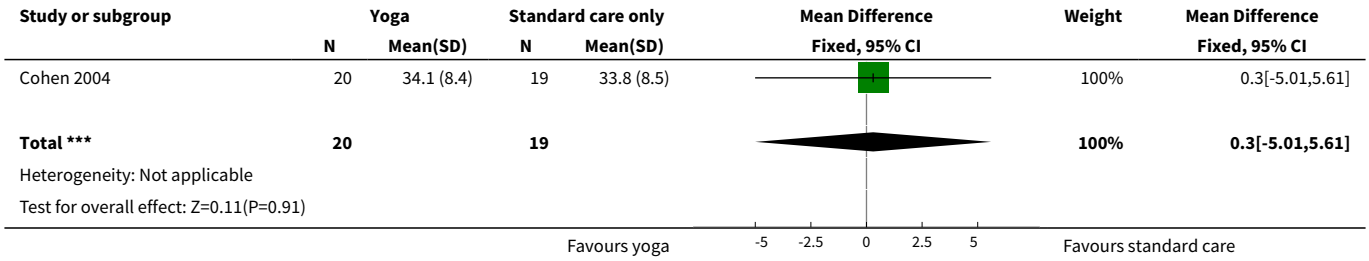
Favours yoga — Favours standard care

Analysis 1.2. Comparison 1 Yoga in addition to standard care versus standard care only, Outcome 2 Fatigue.

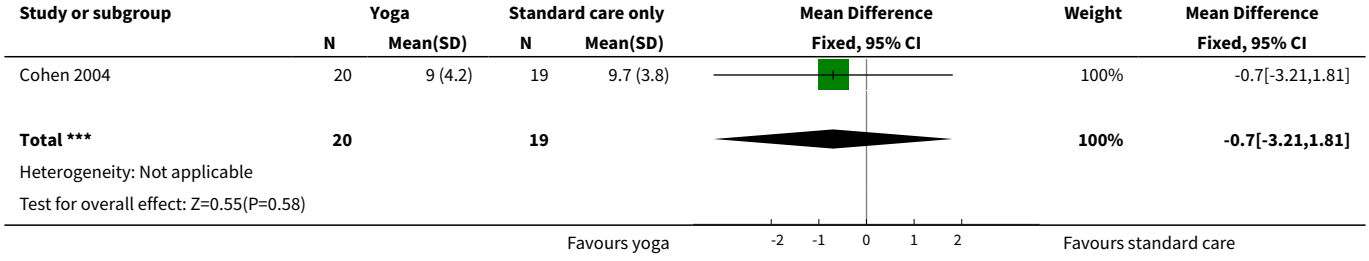
Study or subgroup	Yoga		Standard care only		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Cohen 2004	20	3.1 (1.5)	19	3.1 (1.5)		100%	0[-0.94,0.94]
Total ***	**20**		**19**			**100%**	**0[-0.94,0.94]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favours yoga — Favours standard care

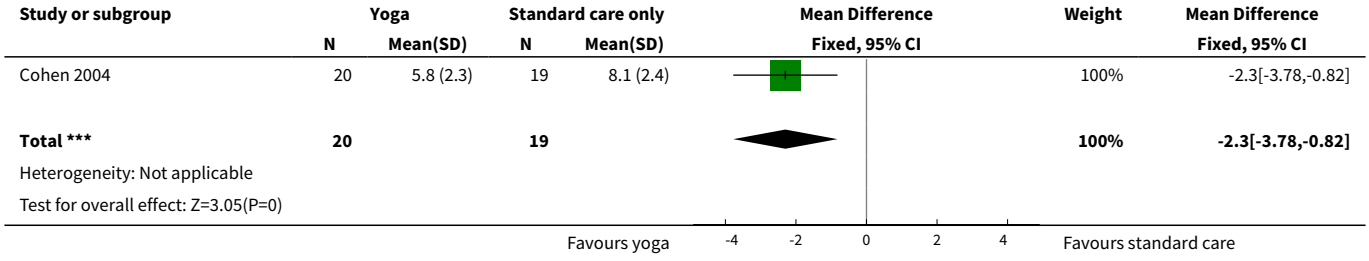
Analysis 1.3. Comparison 1 Yoga in addition to standard care versus standard care only, Outcome 3 Anxiety.



Analysis 1.4. Comparison 1 Yoga in addition to standard care versus standard care only, Outcome 4 Depression.



Analysis 1.5. Comparison 1 Yoga in addition to standard care versus standard care only, Outcome 5 Quality of sleep.



ADDITIONAL TABLES

Table 1. Subscale outcomes for the Pittsburgh Sleep Quality Index (PSQI)

Subscale	Effect estimate	P value
Sleep quality	MD -0.41; 95% CI -0.75 to -0.07	0.02
Sleep latency	MD -0.58; 95% CI -1.02 to -0.14	0.009
Sleep duration	MD -0.46; 95% CI -0.86 to -0.06	0.02
Sleep efficacy	MD -0.08; 95% CI -0.50 to 0.34	0.71
Sleep disturbances	MD -0.10; 95% CI -0.34 to 0.14	0.42

Table 1. Subscale outcomes for the Pittsburgh Sleep Quality Index (PSQI) *(Continued)*

Sleeping medications	MD -0.73; 95% CI -1.30 to -0.16	0.01
Daytime dysfunction	MD 0.03; 95% CI -0.36 to 0.42	0.88

MD = mean difference; CI = confidence interval

APPENDICES

Appendix 1. CENTRAL search strategy

ID	Search
#1	MeSH descriptor **Hematologic Diseases** explode all trees
#2	MeSH descriptor **Hematologic Neoplasms** explode all trees
#3	(hematolog* NEAR/1 malignan*) or (hematolog* NEAR/1 neoplas*) or (haematolog* NEAR/1 malignan*) or (haematolog* NEAR/1 neoplas*)
#4	MeSH descriptor **Bone Marrow Diseases** explode all trees
#5	MeSH descriptor **Lymphoma** explode all trees
#6	MeSH descriptor **Leukemia** explode all trees
#7	(hogkin* or hodkin* or hodgin*):ti,ab,kw
#8	lymphogranulomato*
#9	lymphom*
#10	histiocy*
#11	granulom*
#12	non-hodgkin*
#13	nonhodgkin*
#14	reticulosis
#15	reticulosarcom*
#16	(burkitt* NEAR/ (lymph* or tumo*))
#17	brill-symmer*
#18	plasm**ytom*
#19	myelom*
#20	sezary

(Continued)

#21	leuk*em*
#22	myelodysplas*
#23	aplast* an*em*
#24	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)
#25	MeSH descriptor **Yoga** explode all trees
#26	MeSH descriptor **Relaxation Therapy** explode all trees
#27	MeSH descriptor **Meditation** explode all trees
#28	yoga*
#29	relaxation*
#30	meditat*
#31	asana*
#32	pranayama*
#33	yogic*
#34	(#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)
#35	(#24 AND #34)

Update 04.02.2014

ID	Search
#1	MeSH descriptor: [Hematologic Diseases] explode all trees
#2	MeSH descriptor: [Hematologic Neoplasms] explode all trees
#3	(hematolog* near/1 malignan*) OR (hematolog* near/1 neoplas*) OR (haematolog* near/1 malignan*) OR (haematolog* near/1 neoplas*)
#4	MeSH descriptor: [Bone Marrow Diseases] explode all trees
#5	MeSH descriptor: [Lymphoma] explode all trees
#6	MeSH descriptor: [Leukemia] explode all trees
#7	(hogkin* or hodkin* or hodgin*):ti,ab,kw
#8	lymphogranulomato*

(Continued)

#9	lymphom*
#10	histiocy*
#11	granulom*
#12	non-hodgkin*
#13	nonhodgkin*
#14	reticulosis
#15	reticulosarcom*
#16	(burkitt* NEAR/ (lymph* or tumo*))
#17	brill-symmer*
#18	plasm**ytom*
#19	myelom*
#20	sezary
#21	leuk*em*
#22	myelodysplas*
#23	aplast* an*em*
#24	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25	MeSH descriptor: [Yoga] explode all trees
#26	MeSH descriptor: [Relaxation Therapy] explode all trees
#27	MeSH descriptor: [Meditation] explode all trees
#28	yoga*
#29	relaxation*
#30	meditat*
#31	asana*
#32	pranayama*
#33	yogic*
#34	#25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#35	#24 and #34
#36	#35 from 2013 to 2014, in Trials

Appendix 2. MEDLINE search strategy

#	Searches
1	YOGA/
2	RELAXATION TECHNIQUES/
3	MEDITATION/
4	yoga$.tw,kf,ot.
5	relaxation$.tw,kf,ot.
6	meditat$.tw,kf,ot.
7	asana$.tw,kf,ot.
8	pranayama$.tw,kf,ot.
9	yogic$.tw,kf,ot.
10	or/1-9
11	HEMATOLOGIC DISEASES/
12	exp HEMATOLOGIC NEOPLASMS/
13	(hematolog$ adj1 malignan$).tw,kf,ot.
14	(hematolog$ adj1 neoplas$).tw,kf,ot.
15	(haematolog$ adj1 malignan$).tw,kf,ot.
16	(haematolog$ adj1 neoplas$).tw,kf,ot.
17	exp BONE MARROW DISEASES/
18	exp LYMPHOMA/
19	exp LEUKEMIA/
20	hodgkin$.tw,kf,ot.
21	lymphogranulomato$.tw,kf,ot.
22	lymphom$.tw,kf,ot.
23	histiocy$.tw,kf,ot.
24	granulom$.tw,kf,ot.
25	non-hodgkin$.tw,kf,ot.
26	nonhodgkin$.tw,kf,ot.

(Continued)

27	reticulosis.tw,kf,ot.
28	reticulosarcom$.tw,kf,ot.
29	(burkitt$ adj (lymph$ or tumo?r$)).tw,kf,ot.
30	lymphosarcom$.tw,kf,ot.
31	brill-symmer$.tw,kf,ot.
32	plasm##ytom$.tw,kf,ot.
33	myelom$.tw,kf,ot.
34	sezary.tw,kf,ot.
35	leuk?em$.tw,kf,ot.
36	myelodysplas$.tw,kf,ot.
37	aplast$ an?em$.ti,kf,ot.
38	or/11-37
39	randomized controlled trial.pt.
40	controlled clinical trial.pt.
41	randomi?ed.ab.
42	placebo.ab.
43	drug therapy.fs.
44	randomly.ab.
45	trial.ab.
46	groups.ab.
47	or/39-46
48	humans.sh.
49	47 and 48
50	10 and 38 and 49

Update April 2013 to February 2014

#	Searches	Results

(Continued)

1	YOGA/	1433
2	RELAXATION TECHNIQUES/	5633
3	MEDITATION/	1430
4	yoga$.tw,kf,ot.	1444
5	relaxation$.tw,kf,ot.	74985
6	meditat$.tw,kf,ot.	2498
7	asana$.tw,kf,ot.	88
8	pranayama$.tw,kf,ot.	95
9	yogic$.tw,kf,ot.	144
10	or/1-9	81455
11	HEMATOLOGIC DISEASES/	12342
12	exp HEMATOLOGIC NEOPLASMS/	9209
13	(hematolog$ adj1 malignan$).tw,kf,ot.	11374
14	(hematolog$ adj1 neoplas$).tw,kf,ot.	828
15	(haematolog$ adj1 malignan$).tw,kf,ot.	2916
16	(haematolog$ adj1 neoplas$).tw,kf,ot.	180
17	exp BONE MARROW DISEASES/	70394
18	exp LYMPHOMA/	141882
19	exp LEUKEMIA/	192880
20	hodgkin$.tw,kf,ot.	51614
21	lymphogranulomato$.tw,kf,ot.	1963
22	lymphom$.tw,kf,ot.	121956
23	histiocy$.tw,kf,ot.	20497
24	granulom$.tw,kf,ot.	51509
25	non-hodgkin$.tw,kf,ot.	28507
26	nonhodgkin$.tw,kf,ot.	102
27	reticulosis.tw,kf,ot.	1397
28	reticulosarcom$.tw,kf,ot.	1129

(Continued)

29	(burkitt$ adj (lymph$ or tumo?r$)).tw,kf,ot.	7115
30	lymphosarcom$.tw,kf,ot.	4470
31	brill-symmer$.tw,kf,ot.	224
32	plasm##ytom$.tw,kf,ot.	6384
33	myelom$.tw,kf,ot.	44344
34	sezary.tw,kf,ot.	1680
35	leuk?em$.tw,kf,ot.	201862
36	myelodysplas$.tw,kf,ot.	13571
37	aplast$ an?em$.ti,kf,ot.	4822
38	or/11-37	545476
39	randomized controlled trial.pt.	359892
40	controlled clinical trial.pt.	86935
41	randomi?ed.ab	311358
42	randomi?ed.ab.	141347
43	drug therapy.fs.	1652983
44	randomly.ab.	186582
45	trial.ab.	268535
46	groups.ab.	1204649
47	or/39-46	3102203
48	humans.sh.	13101199
49	47 and 48	2536609
50	10 and 38 and 49	86
51	limit 50 to ed=20120524-20130401	5
52	limit 50 to ed=20130401-20140204	2

CONTRIBUTIONS OF AUTHORS

- Steffen Felbel: development and writing of protocol, search strategy
- Joerg J Meerpohl: clinical and methodological input
- Andreas Engert: clinical expertise and advice
- Ina Monsef: development of the search strategy
- Nicole Skoetz: statistical and methodological expertise and advice

DECLARATIONS OF INTEREST

None known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have specified the primary outcome from QoL to HRQoL and defined specific scales. This will be relevant for future updates as neither QoL nor HRQoL have been measured in the included trial.

We added distress as a secondary outcome, as it represents one scale of quality of life.

We removed overall survival from the list of outcomes that were planned to be included in the 'Summary of findings' table, as it has not been mentioned in the included trial and to report less than eight outcomes.

We searched additional conference proceedings for complementary medicine (ECIM and Global Advances in Health and Medicine) and ongoing trials (http://clinicaltrials.gov/).

We calculated continuous outcomes as mean differences, as we included only one trial. If more trials will be included in potential future updates, using different scales to measure one outcome, we will calculate continuous outcomes as standardised mean differences.

INDEX TERMS

Medical Subject Headings (MeSH)

Health Status; Hodgkin Disease [psychology] [*therapy]; Lymphoma, Non-Hodgkin [psychology] [*therapy]; Quality of Life; Randomized Controlled Trials as Topic; Yoga [*psychology]

MeSH check words

Humans; Middle Aged