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Integrative Therapies for Cancer-Related Fatigue

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Abstract

Cancer-related fatigue (CRF) is a common symptom for which cancer patients often use integrative and integrative therapies; however, evidence supporting these therapies is limited. The aim of this review is to provide evidence-based recommendations for integrative interventions during and after cancer treatment for CRF. These recommendations are based on a systematic literature review from 1990 through 2019. Cognitive behavior therapy plus hypnosis and American ginseng can be considered during active treatment, and acupuncture, mindfulness-based cognitive therapy, and qigong/tai chi easy can be considered during post-treatment. Coenzyme Q10 and L-carnitine are not recommended during active-treatment. All other integrative therapies for CRF had insufficient evidence to make a recommendation. While there is increasing evidence for integrative therapies for CRF, because of lack of rigorous trials and replication, no therapies could be definitively recommended. Further rigorously designed integrative therapy research is needed and should consider implementation and dissemination.

Keywords

Acupuncture; American ginseng; cancer-related fatigue; integrative therapies; hypnosis; integrated oncology; mind-body; mindfulness-based cognitive therapy; natural products; qigong/tai chi easy; systematic review

Cancer-related fatigue (CRF) is one of the most commonly reported symptoms impacting cancer survivors.¹ Cancer-related fatigue is estimated to occur in up to 90% of patients during active treatment² and 27% to 82% of patients after treatment.³ Cancer-related fatigue is defined as multidimensional and distressing fatigue related to cancer and/or cancer treatment that interferes with activities of daily living.⁴ It can negatively impact multiple

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facets of a cancer survivor's life, resulting in decreased quality of life.¹ The etiology of CRF is still unclear¹; however, there is evidence that CRF is related to multiple biologic processes including the immune response, inflammation, metabolic, neuroendocrine, and dysfunction within the central nervous system, including elevations in specific neurotransmitters and metabolites.^{5–7} Cancer survivors with CRF may have multiple and sometimes co-occurring causes for their symptom. Along with numerous overlapping causes of CRF, distinct and clinically meaningful fatigue phenotypes have not been defined, which makes effective prevention and treatment of CRF challenging.

Exercise (aerobic and resistance training), cognitive behavioral therapy (CBT), and psychoeducational therapies are currently the only standard evidence-based recommendation to treat CRF.⁸ The National Comprehensive Cancer Network guidelines recommend both massage and yoga as category 1 nonpharmacological treatments for CRF.⁹ However, these interventions have significant limitations/barriers including access to trained providers, needed equipment, limited or no insurance coverage, cost, and scheduling.^{1,10–14} Additionally, both massage and yoga have very limited evidence to support their ability to treat CRF. Many pharmacological interventions, such as treatment with psychostimulants, either have not been effective or have mixed results.^{1,15} These factors highlight the need to identify novel interventions to treat CRF.

Many cancer patients use integrative therapies during and after cancer treatment, including treatments such as natural products (e.g., herbs and supplements) and mind-body practices (e.g., yoga, mindfulness, and acupuncture). A meta-analysis of 32 surveys of cancer patients in North America found a point prevalence of 46% (95% confidence interval, 35%–56%) of integrative therapy use.¹⁶ Moreover, in cancer survivors, the experience of fatigue has been found to predict use of integrative therapies.¹⁷ Despite this high prevalence of use, information about integrative therapy use for CRF is rarely included in usual cancer care, and 62% or more of cancer survivors do not report using integrative therapies to their health care teams.¹⁸ Instead, information about these therapies comes from various sources, most often friends and family.¹⁹ These factors illustrate a great need for cancer care providers to understand the evidence base for integrative therapies for CRF management. The aim of this review is to provide evidence-based recommendations for integrative therapy interventions for CRF.

METHODS

We conducted a systematic review of published randomized controlled trials from January 1, 1990, through April 1, 2019. We searched the following databases: the National Library of Medicine's PubMed, CINAHL (Cumulative Index to Nursing and Allied Health), PsycINFO, and EMBASE using the search strategy outlined in eSupplement I (Supplemental Digital Content 1, <http://links.lww.com/PPO/A31>). Trials were selected for inclusion in the systematic review if they met the following criteria: (1) peer-reviewed published randomized controlled trial; (2) available in English; (3) conducted in adult patients with cancer 18 years or older; (4) used an integrative therapy as an intervention; (5) 50 participants or more in the trial; and (6) measured CRF as a primary outcome using a self-report validated tool. For the purposes of this review, integrative therapies were defined

as therapies not systematically integrated into standard medical care. Studies that tested conventional exercise interventions were not included because there is already an extensive literature base, including review articles and meta-analyses, on this modality.^{20–22} Also excluded were studies that did not have a clear primary outcome or had multiple primary outcomes not powered on CRF. Systematic reviews, meta-analyses, meeting abstracts, and dissertations were not included. We did not include systematic reviews because many of these are based on a compilation of studies where many if not all of the trials included in them have significant flaws beyond small sample sizes, such as inadequate controls and heterogeneous interventions, making their results difficult to interpret.

Quality was assessed using a modified Delphi approach. This approach assessed 5 key quality aspects including randomization, eligibility, blinding, missing data, and analysis with scores ranging from 0 to 8, with higher scores indicating better quality (Table 1). Interventions were scored and then categorized as Recommended for Practice, Likely to Be Effective, Benefits Balanced With Harm, Effectiveness Not Established, or Effectiveness Unlikely using a modified recommendation rubric based on the Oncology Nursing Society's Decision Rules for Summative Evaluation of a Body of Evidence (Fig. 1).²³

RESULTS

The initial search resulted in 5025 studies, with an additional 6 found through hand searching. After removing duplicates, 4713 articles' titles and abstracts were screened by 2 reviewers (N.M.A., T.B.) for inclusion, which left 117 articles. Two of the authors (N. M.A. and D.L.B. or N.M.A. and S.M.Z.) completed the full-text review, which resulted in 30 articles included in this review (Fig. 2). The quality of trials ranged from 2 to 8, with a mean score of 5.3, and the majority of trials scoring between 5 and 7 ($n = 20$) (eSupplement 2, Characteristic of Included Studies, Supplemental Digital Content 2, <http://links.lww.com/PPO/A32>).

Samples sizes ranged from 50 to 376 participants and were conducted in a wide variety of countries, although the majority were in the United States ($n = 13$). Per our inclusion criteria, all trials were conducted in adult cancer patients older than 18 years, nearly half ($n = 14$) included only women with breast cancer, 8 trials included cancer survivors with any cancer diagnosis, 1 a combination of breast and gynecological cancers, 1 a combination of breast and colon cancer, and 1 a combination of lung and gastrointestinal cancers, and there was 1 trial each conducted solely in nasopharyngeal cancer, advance cancer, prostate cancer, lung cancer, and non-Hodgkin lymphoma. The trials were nearly evenly split between those conducted in patients undergoing active treatment ($n = 13$) and those conducted in posttreatment cancer survivors ($n = 11$). Five trials included both people undergoing active cancer treatment and those who were post-cancer treatment, whereas 1 trial did not specify where participants were in their cancer treatments. The majority of trials were conducted in stage 0 to III cancer survivors; however, there was 1 trial that included stage IV nasopharyngeal cancer patients and 2 trials that included advanced stage cancer patients. One of the trials of advanced stage patients included 90 patients undergoing palliative care, and the other included 127 patients, some of whom were undergoing active treatment.

Comparison conditions that controlled for non-specific effects such as time, attention, or expectations were used in 22 of the 30 studies.

Overview of Interventions for CRF During Active Treatment

Likely to Be Effective—Cognitive behavioral therapy in association with hypnosis can be considered in people with cancer undergoing active treatment (i.e., surgery, chemotherapy, radiation; Likely to Be Effective). This recommendation is based on the results from 1 randomized clinical trial completed in 2014.²⁴ In this trial, the effect of CBT plus hypnosis was compared with the effect of an attention control group. The study, which took place in the United States, included 200 women with breast cancer undergoing a 6-week course of radiation therapy. The hypnosis consisted of an initial 30-minute training prior to radiation and then 15-minute sessions twice per week, ending with a 30-minute session at the end of radiation treatment. This was then combined with the ABC model of CBT therapy. Compared with the control group, women in the intervention group reported significant improvement in fatigue at the end of radiation treatment, 4 weeks later, and at 6 months posttreatment, with increasing effects over time. No adverse events were collected; however, when delivered by a properly trained professional (i.e., certified hypnotherapist),²⁵ both hypnosis and CBT have limited evidence of adverse events.²⁶

American ginseng (*Panax quinquefolius*, *Panacis quinquefolis*) can be considered in people with cancer undergoing active treatment (i.e., surgery, chemotherapy, radiation; Likely to Be Effective). American ginseng is a perennial herb native to eastern North America, used as a Chinese herbal medicine. This recommendation is based on the results of 2 trials conducted in the United States in 2010 and 2014.^{15,27} In these studies, doses ranging from 750 to 2000 mg of powdered and encapsulated whole American ginseng root standardized to either 3% or 5% ginsenosides (Ginseng Board of Wisconsin [Wausau, Wis] and manufactured by Beehive Botanicals [Hayward, Wis]) were taken daily for 8 weeks and compared, in both studies, with matching placebo containing white rice flour. The studies recruited both cancer patients under active treatment (radiation and chemotherapy) and posttreatment, but the majority of participants were cancer patients undergoing active treatment: 265 of 364 (2014) in 1 trial and 211 of 282 (2010). The studies took place in the United States and recruited adult cancer patients with diagnoses including breast, colon, lung, prostate, gynecological, and hematological cancers. In the dose-finding pilot study,²⁷ doses of 1000 and 2000 mg of American ginseng improved fatigue compared with placebo capsules, although these results did not reach significance. In the phase III trial using a dose of 2000 mg of American ginseng daily, at 8 weeks there was a significant improvement of fatigue by ~18% to 22% in the American ginseng group compared with 7% to 18% in the placebo group. Greater benefit was reported in patients receiving active cancer treatment compared with those who had completed treatment.¹⁵ Serious adverse events were low (approximately 3%) and did not significantly differ between groups.

Importantly, American ginseng appears not to inhibit the cytochrome p450 system²⁸ and has not been found to impact the effects of tamoxifen, doxorubicin, cyclophosphamide, paclitaxel, 5-fluorouracil, and methotrexate, but was instead synergistic with these agents inhibiting growth in MCF-7 breast cancer cell lines.^{29,30}

Effectiveness Not Established or Effectiveness Unlikely—Numerous treatments, detailed in Figure 3, have insufficient evidence to recommend them for clinical practice in cancer patients during active treatments (Effectiveness Not Established) including Asian ginseng (Panex ginseng),³¹ guarana,³² and Inner power³³ (an amino acid, coenzyme Q10, L-carnitine blend); and music therapy,³⁴ progressive muscle relaxation,^{35–37} qigong,³⁸ reflexology,³⁹ tai chi^{40,41} and yoga,^{42,43} and laser moxibustion.⁴⁴ Also, detailed in Figure 2 are 2 supplements, coenzyme Q10⁴⁵ and L-carnitine⁴⁶ that have research that indicates they are likely ineffective for treating CRF during active cancer treatment (Effectiveness Unlikely).

Overview of Interventions for CRF Posttreatment

Likely to Be Effective—Self-administered acupressure can be considered in posttreatment cancer survivors (i.e., having completed active treatments of surgery, chemotherapy, radiation; Likely to Be Effective). This recommendation is based on 1 trial in 288 women with breast cancer, who had completed active cancer treatments except hormone therapy at least 12 months previously.⁴⁷ This study compared 2 types of self-acupressure (relaxing and stimulating) administered for 6 weeks once daily to usual care. Both acupressure treatments were significantly better than usual care in improving fatigue at the end of 6 weeks, although the 2 acupressure groups were not significantly different from one another. At week 6, the percentages of participants who achieved normal fatigue levels were 66.2% in relaxing acupressure, 60.9% in stimulating acupressure, and 31.3% in usual care group. Acupressure appeared safe, with only 6 adverse events being reported consisting of mild, transient bruising at acupressure sites.

Mindfulness-based cognitive therapy (MBCT) can be considered in people with cancer posttreatment (i.e., having completed active treatments of surgery, chemotherapy, radiation; Likely to Be Effective). This recommendation is based on 2 trials conducted in 2012 and 2017 in the Netherlands.^{48,49} The 2 studies randomized 100 and 167 adult cancer survivors of any diagnosis, who were at least 1 year or 3 months posttreatment, respectively. In the study of van der Lee and Garssen,⁴⁸ 9 weeks of protocolized group MBCT was delivered by a psychologist and compared with a waitlist control group, whereas the 2017 study delivered a 9-week, web-based MBCT designed for CRF (eMBCT) compared with an active comparator group of ambulant activity feedback (AAF). This AAF control condition was designed to gain insight into their physical activity patterns and increase or balance their daily activities. A third arm was included in this study and consisted of participants receiving brief, psychoeducational emails. At the end of 9 weeks, the MBCT intervention was found to be significantly better than a waitlist control group for improving fatigue severity, whereas both the eMBCT and the AAF interventions significantly improved fatigue compared with the psychoeducational emails but were not significantly better than one another. Neither study reported any adverse events.

Qigong/tai chi easy can be considered in people with cancer posttreatment (i.e., having completed active treatments of surgery, chemotherapy, radiation; Likely to Be Effective). This recommendation is based on 1 clinical trial conducted in the United States in 101 breast cancer survivors who had completed active treatment 6 months to 5 years before enrollment

in the trial.⁵⁰ Twelve weeks of twice-weekly group qigong/tai chi easy, for the first 2 weeks, and then once weekly thereafter, was compared with sham group qigong/tai chi easy, which met for the same frequency and duration as the true tai chi group. Both immediately postintervention and at the 3-month follow-up, those in the qigong/tai chi easy group reported significantly improved fatigue compared with the sham tai chi group. Adverse events were not reported for this study. Tai chi is generally considered safe when practiced with an appropriately trained practitioner, as tai chi practitioners have rigorous requirements to become a “licensed tai chi instructor” or a “clinical Qigong practitioner.”⁵¹ As with any physical activity, however, sprains and strains are possible, especially to the knee, and this should be taken into account when recommending this therapy.⁵²

Effectiveness Not Established—Many treatments, detailed in Figure 4, have insufficient evidence to recommend them for clinical practice in posttreatment cancer survivors (Effectiveness Not Established) including the herbal supplements PG2 (*Astragalus membranaceus*)⁵³ and American ginseng,^{15,27} and acupuncture,^{54,55} biofield energy,⁵⁶ massage therapy,⁵⁷ laser moxibustion,⁴⁴ progressive muscle relaxation (PMR),³⁵ reflexology,³⁹ mindfulness-based stress reduction (MBSR),⁵⁸ and a multimodal mind-body medicine, nutrition, and exercise treatment.⁵⁹

DISCUSSION

There are no interventions that can be recommended for practice with confidence. There are 2 interventions that are likely to be effective in the population receiving cancer treatment and 3 interventions that are likely to be effective in the posttreatment population. However, both sets of “likely to be effective” recommendations are based on limited evidence, often consisting of only 1 randomized clinical trial and populations primarily of women. In this review, there were numerous studies excluded because of small sample sizes and/or poor study designs prone to biases. Well-designed studies have often not been replicated to provide greater confidence around the results, nor have positive studies been replicated to expand the ability to generalize to larger populations.

Despite these limitations, people receiving treatment for cancer who find that they are struggling with CRF may find their fatigue improved through the use of CBT that includes hypnosis. While CBT is considered to be a conventional therapy, the inclusion of hypnosis qualified the intervention to be included in this review. The 1 well-designed, well-controlled trial that demonstrates a benefit for this intervention, called CBT plus hypnosis, was not time intensive on a daily or weekly basis. Cognitive behavioral therapy plus hypnosis did require continued treatments throughout the course of radiation therapy and was delivered in person by someone with advanced training in both CBT and hypnosis. This advanced training limits the number of providers available for delivering these interventions, posing a barrier to broad dissemination. Finally, there are contraindications to hypnosis treatment, namely, schizophrenic spectrum and other psychotic disorders where people are prone to dissociative and/or psychotic states.⁶⁰

American ginseng, the other treatment likely to be effective, used a ginseng root product from one source in Wisconsin. The current dietary supplement regulations make

dissemination of this intervention challenging. Agricultural products, including botanicals, are variable by definition because growing conditions can impact the density of the constituents—in this instance, the percent of ginsenosides in ginseng root products. Currently, the public cannot purchase dietary supplements from any retail store and have confidence that the product will be equivalent to that studied. More research is needed to confirm these findings and to further understand American ginseng's mechanism for fatigue reduction.

A majority of the studies' participants were people who have completed their primary cancer treatment (surgery, chemotherapy, and/or radiation). For these cancer survivors, there are 3 treatment options that are likely effective and therefore likely worth trying. One of these options, self-acupressure, would be relatively easy to disseminate—with limited to moderate time commitment and not resource intensive—as it required stimulation of 7 points for 3 minutes daily for 6 weeks, so approximately 30 minutes per day, and is easily taught to cancer survivors. In contrast, requiring both more time and resources were the mindfulness interventions. The mindfulness interventions studied were all slightly different, 1 delivered online and 2 delivered in group format, some requiring a daylong retreat with varying daily and weekly time commitments. Despite the time- and resource-intensive MBSR interventions, when compared with a control group that was matched for even a small amount of attention or support—less than 10 minutes daily—MBSR was not found to be significantly better at reducing fatigue. This raises questions about the resource-benefit ratio of MBSR and whether such a complex, time-intensive intervention is needed. Only 1 study evaluated qigong/tai chi easy posttreatment but used a very rigorous design with a sham control. The intervention was nurse led, delivered in a group format, and required a large time commitment for 12 weeks. It would be interesting to know if a similarly delivered moderate exercise program would have resulted in comparable fatigue effects.

There are several other interventions that have been studied in both those undergoing cancer treatment and those who have completed active treatment, about which no evaluation of efficacy can be made because of small sample sizes, unclear populations, unclear effects, or inadequate control conditions. Some of these interventions could very well hold promise to improve CRF, and this group of evidence should inform future research.

There are several other interventions that have been studied in both those undergoing cancer treatment and those who have completed active treatment about which no evaluation of efficacy can be made because of small sample sizes, unclear populations, unclear effects, or inadequate control conditions. Some of these interventions could very well hold some promise to improve CRF, and this group of evidence should inform future research. Acupuncture is an excellent example. Despite there being 9 randomized clinical trials of acupuncture for CRF,^{54,55,61–67} only 2 of them met our inclusion criteria, and those 2 studies demonstrated mixed results.^{54,55}

In 3 studies, PMR served as the control group for some form of exercise (resistance, aerobic, or progressive) and was included in this review on that basis.^{35–37} In 2 of those studies, PMR decreased fatigue about as well as exercise, as no differences were found between groups. because many people going through treatment find it difficult to be motivated to

exercise because of their fatigue, PMR or even enhanced relaxation therapies, if helpful, would offer perhaps a more palatable option. More research, with control groups other than exercise, would be needed to better understand both the effects on fatigue and the mechanisms through which fatigue was improved with relaxation techniques before this could be widely recommended.

Complex multimodal interventions also offered unique study and conceptual limitations to evaluating their impact on CRF. One study that evaluated a complex treatment included several different modalities such as lectures, group exercises, guided discussions, medical consultations, and integrated meditation, nutrition, mindfulness, naturopathy, and self-help in a 1-day, 6-hour intervention.⁵⁹ The intervention also included education about walking and supervised walking sessions. This comprehensive set of interventions was compared with home walking alone. Despite the intensiveness of the intervention, no differences in fatigue were found after 10 weeks. It is unlikely that a complex intervention that includes many components without targeting any specific mechanisms would be found to be either cost-effective to deliver or time-effective for people to take up and use. While CRF is likely multifactorial and involves more than 1 system of dysregulation, interventions should be purposefully and specifically targeting identifiable mechanisms.

Neither L-carnitine nor coenzyme Q10 is recommended for improving fatigue during treatment because of a lack of effect in clinical trials among cancer patients. Both supplements had 1 well-conducted randomized controlled trial with 100 participants or more (376 for L-carnitine and 236 for coenzyme Q10) showing that these supplements were not efficacious for CRF.^{45,46} There may also be safety concerns with L-carnitine, as there were 3 deaths during the study, with 1 possibly attributed to the intervention.⁴⁶

There were both strengths and limitations related to the methodology of this review. First, 1 limitation is that we included only articles in English. Studies published in other languages could have strengthened or weakened our recommendations. Second, after eligibility was met, we did not exclude articles based on quality, although a majority of the articles included had high-quality scores, with the majority of trials scoring 5 to 7 with a maximum score of 8. One possible limitation is that we did not pull in systematic reviews or meta-analyses, but rather included only the source publication of the clinical trial. This may be a limitation when trying to evaluate homogeneous studies with small sample sizes—it can be, however, viewed as a strength when trying to evaluate highly heterogeneous studies that are often inappropriate to clump together in a meta-analysis. Another eligibility criterion that could be interpreted as either a strength or limitation was excluding studies where fatigue was not the primary outcome, but was a secondary outcome. For example, yoga has been recommended for fatigue,^{8,9} based on evidence that includes fatigue as a secondary outcome. This is problematic because, for example, in cases where sleep is a primary and fatigue is a secondary outcome, an intervention for sleep-induced fatigue may not work for fatigue that is not associated with a sleep disorder. Clear strengths of this review include the inclusion of comprehensive search terms and databases. In addition, 2 experienced researchers screened all of the initial articles, and the 3 coauthors did independent reviews, with every article receiving 2 reviews, and then came to consensus on inclusion, quality, and the recommendations.

Finally, it should be noted that the recommendations in this article vary from other published guidelines on CRF. The primary reason for this is that we limited our evidence to randomized controlled trials, with a primary outcome of CRF and sample sizes of 50 or more.

Recommendations for Future Research

There remains much that we do not know about CRF in terms of what populations are most at risk of fatigue and, most importantly, what are the characteristics (both from a genetic and psychosocial perspective) of those who have prolonged CRF (5–10 years posttreatment) compared with those who experience a normalization of their fatigue levels. Do survivors with various types of cancer experience fatigue similarly? Are there response differences to behavioral and/or pharmacologic interventions based on demographics, clinical, genetic, or psychosocial differences? Another important area for future research is more studies in populations other than those with breast cancer.

Rigorous studies need to be replicated and expanded to relevant populations. In addition, studies should include responder analyses including the characteristics of the population who responded the most to the intervention and what degree of benefit that group received from the intervention. Conversely, what are the characteristics of those who did not respond to the intervention? Understanding more about the physiology of CRF and articulating fatigue phenotypes would help immensely in moving efficacy research to effectiveness and then dissemination. Whenever possible, mechanisms through which interventions decrease fatigue should be included.

Finally, studies that inform the implementation of interventions, particularly those that are resource intensive, need to be done. Questions that still need to be answered are whether interventions should be delivered in groups, in person, online, or through an app or whether people can learn to do them independently in some other form. What is the degree of training required to implement the intervention? What educational preparation or professional experience may be required? Intervention research should proceed with dissemination in mind, remembering that more is not always better, and time and resources are important commodities that are limited.

In summary, while no integrative treatments can be recommended for practice with a high level of confidence, there are some likely to be effective with no known significant adverse effects. Future research should focus on replicating promising interventions, developing more rigorous study designs, expanding beyond breast cancer populations, and answering questions about dissemination and implementation of integrative therapies, especially those that are time and/or resource intensive.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.
Recommendation rubric.

FIGURE 2.
PRISMA diagram.

FIGURE 3.
Active treatment recommendation for CRF.

FIGURE 4.
Posttreatment recommendations for CRF.

TABLE 1.

Modified Delphi Scoring

Was the method of randomization specified?	1 = Yes; 0 = No
Was the eligibility criterion clearly laid out?	1 = Yes, 0 = no
Is the patient blind to study arm; blind hypothesis?	1 = Yes/N/A, 0.5 = don't know, 0 = no
Is the provider blinded to study arm?	1 = Yes/N/A, 0.5 = don't know, 0 = no
Is the sequence of study arm allocation concealed to the treatment assigner?	1 = Yes/N/A, 0.5 = don't know; 0 = No
Was there an objective strategy followed for treating missing data?	1 = Yes, 0 = no
Was the study adequately powered for the primary outcomes?	1 = Yes, 0.5 = don't know, 0 = no
Point estimates and associated variability estimates (CI) presented for the primary outcome measures?	1 = Yes, 0 = no
Modified Delphi quality score	Sum of scores

CI indicates confidence interval.