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TITLE PAGE

Title: Effectiveness of caregiver interventions for people with cancer and non-cancer related chronic pain: a systematic review and meta-analysis.

Running Title: Caregivers and pain management

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ABSTRACT

BACKGROUND: People with chronic pain frequently have difficulties in completing everyday tasks to maintain independence and quality of life. Informal caregivers may provide support to these individuals. However, the effectiveness of interventions to train and support these individuals in caregiving remains unclear. The purpose of this study was to systematically review the evidence to determine the effectiveness of caregiver interventions to support informal caregivers of people with chronic pain.

METHODS: A systematic review of published and unpublished literature databases was undertaken (09 April 2021). Trials reporting clinical outcomes of caregiver interventions to train informal caregivers to support community-dwelling people with chronic pain were included. Meta-analysis was undertaken and each outcome was assessed using GRADE.

RESULTS: 27 studies were eligible (N=3427 patients). Twenty-four studies assessed patients with cancer pain, three with musculoskeletal pain. No other patient groups were identified. There was very low-quality evidence that caregiver interventions were beneficial for caregiver health-related quality of life (standardised mean difference (SMD): 0.26; 95% confidence intervals (CI): 0.01 to 0.52; N=231). There was moderate-quality evidence that caregiving interventions were effective in reducing pain in the short-term (SMD 0.16; 95% CI: -0.29 to -0.03There was low-quality evidence that caregiving interventions had no beneficial effect over usual care for psychological outcomes, fatigue, coping or physical function in the long-term.

CONCLUSION: Caregiving interventions may be effective for patients and caregivers but only in the shorter-term and for a limited number of outcomes. There is insufficient evidence examining the effectiveness of caregiver interventions for people with non-cancer related pain.

Keywords: pain; symptom management; cancer; musculoskeletal; carer; spousal

INTRODUCTION

Chronic pain is complex and multi-factorial in its origin. Previous literature has explored the social dynamics between people with chronic pain and their family members and friends.[1] People with chronic pain frequently have difficulties in managing everyday activities to maintain independence and quality of life.[2] To assist with these, they often access support or caregiving. Such support may include: washing and dressing, preparing meals and assistance in feeding, housework or shopping.[3,4] This caregiving may be formal or informal. Formal care is defined as the provision of care by someone who is paid for such a service. Informal care is provided without a direct cost. This is historically either a care-recipient's spouse or partner, family members or friends. In addition to activities which formal carers may provide, informal caregivers may also assist in other tasks such as assistance in managing money or bills, or other organisational rather than necessarily physical roles.[3]

Invariably caring for and supporting individuals with chronic pain during day-to-day tasks can have a long-term negative impact on them and their caregiver. This can be particularly challenging for caregivers of people with chronic cancer pain. The management of nociceptive and neuropathic pain associated with cancer pain can be particularly challenging; this is amplified emotionally with the stress of caregiving for someone close to that individual who has a life-limiting disease.[5] Previous evidence has centred on the relationship between older married couples and chronic pain.[6,7] Such studies have demonstrated that both members of this dyad report greater pain elevated by depressed mood, challenges in their marital relationships and heightened distress.[1,7] Whybrow et al[8] reported greater challenges in caregiving and overall dissatisfaction between care-recipients and caregivers when the dyad have limited understanding of the presenting medical condition. They suggested that caregivers desire training interventions on caring, to improve knowledge on their care-recipient's condition and symptom management.[9]

Given that chronic pain affects the health and wellbeing of both care-recipients and caregivers,[10] interventions to support this dyad are warranted. No systematic reviews have undertaken such an analysis irrespective of the cause of chronic pain. The purpose of this study was to address this limitation and to systematically review the evidence to determine the effectiveness of caregiver interventions to support informal caregivers of people with chronic pain.

MATERIALS AND METHODS

This systematic review was registered through the International Prospective Register of Systematic Reviews database (PROSPERO Registration: CRD42019136171) and reported following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[11]

Search Strategy

The search was undertaken by one reviewer (MS) using published and unpublished databases including Ovid EMBASE, Ovid MEDLINE, EBSCO CINAHL, OpenGrey, the WHO International Clinical Trial Registry and ClinicalTrials.gov registry. The search strategy for EMBASE is presented in **Supplementary Table 1**. This was modified for each database. Reference lists of all potentially eligible studies were independently reviewed by two reviewers (TS,MP). Corresponding authors from included studies were contacted to identify other studies. The search was conducted from database inception to 09th April 2021.

We placed no restriction on the search in respect to date of publication, risk of bias or language of publication.

Selection Criteria

Two reviewers (MP, TS) independently reviewed all titles and abstracts from the search results. Full-text papers for all potentially eligible studies were independently reviewed by each reviewer to determine final inclusion. Disagreements between the two reviewers were resolved through discussion with an adjudicator (SL).

The eligibility criteria were:

Inclusion criteria

- Randomised or non-randomised controlled trials (RCTs) recruiting informal caregivers of adults (≥18 years) with chronic pain attributed to any pathological origin. Chronic was defined as pain experienced for six months or longer.[12]
- Interventions were enhanced informal caregiver training programmes. These were defined as interventions aimed to improve the understanding and/or practical skills for informal caregivers to manage symptoms of people with chronic pain.
- Control interventions were either usual care (no caregiver intervention) or a comparative intervention such as a non-caregiver training intervention.

Exclusion criteria

- Caregivers of patients with pain or pain derived from an acute origin including childbirth/acute post-surgical. Acute was defined as less than 12 weeks from primary presentation.[12]
- Caregivers of patients with cognitive impairment or intellectual disabilities where a caregiver-patient education programme may require different learning approaches.
- Interventions which were designed to provide training to paid caregivers or clinical health professionals (community or hospital).

Data Extraction

Data were extracted onto a pre-defined data extraction form by two reviewers (MP, JF) and verified by a third (TS). Where the same study was reported across two or more papers, these were classified as a single study to avoid multiple counting.

Data extracted included: country of origin; year of study conduct; number and characteristics of care-recipients including data on: age, gender, principal presenting pathology and medical morbidities (when reported); caregiver characteristics including: age and gender; intervention characteristics (experimental and control); composition, timing, dosage, staff delivery, duration and format of intervention delivered; co-interventions; and outcomes.

Outcome Measures and End-Points

The primary outcome measure was caregiver health-related quality of life (HRQOL). Secondary outcome measures included: care-recipient HRQOL, care-recipient pain and physical function, care-recipient and caregiver anxiety and depression, caregiver burden, coping, self-efficacy, fatigue, perceived stress and cost-effectiveness/health resource utilisation. These diverse outcome domains are warranted to ensure that both care-recipient and caregiver outcomes are measured, whilst also acknowledging the complex social and health needs which this dyad present.[13]

The primary end-point was 12 months (long-term outcome). Outcomes were analysed as short-term (zero to three months post-randomisation), or mid-term (three to 12 months post-randomisation).

Risk of Bias Assessment

Two reviewers (MP, TS) independently critically appraised each included study using the Cochrane Risk of Bias tool.[14] This assesses the risk of bias in research through an assessment of randomisation (selection bias), blinding of participants or personal (performance bias), outcome assessor (detection bias), risk of bias attributed to incomplete outcome data (attrition bias), selective reporting (reporting

bias) or other potential threats.[14] Each is assessed as 'low risk', or 'high risk, or as 'unclear risk', indicating either lack of information or uncertainty over the potential for bias.[14] Disagreements in scoring between the two reviewers were resolved through discussion until consensus was reached.

Statistical Analysis

Data extraction tables were reviewed for study heterogeneity. Through this, between-study variability in participant characteristics, interventions and study design were assessed. Where heterogeneous, a narrative analysis of the results was presented. Where homogeneous, data were pooled for those outcomes using a Mantel-Haenszel approach.[15] For continuous outcomes, a standardised mean difference (SMD) and 95% confidence intervals (Cis) were reported. For dichotomous outcomes, risk ratios (RR) and 95% CIs were presented. All meta-analyses used a random-effect model given the nature of caregiver training interventions to offer flexibility to tailor interventions.[16] Statistical heterogeneity was assessed using the I^2 statistic.

Small sample size publication bias was assessed using funnel plots, when there were a minimum of 10 studies for each outcome.[14] Sensitivity analyses were undertaken for the principal meta-analysis by removing studies with both: high risk of bias for detection bias and those which did not present an *a priori* sample size calculation.

Planned subgroup analyses were:

(A) Patient diagnosis *for example*, musculoskeletal pain versus cancer pain

(B) Type of caregiver intervention (e.g. multicomponent intervention versus single-component intervention; online versus face-to-face interventions).

All analyses were conducted using RevMan (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Assessment of the Quality of Evidence

We assessed the quality of evidence for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.[17] Through this, the certainty of evidence was either increased (upgraded) or decreased (downgraded) against the following five criterion: (1) methodological limitations using the Cochrane Risk of Bias tool (downgraded where there was high risk of bias for three or more items; upgraded where all items demonstrated low risk of bias); (2) indirectness relating to similarity to clinical practice (downgraded where reviewers felt the study design was not generalisable to UK practice; upgraded where study design was generalisable to UK practice); (3) imprecision relating to the number of participants and events (downgraded where outcomes reported less than 300 participants or five events; upgraded where outcomes reported in excess of 450 participants or 20 events); (4) inconsistency in effect estimates across trials for a given analysis (downgraded where the confidence intervals were four-times the magnitude of the effect estimate; upgraded where confidence intervals were two-times the magnitude of the effect estimate); and (5) likelihood of publication bias (downgraded when reviewers observed asymmetry in funnel plot shape; upgraded when reviewers observed symmetry in funnel plot shape).[17]

RESULTS

Search Strategy Results

A summary of the search results is presented in **Figure 1**. A total of 7732 titles and abstracts were reviewed following de-duplication. From these, 30 papers reporting 27 individual studies were eligible and included.

Publication Bias

There were sufficient data to assess small sample size publication bias for two outcomes (pain and depression). As **Figure 2** illustrates, there was moderate evidence of asymmetry for both. The results should therefore be viewed with caution for this potential bias.

Characteristics of included studies

A summary of the 27 included studies is presented in **Table 1**. This included 26 RCTs and one non-RCT.[18] Final follow-up interval ranged from two weeks[19] to 12 months.[20,21] Three studies recruited people with musculoskeletal pain (osteoarthritis of the lower limb or lumbar spine).[20,22,23] Twenty-four studies recruited people with cancer.[18,19,21,24-44] No other disease-group was identified.

In total, 3427 (1399 male/1610 female) care-recipients were included. Mahendran[18] and Hudson[41] did not report the number of care-recipients. Hudson et al[41] did not report the gender of their patient participants. Mean age of the cohorts ranged from 47.4 years[30] to 71.8 years.[23]The number of caregivers recruited was 3361 (873 male/1668 female). de Wit et al[43] did not report the number of caregivers. Gender was not reported in eight trials.[20,21,22,27,35,42,43,44] Mean caregiver age ranged from 42.7 years[30] to 73.8 years.[23]

Twenty-two studies were conducted in the USA,[19-32,34-39,44,45] two studies from Australia,[40,41] and single studies from Singapore,[18] the Netherlands[43] and Norway.[42]

Experimental interventions are summarised in **Supplementary Table 2**. Number of contacts between healthcare professionals and care-recipients/caregivers as part of the interventions ranged from one[34] to 14 contacts.[24] All experimental interventions were designed to provide education and knowledge to the caregiving-dyad to improve symptom self-management. Eleven trial interventions were delivered solely face-to-face.[18,19,20,21,22,23,25,34,35,38,43] Nine employed a psychological element to the

intervention such as cognitive behaviour approaches or psychoeducational interventions.[18,20,22,25,29,30,39,40,41] Three trial experimental interventions were delivered by telephone.[36,39,45] Two trial interventions were delivered by recorded interventions such as DVD, CD materials or a manual.[31,32] Ten trial interventions adopted a blended approach of face-to-face and telephone interventions[24,27,28,29,30,40,41,42] or web-based and telephone calls.[37,44]

Comparators included interventions on self-management which were delivered solely to the care-recipients and not the caregiver in three trials[22,23,26] and no-intervention (usual care) in seven trials.[18,19,21,25,34,40,43] Sixteen trials used a booklet or received general advice rather than the skills-based intervention delivered as part of an 'active' intervention.[20,24,27,28,29,30,31,32,35,36,37,38,41,42,44,45]

Risk of Bias Assessment

A summary of the Cochrane Risk of Bias results is presented in **Table 2**. The included trials presented a high risk of bias for a number of key criteria. Whilst only Mahendran[18] presented with a high risk of bias for random sequence generation, being a non-RCT, only eight trials (30%) reported concealing their allocation.[19,24,25,36,37,40,44,45] No trial blinded their care-recipients or caregivers to the intervention (as would have been impossible given the nature of this 'participatory' intervention). Seven trials (26%) blinded their assessors to group allocation.[19,21,24,36,41,44,45] There was low risk for attrition bias in 13 trials (48%).[21,22,24,29,31,32,34,35,36,37,42,44,45] Selective reporting bias was evident in four trials (15%).[18,39,41,43]

Meta-Analysis

A summary of the meta-analysis results is presented in **Table 3**.

Primary outcome

There was very low-quality (downgraded two levels for risk of bias and imprecision) evidence that caregiver interventions were beneficial for caregiver HRQOL (SMD: 0.26; 95% CI: 0.01 to 0.52; N=231; one trial) in the medium-term. No data were presented to assess this is the longer or shorter-term.

Secondary Outcomes

Caregiver outcomes

There was very low-quality (downgraded two levels for risk of bias and imprecision) evidence that caregiver interventions were beneficial for caregiver general health status (SMD: 0.59; 0.08 to 1.10; N=62; one trial) in the medium-term. There was low- (downgraded two levels for risk of bias and imprecision) to very low-quality evidence (downgraded one level each for risk of bias, imprecision and inconsistency) that caregiver interventions were not beneficial compared to usual care for caregiver anxiety, depression, fatigue or burden (**Table 2**).

Care-recipient outcomes

There was moderate-quality evidence (downgraded one level for risk of bias) that caregiver interventions are effective in reducing care-recipient pain in the short-term (SMD: -0.16; 95% -0.29 to -0.03; N=1344; 11 trials) and low-quality evidence (downgraded two levels for risk of bias and imprecision) that this occurs to a greater effect in the medium-term (SMD: -0.68; 95% CI: -0.99 to -0.38; N=178; one trial). There was no benefit demonstrated at the long-term follow-up (SMD: 0.07; 95% CI: -0.49 to 0.63; N=49; one trial).

There was low-quality evidence (downgraded two levels for risk of bias and imprecision) that caregiver interventions are no more beneficial than usual care in improving patients with chronic pain HRQOL in the short- (SMD: 0.18; 95% CI: -0.27 to 0.64; N=213; two trials), medium (SMD: 0.16; 95% CI: -0.09 to 0.42; N=235; one trial) or long-term (SMD: 0.03; 95% CI: -0.24 to 0.29; N=218; one trial).

There was low (downgraded two levels for risk of bias and imprecision) and very low-quality (downgraded one level each for risk of bias, imprecision and inconsistency) evidence reporting the outcomes of physical disability and physical function (**Table 2**). There was no benefit of caregiver interventions over usual care for physical function in the short- (SMD: 0.16, 95% CI: -0.01 to 0.34; N=485; two trials) or medium-term (SMD: 0.13; 95% CI: -0.40 to 0.66; N=325; two trials). This was mirrored with the assessment of physical disability (**Table 2**). There was low-quality evidence (downgraded two levels for risk of bias and imprecision) that caregiver interventions could improve social functioning compared to usual care in the short- (SMD: 0.20; 95% CI: 0.02 to 0.38; N=485; three trials) and medium-term (SMD: 0.35, 95% CI: 0.10 to 0.61; N=235; one trial).

Care-recipient psychological factors were assessed through four key domains: depression, anxiety, stress, self-efficacy. These outcomes were based on moderate (downgraded one level for risk of bias) and low-quality evidence (downgraded two levels for risk of bias and imprecision) (**Table 2**). There was no evidence that caregiver interventions benefit patients with chronic pain for psychological outcomes compared to usual care (**Table 2**), principally at short- and medium-term follow-ups.

There was very low-quality evidence (downgraded one level each for risk of bias, imprecision and inconsistency) that caregiver interventions are not beneficial over usual care for reducing care-

recipient fatigue either in the short- (SMD: 0.07, 95% CI: -0.13 to 0.26; N=530; five trials) or medium-term (SMD: -0.01, 95% CI: -0.36 to 0.34; N=314; three trials).

There was low-quality evidence (downgraded two levels for risk of bias and imprecision) that caregiver interventions were beneficial for improving care-recipient perceived coping in the short-term (SMD: 0.81; 95% CI: 0.39 to 1.23; N=95; two trials). This benefit was not demonstrated at medium- (SMD: 0.05; 95% CI: -0.20 to 0.31; N=235; one trial) or long-term (SMD: 0.30; 95% CI: -0.20 to 0.62; N=267; two trials).

Subgroup Analysis: Musculoskeletal Pain versus Cancer Pathologies

Two disease groups were identified. Through this, it was possible to undertake a subgroup analysis of outcomes for people with chronic musculoskeletal pain versus chronic cancer pain are presented in **Supplementary Table 3**. The results for people with cancer pain mirror that of the principal analysis with reported benefit for caregiver interventions in pain in the short- (SMD: -0.15, 95% CI: -0.29 to -0.02; N=1225; eight trials) and medium-term (SMD: -0.68, 95% CI: -0.99 to -0.38; N=178; one trial). Similarly, there was a benefit of caregiver interventions for social functioning in the short- (SMD: 0.20; 95% CI: 0.02 to 0.38; N=485; three trials) and medium-term over usual care (SMD: 0.35; 95% CI: 0.10 to 0.61; N=235; one trial). Caregiver interventions were also beneficial to HRQOL (SMD: 0.26, 95% CI: 0.01 to 0.52; N=235; one trial) and general health over usual care (SMD: 0.59; 95% CI: 0.08 to 1.10; N=62; one trial) in the medium-term.

The exceptions to the principal analysis were that caregiver interventions for people with cancer reduced perceived stress in the medium-term (SMD: 0.34; 95% CI: 0.00 to 0.68; N=136; two trials) and physical disability in the long-term (SMD: 0.96; 95% CI: 0.28 to 1.63; N=38; one trial). This was based

on very low-quality evidence (downgraded one level each for risk of bias, imprecision and inconsistency).

When patient-reported outcomes for caregiver interventions were assessed for people with musculoskeletal pain, there was low-quality evidence (downgraded two levels for risk of bias and imprecision) for a benefit in perceived coping for patients allocated to the caregiver interventions compared to usual care both in the short- (SMD: 0.81; 95% CI: 0.39 to 1.23; N=95; two trials) and long-term (SMD: 0.58; 95% CI: 0.01 to 1.15; N=49; one trial). There was low-quality evidence of no benefit of caregiver interventions on outcomes including pain, physical disability, psychological disability or self-efficacy (**Supplementary Table 3**).

Subgroup Analysis: Face-to-Face interventions vs. Online/Telephone/Recorded interventions

It was possible to compare outcomes of face-to-face compared to online/telephone/recorded interventions for eight patient-reported outcomes (**Supplementary Table 4**). The outcomes of both approaches were the same for pain, physical disability, depression, anxiety and fatigue when measured in the short-term. Interventions which were delivered face-to-face demonstrated benefit in medium-term physical function outcomes (SMD: 0.38; 95% CI: 0.12 to 0.64; N=235; one trial) and depression (SMD: -0.39, 95% CI: -0.65 to -0.13; N=235; one trial) compared to online/telephone/recorded interventions which demonstrate no benefit over usual care.

Whilst the outcomes of caregiver interventions were comparable for short-term anxiety, burden and medium-term depression, there was low-quality evidence (downgraded two levels for risk of bias and imprecision) that caregiver interventions delivered face-to-face demonstrated beneficial effects on short-term caregiver depression (SMD: 0.25, 95% CI: 0.01 to 0.50; N=265; two trials) compared to usual care. This benefit was not evident for online/telephone/recorded interventions.

DISCUSSION

Main Findings

To the best of our knowledge, this is the first study to systematically review and quantify the effectiveness of caregiver interventions for people with chronic pain. The evidence is solely based on people with cancer or musculoskeletal-derived chronic pain. The findings suggest caregiver interventions provide short-term benefit to care-recipients in coping. There was very low-quality evidence that caregiver interventions can benefit caregiver general health status and HRQOL. There was no beneficial effect of caregiver interventions on caregiver anxiety, depression, fatigue or caregiver burden. Caregiver interventions did not provide benefit when measured by care-recipient HRQOL, physical function, psychological outcomes or fatigue. The evidence suggests that caregiving interventions are effective in reducing care-recipient pain and improving social function within the first-year post-intervention. Face-to-face interventions may be more beneficial than caregiver interventions which were delivered solely by telephone, online or through recorded interventions such as audio recordings, DVDs or manuals.

Comparison with the Literature

Whilst caregiver interventions may be effective in reducing pain, there is limited evidence that this translates into improved physical function or psychological outcomes. It may be anticipated that with reduced symptoms, care-recipients would have greater capability to be more physically able.[46] Further exploration for this mismatch would be valuable.

Face-to-face interventions demonstrated greater benefit in physical function and depression, with no difference to online/telephone/recorded interventions for all other interventions. Whilst face-to-face interventions may offer a more personal therapeutic alliance between health professional and care-

recipients/caregiver, there are issues regarding scalability of delivery and the convenience which internet-based approaches can offer.[47] Delivering home-based interventions where care-recipients and caregivers are not required to travel to appointments are beneficial, particularly providing care-recipients and caregivers a feeling of independence from formal healthcare services. However, given the heterogeneity in care-recipients/caregiver beliefs relating to pain and its management, ensuring that such interventions are flexible to the needs of participants is important.[48]

There is limited evidence on pain management caregiver programmes for people without cancer pain. Three studies recruited patients with chronic musculoskeletal pain.[20,22,23] All other studies recruited people with cancer pain. No other disease-groups have been previously examined. Whilst cancer and musculoskeletal chronic pain populations share similar symptoms in pain, there are marked differences around health beliefs to movement,[49,50,51] disease progression,[51,52] prognosis[53] and fatigue.[51] Psychologically, whilst both populations may present with depression and anxiety, the basis of these in relation to ongoing healthcare status may differ.[49,51] However, there are also marked differences between these two populations. This is most notable in the relationships and family dynamics between caregivers and individuals with cancer-related chronic pain. In those with cancer-related pain, caregivers frequently experience high levels of emotional distress as they support individuals who they are close to and who are at the end of their lives, often with unplanned health care utilisation or emergency department visits which can increase stress and anxiety.[52,53] Through these differences between cancer and non-cancer associated pain management, further study is warranted to explore the role of caregiver interventions for people with musculoskeletal diseases.

Nine studies employed a psychological element to the intervention such as cognitive behaviour approaches or psychoeducational interventions.[18,20,22,25,29,30,39,40,41] Adopting a psychological principle to underpin an intervention would appear important when interventions are aimed to change

behaviours or health beliefs regarding pain and symptom management.[54] These interventions were education and skills/knowledge programmes rather than behaviour change interventions.[19,20,22] Given that key components to explain positive dyad relationships are based on influencing potential operant conditioning contingencies,[55] a behaviour change intervention may be warranted. Further exploration is a research priority during the development of future caregiver interventions in improving outcomes.

Whilst the majority of interventions were conducted between four to eight weeks.[18,21,23,27,28,29,30,32,36,41,42,44] However, this ranged in time from a one-off intervention[29,37] to as long as the caregiver required to acquire the intervention skills,[35] with Given et al[25] provided a 20-week intervention. There is insufficient evidence to indicate whether there is a substantial difference in outcome, or whether there are differences in the types of outcome generated for these interventions dependant on duration. Whether interventions of longer duration provide greater opportunity for caregivers to acquire mastery of caregiver skills to benefit care-recipients with chronic pain, remains unclear.

The current evidence-base relates to middle-aged care-recipients and caregivers. Only Martire et al[23] investigated care-recipient/caregiver cohorts who had a mean age above 70 years. Caregivers and care-recipients may have different perceptions and capabilities in managing pain.[56] Caregivers who have physical disabilities or cognitive impairment are more frequently seen in older caregiving population.[2] These may have unique perspectives on the caregiving dyad. Further study is therefore warranted to better understand this potential difference in the caregiving dyad for older people with pain compared to the currently studied 'middle-aged' population.

Limitations

This study presents three key limitations. Firstly, the evidence is derived from North European, North American and Australasian cohorts. There remains uncertainty as to whether these findings are transferable to other populations, such as those from southern European countries, Africa, Asia or South America. These populations may have different perspectives to pain and caregiving.[57,58] Such analyses would therefore be valuable to explore whether cultural differences are important in the chronic pain caregiving dyad. Secondly, there remains limited data on caregiver outcomes, with the majority of data presented on patient-reported outcomes. Given that these interventions are dyad interventions, exploring outcomes particularly on burden, would be valuable to better understand the wider implications of these interventions. Finally, the current evidence-base is focused on cancer- and musculoskeletal-derived chronic pain. No studies were identified examining caregiver interventions for people with chronic pain caused by conditions such as inflammatory bowel disease, gastic reflux or ulcers, endometriosis, Lyme diease or headaches. Whilst all may impact on an individual's (and caregiver's) physical and mental health, the management of these through caregiver interventions may (or may not be) different both in the intervention's components and/or outcome. Future study should consider testing caregiver interventions for such patient groups.

CONCLUSIONS

There is low to very-low quality evidence that these have wider effectiveness on physical and psychological wellbeing both on care-recipients with chronic pain and their caregivers. There is moderate to low-quality evidence that caregiver interventions are effective for people with chronic pain, particularly in managing pain symptoms associated with cancer-related pain. There is a paucity of literature examining the effectiveness of caregiver interventions for people with non-cancer related pain such as from musculoskeletal disease. The adoption of caregiver interventions for this population therefore requires further exploration to better understand what interventions can have the greatest

effectiveness for this population who have high, long-term health and social care challenges worldwide.

FIGURE AND TABLE LEGENDS

Figure 1: PRISMA Flow-Chart

Figure 2: Funnel plot for the assessment of publication bias: pain (left) and depression (right)

Table 1: Characteristics of included studies

Table 2: Summary of the assessment of risk of bias

Table 3: Meta-analysis results (Principal Analysis)

Supplementary Table 1: MEDLINE search strategy

Supplementary Table 2: Summary of the interventions (experimental and control) delivered in the included trials

Supplementary Table 3: Meta-analysis results (subgroup for trials recruiting people with cancer or musculoskeletal pain)

Supplementary Table 4: Subgroup analysis by face-to-face vs. online/telephone/recorded delivery approaches

Supplementary File – PRISMA Reporting Checklist

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Figure 1: PRISMA Flow-Chart

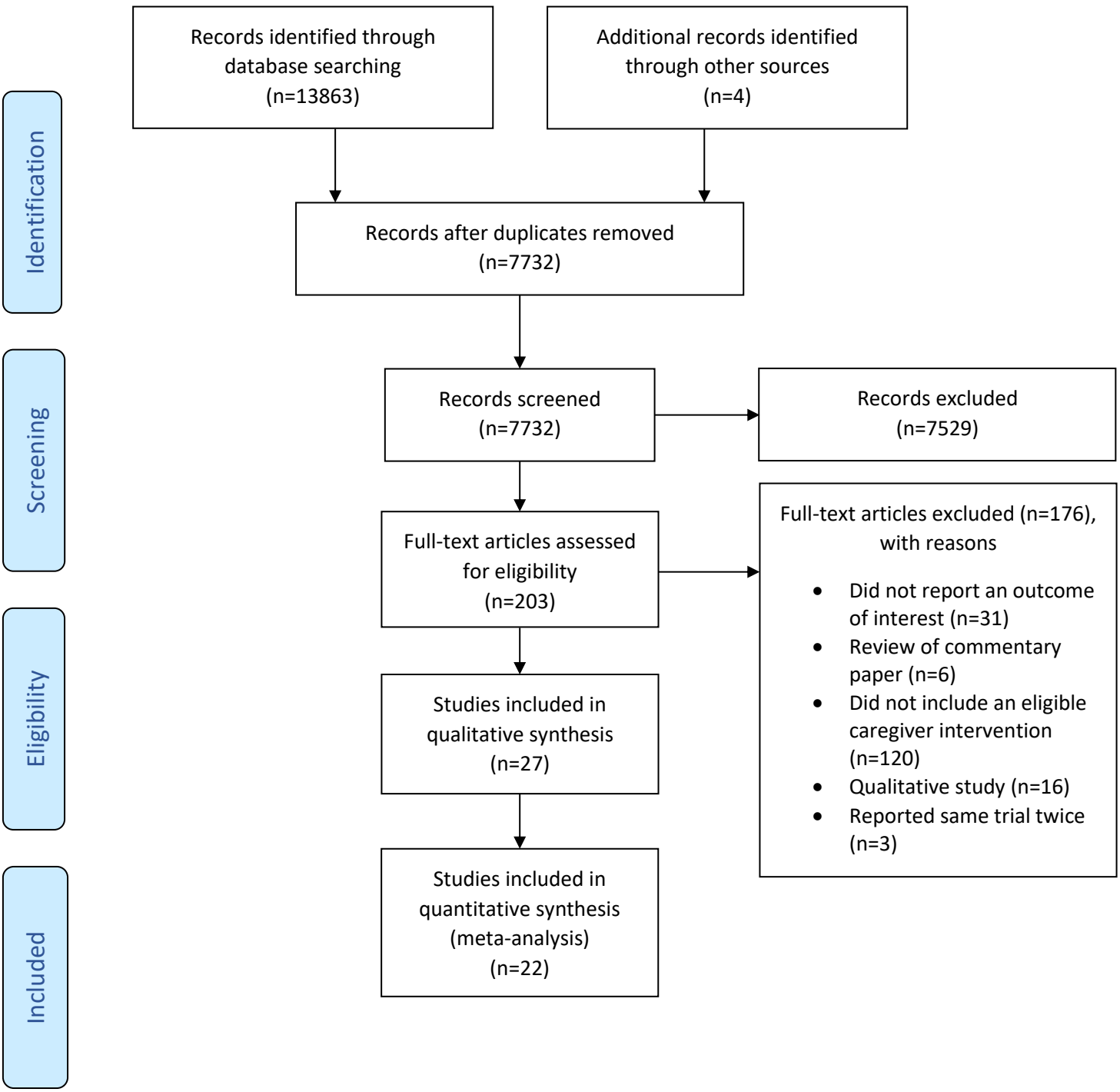

Figure 2: Funnel plot for the assessment of publication bias: pain (left) and depression (right)

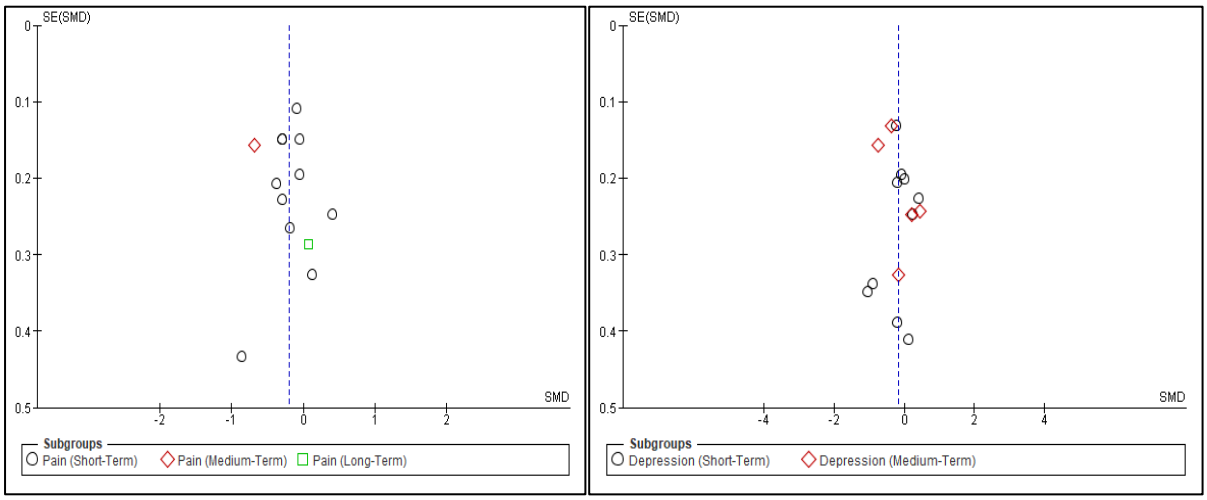

Table 1: Characteristics of included studies

Study	Country of origin	Patient Participants			Caregiver Participants			Diagnosis	Follow-up period
		N	Gender (m/f)	Mean age (yrs) (SD)	N	Gender (m/f)	Mean age (yrs) (SD)		
Badger [29]	USA	71	71/0	67.0 (9.6)	71	4/65	61.1 (10.9)	Prostate cancer	16 weeks
Badger [28]	USA	52	0/52	53	52	21/28	Range: 50, 51, 53	Breast cancer	16 weeks
Badger [30]	USA	80	0/80	47.4 (10.5)	80	37/43	42.7 (12.7)	Breast cancer	16 weeks
Badr [32]	USA	39	10/29	68.2 (10.3)	39	12/27	51.5 (10.2)	Advance lung cancer	8 weeks
Belgacen [35]	USA	67	28/39	59.6 (19.3)	67	N/D	N/D	Haematological cancer	3 months
Budin [39]	USA	249	0/249	53.8 (11.7)	249	122/87	51.6 (12.0)	Breast cancer and their partners	6 months
Collinge [31]	USA	97	23/74	54.7 (11.6)	97	43/54	51.5 (13.6)	Cancer	4 weeks
Given [25]; Kurtz [59]	USA	237	63/172	59.6 (10.5)	237	110/127	55.2 (13.7)	Cancer	20 weeks
Hendrix [38]	USA	119	85/34	N/D	120	20/100	N/D	Haematological malignancy cancer patients	4 weeks
Hudson [40]	Australia	106	49/57	69.1 (13.5)	106	37/69	60.8 (14.0)	Advanced cancer admitted to a community (home-based) palliative care service	8 weeks
Hudson [41]	Australia	N/D	N/D	N/D	298	85/211 (2 unknown)	59.0 (13.9)	Advanced cancer receiving home-based palliative care.	Death
Keefe [20,60]	USA	88	34/54	62.6 (10.1)	88	N/D	N/D	Osteoarthritis Knee	12 months
Keefe [22]	USA	72	33/39	Range: 57.6 to 60.3	72	N/D	N/D	Osteoarthritis Knee	12 weeks

Keefe [19]	USA	78	44/34	60.5	78	30/48	58.5	Advanced cancer	2 weeks
Mahendran [18]	Singapore	N/D	N/D	N/D	97	34/63	N/D	Cancer	4 weeks
Martire [23]	USA	24	0/24	71.8 (7.8)	24	24/0	73.8 (6.8)	Lower limb or lumbar osteoarthritis	6 weeks
Mosher [33,45]	USA	106	50/56	Range: 63.5 (7.7) and 62.0 (8.2)	106	29/77	Range: 56.3 (14) and 56.8 (13)	Small cell or non-small cell lung cancer	6 weeks
Mosher [36]	USA	50	31/19	Range: 58.9 (11.5) and 57.5 (11.7)	50	17/33	Range: 55.3 (12.2) and 52.4 (15.1)	Stage 4 gastrointestinal cancer	5 weeks
Northhouse [21]	USA	235	235/0	63 (9.1)	235	N/D	59 (9.7)	Prostate cancer	12 months
Parker [37]	USA	416	N/D	N/D	446	96/350	Range: 60.1 (12.5) and 59.2 (13.3)	Cancer	Average 18.5 days)
Porter [24]	USA	233	123/110	65.3 (9.5)	233	72/161	59.3 (12.3)	Lung cancer	4 months
Rustøen [42]	Norway	179	92/87	N/D	N/D	N/D	N/D	Bone metastases	6 weeks
Schenker [34]	USA	30	15/15	63 (11)	30	14/16	62 (12)	Advancer pancreatic cancer	3 months
Steel [44]	USA	261	190/71	61 (11)	261	N/D	N/D	Hepatocellular, cholangiocarcinoma, gallbladder, neuroendocrine, pancreatic, or other primary carcinoma that had metastasized to the liver	6 months
Ward [26]	USA	161	64/97	58.5 (11.8)	161	64/97	55.6 (14.1)	Cancer	4 weeks
Wells [27]	USA	64	42/22	53 (14.5)	64	N/D	N/D	Cancer	6 months
Wit [43]	Netherlands	313	117/196	55.5 (12.4)	N/D	N/D	N/D	Cancer	8 weeks

F – female; M – male; N –number; N/D – not documented; SD – standard deviation; USA – United States of America; yrs - years

Table 2: Summary of the assessment of risk of bias

Study	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding of outcome assessors	Incomplete outcome data addressed	Selective reporting bias
Badger [29]	Unclear Risk	High Risk	High Risk	High Risk	Low Risk	Unclear Risk
Badger [28]	Unclear Risk	High Risk	High Risk	High Risk	Unclear Risk	Unclear Risk
Badger [30]	Unclear Risk	High Risk	High Risk	High Risk	Unclear Risk	Unclear Risk
Badr [32]	Unclear Risk	High Risk	High Risk	Unclear Risk	Low Risk	Unclear Risk
Belgacen [35]	Unclear Risk	High Risk	High Risk	High Risk	Low Risk	Unclear Risk
Budin [39]	Low Risk	High Risk	High Risk	High Risk	Unclear Risk	High Risk
Collinge [31]	Unclear Risk	High Risk	High Risk	Unclear Risk	Low Risk	Unclear Risk
Given [25]; Kurtz [59]	Low Risk	Low Risk	High Risk	High Risk	Unclear Risk	Unclear Risk
Hendrix [38]	Low Risk	High Risk	High Risk	High Risk	Unclear Risk	Unclear Risk
Hudson [40]	Low Risk	Low Risk	High Risk	High Risk	Unclear Risk	Unclear Risk
Hudson [41]	Unclear Risk	High Risk	High Risk	Low Risk	High Risk	High Risk
Keefe [20,60]	Unclear Risk	High Risk	High Risk	High Risk	High Risk	Unclear Risk
Keefe [22]	Unclear Risk	High Risk	High Risk	High Risk	Low Risk	Unclear Risk
Keefe [19]	Low Risk	Low Risk	High Risk	Low Risk	Unclear Risk	Unclear Risk
Mahendran [18]	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk
Martire [23]	Unclear Risk	High Risk	High Risk	High Risk	Unclear Risk	Unclear Risk
Mosher [33,45]	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Unclear Risk

Mosher [36]	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Unclear Risk
Northhouse [21]	Unclear Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear Risk
Parker [37]	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Unclear Risk
Porter [24]	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Unclear Risk
Rustøen [42]	Low Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk
Schenker [34]	Low Risk	High Risk	High Risk	Unclear Risk	Low Risk	Low Risk
Steel [44]	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Unclear Risk
Ward [26]	Low Risk	High Risk	High Risk	High Risk	Unclear Risk	Unclear Risk
Wells [27]	Unclear Risk	High Risk	High Risk	High Risk	Unclear Risk	Unclear Risk
Wit [43]	Unclear Risk	High Risk	High Risk	High Risk	Unclear Risk	High Risk

Table 3: Meta-analysis results (Principal Analysis)

Outcome	Time-point	N (Trials)	Std MD (95% CI)	I^2	GRADE Interpretation	Sensitivity Analysis	
						N (Trials)	Std MD (95% CI)
Caregiver Outcomes							
Quality of Life	Medium-Term	231 (1)	0.26 (0.01, 0.52)	NE	Very Low	231 (1)	0.26 (0.01, 0.52)
	Longer-Term	218 (1)	0.14 (-0.13, 0.40)	NE	Very Low	218 (1)	0.14 (-0.13, 0.40)
Anxiety	Short-Term	664 (6)	-0.10 (-0.40, 0.20)	65	Low	106 (1)	-0.15 (-0.53, 0.23)
	Long-Term	70 (1)	0.35 (-0.12, 0.82)	NE	Low	NA	-
Depression	Short-Term	594 (7)	-0.01 (-0.33, 0.30)	67	Very Low	106 (1)	-0.15 (-0.53, 0.23)
	Medium-Term	587 (5)	-0.12 (-0.55, 0.31)	83	Very Low	NA	-
Burden	Short-Term	472 (8)	-0.03 (-0.29, 0.23)	46	Low	233 (3)	-0.15 (-0.51, 0.22)
	Medium-Term	314 (3)	-0.13 (-0.09, 0.65)	90	Low	NA	-
Fatigue	Short-Term	66 (1)	0.00 (-6.85, 6.85)	NE	Very Low	NA	-
	Medium-Term	66 (1)	4.86 (-3.05, 12.77)	NE	Very Low	NA	-
General Health	Medium-Term	62 (1)	0.59 (0.08, 1.10)	NE	Very Low	NA	-
Patient (care-recipient) Outcomes							
Pain	Short-Term	1344 (11)	-0.16 (-0.29,-0.03)	22	Moderate	184 (2)	-0.16 (-0.45, 0.13)
	Medium-Term	178 (1)	-0.68 (-0.99, -0.38)	NE	Low	NA	-
	Long-Term	49 (1)	0.07 (-0.49, 0.63)	NE	Low	NA	-
Quality of Life	Short-Term	213 (2)	0.18 (-0.27, 0.64)	36	Low	NA	-

	Medium-Term	235 (1)	0.16 (-0.09, 0.42)	NE	Low	235 (1)	0.16 (-0.09, 0.42)
	Long-Term	218 (1)	0.03 (-0.24, 0.29)	NE	Low	218 (1)	0.03 (-0.24, 0.29)
Physical Function	Short-Term	485 (2)	0.16 (-0.01, 0.34)	0	Low	NA	-
	Medium-Term	325 (2)	0.13 (-0.40, 0.66)	79	Very Low	NA	-
Physical Disability	Short-Term	215 (4)	0.03 (-0.30, 0.36)	28	Very Low	NA	-
	Long-Term	87 (2)	0.40 (-0.66, 1.46)	83	Very Low	NA	-
Social Functioning	Short-Term	485 (3)	0.20 (0.02, 0.38)	0	Low	NA	-
	Medium-Term	235 (1)	0.35 (0.10, 0.61)	NE	Low	NA	-
Depression	Short-Term	812 (10)	-0.15 (-0.38, 0.08)	58	Moderate	106 (1)	-0.09 (-0.47, 0.29)
	Medium-Term	587 (5)	-0.16 (-0.58, 0.25)	82	Moderate	NA	-
Anxiety	Short-Term	324 (4)	-0.08 (-0.38, 0.23)	46	Low	106 (1)	-0.27 (-0.66, 0.11)
	Medium-Term	70 (1)	0.29 (-0.18, 0.76)	NE	Low	NA	-
Perceived Stress	Short-Term	146 (2)	0.28 (-0.04, 0.61)	0	Low	NA	-
	Medium-Term	136 (2)	0.34 (0.00, 0.68)	0	Low	NA	-
Fatigue	Short-Term	530 (5)	0.07 (-0.13, 0.26)	21	Low	106 (1)	0.24 (-0.14, 0.62)
	Medium-Term	314 (3)	-0.01 (-0.36, 0.34)	54	Low	NA	-
Self-Efficacy	Short-Term	371 (6)	0.28 (-0.03, 0.59)	52	Moderate	156 (2)	-0.03 (-0.34, 0.29)
	Medium-Term	235 (1)	0.01 (-0.25, 0.26)	NE	Low	235 (1)	0.01 (-0.25, 0.26)
	Long-Term	267 (2)	0.04 (-0.30, 0.37)	30	Low	218 (1)	-0.07 (-0.34, 0.20)
Coping	Short-Term	95 (2)	0.81 (0.39, 1.23)	0	Low	NA	-

	Medium-Term	235 (1)	0.05 (-0.20, 0.31)	NE	Low	235 (1)	0.05 (-0.20, 0.31)
	Long-Term	267 (2)	0.30 (-0.20, 0.62)	25	Low	218 (1)	0.21 (-0.06, 0.47)

CI – confidence interval; I^2 – inconsistency value; N – number; NA – not assessed; NE – not estimated; Std MD – standardised mean difference

Supplementary Table 1: MEDLINE search strategy

1. exp Pain/
2. pain*.mp.
3. or/1-2
3. exp Neoplasms/
4. (neoplasm* or malignan* or oncolog* or tumo?r or cancer* or carcinoma).ti,ab.5. exp Arthritis, Rheumatoid/
6. exp Fibromyalgia
7. exp Osteoarthritis
8. exp Musculoskeletal Disease/
9. exp Arthritis/
10. or/3-9
11. Caregivers/
12. (care?giver* or carer* or spouse* or spousal or partner* or significant other).ti,ab.
13. or/6-7
14. (intervention* or educat* or train*).ti,ab.
15. and/3,10,13,14
16. (randomized controlled trial or controlled clinical trial).pt. or (experiment* or control* or random* or blind* or mask* or control* study or groups or assign* or allocate* or interrupted time series).ti,ab.
17. exp animals/
18. humans.sh.
18. 18 not 17
19. and/15,16,18

Supplementary Table 2: Summary of the interventions (experimental and control) delivered in the included trials

Study	Intervention	Comparator
Badger [29]	The 8-week telephone interpersonal counselling (TIP-C) intervention was developed from standard interpersonal psychotherapy (IPT), combined with cancer education. Master's prepared nurse or social worker with psychiatric and oncology expertise delivered the intervention. After the baseline assessment (average of 56 min), sessions averaged 31 min.	The second intervention was an 8-week health education attention condition (HEAC), delivered over the telephone. Participants received written materials from the National Cancer Institute about prostate cancer diagnosis and treatments, and health-related topics such as nutrition during cancer, exercise to decrease fatigue resources for cancer survivors, and quitting smoking. Survivors received weekly telephone calls to review these materials. After the baseline assessment (average of 59 min), sessions averaged 28 min
Badger [28]	Group 1: 8 weekly sessions of health education and their partners received 4 sessions every other week by telephone. Group 2: 8 weekly sessions of one to one counselling by videophone and their partners received 4 sessions every other week (30mins). All sessions lasted approximately 30 min. Written information was provided additionally.	Participants received 8 weekly sessions of one to one counselling by telephone and their partners received 4 sessions every other week (30mins).
Badger [30]	The 8-week telephone interpersonal counselling (TIP-C) intervention was developed from standard interpersonal psychotherapy (IPT), combined with cancer education. A bilingual masters prepared social worker delivered the intervention	All survivors and their SPs received the health education (THE) intervention delivered by two bilingual bicultural paraprofessionals. Adult educational techniques guided the teaching. Standardized educational materials were sent to the participants in Spanish or English before the first session, and these materials were reviewed over the telephone.
Badr [32]	Separate standardized, tailored manuals for patients and caregivers. The manuals were divided into 6 sections. The topics were self-care, stress and coping, symptom management, effective communication, problem solving, and maintaining and enhancing relationships. Patients and	Usual care: consists of standard oncologic care and primary palliative care for the patient from the point of the diagnosis of advanced LC.

	caregivers in the intervention group each received their own tailored manuals and participated together in 6 weekly 60-mins telephone counselling sessions with a trained interventionist who had a masters degree in mental health counselling.	Primary palliative care is provided by the patient's medical oncologist and includes the basic management of pain and other symptoms, including depression and anxiety, as well as basic discussions about the prognosis and goals of treatment. In addition, patients may be referred to the outpatient supportive oncology practice for a specialty palliative care consultation according to need as determined by the treating oncologist
Belgacen [35]	The caregiver educational programme was based on the teaching of care classified into four categories: meal support, nursing care, welfare care, and symptom management. The educational sessions took place in the ward where the patient was undergoing treatment and elsewhere in the hospital during the rest of their stay. The educational process lasted as long as the caregiver needed to acquire the skills to perform care independently.	Not specified
Budin [39]	Group 1: Standard psychological education by video consisted of four phase-specific psychoeducation videos: (a) coping with your diagnosis, (b) recovering from surgery, (c) understanding adjuvant therapy, and (d) your ongoing recovery. Consistent with the theoretical framework, the content of each video was organized under three broad topics: (a) health-relevant information, (b) information on skill development to facilitate effectiveness of coping, and (c) psychosocial support. The objectives of the SE by video intervention were to provide phase specific evidence-based information that addressed concerns unique to both patients with breast cancer and their partners (Hoskins et al., 2001). Group 2: Telephone Counselling (TC) intervention was individualized using a crisis intervention model designed to enhance the patient's and partner's sense of control and mastery over the breast cancer experience and its associated events. The TC intervention protocol consists of four standardized phase-specific TC sessions for each patient and partner. Separate scripts were tailor-made for patients and partners to address the unique phase specific individual needs of patients and partners. The sessions were conducted by a nurse interventionist trained and supervised in individualized TC approaches. Within a framework of providing health-relevant information, skill development, and psychosocial support, the objectives of the TC intervention were to (a) reduce anxiety, (b) shape reality-based appraisals, (c) facilitate	Treatment as usual.

	coping strategies and attainment of support, (d) process information, (e) encourage adaptive behavioural change, (f) promote functional communication, and (g) promote reintegration of a holistic concept of self. Group 3: Standard psych education + telephone counselling provided disease management along with SPE by video and TC as described above. (2) Disease management (DM) was standardized across data collection sites; that is, surgeons, radiologists, and oncologists adhered to evidence-based national treatment protocols for the diagnosis and treatment of breast cancer, thereby ensuring consistency of the DM for the control group and consistency of DM, which was provided to patients in the three intervention groups.	
Collinge [31]	A multilingual 78-mins DVD and 66-page manual were produced for homebased instruction. Content addresses attitudes and communication about touch in cancer, psychological preparation for giving and receiving touch, safety precautions, massage techniques for comfort and relaxation, acupressure for specific cancer-related symptoms, and practice in the home setting. Suggested duration of sessions was 20 mins, but they were told that as little as 5 mins could be beneficial.	Written instructions to read to the patient at least three times per week. Suggested duration of sessions was 20 min, but they were told that as little as 5 min could be beneficial.
Given [25]; Kurtz [59]	A cognitive behavioural approach, based on Bandura's framework. 20 weeks of intervention with 10 contacts (5 in person and 5 by telephone). Delivered to carer by intervention nurse (registered nurse with experience in oncology); focusing on 2 components, prioritizing patient's needs and strategies carers can adopt, and dimensions of burden.	Standard care – unclear what consisted of.
Hendrix [38]	Caregiver training on strategies for managing patients' cancer symptoms, with four major components: prevention of infection, pain control, maintenance of nutrition, and adequate elimination. Tailored to care givers needs. Training lasted 2 to 3 hours and was delivered in one to two sessions, depending on caregiver preference	1 to 2 sessions over 2-3 hours. Provided standard information about healthy lifestyle, community resources for caregiving, including, but not limited to, home health agencies, respite care, and caregiver support services. Tailored to caregivers needs.
Hudson [40]	Psycho-educational intervention for family. Nurse-delivered intervention consisted of two home visits supplemented by a follow-up phone call between the two visits. A caregiver guidebook and audiotape were used to complement the nurse interactions.	Usual Care. Included access to 24-hour phone advice and emergency visits from nurses in addition to pre-scheduled home visits from specialist nurses, doctors, and allied health professionals.

Hudson [41]	Psychoeducational intervention and standard care that incorporated tailored information and resources given to family caregivers to promote psychological well-being. The intervention was delivered in two versions given that in rural and remote areas where, because of limited resources, telephone contact rather than face to face may be more feasible. Intervention 1 consisted of one visit and three phone calls, and intervention two consisted of two visits and two phone calls. For both groups, the first contact was a face-to face visit, and in the latter group, the final contact was also a home visit.	Standard care: Comprised multidisciplinary specialist support for patients with advanced, non-curative disease and their families. Services included an initial assessment, scheduled home visits and access to a health care professional after hours for advice. Specific caregiver support strategies varied within services and were not always systematic or comprehensive
Keefe [20,60]	Spouse-assisted pain coping skills training; Conventional pain coping strategy training with no spouse involvement (all 10-weekly, 2-hour, group sessions). Both pain-coping strategies are grounded in cognitive-behaviour principles, led by psychologist and nurse covering attentive diversion skills, activity-based skills, cognitive coping strategies.	Arthritis education-spousal support control (all 10-weekly, 2-hour sessions). Spouse in attendance and covering education but not with a cognitive behaviour element.
Keefe [22]	Spouse-assisted pain coping skills training; (12-weekly, 2-hour, group sessions). Pain-coping strategies are grounded in cognitive-behaviour principles, led by psychologist and nurse covering attentive diversion skills, activity-based skills, cognitive coping strategies.	12 weekly sessions comprising of Spouse assisted pain coping skills plus exercise session consisting of strengthening and aerobic activities; exercise session alone, or standard care.
Keefe [19]	Patients and their partners in this condition received three face-to-face sessions for training in pain management strategies. The sessions were structured to last for 45 to 60 mins and to be delivered over approximately one to two weeks. Delivered in the patient's home by a registered nurse-level nurse educator knowledgeable about cancer pain and skilled in coping skills training interventions.	Patients and partners in this condition received the routine care provided through their medical outpatient or hospice program.
Mahendran [18]	Pilot psychoeducational support group intervention for family caregivers of cancer patients. "COPE" intervention. Four weekly sessions simultaneously targeting psychoeducation, skills training, and supportive therapy.	Waiting list control
Martire [23]	Group Arthritis Self-Help Course (6-weekly, 2-hour sessions). Trained person (professional or non-professional) delivering arthritis education (coping and management). Each session also had a 20-mins couples' session which augmented the group session with focus on spouse role.	Experimental intervention (6-weekly, 2-hour sessions) attended by the patient but without their husbands and without the 20-mins couples' session.

Mosher [33,45]	Telephone Symptom Management. Participants received instruction in symptom management strategies. Each person was mailed identical handouts detailing major points discussed during the sessions, home practice assignments and a CD with instructions for relaxation exercises. This involved 4x45 mins telephone sessions with both carer and participant.	The primary goal of this intervention was to direct participants to resources for practical and health information and psychosocial services. This involved 4x45 mins telephone sessions with both carer and participant.
Mosher [36]	Participants in both study groups were asked to complete five weekly 50 to 60 mins telephone sessions. Both dyad members participated simultaneously via speakerphone, and all sessions were audio recorded. Dyads in the intervention condition helped create an informational resource on various QoL issues for other patients and caregivers coping with cancer over 5 sessions. Participants used these sessions to create a coping resource for peers.	Dyads in the coping skills condition discussed the same topics as the intervention, but did not help create an informational resource for other patients and caregivers.
Northhouse [21]	Standard clinic care plus a family-based intervention called the FOCUS Program, a supportive-educative intervention. The program consists of 3 x 90-mins home visits and 2 x 30-mins telephone sessions spaced 2 weeks apart and delivered between baseline and 4 months	Control group received standard clinic care at their cancer centre that addressed primarily diagnosis and treatment of patients' disease
Parker [37]	Web-based conferencing/ telephone conferencing regarding patient management. An assigned hospice staff member (usually a nurse) would give a brief report on the patient's condition and identify any concerns for discussion. Family members were encouraged to provide feedback and ask questions before a final plan of care was agreed upon	No involvement in hospice care meetings. Usual care: not documented what this involved.
Porter [24]	14 telephone-based sessions of caregiver-assisted coping skills training (CST) of 45 mins. Involved training in symptom management strategies. Sessions were supplemented with written materials (e.g., handouts), provided to the participants before the sessions, which highlighted the major points discussed in the sessions and detailed home practice assignments. Participants also received a CD (or audiotape) with instructions for progressive muscle relaxation.	Cancer education/ support including the (14 x 45-mins sessions). The primary goal of this intervention was to provide participants with information regarding lung cancer and its treatment in a supportive environment in which patients and caregivers were encouraged to discuss the patient's treatment. Sessions were supplemented with handouts summarizing the major points and listing additional resources (e.g., Web sites and books)
Rustøen [42]	Norwegian version of the PRO-SELF PCP. Nurse-visits in patient's homes in weeks 1, 3 and 6. At the initial session, the nurse identified knowledge deficits to provide knowledge on pain and side effect management, how to use weekly pillbox, communication aids with physicians on	Booklet provided on cancer pain management and diary to record pain. Nurse visits in patients' homes at weeks 1, 3 and 6 and telephone calls at

	pain relief and medication. These were re-enforced and developed in the subsequent sessions. Telephone interviews were conducted at weeks 2, 4 and 5. During these educational support was re-enforced and skill son pain management provided. Patients completed a pain management diary.	Weeks 2, 4 and 5 to re-enforce the use of the diaries.
Schenker [34]	In-person palliative care visits with a specialty-trained palliative care physician. Follow-up intervention visits scheduled monthly for the first three months, and as needed thereafter. More frequent palliative care visits were allowed in the event that additional needs were identified. Visit content included (1) relationships and rapport building; (2) illness understanding, preferences, and concerns; (3) patient and caregiver needs, including physical symptoms, psychological/ emotional distress, and social/financial/caregiver burden; and (4) resources, review, and next steps.	Usual care included standard oncology care. Usual care participants had access to any palliative care service that was deemed appropriate
Steel [44]	A web-based collaborative care intervention. The web-based collaborative care intervention included access to a psychoeducational web site and to a collaborative care coordinator with training and experience with cognitive-behavioural therapy (CBT) and psycho-oncology. The patient had telephone contact with the care coordinator approximately every 2 weeks and face-to-face contact with the care coordinator in the oncology outpatient clinic and/or hospital approximately every 2 months. Frequency of visits increased if required.	Usual care provided by the medical team. if a patient or caregiver scored high on the CES-D or the BPI average pain score, the patient was contacted by a care coordinator and was provided education about the symptoms and referrals to a mental health professional in the patient's community or to the patient's Primary care physician for pharmacological treatment for depression. If the patient scored high on the BPI average pain item, the patient was referred to a pain centre or an expert in symptom management if it was cancer related.
Ward [26]	Solo RIDcancerPAIN + intervention. The intervention was based on the Representational Approach to patient education (Donovan 2007). Patient and significant other received 20-80-minute intervention plus 2 x 5-10 mins follow up calls at 2 weeks and 4 weeks post intervention session. Second arm with Solo RIDcancerPAIN+- intervention but without significant other.	Treatment as usual
Wells [27]	Three treatment arms: a) pain education alone, b) pain education with access to a pain hot line(4 calls over a month), or c) pain education followed by routine provider-initiated	Initial pain management education session for all participants.

	telephone follow-up calls. All patients and their caregivers participated in the pain education program, 20-30 mins in duration.	
Wit [43]	Four study groups were distinguished: (1) a control group without district nursing; (2) an intervention group without district nursing; (3) a control group with district nursing; and (4) an intervention group with district nursing. Intervention: information was provided in a one-to-one setting lasting between 30 and 60 mins. Follow up calls made at 3- and 7-days post-discharge. Intervention was delivered by specialist nurses trained as pain counsellors to educate and instruct patients about pain and pain treatment. The intervention aimed to improve pain knowledge, reporting and help seeking behaviour.	Treatment as usual

Supplementary Table 3: Meta-analysis results (subgroup for trials recruiting people with cancer or musculoskeletal pain)

Outcome	Time-point	N (Trials)	Std MD (95% CI)	I^2	GRADE Interpretation
Caregiver of Patients with Cancer Outcomes					
Quality of Life	Medium-Term	235 (1)	0.26 (0.01, 0.52)	NE	Very Low
	Longer-Term	218 (1)	0.14 (-0.13, 0.40)	NE	Very Low
Anxiety	Short-Term	664 (6)	-0.10 (-0.40, 0.20)	65	Low
	Long-Term	70 (1)	0.35 (-0.12, 0.82)	NE	Low
Depression	Short-Term	594 (7)	-0.01 (-0.33, 0.30)	67	Very Low
	Medium-Term	587 (5)	-0.12 (-0.55, 0.31)	83	Very Low
Burden	Short-Term	448 (7)	-0.03 (-0.31, 0.26)	54	Low
	Medium-Term	314 (3)	-0.13 (-0.90, 0.65)	90	Low
Fatigue	Short-Term	66 (1)	0.00 (-0.48, 0.48)	NE	Very Low
	Medium-Term	66 (1)	0.29 (-0.19, 0.78)	NE	Very Low
General Health	Medium-Term	62 (1)	0.59 (0.08, 1.10)	NE	Very Low
Patients (care-recipients) in Cancer Outcomes					
Pain	Short-Term	1225 (8)	-0.15 (-0.29, -0.02)	25	Moderate
	Medium-Term	178 (1)	-0.68 (-0.99, -0.38)	NE	Low
Quality of Life	Short-Term	213 (2)	0.18 (-0.27, 0.64)	36	Low
	Medium-Term	235 (1)	0.16 (-0.09, 0.42)	NE	Low
	Long-Term	218 (1)	0.03 (-0.24, 0.29)	NE	Low
Physical Function	Short-Term	485 (3)	0.16 (-0.01, 0.34)	0	Low
	Medium-Term	325 (2)	0.13 (-0.40, 0.66)	79	Very Low
Physical Disability	Short-Term	134 (2)	0.09 (-0.40, 0.58)	43	Very Low
	Long-Term	38 (1)	0.96 (0.28, 1.63)	NE	Very Low
Social Functioning	Short-Term	485 (3)	0.20 (0.02, 0.38)	0	Low
	Medium-Term	235 (1)	0.35 (0.10, 0.61)	NE	Low
	Long-Term	218 (1)	-0.07 (-0.34, 0.20)	NE	Low
Depression	Short-Term	788 (9)	-0.16 (-0.41, 0.08)	62	Moderate
	Medium-Term	587 (5)	-0.16 (-0.58, 0.25)	82	Moderate

Anxiety	Short-Term	324 (4)	-0.08 (-0.38, 0.23)	46	Low
	Medium-Term	70 (1)	0.29 (-0.18, 0.78)	NE	Low
Perceived Stress	Short-Term	146 (2)	0.28 (-0.04, 0.61)	0	Low
	Medium-Term	136 (2)	0.34 (0.00, 0.68)	0	Low
Fatigue	Short-Term	530 (5)	0.07 (-0.13, 0.26)	21	Very Low
	Medium-Term	314 (3)	-0.01 (-0.36, 0.34)	54	Very Low
Self-Efficacy	Short-Term	255 (1)	0.11 (-0.13, 0.36)	0	Moderate
	Medium-Term	235 (1)	0.01 (-0.25, 0.26)	NE	Low
Coping	Medium-Term	235 (1)	0.05 (-0.20, 0.31)	NE	Low
	Long-Term	218 (1)	0.21 (-0.06, 0.47)	NE	Low
Caregiver of Patients with Cancer Outcomes					
Quality of Life	Medium-Term	235 (1)	0.26 (0.01, 0.52)	NE	Very Low
	Longer-Term	218 (1)	0.14 (-0.13, 0.40)	NE	Very Low
Anxiety	Short-Term	664 (6)	-0.10 (-0.40, 0.20)	65	Low
	Long-Term	70 (1)	0.35 (-0.12, 0.82)	NE	Low
Depression	Short-Term	594 (7)	-0.01 (-0.33, 0.30)	67	Very Low
	Medium-Term	587 (5)	-0.12 (-0.55, 0.31)	83	Very Low
Burden	Short-Term	448 (7)	-0.03 (-0.31, 0.26)	54	Low
	Medium-Term	314 (3)	-0.13 (-0.90, 0.65)	90	Low
Fatigue	Short-Term	66 (1)	0.00 (-0.48, 0.48)	NE	Very Low
	Medium-Term	66 (1)	0.29 (-0.19, 0.78)	NE	Very Low
General Health	Medium-Term	62 (1)	0.59 (0.08, 1.10)	NE	Very Low
Patients (care-recipients) with Musculoskeletal Pain					
Pain	Short-Term	119 (3)	0.24 (-0.73, 0.25)	41	Moderate
	Long-Term	49 (1)	0.07 (-0.49, 0.63)	NE	Low
Physical Disability	Short-Term	81 (2)	0.09 (-0.83, 0.64)	58	Low
	Long-Term	49 (1)	0.112 (-0.68, 0.44)	NE	Low
Psychological Disability	Short-Term	119 (3)	0.13 (-0.71, 0.45)	57	Low
	Long-Term	49 (1)	0.04 (-0.61, 0.52)	NE	Low
Self-Efficacy	Short-Term	116 (3)	0.61 (-0.06, 1.28)	65	Low
	Long-Term	49 (1)	0.31 (-0.25, 0.87)	NE	Low

Coping	Short-Term	95 (2)	0.81 (0.39, 1.23)	0	Low
	Long-Term	49 (1)	0.58 (0.01, 1.15)	NE	Low

CI – confidence interval; I^2 – inconsistency value; N – number; NA – not assessed; NE – not estimated; Std MD – standardised mean difference

Supplementary Table 4: Subgroup analysis by face-to-face vs. online/telephone/recorded delivery approaches

Outcome	Time-point	Face-to-Face			Online/Telephone/Recorded		
		N (Trials)	Std MD (95% CI)	I^2	N (Trials)	Std MD (95% CI)	I^2
Caregiver of Patients with Cancer Outcomes							
Quality of Life	Medium-Term	235 (1)	0.26 (0.01, 0.52)	NE	NA	-	-
	Longer-Term	218 (1)	0.14 (-0.13, 0.40)	NE	NA	-	-
Anxiety	Short-Term	105 (2)	0.07 (-0.38, 0.53)	19	559	-0.19 (-0.59, 0.21)	76
	Long-Term	NA	-	-	49 (1)	0.07 (-0.49, 0.63)	NE
Depression	Short-Term	265 (2)	0.25 (0.01, 0.50)	0	329 (5)	-0.14 (-0.58, 0.29)	73
	Medium-Term	235 (1)	-0.04 (-0.30, 0.21)	NE	352 (4)	-0.16 (-0.79, 0.48)	87
Burden	Short-Term	107 (2)	-0.10 (-1.00, 0.80)	76	341 (5)	0.03 (-0.26, 0.32)	42
	Medium-Term	NA	-	-	314 (3)	-0.13 (-0.90, 0.65)	90
Fatigue	Short-Term	NA	-	-	66 (1)	0.00 (-0.48, 0.48)	NE
	Medium-Term	NA	-	-	66 (1)	0.29 (-0.19, 0.78)	NE
General Health	Medium-Term	NA	-	-	62 (1)	0.59 (0.08, 1.10)	NE
Patients (care-recipients) in Cancer Outcomes							
Pain	Short-Term	690 (5)	-0.15 (-0.36, 0.07)	48	535 (3)	-0.14 (-0.31, 0.03)	0
	Medium-Term	178 (1)	-0.68 (-0.99, -0.38)	NE	NA	-	-
Quality of Life	Short-Term	213 (2)	0.18 (-0.27, 0.64)	36	NA	-	-
	Medium-Term	235 (1)	0.16 (-0.09, 0.42)	NE	NA	-	-
	Long-Term	218 (1)	0.03 (-0.24, 0.29)	NE	NA	-	-
Physical Function	Short-Term	485 (3)	0.16 (-0.01, 0.34)	0	NA	-	-
	Medium-Term	235 (1)	0.38 (0.12, 0.64)	NE	90 (1)	-0.16 (-0.58, 0.25)	NE
Physical Disability	Short-Term	38 (1)	0.41 (-0.23, 1.06)	NE	96 (1)	-0.10 (-0.50, 0.30)	NE
	Long-Term	NA	-	-	38 (1)	0.96 (0.28, 1.63)	NE
Social Functioning	Short-Term	485 (3)	0.20 (0.02, 0.38)	0	NA	-	-
	Medium-Term	235 (1)	0.35 (0.10, 0.61)	NE	NA	-	-
Depression	Short-Term	364 (3)	-0.17 (-0.37, 0.04)	0	424 (6)	-0.21 (-0.60, 0.19)	75
	Medium-Term	235 (1)	-0.39 (-0.65, -0.13)	NE	352 (4)	-0.08 (-0.69, 0.52)	86
Anxiety	Short-Term	99 (1)	0.22 (-0.17, 0.62)	NE	225 (3)	-0.19 (-0.51, 0.13)	28

	Medium-Term	NA	-	-	70 (1)	0.29 (-0.18, 0.78)	NE
Perceived Stress	Short-Term	NA	-	-	146 (2)	0.28 (-0.04, 0.61)	0
	Medium-Term	NA	-	-	136 (2)	0.34 (0.00, 0.68)	0
Fatigue	Short-Term	183 (1)	0.03 (-0.26, 0.32)	NE	347 (4)	0.09 (-0.19, 0.36)	39
	Medium-Term	NA	-	-	314 (3)	-0.01 (-0.36, 0.34)	54
Self-Efficacy	Short-Term	99 (1)	0.34 (-0.06, 0.73)	NE	156 (2)	-0.03 (-0.34, 0.29)	0
	Medium-Term	235 (1)	0.01 (-0.25, 0.26)	NE	NA	-	-
	Long-Term	218 (1)	-0.07 (-0.34, 0.20)	NE	NA	-	-
Coping	Medium-Term	235 (1)	0.05 (-0.20, 0.31)	NE	NA	-	-
	Long-Term	218 (1)	0.21 (-0.06, 0.47)	NE	NA	-	-

CI – confidence interval; I^2 – inconsistency value; N – number; NA – not assessed; NE – not estimated; Std MD – standardised mean difference

Supplementary File – PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Intro Para 1&2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Intro Para 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods Para 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods; Selection Criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods; Search Strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods; Selection Criteria

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods; Data Extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods; Data Extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods; Methodological Quality Assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods; Data Analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods Data Analysis

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods Quality Assessment and Assessment of GRADE
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods Data Analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results Search Strategy Results & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results; Characteristics of Studies &

			Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results; Methodological Quality
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results, Principal Meta-Analysis
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results, Principal Meta-Analysis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results; Methodological Quality & Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results: Subgroup analyses
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion Para 1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion Para 7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion Para 2-6
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Declarations

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097