

## Home-based physical symptom management for family caregivers: systematic review and meta-analysis

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### Abstract

**Background.** Patients with life-limiting conditions are often cared for at home by family, typically without adequate training to carry out the challenging tasks performed. This systematic review assessed the efficacy of interventions designed to help family caregivers manage pain and other symptoms in adults and children with life-limiting conditions at home. **Methods.** A systematic search was performed on seven databases. A narrative synthesis was conducted, along with a meta-analysis comparing outcomes in those who received an intervention to those who did not, or to pre-intervention scores. **Results.** Eighty-four eligible studies were identified. Significant improvements in cancer patients' pain and fatigue were found compared to patients in the control group and compared to baseline. Cancer patient caregivers receiving an intervention, compared control group caregivers, showed significant improvements in self-efficacy and active coping, and lower avoidant coping. This group also showed significant improvements in burden, self-efficacy, anxiety, and depression, and decreases in avoidant coping pre- to post-intervention. Dementia patients whose caregivers received an intervention showed significantly reduced pain intensity and improvements in quality of life pre- to post-intervention. Caregivers of patients with dementia showed significantly reduced distress pre- to post-intervention. No beneficial effects were found for caregivers of patients with Parkinson's disease or heart failure, although only limited analyses could be performed. **Conclusions.** Interventions targeting family caregivers can improve both patient symptoms and caregiver outcomes, as demonstrated in cancer and dementia care. Future mixed-methods research should collect data from caregiver and patient dyads, identifying key intervention components. There is also need for more studies on caregivers of paediatric patients.

**Keywords:** Family caregivers, Symptom management, Home care, Life limiting condition, Systematic review, Meta-analysis

## **Key Messages**

**What is already known on this topic.** Informal caregivers play a vital role in caring for patients with life-limiting conditions, though research mostly focuses on those caring for adults with cancer.

**What this study adds.** (i) Meta-analysis showed interventions targeting family caregivers of patients with cancer and dementia are efficacious at improving both patient symptoms (e.g., pain, fatigue) and caregiver outcomes (e.g., emotional distress); (ii) A comprehensive review of the outcome domains and outcomes measures used in studies evaluating the efficacy of interventions designed to help family caregivers manage pain and other symptoms in adults and children with life-limiting conditions at home. This will serve as a first-step in developing a core outcome set.

**How this study might affect research, practice or policy.** Key areas for future research include developing and evaluating interventions for young caregivers and parents of paediatric patients, as well as developing a core outcome set for patients and caregivers.

Patients with life-limiting conditions (LLCs) are often cared for at home by family caregivers including spouses, parents, offspring or friends. Home-based care offers several advantages for both caregivers and patients, including increased flexibility, familiarity and comfort, and reduced transportation and financial burden. It also comes with its challenges however, as compared to the education and training formal caregivers such as nurses receive, family caregivers rarely receive adequate training or support to carry out the often complex and challenging tasks required of them [1, 2]. Tasks including assessing and managing symptoms and administering medication can be difficult for caregivers [3], who may be balancing this care alongside their own health needs and/or emotional or psychological difficulties that come with the prospect of a dying relative or friend [4]. Providing care for a family member is often a lonely endeavour [5] associated with considerable burden, including demand on time and resources, physical and mental exhaustion, and health deterioration [6]. When caregivers are adequately supported to perform their caregiving role, caregiving can be viewed as a positive experience however [7].

Numerous studies have developed and evaluated interventions to support the needs of family caregivers, although fewer have examined their efficacy in helping caregivers manage patient symptoms at home. This is important as complex care has increasingly moved from hospitals to homes, leading to a rise in patient self-management and family care [8]. Recent reviews show interventions aimed at caregivers have significant benefits, including improvements in quality of life, depression and anxiety in both caregivers [9] and patients [10]. Interventions have been developed specifically to support caregivers with management of pain medications, with one review suggesting they may have positive impacts on family caregiver knowledge and self-efficacy, even though no effect on patient pain outcomes was found [11]. A meta-analysis of caregiver interventions for individuals with cancer and non-cancer-related chronic pain reported moderate-quality evidence that such interventions were effective in

reducing patient pain in the short-term, and very low-quality evidence they were beneficial for caregiver health-related quality of life [12].

While previous reviews of interventions for family caregivers of patients with LLCs have generally reported positive outcomes for both patient symptom management and caregiver wellbeing, most have specifically focused on caregiving of adult cancer patients. Little is known about the efficacy of interventions developed for caregivers of patients with different LLCs irrespective of age. The outcomes of interventions targeting caregivers should be insightful and, to some extent, applicable across various conditions and patient age. This is because LLCs often share significant characteristics and requirements for care [13]. This systematic review focused on interventions developed and tested to support family caregivers manage pain and other physical symptoms in adult and paediatric patients with any LLC when caring for them at home. It addressed the following questions:

- 1) Are interventions for family caregivers of patients with LLCs efficacious at improving patients' pain and other physical symptoms?
- 2) Are interventions for family caregivers of patients with LLCs efficacious at improving caregiver outcomes such as coping or self-efficacy?

### **Method**

This systematic review was conducted in accordance with guidelines from the Cochrane Collaboration [14], followed PRISMA reporting guidelines [15] and the protocol was registered on PROSPERO (ID: CRD42020169950 [16]). While there were no major protocol deviations, we used the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group [17] to assess methodological quality of single-group studies, which was not stated in the protocol. This review forms part of a large multi-centre study aiming to improve at-home paediatric palliative care pain management (PARAMOUNT) [18, 19].

### **Literature Search**

Searches of the Cochrane Library (title, abstract, keyword), Embase (title), MEDLINE, CINHALL, PsycINFO (title), ProQuest Dissertations & Theses Database (main search field), and OpenGrey (main search field) were conducted from database inception to 27<sup>th</sup> November 2023. The search strategy is presented in Supplementary Material 1. Relevant keywords were combined from four blocks of search terms that related to: i) life-limiting conditions, ii) informal caregivers, iii) interventions, and iv) symptoms. Secondary searches included checking the reference list of all included studies and related reviews.

### **Inclusion Criteria**

Studies were eligible for inclusion if they met the following criteria:

1. Included family caregivers of patients with any condition, illness or disease considered life-limiting or life threatening. All patient and carer age ranges were eligible.
2. Described an intervention in any format (delivered by a healthcare professional face to face, in person or online; paper-based or online) that includes support for carers to carry out tasks relating to physical symptom management in the home. (Interventions were operationalised as any task intended to manage physical symptoms, such as assessing levels of pain and other symptoms, administering medications, performing nursing duties, facilitating physical interventions such as physiotherapy and repositioning, or facilitating psychological interventions such as breathing exercises, relaxation strategies and others).
3. Available in English language.

In this review ‘life-limiting’ was considered any condition that has the potential to shorten a person’s life [20]. ‘Home-based’ was considered any situation in which the patient is cared for either in their own place of residence or the residence of an informal caregiver. Qualitative, quantitative and mixed-method studies were all eligible for inclusion. Studies only including healthcare professionals were not eligible, neither were interventions exclusively providing a

health service, rather than an aim to bring about a change in carer behaviour. Studies featuring a controlled or uncontrolled (pre-post) design were eligible for inclusion. PhD theses were eligible, but Masters' theses and conference presentations were not. All potentially relevant articles were reviewed by DES or SH and checked by CL.

### **Data Extraction**

Data and information were extracted using standardised forms. Table S1 presents characteristics of studies included in the systematic review. Table S2 presents a description of the intervention used in each study and comments on the Template for Intervention Description and Replication (TIDieR) review and results [21]. Information in Tables S1 and S2 were extracted by SH and checked by DES, or extracted by DES and checked by CL. Raw numerical outcome data was extracted by DES and checked by SH or CL.

### **Study Quality Assessment**

The quality of randomised controlled trials were assessed via the Cochrane Risk of Bias 2 (RoB2) tool [22], and single-group studies were assessed using the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group [17]. For both tools, studies were assessed by two authors and checked by a third author. Full details are provided in Supplementary Material 2

### **Outcome Variables and their psychometric properties**

To explore outcome heterogeneity, a list of patient and caregiver outcome domains and measures used in the studies, along with any psychometric properties reported, was extracted by SH, DES or ELS, with details provided in Table S3.

### **Data-analysis and Synthesis**

The Cochrane Handbook for Systematic Reviews and Interventions was followed [14]. For between-group comparisons, Hedges'  $g$  effect sizes (standardized mean difference) were computed using group means and standard deviations in Comprehensive Meta-Analysis 3.0

[23]. Random-effects models were used which assumes the average effect size varies between studies and therefore heterogeneity is to be expected [24, 25]. Cochrane's Q and the  $I^2$  statistic were used to assess study heterogeneity. Cochrane's Q is the traditional test for statistical heterogeneity, with a significant result indicative of heterogeneity. The  $I^2$  statistic describes the percentage of variability in effect estimates due to heterogeneity as opposed to sampling error [26]. The Cochrane Collaboration suggest as a rough guide 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity [14]. However, uncertainty in  $I^2$  is considerable when the number of studies is small. Several studies included more than one intervention group. As it is not appropriate to include data from the same control group more than once in an analysis, in such instances the meta-analysis was conducted separately with data from each intervention group along with the control group.

For pre- versus post-intervention comparisons, Cohen's  $d$  effect sizes (standardized mean difference) were computed based on study means and the average standard deviations [27, 28]. Random-effects models were used to compute average effect sizes using ESCI [27]. An unbiased estimate of the population effect size, referred to as  $d_{\text{unb}}$ , was calculated [27]. As  $d$  overestimates the population effect size, especially for smaller sample sizes, the adjustment is advocated [27, 29, 30]. Cochrane's Q and the  $I^2$  statistic were used to assess study heterogeneity.

Analyses were stratified by disease to capture the similarities of specific diseases in their symptoms, progression, and prognosis, along with similarities in care requirements and associated physical and emotional caregiver burden. We were unable to further stratify analyses by caregiver type because many studies recruited informal caregivers who had a range of different relationships with the patients, with data only provided as an overall group.

## Results

## Search Results

A PRISMA 2020 [15] flow diagram depicting the literature search and study selection process is shown in Figure 1. From an initial identification of 24,346 records, 84 studies were eligible for inclusion. Additional articles reporting secondary data or further analyses were also identified and used for study extraction where relevant (five interventions published data across multiple articles).

## Summary of Identified Studies

Characteristics of the 84 eligible studies are shown in Table S1. Full extracted study details are available on the Open Science Framework (OSF)[31] (<http://tinyurl.com/nc3cjz79>). Fifty-eight studies were conducted in the USA (one of which was also include a site in Canada), three in Hong Kong, Colombia and India, two in Iran, and one study each was conducted in Australia, Colombia, Demark, France, Indonesia, Ireland, Italy, Malawi, the Republic of Korea, Singapore, Sweden, Switzerland, Taiwan, Turkey, Uganda, and the United Kingdom. Seventy-eight studies recruited caregivers of adult patients, of which 58 studies included a patient population with a type of cancer, four studies patients with dementia, four studies patients with heart failure, two studies patients with idiopathic pulmonary fibrosis, two studies with patients with Parkinson’s disease, and one study each including patients with end stage renal disease, HIV/AIDS, stroke, patients who underwent lung resection surgery, and five studies recruiting patients with mixed life limiting diseases (one of which recruited frail older adults with serious illness, but did not provide further details). Six studies recruited caregivers of paediatric patients, including four studies with children with sickle cell disease, one study with children scheduled for cardiac surgery, and one study with children with coagulation factor deficiencies. Thirty-eight studies recruited a mixed sample of informal caregivers, 22 studies specifically stated family caregivers were recruited, 10 studies recruited partners, two studies recruited

spouses, two studies stated the majority of caregivers were spouses or partners, two studies specifically stated recruiting parents, and for eight studies the caregivers were not clearly stated.

### **Methodological Quality and Intervention Reporting**

Fifty-seven RCTs were assessed via the RoB2 tool [22]. Traffic light plots of the domain-level judgements for each individual study are provided in Figure 2. Twenty-seven non-RCTs studies were assessed using the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group [17], with assessors' agreed judgments presented in Table S4. Full results are provided in Supplementary Material 2. Intervention reporting was considered via the TIDieR checklist [21] and is summarised in Table S2. All published reports provided a clear rationale for the intervention implemented, and key details such as number of sessions and intervention locations were frequently reported. Several common problems were identified, however. Full intervention materials were provided or accessible in very few publications, making replication difficult without collaboration with the original researchers. Furthermore, many publications did not specifically state whether the intervention was modified in way during the course of the study, or whether assessments of intervention fidelity or adherence were planned or actually conducted.

### **Outcome Domains and Outcome Measures and their Psychometric Properties**

A wide range of outcomes were assessed for both patients and caregivers, often via established and validated measures (see OSF [31]: <http://tinyurl.com/nc3cjz79>). For patient outcomes, 13 outcome domains were assessed (e.g., emotional functioning, quality of life), including 76 sub-domains (e.g., anxiety, depression) assessed via numerous outcome measures (ranging from 56 measures of emotional functioning, to 1 measure each of financial well-being and preferred place of care). For caregiver outcomes, 11 outcome domains were assessed (e.g., caregiving experience and attitudes, interpersonal functioning), including 53 sub-domains (e.g., self-efficacy, burden) also assessed via numerous outcome measures (ranging from 53 measures

of emotional functioning to 1 measure each of physical well-being, patient pain, preferred place of care and spiritual well-being). It is notable that across patients and caregivers certain potentially important domains were rarely assessed, including spiritual well-being and financial well-being. Tree charts depicting caregiver and patient domains and sub-domains are shown in Supplementary Figures 1 and 2 respectively. Researchers often provided rationale for their choice of specific outcome domains and measures. Table S3 provides the reported psychometric properties of the outcome measures used in each study as computed on the specific samples recruited. Many studies did not compute and report psychometric properties, although when performed was most frequently internal consistency via Cronbach's alpha. While internal consistency was acceptable or better in many cases, several studies reported Cronbach's alpha values  $<.70$ , indicating questionable reliability. Test-retest reliability was less commonly assessed, although most would be considered good or better ( $<.70$ ).

### **Narrative Review Summary**

A narrative review providing a summary of the 84 studies is provided on the OSF [31] (<http://tinyurl.com/nc3cjz79>). Interventions varied widely in their aims and design, although most reported one or more statistically significant beneficial outcomes. Many interventions were aimed at caregivers caring for adult patients with cancer and which report beneficial outcomes for patients and caregivers, although individual studies also typically report numerous outcomes which did not show statistically significant improvements. Fewer interventions were aimed at caregivers of patients with other medical conditions, although at least some benefits have been reported by caregivers or patients with dementia, AIDS/HIV, end stage renal failure, stroke, Parkinson's disease, and idiopathic pulmonary fibrosis. Only six studies provided interventions to support informal caregivers of paediatric patients with LLCs. One reported significant increases in knowledge and attitudes towards pain medication from pre- to post-intervention in parents managing pain after their child's cardiac surgery [32]. Another reported

significant reduction in caregiver burden and improvements in social adjustment were reported by caregivers in the intervention group compared to caregivers in the control group, along with significant decreases in patient acute pain and bleeds [33]. The remaining four studies explored interventions for children with sickle cell disease, all of which reported some positive outcomes [34-37].

### **Meta-Analyses of Patient Outcomes**

#### **Within-group Analyses**

Statistical analyses for within-groups analyses are provided in Table S5 and overall pooled effect sizes in Figure 3. Full written analyses are provided in Supplementary Material 3, and individual forest plots in Supplementary Figure 3. The only significant effects were for cancer and dementia populations. Cancer patients whose caregivers received an intervention reported significant improvements in pain and fatigue pre- to post-intervention. Cancer patients whose caregivers were allocated to a control group also showed significant reductions in pain pre- to post-intervention, but this was only after a sensitivity analysis removed one study with a large effect size that could be considered an outlier and should be interpreted with caution. Caregivers of cancer patients receiving an intervention showed significant improvements pre- to post-intervention in burden, self-efficacy, anxiety and depression, and decreases in avoidant coping. The improvement in self-efficacy was no longer statistically significant however after a sensitivity analysis was performed removing one study with a large effect size that could be considered an outlier. Dementia patients whose caregivers received an intervention showed significantly reduced pain intensity and improvements in quality of life from pre- to post-intervention. Caregivers of patients with dementia showed significantly reduced distress from pre- to post-intervention.

#### **Between-groups Analyses – Patient Outcomes**

Full statistical results are presented in Table S6, overall pooled effect sizes in Figure 4, and forest plots for individual analyses in Supplementary Figure 4.

**Cancer – Patient-reported pain and fatigue outcomes.** Six studies provided data comparing pain outcomes in patients whose caregivers received an intervention to patients whose caregivers were in a control group [38-43]. Patient pain intensity was significantly lower in the intervention group than the control group (Hedges'  $g = -0.421$  (95% CI = -0.783, -0.059),  $p < .023$ ). A sensitivity analysis was conducted removing studies which provided attentional control or enhanced treatment-as-usual comparison conditions [41-43], with the results remaining significant ( $g = -0.404$  (95% CI = -0.709, -0.098),  $p = .010$ ).

Four studies provided data comparing fatigue outcomes in patients whose caregivers received an intervention to patients whose caregivers were in a control group [39, 42-44], one of which randomised patients and caregivers to either reflexology or meditative practice intervention groups [44]. Patients in the intervention group reported significantly lower fatigue post-intervention than patients in the control group when data was included from the reflexology group ( $g = -0.278$  (95% CI = -0.466, -0.091),  $p = .004$ ), and meditative practice group ( $g = -0.232$  (95% CI = -0.421, -0.044),  $p = .016$ ).

### **Between-groups Analyses – Caregiver Outcomes**

**Cancer – Caregiver burden.** Five studies provided burden data for caregivers of cancer patients who received an intervention compared to caregivers in a control group [39, 41, 42, 45, 46], one of which included reflexology and meditative practice intervention groups [46]. No significant difference was found in caregiver burden post-intervention between intervention and control groups, either when data was included from the reflexology group ( $g = -0.286$  (95% CI = -0.748, 0.176),  $p = .225$ ) or the meditative practice group ( $g = -0.309$  (95% CI = -0.763, 0.145),  $p = .182$ ). The analyses were repeated removing studies which included control groups featuring a sixty minute reading session to the patient [42] or enhanced treatment-as-usual [41].

The results remained non-significant when data was included from the reflexology group ( $g = -0.278$  (95% CI = -1.226, 0.671),  $p = .566$ ) or the meditative practice group ( $g = -0.316$  (95% CI = -1.230, 0.598),  $p = .498$ ).

**Cancer – Caregiver self-efficacy.** Six studies provided self-efficacy data for caregivers of cancer patients who received an intervention compared to caregivers of cancer patients who received usual care [40, 41, 47-50], one of which included extensive FOCUS and brief FOCUS intervention groups [49]. With data from the extensive FOCUS group included, caregivers receiving the intervention reported significantly greater self-efficacy post-intervention compared to caregivers in the usual care condition ( $g = 0.301$  (95% CI = 0.036, 0.565),  $p = .026$ ). No significant effect was found when data from brief FOCUS group was included [49] ( $g = 0.289$  (95% CI = -0.017, 0.595),  $p = .064$ ).

These analyses were repeated excluding one study which included an enhanced treatment-as-usual control condition [41]. The result remained significant when including the extensive FOCUS group ( $g = 0.378$  (95% CI = 0.025, 0.732),  $p = .036$ ), and non-significant when including the brief FOCUS group ( $g = 0.365$  (95% CI = -0.048, 0.777),  $p = .083$ ). The analysis was repeated with data from three studies recruiting patients with prostate cancer specifically [47, 48, 50], with no significant difference found between groups ( $g = 0.356$  (95% CI = -0.086, 0.798),  $p = .114$ ).

**Cancer – Caregiver anxiety.** Five studies provided anxiety data for caregivers of cancer patients who received an intervention compared to caregivers of cancer patients who received usual care [41, 45-47, 51]. No significant difference was found in caregiver anxiety post-intervention between caregivers receiving interventions and those in a control group, either when data from the reflexology group ( $g = 0.105$  (95% CI = -0.260, 0.470),  $p = .572$ ) or the meditative practice group ( $g = 0.072$  (95% CI = -0.269, 0.413),  $p = .679$ ) was included from one study [46]. The analyses were repeated removing one study which included an enhanced

treatment-as-usual control condition [41]. The results remained non-significant when data was included from the reflexology group ( $g = 0.268$  (95% CI = -0.068, 0.604),  $p = .118$ ) or the meditative practice group ( $g = 0.226$  (95% CI = -0.104, 0.556),  $p = .180$ ).

**Cancer – Caregiver depression.** Six studies provided depression data for caregivers of cancer patients who received an intervention compared to caregivers of cancer patients who received usual care [41, 45-47, 51, 52]. No significant difference was found in caregiver depression post-intervention between caregivers receiving interventions and those in a control group, either when data from the reflexology group ( $g = 0.002$  (95% CI = -0.289, 0.292),  $p = .992$ ) or the meditative practice group ( $g = -0.108$  (95% CI = -0.300, 0.084),  $p = .270$ ) was included [46]. The analyses were repeated removing one study which included an enhanced treatment-as-usual control condition [41]. The results remained non-significant when data was included from the reflexology group ( $g = 0.081$  (95% CI = -0.254, 0.416),  $p = .636$ ) or the meditative practice group ( $g = -0.034$  (95% CI = -0.283, 0.215),  $p = .789$ ).

**Cancer – Caregiver coping.** Three studies provided data for caregivers of cancer patients who received an intervention compared to caregivers of cancer patients who received usual care [49, 50, 53], one of which included extensive FOCUS and brief FOCUS interventions [49]. Significantly higher active coping was reported by caregivers in the intervention group than the usual care group when data was included from the extensive FOCUS group ( $g = 0.214$  (95% CI = 0.054, 0.374),  $p = .009$ ) and brief FOCUS group ( $g = 0.249$  (95% CI = 0.088, 0.409),  $p = .002$ ). Analysis with data from the extensive FOCUS group included revealed significantly lower avoidant coping reported by caregivers in the intervention group than the usual care group ( $g = -0.215$  (95% CI = -0.405, -0.024),  $p = .027$ ). When data from the brief FOCUS group was included, no significant difference was found ( $g = -0.080$  (95% CI = -0.241, 0.080),  $p = .325$ ).

**Heart failure.** Two studies provided data for caregivers who received an intervention compared to caregivers who received usual care [54, 55]. No significant difference was found

between the intervention and usual care conditions for anxiety ( $g = 0.170$  (95% CI = -0.181, 0.521),  $p = .342$ ), depression ( $g = 0.036$  (95% CI = -0.315, 0.386),  $p = .841$ ), burden (stress) ( $g = -0.095$  (95% CI = -0.433, 0.243),  $p = .582$ ), or quality of life ( $g = 0.211$  (95% CI = -0.316, 0.738),  $p = .433$ ).

## Discussion

Interventions targeting family caregivers can improve both patient symptoms and caregiver outcomes. Cancer patients whose caregivers received an intervention reported significantly lower pain and fatigue post-intervention compared to patients whose caregivers were allocated to a usual care control group with small to medium effect sizes, and also compared to pre-intervention scores with small effect sizes. Caregivers of cancer patients receiving an intervention reported significantly greater self-efficacy and active coping, and significantly lower avoidant coping, post-intervention compared to caregivers allocated to a usual care condition. Caregivers receiving an intervention also reported significant increases in self-efficacy (although this effect was no longer statistically significant after a sensitivity analysis was performed), and significant decreases in caregiver burden, anxiety, depression and avoidant coping, pre- to post-intervention. These results were associated with small effect sizes and align with previous reviews which report a range of beneficial outcomes for caregivers (e.g., [10, 11, 56-58]), although former reviews assessing patient outcomes produced mixed results and conclusions (e.g., [12, 59, 60]).

Dementia patients whose caregivers received an intervention experienced significant reduction in pain intensity and improvements in quality of life post-intervention with medium effect sizes. Additionally, caregivers of these patients reported significantly less distress post-intervention with a medium effect size. These preliminary results are promising considering the high prevalence of pain in individuals with dementia living in the community and its impact on both patients and caregivers [61]. Indeed, family members wish for more involvement in pain

management, but fear analgesics' side effects (61). It is crucial to develop pain management interventions for patients with dementia, facilitated by caregivers [62]. Most current research on pain evaluation and management in people with dementia focuses on those in advanced stages of the disease residing in long-term care facilities however [63], and as such we were able to conduct only a few analyses.

With appropriate clinical support, family caregivers can assist in the management of patient pain and other symptoms at home. While meta-analyses did not show significant improvements for caregivers for patients with Parkinson's disease or heart failure, only limited analyses could be conducted on data from a small number of studies. Inspection of individual studies does show, in certain instances, beneficial outcomes in patients with Parkinson's disease and their caregivers [64] and patients with heart disease and their caregivers [65], although not in all studies [54, 66, 67]. Beneficial outcomes have also been reported in individual studies exploring interventions for other LLCs that we were unable to meta-analyse, including for example stroke [68], HIV/AIDS [69], and end-stage renal disease [70]. Overall, these findings are especially important as, due in part to rapidly aging populations, many Western countries aim to meet the needs of long-term care via informal/family caregivers [71]. Many individuals who are dying also express a wish to die at home [72]. Appropriate support is therefore vital for the patient. As family caregivers are not professionally trained however, they may experience clinically significant levels of distress and impairments in quality of life [73], and associations between caregiver distress and patient outcomes are frequently reported (e.g., [74-76]).

Despite an increasing prevalence of LLCs in children and adolescents (67), only six studies in this review involved interventions targeting caregivers of paediatric patients. Although some positive outcomes were reported in all studies, it was not possible to perform any meta-analyses. Pain is a common symptom reported in children with LLCs, management of which is essential [77]. A recent review [19, 78] explored barriers and facilitators of paediatric

pain and other symptom management at end of life, and providing medication was viewed as helpful by family caregivers in improving or managing the child's symptoms. Barriers included inadequate assistance with administering or managing treatment, and treatment side effects.

Additional fears when caring for their child at home included failure to control symptoms such as pain, or potentially making their child worse if they gave too much medication. Symptom management was facilitated when parents received information, advice or education from healthcare professionals or disease-specific organisations. Overall, it was concluded families would benefit from increased education and training, along with social and practical support.

Methodological quality assessment of the reviewed studies revealed several important limitations. First, not all studies reported following an intervention development framework such as the Medical Research Council's framework for the development and evaluation of complex interventions [79, 80]. Second, while interventions were well-described in most reports, access to the actual intervention material such as treatment manuals, websites, videos or audio recordings were not provided. Full details are necessary to comprehend, replicate, and expand upon the reported interventions [81, 82]. Third, not all studies collected data at multiple follow-up points. While most studies provided evidence for some beneficial patient or caregiver outcomes following the intervention, it is important to ascertain whether these are maintained across time. Fourth, the use of heterogeneous outcomes across interventions can lead to research waste, restricting the comparison and combination of results in meta-analyses [83, 84]. The development of a core outcome set for caregivers is now timely, and this systematic review provides a comprehensive foundation of outcome domains and measures used to date [85]. Certain outcomes such as quality of life and self-esteem were frequently assessed by studies, although other important outcomes such as spiritual well-being, financial functioning and even intervention feedback were much less commonly assessed. Furthermore, while most studies used validated outcome measures with established psychometric properties, they often failed to report specific properties like Cronbach's alpha. We recommend that all studies—particularly

those using modified versions of established measures or bespoke outcome measures—should report psychometric properties as standard practice.

**Strengths and Limitations.** Strengths of this review include the breadth of focus on all life-limiting conditions and the inclusion of informal caregivers of both adult and paediatric patients. Additionally, this review included both RCTs and observational studies, enabling us to comment on both the effectiveness and efficacy of interventions respectively. RCTs with a low risk of bias are undoubtedly the most methodologically robust design for evaluating health interventions due to random allocation and causal inference. Meta-analysis of RCTs is vital but limited by strict patient selection criteria, generally short follow-ups, and high costs for the identification of rare events. Non-randomised studies of interventions (NRSIs) may better represent real-world clinical practice and can complement or replace RCTs, especially when RCTs are impractical or unethical. Both RCTs and NRSIs are valuable, and efforts exist to integrate them to enhance evidence certainty (e.g., [86-89]). Unlike other recent reviews (e.g., [9, 10, 57, 58, 90, 91]), this review provides a comprehensive list of patient and caregiver outcome domains and measures, including their psychometric properties. This represents a crucial first step toward developing a core outcome set. A limitation of this review is that many of the meta-analyses conducted were based on a small number of studies, many of which showed high statistical heterogeneity. While we acknowledge the limitations of such analyses which warrant caution in their interpretation, we believe it is important to perform and report meta-analyses where they are conceptually and theoretically meaningful.

**Future Research.** Research is needed to elucidate which individual components of a successful intervention are the most important in terms of overall observed effects, as it is possible that time-consuming and expensive components may contribute very little to the beneficial outcomes observed [92]. Several different approaches may help address this. Involving patients in intervention design and development is crucial for identifying appropriate

research questions and assessment outcomes, and we suggest including family caregivers as well wherever possible. [93, 94]. Furthermore, following a framework such as the multiphase optimization strategy (MOST) would allow researchers to evaluate and optimise their interventions [92, 95]; none of the interventions described in the present review reported following a framework such as MOST. Many interventions include ‘bundled’ content, which is typically compared to a comparator in an RCT to determine overall efficacy. Such an approach cannot definitively guide subsequent steps to improve the effectiveness, efficiency, economy, or scalability of the intervention [95].

Young carers are increasingly included in caregiving tasks [96] which is perceived as challenging and complex [97]. This review did not find any interventions specifically targeted to young people however, which is a critical area for future research. Additionally, to develop, evaluate and implement interventions that address the complex network of direct and indirect factors impacting the health and well-being of caregivers and patients, future research needs to be guided by caregiving theoretical frameworks [98, 99]. Regardless of whether the primary goal is to improve patient symptoms or caregiver coping, we recommend outcome measures for both patients and caregivers are standardized. A reciprocal relationship exists between the wellbeing of patients with LLCs and the wellbeing of their family caregivers (e.g., [100, 101]). We also recommend more studies add qualitative components to their intervention evaluations, interviewing both patients and caregivers regarding their thoughts and experiences. Only eight studies used a mixed-methods approach in this review (and one used qualitative methods only), although methods such as interviews and focus groups can help identify factors affecting outcomes such as variation in intervention delivery and engagement, contexts helping or hindering intervention delivery, and participants’ interactions with different intervention components [102, 103].

Researchers should also carefully consider data collection points and provide clear theoretical or clinical justifications for their decisions. In this meta-analysis post-intervention data collection points varied between studies, and also within some studies (e.g., [39, 40]). While this was a source of heterogeneity between studies, heterogeneity statistics were not always significant/high in the meta-analyses conducted. Furthermore, the first follow-up point utilised in the analyses was the one the authors expected to see results from their intervention, and even though they are not chronologically the same across studies they are conceptually equivalent. Finally, long-term follow-ups are needed, although cost-effectiveness is a pragmatic constraint to their implementation [104, 105].

**Conclusion.** Interventions targeting family caregivers of patients with LLCs such as cancer and dementia are effective at improving patient symptoms and caregiver outcomes. Future research using mixed-method methodologies should aim to collect data from patient and caregiver dyads, identifying key components of complex interventions, and involving patients and caregivers in the design and evaluation of interventions as equal partners with researchers and clinicians. There is also an urgent need for studies on paediatric patients and their caregivers.

### **Declarations**

**Ethical approval:** This study does not involve human participants

**Consent for publication:** All authors contributed to the final written manuscript and have provided approval for publication.

**Availability of data and materials:** Data and materials are available from the corresponding author on reasonable request. Additional supplementary material is available on the Open Science Framework (<http://tinyurl.com/nc3cjz79>).

**Funding:** This review is supported by Great Ormond Street Children's Charity (Grant number: V5118).

**Author contributions:** CL is the Chief Investigator of the PARAMOUNT study and conceived the project, designed the protocol and takes overall responsibility for the conduct of this systematic review and meta-analysis. CL is responsible for the overall content and is the guarantor. DES and SH planned and designed the study protocol, planned and performed the data extraction and statistical analyses and wrote drafts of the manuscript. ELS performed data extraction, contributed to data analysis and interpretation, and assisted in manuscript write-up. KR, SSJ, MJ and EH provided critical insights. All authors have approved and contributed to the final written manuscript.

**Competing interests:** The authors declare that they have no competing interests.

## **Figures**

Figure 1. PRISMA 2020 flow of records for inclusion in the systematic review and meta-analyses of home-based physical symptom management interventions for family caregivers of patients with life limiting conditions

Figure 2. Traffic light plots of the domain-level judgements for each individual randomised controlled study assessed via the Cochrane Risk of Bias 2 tool

Figure 3. Forest plot showing overall pooled effect sizes for each patient and caregiver within-group analysis conducted in a meta-analysis of home-based physical symptom management interventions for family caregivers of patients with life limiting conditions

Figure 4. Forest plot showing overall pooled effect sizes for each patient and caregiver between-groups analysis conducted in a meta-analysis of home-based physical symptom management interventions for family caregivers of patients with life limiting conditions

## **Supplementary Materials**

Supplementary Material 1. Search strategy.

Supplementary Material 2. Study Quality Assessment Tools, Procedures and Results

Supplementary Material 3. Within-groups analyses

Supplementary Figure 1. A tree chart showing outcome domains (inner circle) and where applicable sub-domains (outer circle) assessed in caregivers of patients with life-limiting conditions

Supplementary Figure 2. A tree chart showing outcome domains (inner circle) and where applicable sub-domains (outer circle) assessed in patients with life-limiting conditions

Supplementary Figure 3. Within-group forest plots for individual analyses

Supplementary Figure 4. Between-groups forest plots for individual analyses

Table S1. Characteristics of eligible studies included in the systematic review

Table S2. Description of the intervention used in each study, comments on Template for Intervention Description and Replication (TIDieR) review and results

Table S3. Reported psychometric properties of patient and parent outcome variables used in each study included in a systematic review and meta-analysis of home-based physical symptom management interventions for family caregivers of patients with life limiting conditions.

Table S4. Methodological quality assessments for pre-post single group interventions included in a systematic review and meta-analysis of home-based physical symptom management interventions for family caregivers of patients with life limiting conditions.

Table S5. Within-groups meta-analyses of pre- to post-intervention change scores for patient and caregiver outcomes

Table S6. Between-groups meta-analysis effect sizes for patient and caregiver outcomes

## References

1. Harrop E, Byrne A, Nelson A. “It’s alright to ask for help”: findings from a qualitative study exploring the information and support needs of family carers at the end of life. *BMC palliative care*. 2014;13(1):22.
2. Roth DL, Fredman L, Haley WE. Informal caregiving and its impact on health: a reappraisal from population-based studies. *Gerontologist*. 2015;55(2):309-19.
3. Payne S, Turner M, Seamark D, Thomas C, Brearley S, Wang X, et al. Managing end of life medications at home—accounts of bereaved family carers: a qualitative interview study. *BMJ supportive & palliative care*. 2015;5(2):181-8.
4. Cai Y, Simons A, Toland S, Zhang J, Zheng K. Informal caregivers’ quality of life and management strategies following the transformation of their cancer caregiving role: A qualitative systematic review. *International Journal of Nursing Sciences*. 2021.
5. Hajek A, Kretzler B, König HH. Informal Caregiving, Loneliness and Social Isolation: A Systematic Review. *Int J Environ Res Public Health*. 2021;18(22).
6. Jika BM, Khan HT, Lawal M. Exploring experiences of family caregivers for older adults with chronic illness: A scoping review. *Geriatric Nursing*. 2021;42(6):1525-32.
7. Quinn C, Nelis SM, Martyr A, Victor C, Morris RG, Clare L. Influence of Positive and Negative Dimensions of Dementia Caregiving on Caregiver Well-Being and Satisfaction With Life: Findings From the IDEAL Study. *Am J Geriatr Psychiatry*. 2019;27(8):838-48.
8. Page BF, Hinton L, Harrop E, Vincent C. The challenges of caring for children who require complex medical care at home: ‘The go between for everyone is the parent and as the parent that’s an awful lot of responsibility’. *Health Expectations*. 2020;23(5):1144-54.
9. Liu Q, Ye F, Jiang X, Zhong C, Zou J. Effects of psychosocial interventions for caregivers of breast cancer patients: A systematic review and meta-analysis. *Heliyon*. 2023;9(2):e13715.
10. Hu Y, Liu T, Li F. Association between dyadic interventions and outcomes in cancer patients: a meta-analysis. *Supportive Care in Cancer*. 2019;27(3):745-61.
11. Latter S, Hopkinson JB, Richardson A, Hughes JA, Lowson E, Edwards D. How can we help family carers manage pain medicines for patients with advanced cancer? A systematic review of intervention studies. *BMJ supportive & palliative care*. 2016;6(3):263-75.
12. Smith TO, Pearson M, Smith MJ, Fletcher J, Irving L, Lister S. Effectiveness of caregiver interventions for people with cancer and non-cancer-related chronic pain: a systematic review and meta-analysis. *British Journal of Pain*. 2021:20494637211022771.
13. Verberne LM, Kars MC, Schouten-van Meeteren AY, Bosman DK, Colenbrander DA, Grootenhuis MA, van Delden JJ. Aims and tasks in parental caregiving for children receiving palliative care at home: a qualitative study. *Eur J Pediatr*. 2017;176:343-54.

14. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane handbook for systematic reviews of interventions 6.4 (updated August 2023)2023. Available from: Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *International Journal of Surgery*. 2021;88:105906.
16. Holley S, Schoth DE, Harrop E, Greenfield K, Liossi C. A systematic review and meta-analysis of home-based physical symptom management interventions for informal (family) caregivers of patients with life limiting conditions. PROSPERO: International prospective register of systematic reviews. 2020;CRD42020169950.
17. National Heart LaBI. Quality assessment tool for before-after (pre-post) studies with no control group. *Systematic Evidence Reviews and Clinical Practice Guidelines* 2014.
18. Greenfield K, Carter B, Harrop E, Jassal S, Bayliss MJ, Renton K, et al. Healthcare professionals' experiences of the barriers and facilitators to paediatric pain management in the community at end-of-life: a qualitative interview study. *J Pain Symptom Manage*. 2022;63(1):98-105.
19. Greenfield K, Holley S, Schoth DE, Harrop E, Howard RF, Bayliss J, et al. A mixed-methods systematic review and meta-analysis of barriers and facilitators to paediatric symptom management at end of life. *Palliat Med*. 2020;34(6):689-707.
20. Hain R, Devins M, Hastings R, Noyes J. Paediatric palliative care: development and pilot study of a 'Directory' of life-limiting conditions. *BMC Palliative Care*. 2013;12(1):43.
21. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687.
22. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366(14898).
23. Borenstein M, Hedges L, Higgins J, Rothstein HR. *Comprehensive Meta-Analysis Version 3*. Englewood, New Jersey: Biostat; 2013.
24. Borenstein M, Hedges LV, Higgins J, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*. 2010;1(2):97-111.
25. Borenstein M, Hedges LV, Higgins J, Rothstein HR. *Introduction to meta-analysis*. Cornwall: Wiley Online Library; 2009.
26. Deeks JJ, Higgins JP, Altman DG, Group CSM. Analysing data and undertaking meta-analyses. *Cochrane handbook for systematic reviews of interventions*. 2019:241-84.
27. Cumming G. *Understanding the new statistics: effect sizes, confidence intervals, and meta-analysis*. New York: Routledge; 2012.
28. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol*. 2013;4(Article 863):1-12.

29. Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. *Journal of Educational Statistics*. 1981;6(2):107-28.
30. Cumming G. The new statistics: Why and how. *Psychol Sci*. 2014;25(1):7-29.
- [DATASET] 31. Schoth DE, Holley S, Johnson M, Stibbs EL, Renton K, Harrop E, Liossi C. Data from: A systematic review and meta-analysis of home-based physical symptom management interventions for family caregivers of patients with life limiting conditions. 2024.
32. Huth MM, Broome ME, Mussatto KA, Morgan SW. A study of the effectiveness of a pain management education booklet for parents of children having cardiac surgery. *Pain Management Nursing*. 2003;4(1):31-9.
33. Rambod M, Pasyar N, Irannejad Parizi F, Edraki M, Khair K, von Mackensen S. The effect of a virtual child disease management programme on burden and social adjustment of caregivers of children with coagulation factor deficiencies. *Haemophilia*. 2022;29(1):199-209.
34. Palermo TM, Dudeney J, Santanelli JP, Carletti A, Zempsky WT. Feasibility and Acceptability of Internet-delivered Cognitive Behavioral Therapy for Chronic Pain in Adolescents With Sickle Cell Disease and Their Parents. *Journal of Pediatric Hematology/Oncology*. 2018;40(2):122-7.
35. Palermo TM, Lalloo C, Zhou C, Dampier C, Zempsky W, Badawy SM, et al. A cognitive-behavioral digital health intervention for sickle cell disease pain in adolescents: a randomized, controlled, multicenter trial. *PAIN*. 2024;165(1):164-76.
36. Johnston JD, Schatz J, Bills SE, Frye BG, Carrara GC. Preschool Pain Management Program for Young Children with Sickle Cell Disease: A Pre-Post Feasibility Study. *Journal of Pediatric Psychology*. 2023;48(4):330-40.
37. Connolly ME, Forman S, Sharkey CM, Merwin S, Darbari DS, Hardy SJ. Feasibility and preliminary efficacy of the Balance Program to reduce pain-related disability in pediatric sickle cell disease. *Pediatric Blood & Cancer*. 2023;70(12):e30667.
38. Jeong J-H, Yoo W-G. Effects of pulmonary rehabilitation education for caregivers on pulmonary function and pain in patients with lung cancer following lung resection. *Journal of Physical Therapy Science*. 2015;27(2):489-90.
39. Belgacem B, Auclair C, Fedor M-C, Brugnon D, Blanquet M, Tournilhac O, Gerbaud L. A caregiver educational program improves quality of life and burden for cancer patients and their caregivers: a randomised clinical trial. *European Journal of Oncology Nursing*. 2013;17(6):870-6.
40. Keefe FJ, Ahles TA, Sutton L, Dalton J, Baucom D, Pope MS, et al. Partner-guided cancer pain management at the end of life: a preliminary study. *Journal of Pain and Symptom Management*. 2005;29(3):263-72.
41. Porter LS, Steel JL, Fairclough DL, LeBlanc TW, Bull J, Hanson LC, et al. Caregiver-guided pain coping skills training for patients with advanced cancer: Results from a randomized clinical trial. *Palliative Medicine*. 2021;35(5):952-61.

42. Samancioglu Baglama S, Bakir E. Caregiver-Delivered Foot Reflexology: Effects on Patients and Caregivers. *Holistic Nursing Practice*. 2019;33(6):338-45.
43. Wyatt G, Sikorskii A, Tesnjak I, Frambes D, Holmstrom A, Luo Z, et al. A Randomized Clinical Trial of Caregiver-Delivered Reflexology for Symptom Management During Breast Cancer Treatment. *Journal of Pain and Symptom Management*. 2017;54(5):670-9.
44. Wyatt G, Lehto R, Guha-Niyogi P, Brewer S, Victorson D, Pace T, et al. Reflexology and meditative practices for symptom management among people with cancer: Results from a sequential multiple assignment randomized trial. *Research in Nursing & Health*. 2021;44(5):796-810.
45. Schenker Y, Bahary N, Claxton R, Childers J, Chu E, Kavalieratos D, et al. A Pilot Trial of Early Specialty Palliative Care for Patients with Advanced Pancreatic Cancer: Challenges Encountered and Lessons Learned. *Journal of Palliative Medicine*. 2018;21(1):28-36.
46. Thana K, Sikorskii A, Lehto R, Guhaniyogi P, Brewer S, Victorson D, et al. Family caregivers of those with cancer: quality of life outcomes from a sequential multiple assignment randomized trial. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2022;30(7):5891-902.
47. Campbell LC, Keefe FJ, Scipio C, McKee DC, Edwards CL, Herman SH, et al. Facilitating research participation and improving quality of life for African American prostate cancer survivors and their intimate partners. A pilot study of telephone-based coping skills training United States2007 [414-24].
48. McCaughan E, Curran C, Northouse L, Parahoo K. Evaluating a psychosocial intervention for men with prostate cancer and their partners: Outcomes and lessons learned from a randomized controlled trial. *Applied Nursing Research*. 2018;40(6iv, 8901557):143-51.
49. Northouse LL, Mood DW, Schafenacker A, Kalemkerian G, Zalupski M, LoRusso P, et al. Randomized clinical trial of a brief and extensive dyadic intervention for advanced cancer patients and their family caregivers. *Psycho-Oncology*. 2013;22(3):555-63.
50. Northouse LL, Mood DW, Schafenacker A, Montie JE, Sandler HM, Forman JD, et al. Randomized clinical trial of a family intervention for prostate cancer patients and their spouses. *Cancer*. 2007;110(12):2809-18.
51. Badr H, Herbert K, Chhabria K, Sandulache VC, Chiao EY, Wagner T. Self-management intervention for head and neck cancer couples: Results of a randomized pilot trial. *Cancer*. 2019;125(7):1176-84.
52. Kozachik SL, Given CW, Given BA, Pierce SJ, Azzouz F, Rawl SM, Champion VL, editors. Improving depressive symptoms among caregivers of patients with cancer: results of a randomized clinical trial. *Oncology Nursing Forum*; 2001.
53. Northouse L, Kershaw T, Mood D, Schafenacker A. Effects of a family intervention on the quality of life of women with recurrent breast cancer and their family caregivers. *Psycho-Oncology*. 2005;14(6):478-91.

54. McMillan SC, Small BJ, Haley WE, Zambroskio C, Buck HG. The COPE Intervention for Caregivers of Patients With Heart Failure. *Journal of Hospice & Palliative Nursing*. 2013;15(4):196-206.
55. Dionne-Odom JN, Ejem DB, Wells R, Azuero A, Stockdill ML, Keebler K, et al. Effects of a telehealth early palliative care intervention for family caregivers of persons with advanced heart failure: the ENABLE CHF-PC randomized clinical trial. *JAMA network open*. 2020;3(4):e202583-e.
56. Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. *CA Cancer J Clin*. 2010;60(5):317-39.
57. Ahn S, Romo RD, Campbell CL. A systematic review of interventions for family caregivers who care for patients with advanced cancer at home. *Patient Education and Counseling*. 2020;103(8):1518-30.
58. Secinti E, Fischer IC, Brennan EA, Christon L, Balliet W. The efficacy of psychosocial interventions for cancer caregiver burden: A systematic review and meta-analysis of randomized controlled trials. *Clinical Psychology Review*. 2023;99:102237.
59. Griffin JM, Meis LA, MacDonald R, Greer N, Jensen A, Rutks I, Wilt TJ. Effectiveness of family and caregiver interventions on patient outcomes in adults with cancer: A systematic review. *J Gen Intern Med*. 2014;29(9):1274-82.
60. Lamson AL, Hodgson JL, Pratt KJ, Mendenhall TJ, Wong AG, Sesemann EM, et al. Couple and family interventions for high mortality health conditions: A strategic review (2010–2019). *J Marital Fam Ther*. 2022.
61. Kerckhove N, Bornier N, Mulliez A, Elyn A, Teixeira S, Authier N, et al. Prevalence of Chronic Pain Among People with Dementia: A Nationwide Study Using French Administrative Data. *Am J Geriatr Psychiatry*. 2023;31(12):1149-63.
62. Riffin C, Brody L, Mukhi P, Herr K, Pillemer K, Rogers M, et al. Establishing the Feasibility and Acceptability of a Caregiver Targeted Intervention to Improve Pain Assessment Among Persons With Dementia. *Innov Aging*. 2023;7(10):igad074.
63. Husebo BS, Achterberg W, Flo E. Identifying and Managing Pain in People with Alzheimer's Disease and Other Types of Dementia: A Systematic Review. *CNS Drugs*. 2016;30(6):481-97.
64. De Pandis MF, Torti M, Rotondo R, Iodice L, Levi Della Vida M, Casali M, et al. Therapeutic education for empowerment and engagement in patients with Parkinson's disease: A non-pharmacological, interventional, multicentric, randomized controlled trial. *Frontiers in Neurology*. 2023;14:1167685.
65. Bakitas M, Dionne-Odom JN, Pamboukian SV, Tallaj J, Kvale E, Swetz KM, et al. Engaging patients and families to create a feasible clinical trial integrating palliative and heart failure care: results of the ENABLE CHF-PC pilot clinical trial. *BMC Palliative Care*. 2017;16(1):45.
66. Fleisher JE, Suresh M, Klostermann EC, Lee J, Hess SP, Myrick E, et al. IN-HOME-PD Caregivers: The effects of a combined home visit and peer mentoring intervention for caregivers of homebound individuals with advanced Parkinson's disease. *Parkinsonism & Related Disorders*. 2023;106:105222.

67. Dionne-Odom JN, Ejem DB, Wells R, Azuero A, Stockdill ML, Keebler K, et al. Effects of a Telehealth Early Palliative Care Intervention for Family Caregivers of Persons With Advanced Heart Failure: The ENABLE CHF-PC Randomized Clinical Trial. *JAMA Network Open*. 2020:e202583-e.
68. Galvin R, Stokes E, Cusack T. Family-Mediated Exercises (FAME): an exploration of participant's involvement in a novel form of exercise delivery after stroke. *Topics in stroke rehabilitation*. 2014;21(1):63-74.
69. Nkhoma K, Seymour J, Arthur A. An Educational Intervention to Reduce Pain and Improve Pain Management for Malawian People Living With HIV/AIDS and Their Family Carers: A Randomized Controlled Trial. *Journal of Pain and Symptom Management*. 2015;50(1):80-90.e4.
70. Chan K-Y, Yip T, Yap DY, Sham MK, Tsang KW. A Pilot Comprehensive Psychoeducation Program for Fluid Management in Renal Palliative Care Patients: Impact on Health Care Utilization. *Journal of Palliative Medicine*. 2020.
71. Bom J, Stöckel J. Is the grass greener on the other side? The health impact of providing informal care in the UK and the Netherlands. *Social Science & Medicine*. 2021;269:113562.
72. Gomes B, Calanzani N, Gysels M, Hall S, Higginson IJ. Heterogeneity and changes in preferences for dying at home: a systematic review. *BMC palliative care*. 2013;12(1):1-13.
73. Ullrich A, Ascherfeld L, Marx G, Bokemeyer C, Bergelt C, Oechsle K. Quality of life, psychological burden, needs, and satisfaction during specialized inpatient palliative care in family caregivers of advanced cancer patients. *BMC palliative care*. 2017;16(1):1-10.
74. Bidwell JT, Lyons KS, Lee CS. Caregiver well-being and patient outcomes in heart failure: a meta-analysis. *The Journal of cardiovascular nursing*. 2017;32(4):372.
75. Stall NM, Kim SJ, Hardacre KA, Shah PS, Straus SE, Bronskill SE, et al. Association of informal caregiver distress with health outcomes of community-dwelling dementia care recipients: a systematic review. *Journal of the American Geriatrics Society*. 2019;67(3):609-17.
76. Bouchard K, Greenman PS, Pipe A, Johnson SM, Tulloch H. Reducing Caregiver Distress and Cardiovascular Risk: A Focus on Caregiver-Patient Relationship Quality. *Canadian Journal of Cardiology*. 2019;35(10):1409-11.
77. Downing J, Jassal SS, Mathews L, Brits H, Friedrichsdorf SJ. Pediatric pain management in palliative care. *Pain management*. 2015;5(1):23-35.
78. Greenfield K, Holley S, Schoth DE, Harrop E, Howard R, Bayliss J, et al. Barriers and facilitators experienced by patients, carers and healthcare professionals when managing symptoms in infants, children and young people at end-of-life: a mixed methods systematic review protocol. *BMJ open*. 2019;9(7):e030566.
79. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. Framework for the development and evaluation of complex interventions: gap analysis, workshop and consultation-informed update. *Health Technology Assessment*. 2021;25(57):1-132.

80. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337.
81. Montgomery P, Grant S, Mayo-Wilson E, Macdonald G, Michie S, Hopewell S, Moher D. Reporting randomised trials of social and psychological interventions: the CONSORT-SPI 2018 Extension. *Trials*. 2018;19(1):1-14.
82. Hoffmann T, English T, Glasziou P. Reporting of interventions in randomised trials: an audit of journal instructions to authors. *Trials*. 2014;15(1):1-6.
83. Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S, et al. Reducing waste from incomplete or unusable reports of biomedical research. *The Lancet*. 2014;383(9913):267-76.
84. Clarke M, Williamson PR. Core outcome sets and systematic reviews. *Systematic reviews*. 2016;5:1-4.
85. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the quality and relevance of research through the use of agreed core outcomes. Sage Publications Sage UK: London, England; 2012. p. 1-2.
86. Lopez-Olivo MA, Kachira JJ, Abdel-Wahab N, Pundole X, Aldrich JD, Carey P, et al. A Systematic Review and Meta-analysis of Observational Studies and Uncontrolled Trials Reporting on the Use of Checkpoint Blockers in Patients with Cancer and Pre-existing Autoimmune Disease. *Eur J Cancer*. 2024:114148.
87. Lv J, Liu Q, Zeng X, Oei TP, Liu Y, Xu K, et al. The effect of four Immeasurables meditations on depressive symptoms: A systematic review and meta-analysis. *Clin Psychol Rev*. 2020;76:101814.
88. Behnood SA, Shafran R, Bennett S, Zhang AX, O'Mahoney LL, Stephenson TJ, et al. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: a meta-analysis of controlled and uncontrolled studies. *J Infect*. 2022;84(2):158-70.
89. Xuan R, Li X, Qiao Y, Guo Q, Liu X, Deng W, et al. Mindfulness-based cognitive therapy for bipolar disorder: A systematic review and meta-analysis. *Psychiatry Res*. 2020;290:113116.
90. Kusi G, Atenafu EG, Boamah Mensah AB, Lee CT, Viswabandya A, Puts M, Mayo S. The effectiveness of psychoeducational interventions on caregiver-oriented outcomes in caregivers of adult cancer patients: A systematic review and meta-analysis. *Psycho-Oncology*. 2023;32(2):189-202.
91. Tang WP, Chan CW, Leung DY, Chan DN. The effects of psychoeducational interventions on caregivers of children with cancer: A meta-analysis of randomized controlled trials. *Journal of Child Health Care*. 2020;24(1):123-42.
92. Collins LM, Trail JB, Kugler KC, Baker TB, Piper ME, Mermelstein RJ. Evaluating individual intervention components: making decisions based on the results of a factorial screening experiment. *Translational behavioral medicine*. 2014;4(3):238-51.
93. Sacristán JA, Aguarón A, Avendaño-Solá C, Garrido P, Carrión J, Gutiérrez A, et al. Patient involvement in clinical research: why, when, and how. *Patient preference and adherence*. 2016:631-40.

94. Tinetti ME, Basch E. Patients' responsibility to participate in decision making and research. *Jama*. 2013;309(22):2331-2.
95. Wells RD, Guastaferro K, Azuero A, Rini C, Hendricks BA, Dosse C, et al. Applying the Multiphase Optimization Strategy for the Development of Optimized Interventions in Palliative Care. *Journal of Pain and Symptom Management*. 2021;62(1):174-82.
96. D'Amen B, Socci M, Santini S. Intergenerational caring: A systematic literature review on young and young adult caregivers of older people. *BMC Geriatr*. 2021;21(1):105.
97. Saragosa M, Frew M, Hahn-Goldberg S, Orchanian-Cheff A, Abrams H, Okrainec K. The young carers' journey: a systematic review and meta ethnography. *Int J Environ Res Public Health*. 2022;19(10):5826.
98. Charalambous A. Caregiving and Caregivers: Concepts, Caregiving Models, and Systems. *Informal Caregivers: From Hidden Heroes to Integral Part of Care*: Springer; 2023. p. 1-11.
99. Raina P, O'Donnell M, Schwellnus H, Rosenbaum P, King G, Brehaut J, et al. Caregiving process and caregiver burden: conceptual models to guide research and practice. *BMC pediatrics*. 2004;4:1-13.
100. Litzelman K, Kent EE, Mollica M, Rowland JH. How does caregiver well-being relate to perceived quality of care in patients with cancer? Exploring associations and pathways. *Journal of Clinical Oncology*. 2016;34(29):3554.
101. Litzelman K, Green PA, Yabroff KR. Cancer and quality of life in spousal dyads: spillover in couples with and without cancer-related health problems. *Supportive Care in Cancer*. 2016;24(2):763-71.
102. Bonell C, Fletcher A, Morton M, Lorenc T, Moore L. Realist randomised controlled trials: a new approach to evaluating complex public health interventions. *Soc Sci Med*. 2012;75(12):2299-306.
103. Renjith V, Yesodharan R, Noronha JA, Ladd E, George A. Qualitative methods in health care research. *Int J Prev Med*. 2021;12(1):20.
104. Llewellyn-Bennett R, Edwards D, Roberts N, Hainsworth AH, Bulbulia R, Bowman L. Post-trial follow-up methodology in large randomised controlled trials: a systematic review. *Trials*. 2018;19:1-12.
105. Hill KG, Woodward D, Woelfel T, Hawkins JD, Green S. Planning for long-term follow-up: Strategies learned from longitudinal studies. *Prevention Science*. 2016;17:806-18.