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Palliative Care Interventions Effects on Psychological Distress: A Systematic Review & Meta-Analysis

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**Abstract:**

**Background:** Managing psychological distress is an objective of palliative care. No meta-analysis has evaluated whether palliative care reduces psychological distress.

**Objectives:** Examine the effects of palliative care on depression, anxiety, and general psychological distress for adults with life-limiting illnesses and their caregivers.

**Design:** We searched PubMed, PsycInfo, Embase, and CINAHL for randomized clinical trials (RCTs) of palliative care interventions. RCTs were included if they enrolled adults with life-limiting illnesses or their caregivers, reported data on psychological distress at 3 months after study intake, and if authors had described the intervention as 'palliative care.'

**Results:** We identified 38 RCTs meeting our inclusion criteria. Many (14/38) included studies excluded participants with common mental health conditions. There were no statistically significant improvements in patient or caregiver anxiety (patient SMD:  $-.008$ ,  $p=.96$ ; caregiver SMD:  $-.21$ ,  $p=.79$ ), depression (patient SMD:  $-.13$ ,  $p=.25$ ; caregiver SMD  $-.27$ ,  $p=.08$ ), or psychological distress (patient SMD:  $.26$ ,  $p=.59$ ; caregiver SMD:  $.04$ ,  $p=.78$ ).

**Conclusions:** Psychological distress is not likely to be reduced in the context of a typical palliative care intervention. The systemic exclusion of patients with common mental health conditions in more than 1/3 of the studies raises ethical questions about the goals of palliative care RCTS and could perpetuate inequalities.

**Keywords:** meta-analysis, palliative care interventions, anxiety, depression, patient, caregiver, psychological distress

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## Introduction

Palliative care clinicians encounter psychological distress regularly in their practices.<sup>1</sup> Psychological distress can include depression, sadness, anxiety, negative affect, and fear.<sup>2</sup> Approximately 30-40% of patients with cancer experience a mood disorder,<sup>3</sup> and depression is similarly common among patients with chronic heart failure and chronic obstructive pulmonary disease (COPD).<sup>4</sup> In addition, patients with cancers, heart failure, and lung disease frequently experience increased depression symptoms as they approach the end of life.<sup>5</sup> Goals of palliative care include identifying, assessing, and managing pain and physical, psychological, social, and spiritual concerns among patients experiencing serious illnesses and their families.<sup>6,7</sup> Some studies have shown that palliative care may improve mental health symptoms<sup>8,9</sup> and may even be associated with reduced likelihood of death by suicide among people with serious illnesses.<sup>10-12</sup>

Prior systematic reviews and meta-analyses have evaluated the effects of palliative care on improving quality of life with mixed findings.<sup>13-17</sup> Among patients with cancer, outpatient palliative care interventions had a positive impact on quality of life.<sup>17</sup> Three systematic reviews found some evidence for palliative care improving quality of life among mixed-disease samples (including cancer and non-cancer patients).<sup>13,14,16</sup> The single review specifically investigating palliative care interventions among non-cancer patients found no effect of palliative care on quality of life.<sup>15</sup> One review of 23 trials on patient mood outcomes<sup>13</sup> found mixed evidence, but 4 of the 5 trials at low risk of bias reported statistically significantly improved mood. However, patient mood was not a primary outcome analyzed in this review, so the authors did not perform a meta-analysis.

We performed a systematic review and meta-analysis of palliative care randomized controlled trials (RCTs) and estimated the association between palliative care and psychological distress symptoms in adult patients with life-limiting illnesses and their caregivers. We also conducted several moderator analyses to examine differences in effect sizes between studies focusing on patients with cancer vs. non-cancer illnesses, examining psychological distress as a primary vs. secondary outcome, using a manualized therapeutic psychosocial intervention, including a specialty mental health clinician on the intervention team, and specifying

a theoretical basis for the psychological component of the intervention. We also examined the moderating role of the study's risk of bias.

We hypothesized that studies focusing on cancer populations would have more improvement in psychological distress than those focused on patients with non-cancer illnesses because cancer care is better integrated within palliative care<sup>18-20</sup> and trajectories of decline are better established for cancer.<sup>21-23</sup> Consequently, palliative care may be better positioned to address psychological distress symptoms at the right times in cancer settings. We also hypothesized that studies using a manualized therapeutic intervention to target psychological distress would have improved outcomes relative to those that did not as the psychological component of the intervention would be standardized, leading to less heterogeneity. It was hypothesized that the inclusion of a specialty mental health clinician on the intervention team would be associated with improved outcomes because participants would be receiving care from a clinician trained to manage psychological distress. We hypothesized that studies with theoretical bases for the psychological component of the intervention would have improved outcomes relative to those without because the mechanism through which the intervention would work is specified. We hypothesized that studies with psychological distress identified as a primary outcome would have stronger outcomes because the intervention would be tailored for psychological distress. And finally, we expected that studies with lower risk of bias would have more precise estimates of the intervention effect because studies with lower risk of bias are less likely to over-estimate effects.<sup>24</sup>

## **Methods**

### *Protocol and registration*

This study is a protocol-based systematic review and meta-analysis (PROSPERO ID: CRD42021255958) conducted according to the Cochrane Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Review and Meta-Analysis statement 27-item checklist.<sup>25</sup>

### *Search strategy*

PubMed, PsycInfo, Embase, and CINAHL were searched for articles published anytime from inception to June 11, 2021. The primary author (M.A.N.) conducted the searches with assistance from a research librarian (see appendix for search examples). The primary author also screened other resources, including searching the

NIH Clinical Trials registration webpage<sup>26</sup> and bibliographic references from prior systematic reviews on similar topics and from retrieved papers of interest, for additional studies and data not identified in the original search strategy. An example of the search strategy can be found in the appendix.

### *Study selection*

Two of the reviewers (M.A.N. and either S.K. or an undergraduate research assistant) screened and independently evaluated all records for eligibility criteria. Disagreements between the two primary reviewers were adjudicated by the third. Studies were included for full review if they had a RCT or cluster RCT study design, the patient population was adults with a life-limiting illness, and the study evaluated a palliative care intervention (as defined by the authors of the included study), and assessed psychological distress symptoms 3 months post-intervention. Life-limiting illnesses were defined as an incurable condition that would likely limit lifespan.<sup>27</sup> Studies of palliative care interventions selected for full review were subsequently included if the intervention was delivered by at least one person who had received palliative care training. This criterion included interventions using palliative care-boarded and/or experienced physicians, nurses, or other clinicians to deliver the intervention. It also included studies in which the individuals delivering the intervention received a study-specific palliative care training, even if they did not have prior palliative care experience. Studies reporting at least one of the following outcomes for either the patient or the patient's caregiver were included: depression symptoms, anxiety symptoms, mood symptoms, or psychological distress symptoms. Studies using an overall symptom or quality of life scale, such as the Edmonton Symptom Assessment Scale, were included only if they reported results from a psychological symptoms sub-scale. Studies reporting a diagnosis of depression or anxiety were included only if they also reported a dimensional assessment of symptoms. There were no limitations placed on types of comparison groups; we allowed both active and non-active controls. Studies were excluded if psychological distress symptoms were not assessed at 3 months (plus or minus one month) after study intake. Studies involving pediatric patients were excluded due to differences in pediatric and adult palliative care.<sup>28</sup> Studies not written in English were also excluded, as the investigative team did not have multiple speakers of other languages. Two authors (M.A.N. and S.K.) extracted all the data.

### *Risk of bias assessment*

Risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials.<sup>29</sup> This checklist includes 12 characteristics: true randomization, concealment of allocation, treatment groups similar at baseline, participants blind to assignment, assessors blind to assignment, groups treated identically except for intervention, follow up complete, intention-to-treat analysis, outcome measurement same for treatment groups, reliable assessment of outcomes, appropriate statistical analysis, and appropriate trial design. Of these 12 characteristics, 11 were applicable to the studies included in this meta-analysis, as it is not reasonable to blind participants to their treatment assignment in a behavioral RCT. Each study was assessed (yes, no, unclear) on all 11 characteristics. The total number of ‘yes’ categorizations within each study were summed, and studies with 7 or more characteristics were considered lower risk of bias, while those with 6 or fewer were considered higher risk of bias. This approach has been used previously.<sup>30</sup>

### *Synthesis of results*

A narrative synthesis was performed to describe the populations, diseases studied, nature of the palliative care interventions, and psychological distress outcomes for the included studies. For the meta-analysis, psychological distress symptoms were selected as the focal outcome, even if they were not the primary outcome of the included palliative care intervention.

### *Summary measures*

Given that several instruments were used to measure psychological distress, standardized mean differences (SMDs) were calculated using Hedge’s adjusted  $g$  estimator to correct for small sample bias.<sup>31</sup> Among studies that did not report SMDs, means and standard deviations or other summary statistics of outcome measures were collected and SMDs calculated according to the Cochrane training handbook.<sup>32</sup> When studies included multiple psychological distress measures and multiple time points within the 2-4 months after study intake, estimates were pooled,<sup>33</sup> based on the imputation of an estimate of intercorrelation among the outcome measures. Based on the prior literature,<sup>34,35</sup> we used an estimate of  $r=0.8$  and conducted sensitivity analyses for  $r=0.5$ . When necessary, individual studies were directionally corrected such that lower scores on distress measures represented lower levels of psychological distress. For studies that did not report numeric data on the psychological distress outcomes in the paper (e.g., only reported results were “not significant”), authors were

contacted and asked to share their data. If authors did not respond or did not agree to share their data, the study was not included in the meta-analysis. Because we used SMDs as the outcome, studies that did not report change scores or psychological distress measures at study intake were excluded.

### *Statistical analysis*

Six separate meta-analyses were performed for patient anxiety, patient depression, general patient psychological distress, caregiver anxiety, caregiver depression, and general caregiver psychological distress. Six potential moderators of patient anxiety and depression outcomes were explored: risk of bias (lower vs. higher risk of bias), illness type (cancer or non-cancer), whether a manualized therapeutic intervention was included, whether a specialty mental health clinician was part of the study team, whether the authors specified a theoretical basis for the psychological component of the intervention, and whether psychological distress was indicated as a primary outcome. Moderators of caregiver outcomes and general distress outcomes were not explored because there were few studies.<sup>36</sup> Heterogeneity was examined using the  $I^2$  statistic value and chi-square tests p-values from each meta-analysis. Heterogeneity is considered high at values over 75%. Outcomes were pooled using a random-effects model including a random study effect to account for heterogeneity among studies.<sup>31</sup> Forest plots and funnel plots were created for each of the main analyses. The analysis was carried out using R (version 4.0.1),<sup>37</sup> the **metafor** package (version 3.0.2),<sup>38</sup> and the **dmatar** package.<sup>39</sup> All analyses used a two-sided p-value of 0.05.

### **Results**

There were 2,806 unique records identified from the literature search, of which 224 were deemed eligible for full review (see Figure 1 for more detail). A total of 38 studies with 6,336 patients and 1,667 caregivers were included. Study characteristics can be found in Table 1 and in Appendix Table 1. Twenty-one (55.3%) were conducted in the US,<sup>8,9,40-59</sup> three (7.9%) in Denmark,<sup>60-62</sup> two (5.3%) in each of Canada,<sup>63,64</sup> Italy,<sup>65,66</sup> Hong Kong,<sup>67,68</sup> and Belgium.<sup>69,70</sup> More than two-thirds of the included studies (N=26, 68.4%) enrolled patients with cancer.<sup>8,9,42,43,45-49,52-54,56,58-65,70-75</sup> Six (15.8%) studies enrolled heart failure patients.<sup>40,44,51,55,57,68</sup> The remaining six studies were evenly divided among neurological conditions,<sup>66,76</sup> pulmonary



conditions,<sup>50,69</sup> and other conditions.<sup>41,67</sup> Most (23) studies had a higher or unclear risk of bias<sup>8,9,42,43,46–48,50,53–55,57–61,65,67,69,71–75</sup> and 15 had a lower risk of bias.<sup>40,41,44,45,49,51,52,56,62–64,66,68,70,76</sup>

[Insert Figure 1 here].

*Intervention Characteristics.* Twelve studies (31.6%) described a theoretical background for the psychological component of the intervention such as the chronic care model or Lazarus's stress and coping theory,<sup>8,9,40,44,51,56,58,60,61,68,74,76</sup> while the other 26 (68.4%) did not. Only 9 studies (23.7%) included a specialty mental health clinician (inclusive of psychologists, social workers providing structured psychosocial care, and psychiatric nurses) on the intervention team.<sup>40,54,61,62,64,66,69,71,74</sup> Ten studies (26.3%) included a manualized educational, behavioral, or therapeutic intervention such as problem-solving therapy or cognitive behavioral therapy (CBT).<sup>9,42–44,51,52,54,62,64,73,74</sup> Most interventions (N=26, 68.4%) included interdisciplinary teams of at least 2 types of clinicians,<sup>8,40,41,47–59,61–64,66,67,69,72,76</sup> while 7 (17.9%) were performed only by nurses;<sup>9,42–44,60,68,70,73</sup> 4 (10.3%) by palliative care physicians,<sup>65,71,74,75</sup> and two had either a physician or a nurse.<sup>45,46</sup> Fifteen studies (39.5%) were conducted in a mix of settings (e.g., inpatient and outpatient),<sup>40,44,44,44,52,53,55,58,61,62,64,68,70,72,77</sup> four (10.5%) were conducted in an outpatient setting,<sup>8,50,56,71</sup> six (15.8%) in an inpatient setting,<sup>51,57,64,72</sup> three (7.9%) were performed in-home,<sup>54,66,69</sup> two (5.3%) by telemedicine,<sup>42,43,73</sup> and eight (21.1%) did not specify a setting.<sup>9,41,45,60,65,74,75</sup> Most interventions (N=21, 55.3%) explicitly included content aimed at improving psychological distress.<sup>8,9,40,42–44,46,51,52,55,57,60,62,64,68–71,74,75,77</sup>

*Outcome Assessments.* Most included studies (N=32, 84.2%) had been pre-registered on ClinicalTrials.gov or another similar trial registration webpage,<sup>8,9,40–49,51,52,54–56,58–66,68,70,73–77</sup> 10 of which included a psychological distress measure as a primary outcome.<sup>41–44,48,49,51,55,73,74,77</sup> Five (50%) studies that pre-specified a primary psychological outcome included a manualized therapeutic intervention.<sup>42–44,51,73,74</sup> The majority of studies considered quality of life as a primary outcome and psychological distress as a secondary outcome. Of the 38 included studies, 6 (15.8%) investigated only depression symptoms,<sup>9,42,43,49,52,57,64</sup> 27 (71.5%) evaluated both depression and anxiety symptoms.<sup>8,40,40,44–47,50,51,53,55,56,58–62,65,66,68–71,73,74,76,77</sup> and 5 (13.2%) assessed general psychological distress.<sup>41,54,63,72,78</sup> No study had an inclusion criterion that required an elevated score on a psychological distress outcome, while fourteen (36.8%) excluded potential subjects with

certain diagnosed mental or behavioral health diagnoses, including depression, anxiety, and substance use disorders.

[Insert Table 1 here.]

Most included studies (N=24, 63.2%) did not find a significant difference in psychological distress symptoms among the intervention and control group.<sup>41,44,49,51–56,58,60,61,63–66,68–72,74–76</sup> Eight studies (21.1%) found a positive effect of the intervention on the corresponding psychological distress outcome, meaning distress was lowered in the intervention group relative to the control.<sup>8,9,40,42,43,47,48,57,62</sup> Six studies (15.7%) found a mix of effects,<sup>45,46,50,59,73,77</sup> with four studies having both a finding that distress decreased on one measure and didn't change on another.<sup>45,46,59,67</sup> The other two studies with mixed results found distress increased on one measure and didn't change on another.<sup>50,73</sup>

[Insert Table 2 here.]

#### *Statistical results: Intervention Effects*

Meta-analytic pooling of effects of a palliative care intervention on psychological distress symptoms can be found in Table 3. None of the SMDs for any effects were statistically significant. However, the anxiety and depression SMDs were all negative, i.e., in the predicted direction. The strongest effect was observed in the five studies that examined caregiver depression, with an SMD of  $-.27$  ( $p=.08$ ). In addition, five of the six primary analyses had statistically significant heterogeneity, and four had heterogeneity statistics higher than 75%, indicating possible substantial to considerable heterogeneity.<sup>32</sup> Figures 1-6 show the forest plot results for each of the main outcomes.

#### *Statistical results: Moderator Analyses*

None of the moderator analyses resulted in significant findings, and as such, none aligned with our hypotheses. However, for both patient anxiety and depression, studies enrolling only cancer patients had negative (i.e., favorable) SMDs with small effect sizes, while non-cancer studies had positive SMDs. Despite not being statistically significant, these findings are in the direction we expected. In addition, studies with lower risk of bias had larger (though not statistically significant) effect sizes for both patient anxiety (SMD of  $-.47$  for lower risk of bias vs. SMD of  $.12$  for higher risk of bias) and patient depression (SMD of  $-.28$  for lower risk of

bias vs. SMD of -.05 for higher risk of bias). The direction of these nonsignificant findings is consistent with our predictions. A similar pattern was seen for patients with depression, with more favorable findings emerging studies with a lower risk of bias than those with a higher or unclear risk of bias. We also conducted moderator analyses to compare studies that indicated psychological distress was a primary outcome vs. those with psychological distress as a secondary outcome for both patient anxiety (SMD of .01 for primary outcome vs. SMD of -.03 for secondary outcome) and patient depression (SMD of .52 for primary outcome vs. -.23 for secondary outcome). This finding did not align with our predicted direction of effect. Moderator analyses comparing interventions with and without a specialty mental health clinician for patient anxiety (SMD of -.07 for a specialty mental health clinician vs -.007 for no specialty mental health clinician) did not support our hypothesis. When depression was the outcome (SMD of .08 for specialty mental health clinician vs. -.22 for no specialty mental health clinician), the direction of effect was inconsistent with predictions. Finally, identifying a theoretical basis for the psychological component of the intervention was not statistically significant for patient anxiety (SMD -.09 for theory vs. SMD .02 for no theory) or patient depression (SMD of -.27 for theory vs. SMD of -.03 for no theory). However, the direction of these effects was as expected. Nearly all moderator analyses had heterogeneity statistics indicating substantial to considerable heterogeneity. However, four subgroups in the patient anxiety moderator analyses saw less heterogeneity: distress as primary outcome ( $I^2=32\%$ ), those with a theoretical basis ( $I^2=13\%$ ), those without a manualized intervention ( $I^2=42\%$ ), and those with a specialty mental health clinician ( $I^2=20\%$ ).

[Inset Table 3 and Table 4 here.]

[Insert Figures 2-7 here.]

## Discussion

Our analyses spanned 38 RCTs, with more than 6,000 patients and 1,500 caregivers. Only one-quarter of included studies found a significant improvement in psychological distress symptoms, and the current meta-analysis suggests that, on average, palliative care interventions do not lead to reductions in psychological distress. While not statistically significant, studies focusing on caregiver anxiety and depression had moderate

effect sizes in favor of the intervention. In addition, four of the six primary analyses had heterogeneity statistics higher than 75%, which is likely attributable to the variety of diseases, treatment settings, and interventions included in the meta-analysis studied. In our moderator analyses, we did observe some findings favoring intervention, though none rose to the level of statistical significance. Standardized mean differences in patients with cancer and among studies with lower risk of bias trended toward favoring intervention, with small to moderate effect sizes (from -.21 to -.47).

The overall null pattern of findings can be partially explained by the fact that none of the studies required elevated psychological distress scores for study entry. Moreover, some studies systematically *excluded* individuals with common anxiety and depression diagnoses. This could lead to a floor effect with no improvements in symptoms to detect.

The exclusion of patients with mental health conditions not only decreases variability on the outcome variable, but it also raises troubling ethical concerns. One of the goals of palliative care is to address psychological symptoms.<sup>6,7</sup> RCTs, such as those included in the current study, often influence medical care and inform evidence based practice. When studies exclude patients with psychological disorders, as over 1/3 of the studies in this review did, then the very individuals who may be most in need of palliative care's integrative approach to suffering are not represented in the clinical trial. The systematic exclusion of individuals with psychopathology is not uncommon,<sup>79</sup> even in trials of treatments for mental health conditions,<sup>80</sup> and likely contributes to and perpetuates health inequities.

In addition, the included studies also had a wide variety of intervention approaches to address psychological distress among enrolled subjects, which constitutes a challenge for conducting a systematic review and meta-analysis.<sup>81</sup> This issue is underscored by the large heterogeneity statistics for most of the analyses. This may have added more difficulty to determining an effect of interventions on psychological distress outcomes because the interventions themselves varied greatly, possibly diffusing effects.

Our findings from specialty mental health clinician moderator analyses were non-significant. This may be due to the lack of specificity of training background of clinicians (inclusive of psychologists, social workers, and psychiatric nurses). Furthermore, some mental health clinicians may offer general support while others may

offer medication management or evidence-based psychotherapies. Just over one quarter of studies included a manualized therapeutic or behavioral intervention such as cognitive behavioral therapy. In palliative care, general psychosocial support is often offered,<sup>1</sup> but less effective than CBT in managing anxiety symptoms.<sup>82</sup> Future studies should consider the type of psychological intervention as a potential moderator of the effect of palliative care on psychological distress symptoms, and its specificity in addressing different distress outcomes (e.g. symptoms of anxiety, depression, PTSD, etc.).

The current findings seem to contrast with preliminary evidence from observational studies that have demonstrated that palliative care service use may reduce suicidal self-violence among veterans with<sup>11,83</sup> and without<sup>10</sup> cancer diagnoses. If palliative care does indeed decrease suicide risk, but does not reliably decrease psychological distress, it will be important to examine alternative mechanisms by which palliative care mitigates suicide risk (e.g., reducing pain; increasing social connection).

The current study is consistent with and extends prior work on mental health services in palliative care. A 2018 review of psychological interventions in palliative care found that many studies failed to describe how psychological symptoms were identified and treated, which team member within the palliative care team delivered psychological treatment, and whether symptoms improved as a result.<sup>84</sup> In the current systematic review, we similarly observed that descriptions of the palliative care interventions often lack enough detail to determine who is delivering particular components of the intervention and whether there is a specific psychological treatment component of the intervention, let alone if the psychological treatment is manualized or evidence-based. However, there seems to be improvement over the last few years, with several of the more recent RCTs providing more detail than earlier studies. Our findings add to the literature by including more studies and a meta-analysis to quantify the effect of the interventions.

Our study demonstrated a need to carefully consider whether improvement in psychological distress symptoms is a realistic outcome of general palliative care interventions or if perhaps non-worsening psychological symptoms may be a more realistic goal for patients nearing end of life. If study participants are enrolled late in their illness trajectory, as would be expected in many palliative care studies, it may be more difficult to reduce psychological distress at that point in the disease trajectory given that distress tends to

increase as end of life approaches, especially in illnesses with high symptom burden.<sup>5,85</sup> Furthermore, researchers should consider *how* they expect palliative care to impact psychological symptoms, whether directly through psychosocial treatment or indirectly through other symptom management, and design RCTs accordingly. We recommend that researchers include the mechanism through which they expect to impact psychological symptoms. More research is needed in efficacy trials to identify effective and appropriate psychological interventions for use in palliative care settings.

*Limitations.* This study is subject to some limitations. First, only RCTs published in English were included due to language limitations of the study team. Future work should include studies written in many languages. Next, studies were included only if they reported outcomes between 2 and 4 months after study intake. The longer-term effects of palliative care interventions on psychological distress are not yet estimated in a meta-analysis. Next, this meta-analysis investigated the effects of heterogeneous interventions on heterogeneous populations seen in heterogeneous settings by heterogeneous palliative care teams. While several moderator analyses were performed to investigate the effects of some dimensions of variation among both interventions and populations, future work could focus on specific aspects of palliative care interventions or on specific populations.

*Implications for policy, practice, and future research.*

Palliative care is a relatively new field which has demonstrated efficacy for managing burdensome symptoms and improving quality of life for people with serious illness. While psychological science and psychiatry have made strides in improving psychological distress symptoms, these advances have not been fully integrated into palliative care. Future RCTs may benefit from including theoretically-grounded psychological interventions that are adapted for and integrated into palliative care settings. The field will also benefit from increasing transparency and accountability through trial pre-registration, providing sample size estimates to detect an effect in the psychological distress variable, and specifying a basis for the assessment time points. We also believe that research teams must include patients with existing mental health conditions in their studies to improve quality of care for this group that is often under-represented in clinical trials.

In conclusion, this systematic review and meta-analysis uncovered no evidence to support the idea that palliative care interventions reduce psychological distress, but we did identify conceptual and methodological problems in the literature that could be remedied. More work is needed to adapt and integrate theoretically-grounded, evidence-based psychological interventions into studies of palliative care and rigorously evaluate outcomes in seriously ill populations.

#### Disclosure/Conflict of Interest Statement

The authors have no financial relationships to disclose. The authors also have no conflicts of interest to disclose.

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## References

1. Kozlov E, Eghan C, Moran S, Herr K, Reid MC. Palliative Care Providers' Practices Surrounding Psychological Distress Screening and Treatment: A National Survey. *Am J Hosp Palliat Med*. 2018;35(7):938-944. doi:10.1177/1049909117743960
2. Ridner SH. Psychological distress: concept analysis. *J Adv Nurs*. 2004;45(5):536-545. doi:10.1046/j.1365-2648.2003.02938.x
3. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol*. 2011;12(2):160-174. doi:10.1016/S1470-2045(11)70002-X
4. Yohannes AM, Willgoss TG, Baldwin RC, Connolly MJ. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psychiatry*. 2010;25(12):1209-1221. doi:10.1002/gps.2463
5. Kozlov E, Dong X, Kelley AS, Ankuda CK. The Epidemiology of Depressive Symptoms in the Last Year of Life. *J Am Geriatr Soc*. 2020;68(2):321-328. doi:https://doi.org/10.1111/jgs.16197
6. National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care, 4th Edition*. National Coalition for Hospice and Palliative Care; 2018. <https://www.nationalcoalitionhpc.org/ncp>.
7. World Health Organization. Palliative Care. Published 2020. Accessed November 20, 2021. <https://www.who.int/news-room/fact-sheets/detail/palliative-care>
8. Temel JS, Greer JA, Muzikansky A, et al. Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2010;363(8):733-742. doi:10.1056/NEJMoa1000678
9. Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *JAMA*. 2009;302(7):741-749. doi:10.1001/jama.2009.1198
10. Kutney-Lee A, Khazanov GK, Carpenter JG, et al. Palliative Care and Documented Suicide: Association Among Veterans with High Mortality Risk. *J Pain Symptom Manage*. Published online April 28, 2022. doi:10.1016/j.jpainsymman.2022.04.179
11. Sullivan DR, Forsberg CW, Golden SE, Ganzini L, Dobscha SK, Slatore CG. Incidence of Suicide and Association with Palliative Care among Patients with Advanced Lung Cancer. *Ann Am Thorac Soc*. 2018;15(11):1357-1359. doi:10.1513/AnnalsATS.201805-299RL
12. Nugent SM, Morasco BJ, Handley R, et al. Risk of Suicidal Self-directed Violence Among US Veteran Survivors of Head and Neck Cancer. *JAMA Otolaryngol Neck Surg*. Published online October 7, 2021. doi:10.1001/jamaoto.2021.2625
13. Kavalieratos D, Corbelli J, Zhang D, et al. Association Between Palliative Care and Patient and Caregiver Outcomes: A Systematic Review and Meta-analysis. *JAMA*. 2016;316(20):2104. doi:10.1001/jama.2016.16840
14. Gaertner J, Siemens W, Meerpohl JJ, et al. Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis. *BMJ*. Published online July 4, 2017;j2925. doi:10.1136/bmj.j2925



15. Quinn KL, Shurrab M, Gitau K, et al. Association of Receipt of Palliative Care Interventions With Health Care Use, Quality of Life, and Symptom Burden Among Adults With Chronic Noncancer Illness: A Systematic Review and Meta-analysis. *JAMA*. 2020;324(14):1439-1450. doi:10.1001/jama.2020.14205
16. Singer AE, Goebel JR, Kim YS, et al. Populations and Interventions for Palliative and End-of-Life Care: A Systematic Review. *J Palliat Med*. 2016;19(9):995-1008. doi:10.1089/jpm.2015.0367
17. Hoerger M, Wayser G, Schwing G, Suzuki A, Perry L. Impact of Interdisciplinary Outpatient Specialty Palliative Care on Survival and Quality of Life in Adults With Advanced Cancer: A Meta-Analysis of Randomized Controlled Trials. *Ann Behav Med*. 2019;53(7):674-685. doi:10.1093/abm/kay077
18. Hui D, Bruera E. Models of integration of oncology and palliative care. *Ann Palliat Med*. 2015;4(3):898-898.
19. Kaasa S, Loge J, Aapro M, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. *LANCET Oncol*. 2018;19(11):E588-E653. doi:10.1016/S1470-2045(18)30415-7
20. Hui D, Kim Y, Park J, et al. Integration of Oncology and Palliative Care: A Systematic Review. *ONCOLOGIST*. 2015;20(1):77-83. doi:10.1634/theoncologist.2014-0312
21. Lunney JR, Lynn J, Foley DJ, Lipson S, Guralnik JM. Patterns of Functional Decline at the End of Life. *JAMA*. 2003;289(18):2387-2392. doi:10.1001/jama.289.18.2387
22. Cagle JG, Bunting M, Kelemen A, Lee J, Terry D, Harris R. Psychosocial needs and interventions for heart failure patients and families receiving palliative care support: a systematic review. *Heart Fail Rev*. 2017;22(5):565-580. doi:10.1007/s10741-017-9596-5
23. Garland EL, Bruce A, Stajduhar K. Exposing barriers to end-of-life communication in heart failure: an integrative review. *Can J Cardiovasc Nurs J Can En Soins Infirm Cardio-Vasc*. 2013;23(1):12-18.
24. Savović J, Turner RM, Mawdsley D, et al. Association Between Risk-of-Bias Assessments and Results of Randomized Trials in Cochrane Reviews: The ROBES Meta-Epidemiologic Study. *Am J Epidemiol*. 2018;187(5):1113-1122. doi:10.1093/aje/kwx344
25. PRISMA. Accessed September 19, 2021. <http://prisma-statement.org/prismastatement/Checklist.aspx>
26. NIH U.S. National Library of Medicine. Home - ClinicalTrials.gov. Accessed April 5, 2022. <https://clinicaltrials.gov/>
27. Zwakman M, Jabbarian L, van Delden J, et al. Advance care planning: A systematic review about experiences of patients with a life-threatening or life-limiting illness. *Palliat Med*. 2018;32(8):1305-1321. doi:10.1177/0269216318784474
28. Mellor C, Hain R. Paediatric palliative care: not so different from adult palliative care? *Br J Hosp Med*. 2010;71(1):36-39. doi:10.12968/hmed.2010.71.1.45971
29. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: *Joanna Briggs Institute Reviewer's Manual*. The Joanna Briggs Institute; 2017. <https://reviewersmanual.joannabriggs.org/>
30. Xiang B, Wong HM, Perfecto AP, McGrath CPJ. The effectiveness of behavioral interventions to improve oral health in adolescents at different periods of follow-up: A systematic review and meta-analysis. *Patient Educ Couns*. 2020;103(4):725-733. doi:10.1016/j.pec.2019.11.030

31. Borenstein M, ed. *Introduction to Meta-Analysis*. John Wiley & Sons; 2009.
32. Cochrane Handbook for Systematic Reviews of Interventions. Accessed December 18, 2022. <https://training.cochrane.org/handbook/current>
33. Borenstein M, Hedges L, Higgins J, Rothstein H. Multiple outcomes or time-points within a study. In: *Introduction to Meta-Analysis*. John Wiley & Sons, Ltd; 2009:225-238.
34. Terrill AL, Hartoonian N, Beier M, Salem R, Alschuler K. The 7-Item Generalized Anxiety Disorder Scale as a Tool for Measuring Generalized Anxiety in Multiple Sclerosis. *Int J MS Care*. 2015;17(2):49-56. doi:10.7224/1537-2073.2014-008
35. Cameron IM, Crawford JR, Lawton K, Reid IC. Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care. *Br J Gen Pract*. 2008;58(546):32-36. doi:10.3399/bjgp08X263794
36. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011;64(11):1187-1197. doi:10.1016/j.jclinepi.2010.08.010
37. R Core Team. R: A language and environment for statistical computing. Published online 2020. <https://www.R-project.org/>
38. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw*. 2010;36(3). doi:10.18637/jss.v036.i03
39. Harrer M, Cuijpers P, Furukawa T, Ebert DD. dmetar: Companion R Package For the Guide “Doing Meta-Analysis in R.” Published online 2019. <http://dmetar.protectlab.org/>
40. Bekelman DB, Allen LA, McBryde CF, et al. Effect of a Collaborative Care Intervention vs Usual Care on Health Status of Patients With Chronic Heart Failure: The CASA Randomized Clinical Trial. *JAMA Intern Med*. 2018;178(4):511-519. doi:10.1001/jamainternmed.2017.8667
41. Carson SS, Cox CE, Wallenstein S, et al. Effect of Palliative Care-Led Meetings for Families of Patients With Chronic Critical Illness: A Randomized Clinical Trial. *JAMA*. 2016;316(1):51-62. doi:10.1001/jama.2016.8474
42. Dionne-Odom JN, Azuero A, Lyons KD, et al. Benefits of Early Versus Delayed Palliative Care to Informal Family Caregivers of Patients With Advanced Cancer: Outcomes From the ENABLE III Randomized Controlled Trial. *J Clin Oncol Off J Am Soc Clin Oncol*. 2015;33(13):1446-1452. doi:10.1200/JCO.2014.58.7824
43. Dionne-Odom JN, Azuero A, Lyons KD, et al. Family Caregiver Depressive Symptom and Grief Outcomes From the ENABLE III Randomized Controlled Trial. *J Pain Symptom Manage*. 2016;52(3):378-385. doi:10.1016/j.jpainsymman.2016.03.014
44. Dionne-Odom JN, Ejem DB, Wells R, 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 Netw Open*. 2020;3(4):e202583. doi:10.1001/jamanetworkopen.2020.2583
45. El-Jawahri A, Greer JA, Pirl WF, et al. Effects of Early Integrated Palliative Care on Caregivers of Patients with Lung and Gastrointestinal Cancer: A Randomized Clinical Trial. *The oncologist*. 2017;22(12):1528-1534. doi:10.1634/theoncologist.2017-0227

46. El-Jawahri A, LeBlanc T, VanDusen H, et al. Effect of Inpatient Palliative Care on Quality of Life 2 Weeks After Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. *JAMA*. 2016;316(20):2094-2103. doi:10.1001/jama.2016.16786
47. El-Jawahri A, LeBlanc TW, Kavanaugh A, et al. Effectiveness of Integrated Palliative and Oncology Care for Patients With Acute Myeloid Leukemia: A Randomized Clinical Trial. *JAMA Oncol*. 2021;7(2):238-245. doi:10.1001/jamaoncol.2020.6343
48. Ferrell B, Chung V, Hughes MT, et al. A Palliative Care Intervention for Patients on Phase 1 Studies. *J Palliat Med*. 2021;24(6):846-856. doi:10.1089/jpm.2020.0597
49. Grudzen CR, Richardson LD, Johnson PN, et al. Emergency Department–Initiated Palliative Care in Advanced Cancer: A Randomized Clinical Trial. *JAMA Oncol*. 2016;2(5):591-598. doi:10.1001/jamaoncol.2015.5252
50. Janssen K, Rosielle D, Wang Q, Kim HJ. The impact of palliative care on quality of life, anxiety, and depression in idiopathic pulmonary fibrosis: a randomized controlled pilot study. *Respir Res*. 2020;21(1):2. doi:10.1186/s12931-019-1266-9
51. Bakitas MA, Dionne-Odom JN, Ejem DB, et al. Effect of an Early Palliative Care Telehealth Intervention vs Usual Care on Patients With Heart Failure: The ENABLE CHF-PC Randomized Clinical Trial. *JAMA Intern Med*. 2020;180(9):1203-1213. doi:10.1001/jamainternmed.2020.2861
52. Bakitas MA, Tosteson TD, Li Z, et al. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol*. Published online March 23, 2015. doi:10.1200/JCO.2014.58.6362
53. McCorkle R, Jeon S, Ercolano E, et al. An Advanced Practice Nurse Coordinated Multidisciplinary Intervention for Patients with Late-Stage Cancer: A Cluster Randomized Trial. *J Palliat Med*. 2015;18(11):962-969. doi:10.1089/jpm.2015.0113
54. Nordly M, Skov Benthien K, Vadstrup ES, et al. Systematic fast-track transition from oncological treatment to dyadic specialized palliative home care: DOMUS - a randomized clinical trial. *Palliat Med*. 2019;33(2):135-149. doi:10.1177/0269216318811269
55. O’Riordan DL, Rathfon MA, Joseph DM, et al. Feasibility of Implementing a Palliative Care Intervention for People with Heart Failure: Learnings from a Pilot Randomized Clinical Trial. *J Palliat Med*. 2019;22(12):1583-1588. doi:10.1089/jpm.2018.0633
56. Schenker Y, Althouse AD, Rosenzweig M, et al. Effect of an Oncology Nurse–Led Primary Palliative Care Intervention on Patients With Advanced Cancer: The CONNECT Cluster Randomized Clinical Trial. *JAMA Intern Med*. 2021;181(11):1451. doi:10.1001/jamainternmed.2021.5185
57. Sidebottom AC, Jorgenson A, Richards H, Kirven J, Sillah A. Inpatient palliative care for patients with acute heart failure: outcomes from a randomized trial. *J Palliat Med*. 2015;18(2):134-142. doi:10.1089/jpm.2014.0192
58. Temel JS, Greer JA, El-Jawahri A, et al. Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial. *J Clin Oncol Off J Am Soc Clin Oncol*. 2017;35(8):834-841. doi:10.1200/JCO.2016.70.5046

59. Temel JS, Sloan J, Zemla T, et al. Multisite, Randomized Trial of Early Integrated Palliative and Oncology Care in Patients with Advanced Lung and Gastrointestinal Cancer: Alliance A221303. *J Palliat Med.* 2020;23(7):922-929. doi:10.1089/jpm.2019.0377
60. Ammari ABH, Hendriksen C, Rydahl-Hansen S. Results from the family and coping oriented palliative homecare intervention study (FamCope)-A randomized controlled trial. *J Psychosoc Oncol.* 2018;36(5):557-581. doi:10.1080/07347332.2018.1460003
61. Johnsen AT, Petersen MA, Sjøgren P, et al. Exploratory analyses of the Danish Palliative Care Trial (DanPaCT): a randomized trial of early specialized palliative care plus standard care versus standard care in advanced cancer patients. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer.* 2020;28(5):2145-2155. doi:10.1007/s00520-019-05021-7
62. von Heymann-Horan A, Bidstrup P, Guldin MB, et al. Effect of home-based specialised palliative care and dyadic psychological intervention on caregiver anxiety and depression: a randomised controlled trial. *Br J Cancer.* 2018;119(11):1307-1315. doi:10.1038/s41416-018-0193-8
63. McDonald J, Swami N, Hannon B, et al. Impact of early palliative care on caregivers of patients with advanced cancer: cluster randomised trial. *Ann Oncol Off J Eur Soc Med Oncol.* 2017;28(1):163-168. doi:10.1093/annonc/mdw438
64. Rodin G, Malfitano C, Rydall A, et al. Emotion And Symptom-focused Engagement (EASE): a randomized phase II trial of an integrated psychological and palliative care intervention for patients with acute leukemia. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer.* 2020;28(1):163-176. doi:10.1007/s00520-019-04723-2
65. Maltoni M, Scarpi E, Dall'Agata M, et al. Systematic versus on-demand early palliative care: results from a multicentre, randomised clinical trial. *Eur J Cancer Oxf Engl 1990.* 2016;65:61-68. doi:10.1016/j.ejca.2016.06.007
66. Solari A, Giordano A, Patti F, et al. Randomized controlled trial of a home-based palliative approach for people with severe multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl.* 2018;24(5):663-674. doi:10.1177/1352458517704078
67. Chan KY, Yip T, Yap DYH, et al. Enhanced Psychosocial Support for Caregiver Burden for Patients With Chronic Kidney Failure Choosing Not to Be Treated by Dialysis or Transplantation: A Pilot Randomized Controlled Trial. *Am J Kidney Dis Off J Natl Kidney Found.* 2016;67(4):585-592. doi:10.1053/j.ajkd.2015.09.021
68. Ng AYM, Wong FKY. Effects of a Home-Based Palliative Heart Failure Program on Quality of Life, Symptom Burden, Satisfaction and Caregiver Burden: A Randomized Controlled Trial. *J Pain Symptom Manage.* 2018;55(1):1-11. doi:10.1016/j.jpainsymman.2017.07.047
69. Scheerens C, Pype P, Van Cauwenberg J, et al. Early Integrated Palliative Home Care and Standard Care for End-Stage COPD (EPIC): A Phase II Pilot RCT Testing Feasibility, Acceptability, and Effectiveness. *J Pain Symptom Manage.* 2020;59(2):206-+. doi:10.1016/j.jpainsymman.2019.09.012
70. Vanbutsele G, Pardon K, Van Belle S, et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. *Lancet Oncol.* 2018;19(3):394-404. doi:10.1016/S1470-2045(18)30060-3

71. Slama O, Pochop L, Sedo J, et al. Effects of Early and Systematic Integration of Specialist Palliative Care in Patients with Advanced Cancer: Randomized Controlled Trial PALINT. *J Palliat Med.* 2020;23(12):1586-1593. doi:10.1089/jpm.2019.0697
72. Jordhøy MS, Fayers P, Loge JH, Ahlner-Elmqvist M, Kaasa S. Quality of life in palliative cancer care: results from a cluster randomized trial. *J Clin Oncol Off J Am Soc Clin Oncol.* 2001;19(18):3884-3894. doi:10.1200/JCO.2001.19.18.3884
73. Hoek PD, Schers HJ, Bronkhorst EM, Vissers KCP, Hasselaar JGJ. The effect of weekly specialist palliative care teleconsultations in patients with advanced cancer -a randomized clinical trial. *BMC Med.* 2017;15(1):119. doi:10.1186/s12916-017-0866-9
74. do Carmo TM, Paiva BSR, de Oliveira CZ, Nascimento MS de A, Paiva CE. The feasibility and benefit of a brief psychosocial intervention in addition to early palliative care in patients with advanced cancer to reduce depressive symptoms: a pilot randomized controlled clinical trial. *BMC Cancer.* 2017;17(1):564. doi:10.1186/s12885-017-3560-6
75. Brims F, Gunatilake S, Lawrie I, et al. Early specialist palliative care on quality of life for malignant pleural mesothelioma: a randomised controlled trial. *Thorax.* 2019;74(4):354-361. doi:10.1136/thoraxjnl-2018-212380
76. Gao W, Wilson R, Hepgul N, et al. Effect of Short-term Integrated Palliative Care on Patient-Reported Outcomes Among Patients Severely Affected With Long-term Neurological Conditions: A Randomized Clinical Trial. *JAMA Netw Open.* 2020;3(8):e2015061. doi:10.1001/jamanetworkopen.2020.15061
77. Chan KY, Yip T, Yap DYH, et al. Enhanced Psychosocial Support for Caregiver Burden for Patients With Chronic Kidney Failure Choosing Not to Be Treated by Dialysis or Transplantation: A Pilot Randomized Controlled Trial. *Am J Kidney Dis Off J Natl Kidney Found.* 2016;67(4):585-592. doi:10.1053/j.ajkd.2015.09.021
78. Ferrell BR, Paterson CL, Hughes MT, Chung V, Koczywas M, Smith TJ. Characteristics of Participants Enrolled onto a Randomized Controlled Trial of Palliative Care for Patients on Phase I Studies. *J Palliat Med.* 2017;20(12):1338-1344. doi:10.1089/jpm.2017.0158
79. Humphreys K, Blodgett JC, Roberts LW. The exclusion of people with psychiatric disorders from medical research. *J Psychiatr Res.* 2015;70:28-32. doi:10.1016/j.jpsychires.2015.08.005
80. Iltis AS, McCall WV, Deria R. Suicidality, Depression, and the FDA: Health Inequities and the Ethical Conduct of Research. *J Clin Psychiatry.* 2020;81(2):20306. doi:10.4088/JCP.19m13050
81. Fletcher J. What is heterogeneity and is it important? *BMJ.* 2007;334(7584):94-96. doi:10.1136/bmj.39057.406644.68
82. Ayers CR, Sorrell JT, Thorp SR, Wetherell JL. Evidence-based psychological treatments for late-life anxiety. *Psychol Aging.* 2007;22(1):8-17. doi:10.1037/0882-7974.22.1.8
83. Nugent SM, Morasco BJ, Handley R, et al. Risk of Suicidal Self-directed Violence Among US Veteran Survivors of Head and Neck Cancer. *JAMA Otolaryngol Neck Surg.* Published online October 7, 2021. doi:10.1001/jamaoto.2021.2625
84. Kozlov E, Niknejad B, Reid MC. Palliative Care Gaps in Providing Psychological Treatment: A Review of the Current State of Research in Multidisciplinary Palliative Care. *Am J Hosp Palliat Med.* 2018;35(3):505-510. doi:10.1177/1049909117723860

85. Kozlov E, Phongtankuel V, Prigerson H, et al. Prevalence, Severity, and Correlates of Symptoms of Anxiety and Depression at the Very End of Life. *J Pain Symptom Manage*. 2019;58(1):80-85. doi:10.1016/j.jpainsymman.2019.04.012

Journal Pre-proof

Study	# Subjects	Patient Illness(es)	Patient or Caregiver Outcomes	Specialty MH clinician?	Primary outcome distress?	Manualized psychological intervention	Theoretical or Conceptual Background	Care delivery team	Content of intervention	Excluded elevated distress?	Baseline Distress Measures
Ammari et al., 2018 <sup>60</sup>	57	Advanced solid cancer patients	Patient	no	no	--	Lazarus's stress and coping theory	Nurses	appraise and cope with problems, support	no	Intervention HADS-D: 6.89 (2.86) Intervention HADS-A: 6.36 (4.56); Control D: 6.86 (2.72), A: 4.66 (3.68)
Bakitas et al., 2009 <sup>9</sup>	279	Advanced cancer patients	Patient	no	no	problem solving therapy	chronic care model	APN with specialty in PC	problem solving, communication and social support, symptom management, advance care planning, unfinished business	excluded axis I diagnoses and people with substance use	not reported alone, only change reported
Bakitas et al., 2015 <sup>52</sup>	207	Advanced cancer	Patient	no	no	problem solving therapy	--	Board-certified PC clinician, APN coach	problem solving, self care, local resources, communication, decision making, ACP; life review and creating legacy	excluded if active axis I diagnosis or active substance use disorder	Intervention CESD: 14.99(10.64); Control: 13.42(9.47)

Bakitas et al., 2020 <sup>31</sup>	415	Advanced heart failure	Patient	no	yes	problem solving therapy	chronic care model, National Consensus Project Guidelines for Quality Palliative Care, Outlook intervention	PC clinician, nurse coach	COPE (creativity, optimism, planning, expert information); self-care (healthy eating, exercise, meditation, spirituality and partnering); physical and emotional symptom management; decision making; life review and creating legacy	excluded if untreated axis I diagnosis or active substance use disorder	Intervention: HADS-A:6.6 (3.5), HADS-D:5.7(4.3); Control: HADS-A:6.8(3.7), HADS-D:5.8(4.2)
Bekelman et al., 2018 <sup>40</sup>	314	Chronic heart failure patients	Patient	yes	no	--	interpersonal and behavioral activation psychotherapies	Team: nurse, primary care clinician, social worker, PC specialist, cardiologist	symptom management, grief and loss, change in role, behavioral activation, pacing, medical review	excluded those with substance use and SMI	phq-9 at baseline: median IQR: 9 (5-14)
Brims et al., 2019 <sup>75</sup>	174	Mesothelioma	Caregiver	no	no	--	--	PC physician	assessment of patient physical, psychological, social, and spiritual needs	excluded those with a psych-related hospitalization in last 12 months	didn't report baseline
Carson et al., 2016 <sup>41</sup>	365	Chronic critical illness that required mechanical ventilation	Caregiver*	no	yes	--	--	PC physician and NP; team could also include social workers, chaplains, and other disciplines as needed		no	Intervention HADS total: 16.0 (8.1) Control: 16.4 (8.4)



Chan et al., 2016 <sup>67</sup>	29	Kidney failure	Caregiver*	no	yes	--	--	PC nurse, social worker, PC physician	enhanced psychosocial support (including education), symptom advice and prevention, psychosocial-spiritual support, social support and advice about financial issues	no	Intervention HADS-A:9.9 (3.3), HADS-D: 5.4 (4.5); Control: HADS-A: 9.1 (2.3), HADS-D:6.4 (2.9)
Dionne-Odom et al., 2015; <sup>42</sup> Dionne-Odom et al., 2016 <sup>43</sup>	122	Advanced cancer	Caregiver*	no	yes	problem solving therapy	--	nurse coaches	COPE (creativity, optimism, planning, expert information); self-care (healthy eating, exercise, meditation, spirituality and partnering); communication; decision making; decision support; ACP	excluded if untreated axis I diagnosis or active substance use disorder	Early group: CESD: 13.4 (SE 1.3), Delayed group: 15.9 (1.4)
Dionne-Odom et al., 2020 <sup>44</sup>	158	Advanced heart failure	Caregiver*	no	yes	problem solving therapy	Wagner's chronic care model; National Consensus Project Guidelines for Quality Palliative Care	Nurse coaches with specific training for this PC intervention	COPE (creativity, optimism, planning, expert information); self-care (healthy eating, exercise, meditation, spirituality and partnering); communication; decision making; decision support; ACP	excluded documented active axis I disorder	Intervention: HADS-A: 3.9(3.1), HADS-D: 4.7 (3.1); Control: HADS-A: 3.7(2.9), HADS-D: 4.8 (3.3)

do Carmo et al., 2017 <sup>74</sup>	63	Advanced cancer	Patient	yes	yes	CBT	session structure method	PC Physician	psychoeducation; discuss functioning of anxiety and techniques to manage symptoms, discuss depressive symptoms	excluded if receiving psychological treatment for any psych disorder or any pharmacological antidepressants for depression and/or anxiety	Arm A: HADS-A:5.79 (3.92), HADS-D:5.11 (4.51), PHQ-9:9.7 (6.5); Arm B: HADS-A: 7.14 (3.41), HADS-D: 7.14 (4.12), PHQ-9: 10.3 (6.0); Arm C: HADS-A:6.27 (4.84), HADS-D: 7.18 (4.92), PHQ-9: 9.8 (6.5)
El-Jawahri et al., 2017 <sup>45</sup>	137	Incurable lung or non-colorectal GI cancer	Caregiver	no	no	--	--	Boarded PC physician or APN	addressing symptoms, enhancing coping efforts, establishing rapport, illness and prognostic understanding, treatment decisions, ACP, discussing disposition	none for CG	not reported alone, only change reported
El-Jawahri et al., 2016 <sup>46</sup>	160	Hematologic Cancer	Patient	no	no	--	--	Inpatient PC physician or APN	managing physical and psychological symptoms	those with existing psych condition the oncologist thought may interfere were excluded	Control: PHQ-9 5.4 (4.7), HADS-D: 4.9(4.1), HADS-A:5.4(3.8); Intervention PHQ-9: 4.8 (4.4), HADS-D: 4.0 (3.2), HADS-A:4.6(3.6)

El-Jawahri et al., 2021 <sup>47</sup>	160	cancer	Patient	no	no	--	--	PC physician, inpatient palliative care physician, advance practice nurse, or physician assistant	address symptoms, assess understanding, goals and expectations, decision-making	those with existing psych condition the oncologist thought may interfere were excluded	Intervention: HADS-A: 6.4 (4.6), HADS-D: 5.5 (3.9), PHQ-9:6.3 (5.0); Control: HADS-A:6.2 (4.1), HADS-D:5.6 (3.3), PHQ-9:6.9 (4.9)
Ferrell et al., 2021 <sup>48</sup>	479	Cancer	Patient	no	yes	--	--	nurses, chaplain, SW, oncologist	teaching sessions addressing symptoms and QOL	not clear	did not report distress at study intake
Gao et al., 2020 <sup>76</sup>	350	long-term neurological conditions (any advanced stage MS, motor neuron disease, idiopathic Parkinson disease multiple system atrophy, or progressive supranuclear palsy)	Patient	no	no	--	Medical Research Council framework for evaluating complex interventions	Existing multidisciplinary PC teams	assessment, personalized care planning, case management/care coordination, advising existing care providers	no	Intervention: HADS-A: 7.78(6.78,8.77), HADS-D: 8.13(7.29, 8.97); Control: HADS-A: 7.51 (6.52, 8.50), HADS-D: 8.31 (7.47, 9.16)

Grudzen et al., 2016 <sup>49</sup>	136	cancer	Patient	no	yes	--	--	physician, NP, social worker, chaplain	symptom assessment/treatment, goals of care and ACP, and transition planning	no	Intervention: 35% had MDD, Control: 29% with MDD
Hoek et al., 2017 <sup>73</sup>	74	Advanced cancer	Patient	no	yes	yes	--	mostly delivered by nurse, but GP was involved when possible		no	Intervention: HADS-A:7.24 (4.7), HADS-D: 7.66(3.87); Control: HADS-A:6.22 (3.91), HADS-D:6.49(4.57)
Janssen et al., 2020 <sup>50</sup>	22	Idiopathic pulmonary fibrosis	Patient	no	no	--	--	physicians, nurses, SWs	intro to PC, symptom and QOL assessment, support network assessment, prognostic understanding, planning decisions, care goals	no	HADS-A: 5.3 (4.3), HADS-D:4.0(3.2), PHQ-9: 5.4(5.3)
Johnsen et al., 2020 <sup>61</sup>	297	Stage IV cancer or stage III/IV CNS cancer	Patient	yes	no	--	European Association for Palliative Care and WHO guidelines	at least 4 different disciplines, always including nurses, physicians, all had psychologist		no	Intervention HADS-A: 6.9 (4.1), HADS-D: 6.3 (3.9); Control: HADS-A: 6.8 (3.9), HADS-D: 6.3 (3.7)
Jordhoy et al., 2001 <sup>72</sup>	434	Advanced cancer	Patient	no	no	--	--	PC Program includes GPs, home care nurses, nursing homes, Pall medicine unit physician & nurse		no	Intervention: IES-Avoidance:17(11), IES-Intrusion:14(10); Control: IES-Avoidance:18(11), IES-Intrusion: 15(10)

Maltoni et al., 2016 <sup>65</sup>	186	Advanced/metastatic pancreatic cancer	Patient	no	no	--	--	PC specialist		no	Intervention elevated HADS-A:42.3%, HADS-D:39.4%; Control HADS-A:45.3%, HADS-D:28%
McCorkle et al., 2015 <sup>33</sup>	146	Late stage gynecological and lung cancer	Patient	no	no	--	--	APNs, Pas, MSWs	symptom management, teaching patients and caregivers, enhancing QOL, goals of care; enhance patient problem solving, decision making, and self-efficacy	no	PHQ-9:5.10(4.33)
McDonald et al., 2017 <sup>65</sup>	182	Stage IV cancer or stage III cancer with poor prognosis	Caregiver	no	no	--	--	PC physician and nurse	symptom management, goals of care, ACP, social/emotional/spiritual needs	no	Intervention: 43.5 (40.7-46.3); Control: 42.7(40.1, 45.2)
Ng & Wong, 2018 <sup>68</sup>	84	End-stage heart failure	Patient	no	no	--	Omaha system	PC nurse case managers and trained volunteer nursing students	physical and psychological symptoms management, social support, spiritual support, goals of care, treatment preference and EOL issues	excluded those with psych disorder requiring active treatment	Median and IQR. Intervention: ESAS-A: 2 (0,6), ESAS-D: 2 (0,6); Control: ESAS-A: 3 (0,6), ESAS-D: 3, (0,6)
Nordly et al., 2019 <sup>34</sup>	322	Cancer	Patient	yes	no	existential-phenomenological therapy	--	nurse, GP, psychologist, in addition to specialized PC team		no	Intervention HADS-A:5.8 (3.8), HADS-D: 4.5(3.6); Control HADS-A:

											5.0(4.0), HADS-D: 4.4(3.6)
O'Riordan et al., 2019 <sup>55</sup>	30	Heart failure	Patient	no	yes	--	--	Interdisciplinary PC team including NP, physician, social worker, chaplain	meds for symptoms, ACP, psychosocial and spiritual support	no, just excluded active illicit drug use	Intervention: HADS-A: 5.9(3.5-8.2), HADS-D: 5.4(3.4-7.4); Control: HADS-A: 7.4(4.9-9.9) HADS-D: 6.5(4.-8.6);
Rodin et al., 2020 <sup>64</sup>	42	Acute leukemia	Patient	yes	no	supportive psychotherapy and CBT, based on Anxiety Reduction Treatment for Acute Trauma intervention	--	MSW as psychosocial clinician, hematology physicians, nurses, allied health; consultation with PC nurses and PC physicians in 1st week and as needed	problem solving, education, modulate emotions	excluded those already receiving psychological or psychiatric care	Intervention BDI:10.25 (SE 1.73); Control: 13.20(SE 1.83)
Scheerens et al., 2020 <sup>69</sup>	39	COPD	Patient	yes	no	--	--	HCNs, PHC physicians, and psychologists	disease insight and coping, symptom management, care planning, caregiver support, psychosocial/existential/spiritual support	no	Intervention: HADS-A: 8.5(5.4, 11.6), HADS-D: 7.9 (5.8,10.0); Control: HADS-A: 8.3(5.2,11.4), HADS-D: 10.2 (8.1, 12.3)

Schenker et al., 2021 <sup>56</sup>	672	cancer	Patient	no	no	--	chronic care model	nurse delivered, shared plans with oncologists	establish rapport, addressing symptom needs, choosing surrogate decision maker, treatment preferences, completion of AD	no	HADS-A: 5.78 (3.90), HADS-D: 5.41(3.75)
Sidebottom et al., 2015 <sup>57</sup>	232	Acute heart failure	Patient	no	no	--	--	PC team: 4 HPM boarded physicians, 2 AP PC nurses, social worker, chaplain	symptom burdens, emotional/spiritual/psychosocial aspects of care, coordination of care, recommendations in treatment, referrals, care planning	no	PHQ-9: 8.3(5.2)
Slama et al., 2020 <sup>71</sup>	126	cancer	Patient	yes	no	--	--	referred out from PC physician to SW, psychologist etc as needed	pain and symptom management, coping strategies, need for psychosocial support	no	Intervention: elevated anxiety:35.7% , elevated depression: 28.3%; Control: elevated anxiety: 34.8%, elevated depression: 28.8%
Solari et al., 2018 <sup>66</sup>	78	Severe MS	Patient	yes	no	--	--	Home-based PC team including a physician (neurology, psychiatrist), nurse with specialty training in PC, psychologist, social worker		no	Intervention: HADS-A: 6.4 (3.9), HADS-D: 6.9 (4.4); Control: HADS-A: 6.6 (3.9), HADS-D: 7.1(3.6)

Temel et al., 2017 <sup>58</sup>	350	Newly diagnosed incurable lung or non-colorectal GI cancer	Patient	no	no	--	National Consensus Project for Quality Palliative Care	physicians and APNs	illness understanding/education, symptom management, decision-making, coping with life-threatening illness, referrals/prescription	excluded if significant psychiatric condition prohibiting participation	Intervention: PHQ-9:6.39 (5.49), HADS-D: 4.72(4.28), HADS-A: 5.05(3.95); Control: PHQ-9: 6.50(5.19), HADS-D: 4.58(3.73), HADS-A: 5.57(3.88)
Temel et al., 2010 <sup>8</sup>	151	Metastatic non-small cell lung cancer	Patient	no	no	--	National Consensus Project for Quality Palliative Care	PC physicians and APNs	physical and psychosocial symptoms, goals of care, decision-making, and coordinating care	no	Intervention HADS-A:36% elevated, HADS-D: 22%, PHQ-9: 12%; Control: HADS-A:33%, HADS-D: 25%, PHQ-9: 17%
Temel et al., 2020 <sup>59</sup>	405	cancer	Patient	no	no	--	--	PC physicians and APNs	symptom assessment/treatment, support of coping with advanced cancer, prognostic awareness, decision-making, planning for EOL care	no	Intervention HADS-A: 7.2(3.3), HADS-D: 5.4 (4.2); Control: HADS-A:7.2 (3.7), HADS-D: 5.8 (4.2)
Vanbuts ele et al., 2018 <sup>70</sup>	186	Advanced cancer	Patient	no	no	--	--	PC nurse with ability to refer to PC physician as needed	illness understanding, symptom burden, psychological coping, spiritual coping, decision making	no	not reported alone, only change reported



von Heyman-Horan et al. 2018 <sup>62</sup>	340	Incurable cancer	Caregiver	yes	no	existential-phenomenological therapy	--	Specialized PC teams which included physicians, and at least 2 other professions (e.g. psychologists, social workers)	psych intervention aiming to decrease distress in patients and caregivers	no	Intervention: Anxiety elevated: 28%, depression elevated: 24%; Control: anxiety elevated: 27%, depression elevated: 23%
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Table 1. Characteristics of interventions and their samples. Abbreviations: CNS: centra nervous system, PC: palliative care, ACP: advance care planning, APN: advanced practice nurse, NP: nurse practitioner, MSW: masters in social work, SW: social worker, GI: gastro-intestinal, PA: physician assistant, MS: multiple sclerosis, GP: general practitioner, EOL: end of life, CBT: cognitive behavioral therapy, \*denotes that caregivers were primary target of intervention

Study	Study	Psych distress outcome measure(s)	Time period(s) for outcome	Symptoms decreased	Symptoms increased	No change in symptoms
Ammari et al. 2018 <sup>60</sup>	Ammari et al. 2018	HADS-A, HADS-D	16 weeks			No differences
Bakitas et al., 2009 <sup>9</sup>	Bakitas et al., 2009	CESD	4 months	Mood improved both in longitudinal analyses and in one month look-back analyses from time of death		
Bakitas et al., 2015 <sup>52</sup>	Bakitas et al., 2015	CESD	3 months			No difference
Bakitas et al., 2020 <sup>51</sup>	Bakitas et al., 2020	HADS-A, HADS-D	8 weeks, 16 weeks (endpoints combined as an average of the two)			No differences at combined endpoint
Bekelman et al., 2018 <sup>40</sup>	Bekelman et al., 2018	PHQ-9, GAD-7	3 months	PHQ-9, GAD-7		
Brims et al., 2019 <sup>75</sup>	Brims et al., 2019	GHQ-12	12 weeks			No difference
Carson et al., 2016 <sup>41</sup>	Carson et al., 2016	HADS	3 months			No difference
Chan et al., 2016 <sup>67</sup>	Chan et al., 2016	HADS-A; HADS-D	3 months	HADS-A		No difference in HADS-D
Dionne-Odom et al., 2015; <sup>42</sup> Dionne-Odom et al., 2016 <sup>43</sup>	Dionne-Odom et al., 2015; Dionne-Odom et al., 2016	CESD	3 months	CESD		
Dionne-Odom et al. 2020 <sup>44</sup>	Dionne-Odom et al. 2020	HADS-A, HADS-D	8 weeks and 16 weeks			No differences at either time point
do Carmo et al., 2017 <sup>74</sup>	do Carmo et al., 2017	PHQ-9, HADS-D, HADS-A	90 and 120 days after baseline			No differences
El-Jawahri et al., 2017 <sup>45</sup>	El-Jawahri et al., 2017	HADS-A, HADS-D	3 months	HADS-D		No difference in HADS-A
El-Jawahri et al., 2016 <sup>46</sup>	El-Jawahri et al., 2016	HADS-A, HADS-D, PHQ-9	12 weeks after baseline	HADS-D, PHQ-9		No difference in HADS-A
El-Jawahri et al., 2021 <sup>47</sup>	El-Jawahri et al., 2021	HADS-A, HADS-D	12 weeks	HADS-D, HADS-A		
Ferrell et al., 2021 <sup>48</sup>	Ferrell et al., 2021	Distress thermometer	12 weeks	Distress thermometer		
Gao et al., 2020 <sup>76</sup>	Gao et al., 2020	HADS-D, HADS-A	12 weeks			No differences
Grudzen et al., 2016 <sup>49</sup>	Grudzen et al., 2016	PHQ-9	12 weeks			No differences
Hoek et al., 2017 <sup>73</sup>	Hoek et al., 2017	HADS-A, HADS-D	12 weeks		HADS-A	HADS-D
Janssen et al., 2020 <sup>50</sup>	Janssen et al., 2020	HADS-A, HADS-D, PHQ-9	3 months		PHQ-9	HADS-A, HADS-D
Johnsen et al., 2020 <sup>61</sup>	Johnsen et al., 2020	HADS-A and HADS-D	8 weeks			No differences
Jordhoy et al., 2001 <sup>72</sup>	Jordhoy et al., 2001	IES	4 months			No difference
Maltoni et al., 2016 <sup>65</sup>	Maltoni et al., 2016	HADS-A, HADS-D	12 weeks			No differences
McCorkle et al., 2015 <sup>53</sup>	McCorkle et al., 2015	HADS-A, PHQ-9	3 months			No differences
McDonald et al., 2017 <sup>63</sup>	McDonald et al., 2017	SF-36 MCS	3 and 4 months			No differences at either time point
Ng & Wong, 2018 <sup>68</sup>	Ng & Wong, 2018	ESAS-A, ESAS-D	12 weeks			ESAS-A, ESAS-D
Nordly et al., 2019 <sup>54</sup>	Nordly et al., 2019	HADS QOL	8 weeks			No difference
O'Riordan et al., 2019 <sup>55</sup>	O'Riordan et al., 2019	HADS-A, HADS-D	3 months			No differences

Rodin et al., 2020 <sup>64</sup>	Rodin et al., 2020	BDI-II	8, 12 weeks			No differences
Scheerens et al, 2020 <sup>69</sup>	Scheerens et al, 2020	HADS-A, HADS-D	12 week			No differences
Schenker et al., 2021 <sup>56</sup>	Schenker et al., 2021	HADS-A, HADS-D	3 months			No differences
Sidebottom et al., 2015 <sup>57</sup>	Sidebottom et al., 2015	PHQ-9	3 months	PHQ-9		
Slama et al., 2020 <sup>71</sup>	Slama et al., 2020	HADS-A, HADS-D	3 months			No differences
Solari et al., 2018 <sup>66</sup>	Solari et al., 2018	HADS-A, HADS-D	3 months			No differences
Temel et al., 2017 <sup>58</sup>	Temel et al., 2010	HADS-total, PHQ-9	12 weeks	PHQ-9 and HAD (dichotomized)		
Temel et al., 2010 <sup>8</sup>	Temel et al., 2017	HADS-A, HADS-D, PHQ-9	12 weeks			No differences
Temel et al., 2020 <sup>59</sup>	Temel et al., 2020	HADS A, HADS D	12 weeks	HADS-A significantly decreased at 12 week		HADS-D, PHQ-9
Vanbutsele et al., 2018 <sup>70</sup>	Vanbutsele et al., 2018	HADS, PHQ-9	12 weeks			No differences
von Heymann-Horan et al. 2018 <sup>62</sup>	von Heymann-Horan et al. 2018	Anxiety and depression subscales of Symptom Checklist-92 (SCL-92)	8 weeks	Anxiety and Depression		

Table 2. Study outcomes for each included study.

Outcome	Standardized Mean Difference	95% CI	p-value	I <sup>2</sup> statistic, p-value
Patient anxiety (N=17)	-.008	(-.37, .36)	.96	95%, p<0.001
Caregiver anxiety (N=4)	-.21	(-1.79, 1.36)	.79	98%, p<0.001
Patient depression (N=22)	-.13	(-.34, .09)	.25	88%, p<0.001
Caregiver depression (N=5)	-.27	(-.57, .03)	.08	64%, p=0.02
Patient psychological distress (N=2)	.26	(-.70, 1.23)	.59	94%, p<0.001
Caregiver psychological distress (N=3)	.04	(-.25, .33)	.78	62%, p=0.07

Table 3. Pooled effect sizes and precision for each outcome type, with p-value for significantly different from null.

Outcome	Subgroup	Standardized Mean Difference	95% CI	p-value	I <sup>2</sup> statistic	
Patient anxiety	Cancer (N=7)	-.28	(-.87, .31)	.14	96%	
	Non-cancer (N=7)	.23	(-.09, .54)		80%	
	Higher risk of bias (N=12)	.12	(-.13, .37)	.18	72%	
	Lower risk of bias (N=5)	-.47	(-1.30, .36)		98%	
	Distress primary outcome (N=4)	.01	(-.35, .38)	.87	32%	
	Distress not primary outcome (N=13)	-.03	(-.47, .40)		96%	
	Theoretical basis (N=6)	-.09	(-.22, .04)	.74	13%	
	No theoretical basis (N=11)	.02	(-.58, .62)		96%	
	Manualized therapy (N=5)	-.003	(-1.09, 1.08)	.88	98%	
	No manualized therapy (N=12)	-.09	(-.23, .06)		42%	
	Specialty MH clinician on team (N=6)	-.07	(-.24, .11)	.82	20%	
	No specialty MH clinician (N=11)	-.007	(-.54, .52)		97%	
	Patient depression	Cancer (N=13)	-.23	(-.53, .07)	.25	91%
		Non-cancer (N=9)	.003	(-.26, .26)		75%
Higher risk of bias (N=16)		-.04	(-.33, .24)	.32	88%	
Lower risk of bias (N=6)		-.28	(-.64, .09)		91%	
Distress primary outcome (N=4)		.52	(-.27, 1.30)	.07	86%	
Distress not primary outcome (N=18)		-.23	(-.46, -.01)		88%	
Theoretical basis (N=9)		-.27	(-.62, .08)	.25	93%	
No theoretical basis (N=13)		-.03	(-.25, .20)		71%	
Manualized therapy (N=6)		-.02	(-.32, .28)	.47	75%	
No manualized therapy (N=16)		-.17	(-.43, .10)		90%	
Specialty MH clinician on team (N=7)		.08	(-.24, .41)	.16	74%	
No specialty MH clinician (N=15)		-.22	(-.48, .04)		90%	

Table 4. Moderator analyses results for patient outcomes, with SMDs and 95% CI for subgroup effects and p-values for between subgroup differences.

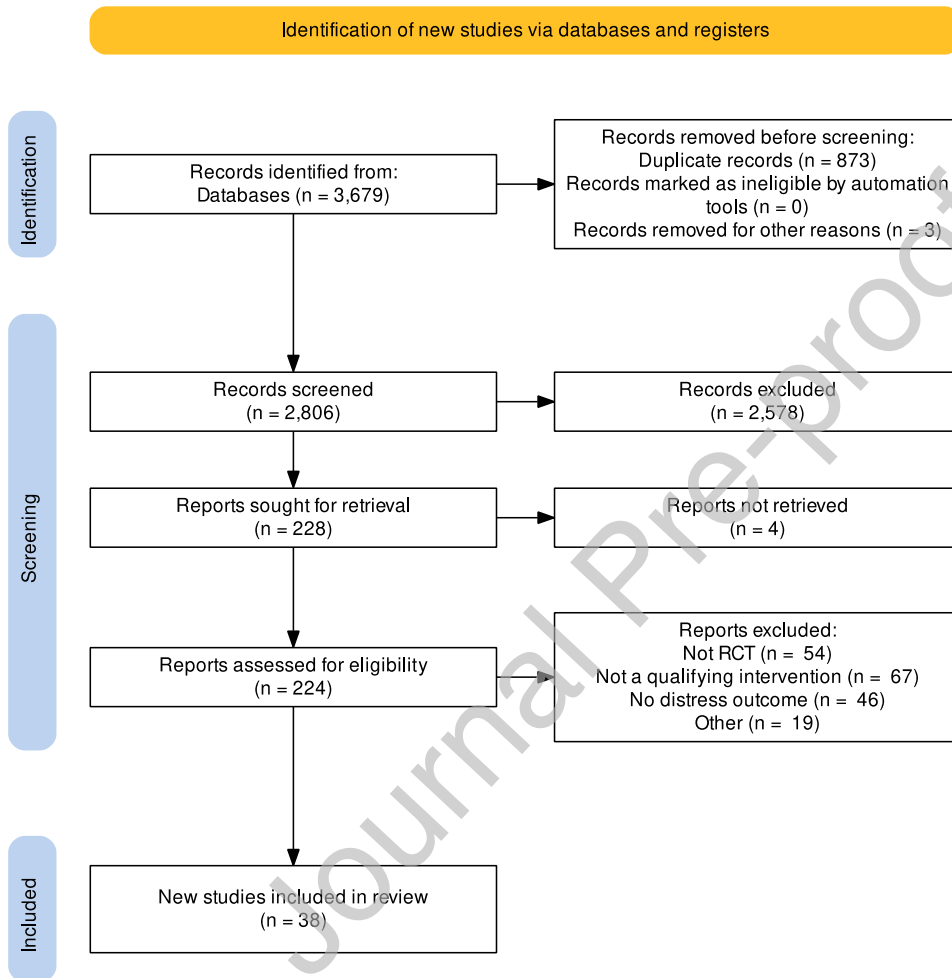


Figure 1. PRISMA flow diagram of included studies

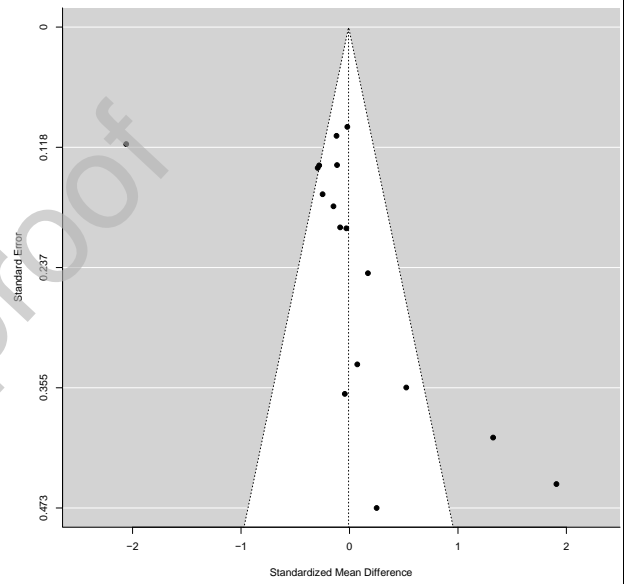
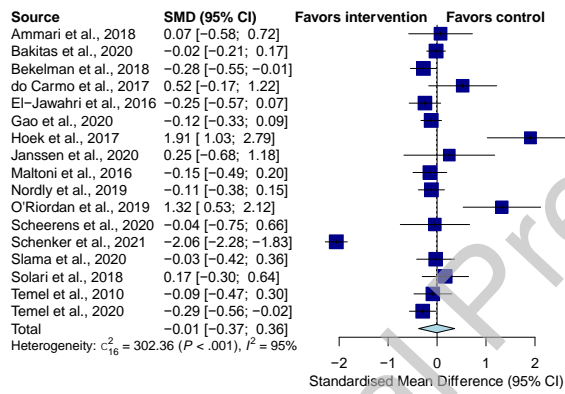


Figure 2a. Forest plot for patient anxiety symptoms

Figure 2b. Funnel plot for patient anxiety symptoms

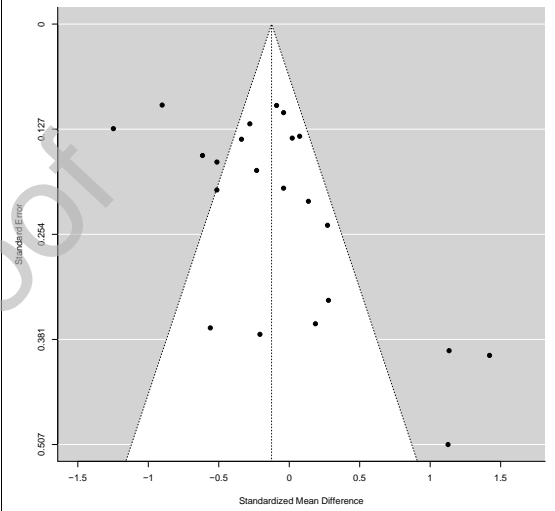
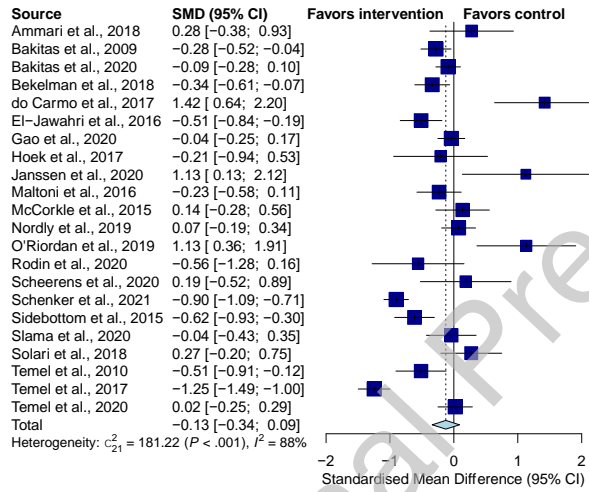


Figure 3a. Forest plot for patient depression symptoms

Figure 3b. Funnel plot for patient depression symptoms

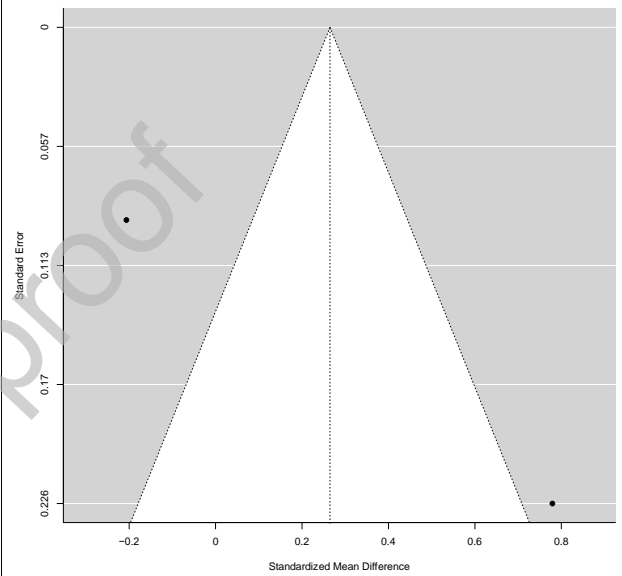
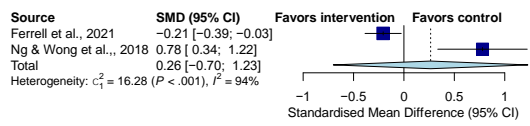


Figure 4a. Forest plot for patient distress symptoms

Figure 4b. Funnel plot for patient distress symptoms



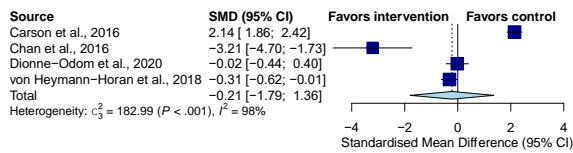


Figure 5a. Forest plot for caregiver anxiety symptoms

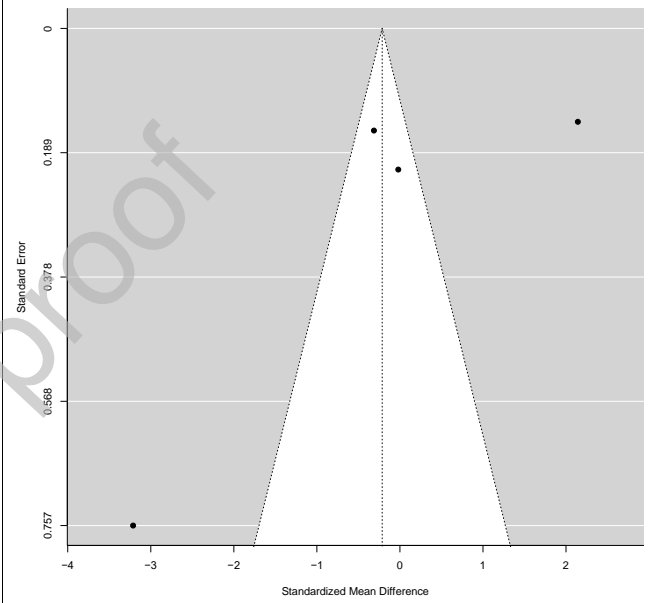


Figure 5b. Funnel plot for caregiver anxiety symptoms

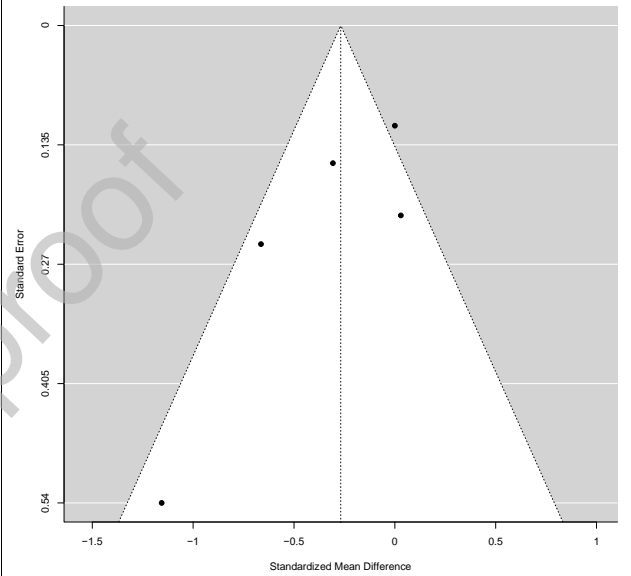
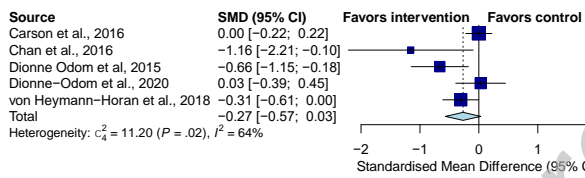


Figure 6a. Forest plot for caregiver depression symptoms

Figure 6b. Funnel plot for caregiver depression symptoms

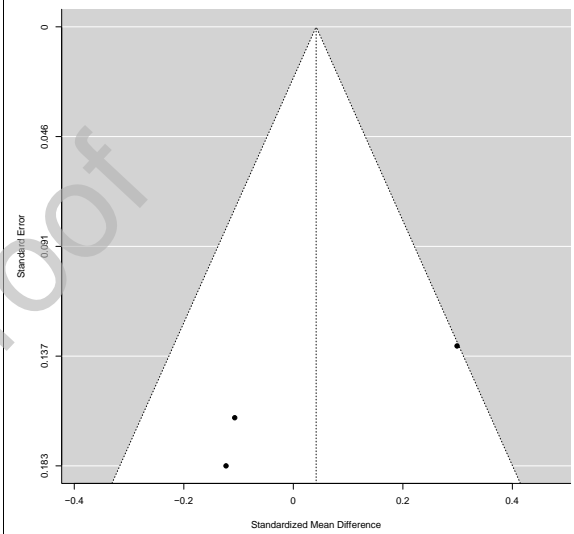
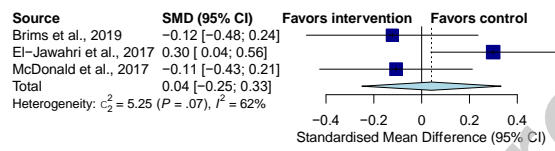


Figure 7a. Forest plot for caregiver distress symptoms

Figure 7b. Funnel plot for caregiver distress symptoms

## Appendix Items

PubMed:

(palliative care [MeSH] OR palliative [TiAb]) AND ((depression) OR (anxiety) OR (distress) OR (quality of life) OR (mood))

Randomized Controlled Trial filter ON

-896 results

Appendix Table 1

Study	Country	Mean Age	Baseline psychological distress, mean (SD)	Racial Group	Ethnicity	Gender Distribution	Marital Status	Educational Attainment	SES
Ammari et al., 2018	Denmark	67.4		NA	NA	68% men	NA	NA	NA
Bakitas et al., 2009	USA	Intervention: 65.4 Control: 65.2		Intervention: 98.6% White Control: 98.5% White	No Hispanic participants	Intervention: 62.1% men Control: 58.2% men	Intervention: 73.1% married Control: 67.2% married	Intervention: 57.2% HS+ Control: 55.2% HS+	NA
Bekelman et al., 2018	USA	Intervention: 64.5 Control: 66.5		NA	NA	intervention: 81.5% men Control: 75.8% men	NA	Intervention: 33.1% HS graduate or less Control: 27.4% HS graduate or less	Intervention: 41.6% less than \$20k Control: 44.0% less than \$20k
Brims et al., 2019	UK and Australia	Intervention: 72.1 Control: 72.8		NA	NA	Intervention: 77% male Control: 82.8% male	NA	NA	NA

Carson et al., 2016	USA	51		NA	int: 15% Hispanic, control: 13%	Intervention: 70% female Control: 72% female	Intervention: 59% married Control: 66% married	NA	Intervention: 57% employed Control: 51% employed
Chan et al., 2016	Hong Kong	45% 40-59 years, 38% 60-79 years		NA	NA	76% female	79% married	80% HS education or lower	NA
Dionne-Odom et al., 2015; Dionne-Odom et al., 2016	USA	Intervention: 61 Control: 57.9		Intervention: 90.2% white Control: 95.1% white	NA	Intervention: 77% women Control: 80.3% women	Intervention: 88.5% married Control: 95.1% married/cohabitating	Intervention: 60.7% some college or less Control: 54.1% some college or less	Intervention: 37.7% employed Control: 60.7% employed
Dionne-Odom et al. 2020	USA	Intervention: 58.2 Control: 57.6		Intervention: 39% white, 56.1% Black Control: 50% white, 47.4% Black	NA	Intervention: 89% women Control: 81.6% women	Intervention: 69.5% married/cohabitating Control: 72.4% married/cohabitating	Intervention: 36.5% HS or less Control: 36.3% HS or less	Intervention: 30.5% employed Control: 39.5% employed

do Carmo et al., 2017	Brazil	Intervention group1: 49.1 Intervention group 2: 52.7 Control: 57		Intervention group 1:63.2% white, 15.8% Black Intervention group 2: 45.5% white, 36.4% Black Control: 68.2% White, 9.1% Black	recorded with race	Intervention group 1: 68.4% women Intervention group 2: 62.6% women Control: 63.6% women	Intervention group 1:68.5% married/stable union Intervention group 2: 59.1% married/stable union Control: 72.7% married/stable union	Intervention 1: 57.9% "low educational level" Intervention 2: 45.5% "low educational level" Control: 54.5% "low educational level"	Intervention 1:42.1% employed Intervention 2: 36.4% employed Control: 54.5% employed
El-Jawahri et al., 2017	USA	Intervention: 57.5 Control: 57.2		Intervention: 92.7% white Control: 92.8% white	1.5% (PC) Hispanic; 2.2% (UC) Hispanic	Intervention: 68.6% women Control: 69.6% women	NA	Intervention: 19% HS, 54.7% college Control: 34.1% HS, 45.7% college	Intervention: 54.0% working Control: 50% working
El-Jawahri et al., 2016	USA	Intervention: 57.2 Control: 56.9		Intervention: 85.2% white Control: 88.6% white	NA	Intervention: 59.3% women Control: 54.4% women	Intervention: 77.8% married Control: 69.6% married	Intervention: 28.4% HS, 43.2% college Control: 30.4% HS, 53.2% college	Intervention: 27.4% less than \$51k Control: 40.3% less than \$51K

El-Jawahri et al., 2021	USA	Median (IQR): 64.4 (19.7-80.1)		86.2% white	NA	40.0% women	NA	NA	NA
Ferrell et al., 2021	USA	Median (IQR): 62 (53-69)		7.1% African American, 9.6% Asian, 69.3% Caucasian, 9.0% Hispanic/Latino, 1.3% Native Hawaiian, 2.5% Mixed race, 1.3% Other	Hispanic Latino 43 (9.0%)	56.8% women	74.9% married/living with partner	22.8% HS grad, 53.9% college grad, 20.0% graduate school	60.3% greater than \$50k
Gao et al., 2020	UK	Intervention: 67.3 Control: 66.4		Intervention: 94.3% NH white Control: 86.2% NH white	combined with race	PC: 48.9% M, UC: 53.5% M	Intervention: 64.8% married/civil partner Control: 67.2% married/civil partner	Intervention: 38.1% no formal education Control: 41.4% no formal education	Intervention: 98.3% not employed Control: 96.0% not employed

Grudzen et al., 2016	USA	Intervention: 55.1 Control: 57.8		Intervention: 34% white, 27% Black, 6% Asian, 1% AI/AN, 1% multi-racial, 30% other Control: 30% white, 23% Black, 3% Asian, 3% AI/AN, 1% multi-racial, 38% other	Hispanic or Latino control 29 (43%) Intervention 20 (29%)	Intervention: 57% women Control: 55% women	NA	Intervention: 46% HS or less Control: 54% HS or less	Intervention: 62% <\$50k Control: 61% <\$50k
Hoek et al., 2017	Netherlands	Intervention: 62.3 Control: 61.9	NA	NA	NA	Intervention: 29% women Control: 39% women	Intervention: 71% married/permanent relationship Control: 81% married/permanent relationship	Intervention: 24% college+ Control: 25% college+	NA



Janssen et al., 2020	USA	71.1		NA	NA	90% Male	NA	NA	NA
Johnsen et al., 2020	Denmark	Modal range: 60-69		NA	NA	Intervention: 57% women Control: 59% women	NA	Intervention: 18% didn't go beyond mandatory education Control: 12%	NA
Jordhoy et al., 2001	Norway	Median Intervention: 70 Control: 69		NA	NA	Intervention: 44% women Control: 51% women	NA	Intervention: 13% 13 years or more Control: 17%	NA
Bakitas et al., 2020	USA	Intervention: 63.5 Control: 64.1		Intervention: 44.2% white, 54.3% Black Control: 44.4% white, 54.6% Black	NA	Intervention: 53.4% male Control: 53.1% male	Intervention: 50.5% married/living with partner Control: 46.4% married/living with partner	Intervention: 53.3% HS or less Control: 38.2%	Intervention: 2.9% unemployed 48.6% disabled Control: 2.4% unemployed, 46.9% disabled

Bakitas et al., 2015	USA	Intervention: 64.03 Control: 64.6		Intervention: 90.08% white Control: 95.15% white	NA	Intervention: 53.85% male Control: 51.46% male	Intervention: 66.35% married/living with partner Control: 64.08%	Intervention: 66.34% HS or less Control: 51.45%	Intervention: 24.04% employed, 47.12% retired Control: 23.3% employed, 48.54% retired
Maltoni et al., 2016	Italy	Intervention: 67 Control: 66		NA	NA	Intervention: 61.5% male Control: 52.8% male	Intervention: 76.9% married Control: 78.6% married	NA	NA
McCorkle et al., 2015	USA	62.3% younger than 65, 37.7% 65+		NH white: 85.9%, other: 15.1%	combined with race	56.2% Female	56.2% married, 43.8% single/widowed/divorced	28.8% HS or less, 71.2% college or more	34.2% working, 31.6% retired, 34.2% other
McDonald et al., 2017	Canada	Median Intervention: 58 Control: 57		NA	int: 80.9% "European ethnicity", 88.2% control	Intervention: 61.7% women Control: 69.3% women	Intervention: 94.5% married Control: 96.6% married	Intervention: 73.1% greater than HS Control: 56.5% greater than HS	Intervention: 39.4% retired, 52.1% employed Control: 31.8% retired, 47.7% employed

Ng & Wong, 2018	Hog Kong	Intervention: 78.3 Control: 78.4		NA	NA	Intervention: 43.9% male Control: 61.90% male	Intervention: 62.8% married, 30.2% widowed Control: 68.3% married, 22.1% widowed	Intervention: 44.2% no schooling, 37.2% primary, 16.3% secondary Control: 29.3% no schooling, 48.8% primary, 17.1% secondary	Intervention: 25.6% make more than enough money Control: 24.4% make more than enough money
Nordly et al, 2019	USA	Intervention: 66.3 Control: 65.2		NA	NA	Intervention: Male 48.7 % Control: Male 48.8%	Intervention: 69.8% married Control: 66% married	Intervention: 58.3% with at least some higher education Control: 51.9%	NA
O'Riordan et al., 2019	USA, California	Intervention: 71 Control: 59		Intervention: 44% white Control: 43% white	NA	Intervention: 69% female Control: 28% female	NA	Intervention: 81% 4 year degree Control: 64% 4-year degree	NA
Rodin et al., 2020	Canada, Toronto	52.86		76.2% white	combined with race	38.1% female	71.4% married/common law	66.7% post-secondary education	54.8% employed, 43.3% with income less than 60k

Scheerens et al., 2020	Belgium	Intervention: 67.5 Control: 67		NA	NA	Intervention: 55% male Control: 57.9% male	Intervention: 65% married Control 73.7% married	Intervention: 45.0% Lower secondary, primary education, or less Control: 73.7% lower secondary, primary education, or less	NA
Schencker et al., 2021	USA	69.3		4.9% Black, 0.7% Asian, 94% white	Latino 9 (1.3%) others - non latino 663 (98.7%)	53.6% women	56.8% married	High school/GED or less (49.8%), Some college or college degree 289 (43.0%), Graduate or professional degree 41 (6.1%)	6.8% Cannot make ends meet, 33.6% Just manage to get by
Sidebottom et al., 2015	USA, Minnesota	73.4		93.9% white, 4.3% Black, 1.3% American Indian	0.9% Hispanic	47.4% female	53% married/partnered	NA	NA

Slama et al., 2020	Czech Republic	Intervention: 61.1 Control: 63.5		NA	NA	InterventionL 61.7% male Control: 57.6% male	NA	NA	NA
Solari et al., 2018	Italy	Intervention: 60.5 Control: 56.8		NA	NA	Intervention: 62% female Control: 46% female	NA	Intervention: 20% university Control: 24% university	Intervention: 78% retired due to disability Control: 85% retired due to disability
Temel et al., 2017	USA, Massachusetts	Intervention: 65.64 Control: 64.03		Intervention: 89.1% white, 3.4% Black, 4% Hispanic, 2.9% Asian, 2.3% American Indian Control : 95.4% White, 1.7% Asian, 2.3% Black, 1.1% Hispanic	combined with race	Intervention: 52% male Control: 56% male	Intervention: 69.1% married Control: 70.9% married	Intervention: 33.1% HS or less, 43.3% some or completed college Control: 41.7% HS or less, 39.4% some or completed college	NA

Temel et al., 2010	USA, Massachusetts	Intervention: 64.98 Control: 64.87		Intervention: 100% white Control: 95% white, 4% Black, 1% Asian	both groups 1% Hispanic	Intervention: 55% female Control: 49% female	Intervention: 62% married Control: 61% married	NA	NA
Temel et al., 2020	USA	Intervention: 65.5 Control: 65		Intervention: 75.9% white, 12.3% Black, 6.2% unknown, 4.6% Asian, 1% AI/AN Control: 79.1% white, 11.2% Black, 4.6% unknown, 3.1% AI/AN, 1% Native Hawaiian	Hispanic intervention 8 (4.1%) Control 6 (3.1%)	Intervention: 58.5% male Control: 54.6% male	Intervention: 61.6% married/partner Control: 59.2% married/partner	Intervention: HS or less 37.4% Control: HS or less 41.4%	NA

Vanbutsele et al., 2018	Belgium	Intervention: 64.5 Control: 65.0		NA	NA	NA	NA	Intervention: 26% college or higher Control: 32% college or higher	NA
von Heymann-Horan et al. 2018	Denmark	Intervention: 61 Control: 62		NA	NA	Intervention: 63% female Control: 65% female	Intervention: 92% married/cohabitating Control: 90% married/cohabitating	Intervention; 38% HS or less Control: 41% HS or less	NA

Authors	True randomization?	Allocation to treatment groups concealed?	Treatment groups similar at baseline?	Outcomes assessors blind to treatment assignment?	Treatment groups treated identically other than intervention?	Follow up complete, if not were differences btwn groups in terms of their follow up adequately described and analyzed?	Participants analyzed in the groups to which they were randomized?	Were outcomes measured in the same way for treatment groups?	Were outcomes measured in a reliable way?	Was appropriate statistical analysis used?	Was trial design appropriate, and any deviations from standard RCT design accounted for in conduct and analysis of the trial?
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Ammari et al. 2018 <sup>11</sup>	yes	unclear	yes	no	yes	unclear	yes	yes	unclear	no	yes
Bakitas et al., 2009 <sup>12</sup>	yes	unclear	yes	no	unclear	no	yes	yes	yes	no	yes
Bekelman et al., 2018 <sup>13</sup>	yes	yes	yes	no	unclear	unclear	yes	yes	unclear	yes	yes
Brims et al., 2019 <sup>16</sup>	yes	unclear	yes	no	unclear	unclear	yes	yes	unclear	yes	yes
Carson et al., 2016 <sup>17</sup>	yes	yes	yes	no	unclear	no	yes	yes	unclear	yes	yes
Chan et al., 2016 <sup>18</sup>	yes	unclear	yes	no	unclear	no	unclear	yes	unclear	unclear	yes
Dionne-Odom et al., 2015 <sup>19</sup> ; Dionne-Odom et al., 2016 <sup>20</sup>	unclear	unclear	yes	no	unclear	no	yes	yes	unclear	yes	yes
Dionne-Odom et al. 2020 <sup>21</sup>	yes	yes	yes	no	unclear	unclear	yes	yes	unclear	yes	yes
do Carmo et al., 2017 <sup>22</sup>	yes	unclear	no	no	unclear	unclear	yes	yes	yes	yes	yes
El-Jawahri et al., 2017 <sup>23</sup>	yes	yes	yes	no	yes	no	unclear	yes	unclear	yes	yes
El-Jawahri et al., 2016	yes	unclear	yes	no	unclear	no	unclear	yes	unclear	yes	yes
El-Jawahri et al., 2021	yes	unclear	yes	no	unclear	no	unclear	yes	unclear	yes	yes
Ferrell et al., 2021	yes	unclear	yes	unclear	unclear	no	yes	yes	unclear	yes	yes
Gao et al., 2020 <sup>25</sup> ; patient	yes	unclear	yes	yes	unclear	no	yes	yes	unclear	yes	yes
Grudzen et al., 2016	yes	yes	yes	yes	yes	no	yes	yes	unclear	yes	yes



Hoek et al., 2017 <sup>26</sup>	yes	yes	no	unclear	yes	no	unclear	yes	unclear	yes	yes
Janssen et al., 2020 <sup>27</sup>	unclear	unclear	no	unclear	unclear	no	yes	yes	unclear	yes	yes
Johnsen et al., 2020 <sup>29</sup>	yes	unclear	yes	no	yes	no	no	yes	unclear	unclear	yes
Jordhoy et al., 2001 <sup>30</sup>	unclear	no	yes	unclear	unclear	no	unclear	yes	unclear	unclear	yes
Bakitas et al., 2020 <sup>32</sup>	yes	yes	yes	yes	unclear	no	yes	yes	unclear	yes	yes
Bakitas et al., 2015 <sup>33</sup>	yes	unclear	yes	yes	yes	no	yes	yes	unclear	yes	yes
Maltoni et al., 2016 <sup>34</sup>	yes	no	yes	no	unclear	no	yes	yes	unclear	yes	yes
McCorkle et al., 2015 <sup>35</sup>	yes	no	no	unclear	yes	no	unclear	yes	yes	maybe	unclear
McDonald et al., 2017 <sup>36</sup>	yes	unclear	yes	no	yes	no	yes	yes	unclear	yes	yes
Ng & Wong, 2018 <sup>37</sup>	yes	yes	yes	no	yes	no	yes	yes	unclear	yes	yes
Nordly et al., 2019	yes	yes	yes	no	unclear	no	no	yes	unclear	yes	yes
O'Riordan et al., 2019 <sup>39</sup>	yes	unclear	no	yes	unclear	no	unclear	yes	unclear	yes	yes
Rodin et al., 2020 <sup>42</sup>	yes	yes	yes	no	yes	no	yes	yes	unclear	no	yes
Scheerens et al., 2020	yes	yes	no	no	yes	no	unclear	yes	unclear	yes	yes
Schencker et al., 2021	yes	yes	no	yes	unclear	no	yes	yes	unclear	yes	yes
Sidebottom et al., 2015 <sup>44</sup>	unclear	yes	no	unclear	yes	no	yes	yes	un	yes	yes
Slama et al., 2020	yes	unclear	yes	no	unclear	no	unclear	yes	unclear	non	yes

Solari et al., 2018 <sup>45</sup>	yes	yes	no	yes	unclear	no	yes	yes	unclear	yes	yes
Temel et al., 2017 <sup>46</sup>	yes	yes	no	unclear	yes	no	unclear	yes	unclear	yes	yes
Temel et al., 2010 <sup>47</sup>	yes	unclear	yes	no	unclear	no	yes	yes	un	yes	yes
Temel et al., 2020	yes	unclear	no	no	unclear	no	unclear	yes	unclear	yes	yes
Vanbutsele et al., 2018 <sup>48</sup>	yes	yes	no	no	yes	no	yes	yes	un	yes	yes
von Heymann-Horan et al. 2018 <sup>49</sup>	yes	yes	yes	no	yes	no	yes	yes	unclear	yes	yes

Appendix table 2. Risk of bias for each included study.