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PHD THESIS

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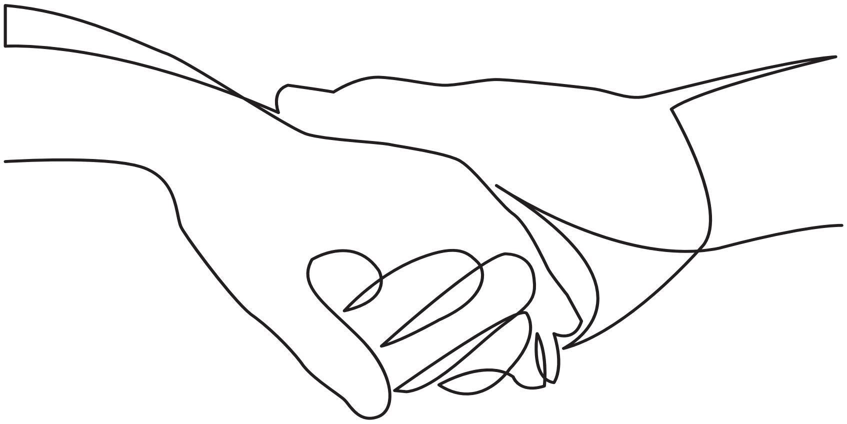

INTEGRATION OF PSYCHOLOGICAL INTERVENTION IN SPECIALIZED PALLIATIVE CARE

EFFECTS ON CAREGIVER DISTRESS AND DYADIC COPING

Submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, February 28th 2018.

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PhD thesis

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LIST OF ABBREVIATIONS

ANOVA Analysis of variance

CI Confidence interval

DCI Dyadic Coping Inventory

EPT Existential phenomenological therapy

ITT Intention to treat

OR Odds ratio

RCT Randomized controlled trial

SCL Symptom Checklist

SPC Specialized palliative care

SPI Specialiseret palliativ indsats

STM Systemic transactional model

WHO World Health Organization

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If I have learned anything during my PhD, it is that research takes enormous amounts of time, effort, and collaboration by a lot of dedicated people. This work is no exception and I owe thanks to many for helping prepare, inspire, and complete the work and letting me reach the milestone of handing in my thesis.

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SUMMARY

Advanced cancer profoundly affects not only patients but also their caregivers, who may be partners, adult children or other family and friends. Symptoms of psychological distress are prevalent and psychological well-being related in patient-caregiver dyads, who may cope with the disease through both individual and dyadic coping efforts. Palliative care is a multidisciplinary approach that aims to alleviate suffering in patients and families, but psychological interventions in trials of specialized palliative care (SPC) are rarely well-described, and often lack a focus on the dyad. Limited knowledge exists about the effects of SPC on psychological distress in caregivers and although patients and caregivers are increasingly included in SPC trials together, the effects of these interventions on dyadic interactions and coping are unknown.

The 'Domus' randomized controlled trial (RCT) was conducted to investigate effects of SPC and psychological intervention on patients with advanced cancer and their caregivers. Adult patients seen at the Department of Oncology at Rigshospitalet, Copenhagen University Hospital, who had incurable cancer and limited antineoplastic treatments options were recruited and could invite a caregiver to participate. Participants were randomized to the intervention or care as usual. In the intervention arm, home-based palliative care was initiated through an accelerated, coordinated process, and psychological intervention was provided as an integrated part of home-based SPC. The intervention was based on existential-phenomenological therapy and aimed to alleviate distress in patients and caregivers by addressing the specific issues challenging each dyad's psychological adaptation when needs arose. Two sessions were planned within a month of randomization and followed by monthly needs assessments or needs-based sessions until early bereavement. Patients and caregivers completed questionnaires before randomization and up to six months later. Bereaved caregivers completed questionnaires up to 19 months after the patient's death. Questionnaires included the anxiety and depression subscales of the *Symptom Checklist* (SCL) 92, and subscales of the *Dyadic Coping Inventory* (DCI) measuring communication of stress, common coping, and satisfaction with dyadic coping. Intervention effects on caregivers' symptoms of anxiety and depression and on the measured aspects of dyadic coping, were estimated with 95% confidence intervals (CI) in mixed effects models. We estimated direct and indirect intervention effects in path analyses to investigate whether effects of anxiety and depression were mediated by effects on dyadic coping.

From June 2013 to August 2016, 340 patients were recruited, of whom 258 (76%) participated with a caregiver. Mixed effects models found significant intervention effects on caregivers' symptoms of anxiety throughout follow-up (estimated difference, -0.12 ; 95% CI; -0.22 to -0.01; Cohen's d, -0.19), and symptoms of depression eight weeks (-0.17; 95% CI, -0.33 to -0.02; Cohen's d, -0.26) and six months (-0.27; 95% CI, -0.49 to -0.05;

Cohen's d, -0.41) after randomization. Symptoms of depression were also significantly lowered in bereavement, two weeks (-0.28; 95% CI, -0.52 to -0.03; Cohen's d, -0.42), and two months (-0.24; 95% CI, -0.48 to -0.01; Cohen's d, -0.37) after the patient's death. The intervention had no significant main effects on measures of dyadic coping, but significant effects in subgroups of dyads. Among couples, the intervention significantly increased common coping (estimated difference, 0.68; 95% CI, 0.11 to 1.24), albeit to a small extent. Further, for caregivers in couples the intervention significantly increased stress communication (0.97; 95% CI, 0.24 to 1.71), while decreasing stress communication in parents cared for by an adult child (-2.54; 95% CI, -4.19 to -0.90). Mediation analyses showed no evidence for mediation.

The Domus RCT demonstrated that SPC and dyadic psychological intervention can significantly decrease psychological distress in caregivers of patients with advanced cancer, and may affect certain aspects of dyadic coping. Increases in dyadic coping did not prove to be the mechanisms through which the Domus intervention affected caregivers' symptoms of anxiety and depression. The findings presented underscore that caregivers should be considered targets of intervention in palliative care, and that beneficial effects of specialized palliative care with integrated psychological support can extend even into bereavement. Further, the findings suggest that interventions tailored to the individual dyad and its needs may be appropriate in specialized palliative care. However, future research should investigate whether dyads in different relationships, such as couples or parents cared for by adult children, benefit equally from the same interventions, or whether interventions need to be adapted to each dyad type.

DANSK RESUMÉ

At leve med fremskreden kræft påvirker ikke kun patienter, men også deres pårørende. Psykologisk belastning er udbredt blandt både patienter og pårørende og forringet psykologisk velbefindende hos den ene påvirker også den anden, men patienter og pårørende kan håndtere belastningen både igennem individuelle og fælles (dyadiske) strategier. Palliativ indsats er en multifaglig tilgang der sigter efter at lindre lidelse hos patienter og deres familier, men psykologiske interventioner i undersøgelser af specialiseret palliativ indsats (SPI) er ofte dårligt beskrevne og mangler fokus på dyaden. Der findes kun lidt viden om hvordan SPI påvirker pårørendes psykologiske velbefindende og selvom patienter og pårørende i stigende grad deltager sammen i undersøgelserne er effekten af disse interventioner på dyadernes interaktion og stresshåndtering ikke kendt.

'Domus' er en lodtrækningsundersøgelse der blev gennemført for at undersøge hvordan SPI og psykologisk intervention påvirker patienter med fremskreden kræft og deres pårørende. Voksne patienter tilknyttet Onkologisk klinik på Rigshospitalet, som havde uhelbredelig kræft og begrænsede antineoplastiske behandlingsmuligheder kunne deltage i undersøgelsen og vælge at invitere en pårørende. Alle deltagere blev randomiseret til interventionen eller standard behandling i kontrolgruppen. For patienter i interventionsgruppen blev SPI i hjemmet påbegyndt i en accelereret og koordineret proces, og psykologisk intervention tilbudt som del af SPI. Interventionen var baseret på Eksistentiel fænomenologisk terapi og havde til formål at forbedre det psykologiske velbefindende hos patienter og pårørende ved at adressere de specifikke problemstillinger der forhindrede hver dyade i at tilpasse sig deres situation på bedste vis. To samtaler blev planlagt i løbet af den første måned efter randomisering og fulgt op af månedlige telefoniske behovsvurderinger og, ved behov, samtaler indtil den første tid efter patientens død. Patienter og pårørende udfyldte spørgeskemaer inden randomisering, samt op til seks måneder derefter. Efterladte pårørende udfyldte spørgeskemaer op til 19 måneder efter patientens død. Spørgeskemaerne inkluderede angst og depressionssubskalaerne i *'Symptom Checklist' (SCL) 92* og subskaler fra *'Dyadic Coping Inventory' (DCI)*, der måler kommunikation af stress, fælles stresshåndtering og tilfredshed med dyadisk stresshåndtering. Vi estimerede effekten af interventionen på pårørendes angst og depression, samt dyadernes stresshåndtering i *'mixed effects'* modeller med 95% konfidensintervaller (CI). Endvidere estimerede vi direkte og indirekte interventionseffekter i *'path'* analyser for at undersøge om effekter på dyadisk stresshåndtering medierede effekten på angst og depression.

Fra juni 2013 til august 2016 deltog 340 patienter i undersøgelsen, heraf 258 (76%) sammen med en pårørende. I *mixed effect* modeller fandt vi signifikante effekter af interventionen på pårørendes

angstsymptomer over hele opfølgningsperioden (estimeret forskel, -0.12 ; 95% CI; -0.22 to -0.01; Cohen's d, -0.19), og på depressionssymptomer otte uger (-0.17; 95% CI, -0.33 to -0.02; Cohen's d, -0.26) og seks måneder (-0.27; 95% CI, -0.49 to -0.05; Cohen's d, -0.41) efter randomisering. Interventionen mindskede ligeledes symptomer på depression to uger (-0.28; 95% CI, -0.52 to -0.03; Cohen's d, -0.42) og to måneder (-0.24; 95% CI, -0.48 to -0.01; Cohen's d, -0.37) efter patientens død. Vi fandt kun signifikante effekter på dyadisk stresshåndtering blandt par og forældre med voksne børn. Blandt parrene medførte intervention signifikant øget fælles stresshåndtering (estimeret forskel, 0.68; 95% CI, 0.11 to 1.24). Endvidere øgede interventionen pårørende partneres stress kommunikation (0.97; 95% CI, 0.24 to 1.71), mens den mindskede stresskommunikationen hos forældre med pårørende voksne børn (-2.54; 95% CI, -4.19 to -0.90). Vi fandt ingen indikation på mediation.

Domus undersøgelsen har vist, at SPI og dyadisk psykologintervention mindsker symptomer på angst og depression signifikant blandt pårørende til patienter med fremskreden kræft og kan påvirke dele af den dyadiske stresshåndtering. Ændringerne i den dyadiske stresshåndtering syntes imidlertid ikke at medvirke til ændringerne i pårørendes angst og depression. Undersøgelsens resultater understreger at pårørende bør støttes i SPI og at de positive effekter af SPI og psykologisk intervention strækker sig ind i livet som efterladt. Resultaterne peger på at interventioner bør skræddersyes til den enkelte patient-pårørende dyade og dennes specifikke behov. Fremtidige studier må undersøge om patienter og pårørende i forskellige relationer har gavn af de samme interventioner eller om interventioner må differentieres for at have bedst effect.

CONTENTS

1

INTRODUCTION

Cancer affects not only patients but also their loved ones. Many patients with incurable cancer need extensive support, not only from health care providers, but also from their spouses, partners, other family members, and friends. In their remaining time together, patients and caregivers face physical, emotional, and existential challenges. Among these, symptoms of anxiety and depression represent widespread problems. Psychological distress within patient-caregiver dyads is linked, and dyads are increasingly understood to cope with the disease together.

When cure is no longer an option, palliative care comes center stage in patients' treatment. Palliative care aims to reduce suffering and promote quality of life for patients with life-threatening diseases and their families. In order to provide comprehensive psychological support, palliative care needs to include attention to caregivers and their dyadic interaction with patients. Well-described psychosocial interventions that can be replicated and eventually implemented in clinical practice are necessary. Psychological interventions for patients, caregivers, and dyads have had beneficial effects outside specialized palliative care (SPC), and psychological intervention based on existential approaches may be particularly relevant. To date, randomized controlled trials (RCTs) testing SPC interventions have mostly focused on the patient, and while they increasingly include caregivers, none have targeted psychosocial support to the patient-caregiver dyad. In the large majority of trials, descriptions of the psychosocial care provided are vague and effects on dyadic interactions as well as on caregivers in bereavement are not explored. Therefore, it remains unclear what psychosocial support is effective in helping patients and caregivers in specialized palliative care.

As part of 'Domus', a largescale RCT of home-based SPC, this PhD aims to address the gap in knowledge to contribute to alleviating suffering in patients and caregivers coping with advanced cancer.

2

AIMS

This PhD thesis aims to contribute to the development of psychological support for patients with advanced cancer and their caregivers by developing and evaluating a psychological intervention that targets the patient-caregiver dyad as part of specialized palliative care.

The overall aim comprises four specific aims:

a) To develop a psychological intervention that can be provided as part of home-based SPC for patients with advanced cancer and their caregivers and explore its feasibility as part of an RCT.
b) To investigate the effect of home-based SPC with integrated dyadic psychological support on symptoms of anxiety and depression in caregivers of patients with advanced cancer.
c) To investigate the effect of home-based SPC with integrated dyadic psychological support on aspects of dyadic coping in patient-caregiver dyads with advanced cancer and whether this effect was modified by characteristics of the dyad.
d) To investigate whether effects on aspects of dyadic coping mediated the effect on symptoms of anxiety and depression in caregivers.

3

BACKGROUND

The following chapter presents the context for the work presented in this PhD thesis. First, I introduce specialized palliative care and outline its provision in Denmark. Second, I present literature concerned with the psychological distress experienced by patients with advanced cancer and their informal caregivers. Third, I briefly outline two frameworks that are used in this thesis. One forms the understanding of the dyadic nature of patient-caregiver coping, the other provides the therapeutic approach for the psychological intervention presented. Finally, I provide an overview of relevant findings from two fields of intervention research at the intersection of which this thesis is situated: research investigating effects of specialized palliative care and research investigating the effect of stand-alone psychological and psychosocial interventions for patients and caregivers.

3.1 PALLIATIVE CARE

The World Health Organization (WHO) defines palliative care as *"an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."*[1] This definition highlights several important features of palliative care today: palliative care is not defined by the end of life alone, but rather extends earlier into the trajectory of illnesses that are life threatening. In accordance, the provision of palliative care is increasingly advocated alongside disease-directed treatment, progressively becoming the focus of treatment as the symptom burden for patients with cancer increases toward death.[2] The WHO's definition also highlights that the focus of palliative care includes the patient's family. Palliative care is inherently patient-focused and responds to the specific needs of patients and their families,[3] including not only symptom management for patients, but also social, psychological and spiritual care for patients and caregivers, extending into bereavement.[1] An interdisciplinary team of providers is thus central to palliative care.[4,5] *Basic* or *primary* palliative care, that can be provided by all health care professionals, is often distinguished from the *specialized* care provided by multidisciplinary teams with specialist training,[6] or who work primarily in palliative care,[7] and provide care for patients with greater complexity or duration of symptoms.[6] The need for palliative care has been projected to increase dramatically over the next decades, as morbidity and the number of persons dying from cancer as well as other chronic diseases rise in the aging population.[8]

3.1.1 Palliative care in Denmark

Palliative care in Denmark is provided as part of the tax-financed, free health care service, including general practitioners, hospital services, home nursing and care, as well as hospice services. National guidelines for the provision of palliative care in Denmark are based on the WHO definition,[1] and thus also emphasize early initiation, holistic, multidisciplinary care including physical, psychological, social, and existential care, and family-involvement.[9,10] SPC is provided by multidisciplinary teams, consisting of two professions, in addition to nurses and physicians, based either at hospitals or inpatient hospices, in accordance with clinical guidelines.[9,11] Physician referral is necessary and criteria for most SPC units' include the presence of complex symptoms.[12] Palliative care is not a separate medical specialty, but rather a subspecialty within oncology or anesthesiology.[9] Basic palliative care is provided by health care professionals such as general practitioners, non-palliative hospital clinics, and nursing services based in municipalities.[9] The general practitioner is intended to remain the primary coordinator, even if patients are referred to SPC teams, but only a minority of general practitioners may attend home care conferences initiated by SPC teams.[13] Nursing or help with activities of daily living in the home is provided to patients in need by municipalities.[14]

3.1.2 Guidelines for psychosocial care and bereavement support in palliative care

National and international guidelines for palliative care provision include or are specific to psychosocial support provided to patients and caregivers in palliative care.[9,15–19] These guidelines advocate treatment of psychiatric diagnosis regardless of whether these are a result of the illness or a preexisting comorbidity,[19] the explicit inclusion of caregivers in palliative care as targets of care in their own right,[9,10,16] intermittent or continuously performed structured patient and/or caregiver screening and needs assessments,[10,18,19] development of caregiver care plans emphasizing caregivers' own well-being,[16] and screening for risk for complicated grief.[19] After the patient's death, guidelines emphasize needs assessments in bereavement.[16,18]

3.1.3 Place of death

Treatment and care of cancer are increasingly moved from the clinical to the home-setting,[20] and home death is often considered a characteristic of a 'good death'.[21] In studies of Danish patients with cancer, most (71-81%) report a preference for home death.[22,23] Yet, between 2007 and 2011, the majority of patients with cancer died in hospitals (57%), while only one in four died at home.[24] Findings from other countries also show that preferences and actual home deaths stand in contrast to each other.[25,26] Home death has been associated with patient characteristics, such as preferences and lower functional status, characteristics of medical care, such as early referral to SPC, hospital admissions, and with family-related factors, like living with relatives, having family support, and caregivers' coping ressource.[27,28]

3.2 PSYCHOLOGICAL DISTRESS IN PATIENTS WITH ADVANCED CANCER AND THEIR CAREGIVERS

3.2.1 Symptoms and needs of patients with advanced cancer

Patients with advanced cancer suffer from a range of physical and emotional symptoms such as pain, fatigue, anorexia, weight loss, anxiety, depression, and meaninglessness.[29–31] Many symptoms worsen with increasing proximity to death, and patients' performance status, i.e. their ability to perform their daily life activities, declines most rapidly throughout the last month of life.[32] As a consequence of worsening symptoms, patients have also been found to experience increased existential distress closer to death.[33]

3.2.1.1 Psychological distress in patients with advanced cancer

Psychological distress can be defined as a *"multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope effectively with cancer"*,[34] and includes symptoms of anxiety and depression. The prevalence of anxiety and depression among patients with advanced cancer has been estimated at between 10 and 30% and 17 and 39%, respectively, in both large prospective studies, systematic reviews and meta-analyses.[29,31,32] Symptoms of anxiety and depression in and of themselves cause suffering, but they may also impact satisfaction with care,[35] treatment choices,[36] length of hospital stays,[37] and suicidal ideation.[38] Among patients with advanced cancer, depression has been found to be significantly correlated with pain, lower performance status,[39] desire for hastened death,[40] and mortality.[41,42] In spite of the prevalence and accompanying issues of psychological distress, perceptions of the availability and potential benefit of psychosocial support as well as social constraints and stigma, can prevent patients from seeking help.[43]

3.2.2 Informal caregivers

Informal caregivers of patients with cancer are those individuals who provide unpaid care to patients and are most often patients' spouses, non-marital partners or their adult children.[44,45] Caregivers provide patients with a wide range of help, such as practical support in daily activities, help with medical decision making and symptom management,[46] as well as emotional support.[47] As treatment and care for patients is moved out of hospitals and into the home,[48] caregivers take on a growing amount of caregiving tasks. Cancer caregiving has been conceptualized as a stress process that encompasses both primary stressors, the symptoms of cancer and ensuing care requirements, as well as secondary stressors, not stemming directly from the disease.[49] The disease and caregiving may result in changed family roles,[46] work impairment,[50] and challenges for caregivers to maintain social and leisure activities.[47,51] Different perceptions of caregiving as a rewarding experience,[52] or a burden,[53] and different levels of caregiving competence and preparedness,[54] influence caregivers' outcomes.[49] Throughout the trajectory of the disease, transitions such as that from curatively intended treatment to palliative care, may mark periods of increased vulnerability.[49] The impending death of the patient may evoke existential distress and concerns related to the loss of a common future as well as caregivers' own mortality.[55] Caregivers of patients receiving palliative care may thus be especially burdened, but may play an important role in facilitating home-based care and home death.[56–59] Some caregivers may feel pressured to provide care at home by prevailing societal discourse[60] and assume responsibilities they may not be comfortable with.[61] Home care may also, however, provide an opportunity for families to preserve normality in some aspects of life,[62] and fulfilling the patient's wish for their place of care may be rewarding.[63] Home death may thus be both beneficial and detrimental to caregivers' mental health.[64–69]

3.2.2.1 Psychological distress in informal caregivers

Between 3.5 to 42% and 4.1 to 39% of caregivers may suffer from elevated symptoms of anxiety and depression, respectively.[30,70–75] Differences in caregiver characteristics may be related to distress,[76] and spousal and parental caregivers may experience greater psychological distress than other caregivers.[30,73] Depression and anxiety have been found to increase as death approaches.[53] Compared to the general population, the risk for psychiatric disorder among caregivers of patients with advanced cancer may be almost eightfold increased for a first episode of major depression and threefold increased for generalized anxiety disorder.[71] Even so less than half of caregivers with a psychiatric disorder may receive mental health care.[70] Caregivers may perceive their needs as secondary compared to those of the patient and feel less entitled to ask for and receive support for themselves.[77,78] Recent findings indicate, that caregivers' symptoms of depression may also affect quality of care reported by patients.[79]

3.2.2.2 Psychological distress in bereaved caregivers

Caregivers' increased risk of psychological distress extends beyond the patient's death, into bereavement. Elevated distress, corresponding to potential psychiatric disorder, has been found among 44% of bereaved spouses.[80] Among caregivers of patients in palliative care, 15% have been found to be likely to have moderate to severe depression six months after bereavement,[81] and significantly more bereaved family members self-report experiencing depressive mood compared to the general population.[82] Caregivers' risk of using antidepressant and anxiolytic medication has also been found to increase significantly in bereavement.[83,84] A systematic review found that higher burden experienced during caregiving is significantly associated with worse mental health in bereavement.[85]

3.3 THEORETICAL AND THERAPEUTIC FRAMEWORKS USED IN THIS THESIS

3.3.1 Dyadic coping as framework to understand patient and caregiver interaction

Cancer has been conceptualized as a "we-disease", affecting both patient and caregiver and their relationship.[86] A meta-analysis found a moderate, statistically significant association between distress in patients and their partners, which supports the notion of couples coping as an "emotional system".[87] This emotional interdependence has led to the hypothesis that involving patients and caregivers in joint interventions could benefit both dyad members.[88,89] Couples in which one partner suffers from a chronic illness are increasingly viewed as coping not only as individuals but in relation with each other.[90] This notion of *dyadic coping* expands the view of an individual's coping process to include the reciprocal effects of appraisal of stressors, coping and outcomes between two individuals.[90] The Systemic Transactional Model (STM) of dyadic coping describes the process of couples' coping with stressors affecting either one or both partners.[91] The STM defines dyadic coping as the sum of individual and dyadic coping efforts by both members of the dyad, that aim to maintain or restore equilibrium in the dyad as well as in each partner.[91] This includes the verbal or nonverbal communication about stress by one partner to the other, and that partner's reaction. Dyadic coping efforts are categorized as common, i.e. the collaborative attempt to resolve the situation, delegated, when one partner asks the other to resolve the situation for them, or supportive, when assistance is given by one partner to the other.[91] Communication of stress between partners in the STM serves to elicit support, and is thus a precursor to dyadic coping efforts.

3.3.1.1 Dyadic stress communication and coping in palliative care

Increasing knowledge exists about the importance of dyadic coping in patients with cancer and their caregivers. Systematic reviews have found that constructive communication and supportive and common coping behaviors have been frequently linked with better relationship functioning in studies of couples coping with cancer.[92,93] One review found evidence for associations between better marital adjustment and lower levels of distress and satisfactory communication among couples.[93] Although communication is likely associated with better outcomes, caregivers have been found to attempt to 'buffer' patients from their concerns, or 'overprotect' them, which has been related to greater distress in patients.[94] Few studies have investigated these associations in samples of advanced cancer patients. One study found that greater positive common coping efforts significantly predicted subsequent distress, decreasing distress in caregivers, but increasing distress in patients.[95] Stress communication among patients with advanced breast cancer and their caregivers has been found to predict better adjustment in both.[95] And while patients may often disclose more concerns than caregivers, in dyads where they hold back these concerns, caregivers are more likely to experience avoidance of thoughts related to cancer.[96] In dyadic interventions for couples coping with disease, communication and disclosure of concerns have been identified as a necessary component.[97]

3.3.2 Psychotherapeutic framework: The Existential phenomenological approach

As advanced cancer may engender questions and doubts about the meaning of life and death, existentially based approaches have been specifically advocated for this population.[98–100] Existential therapies encompass a wide range of therapeutic approaches,[101] some of which have formed the basis for interventions for patients with cancer.[102,103] The psychological intervention included in the work behind this PhD thesis employs the Existential phenomenological therapeutic (EPT) approach. EPT is based on existential philosophy, and thus on understanding life within the boundaries of human *givens*, i.e. the basic premises (social relatedness, uncertainty, ultimately death) that delimit human life.[101,104] Existential phenomenological therapy proceeds from an understanding of the person, and their autonomy and choice, within the physical, social, personal, and spiritual aspects of life.[104,105] EPT further builds on the understanding that life is in constant change, and to create predictability, is understood from within a stable world-view made up of beliefs, values, attitudes, and meanings about self, others, and the world.[104] Inevitably, the world-view imposes a certain set of restrictions on life that can become problematic, when new life circumstances require an adaptation. EPT aims to help clients explore and become open to alternative ways of relating to themselves, their relationships and their world.[104] Central to EPT as practiced in the Domus intervention is working phenomenologically to meet the dyads in their experience through an authentic therapeutic relationship. This involves the psychologist's attempt to stay with the lived experience of the dyad by suspending previous judgements and hypotheses (*bracketing*), refraining from abstracting the experience (*description*), and not valuing certain aspects of it above others (*equalizing*).[104,105] When the relationship between psychologist and dyad is well-established, the psychologist may begin to challenge restrictions in the dyad's world-view.[104]

3.3.2.1 EPT in advanced cancer

Using EPT as a therapeutic framework in this population was based on the premise within EPT that not all suffering can be removed, but that we can explore ways to live with it. A diagnosis of advanced cancer presents a fundamentally unpredictable situation, and the world-views of dyads with advanced cancer may be particularly challenged. Existential phenomenological therapy can help patient-caregiver dyads explore the restrictions imposed by their world-view, and the consequences they have, thereby increasing dyads' flexibility to adapt and the range of ways in which they can bear their life. For instance, a belief about the primacy of personal control and independence could prevent a patient from accepting outside help in order to retain their self-view, even while they may suffer from increasingly burdensome symptoms and limited ability to perform usual activities. EPT emphasizes the person's autonomy and choice while acknowledging the existential givens that cannot be changed. This means that e.g. a patient's fears of death and loss are approached, not as thoughts that need to be restructured as might be the focus in for instance some cognitive therapies. Rather they are seen as the legitimate expression of the patient's encounter with a given of existence, that they may live with in different ways, but that in itself cannot be changed.

3.4 PREVIOUS PSYCHOSOCIAL AND PSYCHOLOGICAL INTERVENTIONS WITHIN AND OUTSIDE PALLIATIVE CARE

Psychosocial or psychological interventions for patients with cancer have been variously defined and can broadly range from educational programs, through social support and coping skills training, to psychotherapeutic interventions.[106,107] Here, I define psychosocial interventions as any intervention conducted by professionals in personal interaction, face-to-face or through telephone/video-conferencing, to target psychological or social issues, such as emotional distress or relational interactions, and using interpersonal communication or relation as the mechanism of delivery or change.[106] Psychological interventions form a subgroup of these interventions that target psychological well-being through psychotherapeutic methods and are performed by mental health professionals such as psychologists or psychiatrists. I include both types of interventions in this overview because they often share some of their methods and goals and are frequently not distinguished and summarized together in reviews and meta-analyses.[108] In the following, I review first effects on psychological distress of specialized palliative care interventions and the psychosocial interventions or intervention elements they include, and second, effects of stand-alone psychological and psychosocial interventions.

3.4.1 Effects of specialized palliative care

A number of meta-analyses have been completed that document effects of SPC defined in various ways, such as multi-professional coordination or provision of comprehensive care,[109] home-based-,[110] or early palliative care.[111] These meta-analyses documented effects on patients' quality of life, symptom burden, and the number of home deaths.[109–111] No or inconclusive effects were found for patients' anxiety and depression as well as caregivers' grief, and limited effects for other caregiver outcomes.[109–111] Below, I inspect more closely those SPC interventions that encompass multidisciplinary care for outpatients or patients cared for at home.

3.4.1.1 Psychosocial interventions in RCTs of specialized palliative care

Eight RCTs of specialized home-based or outpatient palliative care with interventions provided by multidisciplinary teams have been published to date (appendix 1).[112–119] The majority (n = 5) of these trials were conducted in the USA,[112,114,116–118] while one trial each was conducted in Canada,[115] Norway,[119] and Denmark.[113] Although all interventions addressed multiple domains of care, and some explicitly included psychosocial assessment,[112,113,115–117,119] for instance as part of adhering to professional guidelines,[112,113,117] only two trials included specified descriptions of psychosocial interventions. These psychosocial interventions consisted of four[118] or six[114] weekly telephone coaching sessions with predefined educational and coaching content and monthly follow-up.[114,118] Only one intervention systematically targeted caregivers themselves in separate sessions,[120] while the other encouraged caregivers to participate, but did not specifically target them.[118,121] Symptoms of anxiety or depression in patients were assessed and reported specifically in one[112] and five[112,114,116–118] of the previous trials, respectively. No effects on symptoms of anxiety, but significant effects on symptoms of depression were found in three RCTs,[112,117,118] and one RCT found a significant effect on a combined measure of anxiety and depression.[117] In five trials, outcomes for caregivers were assessed in addition to patient-outcomes.[112,120–123] Two included a measure of anxiety and/or depression and found significant short-term effects.[120,124] Finally, one study assessed caregivers eight to twelve weeks into bereavement, with no effect for symptoms of depression.[125]

3.4.1.2 Limitations in previous studies

While some effects of home-based or outpatient SPC have been demonstrated for symptoms of depression in patients, limited evidence exists for effects on patients' symptoms of anxiety. Evidence is also limited for effects on caregivers' symptoms of anxiety and depression, particularly in bereavement. No interventions have focused on supporting the patient-caregiver dyad together, and no trials have assessed dyadic effects. Neither mediation nor moderation of effects has been assessed in any trials to date, leaving a large gap in evidence for the mechanisms through which effects are achieved, and whether or not interventions are equally beneficial across subgroups. The lack of well-described psychosocial interventions limits the knowledge about the proposed content, delivery, and mechanisms of the psychosocial support, and thus impedes replication and translation into clinical practice. For both patients and caregivers, anxiety and/or depression have only been assessed in trials conducted in the USA, mainly in regionally confined, socioeconomically homogenous populations,[112,114,116–118] limiting the generalizability of results and the applicability in other settings, e.g. with different medical systems.

In summary, there is a paucity of well-described psychosocial interventions in RCTs of SPC, especially focusing on informal caregivers and patient-caregiver dyads. Available evidence for effects on caregivers' anxiety and depression is largely confined to the time before the patient's death, with no long-term bereavement follow-up, and stems chiefly from RCTs conducted in populations and settings that may not be generalizable to the Danish setting.

3.4.2 Psychosocial intervention in advanced cancer

While there is a lack of well-described psychosocial interventions integrated in RCTs of SPC, many stand-alone psychosocial interventions for patients with advanced cancer and their caregivers have been tested.

Below, I present meta-analyses or reviews to outline the knowledge on psychosocial interventions in advanced cancer, and highlight a few interventions of particular relevance to SPC.

3.4.2.1 Reviews of patient and caregiver interventions in advanced cancer and palliative care

The effect of psychotherapy for patients with advanced cancer has been investigated in two meta-analyses that found significant, moderate effects on depression, as well as significant effects on general distress and anxiety.[126,127] Across three reviews and/or meta-analyses of psychosocial and psychological interventions for caregivers of patients in palliative care, patients in terminal stages of disease (7/8 studies in advanced cancer), and patients receiving home-based SPC, only limited effects were found.[110,128,129] The review summarizing home-based SPC identified four studies that compared caregiver focused intervention delivered in addition to SPC with SPC alone.[110] These interventions, and a subsequent extension of one of them,[130,131] targeted caregivers alone and focused on support, psychoeducation about caregiving, and coping skills, most covering predefined content in a limited number of sessions.[132–135] Few significant effects were found for caregiver's quality of life, burden,[133] psychological well-being in bereavement,[130] and experience of caregiving rewards.

3.4.2.2 Review of dyadic or family based interventions in advanced cancer

To the best of my knowledge, no meta-analysis or systematic review of dyadic or family-based interventions limited to patients with advanced cancer exist, but a meta-analysis of couple based interventions across cancer stages found significant small intervention effects for both patients and caregivers.[136] A narrative review of dyadic and family-based psychosocial interventions for patients with advanced cancer and their caregivers identified eight RCTs and found some effects, chiefly on relationship functioning, patients' distress and caregiver burden.[89] The interventions reviewed focused on teaching of communication and coping skills as well as information provision. The review concluded that dyadic and family-based interventions were promising, but had yet to be sufficiently refined and integrated into clinical care.[89]

3.4.2.3 Existentially focused interventions

Interventions for patients with advanced cancer incorporating an existential component range from those addressing existential and/or spiritual concerns as one of several topics,[137,138] or the main concern underpinning the intervention,[139–142] to those basing the intervention on existential theory,[102,103] at times in combination with other psychological approaches.[143,144] Many recent interventions focus on facilitating the creation of meaning, and have shown effects on a variety of outcomes from anxiety, depression and quality of life to symptom distress.[100,102,103,143] One systematic review and meta-analysis found some evidence for effects of interventions using group therapy incorporating existential dimensions on psychological distress in women with metastatic breast cancer.[145] A meta-analysis of existential therapies, conducted in mostly patients with advanced cancer (6/10 studies), found a significant small standardized effect on symptoms of anxiety and depression.[146] To the best of my knowledge, only one existentially based intervention to date has targeted caregivers of patients with advanced cancer, finding significant medium to large intervention effects in the short term on anxiety and in the long term on depression.[143] Some interventions have included optional family sessions, but no assessment of effects on caregivers,[147,148] and none have targeted the patient-caregiver dyad.

3.4.3 Evidence for mediation and moderation of intervention effects

Several mechanisms may underlie the effect of an intervention, particularly those with multiple components. Clarifying which mechanisms contribute to an effect can guide intervention development to establish the most beneficial interventions. Two approaches can help elucidate this issue.[149] Analyzing whether subgroups of patients and caregivers benefit more from interventions than others, i.e. whether certain participant characteristics moderate effects, can point toward effective (or ineffective) intervention components. Analyses of mediation, i.e. when effects on the outcome are carried, in total or in part, by effects on an intermediate variable, can contribute to elucidating causal mechanisms. Such analyses of mediation and moderation are scarce in the literature outlined above. However, in single studies moderating effects have been found of cancer type,[112] baseline levels of psychological distress[150] and communication,[151] risk for distress and caregiver vs. patient-role.[152] Two meta-analyses of caregiver interventions explored moderation and found that longer interventions increased effects on coping, while however also increasing depression,[153] and that age and percentage of women participants modified overall effects.[154] While some studies thus address moderation, mediation is less frequently investigated. Among the existentially based interventions, specific proposed intervention mechanisms, such as sense of meaning and peace and mindfulness, have been found to mediate the intervention effect on psychological distress and quality of life.[155,156] Such evidence on proposed mediators is missing for many other interventions.[89,129]

3.5 SECTION SUMMARY

Patients with advanced cancer and their caregivers are experiencing a difficult life situation and the prevalence of symptoms of anxiety and depression in both groups is considerable. Patients and caregivers are increasingly understood to be interdependent in their outcomes, such as psychological distress, as well as in their coping efforts. Symptoms of anxiety and depression not only induce suffering in and of themselves, but may be related to patients' wishes for hastened death, quality of care, and long-term outcomes in caregivers, even reaching bereavement. Therefore, psychological distress and symptoms of anxiety and depression are important targets for treatment and prevention.

Specialized palliative care is a multidisciplinary approach that seeks to alleviate suffering in patients with life threatening illness and their families. Recent RCTs have demonstrated beneficial effects of SPC interventions, but the evidence for effects on anxiety and depression is limited and psychosocial interventions are rarely well-described. More evidence exists for effects on distress of individual and dyadic interventions in advanced cancer populations provided outside of SPC, including those with an existential focus. Such stand-alone psychosocial or psychological interventions are, however, frequently not integrated into clinical care. Caregivers are most often secondary targets of SPC interventions, and dyadic interventions are absent from trials of SPC.

Little is known about factors that may moderate intervention effects, with available results from trials and reviews outside SPC indicating differential effects by intervention length, for patients or caregivers, and for those at risk for distress, but not for different caregiver types or cancer diagnoses. Evidence of mechanisms that mediate intervention effects is even more scant.

Randomized controlled trials in palliative care are needed that test whether providing psychological interventions integrated into SPC to patient-caregiver dyads can improve outcomes for both patients and caregivers.

4

METHODS

The following chapter will describe the methodology and design of the Domus RCT, within which the work for this PhD was completed, the psychological intervention, as well as summarize the methods of the individual papers included in this PhD thesis.

4.1 THE DOMUS RANDOMIZED CONTROLLED TRIAL

The Domus study was an RCT comparing accelerated transition to SPC with dyadic psychological intervention to care as usual.[157] The primary outcome was patients' place of care and death. Specifically, the RCT aimed to increase the time patients spent at home, as opposed to in hospital or other places, and the number of patients who died in their own homes. The primary outcomes and most intervention effects for patients are the subject of others' work.

4.1.1 Study population

Patients who attended the Department of Oncology at Rigshospitalet, Copenhagen University Hospital were screened for eligibility. The Department of Oncology treats adult patients with cancer, averaging 4000 new patients and 52,000 outpatient visits per year, and has 54 inpatient beds.[158] The department consists of eight different clinics, five specializing in different cancer sites, a radiotherapy clinic, a phase-1 trial unit, and a palliative care unit. Patients were eligible to participate if they had incurable cancer, were at least 18 years of age, and lived in the Capital Region of Denmark. Further, patients had to have limited antineoplastic treatment options, which were defined for each major cancer group as progression on a specific line of treatment after the patient had been diagnosed with metastatic or advanced cancer.[157] For instance, for lung cancer: progression on the first line of chemotherapy after diagnosis of advanced or metastatic disease. Inclusion criteria are listed in box 1. Patients were free to choose to invite a caregiver or not. Inclusion criteria for caregivers were limited to at least 18 years of age and written informed consent.

4.1.1.1 Screening and inclusion procedures

Screening for the Domus study was conducted systematically by project nurses reviewing medical records for all inpatients on a daily basis. Outpatients' medical records were screened sequentially for all patients with prospective appointments in the five site-specific clinics as well as the phase-1 trial clinic. An alternation procedure ensured equal screening frequency across clinics. Patients were approached during hospital visits or by telephone prior to outpatient visits, to inform about the study. Recruitment took place from June 2013 until August 2016.

Box 1. Domus patient inclusion criteria

Eligible patients:

- are treated at the department of oncology, Rigshospitalet
- are diagnosed with incurable cancer
- are at least 18 years of age
- have no or limited antineoplastic treatment options (see below) *or* have chosen to forgo antineoplastic treatment
- reside in the Capital Region of Denmark
- wish to spend as much time at home as possible
- provide written informed consent

Patients were excluded if they had already been referred to SPC, were hospitalized at a hospital other than Rigshospitalet, were not able to be discharged to their home, or were incapable of cooperating e.g. due to language barriers.

Site/disease-specific definitions of limited antineoplastic treatment options

Site/Disease	Refractory to…
Breast cancer	3rd line antineoplastic treatment for metastatic disease
Lung cancer	1st line chemotherapy for metastatic/advanced disease
Gastrointestinal cancer	1st line chemotherapy for metastatic/advanced disease
Ovarian or uterine cancer	2nd line chemotherapy for metastatic/advanced disease
Cervical or vulvar cancer	1st line chemotherapy for metastatic/advanced disease
Central nervous system cancer	concomitant/adjuvant chemotherapy
Prostate, bladder, penile or thyme cancer and adrenal carcinoma	1st line chemotherapy for metastatic/advanced disease
Head and neck cancer	1st line chemotherapy for metastatic/advanced disease
Cancer of unknown primary origin	radiation therapy or surgery with curative intent

Adapted from Nordly et al. (2014)[157]

4.1.1.2 *Target sample size and randomization procedure*

Power calculations were used to determine the necessary sample size to detect a 15% difference (with 80% power, $\alpha = 0.05$) in the number of home deaths between the intervention and control group.[157] One hundred seventy patients were required for each group. To allow for an expected dropout rate of 10-15%, the target sample size was initially set to n = 380, although inclusion was stopped at n = 340 due to lower than anticipated drop-out. Upon written consent and completion of baseline questionnaires, nurses randomized patients and caregivers using sequentially numbered, sealed, and opaque envelopes, based on a computer-generated 1:1 randomization sequence with varying block size, unknown to project nurses.

4.1.2 SPC intervention component: Accelerated referral to SPC

Patients who were randomized to the intervention group were referred to one of nine participating SPC teams, based on a) uptake area and b) capacity, and were appointed a project psychologist. Project nurses further informed nursing services in the patient's home municipality and the patient's general practitioner, and coordinated a home care conference within five days of randomization with the patient (and caregiver), representative(s) of the SPC team and municipal nursing services, and if possible the general practitioner and project psychologist. The aim of the home care conference was not further described, but is defined by national guidelines as providing patients and caregivers with information about services and responsibilities of each health care provider, creating a care plan based on needs assessment, discussion of topics such as leave for caregivers, and coordination of care responsibilities.[9] After the home care conference, SPC teams in collaboration with general practitioners were responsible for patients' care. The participating SPC teams were not asked to change their practice other than with regard to this referral and initiation process. Figure 1 displays the structure of the Domus intervention.

4.1.2.1 Specialized palliative care in the Capital Region of Denmark – Care as usual

The Domus study was conducted in the Capital Region of Denmark, in which nine specialized palliative care teams operate, five of which are hospital-based and four hospice-based. All teams offer outpatient and home-based care from physicians and nurses, and all but one team had either inpatient palliative care unit beds or hospice beds. The *'EORTC-QLQ-C15PAL'*, a symptom and quality of life questionnaire,[159] is frequently used for symptom screening, and was completed by 55% of patients seen by SPC teams in the Capital Region within three days of referral in 2015.[160] The presence of other professions in the team varied between teams and throughout the study period, including but not limited to psychologists, physical therapists, and social workers ('socialrådgivere'). Whereas all hospital-based teams employed a psychologist at least part-time, psychologists were not part of hospice-based teams. Referral criteria for psychologists within the teams are not formalized and treatment by a psychologist was thus not systematic.

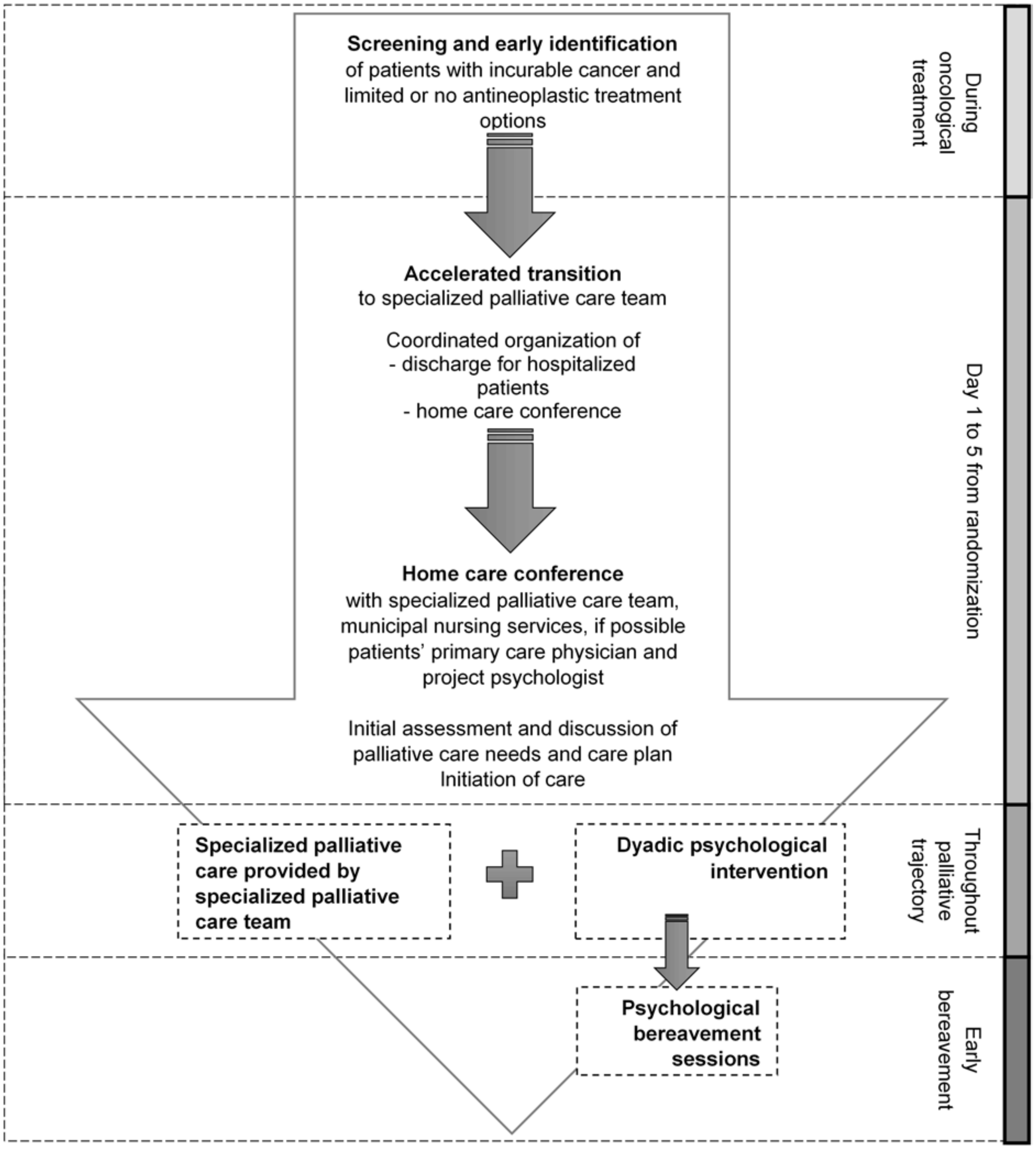


Figure 1. The Domus palliative care model[161]

4.2 THE PSYCHOLOGICAL INTERVENTION (PAPER 1)

4.2.1 Aims of the overall Domus RCT and the psychological intervention

The psychological intervention was included in the Domus RCT to provide home-based psychological support to patients and their caregivers. The primary target of the psychological intervention was to alleviate psychological distress and improve quality of life. We hypothesized that decreasing patient and caregiver distress and preventing its escalation would enhance their emotional resources to cope with care and death in the home, e.g. by reducing unplanned admissions due to reduced psychosocial resources in caregivers.[59] However, the psychological intervention would also be able to affect e.g. home death more directly, by creating a space within which patients and caregivers could discuss e.g. wishes for care at the end of life, if they chose. As such, the psychological intervention represents one mechanism through which the overall Domus intervention sought to achieve its primary outcome.

4.2.2 Development of the psychological intervention manual

Complex interventions and their evaluation require the consideration and/or development of a theoretical basis for the processes that will lead to change, as well as an understanding of the context in which the intervention will be implemented.[162] Theory forms the basis for identifying mediators and mechanisms of change which may focus intervention efforts both to increase the efficacy of an intervention, and to translate it into clinical practice.[149] An intervention manual (appendix 3) was developed for the psychological intervention, describing relevant literature, the existential phenomenological psychotherapeutic framework, as well as the structure of the intervention, and its' integration within the organizational context of SPC. In addition to the regional context, the development of the psychological intervention considered guidelines for psychosocial support[9] and caregiver support in palliative care,[16] as well as needs assessment and bereavement support.[17,18]

4.2.3 Summary of psychological intervention mechanisms and structure

The following will summarize key features of the psychological intervention related to its format, structure, mechanism, and delivery.

4.2.3.1 Intervention format and structure

To create an initial therapeutic relationship, two meetings within the first month after randomization were planned, with attendance of both patient and caregiver. If possible, psychologists attended the home care conference. Continuous needs assessment was used to identify needs for subsequent intervention sessions.

Needs were defined within two broad areas: a) Psychological distress, encompassing both diagnosable psychiatric disorders as by criteria in the 10th revision of the International Classification of Diseases,[163] and psychological distress defined as unpleasant emotional experience preventing adaptation to the illness and its consequences.[34] b) Psychosocial barriers to receiving care, including issues related to health care professionals, such as communication, and relational and other psychological or social issues that impeded care receipt, such as disagreements within the dyad. In order for psychologists to be able to offer sessions to prevent distress from escalating, assessment of risk for distress was also included. Risk for distress was defined through previously identified risk factors for distress and adverse bereavement outcomes, as presented in key literature[76,164,165] and guidelines.[17,34] If no needs for intervention were identified, phone-based assessments of patients' and caregivers' needs were completed monthly.

4.2.3.2 *Hypothesized intervention mechanisms*

A number of mechanisms were hypothesized to create change within the psychological intervention (figure 2), ultimately aiming to increase time at home and home deaths, as defined in the primary outcome of the Domus RCT.

- Addressing the specific issues related to the distress experienced by each dyad would lower distress.
- Continuous needs and risk assessment would let the intervention target dyads in need, and prevent escalation of distress.
- Using EPT would decrease distress by helping patients and caregivers find alternative ways of relating to their situation.
- Including patients and caregivers in the intervention together would support aspects of their dyadic coping, such as communication and common coping, which would decrease distress.
- Legitimizing psychosocial needs and help seeking, and creating a therapeutic relationship with psychologists would increase patient's and caregivers' acceptance of support and care.

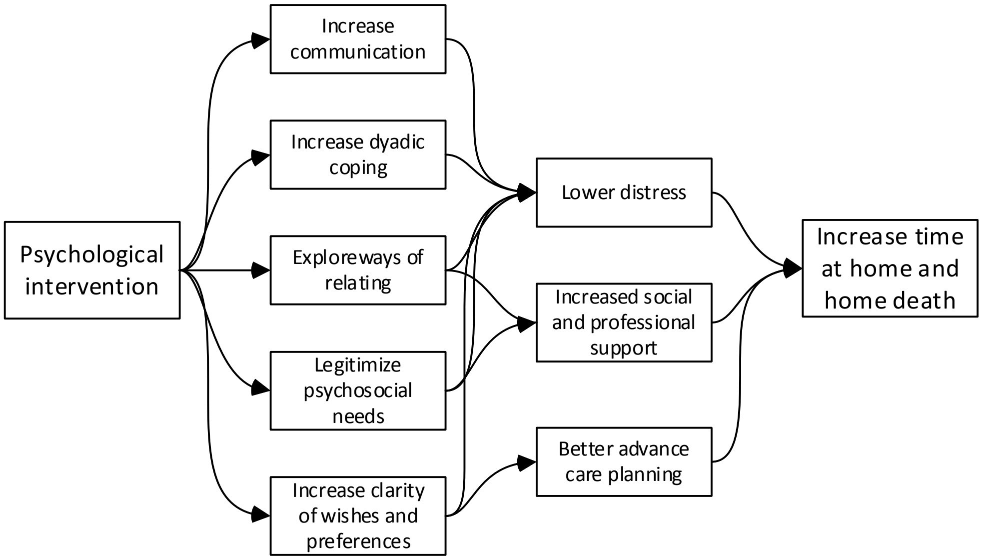


Figure 2. Selected hypothesized pathways for effects of the psychological intervention (NB: although certainly present, no relations among the different pathways, e.g. communication increasing dyadic coping or increased professional support leading to better advance care planning, are drawn)

4.2.4 Delivery of the psychological intervention

Over the course of the trial, seven psychologists were involved in providing the psychological intervention. All held a master's degree in psychology (Danish *Cand.psych.)*, which is the final university degree required to practice using the title 'psychologist' in Denmark. In addition, the psychologists had varying levels of previous psychotherapeutic experience during and after their university education, such as conducting couples therapy, bereavement counseling, and psychotherapy in private practice, oncological departments, pain clinics, or SPC teams.

4.2.4.1 Therapist training and intervention adherence

All psychologists underwent training in the principles of EPT in general, and applied to patients and caregivers coping with life-threatening illness. Central foci were the phenomenological method of inquiry, an understanding of the dyad within the physical, psychological, social, and spiritual domains,[105] as well as the importance of continua of relating such as closeness-distance and hope-hopelessness.[104] Senior psychologists with expert-level EPT experience and extensive experience in supervision and teaching conducted the training, the length of which was adapted to the number of psychologist trained at any point during the trial.

Intervention adherence was not formally checked, but group-supervision was conducted on average every other week, in which adherence to the principles of EPT and the manual, e.g. relating to needs assessment, was reinforced through discussion of particular cases as well as themes. In addition, regular meetings were held within the group of psychologists, discussing issues related to the manual, to ensure that intervention practices did not drift throughout the trial period.

4.2.4.2 Collaboration with specialized palliative care teams

Each psychologist collaborated with the SPC teams that were assigned to their dyads. Psychologists used the medical records already used by the team to ensure information sharing. The amount and nature of contact beyond medical records was determined by the needs of each dyad and could vary from face-to-face discussion of cases to phone consultation. Psychologists could also participate in sessions conducted jointly with another SPC team member, such as a physician or nurse, as well as facilitate referral to other team professionals, such as social workers. In addition to training in EPT, psychologists new to the RCT visited several of the participating SPT teams to shadow nurses in their daily practice and become acquainted with team members as well as the teams' organization.

4.3 CHANGES THROUGHOUT THE RCT

Two amendments to the Domus RCT and intervention were decided during the course of the trial. The first amendment concerned the psychological intervention component. The initial structure of the psychological intervention was based on documentation of a median survival of 35 days in patients referred to SPC teams in 2011.[166] It was hypothesized that the intervention would need to focus on the time immediately after randomization to achieve effects within a timeframe this short. Therefore, weekly meetings during the first month were planned, succeeded by less frequent sessions (every three weeks). In the first months of intervention, it became evident that patients participating in the Domus RCT had longer survival than expected. In response, the structure of the psychological intervention was changed from October 2013 to allow for greater flexibility and tailoring to the individual dyads' needs. The content of the intervention was unchanged.

The second amendment concerned the inclusion criteria for the RCT. Until October 2014, to be eligible patients had to be classified as performance status 2-4 (Eastern Cooperate Oncology Group).[167] Due to slow enrollment, this criterion was discontinued, and patients were included regardless of their performance status.

4.4 DATA SOURCES

4.4.1 Inclusion database

Project nurses registered information about patients (e.g. diagnosis, gender, date of birth) and caregivers (caregiver type, gender, date of birth) at inclusion. Further, for patients who declined participation or dropped out of the trial after randomization and offered a reason to do so, this was recorded.

4.4.2 Registration of psychological intervention sessions

Psychologists registered each completed session and needs assessment during the intervention. For each session, date and participants (dyad, patient or caregiver) were documented. Further, deviations from the planned intervention structure were documented in the following categories: initial two sessions not completed within a month of randomization, monthly contact (session or needs assessment) not completed, psychological intervention ended (by dyad, patient or caregiver), and bereavement sessions not completed. The reason for each deviation was also registered.

4.4.3 Data collection

After randomization, patients and caregivers were asked to complete mailed questionnaires at two, four, and eight weeks, as well as six months of follow-up (table 1). When a patient died, pre-bereavement questionnaires were discontinued and bereaved caregivers received questionnaires two weeks, two, seven, 13, and 19 months into bereavement.

4.4.3.1 Caregivers' anxiety and depression

Questionnaires for caregivers from baseline until six months after randomization contained the anxiety and depression subscales of the '*Symptom Checklist-92*' (SCL-92), a Danish translation and combination of the '*Symptom Checklist-90*' and the subsequent '*Symptom Checklist-90R*'.[168] The SCL-92 anxiety and depression subscales consist of 12 and 13 items, respectively, probing the extent to which a certain symptom has been experienced over the past week. For anxiety, items range from experiences of feeling nervous and jittery to experiences of panic, and for depression, from feeling sad to having suicidal ideation (appendix 4). Items are scored on a five point Likert scale, with values from 0, 'not at all', to 4, 'extremely'. Summary scores are created as the mean score across each subscale and can thus range from 0 to 4. The SCL-92 has been validated in a random sample of the Danish population.[168] Using item-response analyses, all subscales, except for 'psychoticism' were found to have good to acceptable functioning, indicating that each subscale measures a distinct dimension. Raw-score criteria for caseness, i.e. elevated scores approximating clinical diagnosis, have been identified based on the Danish normative material. They are derived from the standard case-finding criteria in the SCL-90R, with t-scores above 63, a score 1.3 standard deviations above the normative mean.[169]

Table 1 Items and scales from Domus questionnaires used in this thesis

Follow-up time	Caregivers	Patients
Baseline	**Single items assessing:** • marital status *(single, married/cohabiting, widowed, divorced/separated)* • children living at home *(yes, no, no children)* • highest completed education *(primary/secondary school (9/10 years), vocational, high school, further education (2 years, 2-4½ years, and 5 years or more))* • length of relationship between patient and caregiver • Relationship Ladder (relationship quality)	
Baseline & Week 2, 4, 8, month 6 after randomization	**Scales** • Dyadic coping inventory subscales *(subscales: own stress communication, dyad's common coping, satisfaction with common coping)*	
	• Symptom Checklist 92 *(subscales: anxiety and depression)*	-
Week 2, months 2, 7, 13, 19 after the patient's death	**Scales** • Symptom Checklist 92 *(subscales: anxiety and depression)*	-

4.4.3.2 *Dyadic measures*

Dyadic stress communication, common coping, and overall satisfaction with dyadic coping were measured using subscales from the '*Dyadic Coping Inventory*' (DCI). The DCI has been validated in several languages,[170-172] translated into Danish according to standard backward and forward translation procedures,[173] but has not yet been validated in Denmark. Each dyad-member (patient or caregiver) reported their experience of their own stress communication to the other, the dyads' common coping, and overall satisfaction with dyadic coping. Items were rated on a 5 point scale from 1 'very rarely' to 5 'very frequently'. Items assessing stress communication concerned asking for assistance due to stress or telling the other about feeling stressed (appendix 4). Items assessing common coping concerned e.g. attempts to solve a problem together and doing relaxing things together. Items assessing satisfaction with coping asked about satisfaction with and perceived effectiveness of overall dyadic coping. The DCI was originally created for use with couples, and two items on the common coping scale were changed from activities specific to couples to more widely applicable activities reflective of the same underlying construct after consultation with the scale's original author (personal communication) (kissing and cuddling to being physically close e.g. by giving a hug; taking a bath together to relaxing e.g. by watching television). Subscales are scored by addition of item scores and range from 5 to 25 for common coping and stress communication and 2 to 10 for satisfaction with dyadic coping.

4.4.3.3 Relationship ladder

The perceived quality of the relationship between patient and caregiver was assessed by each dyad member at baseline, using the *'Relationship ladder'* (appendix 4). This is a measure of global relationship quality, which allows each person to evaluate the relationship based on their own quality criteria.[174] The measure is presented as a ladder with scores from 0 'worst imaginable quality' to 10 'best imaginable quality'. The scale has previously been used as an outcome measure and found to perform well in an intervention for couples coping with cancer.[174] For dyads in non-intimate relationships, the introductory text for the measure was reworded to apply to "the relationship to the person you are participating in this study with".

4.5 SUMMARY OF STATISTICAL ANALYSES

The following describes the methods of statistical analysis used in the three papers: descriptive statistics, mixed effects models, and path analyses.

4.5.1 Descriptive analyses of the psychological intervention component (paper 1)

A feasibility assessment for the psychological intervention component was conducted when more than two thirds of the target number of patients had been included in the trial. Data from the inclusion database on reasons for declining and reasons for discontinuing study participation were used. To determine whether the intervention was acceptable, we calculated the number and percent of patients or dyads declining participation due to the psychological intervention or discontinuing the psychological intervention. Registrations of sessions for patients or dyads who had completed the intervention (i.e. participated until the death of the patient) were used to inspect deviations from the intervention structure and reasons for these deviations. To determine whether the intervention was feasible, we calculated the proportion of deviations from the planned intervention structure.

After completion of the RCT, the mean number of needs-based sessions (excluding the initial two sessions) received per month participation in the RCT was calculated for all participating dyads.

4.5.2 Descriptive analyses of baseline scores

In keeping with the *'Consolidated Standards of Reporting Trials' (CONSORT)* recommendations,[175] we did not perform statistical tests of differences between participants in the intervention and control groups. To test for differences in baseline scores on the DCI between patients and caregivers across randomization groups and dyad types, we performed paired t-tests of differences in measures of dyadic coping (common coping, stress communication, satisfaction). Based on significant differences in these t-tests, we investigated differences among dyads types for patients and caregivers separately using one-way analysis of variance (ANOVA) and post-hoc Tukeys Honestly Significant Difference-tests to explore results of significant ANOVAs. Caregivers' baseline scores on the SCL-92 were likewise compared between dyad types using ANOVAs. Descriptive analyses were completed in *'R'* version 3.3.3.

4.5.3 Mixed effects models (paper 2 & 3)

To compare changes in outcomes between the intervention and the control group, we used mixed effects models. These models take into account the correlation between repeated measures from an individual due to repeated follow-up assessments.[176] We estimated main intervention effects for the change from baseline across all follow-up times with 95% confidence intervals (CI). Model fit was assessed using residual plots. We calculated effect sizes (Cohen's d)[177] using the variance from the baseline assessment in the control group, as done by Friedman et al.[178] All effect analyses were conducted based on the 'intention to treat' (ITT) principle, such that dyads were analyzed in the group they were randomized to, regardless of whether and to what extent they received the intervention. As adjusting analyses in RCTs for known predictors of the outcome may increase power and minimize bias,[179] we adjusted analyses for variables expected to predict the outcome. All outcome analyses were planned in collaboration with and conducted by Senior Statistician Elisabeth Anne Wreford Andersen, from the Statistics and Pharmacoepidemiology Unit at the Danish Cancer Society Research Center, in SAS (version 9.4) using PROC MIXED.

4.5.3.1 Effect on anxiety and depression (paper 2)

We completed separate mixed effect models for anxiety and depression. We included fixed effects of caregivers' sex, age, their relationship to the patient (spouse, adult child, other), baseline score for anxiety or depression, randomization group (intervention or control), and follow-up time (categorical; 2, 4, 8 weeks, and 6 months after randomization, 2 weeks, 2, seven, 13 and 19 months after the patient's death). Further, we included the interaction between follow-up time and randomization group to estimate effects at each follow-up time and to investigate whether effects of the intervention were constant throughout follow-up.

The mixed models account for data missing at random. However, to study the effect of missing data due to non-completion of questionnaires (as opposed to a patient's death[180]), we conducted sensitivity analyses with imputed data for anxiety or depression under an assumption of missing not at random. Data were imputed in two different models, one assuming missing at random, and one assuming that missing values would be slightly elevated. The latter modelled the expected situation that caregivers refrain from answering questionnaires because they are experiencing higher symptoms, and missing data were shifted upward by a random value from a normal distribution with mean 0.1 and variance 0.005^2. Mixed effects models were repeated on the imputed data.

To investigate whether more caregivers scored above cut-offs approximating clinical diagnosis, we dichotomized outcomes for anxiety and depression, based on gender-specific cut-off scores. The repeated observations of the binary outcomes were analyzed using logistic regression models including the same covariates as for the continuous outcomes and using General Estimation Equation methods to account for the repeated observation.[176] We estimated population average odds ratios (ORs) with 95% CIs for the overall intervention effect. We also included the interaction between follow-up times and randomization group to estimate the intervention effect at each follow-up assessment.

4.5.3.2 *Dyadic effects (paper 3)*

We conducted mixed effects models to investigate intervention effects on stress communication, common coping, and satisfaction with dyadic coping. These models included the fixed effects of dyad member (caregiver or patient), age, sex, relationship (spouse, adult child or other caregiver), relationship quality, follow-up assessment (two, four, eight weeks, and six months after randomization) and randomization group. As measures of persons within one dyad cannot be assumed to be independent, a hierarchical model was used with follow-up assessments nested within each dyad member, nested within the dyad. Because dyad members are distinguishable as patients or caregivers,[181] we included the interaction between dyad member and the remaining variables in an initial model, and non-significant interactions were excluded in stepwise testing to yield a final model. In the final model, we tested for effect modification by including interactions between randomization group and type of dyad (couple, parent-child, other), age, and sex. Interactions significant at p = 0.1 were included in the final model.

4.5.4 Mediation of effects on anxiety and depression by dyadic coping (paper 3)

An intervention may affect a given outcome directly (figure 3, effect C) and indirectly by effects on a third variable, the mediator (effect A), which in turn may affect the outcome (effect B) (figure 3). The indirect effect of the intervention on the outcome corresponds to the product of effects A and B.

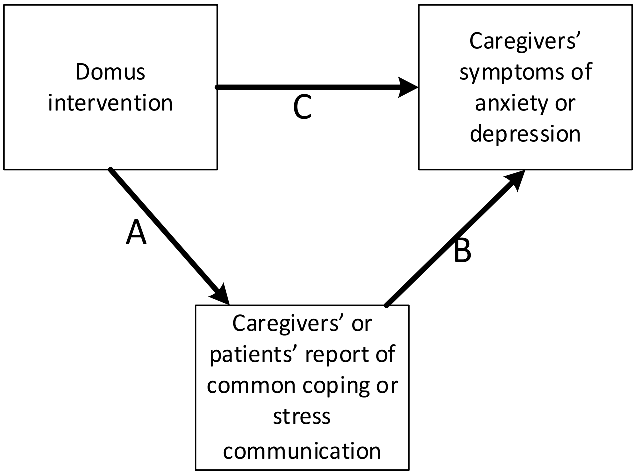


Figure 3. Illustration of mediation framework

We used path analysis to estimate direct effects on anxiety and depression at six months, and indirect effects, mediated through common coping or stress communication at eight weeks. We completed separate models for couples and parent-child-dyads, and adjusted for baseline values of the mediator and outcome, gender, and age of the caregiver. We completed the primary models with complete cases, and in addition conducted sensitivity analyses with missing observations handled using an assumption of joint normality and missing at random. Further, we investigated mediation of effects on anxiety or depression at eight weeks by dyadic measures at four weeks in addition to our primary mediation models. The analyses were carried out by Senior Statistician Elisabeth Anne Wreford Andersen using the 'sem' commands in Stata, release 14.

4.6 ETHICAL CONSIDERATIONS AND TRIAL REGISTRATIONS

Randomized controlled trials in palliative care have been described as a particular ethical challenge because of the vulnerable state of patients approaching the end of life and their caregivers, but it has also been argued that withholding the opportunity for research from this population is equally, or more, problematic.[180] The Domus RCT was conducted in compliance with the Helsinki Declaration on medical research with human subjects.[182]

4.6.1 Ethical considerations in the psychological intervention

Certain specific ethical considerations were necessary regarding the psychological intervention. Firstly, it was stressed to all psychologists performing the intervention that the primary outcome of the Domus RCT, home death and time at home, could never be prioritized above the individual wishes of patients and caregivers. Clinical actions were thus always based on patients' and caregivers' best interests rather than those of the trial. A special situation was the overlap between scientific and clinical work for three psychologists affiliated with the project, including myself. In addition to being PhD students, we all provided parts of the clinical psychological intervention. This required an explicit acknowledgment of the potential conflict inherent in the two roles. For instance, we emphasized our role as clinicians toward patients and caregivers, and deferred to other project staff when e.g. technical question arose about trial participation.

4.6.2 Trial registrations and ethical approvals

The Domus RCT was approved by the Danish Data Protection Agency (reference 2007-58-0015), and the Danish National Committee on Health Research Ethics (reference 37237). The trial was registered at clinicaltrials.gov (identifier NCT01885637).

4.7 SECTION SUMMARY

The Domus study was an RCT of SPC with an integrated psychological intervention for patients with advanced cancer and limited treatment options and their caregivers. The intervention consisted of an accelerated and coordinated transition from hospital based oncological treatment to home-based SPC, as well as a needs-based, dyadic psychological intervention based on EPT. The effect on caregivers' symptoms of anxiety and depression as well as aspects of patients' and caregivers' dyadic coping was assessed two, four, and eight weeks, as well as six months after randomization. Caregivers' symptoms of anxiety and depression were likewise assessed two weeks, two, seven, 13, and 19 months into bereavement. Mixed effects models were used to investigate effects on anxiety, depression, and dyadic coping, and path analyses were used to evaluate whether dyadic measures mediated the effect on anxiety and depression.

5

SUMMARY OF RESULTS

The results of the work conducted in this PhD are presented in the three papers that form the basis of this thesis (appendix 2). The following briefly outlines the Domus study population and key findings of the papers.

5.1 THE DOMUS STUDY POPULATION

5.1.1 Inclusion, randomization and exclusions

From June 19th, 2013 until August 22nd, 2016, 10,889 patients were screened for eligibility, of whom the large majority (84%) were ineligible due to curable disease or further treatment options. A total of 598 eligible patients received information about of the study. The percentage consenting to participate was 57% and 340 patients were included and randomized.[183] Six (2%) consenting patients reported not to have a caregiver, 64 (19%) did not wish to include an available caregiver, and 270 (79%) invited a caregiver to participate (flowchart, figure 4). Twelve caregivers (4%) declined participation, resulting in 258 included caregivers. The following results, with exception of results from the assessment of feasibility and acceptability in paper 1, stem from the subgroup of dyads participating in the Domus RCT, and patients participating alone will thus not be included from this point.

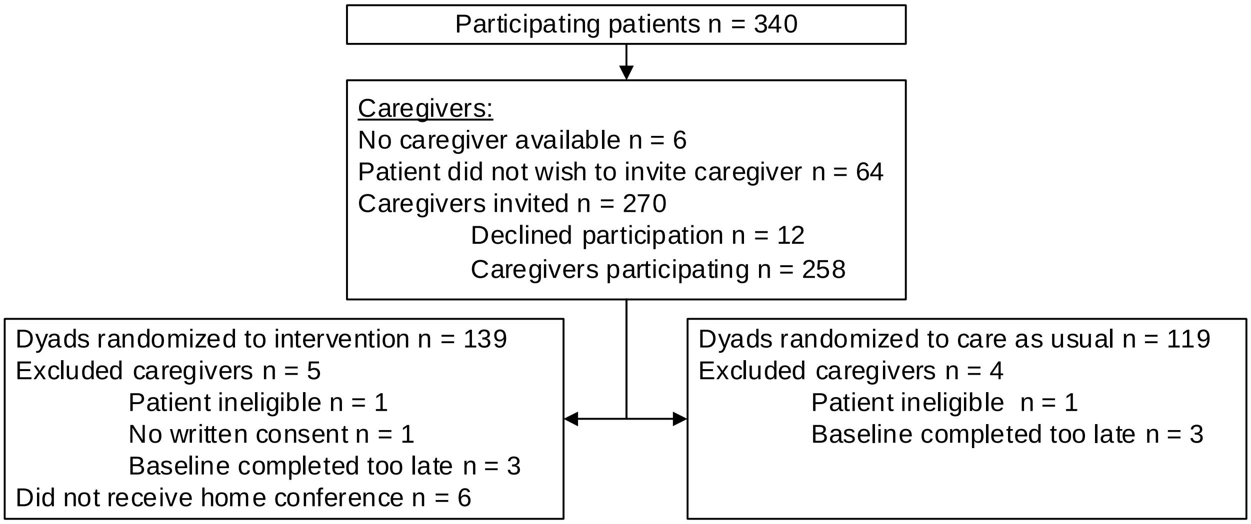


Figure 4. Flowchart of caregivers participating in the Domus RCT

5.1.2 Characteristics of the population

Of the 249 dyads available for analyses, 78% were in a romantic relationship, 14% were parents participating with their adult child as a caregiver, 8% were siblings, friends or other caregivers (table 2). Because randomization was not stratified for the participation of a caregiver, the number of dyads in the intervention and control group was unequal. Aside from this, the intervention and control groups were well balanced with regard to baseline characteristics with only slight differences. Slightly more patients with diagnoses of prostate and other cancers were randomized to the intervention group, and slightly more patients with

Table 2. Baseline characteristics of 249 dyads in the Domus RCT

		Patients		**Caregivers**	
		Intervention N = 134 *†*	**Control N = 115** *†*	**Intervention N = 134** *†*	**Control N = 115** *†*
Age, years	Mean (SD)	66 (10)	65 (11)	61 (12)	62 (13)
Sex N (%)	Male	66 (49)	50 (43)	49 (37)	40 (39)
	Female	68 (51)	65 (57)	85 (63)	75 (65)
Marital status N (%)	Married/cohabiting	108 (81)	93 (81)	123 (92)	103 (90)
	Single	6 (4)	14 (12)	7 (5)	7 (6)
	Divorced	7 (5)	3 (3)	1 (2)	3 (3)
	Widow(er)	11 (8)	5 (4)	-	2 (2)
	Missing information	3 (2)	-	3 (2)	-
Children N (%)	Children	114 (85)	95 (83)	110 (82)	97 (84)
	*living at home **	16 (12)	19 (17)	*27 (20)*	*24 (21)*
	*not living at home **	102 (76)	81 (70)	*86 (64)*	*78 (68)*
	No children	17 (13)	20 (17)	19 (14)	17 (15)
	Missing information	3 (2)	-	5 (3)	1 (1)
Highest education N (%)	Elementary/middle school (9 yrs)	24 (18)	20 (17)	14 (10)	14 (12)
	Vocational	28 (21)	30 (26)	35 (26)	31 (27)
	High school	3 (2)	3 (3)	2 (2)	2 (2)
	Further education (-4.5 years)	56 (42)	45 (39)	48 (36)	47 (41)
	Higher education (≥5 years)	21 (16)	17 (15)	27 (20)	16 (14)
	Missing information	2 (2)	-	8 (6)	5 (4)
Caregiver relationship N (%)	Spouse/Partner			103 (77)	92 (80)
	Son/daughter			24 (18)	10 (9)
	Other			7 (5)	13 (11)
Dyad cohabiting N (%)	Yes			103 (77)	91 (79)
	No			25 (19)	22 (19)
	Missing information			6 (5)	2 (2)
Relationship length, years	Mean (SD)			38 (15)	38 (16)
	Range			5-63	2-64
	Missing information			5	3
Relationship quality	Mean (SD)	9 (2)	9 (1)	8 (2)	8 (2)
	Missing information	2	1	4	6
Diagnosis N (%)	Breast	5 (4)	7 (6)		
	CNS	16 (12)	21 (18)		
	Connective tissue	5 (4)	8 (7)		
	Female genitalia	18 (13)	13 (11)		
	Head and neck	6 (5)	9 (8)		
	Lower gastrointestinal	15 (11)	13 (11)		
	Lung	28 (21)	25 (22)		
	Other	11 (8)	1 (1)		
	Prostate	17 (13)	5 (4)		
	Upper gastrointestinal	13 (10)	13 (11)		
Performance status N (%)	0 - 1	68 (51)	59 (51)		
	2 - 3	66 (49)	56 (49)		
Symptoms of anxiety	Mean (SD)			0.84 (0.69)	0.8 (0.64)
	N above cut-off (%)			36 (27)	31 (27)
Symptoms of depression	Mean (SD)			1.00 (0.66)	0.94 (0.66)
	N above cut-off (%)			32 (24)	26 (23)
Dyadic coping	Common coping, mean (SD)	18 (5)	18(5)	17 (5)	18 (5)
	Missing information	7	4	10	6
	Stress communication, mean (SD)	14 (3)	13 (4)	10 (3)	10 (3)
	Missing information	7	5	6	6
	Satisfaction, mean (SD)	8 (2)	8 (2)	8 (2)	7 (2)
	Missing information	7	5	5	4

* Categories not mutually exclusive

† Percentages may not add up to 100 due to rounding

central nervous systems (CNS) tumors to the control group. The intervention group consisted of slightly more dyads with an adult child-caregiver, whereas more other caregivers were included in the control group, and more patients in the control group reported being single.

At baseline, caregivers in the intervention and control group reported similar levels of anxiety and depression, with 28% in the intervention group and 27% in the control group exceeding cut-off scores for anxiety, and 24% in the intervention group and 23% in the control group exceeding cut-off scores for depression (table 2). Across randomization groups, patients reported significantly higher levels of common coping, stress communication, and satisfaction with dyadic coping than caregivers. When split into subgroups, patients in 'other' dyads reported significantly lower scores on common coping than patients in couples. Caregivers in couple-dyads reported significantly higher levels of common coping than caregivers in parent-child and other dyads, and no significant differences were found in other dyadic measures as well as anxiety and depression (table 3).

Table 3. Baseline scores on dyadic measures for patients and caregivers, control and intervention group together

Dyad type Measure	All dyads (n=249)		Couples (n=195)	Parent-child (n=34)	Other (n=20)
	Mean (SD)	Difference	Mean (SD)	Mean (SD)	Mean (SD)
Common coping					
Caregiver	17.42 (4.64)	$p < 0.03$	18.2 (4.39)	15.07 (3.99) *	14.37 (5.61) *
Patient	18.09 (4.77)		18.44 (4.57)	17.52 (4.82)	15.39 (5.94) †
Stress communication					
Caregiver	9.94 (3.32)	$p < 0.000$	10.18 (3.25)	9.26 (3.49)	8.74 (3.54)
Patient	13.40 (3.53)		13.62 (3.46)	12.88 (4.19)	12.06 (2.67)
Satisfaction					
Caregiver	7.42 (2.04)	$p < 0.000$	7.56 (2.00)	6.84 (2.11)	7.0 (2.19)
Patient	8.45 (1.73)		8.43 (1.67)	8.67 (1.77)	8.22 (2.29)
Anxiety (caregiver only)			0.84 (0.68)	0.82 (0.66)	0.72 (0.57)
Depression (caregiver only)			0.98 (0.67)	0.97 (0.68)	0.9 (0.6)

* Significantly different from score for caregivers in couple-dyads (p = 0.002)

† Significantly different from score for patients in couple-dyads (p = 0.03)

5.1.3 Bereavement during follow-up

Within six months of randomization, 56 (42%) patients in the intervention died and 50 (43%) in the control group. By the end of follow-up included in papers 2 & 3, 105 caregivers (78%) in the intervention group and 89 (77%) in the control group had been bereaved.

5.2 FEASIBILITY ASSESSMENT: RESULTS OF PAPER 1

The feasibility assessment was conducted when 251 patients, 190 of these with caregivers, had been included in the study and randomized (Figure 5). Reasons for declining participation were available from 79 of 145 patients (54%) who had chosen not to participate. A small minority (5%) cited the psychological intervention as their reason. Of 122 participating patients or dyads randomized to the intervention arm at the time, 4% (n=5) had discontinued the psychological intervention, while remaining in SPC care and in the overall Domus RCT. Reasons for this withdrawal were that session were not helpful (n=2) or wished for (n=1), or seeking treatment with a psychologist outside the project (n=2). Fifty-five patients or dyads had participated in the Domus RCT until the patients' death at the time of the assessment. Among them, the greatest percentage of deviations (36%) from the planned intervention structure was found for dyads who did not complete the two initial sessions within the first month after randomization (though they might have completed them at a later point in time). We concluded that the psychological intervention component had proven feasible to conduct, as well as acceptable to patients and caregivers.

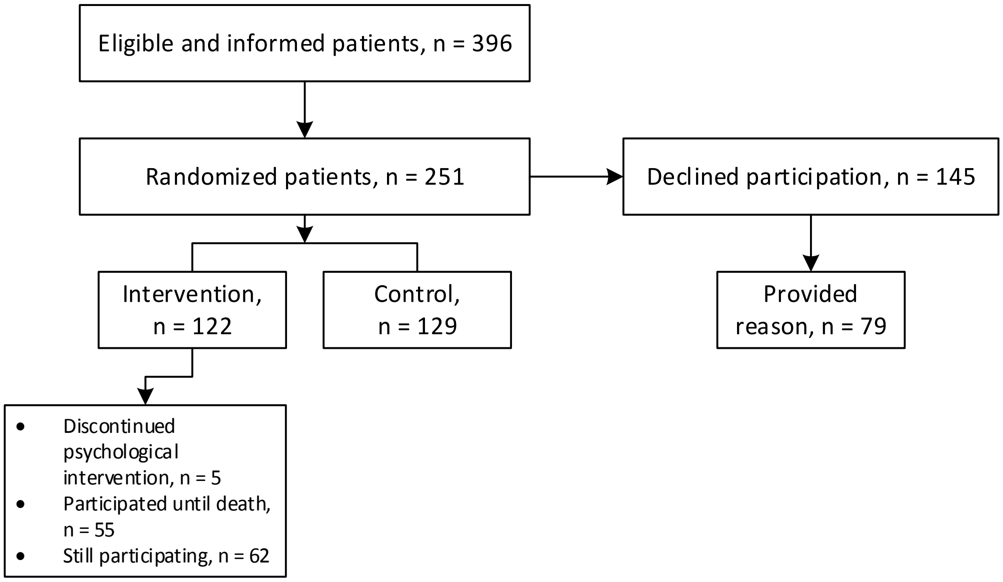


Figure 5. Flow-chart for participants in feasibility assessment

5.3 USE OF THE PSYCHOLOGICAL INTERVENTION THROUGHOUT THE RCT

Among all participating dyads in the intervention group included in analyses presented in this PhD (n=134), the psychological intervention was not initiated in nine patients due to dropout, death, or repeated hospitalizations within the first weeks after randomization. One dyad chose not to receive the psychological intervention. On average, dyads had 1.3 contacts with the psychologist per month participation, and across dyad types most sessions were conducted as common sessions with both dyad members participating (table 4).

Table 4. Mean number of sessions pr. month participation in the psychological intervention

Session type *Mean (min., max.)*		All dyads (n=124)	Couples (n=96)	Parent-Child (n=21)	Other dyads (n=7)
Home Care Conference, *% attended by psychologist*		46	48	38	43
Needs-based sessions	Common	0.6 (0, 2.4)	0.6 (0, 2.2)	0.4 (0, 1.1)	0.8 (0.1, 2.4)
	Patient	0.1 (0, 1.1)	0.1 (0, 1.1)	0.2 (0, 0.7)	0.2 (0, 1)
	Caregiver	0.1 (0, 2.2)	0.1 (0, 1.1)	0.2 (0, 2.2)	0.2 (0, 1)
	Needs assessments	0.4 (0, 1.1)	0.4 (0, 1.1)	0.5 (0, 0.9)	0.3 (0, 0.5)
	Any contacts *	1.3 (0, 3.9)	1.3 (0, 3.8)	1.2 (0, 3.9)	1.4 (0.8, 1)
Bereavement sessions		0.4 (0, 3)	0.4 (0, 3)	0.33 (0, 2)	0.29 (0, 1)

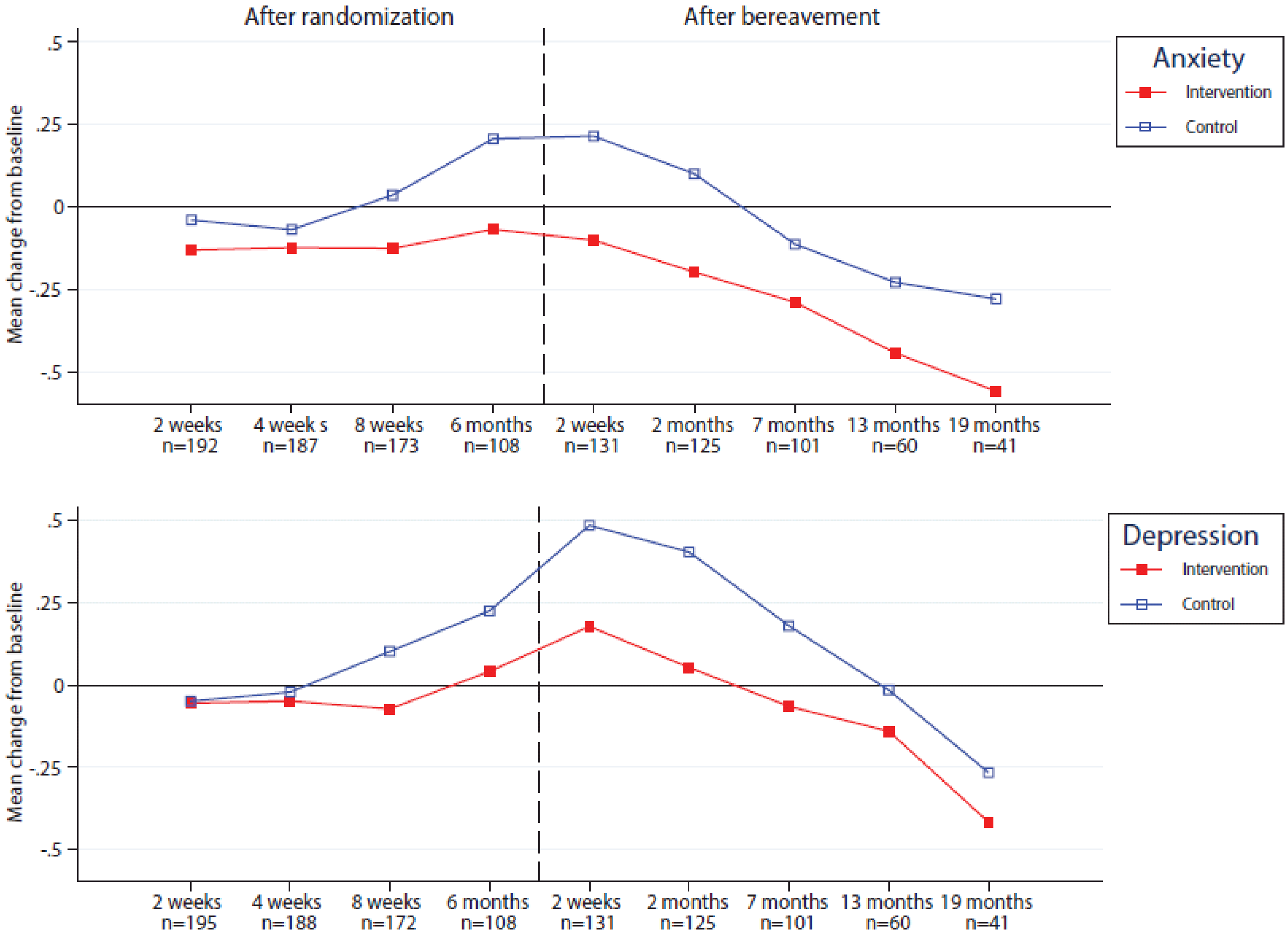
* May not correspond exactly to sum of separate session types due to rounding

5.4 INTERVENTION EFFECTS: RESULTS OF PAPERS 2 & 3

5.4.1 Caregivers' anxiety and depression (paper 2)

Observed mean scores of symptoms of anxiety and depression in the control group, increased in the first six months after randomization, and decreased after the patients' death (figure 6). In the intervention group, the same pattern was seen in the mean symptoms of depression, although with lower observed increases. The mean score for symptoms of anxiety remained close to stable in the intervention group until six months after randomization, and decreased after the patients' death.

Figure 6. Observed mean change scores from baseline in symptoms of anxiety and depression for caregivers in the Domus RCT

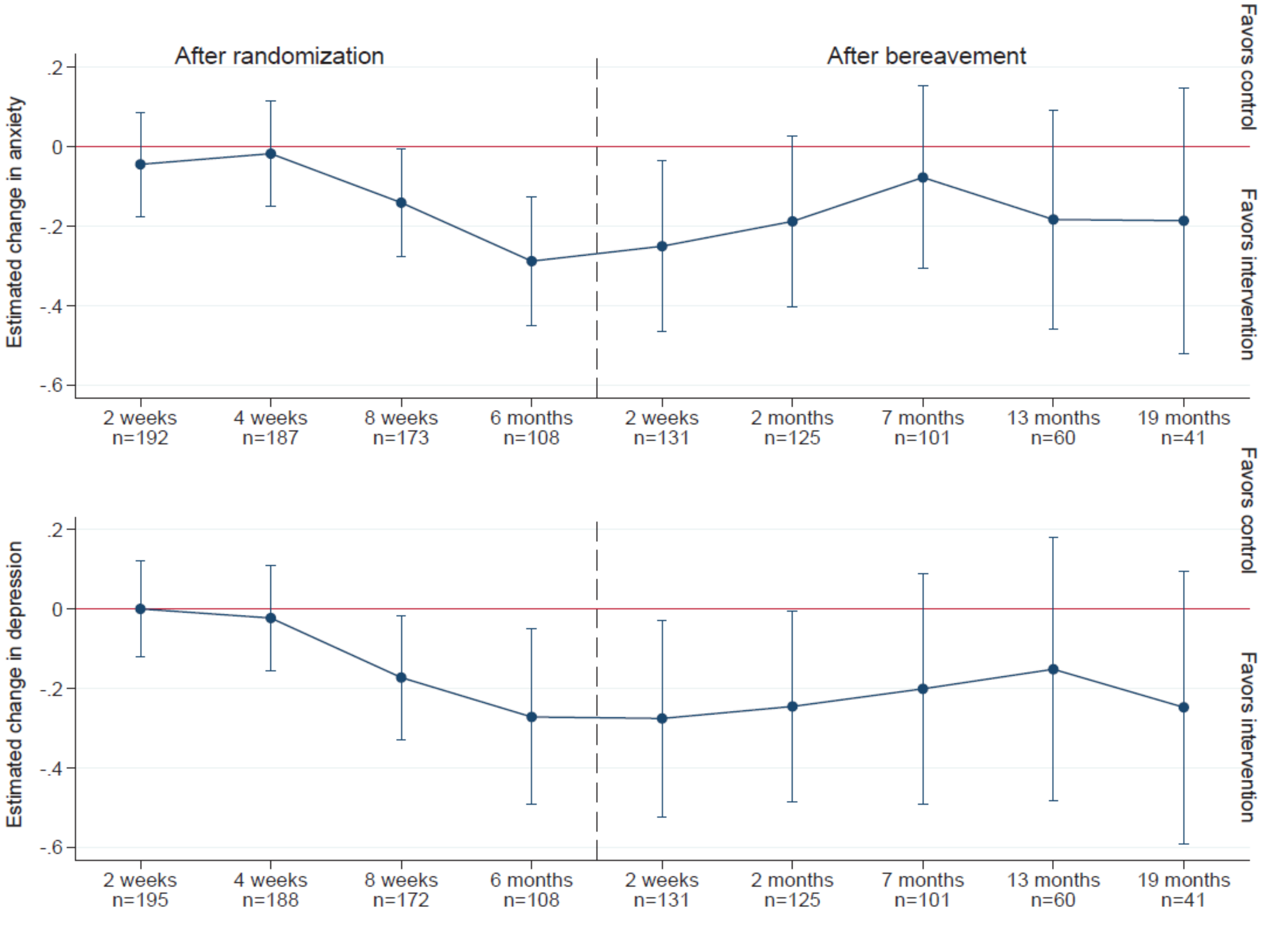


We found a significant main intervention effect in mixed effects models for anxiety. Caregivers in the intervention group had significantly lower symptoms of anxiety (estimated difference, -0.12; 95% CI, -0.22 to -0.01) (figure 7). Estimates for individual follow-up assessments were significant at 8 weeks (-0.14; -0.28 to -0.02), 6 months (-0.29; -0.45 to -0.13), and 2 weeks after the patient's death (-0.25; -0.47 to -0.04) (figure 7). No significant main intervention effect was observed for depression, but caregivers in the intervention group had significantly lower scores at 8 weeks (-0.17; -0.33 to -0.02), and 6 months (-0.27; -0.49 to -0.05) after randomization, and 2 weeks (-0.28; -0.52 to -0.03), and 2 months (-0.24; -0.48 to -0.01) into bereavement. Effect sizes for the significant effects found ranged from -0.19 to -0.45, corresponding to small to medium effects.

5.4.1.1 *Results of sensitivity analyses*

Mixed effects models based on multiple imputations yielded largely similar results for both symptoms of anxiety and depression when missing data were imputed assuming missing at random, although estimates for the intervention effect on symptoms of depression in bereavement were slightly lower than in the main models. Models with missing data imputed based on the assumption that missing values would be slightly lower, yielded larger estimates for almost all effects.

Figure 7. Estimated intervention effect on symptoms of anxiety and depression for caregivers in the Domus RCT, n=246



*adjusted for age, sex, relationship to the patient (spouse, adult child, other), baseline anxiety or depression score

5.4.1.2 *Analyses based on cut-off scores*

In mixed effects models based on dichotomized anxiety scores, caregivers in the intervention group had significantly lower odds of scoring above the cut-off throughout follow-up (OR 0.55; 95% CI 0.39 to 0.78) as well as 2 weeks into bereavement (0.38; 0.15 to 0.97). For depression, the main intervention effect was not statistically significant, but caregivers in the intervention group had significantly lower odds of scoring above the cut-off 8 weeks (0.40; 0.17 to 0.92) and 6 months (0.42; 0.14 to 0.98) after randomization.

5.4.2 Dyadic stress communication and coping (paper 3)

In mixed effects models for dyadic coping measures, no main effects on common coping, stress communication or satisfaction with dyadic coping were found (table 5). However, significant interaction effects between randomization group and dyad type were found for common coping and stress communication. Couples in the intervention group had significantly higher common coping than couples in the control group (estimated difference, 0.68; 95% CI, 0.11 to 1.24). Partner-caregivers in the intervention group reported significantly greater stress communication than partner-caregivers in the control group (0.97; 0.24 to 1.71), and parents in the intervention group who were cared for by an adult child reported significantly lower stress communication than parents with adult child-caregivers in the control group (-2.54; -4.19 to -0.90).

Table 5. Estimated intervention effect on dyadic coping and 95% CI for patient-caregiver dyads

	Overall effect	Effect when including interaction between randomization group and dyad type			
		Couples (n=195)	Parent child dyads (n=34)	Other dyads (n=20)	*p* for interaction between randomization group and dyad type
	Estimated difference (95% CI)	Estimated difference (95% CI)	Estimated difference (95% CI)	Estimated difference (95% CI)	
Common coping *	n=243				
	0.4 (-0.1; 0.9)	0.68 (0.11; 1.24)	-1.16 (-2.73; 0.41)	-0.18 (-2.06; 1.71)	0.0833
Stress communication †	n=245				
Caregiver	0.66 (-0.04, 1.36)	0.97 (0.24; 1.71)	-1.53 (-3.18; 0.12)	0.29 (-1.63; 2.22)	0.0142
Patient	-0.38 (-1.08; 0.32)	-0.04 (-0.78; 0.70)	-2.54 (-4.19; -0.90)	-0.72 (-2.64; 1.20)	
Satisfaction with dyadic coping ‡	n=244				
	0.10 (-0.18; 0.37)	0.25 (-0.05; 0.55)	-0.67 (-1.50; 0.17)	-0.48 (-1.46; 0.50)	0.0636

* *adjusted for dyad member, baseline coping*dyad member, baseline relationship quality, age, gender, follow-up assessment, Included interaction between dyad member and randomization group.*

† *Adjusted for dyad member, baseline communication*dyad member, baseline relationship quality*dyad member, age, gender, follow-up assessment*

‡ *Adjusted for dyad member, baseline satisfaction*dyad member, relationship quality, age*dyad member, dyad type*dyad member, follow-up assessment*

5.5 MEDIATION: RESULTS OF PAPER 3

The mediation analyses consistently showed no evidence of an indirect effect, through common coping or stress communication, whether for anxiety, or depression (table 7). For partner-caregivers, the analyses yielded direct intervention effects on symptoms of anxiety similar to the effects found in mixed effects models (paper 2). For symptoms of depression in partner-caregivers, effects were non-significant and smaller than those found in mixed effects models. For adult children caring for a parent, no clear pattern of direct effects was found. Sensitivity analyses with imputed data did not change conclusions.

Table 7. Direct and indirect intervention effects on caregivers' anxiety and depression at six months, mediated by dyadic measures at eight weeks

	Couple dyads, n = 195			
	Common coping Estimate (96% CI)		Stress Communication Estimate (96% CI)	
Anxiety	Caregiver's view	Patient's view	Caregiver's view	Patient's view
Direct effect	-0.26 (-0.50; -0.03)	-0.28 (-0.52, -0.04)	-0.25 (-0.47, -0.03)	-0.27 (-0.52, -0.02)
Indirect effect	-0.01 (-0.04; 0.02)	-0.02 (-0.06, 0.02)	-0.02 (-0.08, 0.03)	0.01 (-0.02, 0.04)
Depression				
Direct effect	-0.11 (-0.32, 0.11)	-0.16 (-0.39, 0.06)	-0.14 (-0.38, 0.09)	-0.13 (-0.36, 0.09)
Indirect effect	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)	0.01 (-0.04, 0.06)	0.01 (-0.02, 0.04)
	Parent-child dyads, n = 34			
	Common coping Estimate (96% CI)		Stress Communication Estimate (96% CI)	
Anxiety	Caregiver's view *	Patient's view †	Caregiver's view *	Patient's view †
Direct effect	-0.02 (-1.02, 0.99)	0.36 (-0.01, 0.73)	-0.06 (-1.01, 0.91)	0.12 (-0.11, 0.35)
Indirect effect	-0.03 (-0.16, 0.09)	-0.15 (-0.42, 0.12)	-0.03 (-0.10, 0.05)	-0.00 (-0.09, 0.08)
Depression				
Direct effect	-0.30 (-1.33, 0.73)	0.30 (-0.22, 0.82)	-0.25 (-1.21, 0.72)	0.02 (-0.43, 0.48)
Indirect effect	0.01 (-0.09, 0.11)	-0.17 (-0.44, 0.10)	-0.04 (-0.15, 0.08)	0.00 (-0.15, 0.16)

*based on 12 dyads, † only nine dyads available for analyses as 6 months, therefore these are at 8 weeks

5.6 SECTION SUMMARY

Two-hundred and forty-nine dyads who participated in the Domus RCT were analyzed. The intervention and control group were well-balanced except for minor differences in caregiver type and cancer diagnoses. In mixed effects models, we found a significant intervention effect on symptoms of anxiety throughout follow-up, and symptoms of depression from eight weeks after randomization to two months into bereavement. We found that the intervention significantly increased common coping by a small amount in couple-dyads. Further, in parents cared for by an adult child, the intervention significantly decreased stress communication, whereas it increased stress communication in partner-caregivers. In models examining mediation of the effect on anxiety and depression by dyadic measures, no evidence of mediation was found.

6

DISCUSSION OF RESULTS

The next section discusses the main findings presented in this PhD thesis in the context of previous trials in SPC as well as previous dyadic and existential psychological interventions. Further, it discusses aspects of the design of the Domus SPC and psychological intervention that might underlie intervention effects.

6.1 EFFECTS ON CAREGIVERS' PSYCHOLOGICAL DISTRESS AND DYADIC COPING

6.1.1 Effects on anxiety and depression

Compared to the control group, caregivers in the intervention group had significantly lower symptoms of anxiety throughout follow-up. Symptoms of depression were significantly lower eight weeks and six months after randomization, as well as two weeks and two months after the patient's death. The magnitude of effects found corresponds to small to medium standardized effect sizes, in line with the previous RCTs of SPC that reported significant effects on distress in caregivers.[120,124] The only previous RCT that assessed distress in bereavement, had limited power and found only a very small (effect size 0.07) non-significant effect.[125] While previous psychosocial intervention studies conducted alone or in addition to SPC indicated that interventions can alleviate distress both before and after the patient's death, the evidence of effects has been mixed. Among studies in which SPC was compared to SPC with additional psychosocial intervention, one study found effects on psychological distress in bereavement, but not during caregiving.[130,131] One previous study with an existential component likewise found significant effects on symptoms of anxiety and depression, although effects on anxiety were only found immediately post-intervention and effects on depression only in the long-term, and pre- and post-bereavement effects could not be distinguished.[143] In a previous dyadic intervention, large effects on symptoms of anxiety and depression were found eight weeks after the intervention, but caregivers were not followed up in bereavement.[184] The Domus RCT adds to the evidence base by demonstrating intervention effects on both anxiety and depression during caregiving as well as in bereavement.

6.1.1.1 Clinical significance

Statistically significant results may not be clinically relevant. However, we also found a significant intervention effect on odds of having elevated symptoms of anxiety or depression, which supports the clinical significance of our findings. Even small changes in distress may be meaningful for caregivers, who are experiencing a highly stressful situation. Their distress has been found to be significantly related to the experience of caregiving burden,[185] increased levels of unmet needs,[186] and subsequent faster decline in their physical health.[187] Caregiver distress may also affect patients, as it has been found to be significantly associated with caregivers' self-efficacy for symptom management,[188] underestimation of patients' symptoms.[189] Depression in caregivers has also been shown to be related to patients' reports of quality of care.[79] As caregivers' psychological distress may have wide-reaching consequences, even small improvements may be meaningful in clinical practice.

6.1.2 Effects on dyadic coping

We found no main effects of the intervention on three measures of dyadic coping, namely common coping, stress communication, and satisfaction with dyadic coping. These measures represent only certain aspects of dyadic coping and the intervention may have affected other unmeasured dyadic coping efforts. However, significant effects did emerge for couple-dyads and dyads with an adult child caring for a parent (see below). No previous interventions for patients with advanced cancer and their caregivers have assessed outcomes related to the systemic transactional model of dyadic coping. The lack of main effects may be due both to the Domus intervention design and to subgroup effects in differing directions. While the format of the intervention was largely dyadic, with the two initial and most needs-based sessions taking place jointly with patients and caregivers, the content of the intervention was not specified to address dyadic coping. Some previous interventions have focused more explicitly on e.g. communication between partners, by including teaching of communication skills, and might thus be expected to increase communication specifically. These studies have reported significant effects on psychological distress and relationship quality, but did not assess whether communication changed and mediated these effects.[184,190] Because topics were flexible in the Domus intervention, sessions would affect dyadic coping if it was agreed on as a session topic by dyads and psychologists. Alternatively, the intervention format may have had indirect effects on dyadic coping, for instance by increasing the focus on communication simply through the implicit expectation to *talk* during sessions. Indeed, communication may be a necessary component in interventions aiming to target dyads as the unit of care.[89] Such an indirect effect might be what is observed in the increased stress communication by partner-caregivers.

6.1.2.1 Subgroup effects

In couples, the intervention significantly increased common coping as well as stress communication in partner-caregivers. Among parents cared for by an adult child, on the other hand, the intervention significantly decreased stress communication. It may be intuitive, that couples and other dyads react differently to the experience of advanced cancer, because of their different relationship and the differences this implies for caregiving.[191] Understanding the different effects found may require both an examination of such relationship differences and consideration of the assumptions about dyadic coping made in the STM. The STM describes dyadic coping in couples[91] and the model might not be extendable to non-couple dyads. For instance, common coping is assumed to occur when partners share common goals,[91] and couples might more frequently share common goals, e.g. by virtue of their shared daily lives. Further, the STM assumes that dyadic coping serves to safeguard both partner’s well-being as well as that of the relationship itself.[91]

Patients and caregivers in other relationships might not share this fundamental motivation and therefore not engage in dyadic coping to the same extent. Members of a couple may be emotionally closer and each other's primary attachment figures and confidants, as well as more reliant on each other for support. Children caring for their adult parents, on the other hand, may have their primary confidant outside the patient-caregiver dyad. Further, caregiving often represents a shift in the relationship due to role-reversal, with the child assuming the role of caregiver previously held by the parent.[192]

Because of these differences, certain aspects of the Domus intervention may have had different effects on different dyad types. The psychological intervention acknowledged caregivers' needs as equally important as the needs of patients. Partner-caregivers may have experienced the dyadic setting as an encouragement and legitimization to speak about their concerns and experience of stress. Caregivers have previously been found to buffer patients from their concerns[96,193] and caregivers in the Domus study also reported significantly lower stress communication scores than patients at baseline. The intervention may have contributed to decreasing this difference in stress communication among patients and caregivers in couples. In parents cared for by their adult children on the other hand, increased awareness of their children's needs may have led to lower stress communication in order to protect the child from the parents' concerns. This might be an adaptive strategy in parent-child dyads with potentially diverging goals or lower levels of closeness and support in the dyad.

Whether or not the observed changes in dyadic coping were beneficial is not a straightforward question. Some previous research indicates that increased communication is beneficial to dyads' adjustment,[95,96,194] but this may not be unequivocally true. For instance, one-sided disclosure may increase psychological distress,[193] and a more nuanced view of the benefit of communication has been called for.[195] Further, the effects of communication could be different in different dyad types. The Domus intervention did not change satisfaction with coping among couples or parent-child dyads, one indicator that intervention effects did not negatively affect dyads.

6.1.2.2 Intervention effects on adult children caring for a parent

For partner-caregivers, path analyses to investigate mediation replicated the significant direct effects of the intervention on symptoms of anxiety and, while not significant, showed a pattern of effects on depression that was in accordance with the results of mixed effects models. For adult children, no consistent pattern of direct effects was found in these analyses. While the power to detect significant changes was limited in this analysis, it leaves open the possibility that adult children, as opposed to partner-caregivers, did not benefit from the intervention. It has been suggested that dyadic intervention may need to be tailored differently to different types of dyads,[89] and the results from the Domus RCT highlight that this may be an issue in need of further exploration. Future studies should consider investigating moderation by dyad type to further elucidate whether parent-child dyads may experience different outcomes than couples, and investigate whether interventions with a different focus or structure might be more beneficial to parent-child dyads. For instance, it is possible that parent-child dyads benefit more from interventions that address the patient and caregiver separately, to accommodate diverging goals, wishes, and needs between the parent and adult child. Alternatively, parent-child dyads might benefit from more structured interventions that explicitly address the potential conflicts or diverging interests and teach strategies to cope with them. A first step, however, is investigating whether existing interventions that are provided across dyad types have differential effects akin to those found here.

6.2 MEDIATION EFFECTS AND THE RELEVANCE OF DYADIC COPING DURING THE END OF LIFE

We found no evidence for mediation of intervention effects on symptoms of anxiety and depression by the aspects of dyadic coping measured. In part, this may be because effects on dyadic coping were primarily found on stress communication, an antecedent of other dyadic coping efforts, and were very limited for common coping. In addition, the framework of dyadic coping has not yet been systematically related to and investigated within the context of the end of life. It is not clear what the unique challenges related to the ultimate dissolution of the relationship by death may imply for dyadic coping in dyads at very advanced stages of disease. The STM assumes that dyadic coping may at times be asymmetric[91] and one hypothesis could be that the balance of dyadic coping shifts to being less reciprocal at the end of life. Common coping might decrease as the patient gets weaker and death approaches, and stress communication might be impacted by both patients and caregivers seeking to protect one another from burden. In the STM, supportive and delegated coping are proposed as two types of coping efforts where one partner supports the coping of the other, or takes over the other's tasks and solves the problem for them.[91] It may be that caregivers provide more supportive and delegated coping to patients toward the end of life, and that these forms of coping are thus more relevant to dyads' psychological well-being during this time.

The results of our mediation analyses do not speak directly to the importance (or lack thereof) of dyadic coping at the end of life. The scarcity of previous research findings in advanced cancer within which to interpret our findings, however, highlights that much knowledge has yet to be gained on interactive coping efforts and their effects in dyads at the end of life.

6.3 INTEGRATION OF PSYCHOLOGICAL INTERVENTION IN SPC

One of the most prominent differences between the Domus intervention and previous RCTs of SPC interventions is the dyadic psychological intervention component. Several aspects of the psychological intervention component distinguish it from previous interventions and are expected to have influenced outcomes.

6.3.1 Collaboration with SPC team

Because the Domus psychological intervention was integrated in the overall Domus intervention, collaboration between psychologists and SPC team members, such as nurses or physicians, was part of the psychological intervention component. In the previous RCTs in SPC that included a specified psychosocial intervention, nurses providing it could contact clinical teams with the permission of the patient.[120,121] In the Domus RCT, the extent of collaboration differed greatly between dyads and may have depended both on the extent and type of needs present. This collaboration, which is not included in stand-alone psychosocial or psychological interventions allows for an integrated care experience for patients and caregivers. Health professionals can coordinate their care and understanding of patients' physical symptoms and their current treatment can be integrated into the psychological intervention and vice versa.

6.3.2 Needs-based intervention structure and content

The psychological intervention differs from many previous psychological interventions for patients with advanced cancer in structure and content. In large part this difference is rooted in the integration of the intervention in SPC. As a patient-centered approach, palliative care must remain flexible to the individual patients' and their families' developing needs throughout the trajectory of the illness, necessitating continuous assessment of needs and offer of tailored interventions.[3]

6.3.2.1 Intervention timing

The Domus psychological intervention adopted the approach of continuous needs assessment and aimed to target sessions toward dyads when needs arose. In many previous psychological and psychosocial interventions a limited number of sessions was offered.[103,139–144,148,196] In trials of SPC, continuous follow-up until patients' death has been part of the intervention, including the one previous trial in which a manualized psychosocial intervention specifically targeted caregivers.[114,120] In accordance with the finding that psychological intervention may be most effective with patients who are distressed,[197] a previous study offered intervention to only those caregivers who experienced heightened distress at baseline.[134] This study, however, did not find effects. The approach in the Domus intervention was to continuously monitor whether elevated distress emerged, rather than offer intervention based on a one-time assessment. This meant that dyads would also receive intervention, if psychological distress developed over the course of receiving palliative care. While the continuous needs assessment may have underpinned part of the intervention effect, the decision to enroll dyads regardless of needs for psychological support may also have diluted effects. Including only dyads with needs at baseline and thus greater potential to benefit might have resulted in stronger effects. The needs assessments themselves may also have contributed to the intervention effects, as they may have provided a sense of security and comfort even when no needs for intervention were identified. Clarifying how continuous needs assessments benefits dyads, and what prompts psychological intervention sessions, may help to further target assessments and interventions. Future studies might also investigate whether sessions may be particularly needed and helpful at certain points during the trajectory of palliative care to elucidate when heightened attention to needs may be necessary.

6.3.3 Specificity of intervention content

The intervention content of the psychological component may be characterized in terms of its topics, i.e. those issues, themes, and challenges that the intervention addressed, and its method, the EPT approach. As opposed to many recent psychosocial interventions with caregivers of patients with advanced cancer and dyads and the one RCT of SPC targeting caregivers, the psychological intervention in the Domus RCT contained almost no pre-specified content. The completion of the needs assessment necessitated that a range of topics be addressed, especially during the initial two sessions, but in subsequent sessions topics were chosen with the dyad. Thus, when need for intervention arose, sessions could cover precisely the issues that were relevant. Pre-specified content on the other hand may be particularly helpful in preventive interventions that aim to increase e.g. caregivers preparedness and competence for caregiving.[131] The psychological intervention was thus individualized both with regard to timing and content, and we expect that the specificity in content is instrumental to intervention effects. The different effects found for different dyad types are somewhat surprising in light of the tailored nature of the intervention. This may indicate that the basic structure of the intervention, including caregivers in SPC and psychological intervention, might have different implications for different dyad types.

6.3.3.1 Existential phenomenological approach

Existential approaches have previously been advocated for patients with advanced cancer and their caregivers.[98–100] Many existentially based interventions focus on the generation of meaning from the experience of caregiving or suffering from cancer.[146,198] Such an intervention aim may be at risk of making meaning the normative goal. In contrast, the Domus psychological intervention used EPT, which belongs to the less normative approaches among existential therapies.[101] This stance allowed for a flexibility in meeting suffering among patients and caregivers that does not prescribe, however implicitly, that meaning can and should be found in all suffering. Rather it acknowledges that certain life circumstances can be, or be experienced as, devoid of meaning.

6.3.4 Focus on caregivers and dyads

The specific attention paid to caregivers in the Domus study is only found in one other RCT of SPC with a well-described psychosocial intervention.[120] Further, only one RCT with an existentially inspired intervention has targeted caregivers.[143] Within both fields, the dyadic approach has not yet been explored in RCTs. In keeping with the focus on flexibility, the Domus psychological intervention left sessions, other than the two initial ones, open to be conducted either in common or individually, and the finding that many dyads made use of the flexible structure to receive some sessions individually underscores that the needs for individual and dyadic intervention may exist concurrently. Compared to psychologists that conduct sessions solely with the patient or caregiver, the Domus psychologists were familiar with both dyad-members. This knowledge of the other dyad-member meant that the Domus intervention always contained some aspect of dyadic focus, even in individual sessions. In the previous manualized psychosocial intervention in SPC that targeted caregivers, such knowledge was avoided by letting different nurses provide the intervention to patients and caregivers, in order to enhance open sharing of concerns.[120] Confidential sharing of information, however, was also possible in the Domus intervention, as no content from individual sessions would be shared with the other dyad-member unless this was explicitly agreed on. Individual sessions may thus help patients or caregivers better understand their own needs and wishes before sharing them with the other dyad-member.

6.4 PATHWAYS OF EFFECTS IN COMPLEX INTERVENTIONS

6.4.1 A note on complex interventions

The overall Domus intervention was a complex intervention, with multiple interacting components, and multiple pathways could thus explain intervention effects. Specialized palliative care interventions, in accordance with the multidimensional focus of palliative care, are complex and multifaceted, but limited specificity about for instance the training of SPC providers makes SPC interventions difficult to compare.[5] The complexity in these interventions further creates difficulty in ascertaining which intervention components are effective, and especially so when most RCTs provide limited descriptions and specifications of intervention principles and content, and analyses of effect moderation and mediation are rarely performed. While it is challenging to determine the effective components of complex interventions, and comparisons among different complex interventions are difficult, such complex interventions are nonetheless necessary. They provide evidence for treatment situations that approximate clinical conditions more than stand-alone interventions can. Different intervention components might interact with each other, and assessing them one at a time would not provide evidence for their combined effects. Here, I will consider the pathways that could have led to the decrease in symptoms of anxiety and depression among caregivers in the intervention group.

6.4.2 Pathways behind the effect on anxiety and depression

Both the psychological and the SPC team intervention components may have contributed to the observed effects. The pathways of change could be divided into those that directly affect the caregiver and those that affect the caregiver through the patient or through dyadic interactions. The SPC team might have reduced caregivers' symptoms of anxiety or depression directly, by providing knowledge and guidance on e.g. symptom management and increasing caregivers' self-efficacy, which has been found related to distress.[199] The psychological intervention component could have lowered symptoms of anxiety and depression by helping the caregiver find new ways of relating to the weakened patient and their own situation, or by helping them address inflexible assumptions in their world-view about e.g. the amount of support they found acceptable to receive or the way they expected to have to deal with bereavement. Both the psychological and the SPC team intervention components might have increased quality of life for patients,[183] which could affect caregivers, by lowering their caregiving burden and/or their worry for patients. One previous RCT of SPC, in which no psychological or psychosocial intervention was specified for caregivers, but which nonetheless improved caregivers' psychological distress may support such indirect effects through effects on patients.[124]

Although we found no mediation by the measured aspects of dyadic coping, caregivers may have been affected by other dyadic interactions that changed in response to the intervention. In psychological intervention sessions, dyadic disagreements could be discussed and new ways of handling joint challenges explored, e.g. relating to common plans and activities affected by the patient's symptoms, or differences of opinion regarding professional help. Helping to address issues experienced within the dyad might indirectly lower caregivers' anxiety and depression. We explored one such dyadic mechanism, and found no evidence to support the hypothesized mediation of intervention effects by the dyadic measures assessed, i.e. common coping and stress communication. These two concepts, as measured by the DCI, represent small parts of the potential dyadic effects, and ones that were not directly targeted by the psychological intervention component. Thus, we can neither confirm nor reject that SPC and dyadic psychological intervention can affect caregiver outcomes through changes to dyadic interaction.

6.5 SECTION SUMMARY

The Domus psychological intervention component represents an attempt to integrate a psychological intervention that shares features with previous stand-alone psychological interventions and integrates them into SPC. The psychological intervention adopted the patient-centered approach of SPC, which involves continuous needs assessment and the intervention was targeted to needs, both in content and timing. The existential therapeutic approach allowed flexibility with regard to content while addressing the dyad with an understanding of their suffering rooted in existential philosophy.

The differential effects found for different types of dyads likely depend on the differences in the relationship and caregiving situation that couples and parents cared for by adult children are experiencing. It is not clear how the framework of dyadic coping extends to non-couple dyads, and dyads at the end of life, and how the assumptions in the theoretical model underlying our measure of dyadic coping might have affected results. Further, when, in what combination, and to which types of dyads individual or dyadic sessions should be offered to achieve the greatest benefit is a question for future research to address.

The Domus RCT has demonstrated that a flexible dyadic approach, with continuous needs assessment, has significant beneficial effects on caregivers' symptoms of anxiety and depression, and does affect certain aspects of dyadic coping in couples and parent-child dyads. The Domus RCT has extended the evidence for a beneficial effect of SPC and psychological interventions on caregivers' psychological distress to more diverse caregiver populations than previous RCTs of SPC. Further, it has shown that caregivers benefit both while caring for the patients and in bereavement.

7

DISCUSSION OF METHODS

In the following, I discuss central methodological strengths and weaknesses of the Domus RCT and the psychological intervention component and their implications for the results presented in this thesis. I begin by focusing on a few central design aspects of the overall Domus RCT that have implications for the generalizability of findings, then discuss the design of the psychological intervention component in particular, and finally discuss issues surrounding follow-up assessments and statistical methods.

7.1 DESIGN OF THE DOMUS RCT

7.1.1 Population and intervention focus

Patients in the Domus RCT constitute a more varied clinical population than patients in previous RCTs that have investigated effects of SPC on caregivers' symptoms of anxiety and/or depression. Whereas patients in previous trials were referred shortly after diagnosis of advanced disease,[120,124] patients in the Domus RCT were referred at different times during the disease trajectory and the population included patients with worse performance status than in many previous RCTs of SPC.[112–115,117,118] This difference reflects the original focus of the Domus RCT on patients with worse performance status and the primary outcome of place of care and death, while most previous RCTs investigated early initiation of SPC. The shift in the target population of the Domus RCT implies that the study sample is representative of a broader group of patients with advanced cancer, but also that overall timing of the intervention is less specific. Effects of the Domus RCT may thus be more widely generalizable, but reveal less about the optimal timing of SPC initiation than previous studies.

7.1.2 Sample size, screening and participation

The sample size for the Domus RCT was determined for patients and the primary outcome, not for caregivers. However, as small to medium significant effects were detected for caregivers, an adequate sample size was attained. Screening for eligibility was systematically conducted and ensured that all eligible patients were approached to be informed of the study. Fifty-seven percent of informed patients consented to participate, but no analysis was conducted comparing participants and non-participants. This limits our knowledge about potential selection bias in recruitment. Participation among caregivers invited by patients was very high (96%) and comparable to that in previous RCTs, but a large minority of patients (n=82, 24%) chose not to invite an available caregiver. We have no way of knowing the characteristics of caregivers whom patients chose not to invite, and can only speculate that the type and quality of relationship may have played a role. We can, however, be reasonably certain about the generalizability of our findings to caregivers whom patients would to choose to include in their care experience. While some previous RCTs reported higher patient participation, most recruited from geographically and/or socioeconomically selected populations.[112,114,116–118,200112,201] In the context of the Danish health care system with free hospital treatment, the Domus RCT recruited from a socioeconomically diverse patient population, resulting in a socioeconomically diverse sample of caregivers. Two previous RCTs that assessed effects of SPC on caregivers' symptoms of anxiety and depression, reported very high educational attainments among their participating caregivers, with 0-1% having completed less than high school.[120,124] Among caregivers participating in the Domus RCT, 37% reported an elementary or vocational, and no high school education. Thus, our sample extends the generalizability of the beneficial effects compared to previous RCTs.

7.1.3 Randomization and blinding

The randomization sequence was computer generated and project nurses who randomized patients were blinded to the size of changing blocks. However, the use of envelopes as opposed to computer-based real-time randomization represents a potential weakness. The randomization was successful, although some differences in the intervention and control group were found at baseline, which can be expected by chance. The fact that blinding to randomization group was not possible for participants or providers may have increased the effectiveness of the intervention through participants' expectations of benefits, but blinding is rarely, if ever, possible and thus not standard practice in RCTs of palliative care.[110]

7.1.4 The SPC intervention and usual care

Many prior RCTs of SPC were carried out in single institutions,[112,115–117] whereas the Domus intervention was provided by nine different SPC teams, ensuring greater representativeness of SPC practices and thus greater generalizability. The SPC intervention focused on the transition from hospital-based oncological care to home-based SPC. Therefore, the specific content, timing and intensity of continuing SPC in the intervention group was not prescribed a priori, and reflects usual clinical practice. Only adherence to the home care conference could be assessed. Six patients never received the home-conference, as they were either hospitalized or had died. Among all patients included in the intervention (including those participating without a caregiver) almost half (48%) of home care conferences were conducted later than the protocol specified,[183] and SPC teams often had difficulty scheduling it within the allotted time, reflecting the limited SPC capacity in Denmark.[12] Due to ITT analyses, however, this change to the intervention as received would result in under- rather than overestimation of intervention effects. Carry over effects, i.e. changes in the control condition due to the intervention, may have played a role in the Domus RCT. Of patients in the control group (including those participating alone), 60% received SPC, although, on average, 110 days later than the intervention group.[183] While not formally assessed, project nurses reported a drift in the referral of patients by oncologists throughout the study period, both such that more patients were referred before they could be offered study participation, and such that patients allocated to the control condition were more often referred to SPC services after randomization. Thus, with regard to the SPC team intervention, carry over effects may have weakened the intervention effect.

7.2 THE PSYCHOLOGICAL INTERVENTION COMPONENT

The psychological intervention component also contains certain strengths and weaknesses, related to the design, manualization, and adherence of psychologists to the intervention.

7.2.1 Design of the psychological intervention

The focus on dyads and caregivers as well as the existential approach represent strengths in the psychological intervention that have already been discussed. Limitations of the psychological intervention include the lack of a formal feasibility study prior to the full scale RCT. The pilot-test of the intervention was included in the RCT period, which resulted in the necessity to adapt the intervention structure as a result of unexpected survival times. While this represents a departure from the ideal in RCTs and a limitation in the RCT, the change affected mainly the timing of sessions, and did not change the content or theoretical framework of the intervention. It did, however, introduce the necessity of continuous needs assessment, which we believe became a major strength in the psychological intervention component. Only eight patients, including five participating with a caregiver, were enrolled prior to the change and received the psychological intervention for maximally three months before the structure of sessions was changed. The very small number of dyads and caregivers affected limits the impact of the change on our results.

7.2.2 Manualization vs adaptability

Manualization makes interventions reproducible and eases their implementation in clinical practice. The psychological intervention manual contained specifications of the structure of the intervention and the therapeutic approach. While more strict manualization, with specified intervention content, wording of introductions, homework etc., has been carried out for other psychological interventions with patients with advanced cancer and or their caregivers,[133,142,202,203] the psychological intervention in the Domus RCT retained flexibility to target and adapt sessions based on dyads' specific situation and clinical judgement. Certain aspects of the intervention might however have been more specifically described. Existential phenomenological therapy was described as the therapeutic approach, and a dyadic understanding of coping was the theoretical background for providing dyadic sessions. However, neither a specific theory of dyadic coping nor the way in which the intervention made use of EPT with dyads rather than individuals was specified. While existential therapy with couples is by no means rare or new, little has been written about EPT as an approach to couples or other dyads.[204] A meaning-based intervention for couples coping with advanced cancer has recently been shown to be feasible.[205] EPT with individuals, however, already has a strong focus on relations, as EPT is based on an understanding of 'relatedness' as one of the givens of existence.[104] [101] Many principles of EPT are thus applicable to couples, and to the exploration of patients' and caregivers' experience and understanding of their relationship. The application of EPT to dyads was thus left open to the clinical judgment of the intervention psychologists. Another aspect of the intervention that might have been manualized to a greater extent is the assessment of needs and risk used to determine session frequency. Although the needs and risk assessment was based on previously identified risk factors, clinical judgement was likewise allowed to remain central in this assessment. More structured assessments, such as formalized interviews or tools, might identify issues that could be overlooked in a clinical assessment. The strength of the clinical assessment, on the other hand, is the flexibility to adapt it to the individual dyad. The collaboration with the SPC team might also have been specified to a greater extent. This could have strengthened collaboration, e.g. by ensuring that each dyad was discussed at least once with the whole SPC team. While the loose manualization may be seen to represent a limitation with regard to replicating the intervention, it is in keeping with relying on clinical judgement to ensure optimal tailoring of sessions to each dyad, and may ultimately make it easier to implement in clinical practice.

7.2.3 Adherence and competence

Deviations from the structure proscribed in the psychological intervention manual as well as reasons for these were systematically documented and found to be acceptable in the initial feasibility assessment (paper 1). However, adherence to the EPT method was not investigated. The degree of manualization in the psychological intervention meant that formal assessment of adherence was not easily conducted, as no checklists or other measures to quantify existential phenomenological therapy exist. Instead, regular group supervision by senior psychologists who were very experienced existential therapists was used to continually reinforce the therapeutic approach. The competence of intervention psychologists to complete the intervention was ensured through training in EPT and continuous group supervision, but was also not directly assessed.

7.2.4 Psychological care as usual

Whether or not patients and caregivers in the control group received psychological intervention may influence intervention effects. Psychological care as usual is difficult to describe, as it could take place in several different contexts and could have been provided by psychologists in SPC teams or by publicly subsidized psychologist, referral to whom would have been available to many participants. No formal treatment standards exist that apply to both these groups. While referral criteria for publicly subsidized psychologists include severe illness and death in a relative as well as diagnosed anxiety or depression, no referral criteria are formalized across psychologists in SPC teams. Therapeutic approaches can be expected to vary widely between and within the two groups, and no conclusive description of psychological care-as-usual is thus possible. Patients' and caregivers' use of psychological treatment outside the RCT was not assessed, and we cannot determine what effects such treatment might have had on the outcomes.

7.3 FOLLOW-UP AND ASSESSMENT

The measures of symptoms of anxiety and depression and dyadic coping used have certain strengths and limitations. The SCL-92 anxiety and depression subscales, completed by caregivers, have been validated and found to perform well in a randomly selected sample from the general adult Danish population.[168] In addition, a criterion for identifying overall distress has been proposed: two SCL-92 subscales exceeding T-score based cut-offs.[169] We chose to use the cut-off scores separately for each scale, which could lead to overestimating the prevalence of elevated distress. However, we found proportions with elevated scores falling within the range identified in previous studies of caregivers of advanced cancer patients using questionnaires.[30,70–75]

7.3.1 Dyadic coping inventory

The Dyadic Coping Inventory has been validated in several languages,[170–172] and translated into Danish according to standard forward and backward translation guidelines.[173] The scale was originally created for healthy couples,[172] but has previously been used in couples coping with breast cancer[173] and hematological cancer,[206] and its application to couples coping with advanced cancer may thus not be unreasonable. The DCI has not previously been used in patients and caregivers who are not in romantic relationships. Although we adapted the items on the common coping subscale to describe the same type of behaviors in a more inclusive way (e.g. kissing changed to hugging, both behaviors of physical closeness), this represents a limitation. Non-couple dyads might not engage in the behaviors assessed by the DCI to the same extent, or the behaviors might have different meanings. We cannot rule out that the DCI items function differentially among different types of dyads, leading to potential misclassification and bias.

7.3.2 Timing of follow-up assessments

The timing of follow-up assessments may limit the conclusions that can be drawn about our results. Follow-up assessments before the patients' death were chosen to be carried out two, four, and eight weeks as well as six months after randomization. This was based on the initial expectation of relative short survival, which necessitated short-term rather than long-term assessments. Assessing patients and caregivers at regular intervals and adding an assessment at four months after randomization would have given a more complete picture of intervention effects over time. Assessments in bereavement were motivated by the wish to investigate both short- and long-term effects. We included an assessment two weeks as well as two months in bereavement to cover both the period right after the death, as well as the time when the funeral and many practical arrangements have already taken place. Thereafter, we planned assessments every six months, and to avoid the anniversary of the patients' death, these were conducted at seven, 13, and 19 months into bereavement.

7.3.3 Loss to follow-up

Patients and caregivers were lost to follow-up chiefly due to the patient's death, which is expected in trials in palliative care, but should not be considered a limitation in itself, and attrition due to death should be distinguished from attrition from other causes.[180] Considering the length of follow-up, a low proportion of patients (n=11, 4%) and caregivers (n=19, 8%) withdrew consent. Before the patients' death, the proportions of participants who were sent and completed follow-up assessments were relative high, from 73-84%. In bereavement, caregivers who completed follow-up assessments decreased with increasing time from the patients' death, most prominently in the control group, where 57% of caregivers completed the SCL-92 19 months into bereavement. As sensitivity analyses for both anxiety, depression and mediation yielded largely similar results, the missing responses did not seem to introduce bias.

7.4 STATISTICAL METHODS

7.4.1 Mixed effects models

Mixed effects models take into account the variation within repeated non-independent measures,[176] and thus represent an appropriate analysis for intervention effects of the RCT. Recent RCTs in SPC have employed *terminal decline analyses*, which model outcomes as well as survival backward from death.[124,125] Conducting such analyses was outside the scope of the present work, but could have provided additional insight into intervention effects by accounting for the influence of proximity to death on outcomes assessed in questionnaire measures. Below, I discuss a few specific aspects of the mixed effects analyses.

7.4.1.1 Intervention effects on symptoms of anxiety and depression

In models for symptoms of anxiety and depression, we included the interaction between randomization group and follow-up time points to estimate intervention effects at all follow-up times. We interpreted these individual intervention effects in spite of the interaction being non-significant, which would indicate that the effect did not differ between assessment points. However, as the length of psychological interventions has previously been found to moderate intervention effects, we had reason to assume that the intervention would not have had the same effect after two weeks, during which a maximum of one psychological intervention sessions would usually have been possible, as after six months. Neither can it necessarily be expected that effects of psychological interventions persist after the intervention has ended. The pattern found, with significant effects from eight weeks and until early bereavement is consistent with both these assumptions. Sensitivity analyses did not change our conclusions, even when we modelled missing data to reflect higher symptoms of anxiety and depression. This strengthens our confidence in the findings.

7.4.1.2 Intervention effects on aspects of dyadic coping

In mixed effects models of dyadic measures, we investigated moderating effects of participants' age, gender, and relationship (couples, parent-child or other dyads), to investigate whether certain dyads benefitted more from the intervention than others. We found no moderation by age and gender. Although an overall analysis of intervention effects on dyadic measures was planned a priori, the exploration of moderation by dyad type should be considered exploratory, and results should be interpreted with caution.

The conclusions about dyadic outcomes that can be drawn based on the Domus RCT are limited by the fact that separate outcome analyses for patients and caregivers were/will be conducted for all outcomes other than dyadic coping. This prevents us from taking into account the true nested nature of the data, and ultimately from drawing conclusions on the similarity or difference in intervention effects between patients and their caregivers. Dyadic outcome analyses would also enable an investigation of whether or not patients and caregivers within the same dyads profit from the intervention, and whether dyad characteristics might predict differential effects on patients and caregivers.

7.4.2 Path analyses to investigate mediation

We used path analyses to investigate whether the effects found on caregivers' symptoms of anxiety and depression were carried in part or whole by intervention effects on aspects of dyadic coping. We analyzed effects at the six month follow up, and included measures of dyadic coping at the eight week follow-up, to ensure that the measure of the mediator preceded the outcome. It has been argued that mediation analyses should include the outcome assessed simultaneously with the mediator, to establish that the change in the mediator precedes any change in the outcomes variable.[149] As we found no evidence of mediation in our models, however, including symptoms of anxiety and depression measured at the same time as the mediator would likely not have changed our findings.

7.5 SECTION SUMMARY

The strengths of the Domus study includes the randomized controlled design and the explicit description of the theoretical frame and structure of the psychological intervention. This facilitates comparison with other interventions, as well as replication and implementation in clinical practice. Further strengths include the systematic screening in an equitable health care system, which ensured a diverse sample of patients and caregivers. The very high participation among caregivers increases the generalizability of the results of the intervention. The Domus study included follow-up of caregivers after the patient's death and 19 months into bereavement, providing the opportunity to assess long-term effects of SPC. Intervention effects were analyzed using appropriate repeated-measures models.

The RCT was limited by the lack of specification of the SPC team intervention component. Results in long-term bereavement as well as for the subgroup of parent-child dyads are limited by the small sample size, although results of sensitivity analyses imply that the bias introduced is limited, at least for analyses of caregiver anxiety and depression. The lack of data on patients' anxiety and depression limits the ability of this thesis to draw conclusions about the dyadic nature of effects on distress from this dyadically based intervention.

8

CONCLUSIONS AND PERSPECTIVES

8.1 CONCLUSIONS

The work presented in this PhD thesis has described a dyadic psychological intervention based on EPT integrated in SPC throughout the patient's life and in early bereavement. The intervention was found to be acceptable to patients and caregivers and feasible to conduct in this population and setting. The SPC and dyadic psychological intervention significantly decreased caregivers' symptoms of anxiety and depression, both while patients were alive and in bereavement. This extends the previous evidence for the effectiveness of SPC on caregiver distress into bereavement. Further, the Domus RCT has shown that beneficial effects of SPC can extend into diverse caregiver populations.

Intervention effects were furthermore found on some measures of dyadic coping among certain dyad types. Common coping in couple-dyads increased significantly, albeit to a small extent. In partner-caregivers, the intervention significantly increased stress communication, while significant decreases were found in parents cared for by an adult child. Whether the decreased stress communication has a beneficial or detrimental effect on parent-child dyads is not clear from the work reported here.

Finally, we have demonstrated that the Domus intervention effects on anxiety and depression were not mediated by effects on dyadic coping. Thus the mechanisms by which the intervention achieved improvements in caregivers' psychological distress remain unclear. The Domus intervention is distinguished from previous SPC interventions by the integration of the psychological intervention, the central feature of which may have been the provision of targeted sessions, both in content and timing.

Caregivers are central to the care that patients' receive, and decreased distress in caregivers may increase the support they are able to provide to their loved ones during the end of life. Caregivers live on after the loss and with the long-term consequences of caregiving that extend into bereavement. Interventions that decrease caregivers' psychological distress may thus create effects that last beyond palliative care and into their readjustment to life without their loved ones.

8.2 IMPLICATIONS FOR CLINICAL PRACTICE

The results presented in this PhD thesis suggest that routine inclusion of psychological assessment and/or intervention may be warranted for caregivers in specialized palliative care. This finding is in support of many clinical guidelines that already advocate assessing and targeting caregivers in their own right. Effects for caregivers seem to require repeated assessment and intervention in response to need over some time, and psychological interventions that are part of ongoing SPC rather than separate short-term add-ons may be necessary. However, in implementing interventions for dyads in clinical practice, the results presented here suggest that parent-child dyads may require different support than couple-dyads. In clinical practice, this will certainly not be a new consideration, but our results reinforce that it should be remembered when new programs are initiated and applied across dyad types.

In many ways the basic structure of the Domus psychological intervention mirrors how clinical psychologists in SPC teams already work in Denmark today: seeing patients and caregivers when they experience needs. The Domus RCT has demonstrated how such an approach, with continuous assessment of needs for psychological intervention, can be systematically delivered to all patients and caregivers. A more systematic clinical practice with regard to referral and needs assessment for psychological intervention would ensure that all patients and caregivers are assessed and that those in need are offered intervention.

The extent to which the Domus intervention as a whole is applicable in clinical practice depends on the organization of the health care system, as the intervention rests on the organization of home-based SPC in the Danish setting. The applicability of the psychological intervention component necessitates psychologists who can collaborate with the SPC as part of their clinical work. Given such an organizational context, the Domus intervention is applicable across a wide group of cancer diagnoses and socioeconomic populations.

8.3 IMPLICATIONS FOR FUTURE RESEARCH

While the Domus RCT has shown that SPC and dyadic psychological intervention improves anxiety and depression in caregivers, the mechanisms through which the effect was achieved remain unclear. Future RCTs should ensure that components of an SPC intervention are specified to a degree that allows first the identification of specific mechanisms and second the development or choice of measures that can help elucidate whether the proposed mechanisms mediate outcome effects. Identification of specific effective pathways through which interventions achieve their effects as well as comparisons of the relative effect of such pathways is necessary to further enhance the effectiveness of complex SPC interventions.

The Domus RCT may suggest some candidate-features of a psychological intervention that could contribute specifically to effects and could be investigated by future studies. Investigating the effects of continuous assessment of needs on the use and acceptance of psychological intervention among patients and caregivers could shed light on how psychological interventions are best initiated within SPC. Further, clarifying the optimal combination of individual and dyadic intervention components could likely enhance intervention effects. Investigating the collaboration between psychologists and other members of the SPC team could lead to better specification of how such collaboration is ideally organized in clinical practice.

The effects found for dyadic coping measures in the Domus study were based on a very small sample, but they pose the question whether SPC and dyadic psychological interventions have the same effects on dyads in different relations, and whether some effects might be maladaptive in dyads of adult children caring for their parents. Future research is needed to explore whether or not effects of SPC may be different in dyads of adult children caring for their parents. This includes the completion of moderation analyses in trials powered to assess small subgroups of dyads. If true differences between dyad types emerge, the design of future interventions will have to consider e.g. whether interventions with different foci and/or delivery strategies are required for different dyad types to provide optimal psychological support.

9

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10

APPENDICES

APPENDIX 1. OVERVIEW OF RCTS OF SPC

Randomized controlled trials of specialized outpatient palliative care. (Reports from the same trial listed consecutively, with caregiver outcomes in grey)

Study	Population	Setting	Intervention	Outcome measures * indicates primary outcome	Intervention effect † and significance
Temel (2017) RCT	n = 350 (75% consent to participate) Patients within 8 weeks of diagnosis of incurable lung and non-colorectal GI cancer Majority PS 1	USA, Massachusetts General Hospital Well-integrated pall care Education: 35% High school or less, 41% Some/completed college, 21% Graduate School	Early integrated palliative care by physicians and advanced practice nurses. At least monthly meetings based on guidelines. Psychosocial intervention not specified. Control: PC clinician consultation upon request	* FACT-G (12 weeks) FACT-G (24 weeks) PhQ-9 (12 & 24 weeks) End-of-life communication (12 & 24 weeks)	NS Sign. Sign. at 24 weeks Intervention group found prognostic knowledge more helpful at 12 weeks and were more likely to discuss EOL wishes with oncologist at 24 weeks Further: FACT-G and PHQ9 sign. at 12 weeks for GI cancer, but not lung). Terminal decline models found sign. FACT-G at 2 and 4 months before death for entire sample, and 2, 4, and 6 months before death for lung cancer sample.
El-Jawahri (2017)	n = 275 caregivers 18 years old, able to participate, "relative or friend who would likely accompany them to clinic visits" (no information on n consenting to participate)	Relationship: 67% partners, 19% children, 2% parents, 4% siblings, 4% friends, 3% others Education: 27% High school, 50% College, 23% Graduate School	Participation encouraged, not required Providers reported to address both patient and caregiver needs. Intervention or assessment not otherwise described*TRUE?	HADS SF-36 (both 12 & 24 weeks after randomization)	Total HADS 12 weeks, HADS-D 12 weeks, NS at 24 weeks NS Further: Terminal decline model HADS-total, HADS-D, HADS-A 3 and 6 months before death

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Groen-vold (2017) RCT	n = 297 (66% consent to participate) Advanced cancer patients with needs (as defined by EORTC-QLQ-C30) Majority PS 1 (caregivers not included)	DK, multi-center Education: 15% no education, 13% < 1 year, 18% skilled workers, 15% 1-3 years, 28% >3 years, 5% academic, 4% missing	Referral to multidisciplinary PC team, based on local, national, and international guidelines. <u>Control:</u> Care as usual	* change in primary need (highest scoring EORTC-QLQ-C30 item at baseline) EORTC-QLQ-C30 (all 3 & 8 weeks after randomization)	NS Beneficial effect on nausea/vomiting ($p < 0.05$, but above threshold adjusted for multiple comparisons (0.01))
Bakitas (2015) RCT	n = 207 (38% consent to participate) 30-60 days after advanced cancer diagnosis/recurrence/progression & prognosis 6-24 months Karnofsky PS: 81 (mean)	USA, New Hampshire & Vermont, National Cancer Institute cancer center, a Veterans Affairs Medical Center, and community outreach clinics Rural population Education: 5% < high school, 54% high school, 41% college	Initial PC consultation by board certified PC clinician & weekly manualized psychosocial sessions with advance practice nurse (predefined content: problem solving, symptom management, decision making, advance care planning, life review), with monthly follow-up after six sessions. (ENABLE) <u>Control:</u> ENABLE intervention as above, but three months delayed	FACIT-PAL (3 months) FACIT-PAL TOI (3 months) QUAL-E (3 months) CES-D (3 months) 1 year survival Overall survival Resource use Place of death	NS NS NS NS Sign. (15% difference) NS NS NS Further: no sign. effects at 12, 6, or 3 months before death.
Dionne-Odom (2015)	n = 122 (98% consent to participate) “a person who knows you well and is involved in your medical care”	Relationship: 75% spouses, 6% siblings, 11% children, 6% parents, 2% other Education: 1% < high school, 57% high school, 42% college	ENABLE intervention as above, but separate psychosocial intervention for caregivers with three sessions with predefined content addressing problem solving, self-care, supporting patient in symptom management and assessment, decision making, decision support, advance care planning, and monthly follow-up.	CQoL-C (3 months) CES-D (3 months) MBCB (3 months) (all 3 months after randomization)	NS Sign. NS Further: Terminal decline model found sign. effects for depression and stress burden

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Dionne-Odom (2016)	n = 44 (63% of caregivers whose patients died responded)	Relationship: 82% spouses, 16% other close relative, 2% other Education: 43% high school, 57% college		CES-D PG13 (both 8-12 weeks after death)	NS NS
Zimmermann (2014) cRCT	n = 461 (57% overall consent to participate, 48% intervention, 70% control) patients with advanced cancer, PS 0-2 and 6-24 month prognosis Majority PS 1	Canada, Princess Margaret Cancer Center, 24 clinics randomized Education: 9% < high school, 25% high school, 66% college	Consultation and follow-up, at least monthly, by palliative care team (PC physician and nurse). Routine, structured symptom assessment, routine psychosocial assessment (patient and family support needs, coping and distress, intervention not specified). 24hour on-call service. <u>Control:</u> Care as usual	*FACIT-SP (3 months) *FACIT-SP (4 months) QUAL-E (3 & 4 months) ESAS (3 & 4 months) FAMCARE-P16 (3 & 4 months) CARES-MIS (3 & 4 months)	NS Sign. (3&4 months) Sign. (3&4 months) NS 3 months, sign. 4 months Sign. (3&4 months) NS
Mc-Donald (2016)	N = 182 (60/66% participation, depending on inclusion of those who did not complete baseline as non-participants or not) Primary caregiver identified by patient, ≥18 years	Relationship: 84% partner/spouse, 12% child, 4% other Education: 8% < high school, 26% high school, 64% post-secondary	Intervention as above. Focus for caregiver described as "providing social support, emotional care, and providing resources to assist with care of the patient". Intervention or assessment not otherwise described.	FAMCARE (3 & 4 months) SF-36v2 MCS (3 & 4 months) SF-36v2 PCS (3 & 4 months) CQoL-C (3 & 4 months)	Sign 3 & 4 months NS NS NS
Wallen (2012) RCT	n=152 Advanced cancer patients participating in surgical oncology trial (PS and participation percentage not reported) (Caregivers only included in qualitative assessments, otherwise neither assessed, nor systematically targeted.)	USA, Maryland, NIH Clinical Center. Pain and palliative care team available to all patients participating in research. Education: 3% < high school, 28% high school, 17% some college, 26% college, 26% post-graduate	Pall care team (physicians, nurse practitioners, nurse thanatologist), and extended team (spiritual ministry, social work, recreation therapy, counseling, nutrition, acupuncture, acupressure, massage, reiki, rehabilitation medicine). Interviews (consultations?) pre- and postoperatively (from here all in outpatient clinic), 4-6, weeks, 3, 6, 9, 12 months. <u>Control:</u> Care as usual	*GPS *SDS APACHE II CES-D Sources of social support (Qualitative outcomes not included)	NS NS NS NS Sign. greater mean number of sources of social support reported in intervention group at 4-6 weeks (but not at six months)

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Temel (2010) RCT	n=151 (72% consent to participate) Patients within 8 weeks of diagnosis of metastatic non-small-cell-lung-cancer patients & PS 0-2 Majority PS 1 (no caregivers included)	USA, Massachusetts General Hospital Well-integrated pall care (no education information)	Early assignment to palliative care: meetings with palliative care team member (physician and advance practice nurse) within 3 weeks of enrollment and at least monthly until death. Adapted general guidelines from National consensus project on palliative care. Psychosocial symptoms to be assessed, psychosocial intervention not otherwise specified. Control: Care as usual	* TOI (12 weeks) FACT-L (12 weeks) FACT-LCS (12 weeks) HADS (12 weeks) PHQ-9 (12 weeks) Survival Health care use	Sign. Sign. NS (Sign. in unadjusted analyses) Sign. (not for anxiety alone) Sign. Sign. Sign. difference in aggressive end of life care, documentation of resuscitation preference
Bakitas (2009) RCT	n=322 (47% consent to participate) Patients 8 to 12 weeks after diagnosis advanced cancer Karnofsky PS: 77(interv.), 78(control)	USA, New Hampshire & Vermont, Norris Cotton Cancer Center's Tumor board & VA medical center Education: 11% < high school, 49% high school, 25% college, 16% missing	Phone-based, manualized, nurse led intervention with 4 sessions comprising distress screening and pre-specified content: problem solving, communication, advance care planning, unfinished business, supportive care resources. Thereafter at least monthly follow-up. Monthly shared medical appointments by PC physician. (ENABLE II) Control: Care as usual	* FACIT-Pal * ESAS * Resource use CES-D Survival (Questionnaires 1 month after randomization and every three months until death.)	Sign. NS NS Sign. NS Further: significant effects on QoL and depression in subgroup of deceased patients in three assessments before death
O'Hara (2010)	n = 198 (90% of invited caregivers provided data)	Relationship: 71% partner/spouse, 6% friend, 16% child, ,5% parent, .5% grandchild, .5% niece/nephew, 4%other, 1.5% missing Education: 6% < high school, 59% high school, 31% college, 4% missing	ENBALE II intervention as above, presented as "patient-focused" Caregivers invited and encouraged to participate (but not presented as part of the unit of care)	MBCB (1 month after randomization and every three months until death.) After death bereaved family member interview (about quality of care)	Ns Further: ns interaction of patient gender and intervention

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Jord-høy (2000) cRCT	n = 434 Patient with incurable maglignant disease & 2-9 month prognosis (no information on % consenting to participate) Majority Karnofsky PS 60-80	NO, University Hospital, Trondheim, 8 community districts randomized Trial in norway (cluster randomization) and Sweden (non-randomized controlled) Education: 37% ≤ 7 years, 49% 8-12 years, 15% ≥ 13 years	Coordination of PC by newly established multidisciplinary consultant team (physician, nurse, social worker, priest, nutritionist, physical therapist), described as addressing psychological issues, but psychosocial intervention not otherwise specified. Initial meeting with general practitioner, community nurse, team representative, patient, and caregivers. Guidelines for interaction between PC unit and community, not specified. All in-patient care at PC unit if possible. Ongoing education of community professionals. <u>Control:</u> care as usual	* Place of death	Sign.
				Survival	NS
				Time in institutions	Sign. lower proportion in nursing homes in last month. Time at home and hospitalizations NS.
				Admissions	NS
Jord-høy (2001)	(as above)	(as above)	(as above)	* Physical functioning, emotional functioning, pain (EORTC-QLQ-C30) (4 months)	Ns
				* IES (4 months)	Ns
Ringdal (2001) ≠	n = 183 Bereaved relatives or friends (66% consent to participate after patient's death)	Relationship: 63% partner/spouse, 2% friend, 33% child, 1% parent, 2% siblings Education: 18% ≤ 7 years, 36% 8-10 years, 23% 11-12 years, 23% ≥ 13 years	(as above) Family not targeted while patient alive, but encouraged to participate in consultations. Bereavement meeting with responsible providers after patient's death.	Family members grief (TRIG) (1, 3, 6 & 13 months after death)	Ns
Ringdal (2002)	(As Ringdal 2001)	Relationship (as above) Education: 71% 7-10 years, 13% 11-12 years, 23% ≥ 16 years		FAMCARE (1 month after death)	Sign.

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† If not otherwise specified, effects are in favor of intervention group. ‡ Results on health related quality of life from the Jordhøy/Ringdal cRCT were presented combined with a nonrandomized study, and are therefore not included.

ADL, Activies of daily living; APACHE II, Acute physiology and chronic health evaluation (Severity of illness measure); CARES-MIS, Cancer rehabilitation evaluation system medical interaction subscale (problems in interaction with medical team, self-report); CES-D, Center for Epidemiologic Studies Depression Scale (depression self-report); CPAP, California pain assessment profile (symptom self-report); CQoL-C, Caregiver Quality of life scale-cancer; EORTC-QLQ-C30, European organization for research and treatment of cancer, quality of life questionnaire core 30 (QoL self-report); ESAS, Edmonton symptom assessment scale (symptom self-report); FACIT-PAL, Functional assessment of chronic illness therapy-Palliative care (QoL self-report); FACIT-SP, Functional assessment of cancer therapy-Spiritual well-being (Spiritual well-being self-report); FACT-G, Functional assessment of cancer therapy-general (QoL self-report); FACT-L, Functional assessment of cancer therapy-lung (QoL self-report); FACT-LCS, Functional assessment of cancer therapy-lung cancer subscale (QoL self-report); FAMCARE-p16, Satisfaction with care self-report; GI, gastro-intestinal; GPS, Gracely pain scale (pain self-report); HADS, Hospital anxiety and depression scale (-A: anxiety, -D: depression self-report); IES, Impact of events scale (psychological distress self-report); IPS, Interpersonal care scale (self-report); MBCB, Montgomery-Borgatte Caregiver Burden scaleNS, non-significant; PC, Palliative care; PG13, Prolonged grief scale (grief self-report)PHQ-9, Patient health questionnaire (depression self-report); PS, Performance status; QUAL-E, Quality of life at end of life (QoL self-report); SDS, Symptom distress scale (distress associated with symptoms self-report); SF36 & SF36v2, health related quality of life (MCS: Mental component summary, PCS: physical component summary, self-report); RCT, Randomized controlled trial; cRCT, cluster-randomized controlled trial, TOI, Treatment outcome index

APPENDIX 2. INCLUDED PAPERS

PAPER 1

von Heymann-Horan, A. B., Puggaard, L. B., Nissen, K. G., Benthien, K. S., Bidstrup, P., Coyne, J., Johansen, C., Kjellberg, J., Nordly, M., Sjøgren, P., Timm, H., von der Maase, H., & Guldin, M.-B. Dyadic psychological intervention for patients with cancer and caregivers in home-based specialized palliative care: The Domus model. *Palliative & Supportive Care*. 2017 30. March; https://doi.org/10.1017/S1478951517000141 *[E-pub ahead of print]*

PAPER 2

von Heymann-Horan, A., Bidstrup, P. E., Guldin, M., Sjøgren, P., Andersen, E. A. W., Von Der Maase, H., Kjellberg, J., Timm, H. & Johansen, C. Effect of home-based specialized palliative care and dyadic psychological intervention on anxiety and depression in caregivers: A randomized controlled trial. 2018. *Under review, British Journal of Cancer.*

Effect of home-based specialized palliative care and dyadic psychological intervention on caregiver anxiety and depression: A randomized controlled trial

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BACKGROUND Specialized palliative care trials often fail to address intervention effects on caregiver anxiety and depression, particularly in bereavement. We evaluate effects of specialized palliative care and dyadic psychological intervention on caregiver anxiety and depression in a randomized controlled trial (RCT).

METHODS Patients with incurable cancer and limited antineoplastic treatment options and their caregivers, recruited from a university hospital oncology department, were randomized (1:1) to care as usual or accelerated transition from oncological treatment to home-based specialized palliative care. We assessed caregivers' symptoms of anxiety and depression with the Symptom Checklist-92 up to six months after randomization and 19 months into bereavement, and estimated intervention effects in mixed effects models.

RESULTS The 'Domus' trial enrolled 258 patients with caregivers. The intervention significantly decreased caregivers' symptoms of anxiety overall (estimated difference, -0.12; 95% confidence interval, -0.22 to -0.01, *p*=0.0266), and symptoms of depression at eight weeks (-0.17; -0.33 to -0.02; *p*=0.0314), six months (-0.27; -0.49 to -0.05; *p*=0.0165), and in bereavement at two weeks (-0.28; -0.52 to -0.03; *p*=0.0295) and two months (-0.24; 0.48 to -0.01; *p*=0.0448).

CONCLUSION This first RCT evaluating specialized palliative care with dyadic psychological support significantly decreased caregiver anxiety and depression before and during bereavement.

Clinicaltrials.gov: NCT01885637

Background

The majority of patients with advanced cancer require substantial support, often provided by spouses or family members at a cost to caregivers' own mental health. Spouses are at significantly greater risk of antidepressant use and hospitalization for severe depression than the general population,[1,2] even in bereavement.[1–3] Every third to fifth caregiver of patients with advanced cancer experiences elevated symptoms of anxiety or depression.[4] Patients and caregivers may cope with disease in interaction[5] and interventions that lower caregivers' psychological distress could lead to better care for patients as well as prevent negative long-term effects for caregivers.

Palliative care aims to alleviate suffering in patients and families.[6] Still, in eight published randomized controlled trials (RCTs) of out-patient multidisciplinary specialized palliative care identified in PubMed until December 2017, interventions were primarily patient-focused.[7–14] Only two included systematic, well-defined psychosocial intervention extending to caregivers,[10,12] including one manualized intervention.[12] Only two trials assessed symptoms of anxiety or depression in caregivers,[7,12] finding effects on one or both,[15,16] and a single trial assessed depression in bereavement, finding no effect.[17]

Many previous trials included homogenous populations[18] and caregivers' symptoms of anxiety or depression have only been assessed in trials with highly educated participants.[15,16] A recent review highlighted the threat to generalizability posed by low participation rates and non-response-bias.[19] Even with high participation, however, participants may be representative only of selected populations and generalizability may be threatened.

The 'Domus' trial is the first RCT evaluating home-based specialized palliative care with integrated dyadic psychological intervention. It was conducted in a socioeconomically diverse population ensured by a Scandinavian health care setting with equitable access to care. The primary aim was to increase patients' time at home and the number of home deaths, and the psychological intervention targeted distress in patients and caregivers.[20,21] We hypothesized that targeting patients' and caregivers' distress together could improve outcomes for both. This study examines the effect on the secondary outcomes of caregivers' symptoms of anxiety and depression.

Materials and Methods

Study design

The Domus study was a parallel-group RCT, with patients and caregivers recruited from the Department of Oncology at Rigshospitalet, Copenhagen University Hospital, Denmark.[20] The study protocol was approved by the Danish National Committee on Health Research Ethics (File: 37237) and the Danish Data Protection Agency (File: 2007-58-0015). The trial was registered at clinicaltrials.gov (Identifier: NCT01885637).

Participants

All potentially eligible patients attending the Department of Oncology at Rigshospitalet, Copenhagen University Hospital were screened for the following eligibility criteria: 1) incurable cancer; 2) limited antineoplastic treatment options or patient chose to forego antineoplastic treatment; 3) living in the Capital Region of Copenhagen; 4) 18 years or older. Limited antineoplastic treatment options were defined for each group of cancers as disease refractory to a specific treatment line, e.g. 3rd line antineoplastic treatment for metastatic breast cancer.[20] Patients were ineligible if they already received care from a specialized palliative care team, could not be discharged, or were unable to cooperate. Until November 2014, performance status 2-4 was a further inclusion criterion, which was dropped due to slow enrollment. Eligible patients could ask a caregiver, 18 years or older (no other criteria applied), to participate e.g. a partner, adult child or friend. Both provided written consent.

Randomization

Patients and caregivers were assigned to the intervention or care-as-usual control group with a computer generated 1:1 randomization sequence with varying block size, generated by a statistician not affiliated with the project. Project nurses blinded to block size enrolled and randomized participants using numbered, sealed, and opaque envelopes. As the trial included a behavioral intervention, blinding was not possible.

Procedure

The design of the Domus intervention,[20] including the psychological component,[21] has previously been presented in detail. Briefly, patients and caregivers in the intervention group received an accelerated transition from hospital-based oncological treatment to specialized palliative care at home. The transition included a home-care conference within five working days of randomization with representatives from one of nine specialized palliative care teams, municipal nursing services, if possible the general practitioner, and project psychologist. After the home-care conference, patients received continuing needs-based care according to national guidelines[22] from their specialized palliative care team, their oncologist, general practitioner, and municipal nursing services. A manualized psychological intervention targeted the patient-caregiver dyad, aiming to decrease distress in both patients and caregivers. Two sessions within one month of randomization were followed by monthly needs-assessment and/or needs-based sessions until early bereavement. Sessions were based on existential phenomenological therapy and focused on content decided with the dyad.[21] Psychologists collaborated with members of the specialized palliative care team as needed.

The control group received care as usual. The Danish health care system is tax-financed and provides free access to healthcare services including general practitioners, general practitioner out-of-hours services, hospital treatment, as well as in-home nursing, home care, and nursing homes. Home-based specialized palliative care is provided by hospital and hospice-based teams, and patients are free to continue oncological treatment alongside specialized palliative care. Some, but not all, specialized palliative care teams include psychologists, and access to psychological support in specialized palliative care is thus not systematic. Care as usual for patients and caregivers randomized to the control group included the possibility of later referral to specialized palliative care, but neither the accelerated transition process, nor the dyadic psychological intervention.

Patients and caregivers completed self-report questionnaires maximally three days before randomization and four times after randomization (weeks 2, 4, 8, month 6) (Figure 1). In addition, caregivers completed questionnaires five times after the patient’s death (week 2, months 2, 7, 13, 19). Questionnaires included the anxiety and depression subscales of the Symptom Checklist-92 (SCL-92), which has been validated in a population-based Danish sample and includes cut-off scores for likely cases.[23,24] A study presenting patient outcomes is currently in preparation [Nordly et al: Systematic Fast-Track Transition from Oncological Treatment to Specialized Palliative Home Care: DOMUS - A randomized clinical trial].

Statistical Analyses

The target sample size (*n* = 380 patients) was determined through power analysis for the primary outcome (patients' time at home and home deaths) to allow for 10-15% dropout.[20] Descriptive statistics were calculated for baseline characteristics (table 1). Mean change scores for anxiety and depression were plotted according to randomization group and follow-up time. To investigate the intervention effect on change in symptoms of anxiety and depression, we fitted linear mixed effects models of repeated measures using restricted maximum likelihood based on the intention to treat principle. Degrees of freedom were calculated with the Kenward-Rogers method.[25] We estimated main intervention effects for change from baseline with 95% confidence intervals (CI), and calculated effect sizes using the standard deviation of the control group at baseline.[26] Models included fixed effects of caregivers' age, sex, relationship to the patient (partner, adult child, other), baseline anxiety or depression score, and follow-up time points (categorical). We included the interaction between follow-up time points and randomization group to investigate whether effects differed between follow-up times. From this interaction, we estimated intervention effects with 95% CIs and effect sizes for each time point. Based on Aikaike Information Criteria, covariance structures were modelled as a random subject effect together with an autoregressive AR1 by period (before versus after the patient's death) for anxiety, and unstructured for depression. Underlying model assumptions were assessed through visual inspection of residual plots and normal qq-plots. We conducted sensitivity analyses based on two forms of multiple imputation, using fully conditional specification.[27] First, we imputed missing responses on anxiety or depression, unless they were missing in a pre-bereavement assessment because the patient died prior to that assessment. Data were imputed separately for the intervention and the control group, conditional on all nine changes from baseline, baseline observations, age, sex, and caregiver's relationship to patient. Second, to simulate a situation in which caregivers' missing data were related to their levels of anxiety and depression, we shifted all imputed data upward by a value drawn from a normal distribution with mean 0.1 (about one sixth of a standard deviation) and variance 0.005^2. Supplementary logistic models examined the effect on caregivers' odds of exceeding cut-off scores for anxiety and depression.[24] We calculated population average odds ratios using generalized estimation equations with independent working correlation. Models included caregiver sex, age, relation to the patient (partner, adult child, other), baseline anxiety or depression score, group status, and follow-up time (categorical). As in the primary analyses, we included the interaction between follow-up time points and randomization group to investigate whether effects differed between follow-up times, and estimate effects and effects sizes for each follow-up time point. Analyses were conducted in SAS version 9.4.

Results

From June 19, 2013 to August 22, 2016, 340 patients were recruited, of whom 258 (76%) participated with a caregiver. Inclusion was terminated early due to lower than expected drop-out. One hundred thirty-nine dyads were allocated to the intervention, 119 to the control group (Figure 1). Almost all invited caregivers (96%) participated. We excluded nine caregivers from the present analyses: two patients did not fulfill eligibility criteria, one caregiver did not provide written consent, and six caregivers failed to complete baseline assessments before randomization (figure 1). Ten caregivers in the intervention and nine in the control group withdrew consent during follow-up and were excluded from analyses subsequently. Within six months of randomization, 56 patients (42%) in the intervention group and 50 patients (43%) in the control group died (figure 1). During the period of follow-up for this study (until 22 February 2017), a total of 105 (78%) patients in the intervention group and 89 (77%) in the control group had died. At assessments during caregiving, the SCL-92 was completed by between 80 and 84% of available caregivers, who were neither bereaved nor had withdrawn consent. At assessments in bereavement, between 57 and 68% of caregivers completed the measure. Three caregivers were not included in the primary analysis due to missing data on symptoms of anxiety and depression at baseline.

Six dyads in the intervention group did not receive the planned home conference. The number of subsequent visits from the specialized palliative care team differed based on needs. On average, dyads received one psychological intervention session per month participation in the RCT, the majority (63%) of which were attended by the patient and caregiver together. Of patients in the control group (including patients participating alone), 60% received specialized palliative care, beginning on average 110 days later than the intervention group [Nordly et al. in prep.]. Use of psychologists by participants in the control group was not recorded.

Most participating caregivers were patients' partners and the majority women (table 1). At baseline about one fourth of caregivers in the intervention and control group exceeded cut-off scores for anxiety and depression (online figures S1, S2). Caregivers in the intervention group reported more beneficial changes in mean scores for symptoms of anxiety and depression throughout follow-up than caregivers in the control group (figure 2).

Mixed effects models estimated that caregivers in the intervention group experienced significantly lower symptoms of anxiety throughout follow-up (estimated difference -0.12; 95% CI, -0.22 to -0.01; *p* = 0.0266; Cohen's d, -0.19), at eight weeks and six months after randomization, and two weeks into bereavement (figure 3, online table S1). We found no significant overall intervention effect for symptoms of depression (-0.06; 95% CI, -0.17 to 0.05; *p* = 0.2992; Cohen's d, -0.09), but caregivers in the intervention group experienced significantly lower symptoms than caregivers in the control group at eight weeks (-0.17; 0.33 to -0.02; *p* = 0.0314; Cohen's d, -0.26) and six months after randomization (-0.27; -0.49 to -0.05; *p* = 0.0165; Cohen's d, -0.41), as well as two weeks (-0.28; -0.52 to -0.03; *p* = 0.0295; Cohen's d, -0.42) and two months (-0.24; -0.48 to -0.01; *p* = 0.0448; Cohen's d, -0.37) after the patient's death (online table S1). Sensitivity analyses using multiple imputation did not change conclusions (online table S1). In models for dichotomized scores, caregivers in the intervention group were significantly less likely than caregivers in the control group to score above the cut-off for anxiety throughout follow-up (OR 0.55; 95% CI, 0.39 to 0.78), and less likely to score above the cut-off for depression eight weeks (OR 0.4; 0.17 to 0.92), and six months after randomization (OR 0.38; 0.14 to 0.98) (figure 4, online table S2,).

Discussion

We found significantly smaller increases in symptoms of anxiety and depression in caregivers in the intervention group compared to caregivers in the control group both before and after the patient's death. Differences reached significance from eight weeks after randomization to two months after the patient died, as well as for the main effect on symptoms of anxiety.

Our study is the first to demonstrate effects of specialized palliative care with dyadic psychological intervention on caregivers' symptoms of anxiety and depression both before and after the patient's death. We found small to medium effect sizes (0.26 to 0.32 for depression, 0.19 to 0.45 for anxiety, online table S1), which is comparable to effect sizes reported in previous trials (0.30 to 0.39).[15,16] The significantly reduced likelihood of intervention group caregivers exceeding cut-of scores for anxiety and depression at several follow-up points indicates that effects are clinically significant.

Caregivers are at short- and long-term risk of diminished mental health,[3,4] but may not feel entitled to seek support.[28] Although the interactions between follow-up time points and group status in mixed effects models were not significant, our results yield a pattern of increasing effects with time until the six-month follow-up, significant from eight weeks after randomization. This indicates that alleviating caregivers' symptoms of anxiety and depression may require continued needs assessments and intervention over time. It may also reflect greater strain on caregivers, and therefore potential to intervene, in the time surrounding patients' death. Palliative care clinicians see many caregivers through their involvement in patients' care and may be uniquely positioned to refer caregivers to services to prevent mental health problems. Several efficacious caregiver interventions exist,[29] but interventions in RCTs of specialized palliative care focus predominantly on patients. Neither of the previous trials assessing caregivers' symptoms of anxiety and depression focused on support for the patient-caregiver dyad together,[15,16] and one explicitly separated patient and caregiver psychosocial interventions to encourage disclosure of sensitive topics.[16] The similar effect sizes found in our study mostly targeting distress in patients and caregivers together indicates that dyadic interventions may also be appropriate.

The Domus RCT tested a complex intervention and effects cannot be attributed to specific intervention components. This mirrors the nature of specialized palliative care, where multidisciplinary management is central,[6] and complex trials are crucial to solidify the evidence base. The Domus intervention may have affected caregiver distress through multiple pathways, lowering distress directly, indirectly through intervention effects on patients, or through dyadic effects. Examples of such pathways could be (a) direct: lowering caregivers' depression by helping them relate to the weakened patient in new ways or providing them with knowledge about symptom management leading to increased feelings of mastery and diminished anxiety, (b) indirect: reducing patients' physical or psychological symptoms, leading to lower caregiver burden, or (c) dyadic: facilitating communication about wishes for professional support, leading to increased acceptance of care and lower caregiver strain. Future investigations to identify specific mechanisms and their optimal timing could further strengthen effective components of complex specialized palliative care interventions.

Among the strengths of this study is the inclusion of a manualized psychological intervention[21] to ensure that all sessions were based on the same principles and methods. The manual provides a description of the intervention rationale and delivery, and can thus inform clinical practice and future research. Previous trials assessing caregiver anxiety or depression were conducted mostly with highly educated populations,[18,19] biased due to their socioeconomic resources, and the findings cannot be directly generalized to more diverse populations of caregivers. The Domus study was conducted in a Scandinavian health care setting that ensures access and equitable treatment across socioeconomic positions, and affords the opportunity to reach not only those highly educated populations that are well-represented in previous trials, but also patients and caregivers in lower socioeconomic positions of society. As a result, more than one third of participating caregivers had less than high school education,[15,16] and our results may be generalized to socioeconomically diverse caregiver populations. Systematic screening for inclusion of all cancer patients attending the Department of Oncology, Rigshospitalet, Copenhagen University Hospital ensured that all potentially eligible patients were approached and informed of the study and the very high participation rate among invited caregivers (96%) increases our confidence in the generalizability of effects. Our previous investigation of uptake of the psychological intervention component indicated that the intervention was feasible and acceptable to patients and caregivers.[21]

This study is limited by the decreasing number of respondents in bereavement, as some caregivers were not, or only recently, bereaved at the time of analyses. However, sensitivity analyses yielded very similar results. Like previous studies, our sample was recruited in a single location. However, nine different palliative care teams provided the intervention, limiting the effect of the single recruitment site on generalizability. The absence of a diagnostic measure of anxiety and depression according to the DSM5 or ICD10 manuals is a further limitation. However, we used proposed cut-off scores for the background population to approximate clinical diagnoses. Finally, we did not measure intervention adherence, limiting the confidence with which we can attribute effects to specific intervention components. However, psychologists participated in biweekly group-supervision to support the uniform implementation of the psychological intervention component.

We have demonstrated that an accelerated transition to home-based specialized palliative care in combination with dyadic psychological intervention significantly improved caregivers' symptoms of anxiety and depression, both before and after the patient's death. The Domus RCT is the first trial of home-based specialized palliative care to include a manualized psychological intervention that targets the patient-caregiver dyad as the unit of care. Targeting distress in caregivers not only improves their mental health, but may also counteract other negative effects of caregiving, such as increased health care use and work impairments,[30] creating a ripple of public health and societal impacts both during caregiving and in bereavement.

Additional information

Ethics approval and consent to participate

The study protocol was approved by the Danish National Committee on Health Research Ethics (37237) and the Danish Data Protection Agency (2007-58-0015). Written informed consent was obtained from participants, and the study was performed in accordance with the Declaration of Helsinki.

Availability of data and material

The data that support the findings of this study are available on reasonable request from the corresponding author [AH]. The data are not publicly available due to participant privacy and consent.

Conflict of interest

The authors declare no conflicts of interest.

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Authors' contribution

AH, PB, MG, PS and CJ designed the study. PS was principal investigator for the trial, and CJ, HM, JK, and HT were part of the study consortium. EA performed analyses and all authors interpreted data. AH, PB, MG and CJ prepared the manuscript. All authors revised the manuscript and gave final approval for submission.

Supplementary information is available at the journal's website

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TABLES

Number of tables: 1

Table 1 Caption: Baseline characteristics of analyzed caregivers in the DOMUS study, n=249

Legend: * Some percentages do not add up to 100 due to rounding, ** categories are not exclusive

Number of supplementary tables: 2

Table S1 Caption: Estimated intervention effect on change in caregivers’ symptoms of anxiety and depression

Legend: * Interaction of follow-up time point (categorical) and randomization group

Table S2 Caption: Estimated odds ratios for caregivers of scoring above cut-offs (cases) for anxiety and depression

Legend: * Interaction of follow-up time point (categorical) and randomization group

FIGURES

Number of figures: 4

Figure 1 Caption: Trial profile of caregivers participating in the Domus study, n = 258

Legend: Consort flow-chart presenting numbers of caregivers approached for participation, allocated to intervention or control group, excluded from analyses, lost to follow-up due to patient’s death or withdrawn consent, and numbers available for analysis at each follow-up time point.

Figure 2 Caption: Observed mean change scores in caregivers’ symptoms of anxiety and depression

Figure 3 Caption: Estimated difference in change in caregivers’ symptoms of anxiety and depression and 95% confidence intervals

Legend: Estimates adjusted for age, sex, relationship to the patient (spouse, adult child, other), baseline score.

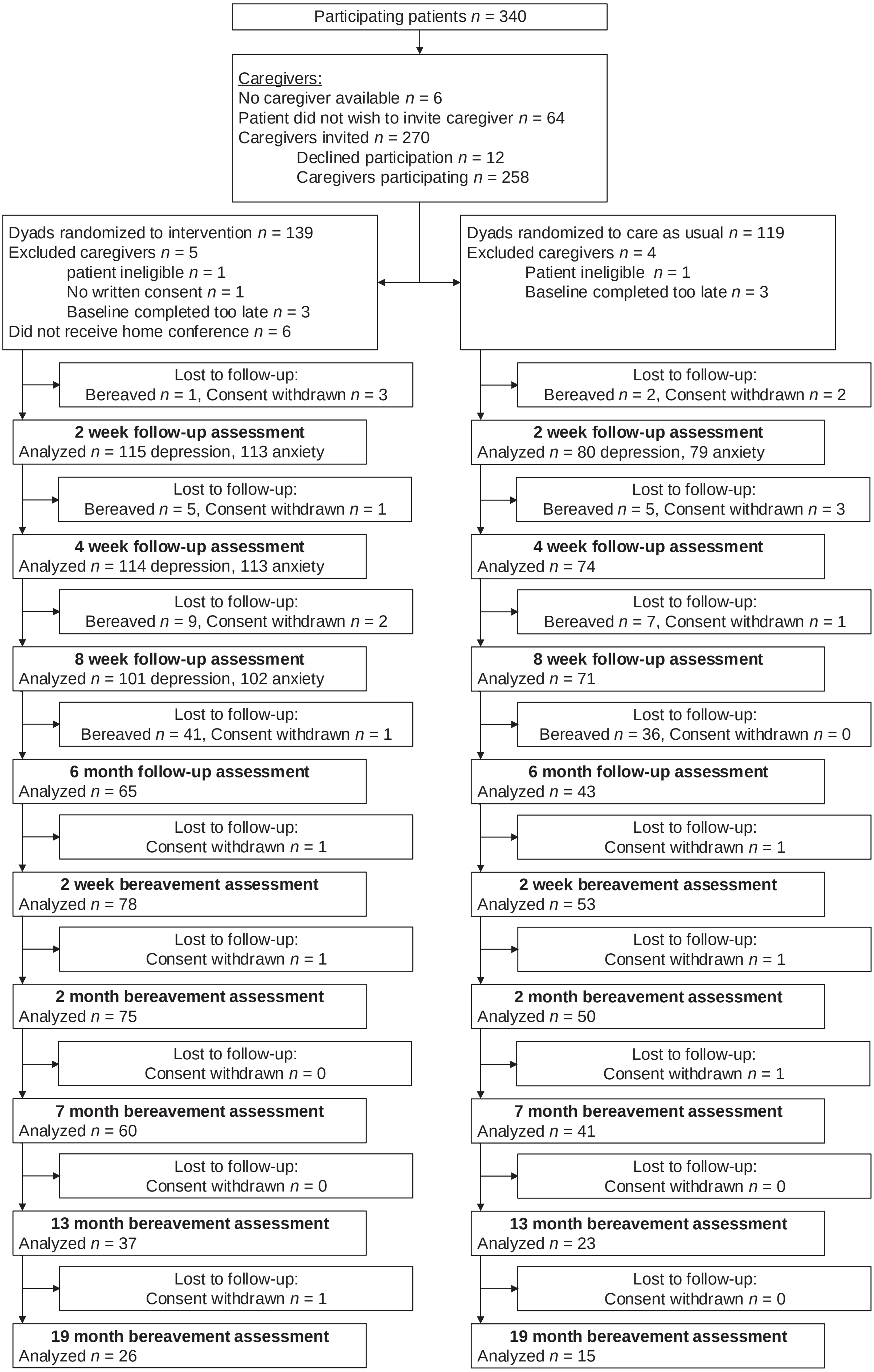
Figure 4 Caption: Estimated change in probability of scoring above cut-offs (cases) for anxiety and depression for caregivers (*n* = 41 - 246)

Legend: Estimates adjusted for age, sex, relationship to the patient (spouse, adult child, other), baseline score.

Number of supplementary figures: 2

Figure S1	Caption: Observed proportion of caregivers scoring above cut-off scores for anxiety
Figure S2	Caption: Observed proportion of caregivers scoring above cut-off scores for depression

Figure 1. Trial profile of caregivers participating in the Domus study, n = 258



Consort flow-chart presenting numbers of caregivers approached for participation, allocated to intervention or control group, excluded from analyses, lost to follow-up due to patient's death or withdrawn consent, and numbers available for analysis at each follow-up time point.

Figure 2. Observed mean change scores in caregivers' symptoms of anxiety and depression

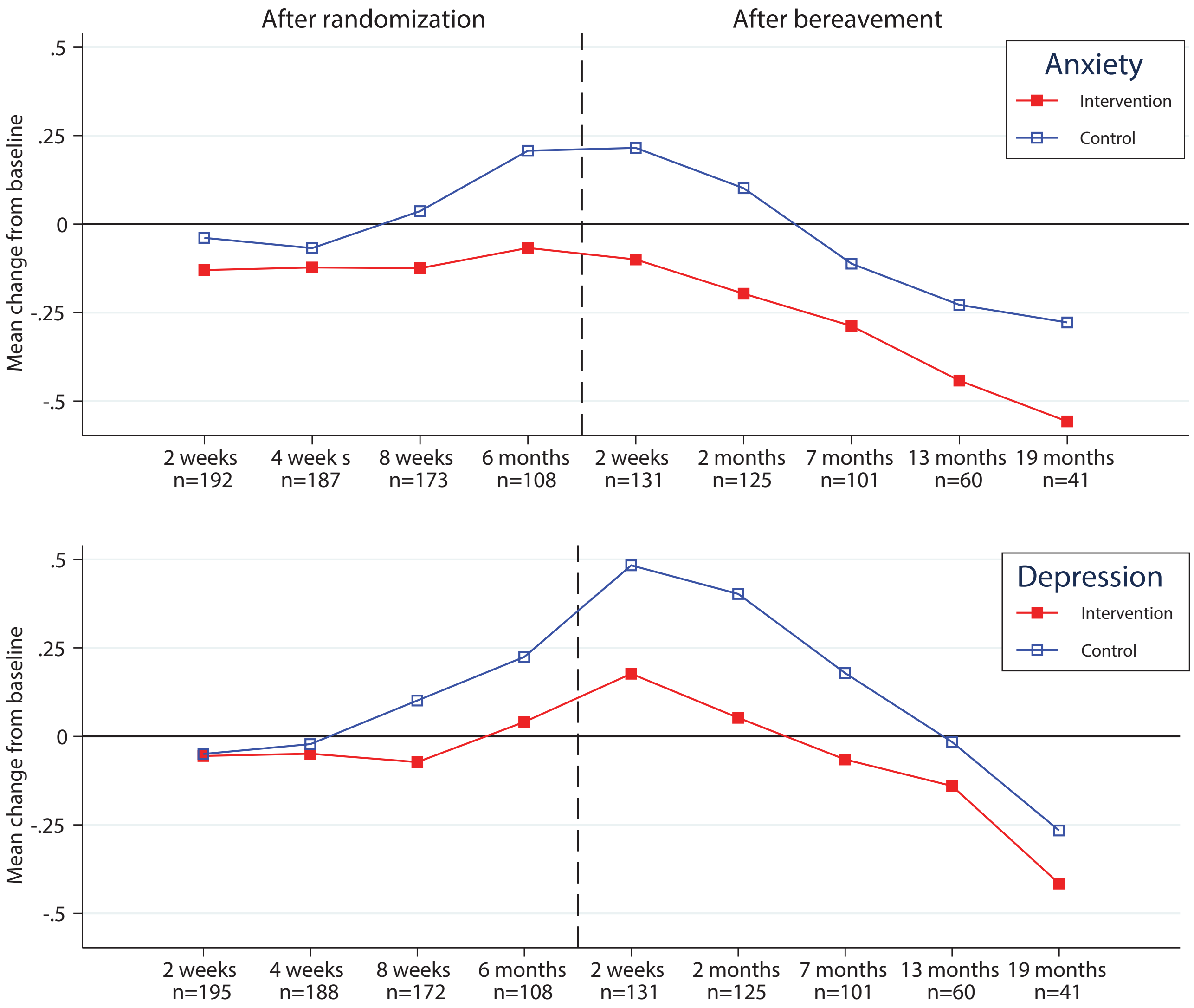
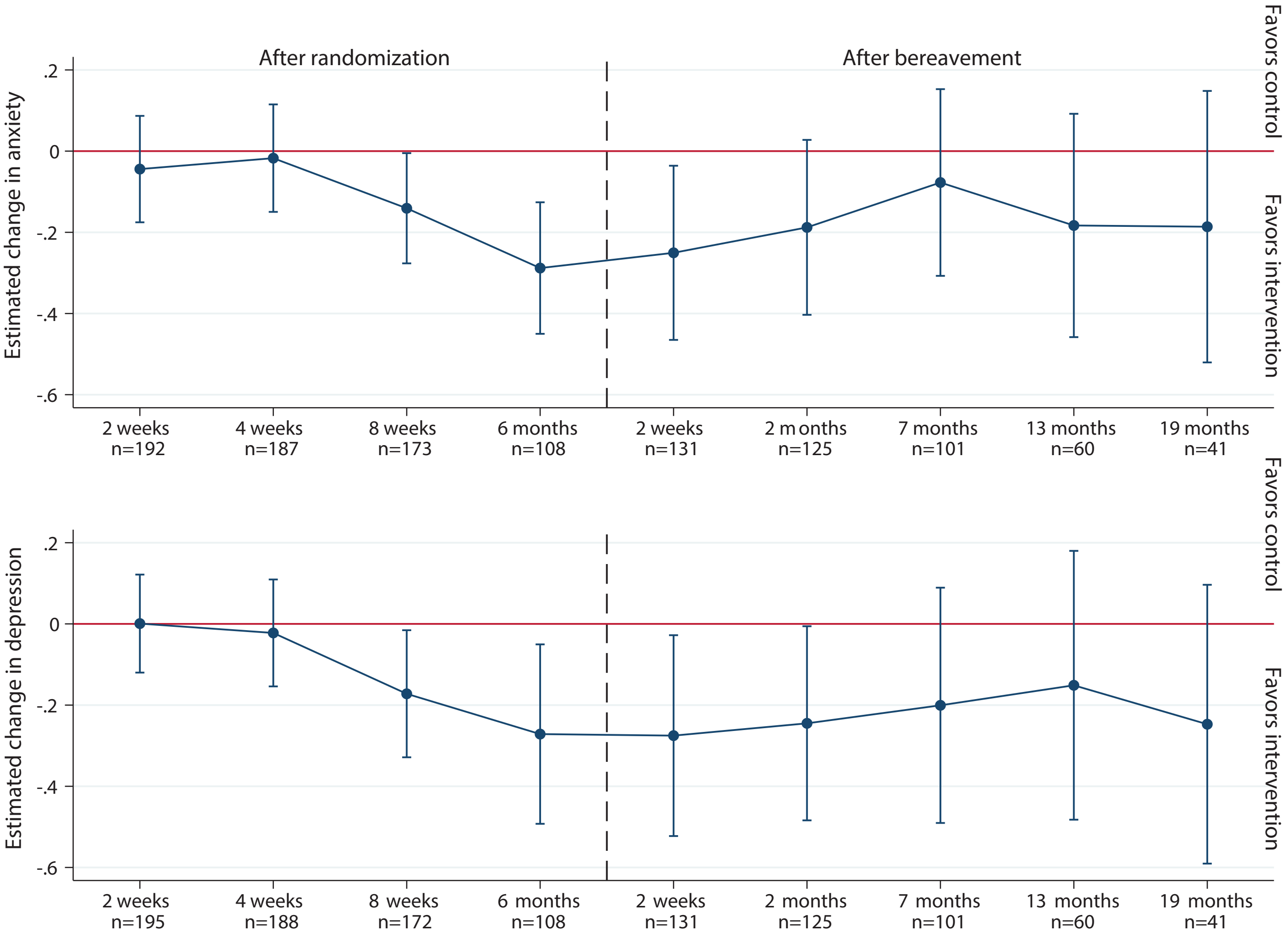
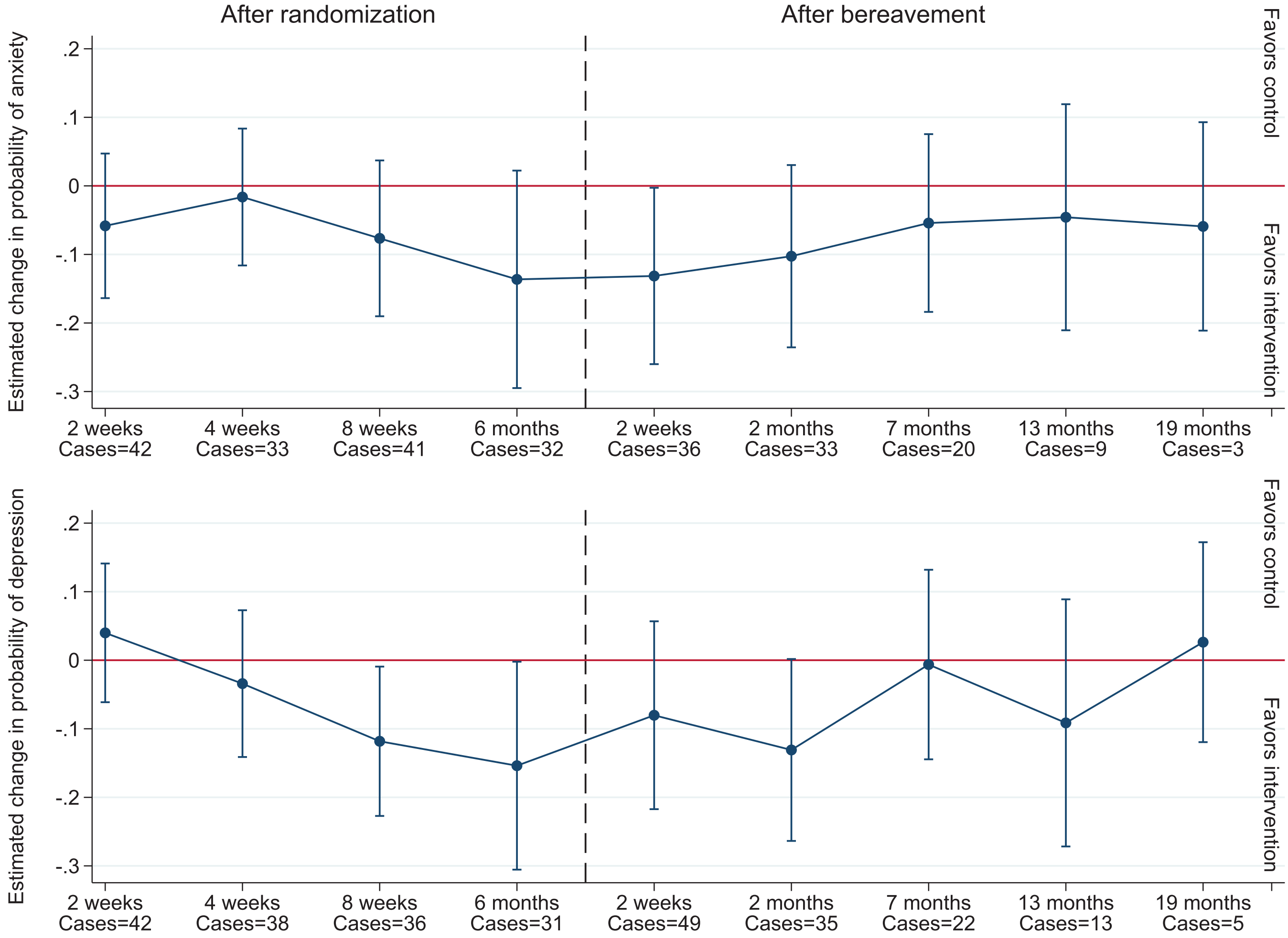


Figure 3. Estimated differences in change in caregivers' symptoms of anxiety and depression and 95% confidence intervals



Estimates adjusted for age, sex, relationship to the patient (spouse, adult child, other), baseline scores

Figure 4. Estimated change in probability of scoring above cut-offs (cases) for anxiety and depression for caregivers (*n* = 41 to 246)



Estimates adjusted for age, sex, relationship to the patient (spouse, adult child, other), baseline scores

Figure S1. Observed proportion of caregivers scoring above cut-off scores for anxiety

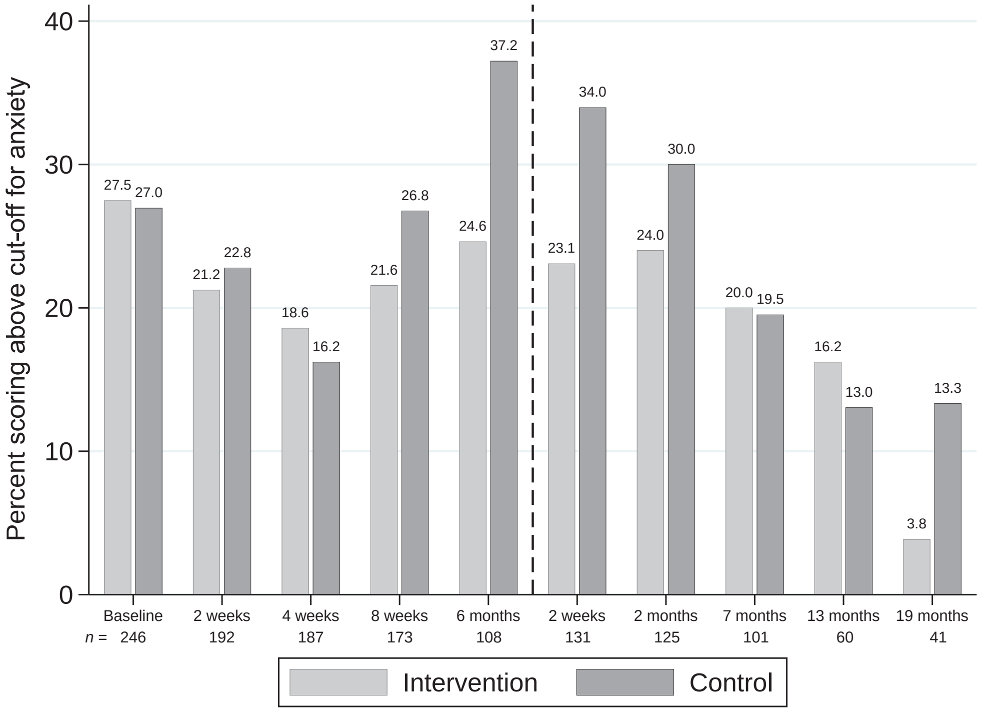


Figure S2. Observed proportion of caregivers scoring above cut-off scores for depression

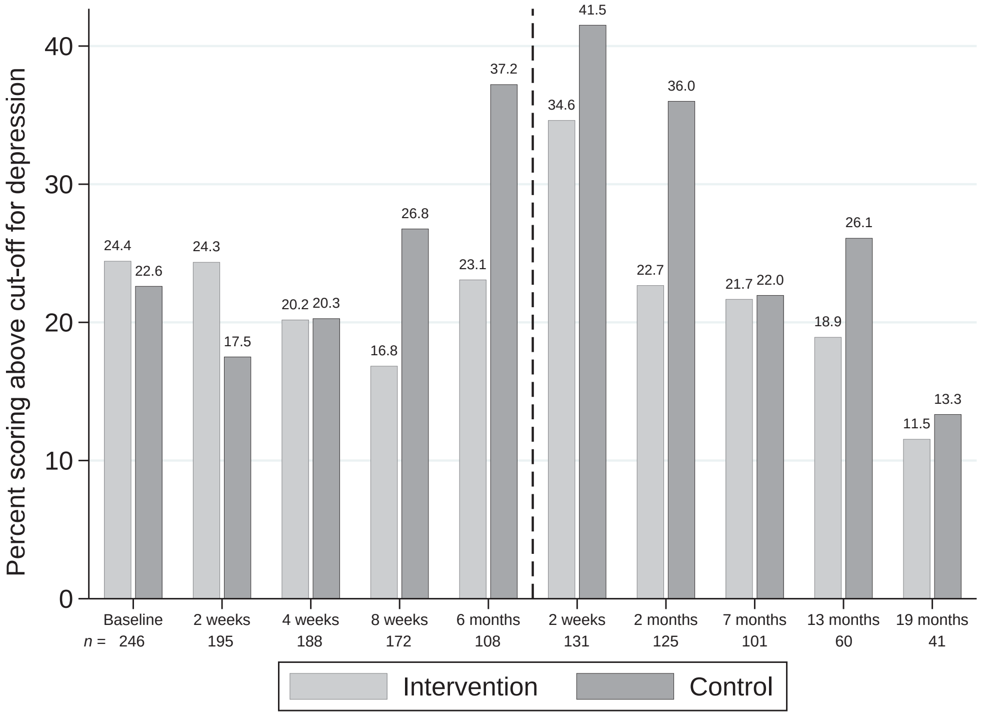


Table 1. Baseline characteristics of analyzed caregivers in the DOMUS study, n=249

	Intervention group *n* = 134*	**Control group *n* = 115***
Age, years Mean (SD)	61 (12)	62 (13)
Sex *n* (%)		
Male	49 (37)	40 (39)
Female	85 (63)	75 (65)
Marital status *n* (%)		
Married/cohabiting	123 (92)	103 (90)
Single	7 (5)	7 (6)
Divorced	1 (2)	3 (3)
Widow(er)	-	2 (2)
Missing information	3 (2)	-
Children *n* (%)		
Children	110 (82)	97 (84)
- living at home[**]	*27 (20)*	*24 (21)*
- not living at home[**]	*86 (64)*	*78 (68)*
No children	19 (14)	17 (15)
Missing information	5 (3)	1 (1)
Highest achieved education *n* (%)		
Element./middle school (9 years)	14 (10)	14 (12)
Vocational	35 (26)	31 (27)
High school	2 (2)	2 (2)
Further education (-4½ years)	48 (36)	47 (41)
Higher education (5- years)	27 (20)	16 (14)
Missing information	8 (6)	5 (4)
Relationship to patient *n* (%)		
Spouse/Partner	103 (77)	92 (80)
Son/daughter	24 (18)	10 (9)
Other	7 (5)	13 (11)
Cohabiting with patient *n* (%)		
Yes	103 (77)	91 (79)
No	25 (19)	22 (19)
Missing information	6 (5)	2 (2)
Length of relationship with patient, years		
Mean (SD, range)	38 (15, 5-63)	38 (16, 2-64)
Missing information	5	3
Patient's cancer diagnosis *n* (%)		
Breast	5 (4)	7 (6)
CNS	16 (12)	21 (18)
Connective tissue	5 (4)	8 (7)
Female genitalia	18 (13)	13 (11)
Head and neck	6 (5)	9 (8)
Lower gastrointestinal	15 (11)	13 (11)
Lung	28 (21)	25 (22)
Other	11 (8)	1 (1)
Prostate	17 (13)	5 (4)
Upper gastrointestinal	13 (10)	13 (11)
Performance Status *n* (%)		
0 - 1	68 (51)	59 (51)
2 - 3	66 (49)	56 (49)
Baseline anxiety symptoms Mean (SD)	1.00 (0.66)	0.94 (0.66)
% scoring above cut-off	28	27
Baseline depression symptoms Mean (SD)	0.84 (0.69)	0.80 (0.64)
% scoring above cut-off	24	23

* Some percentages do not add up to 100 due to rounding
** categories are not exclusive

Table S1. Estimated intervention effect on change in caregivers' symptoms of anxiety and depression (Online only)

	Anxiety					**Depression**				
	Mixed model results			**Multiple imputation**	**Multiple imputation, shifted values**	**Mixed model results**			**Multiple imputation**	**Multiple imputation, shifted values**
Follow-up time point	***n***	**Mean difference (95% CI)**	**Cohen's d**	**Mean difference (95% CI)**	**Mean difference (95% CI)**	***n***	**Mean difference (95% CI)**	**Cohen's d**	**Mean difference (95% CI)**	**Mean difference (95% CI)**
2 weeks	192	-0.04 (-0.18; 0.09)	-0.07	-0.07 (-0.22; 0.08)	-0.28 (-0.55; -0.02)	195	0.00 (-0.12; 0.12)	0.00	-0.01 (-0.13; 0.11)	-0.20 (-0.46; 0.06)
4 weeks	187	-0.02 (-0.15; 0.12)	-0.03	-0.02 (-0.17; 0.13)	-0.21 (-0.46; 0.03)	188	-0.02 (-0.15; 0.11)	-0.03	-0.03 (-0.17; 0.11)	-0.21 (-0.47; 0.05)
8 weeks	173	-0.14 (-0.28; -0.01)	-0.22	-0.20 (-0.36; -0.03)	-0.46 (-0.72; -0.20)	172	-0.17 (-0.33; -0.02)	-0.26	-0.19 (-0.36; -0.02)	-0.49 (-0.78; -0.20)
6 months	108	-0.29 (-0.45; -0.13)	-0.45	-0.35 (-0.61; -0.09)	-0.58 (-1.11; -0.04)	108	-0.27 (-0.49; -0.05)	-0.41	-0.30 (-0.55; -0.05)	-0.44 (-0.91; 0.03)
Bereavement follow-up										
2 weeks	131	-0.25 (-0.47; -0.04)	-0.39	-0.22 (-0.57; 0.12)	-0.90 (-1.64; -0.17)	131	-0.28 (-0.52; -0.03)	-0.42	-0.25 (-0.55; 0.05)	-1.00 (-1.51; -0.49)
2 months	125	-0.19 (-0.40; 0.03)	-0.29	-0.16 (-0.48; 0.17)	-0.86 (-1.55; -0.16)	125	-0.24 (-0.48; -0.01)	-0.37	-0.24 (-0.52; 0.04)	-0.89 (-1.40; -0.38)
7 months	101	-0.08 (-0.31; 0.15)	-0.12	-0.05 (-0.37; 0.28)	-0.63 (-1.32; 0.07)	101	-0.20 (-0.49; 0.09)	-0.30	-0.14 (-0.47; 0.18)	-0.52 (-1.13; 0.10)
13 months	60	-0.18 (-0.46; 0.09)	-0.29	-0.06 (-0.43; 0.32)	-0.13 (-1.32; 1.06)	60	-0.15 (-0.48; 0.18)	-0.23	-0.03 (-0.40; 0.34)	-0.51 (-1.59; 0.58)
19 months	41	-0.19 (-0.52; 0.15)	-0.29	-0.16 (-1.08; 0.76)	-0.83 (-7.34; 5.68)	41	-0.25 (-0.59; 0.10)	-0.37	-0.12 (-1.55; 1.31)	0.15 (-4.37; 4.67)
Test for interaction* in mixed model: F(8, 562) = 1.82 p = 0.0705							F(8, 87.5) = 1.73 p = 0.1022			
Main effect	246	-0.12 (-0.22; -0.01)	-0.19	-0.16 (-0.30; -0.03)	-0.42 (-0.68; -0.16)	246	-0.06 (-0.17; 0.05)	-0.09	-0.04 (-0.19; 0.11)	-0.14 (-0.41; 0.12)

* Interaction of follow-up time point (categorical) and randomization group

Table S2. Estimated odds ratios for caregivers of scoring above cut-offs (cases) for anxiety and depression (Online only)

Follow-up time point	Anxiety		Depression	
	n	**OR (95% CI)**	***n***	**OR (95% CI)**
2 weeks	192	0.63 (0.28; 1.44)	195	1.37 (0.61; 3.11)
4 weeks	187	0.86 (0.35; 2.11)	188	0.77 (0.34; 1.75)
8 weeks	173	0.57 (0.25; 1.30)	172	0.40 (0.17; 0.92)
6 months	108	0.43 (0.16; 1.14)	108	0.38 (0.14; 0.98)
Bereavement follow-up				
2 weeks	131	0.38 (0.15; 0.97)	131	0.62 (0.27; 1.40)
2 months	125	0.48 (0.19; 1.23)	125	0.42 (0.17; 1.00)
7 months	101	0.61 (0.19; 1.96)	101	0.95 (0.33; 2.78)
13 months	60	0.60 (0.11; 3.45)	60	0.50 (0.13; 1.90)
19 months	41	0.28 (0.01; 5.48)	41	1.40 (0.21; 9.35)
Test for interaction*	Chi2(8) = 2.25, *p* = 0.97		Chi2(8) = 10.36, *p* = 0.24	
Main effect	246	0.55 (0.39; 0.78)	246	0.65 (0.40; 1.07)

* Interaction of follow-up time point (categorical) and randomization group

PAPER 3

von Heymann-Horan, A., Bidstrup, P. E., Johansen, C., Rottman, N., Andersen, E. A. W., Sjøgren, P., von der Maase, H., Timm, H., Kjellberg, J. & Guldin, M.. Dyadic effects and mediators in a specialized palliative care intervention for patients with advanced cancer and their caregivers: findings from a randomized controlled trial. 2018. *Submitted.*

Dyadic effects and mediators in a specialized palliative care intervention for patients with advanced cancer and their caregivers: findings from a randomized controlled trial

Running head: Dyadic effects and mediators in palliative care

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Abstract

Background Specialized palliative care (SPC) interventions increasingly include patient–caregiver dyads, but their effects on dyadic coping are unknown. We investigated whether an SPC and dyadic psychological intervention increased aspects of dyadic coping in patients with advanced cancer and their caregivers, whether effects differed between subgroups of dyads and whether dyadic coping mediated significant intervention effects on caregivers' anxiety and depression.

Methods We randomized 258 patients with incurable cancer and their caregivers to care as usual or accelerated transition from oncological treatment to home-based SPC and dyadic psychological support. In mixed-effects models, we estimated intervention effects and 95% confidence intervals (CIs) for communication of stress, common coping, and satisfaction with coping, and moderation by dyad type and demographic characteristics. In path analyses, we investigated whether dyadic coping mediated intervention effects on caregivers' symptoms of anxiety and depression. (Clinicaltrials.gov NCT01885637)

Results We found no main effects on dyadic measures; however, the intervention significantly increased common coping in couples (estimated difference, 0.68; 95% CI, 0.11 to 1.24) and stress communication by partner caregivers (0.97; 0.24 to 1.24), whereas it significantly decreased stress communication by parents cared for by adult children (–2.54.; –4.19 to –0.90). Dyadic measures did not mediate effects on caregivers' anxiety or depression.

Conclusions Our results indicate that effects of SPC and dyadic psychological intervention may vary for dyad types, such as couples or parents and their adult children. The kinds of dyadic interventions that are appropriate and beneficial for different types of dyads in SPC need further investigation.

Background

The stressful life with advanced cancer requires that patients and caregivers cope, using both individual and collaborative efforts.[1,2] Multidisciplinary specialized palliative care (SPC) aims to relieve suffering in patients with life-threatening illness and their families[3] and has been shown to significantly improve quality of life of patients with advanced cancer.[4] As trials of SPC increasingly include patient–caregiver dyads,[5–8] they are likely to affect not only the individual coping and well-being of patients or caregivers but also their interaction. According to the systemic transactional model of coping (STM), couples may cope with stressors such as cancer in individual and interactional ways.[9] Dyadic coping is a reciprocal process comprising each partner's communication of stress and the ensuing positive or negative coping efforts of the partner and dyad. Stress communication serves to elicit support from the other partner, such as helping with or taking over tasks (supportive and delegated coping), and common coping, in which partners manage a problem together in the context of common goals.[9]

Stress communication has been related to improved quality of life in patients with hematological cancer[10] and better dyadic adjustment in patients with advanced breast cancer and their partners.[11] Greater common coping efforts, such as joint problem-solving or relaxation, have been found to significantly predict increased relationship quality and lower depressive symptoms in dyads coping with breast cancer.[12] In patients with advanced breast cancer and their caregivers, however, common coping has been significantly associated with subsequent lower distress in caregivers but increased distress in patients.[11]

Dyadic interactions could be affected by interventions to improve well-being in patient–caregiver dyads and contribute to other outcomes, such as distress. Although caregivers are increasingly included in trials of SPC, no randomized controlled trial (RCT) has yet assessed effects on dyadic interactions. A sizeable minority of the caregivers who participate in trials of SPC are adult children.[5–8] Yet, little is known about whether interventions for dyads with advanced cancer are equally effective for different types of dyads.

We aimed to investigate whether SPC and dyadic psychological intervention increased stress communication, common coping, and overall satisfaction with dyadic coping and whether effects differed according to dyad-characteristics. We recently reported that the Domus intervention significantly reduced symptoms of anxiety and depression in caregivers.[13] In creating the intervention, we hypothesized, that supporting dyadic coping would be one mechanism by which the intervention would decrease distress in dyads.[14] We therefore also investigated whether dyadic effects mediated the effect on caregivers' symptoms of anxiety and depression.

Methods

The Domus study was an RCT of home-based SPC with dyadic psychological support for patients with advanced cancer and their caregivers.[14,15] Dyads were recruited at the Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark. Patients were eligible if they had incurable cancer, limited antineoplastic treatment options, lived in the Capital Region of Copenhagen and were 18 years of age or older. Patients could invite a caregiver to participate. Upon completion of baseline questionnaires and written consent, dyads were randomized 1:1 to care as usual or the intervention. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Danish National Committee on Health Research Ethics (37237) and the Danish Data Protection Agency (2007-58-0015). The trial was registered at clinicaltrials.gov (NCT01885637).

We previously described the design of the Domus RCT[15] and the psychological intervention component in detail.[14] Briefly, the intervention consisted of an accelerated, coordinated transition from hospital-based oncological treatment to home-based SPC, in addition to care as usual.[15] Participants received a dyadic psychological intervention consisting of needs-based sessions with an existential therapeutic approach.[14] The psychological intervention was integrated into SPC and based on a dyadic understanding of coping with cancer; it aimed to decrease distress in both patients and caregivers by addressing issues that were currently salient to the dyad. The intervention was initiated in two dyadic sessions followed by monthly needs assessments by telephone. Subsequent sessions were based on needs and could be either dyadic or individual; the majority (63%) were attended by the patient and the caregiver together.

Measures

Dyads completed questionnaires before randomization and four times during follow-up (weeks 2, 4, and 8, and month 6). The measures included the anxiety and depression subscales of the Symptom Checklist-92[16] and the Relationship Ladder, which assesses overall relationship quality, rated from 0 ‘worst possible’ to 10 ‘best possible’.[17] Three subscales of the Dyadic Coping Inventory (DCI)[18] were also included. Patients and caregivers each reported their own stress communication to the other dyad member (e.g.“I show my relative that I feel stressed and unwell”), their perception of the dyad’s common coping (e.g. “We help each other see the problem in a new light”), and their overall satisfaction with the dyad’s coping efforts (e.g. “I am satisfied with the support of my relative and the way we cope with stress together”). The scores ranged from 5 to 25 for stress communication and common coping and from 2 to 10 for satisfaction. The DCI has been validated in several languages[19,20] but not yet in Danish. It was translated using a forward-and-backward procedure[12] and adapted for use with non-couple dyads for the present study by changing the wording of items to include caregivers. We further changed two items on the common coping subscale that assessed couple specific behaviors, such as relaxing together while bathing or showing affection by making love, to more inclusive behaviors, like listening to music and giving each other a hug.

Statistical analyses

Descriptive statistics were calculated for baseline characteristics, and paired t-tests tested differences in dyadic measures between patients and caregivers. To investigate whether the intervention increased stress communication, common coping, and overall satisfaction with dyadic coping, we used mixed-effects models to estimate intervention effects on the change from baseline and 95% confidence intervals (CIs). The initial models included fixed effects for the dyad member (patient, caregiver), dyad type (couple, parent-adult child, other), age, sex, randomization group (intervention, control), baseline scores for the outcomes, relationship quality at baseline, and follow-up assessments (weeks 2, 4, and 8 and month 6, categorical). Models were hierarchical, with follow-up assessments nested within dyad members, who were nested within the dyad. As dyad members were distinguishable as patients or caregivers, the initial models also included interactions between dyad member and all other variables. We removed nonsignificant interactions by stepwise testing. We investigated effect modification by including interactions between randomization group and age, sex, and dyad type. The final models comprised the initial fixed effects as well as interaction terms significant at $P = 0.1$. Covariance structures were modeled as “unstructured@CS” for common coping and communication (unstructured for follow-up assessments and compound symmetry for dyad members) and based on two random effects for satisfaction (for dyad and dyad member). Underlying model assumptions were assessed by visual inspection of residual plots. We calculated effect sizes from the standard deviation of the baseline assessment for the control group.[21]

To investigate whether the effects on caregivers’ symptoms of anxiety and depression reported earlier[13] were mediated by dyadic effects, we estimated direct and indirect effects of the intervention on symptoms of anxiety and depression. Indirect effects on an outcome are those that are due, in part or wholly, to effects on another variable, the mediator (effect A), which in turn has an effect on the outcome (effect B) (Figure 1). Because of differences found in mixed-effects models, we estimated models separately for couples and for parent–child dyads; but not ‘other’ dyads, as the group was too heterogeneous for meaningful interpretation. We used path analysis with maximum likelihood, adjusting for baseline values of the mediator and outcome, as well as caregivers’ age and gender in analyses of couple dyads. Because of limited power, gender and age were left out of the analyses of parent–child dyads. The Huber–White–Sandwhich estimator,[22] which relaxes assumptions about normally distributed errors, was used to estimate variance and 95% CIs. Model fit was evaluated with model fit statistics (SRMR, coefficient for determination R^2) and possibly improved by consulting modification indices. The primary mediation analyses were carried out for complete cases to investigate effects on symptoms of anxiety and depression at 6 months and their mediation by dyadic coping at 8 weeks. As sensitivity analyses, we completed models for effects on symptoms of anxiety and depression at 8 weeks and their mediation by dyadic coping at 4 weeks. We also estimated models with imputed missing observations on the basis of an assumption of joint normality and data missing at random.

Results

Between 19 June 2013 and 22 August 2016, 340 patients and 258 caregivers were included (supplemental figure 1). Nine dyads were excluded from the analyses because baseline measures were completed after randomization, written informed consent was missing, or the patient did not fulfill eligibility criteria. Data on one or more of the dyadic coping measures at baseline was missing for up to 6% of patients or caregivers. Thus, 243–245 dyads were available for analyses of intervention effects on different aspects of dyadic coping. Small differences between the intervention and control group seemed to occur for cancer diagnosis, caregiver type and patients' marital status (Supplemental table 1). At baseline, caregivers reported significantly lower levels on all measures of dyadic coping than patients (data not shown).

We found no significant main intervention effects in mixed-effects models, and caregivers' age and gender did not moderate the effects; however, when we investigated effect modification by dyad type, significant effects emerged for couples and parent–child dyads for common coping and stress communication. Couples in the intervention group reported significantly higher levels of common coping than couples in the control group (estimated difference, 0.68; 95% CI, 0.11 to 1.24; effect size, 0.15; Table 1). Further, the intervention significantly increased stress communication for partner caregivers (0.97; 0.24 to 1.71; effect size, 0.29), whereas it significantly decreased stress communication in parents cared for by an adult child (–2.54; 4.19 to –0.90; effect size, –0.55).

We found no evidence for mediation of effects on anxiety or depression, in either couples or parent–child dyads, regardless of the outcome or mediator (common coping or stress communication) (Table 2). Figure 1 shows the results of the path model for effects of the intervention on caregivers' symptoms of anxiety 6 months after randomization and mediation by caregivers' reports of common coping at 8 weeks. Sensitivity analyses confirmed the absence of indirect effects (data not shown). The pattern of previously reported intervention effects on caregivers' symptoms of anxiety and depression was confirmed for couples. No conclusive pattern of direct effects was observed for parent–child dyads.

Discussion

We found significant intervention effects in subgroups of dyads, with increased common coping and stress communication among partner caregivers but decreased stress communication among parents cared for by adult children. We found no evidence for mediation of the intervention effect on caregivers' symptoms of anxiety or depression by stress communication or common coping.

The lack of main effects on dyadic measures may be due to the absence of direct training of dyadic coping skills, stress communication or common coping in the intervention. Because dyads were together in the initial and as many of the subsequent sessions as they wished, their communication and common coping efforts were likely to be addressed indirectly, in relation to other topics discussed. The intervention did, however, significantly change common coping and stress communication in different types of dyads. The reason for these differential effects is not immediately evident but may depend on relational differences between dyad types. The STM was developed to describe dyadic coping within couples; it emphasizes the importance of common goals, such as maintaining the couple's relationship, to dyadic coping.[9] Couples might have more common goals than parents and children, making common coping efforts more relevant and frequent in couples and potentially easier to influence through interventions. Couples are likely emotionally closer as primary adult attachment figures, whereas the primary confidant of adult children may be e.g. a romantic partner outside the dyad. Thus, dyadic coping between a parent and child might have different implications than dyadic coping between partners. The different relationship and attachment between couples and parent–child dyads may be particularly salient in dyads in palliative care, as the experience of loss and grief differs for partners and child caregivers.[23,24]

Effects on stress communication

Caregivers often view their needs as secondary to those of patients;[25] and the psychological intervention likely increased dyads' awareness of caregivers' needs. During sessions, partner caregivers may have experienced talking with the patient about their concerns as possible and potentially beneficial. The significant increase in partner caregivers' stress communication can be seen in the light of previous findings that caregivers may engage in protective buffering, i.e. shielding patients from their own concerns,[26] and disclose significantly fewer concerns than patients.[27] Caregivers in the Domus trial also reported less stress communication than patients at baseline, and the intervention may have encouraged them to disclose their needs. In parent–child dyads, however, the increased attention to child caregivers' needs may have prompted parents to shield their children from additional concerns by limiting stress communication. A related hypothesis is that parents (and their adult children, although the estimate was not significant) may each have confided in the psychologist or other members of the care team, thus lowering their stress communication with each other.

Implications of changed stress communication

The effects on stress communication found in the Domus trial may not be unequivocally beneficial or detrimental. Although open communication is often expected to benefit dyads, a more nuanced view may be necessary.[28] In the STM, stress communication is seen as a precursor of dyadic coping efforts and serves to elicit support from the partner.[9] Patients with advanced cancer and their caregivers in the same dyad may experience different needs for communication,[29] and one-sided self-disclosure has been found to increase depressive symptoms,[30] indicating that increased communication within a dyad may sometimes be detrimental. The Domus intervention did not affect satisfaction with dyadic coping, indicating that the effects were not experienced as negative. The optimal level of communication likely depends on each dyad and its unique situation and preferences. Psychologists in the Domus intervention were free to use their clinical judgement and we believe the intervention was in keeping with such a differentiated approach. We found no evidence that common coping or stress communication mediated the effects on caregivers' symptoms of anxiety and depression. While power limitations prevent firm conclusions, we found no clear positive or negative direct intervention effects on symptoms of anxiety and depression in children caring for their parents. This lack of effects might support the hypothesis that changes in stress communication in parent–child dyads were not experienced as negative. It also poses the question, however, of the extent to which children caring for parents benefitted from the intervention. Although many intervention studies in advanced cancer and SPC include dyads with different types of caregivers, to the best of our knowledge, very few have investigated whether dyad type moderates intervention effects. In some previous psychosocial interventions, no moderation was found, although all non-spouse caregivers were analyzed together.[31,32]

Clinical implications

Our results indicate that it might be necessary to investigate whether the effect of dyadic interventions differs for different types of dyads. If different dyad types require different interventions, this has implications both for applying existing interventions in clinical practice and for designing new interventions.

Dyadic coping at the end of life

Applying the concept of dyadic coping at the end of life is a relatively new approach, and it is not clear what role dyadic coping plays at very advanced stages of disease. Stress communication might be affected, as talking about suffering and death may be particularly difficult, and patients and caregivers may wish to protect each other from death-related fears.[33] As patients become progressively weaker and caregivers increasingly burdened, the need for communication and patients' ability to engage in dyadic coping may change and the wish to protect one another may increase. Further, caregivers may already be starting the emotional adaptation to the loss of the patient.[34] Ultimately, the relationship in a dyad at the end of life will cease in its current form, and it is not clear how dyadic coping is affected by the fundamental change and dissolution of the relationship toward the patient's death. Studies are needed to clarify the changes that may occur in dyadic coping during the end of life.

Study limitations and strengths

Our study has certain limitations. The DCI was originally developed for healthy couples and has since been used in e.g. couples coping with breast cancer and hematological cancer[10] but not patients with advanced cancer. A previous version of the questionnaire has, however, been used in dyads with metastatic breast cancer.[11] We adapted the common coping scale to include behaviors that were not exclusive to romantic couples but representative of the same underlying concepts; however, the validity of the DCI in non-spouse dyads is unknown. The lack of mediation effects may be due to the specific measures of dyadic coping used. While a study using the DCI in a Danish sample found that common coping significantly predicted decreased depressive symptoms in both patients with breast cancer and their partners,[12] other aspects of dyadic coping not measured in our study, such as ambivalent or hostile coping, may be more closely related to anxiety and depression.[12,18,35] We had limited statistical power to detect effects in parent–child dyads, and as both mediation and moderation analyses were planned post hoc, results should be interpreted with caution.

The strengths of the study include the RCT design and inclusion of a manualized psychological intervention, which increases the confidence with which we can attribute effects to the intervention. All patients attending the Department of Oncology at Rigshospitalet, Copenhagen University Hospital, were screened systematically for eligibility, and participation of both patients (57%) and caregivers (96%) was good, increasing the generalizability of our findings.

Conclusion

The Domus intervention had significant effects on aspects of dyadic coping, differing for couples and parents cared for by adult children. The effects on dyadic coping did not mediate the previously found significant decreases in caregivers' symptoms of anxiety and depression. To the best of our knowledge, this study represents the first attempt to assess effects of SPC on dyadic coping and to investigate effect moderators for caregivers in a trial of SPC. Psychosocial intervention programs in SPC must accommodate patients and caregivers in all relationships, and tailoring care to patient and caregiver characteristics, such as their relationship, is a core clinical skill. Our results indicate that it is important to investigate whether intervention programs that seek to standardize care have the desired beneficial effects for all types of dyads before they are implemented in the clinic, to ensure that all patient–caregiver dyads receive the best possible care.

Acknowledgements

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Conflict of interest

The authors report no conflicts of interest.

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Table 1. Estimated differences and 95% CI for the effect of the Domus intervention on outcomes for patient–caregiver dyads

	Overall effect	Subgroup effect			
		Couple-dyads (n=195)	Parent-child dyads (n=34)	Other dyads (n=20)	*P* for interaction between intervention and dyad type
	Estimated difference (95% CI)	Estimated difference (95% CI)	Estimated difference (95% CI)	Estimated difference (95% CI)	
Common coping†	n=243				
	0.4 (-0.1; 0.9)	0.68 (0.11; 1.24)	-1.16 (-2.73; 0.41)	-0.18 (-2.06; 1.71)	0.0833
Stress communication‡	n=245				
Caregiver	0.66 (-0.04, 1.36)	0.97 (0.24; 1.71)	-1.53 (-3.18; 0.12)	0.29 (-1.63; 2.22)	0.0142
Patient	-0.38 (-1.08; 0.32)	-0.04 (-0.78; 0.70)	-2.54 (-4.19; -0.90)	-0.72 (-2.64; 1.20)	
Satisfaction with dyadic coping§	n=244				
	0.10 (-0.18; 0.37)	0.25 (-0.05; 0.55)	-0.67 (-1.50; 0.17)	-0.48 (-1.46; 0.50)	0.0636

† adjusted for dyad member, baseline coping*dyad member, baseline relationship quality, age, gender, follow-up assessment

‡ Included interaction between dyad member and randomization group. Adjusted for dyad member, baseline communication*dyad member, baseline relationship quality*dyad member, age, gender, follow-up assessment

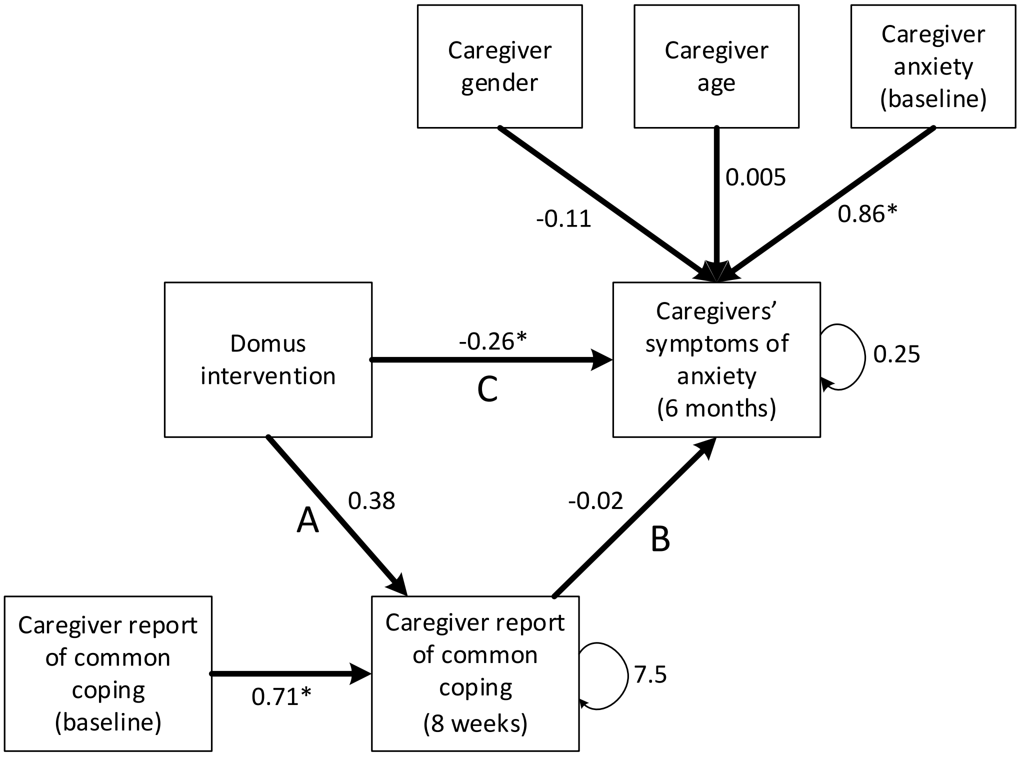
§ Adjusted for dyad member, baseline satisfaction*dyad member, relationship quality, age*dyad member, dyad type*dyad member, follow-up assessment

Table 2. Direct and indirect intervention effects on caregivers’ anxiety and depression at 6 months, mediated by dyadic measures at 8 weeks

	Couple dyads, n = 195				Parent-child dyads, n = 34			
	Common coping Estimate (96% CI)		Stress communication Estimate (96% CI)		Common coping Estimate (96% CI)		Stress communication Estimate (96% CI)	
Anxiety	Caregiver’s view	Patient’s view	Caregiver’s view	Patient’s view	Caregiver’s view†	Patient’s view‡	Caregiver’s view†	Patient’s view‡
Direct effect	-0.26 (-0.50; -0.03)	-0.28 (-0.52, -0.04)	-0.25 (-0.47, -0.03)	-0.27 (-0.52, -0.02)	-0.02 (-1.02, 0.99)	0.36 (-0.01, 0.73)	-0.06 (-1.01, 0.91)	0.12 (-0.11, 0.35)
Indirect effect	-0.01 (-0.04; 0.02)	-0.02 (-0.06, 0.02)	-0.02 (-0.08, 0.03)	0.01 (-0.02, 0.04)	-0.03 (-0.16, 0.09)	-0.15 (-0.42, 0.12)	-0.03 (-0.10, 0.05)	-0.00 (-0.09, 0.08)
Depression								
Direct effect	-0.11 (-0.32, 0.11)	-0.16 (-0.39, 0.06)	-0.14 (-0.38, 0.09)	-0.13 (-0.36, 0.09)	-0.30 (-1.33, 0.73)	0.30 (-0.22, 0.82)	-0.25 (-1.21, 0.72)	0.02 (-0.43, 0.48)
Indirect effect	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)	0.01 (-0.04, 0.06)	0.01 (-0.02, 0.04)	0.01 (-0.09, 0.11)	-0.17 (-0.44, 0.10)	-0.04 (-0.15, 0.08)	0.00 (-0.15, 0.16)

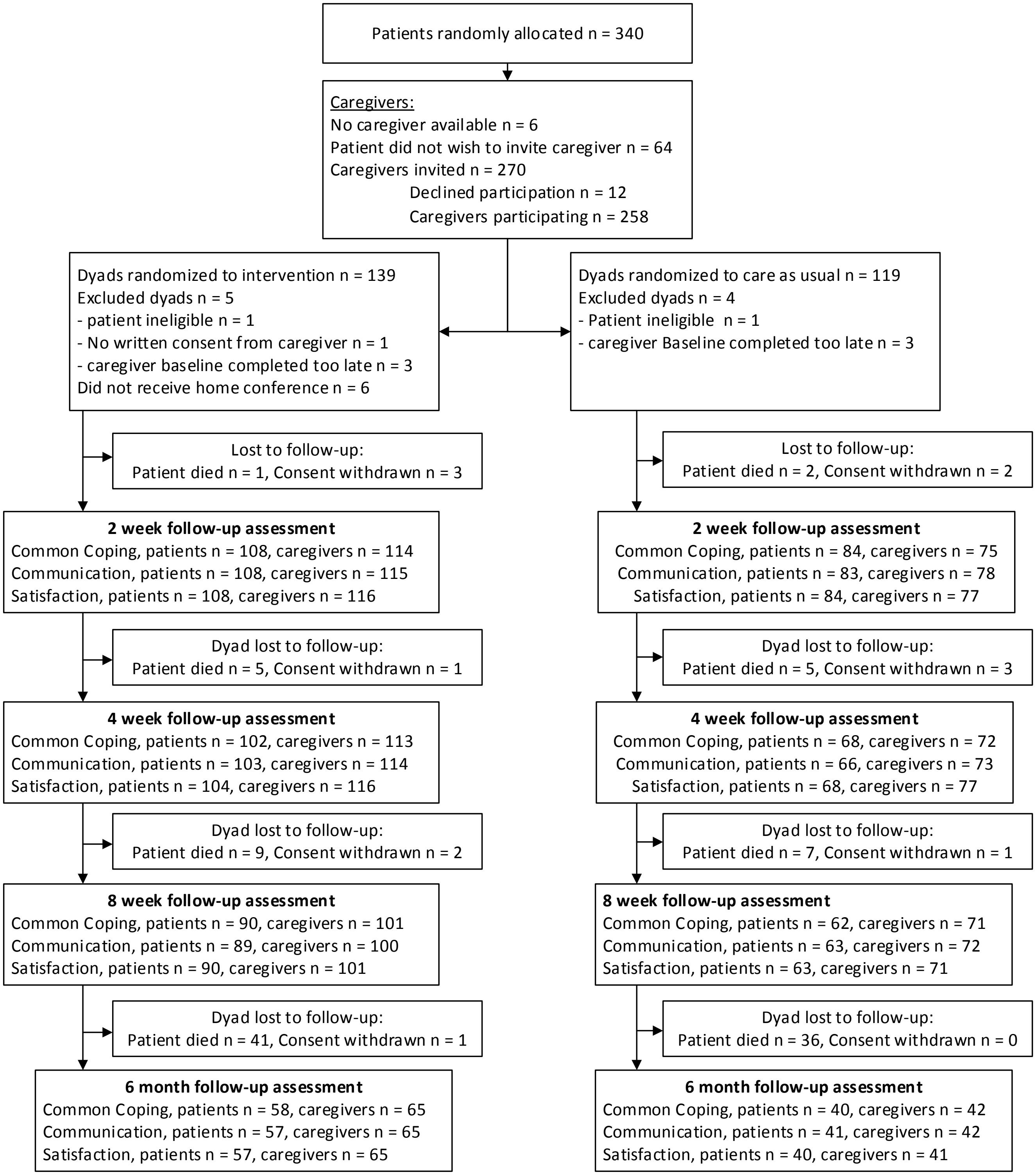
† Based on 12 dyads, ‡ Only nine dyads available for analyses at 6 months, therefore these are at 8 weeks

Figure 1. Direct and indirect intervention effects on caregivers' symptoms of anxiety at 6 months, mediated by caregivers' report of common coping at 8 weeks.



* $p < 0.05$

Supplemental Figure 1. Flow-chart of dyads (n=258) participating in the Domus RCT



APPENDIX 3. THE PSYCHOLOGICAL INTERVENTION DESCRIPTION

EXISTENTIAL-PHENOMENOLOGICAL INTERVENTION FOR CANCER PATIENTS AND THEIR INFORMAL CAREGIVERS IN SPECIALIZED PALLIATIVE HOME CARE

PSYCHOLOGICAL INTERVENTION IN THE DOMUS STUDY

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Copenhagen, April 2013

Revised, May 2014

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INTRODUCTION

The following describes the psychological intervention in the study: ”DOMUS - *A randomized clinical trial of accelerated transition from oncological treatment to continued palliative care at home.”* The DOMUS study investigates, whether accelerated transitions to palliative care teams and sessions with a psychologist for advanced cancer patients and their primary informal caregivers, can help patients receive care and treatment at home, improve symptom control, survival and the possibility for home death.

The psychological intervention aims to help patients remain in their own homes for as long as possible, to improve patients’ and caregivers’ quality of life, and to alleviate psychological and existential suffering, as well as to support bereaved caregivers’ grief process. The intervention consists of existential psychotherapy sessions tailored to the patient’s and informal caregiver’s needs to accommodate the widely varying psychological needs of palliative care patients and their caregivers. The psychological intervention has two parts: a primarily dyadic intervention directed at both the patient and the caregiver while the patient is receiving specialized care and treatment at home (specialized palliative care, SPC) and a bereavement intervention for bereaved caregivers.

The intervention is based on a dyadic understanding of severe illness as a common stressor, which is experienced by and affects both the patient and the caregiver. The disease, its symptoms, and the awareness of the approaching death are burdensome for both patient and caregiver, and may be accentuated by the transition to palliative care. Patient and caregiver are both affected by these burdens, which must therefore be coped with in collaboration.

BACKGROUND

Caregiving during the palliative phase will increasingly take place in patients’ own homes to meet the preference of the majority of cancer patients’ for their place of care and death (Brogaard, Neergaard, Sokolowski, Olesen, & Jensen, 2013; B Gomes et al., 2012; Neergaard et al., 2011). There is evidence that palliative home care increases the likelihood of patients dying in their own homes (Gomes, Calanzani, Curiale, McCrone, & Higginson, 2013). Growing demands may thus be placed on informal caregivers as changes in the health care system shift patient cancer care from in-patient and ambulatory to home settings (Given, Given, & Kozachik, 2001; Stenberg, Ruland, & Miaskowski, 2010). In this document, informal caregivers are defined as any relative or other person providing non-professional care to a patient, for instance a spouse, an adult child, or a friend.

Living with advanced cancer greatly impacts the person afflicted with the disease as well as their informal caregivers. Changes in family roles and the burden placed on informal caregivers may negatively affect quality of life for both the patients and their informal caregivers (Given et al., 2001). In addition to suffering from physical symptoms such as pain, fatigue, weakness, lack of energy, and appetite loss (Teunissen et al., 2007), patients also have to deal with the emotional impact of their illness and poor prognosis. A meta-analysis has estimated the prevalence of common psychological disorders in palliative cancer populations, finding a prevalence of 16.5% of depression, 9.8% of anxiety, and 15.4% of adjustment disorder, with 29% of patients meeting criteria for at least one of these disorders (Mitchell et al., 2011).

The role of informal caregivers has shifted from *“one of custodial care to a complex, multifaceted role”* (Given et al., 2001, p. 216), where the informal caregivers take on a number of direct or indirect caring tasks such as managing symptoms and equipment, transportation, patient advocacy, as well as assuming the patient’s previous duties (Given et al., 2001), such that caregiver play the role of ‘conductor’ in patients’ lives (Lowson et al., 2013). Caregivers may invest a substantial part of their time in taking care of their relative, and have been reported to have greater levels of absenteeism and impairment at work than non-caregivers (Goren, Gilloteau, Lees, & DiBonaventura, 2014). Informal caregivers of cancer patients are at risk for diminished quality of life, increased psychological distress, and use of psychotropic medication and health care services (Braun, Mikulincer, Rydall, Walsh, & Rodin, 2007; Grunfeld et al., 2004; Guldin, Jensen, Zachariae, & Vedsted, 2013; Song et al., 2011). Hence, patients with advanced cancer as well as their informal caregivers can benefit from psychosocial support (Northouse, Katapodi, Schafenacker, & Weiss, 2012; Northouse, Katapodi, Song, Zhang, & Mood, 2010; Uitterhoeve et al., 2004). However, no studies exist that have combined in-home palliative care with psychological interventions targeting patient-caregiver dyads, and the effect of such comprehensive support in a palliative population remains to be tested.

PSYCHOLOGICAL INTERVENTIONS IN STUDIES TARGETING IN-HOME CARE AND BEREAVEMENT

Among previous studies of comprehensive in-home palliative care reviewed by Gomes et al. (2013), four interventions were identified in which standard in-home palliative care was reinforced with additional psychosocial support to caregivers (Harding et al., 2004; Hudson et al., 2005; McMillan & Small, 2007; Walsh et al., 2007). All four studies targeted caregivers alone and were principally psycho-educational or supportive. The review did find some evidence of effects of these interventions on patients' symptom burden and alleviation of caregivers' distress and increase in their satisfaction with caregiving. The remaining studies investigated in-home palliative care as compared to care as usual, with palliative care provided by multidisciplinary palliative care teams, and psychosocial, psychological, and/or family support mostly listed as one of several available services. No interventions in Gomes' review offered psychological support to patients and caregivers as a dyad (Gomes et al., 2013).

PREVIOUS EXISTENTIALLY BASED PSYCHOSOCIAL INTERVENTIONS FOR A PALLIATIVE POPULATION

Existential therapy may be described as “a rich tapestry of intersecting therapeutic practices, all of which orientate themselves around a shared concern: human lived-existence.” (Cooper, 2003, p. 1) This broad description encompasses the approaches collectively referred to as the ‘British School’, represented by Emmy van Deurzen (2010) and Ernesto Spinelli (2007), which form the basis for the DOMUS intervention. The existential therapy practiced in this intervention is a descriptive approach, centered on the phenomenological method of inquiry, that aims to help patients and caregivers become open to and explore alternative ways of living with the challenges posed by the illness. To date, the efficacy of this form of existential therapy has not been investigated in trials for palliative care patients and their caregivers.

Existential aspects, however, have been integrated in psychosocial interventions for advanced cancer patients and/or their informal caregivers in a wide range of ways. Many psychosocial intervention studies have addressed what could be considered existential themes or issues among other aspects, either broadly defined as “spirituality/existential issues”(Steel, Nadeau, Olek, & Carr, 2007), or more narrowly, such as “accepting the finality of life” (Kwak, Salmon, Acquaviva, Brandt, & Egan, 2007, p. 437), and “meaning and purpose” (Rummans et al., 2006, p. 637). Other interventions have addressed existential issues such as meaning (Henry et al., 2010) or dignity (Chochinov et al., 2005, 2011) as the primary intervention aspect. Still other studies have based the psychological intervention on existential theory and/or therapy in supportive-expressive group therapy, focusing on emotional expression, group support and confrontation with existential themes (Classen et al., 2001; Kissane et al., 2004, 2007), and meaning-centered psychotherapy, focusing on enhancing the experience of meaning and purpose (Breitbart et al., 2010, 2012; Greenstein & Breitbart, 2000), or in combination with mindfulness (Fegg et al., 2013), or attachment and relational theory (Lo et al., 2014; Nissim et al., 2012).

The above studies have shown, that interventions for advanced cancer patients, which address existential concerns or are based on existential theory and/or therapy can increase patients' spiritual well-being and meaning and alleviate anxiety and desire for hastened death (Breitbart et al., 2010). They have also been shown to increase spiritual well-being, quality of life, and decrease symptom burden and symptom-related distress (Breitbart et al., 2012). Moreover, they have decreased suffering and depression (Chochinov et al., 2005), decreased traumatic stress symptoms, depression, and death anxiety (Classen et al., 2001), and increased spiritual well-being (Henry et al., 2010; Lo et al., 2014). The one existentially based study targeting informal caregivers showed effects on anxiety and quality of life, depression and negative affect (Fegg et al., 2013).

LIMITATIONS OF EXISTENTIALLY BASED INTERVENTIONS TO DATE

In previous studies, the existentially based interventions have been delivered both in group formats (Breitbart et al., 2010; Classen et al., 2001; Fegg et al., 2013), and individually (Breitbart et al., 2012; Chochinov et al., 2005, 2011; Lo et al., 2014; Nissim et al., 2012). However, none of the interventions mentioned above have targeted the patient-caregiver dyad as the unit of care, although clinical evidence for the feasibility of existentially based therapy with cancer patients and their partners exists (Lantz & Gregoire, 2000). Dyadic interventions focusing on coping, education, emotion-focused therapy or emotional disclosure and equity in palliative patient-caregiver dyads have proven efficacious (Kuijer, Buunk, De Jong, Ybema, & Sanderman, 2004; McLean, Walton, Rodin, Esplen, & Jones, 2013; Northouse et al., 2007; Northouse, Kershaw, Mood, & Schafenacker, 2005; Porter et al., 2009). Among other aspects, effects have been found on marital function and patients' perceptions of caregivers' empathic behavior (McLean et al., 2013), hopelessness and negative appraisal of the illness and caregiving (Northouse et al., 2005), perceptions of equity, relationship quality, and patients' psychological distress (Kuijer et al., 2004).

Further, only one of the existential interventions followed advanced cancer patients throughout their illness and until the end of life (Classen et al., 2001), while the remainder were time-limited interventions. Only some interventions allowed the sessions to address the content, which was most important to participants at the time (Classen et al., 2001; Lo et al., 2014; Nissim et al., 2012), instead of specifying intervention content prior to the intervention. Finally, even though the World Health Organization specifies, that supporting bereaved relatives during their grief is an integrated part of palliative care (Sepúlveda, Marlin, Yoshida, & Ullrich, 2002), none of the previous interventions included the caregiver from pre loss and into bereavement.

The psychological intervention in the DOMUS study addresses these gaps by combining an existential approach with a dyadic focus on the patient and caregiver as the primary unit of care, and providing care throughout the palliative trajectory and into early bereavement.

AIM

The primary aim of the psychological intervention in the DOMUS study is:

To improve quality of life during home care and in early bereavement and assess and relieve distress. We hypothesize that the intervention will enhance the ability of patients and caregivers to receive care in their homes, in correspondence with the aim of the DOMUS study (Nordly et al., 2014).

TEMPORAL AND SPATIAL FRAME OF INTERVENTION

Two sessions are planed within the first month from entering the DOMUS study. These sessions are planned at an initial interdisciplinary meeting in the patient's home. After the initial two sessions, patients and caregivers are contacted monthly by phone in order to assess the dyad's needs and offer additional session if required. Sessions with patients who are participating without a caregiver, will last up to one hour, joint sessions with patients and caregivers will last up to 1½ hours.

The sessions will take place where the patient and caregiver currently reside, as the intention is to support home care in addition to improving QOL. The intervention aims to be non-resource demanding for patients and caregivers in terms of transportation. If the patient is hospitalized or temporarily resides in hospice, the sessions can take place in that setting. If either the patient or caregiver is unable to participate in, or complete, a planned session, the patient or caregiver can participate in the session alone. Otherwise, the session is re-scheduled. As patients reside in their own homes throughout the project, other relatives/persons may be present in the home. However, the present intervention does not include family therapy, thus other relatives are excluded from participating.

The session(s) with the bereaved caregiver takes place approximately one month after the loss. The session will last up to an hour and a half, and take place in a location convenient for the bereaved caregiver.

NEEDS ASSESSMENT AND INDIVIDUAL TAILORING

Palliative care needs develop and change throughout the palliative care phase; likewise, caregiver needs may vary according to the decline of the patient’s functional status (Grunfeld et al., 2004; Oechsle, Goerth, Bokemeyer, & Mehnert, 2013). The present intervention aims to improve QOL and relieve psychological distress in individuals/dyads and therefore, the frequency of sessions is tailored to each individual’s /dyad’s needs and motivation. The initial sessions focus on the therapeutic alliance and the initial needs assessment, followed by an individually tailored course of sessions. Monthly contacts allow for a continuation of the therapeutic alliance and exploration of the dyad’s need within the continuity of the established therapeutic relationship, and may reduce potential barriers to receiving support. Taking into account factors that have been found in the literature to characterize patients and caregivers at risk for distress in the needs assessment allows the psychologist to intensify the intervention for at-risk individuals in order to strengthen the alliance and prevent future distress.

CONTINUAL NEEDS ASSESSMENT THROUGHOUT THE PALLIATIVE PHASE

Needs and risk factors at the individual as well as the dyadic level are assessed during phenomenological interviews in the initial two sessions. When needs have been identified, the next session is planned accordingly and in dialogue with the individual/dyad depending on their motivation to receive support, as well as the urgency of the needs. If no needs are identified, no further sessions are planned at that time. The needs assessment is updated continually through monthly contacts with patient and caregiver, which also aim to maintain the therapeutic alliance for future support needs. These contacts will be planned as telephone calls, or if the needs assessment cannot be completed by phone and/or the continuation of the therapeutic alliance requires a face-to-face contact, a session is scheduled to take place at the residence of the patient. Further sessions are planned according to the continual needs and risk factor assessment.

DEFINITION OF PSYCHOLOGICAL NEEDS

In this intervention, needs are defined in relation to the following areas:

1. Psychological distress

   Psychological distress is defined, as by the National Comprehensive Cancer Network, as *“a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment***.** *Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation,* *and existential and spiritual crisis.''* (National Comprehensive Cancer Network, 2014, p. 7) This definition of distress is applied to patients as well as caregivers, and distress is evaluated for patients and caregivers separately. Further sessions are planned if distress impacts on the individual's or dyad's ability to adjust adequately to circumstances or to minimize a decrease in their quality of life. To aid clinical decision-making diagnosable psychiatric disorders are distinguished from this category (see below).

2. Psychiatric disorders

   Psychiatric conditions are evaluated according to ICD-10 criteria (World Health Organization, 2010), separately for patient and caregiver. Central to psychiatric assessment in palliation are the affective (mood) disorders, notably depression, reactions to severe stress, anxiety disorders and adjustment disorders (Breitbart, Chochinov, & Passik, 2009). These are the disorders, which are within the scope of the intervention. Organic mental disorders (delirium) should always be ruled out or referred to appropriate medical/interdisciplinary treatment. If diagnosable psychiatric conditions are present and currently impact the individual's or dyad's adjustment ability, these are regarded as needs.

3. Psychosocial barriers to receive in-home palliative care

   Psychosocial barriers to palliative care are a complex, multifactorial matter consisting of individual, relational, professional, organizational, as well as political aspects (Graham, Kumar, & Clark, 2009). In this needs assessment, psychosocial barriers are defined as those barriers which are a) relational in nature, such as disagreements or communication problems between patient and caregiver with regard to in-home care, b) related to the individual's/dyad's involvement with health care professionals in the care, for instance their trust in health care providers or willingness to consider treatment options, as well as c) other barriers that are psychosocial in nature, for example challenges to established family roles.

RISK FACTORS FOR DISTRESS AND ADVERSE BEREAVEMENT OUTCOMES

Research has identified a number of risk factors which may predict the individual's or family's outcomes, such as distress or prolonged grief during palliative care and/or during bereavement (Aranda & Milne, 2000; Kissane & Zaider, 2009; National Comprehensive Cancer Network, 2014; Pitceathly & Maguire, 2003; Schulz, Boerner, & Hebert, 2007). Such risk factors are evaluated at the individual as well as the dyadic level, based on those found for distress during palliative care according to the National Comprehensive Cancer Network (2014) and Pitceathly & Maguire (2003), as well as for adverse outcomes in bereaved caregivers as identified by Arandy & Milne (2000), Kissane & Zaider (2009), and Schulz et al. (2007). In this project, a risk factor is defined as any characteristic which predicts a specific occurrence, i.e. increases the probability of psychological distress in patients or caregivers or adverse bereavement outcomes in bereaved caregivers (Aranda & Milne, 2000). Adverse outcomes are defined as negative outcomes associated with the loss and include depressive disorders, anxiety disorders, prolonged grief, and poor physical health (Aranda & Milne, 2000). Examples of the assessed risk factors for distress are a history of psychiatric disorder, cognitive impairment and severity of symptoms in patients, and social issues, such as family or caregiver conflicts (National Comprehensive Cancer Network, 2014; Pitceathly & Maguire, 2003). Risk factors for adverse bereavement outcome include a history of psychiatric disorder, the nature of the death, family or relationship conflicts, history of previous losses, as well as high distress and caregiver burden preceding the death (Aranda & Milne, 2000; Kissane & Zaider, 2009; Schulz et al., 2007).

NEEDS ASSESSMENT DURING BEREAVEMENT

A single bereavement/closing session is offered to all bereaved caregivers, which includes a brief assessment of risk of adverse bereavement outcomes and needs to inform targeted psycho education about grief reactions and available support. This needs assessment is based on risk factors for bereaved caregivers (Aranda & Milne, 2000; Kissane & Zaider, 2009; Schulz et al., 2007). One additional session can be offered to bereaved caregivers who are at increased risk for adverse bereavement outcomes due to circumstances surrounding the death and to help the person into an appropriate support service (Aranda & Milne, 2000; Kissane & Zaider, 2009).

EXISTENTIAL-PHENOMENOLOGICAL PSYCHOTHERAPY

The intervention is based on the British School of existential analysis, chiefly the work of Ernesto Spinelli and Emmy van Deurzen (Spinelli, 2007; van Deurzen, 2010). As the DOMUS study takes place in a context of specialized, palliative care and treatment, existential-phenomenological therapy is employed cognizant of the special requirements and circumstances that arise when therapeutic practice occurs in a medical context, with couples, and in the face of severe physical illness and its ensuing limitations. Existential-phenomenological therapy invites clients to investigate and clarify the assumptions that underlie their being-in-the-world, in order to expand their possibilities of relating to themselves, the world and others (Spinelli, 2007). The following paragraphs present concepts underlying existential-phenomenological therapy, which are central to the practice of existential-phenomenological therapy in this intervention. The presentation is necessarily short and selective and only a short introduction to a complex field.

AN EXISTENTIAL UNDERSTANDING OF HUMAN BEING

Existential-phenomenological therapy is based on an understanding of humans drawn from a variety of existential philosophical theories, such as those put forth by Søren Kierkegaard, Martin Buber, Martin Heidegger, and Maurice Merleau-Ponty, among others (Cooper, 2003) . Central to this understanding are the inescapable givens that delimit human existence, and the way in which we live with them.

EXISTENTIAL GIVENS

Humans are subject to basic conditions, inescapable 'givens' of life (Spinelli, 2007). We are always in the world, in space, in time, in the body, emotionally "attuned", intersubjective and limited by death (Cohn, 1997). These givens are fundamental to existence and cannot be escaped (van Deurzen & Adams, 2011), but we can influence how we choose to deal with these ultimate conditions of life in creating our own specific understanding of the world, our world-view (Spinelli, 2007). Patients and caregivers in palliative care are faced with numerous bodily, psychological, and social losses, and the threat of death. This amplifies the importance of the existential givens, most acutely death, in daily life, and losses and symptoms exist before the backdrop of death.

THREE PRINCIPLES OF EXISTENCE

According to Spinelli (2007), three general principles of existence are of central importance to understanding human being: 1) Existential relatedness, 2) existential uncertainty and 3) existential anxiety. 1) We are always in relatedness with others. Our experiences, knowledge and awareness of self, come from this relatedness, and are understood within it (Spinelli, 2007). 2) Human beings are understood as a constant dynamic process of becoming, they are continually changing, rather than a fixed state. To create predictability and security, each person understands his/her situation from his/her own specific stable 'worldview', made up of his/her beliefs, values, views, attitudes, meanings, assumptions and conclusions and their associated behaviors and emotions (Spinelli, 2007). In the effort to avoid or reduce anxiety, we select fixed truths, facts and statements and distance those experiences that challenge our claims of certainty and fixed meaning (Spinelli, 2007). The worldview provides stability, which the dynamic process of being may not provide without the structure of the worldview. 3). Existential anxiety is the uneasiness or discomfort that stems from the worldview's incomplete attempt to structure the process-like being, resulting in incongruence between the experience of being and the worldview.

PHENOMENOLOGICAL INQUIRY

The intervention proceeds from the phenomenological method of inquiry, which requires that the therapist sets aside her own understanding, prejudice and attitudes, to allow an immediate experience of a given situation (van Deurzen & Adams, 2011). The therapists aims to help the patient describe his or her worldview starting from the patients' immediate experiences of his/her emotions, behavior, actions, and thoughts (van Deurzen & Adams, 2011). The therapist is required to refrain from judging these descriptions as being relevant or not, but explores what is important to the patient at the present time (Spinelli, 2005).

EXISTENTIAL THERAPY IN THIS INTERVENTION

When patients and caregivers are faced with loss and death, their previous assumptions may be challenged and their worldviews may no longer provide the stability that protects them from facing the uncertainty inherent in life. Existential therapy is well positioned to address the experience of patients and caregivers who are forced to face the existential givens of insecurity and death, because of its basis in an understanding of these givens as unavoidable, and its approach toward helping the person to live *with* these givens. The existential therapy practiced in this intervention focuses on helping the patient and/or caregiver become open to the possibility of alternative ways of living within these givens. Existential therapy is, however, not only the facilitation of the person's exploration of existential givens and assumptions, but a flexible approach, responsive to the individual's needs. It spans from this exploration of the person's way of seeing the world 'within' his/her own frame of reference to challenging that worldview from 'without' (Spinelli, 2007). Put differently, it may span from efforts of active listening, over guiding and instructing efforts, to requiring certain actions of the patient (Bugental, 1987).

The psychological intervention can help dyads in palliative care adapt to their current situation, by helping them address fixed assumptions in their worldview (for instance about help seeking or control) that may prevent them from achieving their wishes for their remaining time, as well as helping the dyad to live with the uncertainty and existential anxiety that cannot be removed.

TRAINING, SUPERVISION, AND CONGRUENCY

The intervention psychologists will receive initial intensive training in the fundamental principles of existential phenomenological therapy, by a senior psychologist with 30 years of experience in existential phenomenological practice, and the principles will continually be addressed in ongoing supervision. Supervision by psychologists with long experience in psycho-oncology and specialized palliative care ensures the incorporation of the demands of the medical context into the existential therapy practiced. The supervision is organized as group supervision, planned to take place for an average of three hours on a biweekly basis, to ensure the congruent practice of all psychologists.

COLLABORATION AND BOUNDARIES

RECORD KEEPING AND CONFIDENTIALITY

The psychologists keep written records and will prepare such after each session. The written records are kept for at least three years in accordance with Danish laws governing the practice of psychologists (Socialministeriet, 1994; Social- og Integrationsministeriet, 2012). Documentation that the sessions have taken place is entered into the electronic medical record of the patient, and thus available to the palliative care team. Treatment relevant information, such as information about patients' symptoms that emerges during sessions, about dyads' willingness to seek help, or other needs that require medical or nursing attention, is also shared with the involved palliative care team. Patients and caregivers are informed of this information exchange in the written information materials and the information enclosed with the informed consent form. Further, in the first session, the psychologist will explain to the patient and caregiver how confidentiality and information sharing are handled, while explaining the spatial and temporal scope of the intervention.

TREATMENT RESPONSIBILITY, DIFFERENTIAL DIAGNOSTICS AND REFERRALS – DELIMITING THE INTERVENTION

The intervention includes the ongoing clinical assessment of distress (including anxiety, depression, and adjustment disorder) in patients and caregivers. If other psychiatric conditions are present, which are not within the scope (such as personality disorders, and very severe depressive disorders or psychoses requiring psychiatric care), the psychologist will discuss referral options to treatment outside of the project with the palliative care team.

EVALUATING THE INTERVENTION

The supportive existential-phenomenological intervention is evaluated in three PhD theses based on the DOMUS study (Nordly et al., 2014). As the psychological intervention is taking place alongside the specialized palliative care intervention, home nursing and standard care, it is not possible to isolate the effect of the psychological intervention from the effect of the other aspects of the intervention in the DOMUS trial. Thus, the aim of the DOMUS study is to investigate the effect of the overall intervention (specialized palliative care, psychological intervention etc.). The evaluation of the DOMUS study is described in the study protocol (Nordly et al., 2014).

ETHICAL CONCERNS

The psychological intervention in the DOMUS study takes place within a randomized controlled trial, and therefore requires an explicit ethical stance toward possible conflicts between the best interest of the participants and that of the trial. The psychologists in the intervention work in accordance with the ethical principles agreed upon by the associations of Nordic psychologists (Dansk Psykologforening, 2000). Although the DOMUS study aims to provide palliative care in patients' homes, patients' needs always take priority, also when they are in conflict with the overall aim of the DOMUS study. For instance if a patient needs care and treatment at a hospice or at the hospital, or does not wish to be cared for at home, these needs and wishes are prioritized above the DOMUS aim of remaining at home.

The psychologists who are conducting the therapy are also doing their PhD on data from the DOMUS study. The psychologists are aware of the potential ethical dilemmas of this study and their double role and ensure that the role as researchers in the DOMUS study and the role of clinical psychologists are carried out separately. The psychologists do not have access to the responses on the questionnaires while the DOMUS study is ongoing and have no knowledge of the answers given by their patients during the psychological intervention. Questions regarding t the questionnaires are referred to the project nurses and questionnaires are returned to the researchers independently of the psychological intervention.

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APPENDIX: THE DOMUS STUDY

The intervention described in this document is the psychological component in the study: ”DOMUS” *A randomized clinical trial of accelerated transition from oncological treatment to specialized palliative care at home* (Nordly et al., 2014).

The DOMUS study is a randomized clinical trial. The DOMUS study investigates whether accelerated transitions from oncological treatment to specialized palliative care is effective in helping patients receive care and treatment at home, in accordance with their own wish, to improve symptom control, and increase survival and the possibility for home death.

The study takes place at the Oncological Clinic, Rigshospitalet (Copenhagen University Hospital), where 340 palliative cancer patients will be included.

The DOMUS intervention consists of a consensus meeting, regarding the patient’s and primary informal caregiver’s wishes for care and treatment at home, followed by a home-visit to optimize home-facilities, if necessary. The patient is discharged no more than 5 days after informed consent for participation in the study has been obtained. Upon discharge, the patient, caregiver, homecare nurse, and representatives from the local palliative care team, and if possible the patient’s general practitioner as well as the project psychologist attend a meeting in the patient’s home to coordinate and plan the ensuing palliative care. The control group receives care as usual and is not prevented from receiving referrals to palliative care teams if this is planned with their own treating physician.

Patients in both the intervention and control group are followed by way of questionnaires for up to 6 months. Thus, the last questionnaire for patients is 6 months after the completion of the baseline questionnaire. Informal caregivers will receive follow-up questionnaires for up to 19 months after the patient’s death (Nordly et al., 2014).

INCLUSION CRITERIA FOR THE STUDY POPULATION

Patients

Patients represent the population that is normally seen in the Oncological Clinic at Rigshospitalet. Patients are eligible for inclusion if they have an incurable cancer disease and their WHO performance status is 2-4. (As of November 1st 2014, the performance status inclusion criterion was discarded to boost recruitment.) All patients are 18 years of age or older and must reside in the Capital Region of Denmark. All patients included in the study wish to spend as much time in the palliative care trajectory as possible in their own homes. If the patients are hospitalized, it is assessed whether discharge is possible (Nordly et al., 2014). Patients are treated at the Oncological Clinic at Rigshospitalet and they have different prognosis at inclusion. All patients randomized to the intervention group will receive sessions with a psychologist.

Informal caregivers

Caregivers, who participate in the DOMUS study are informal caregivers appointed by the patient at inclusion (one per patient) (Nordly et al., 2014). Previous Danish studies have shown, that participating caregivers are most often spouses or partners or adult children (Brogaard et al., 2013). Informal caregivers must be 18 years of age, or older and be able to speak and read Danish (Nordly et al., 2014).

Patients, who agree to participate but do not appoint an informal caregiver, participate alone in the DOMUS study (Nordly et al., 2014).

APPENDIX 4. QUESTIONNAIRES

Symptom Checklist 92

De næste spørgsmål handler om dit psykiske velbefindende

Nedenfor er anført en række problemer og gener, som man undertiden kan have. Læs venligst hver enkelt grundigt. Når du har gjort det, bedes du sætte X i den boks, der bedst beskriver, i hvor høj grad det pågældende problem har voldt dig ubehag **i løbet af den sidste uge inklusive i dag**. Afkryds kun én boks for hvert problem.

	I hvilken grad har du været plaget af:	Slet ikke	Lidt	Noget	En hel del	Særdeles meget
1	nervøsitet eller indre uro	☐	☐	☐	☐	☐
2	manglende interesse for eller glæde ved seksualitet	☐	☐	☐	☐	☐
3	en følelse af manglende energi eller af at være langsom	☐	☐	☐	☐	☐
4	tanker om at gøre en ende på dit liv	☐	☐	☐	☐	☐
5	rysten	☐	☐	☐	☐	☐
6	at du let kommer til at græde	☐	☐	☐	☐	☐
7	en følelse af at være fanget i en fælde	☐	☐	☐	☐	☐
8	at du pludselig bliver bange uden grund	☐	☐	☐	☐	☐
9	selvbebrejdelser	☐	☐	☐	☐	☐
10	at føle dig ensom	☐	☐	☐	☐	☐
11	at føle dig nedtrykt	☐	☐	☐	☐	☐
12	at bekymre dig for meget	☐	☐	☐	☐	☐
13	at du ikke føler dig interesseret i noget	☐	☐	☐	☐	☐
14	at føle dig ængstelig	☐	☐	☐	☐	☐
15	hjertebanken	☐	☐	☐	☐	☐
16	at føle dig uden håb for fremtiden	☐	☐	☐	☐	☐

17	at du føler dig anspændt eller opkørt	☐	☐	☐	☐	☐
18	en følelse af, at alting er anstrengende	☐	☐	☐	☐	☐
19	anfald af rædsel eller panik	☐	☐	☐	☐	☐
20	at du føler dig rastløs, at du ikke kan sidde stille	☐	☐	☐	☐	☐
21	en følelse af at være ingenting værd	☐	☐	☐	☐	☐
22	en følelse af, at der vil ske dig noget slemt	☐	☐	☐	☐	☐
23	skræmmende tanker og forestillinger	☐	☐	☐	☐	☐
24	en følelse af, at velkendte ting er fremmede eller uvirkelige	☐	☐	☐	☐	☐
25	at du føler dig presset til at få tingene gjort	☐	☐	☐	☐	☐

Dyadic Coping Inventory

De følgende spørgsmål omhandler din og din pårørendes håndtering af stressede situationer

Med din pårørende menes den person, du er gået ind i denne undersøgelse sammen med.

De efterfølgende spørgsmål sætter fokus på, hvordan du og din pårørende har håndteret stressede situationer (situationer, der er fysisk og/eller følelsesmæssigt belastende) **i løbet af de sidste to uger**. Du bedes besvare alle spørgsmål så spontant som muligt og uden for mange overvejelser.

Hvad gør du, når du føler dig stresset/overanstrengt?

		Meget sjældent	Sjældent	Af og til	Tit	Meget tit
1	Jeg fortæller min pårørende, når jeg er glad for hans/hendes støtte i praktiske ting eller for hans/hendes gode råd og vejledning	☐	☐	☐	☐	☐
2	Jeg beder min pårørende om at overtage opgaver og gøremål, når jeg føler mig overbelastet	☐	☐	☐	☐	☐
3	Jeg viser min pårørende, at jeg føler mig overanstrengt og har det skidt	☐	☐	☐	☐	☐
4	Jeg siger ligeud til min pårørende, når jeg er stresset og har brug for, at han/hun støtter mig følelsesmæssigt	☐	☐	☐	☐	☐

Hvordan håndterer du og din pårørende stress, der angår jer begge to?

		Meget sjældent	Sjældent	Af og til	Tit	Meget tit
9	Vi forsøger at klare problemet i fællesskab og finde konkrete løsninger	☐	☐	☐	☐	☐
10	Vi diskuterer problemet indgående og analyserer, hvad der skal gøres	☐	☐	☐	☐	☐
11	Vi hjælper gensidigt hinanden med at se problemet i et nyt lys	☐	☐	☐	☐	☐
12	Vi slapper af ved at gøre ting sammen, f.eks. at høre musik eller se tv	☐	☐	☐	☐	☐
13	Vi forsøger at bekæmpe stressede situationer ved at være fysisk tæt på hinanden f.eks. give hinanden et kram	☐	☐	☐	☐	☐

Hvordan vurderer du jeres fælles stresshåndtering?

		Meget sjældent	Sjældent	Af og til	Tit	Meget tit
14	Jeg er *tilfreds* med min pårørendes støtte og med den måde, vi sammen klarer stressede situationer på	☐	☐	☐	☐	☐
15	Jeg opfatter min pårørendes støtte og vores fælles håndtering af stressede situationer som *effektiv*	☐	☐	☐	☐	☐

Relationship Ladder

For partners:

Det sidste spørgsmål handler om dit parforhold

For non-partners:

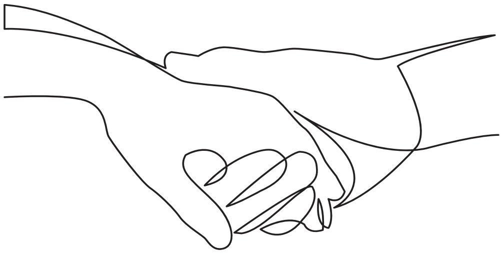
Det sidste spørgsmål handler om dit forhold til den person, du er gået ind i denne undersøgelse sammen med

Herunder er et billede af en “stige”. Det øverste trin på stigen (tallet 10) angiver det, for dig, bedst tænkelige forhold, og det nederste trin (tallet 0) angiver det, for dig, dårligst tænkelige forhold.

x.1 Hvor på stigen befinder jeres forhold sig for øjeblikket?

Det kan du angive ved at sætte et X på det trin på stigen, hvor dit forhold, efter din mening, befinder sig for øjeblikket

10	☐
9	☐
8	☐
7	☐
6	☐
5	☐
4	☐
3	☐
2	☐
1	☐
0	☐



PHD THESIS

ANNIKA VON HEYMANN-HORAN

INTEGRATION OF PSYCHOLOGICAL INTERVENTION IN SPECIALIZED PALLIATIVE CARE

EFFECTS ON CAREGIVER DISTRESS AND DYADIC COPING

Danish Cancer Society Research Center

&

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