PhD dissertation
Nanja Holland Hansen

COMPASSION CULTIVATION TRAINING FOR INFORMAL CAREGIVERS OF PEOPLE WITH A MENTAL ILLNESS

Health, Aarhus University, 2021

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Acknowledgement

A Ph.D. does not happen or exist in a vacuum. It holds a long journey filled with many important people and personal experiences. I would like to share some of my journey here beginning when I was three years old. One night, at the age of three, my mother read The Ugly Duckling by Hans Christian Andersen to me. The story goes, (of course I don't remember this) that I started crying feeling so sad for this little duckling, who was treated poorly and feeling disconnected from himself and the world around him. Fast forward to the eight-grade, when I spent months on a written assignment, researching various kinds of drugs and the lives of drug-users. I even got to speak with some drug-users, whose stories made a strong impression on me. Their lives were filled with so much suffering due to their childhoods, their drug-use and the lifestyle that came with the addiction. Fast forward again, to my undergraduate years at University of Illinois Urbana-Champaign, USA. Here, I signed up for an internship program working with juvenile delinquents living in juvenile detention centers, some charged with first-degree murder. Again, I experienced the great unfairness of the world; how so many of the adolescents in there should not have been there, how unfair the system is, and how the structural and systemic racism was so much part of everyday life for these adolescents. Embarking on graduate school I enrolled in yet another internship program, this time working with young adults in downtown Phoenix Arizona, USA. Again, I was faced with the same unfairness, the same hopelessness and powerlessness, that had permeated the lives of the juvenile delinquents and that so many of these young adults lived with daily. Young men and women trying to make a better life for themselves by getting a high-school diploma and learning a trade. At the same time the social structures of their home environment and cultural heritage made it so that many of them were part of gangs in order to feel protected and connected in their local communities. Native Americans moving away from their reservations trying to learn how to "fit into" White America, attempting to get away from alcoholism and violence. At this point I had become a trained psychologist and felt an immense urge and willingness to engage with the suffering of these young men and women. I also felt overwhelmed and

powerless – how could one person make any kind of change or difference in the daily lives of these individuals?

Fast forward again, I was now married, had two kids, living in California, and working as a psychologist at Stanford University. The suffering here looked very different; parents grooming their children to have the best resumé when they graduated high-school so they could get accepted into an Ivey League School, the stress of having to earn a high income just to be able to live in Silicon Valley, the stress and disconnectedness of having to appear to be "perfect" and have the "perfect life". It was also here that I became acquainted with compassion and compassion-based training programs. Embarking on this training both as a private person and as a healthcare professional added a whole new dimension to my life. Compassion training, teaching and research became a bridge or a red thread of my life and all the experiences I had had up until this point. It evoked a strong sense of wisdom and direction within me. This wisdom and this direction took me on a new journey, the Ph.D. journey. The journey of bringing manualized compassion-based interventions to people, whose daily lives are fraught with suffering – namely informal caregivers. People, who daily, deal with the "hidden" problems of society, where mental illness is still met with stigmatism, where needing help or not knowing how to take acre of oneself is still taboo. The wisdom that rings so true within me is this: We cannot continue to pretend that our lives, our health and our survival does not depend on the quality of our mental health. It is not the responsibility of the individual, it is the responsibility of all societies.

As I said, this journey certainly did not exist in a vacuum, and many people have influenced my life. Therefore, it seems important to mention some of them. First, I would like to acknowledge my grandmothers; Olga Hansen and Mary Elisabeth Duncan. They were both incredibly strong women and they have inspired me throughout my life. My parents; Kurt Hansen and Sally Dean Anderson, who never let me rest, and who urged me to be curious and diligent. To work hard, to play, enjoy life and to love. To my husband; Kennett Sprogøe, whose unwavering love, belief in my capabilities and support, is a daily strength in my life. To my two beautiful kids; Ella Holland Sprogøe and Mateo Holland Sprogøe, who are the most compassionate individuals I know, and provide me daily with so much practice material it makes my head spin. To Dr. William Cabianca (Dr. C) – my beloved mentor and friend. His wisdom and nurturance, is with me daily. To Dr. Andrea Dixon, who saw the student in me and took me serious in my graduate school years. To my main supervisor Lone Overby Fjorback, thank

you for not being risk adverse, for pushing boundaries and for tirelessly working towards bringing good mental health to all people. To my co-advisor, Lise Juul, for her gentle caring, diligence, attention to detail, and guidance. To all my colleagues at the Danish Center for Mindfulness, who in various ways have supported me in this journey. Finally, I would like to acknowledge all the informal caregivers who took part in the research. Without their willingness to sign up, participate, and answer questionnaires this project would not have been able to come about. Their courage, their wisdom and their willingness to be with suffering will forever be part of me.
Thank you all!

Overview

This dissertation investigated the effectiveness, of an eight-week manualized compassion cultivation training (CCT) for informal caregivers of people with a mental illness, on decreasing psychological distress. Part one of the dissertation takes the reader through the background of informal caregivers, interventions, compassion-based training programs and mediators of change. Part two, the current state of the field is explored and highlighted regarding informal caregiver interventions, compassion-based interventions and mediators of change. Limitations and gaps within the field is also addressed. Part three takes the reader into the study design, the aim and the methodology of the RCT. Part four present the three research articles: 1) The effect of mental health interventions on psychological distress for informal caregivers of people with mental illness on: A systematic review and meta-analysis, 2) Effect of a compassion cultivation training program for caregivers of people with mental illness in Denmark: A randomized clinical trial and 3) Mediators for the effect of compassion cultivating training: A longitudinal path analysis in a randomized controlled trial among caregivers of people with mental illness. Part five provides a summary of the findings, including implications for future research, methodological considerations and strengths and limitations. Part six includes a beyond the scope of the Ph.D. project and a lastly a conclusion.

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List of research articles

This work led to the following three research papers:

I. Hansen, N.H., Bjerrekær, L.A., Pallesen, K.J., *Juul, L., & *Fjorback, L.O. (2021). The effect of mental health interventions on psychological distress for informal caregivers of people with mental illness on: A systematic review and meta-analysis (ready for submission).
(*shared last authorship)

II. Hansen, N. H., Juul, L., Pallesen, K. J., & Fjorback, L. O. (2021, Mar 1). Effect of a Compassion Cultivation Training Program for Caregivers of People With Mental Illness in Denmark: A Randomized Clinical Trial. *JAMA Netw Open, 4*(3), e211020. https://doi.org/10.1001/jamanetworkopen.2021.1020 (published)

III. Hansen, N.H., Fjorback, L.O., Frydenberg, M., & Juul, L. (2021). Mediators for the effect of Compassion Cultivating Training: A longitudinal path analysis in a randomized controlled trial among caregivers of people with mental illness (submitted and has received a finalized review process. Awaiting final decision, in Frontiers in Psychiatry - Psychological Therapies).

List of Abbreviation

CCT – Compassion Cultivation Training
SCL- 5 - Symptom Checklist Five
SCS-12 - Self-Compassion Scale- 12
PSS - Perceived Stress Scale
ERQ - Emotion Regulation Questionnaire
FFMQ-15 - Five Facet Mindfulness Questionnaire-15
MCS - Multidimensional Compassion Scale
WHO - World Health Organization
MRC - The Medical Research Council
RCT – Randomized Controlled Trial
CBT - Cognitive Behavioral Therapy
KBM - Kindness-Based Meditations
LKM - Loving Kindness Meditation
CM - Compassion Meditation CM
CFT - Compassion Focused Therapy
MBCT - Mindfulness Based Cognitive Therapy
CBCT Cognitively-Based Compassion Training
MSC - Mindfulness Self Compassion
MAT – Meditation Awareness Training,
MET, Motivational Enhancement Therapy
PTSD – Post Traumatic Stress Disorder
IVP – Intimate Violent Partner
MBSR- Mindfulness-Based Stress Reduction
MBI - Mindfulness-Based Interventions
MDD - Major Depressive Disorder
DASS - Depression Anxiety Stress Scale
BRS - Brief Resilience Scale
WHO-5 - The World Health Organization Five Well-Being Index
SOCS-S and SOCS -O - Sussex-Oxford Compassion Scale for Self and Other

Preface

It is important to include the work that lies before thisPh.D. project. In 2016, very few people were talking about manualized compassion-based training programs in Denmark, let alone taking a course that would help individuals train compassion for their own and others suffering. That same year, Aarhus University, Department of Clinical Medicine, Danish Center for Mindfulness offered the very first Compassion-based intervention, called the Compassion Cultivation Training (CCT) program to self-selected paying participants. This was done to answer one simple question: Was a compassion training course in Denmark feasible?

We translated all course materials into Danish and offered the CCT course. Twelve participants signed up for that very first course with majority of them being healthcare professionals (psychologists and doctors). We collected pilot data, which served two functions: 1) testing of selected measurements for the Ph.D. and 2) did the intervention improve participants mental health? We collected data on 101 self-selected and self-paying participants from 2016-2018. We found that the CCT course yielded a completion rate of ninety-three percent and eighty-four percent completed six weeks or more sessions of the eight-week program. Fifty-four participants were given self-report questionnaires and of those less than fifty percent answered pre-post scores. The included measures were the Symptom Checklist Five (SCL-5) (Parloff, 1954), the Self-Compassion Scale (SCS-12) (Raes et al., 2011), the Perceived Stress Scale (PSS) (Cohen, 1983), the Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003), the Five Facet Mindfulness Questionnaire (FFMQ-15) (Baer et al., 2006) and lastly, we translated, using the World Health Organizations guidelines for translating self-report measures, the Multidimensional Compassion Scale (MCS) (H. Jazaieri, 2018). Results showed a statistically significant effect on self-compassion, but not on any of the other scales. We speculated that the lack of effect might be due to the fact that the people who enrolled in the CCT course were mainly high functioning people with an interest in, or an already established mindfulness and/or compassion

practice. We concluded that the CCT course was feasible and acceptable in Denmark and decided to use another primary outcome measure and to include a self-report measurement measuring overall well-being.

Parallel to this process I was collaborating with The Mental Health Fund (Psykiatrifonden), in writing a book on compassion. The book provides the reader with an overview of compassion, the science and practice of compassion and information on different compassion-based interventions. The book was published in 2017 and called Compassion: Lær at rumme svære følelser (Compassion: Learn to be with difficult emotions) (Hansen, 2017).

This laid the groundwork for the Ph.D. project, which is a novel line of research here in Denmark regarding the effectiveness of a compassion-based intervention for informal caregivers of people with a mental illness on decreasing psychological distress.

Background

Mental health

Poor mental health is a growing problem (World Health Organization, 2021). The association between poor mental health and poor physical health is documented and the cost to society is grave (Prince et al., 2007). It is confirmed that mental illness is a public health issue as serious as cancer and heart disease (Keyes, 2014). The World Health Organization (WHO), defines mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" (World Health Organization, 2021). Three different components of mental health has been identified: 1) emotional well-being, 2) psychological well-being and 3) social well-being (Keyes, 2006). Emotional well-being includes feeling happy and satisfied with one's life, psychological well-being includes liking oneself, having good and healthy relationships with others, and social well-being includes feeling like one is contributing to society and feeling connected to a community (Keyes, 2006)

Informal caregivers

Informal caregivers may be defined as a family member, who provides unpaid care to a loved one, and who play an essential role in the healthcare system (MRC, 2010). Approximately one in four people provide informal care to a loved one (WHO, 2021), and as much as 50% of caregivers may be at risk of developing depression, anxiety and stress. (Clark et al., 2014; Dharmawardene et al., 2016; Sorrell, 2014; Stansfeld et al., 2014). Informal caregiving has come about, as a result of people living longer, and the deinstitutionalization of the health care system. The formal care that once was provided by nurses and other healthcare personnel has now, to a large degree, been given to family members. Caregivers become "hidden patients" (Lancet, 2017) and interventions that provide caregivers with the skills necessary to take care of their own mental health and increase their health-related quality of life is recommended (Sörensen et al., 2002). In Denmark, psychiatric disorders make up the largest disease burden. Thirty-eight percent of the adult population, categorize themselves as an informal caregiver of someone with a mental illness. Sixty-one percent experience psychological distress (Psychiatry, 2020) and it is estimated that $9.17 billion make up the direct and indirect cost of poor mental health in

Denmark (Psykiatrifonden, 2020). Taken together, these findings provide impetus to study interventions to support informal caregivers, particularly preventive interventions that increase their psychological and physical health, thereby decreasing the economic burden on society (Jacobsen, 2011).

Interventions

The definition of a complex intervention is one that "contains several interacting components" (Craig et al., 2008). Complex interventions are often difficult to evaluate and in 2000 The Medical Research Council (MRC) was established. The MRC created a framework to aid researchers in recognizing and supporting relevant methods (Craig et al., 2008), and suggested that some of the important questions to ask when evaluating complex interventions were: 1) are they effective in everyday life of the target population and 2) what are the mediators of the intervention that is creating the effect (Craig et al., 2008)? Preventive interventions target's those vulnerable to mental illness, such as informal caregivers, and compassion-based interventions are an example of a complex intervention.

What is Compassion?

Compassion includes a range of psychological, social and physiological processes (Gilbert, 2017) and is embedded within structures of society such as; medical ethics, departments of health, religion, and educational systems (Strauss et al., 2016). There is a growing research interest in compassion and compassion training but a lack of consensus remains as to the definition of compassion and the lack of psychometrically robust measurements of the construct makes it difficult to assess in empirical research (Strauss et al., 2016). Compassion has been defined in many different ways but there does seem to exist some general consensus that compassion "involves feeling for a person who is suffering and being motivated to act to help" (Strauss et al., 2016). In a review of the numerous definitions of compassion, authors suggested an alternate definition of compassion, involving three processes, namely: a cognitive, affective, and behavioral process, which included five elements that related not only to compassion for others but also to compassion for self. The five elements embedded in the definition were to: 1) recognize that suffering is present, 2) understand that the universality of suffering is a human experience, 3) feel empathy for the person suffering and connect with their distress, 4) tolerate uncomfortable feelings aroused in response to the person who is suffering, thereby remaining open

towards and accepting of the person suffering and 5) feel motivated to act to relieve the suffering (Strauss et al., 2016). Another multidimensional definition of compassion came from Geshe Thupten Jinpa, Tibetan scholar and His Holiness Dalai Lama's principle English translator. He suggested a multidimensional definition of compassion as: "Becoming aware of suffering, within oneself and others, and feeling the wish or motivation to relieve the suffering" (Jazaieri, 2012). The multidimensional definition involves four components: being aware of present suffering (cognitive component), having sympathetic concern for the person suffering (affective component), feeling the wish to see the relief of the suffering (intentional component) and having a responsiveness to relieve the suffering (motivational component) (Jazaieri, 2012; Kirby et al., 2017). This definition of compassion is also the one underlying one of the compassion-based interventions called Compassion Cultivation Training (CCT). This program, amongst others, has been developed with the intention to practice and cultivate compassion (Kirby et al., 2017).

Research on compassion

The last two decades has seen a growing interest in understanding and exploring how compassion is trained, defined, measured and implemented into various settings (Kirby et al., 2017). Clinical scientists are examining the impact compassion training has on the emotional experience, psychological flexibility and emotion regulation (Goldin, 2017). Regarding the psychological processes of compassion, a systemic review investigating the impact of compassion training on the treatment of psychopathology, concluded that compassion interventions might be effective in treating a broad array of mental health concerns. Results suggested an improvement in psychological distress, levels of positive and negative affect, the frequency and intensity of positive thoughts and emotions, empathic accuracy, and interpersonal skills (Shonin et al., 2015).

Regarding the social processes of compassion, studies found that completing a brief compassion exercise increased feelings of social connection and positivity towards strangers (Hutcherson et al., 2008). Moreover, research regarding the physiological processes, showed that feeling compassionate had physiological effects such as; decreased heart rate (Gu et al., 2017), lowered cortisol reactivity and blood pressure, and increased heart rate variability (Cosley et al., 2010). Thus far, research on compassion training point to the potential of being a tool to enhance and sustain mental and physical health (Goldin, 2017; Hoffmann et al., 2010; Kirby et al., 2017), though very little is known regarding

the mediators of change.

The importance of understanding mediators of change

There is a paucity of research on the mediators of change in compassion-based programs. As suggested by the MRC framework, understanding what the active ingredients of an intervention are, is important when evaluating the effectiveness of complex interventions. Mediators are an intervening variable that may statistically account for the relationship between the independent and dependent variable (Kazdin, 2007). Mediators may not, though, explain how the change happened. Mediator analysis is often the first step leading up to investigating mechanisms of change. Mechanisms, compared to mediators, is the process, which is responsible for the change and helps explain how the change happened and how it came about (Kazdin, 2007). Limitations of research on mediators include very few studies using an underlying theory to guide the research question, timelines between a proposed mediator and outcome are often not established, and a variety of statistical test are used to analyze mediators (Kazdin, 2007). Kazdin has therefore proposed a framework for investigating and analyzing mediators including seven points: 1) Use theory as a guide, 2) include measures of potential mediators in treatment studies, 3) establish the timeline of the proposed mediator or mechanism and outcome, 4) assess more than one mediator or mechanism, 5) use designs that are able to evaluate the mediators and mechanisms, 6) examine consistencies across different types of studies, and 7) intervene to change the proposed mediator or mechanisms (Kazdin, 2007).

With this knowledge, we now turn to the current state of the field regarding informal caregiver interventions, compassion-based interventions in general and manualized compassion-based interventions specifically. Lastly, we address the current state of the field on mediators of change within mindfulness-based interventions.

Current state of the field

Caregiver interventions

There are a multitude of interventions for caregivers of people with a mental illness. Research into the effectiveness of interventions for caregiver mental health is inconclusive and confusing. Systematic reviews and meta-analyses of intervention programs for caregivers have found conflicting evidence for the effectiveness of interventions programs on psychological distress (Knight et al., 1993; Sörensen et

al., 2002). Early reviews looked at different types of interventions (i.e. social support, psychoeducational, behavioral, psychotherapy and respite groups) calling for more controlled evaluations of the different interventions. Others found that while caregivers would state that an intervention had been effective there was little evidence of change when measures of effect on psychological distress were used or when the study design included a control group (Knight et al., 1993). Based on these early systematic reviews, a meta-analysis was undertaken, aiming to understand the effectiveness of interventions for caregiver distress in general. Results showed a moderately strong effect for respite care and for individual psychosocial interventions, while group psychosocial interventions showed a small but positive effect (Knight et al., 1993). Subsequent systematic reviews and meta-analysis tended to divide the effectiveness of interventions based on type of mental illness. Broadly there were two categories: 1) caregiver interventions for people with dementia, and 2) caregiver interventions for people with severe mental illness (usually including, schizophrenia, psychosis, bipolar disorder, and depression).

Regarding the first broad category, a systematic review updating the literature of interventions for caregivers of older adults, found that psychoeducational and psychotherapeutic interventions presented consistent short-term effect on all outcome measures, and that the effects were smaller for caregiver interventions of people with dementia. Results further suggested that setting, number of sessions, care-receiver age, gender, initial burden and the caregiver-care-receiver relationship were all characteristics moderating observed effects (Sörensen et al., 2002). As research into different types of interventions modalities flourished, a meta-analysis was undertaken, investigating the effect of the different intervention modalities. Results suggested that on average the effectiveness of caregiver interventions was significant but small on subjective well-being, depression, and knowledge of symptoms. Only multicomponent interventions reduced the risk of institutionalization, and psychoeducational interventions with active participation had the greatest effect (Pinquart & Sörensen, 2006). The following year a systematic review investigated the effect of evidence-based interventions for decreasing psychological distress in informal caregivers (Gallagher-Thompson & Coon, 2007). Three categories emerged 1) psycho-educational, 2) psychotherapy and 3) multicomponent interventions and results suggested that psychoeducational interventions that focused on skills training, anger and depression management were effective in reducing informal caregiver psychological distress.

Moreover, in the psychotherapy category, Cognitive Behavioral Therapy (CBT) was effective and interventions in the multicomponent category showed effect when two different theoretical approaches were included (Gallagher-Thompson & Coon, 2007). In 2013 a systematic review looked at the evidence of psychological interventions and similar results emerged as in the review six years prior. This time though, effect for technology-based interventions was also found (Elvish et al., 2013). Lastly, a current systematic review in this first broad category, reported that psychoeducational interventions improved caregiver's knowledge of illness, helped develop problem-solving skills, and facilitated social support. Moreover, results suggested that technology-based interventions significantly affected burden, while group-based interventions affected depression, anxiety, insomnia, burden, self-efficacy and quality of life (Frias et al., 2020).

The second broad category of informal caregiver intervention studies, were caregivers of people with severe mental illness. The results of a systematic review investigating which components of an intervention was effective in decreasing informal caregiver psychological distress, found that while interventions were effective in decreasing one or more of the selected outcomes, they were not able to find any evidence to suggest that the presence or absence of different components rendered an intervention more or less effective (Lobban et al., 2013). The results of another systematic review found that psychoeducation, support group, and bibliotherapy were effective and showed benefits on psychological distress at 6-month follow-up. The quality of the evidence ranged from low to very low (Yesufu-Udechuku et al., 2015). A third systematic review and meta-analysis concluded that psychoeducation was superior in reducing caregiver subjective burden, negative caregiving experience, and expressed emotion and that findings of the effectiveness of interventions were ambiguous on the outcome for caregiver well-being. In addition, effects beyond pre and post measures were not possible due to lack of available data. Compared to the results found in earlier years a meta-regression revealed no association between intervention modality, contact time, duration and outcomes (Sin et al., 2017). Both broad categories revealed inconsistencies within the literature as to which intervention modality and delivery mode is effective in decreasing informal caregiver psychological distress, and what components of an intervention make it effective.

Compassion-based interventions

Research into training compassion and a compassionate response to suffering has flourished within the last decade. Within the last 10-12 years manualized compassion training programs have emerged and research into the effectiveness of such interventions have been undertaken. To get a sense of whether compassion is effective in addressing psychological distress and well-being Hoffman et al., (2011) published a narrative review on the potential for Loving Kindness Meditation (LKM) and Compassion Meditation (CM) interventions to be utilized as psychological interventions. LKM is a practice of cultivating an inner feeling of love and connectedness with self and all other sentient beings (Salzberg, 2011), while the CM practice is the practice of cultivating a willingness to be with one's own and others suffering and feeling a wish or an intention to relieve that suffering. The results of the narrative review suggested that LKM and CM interventions showed promise for reducing negative affect such as anxiety and stress and improving positive affect (Hoffman et al., 2011). The authors further hypothesized that CM and LKM interventions might be particularly helpful in treating relationship problems and depression and counteract the challenges faced, by not only professional healthcare providers, but informal caregivers of people with long-term caretaking needs (Hoffman et al., 2011).

Three years later a systematic review and meta-analysis was published on the effects of kindness-based meditations (KBM) on health and well-being (Galante, 2014). They included twenty-two RCTs with healthy adults. Ten RCTs included an LKM practice with the shortest duration being a seven-minute single taped session to eight-weeks of practice. Eight RCTs included at CM practice with the shortest duration being between two week and lasting up to eight weeks. One RCT included a stress management program with forgiveness being the goal of the intervention for eight weeks, one RCT practiced the *Four Immeasurables* and *Tonglen* for eight weeks and one RCT practiced mindful self-compassion for eight weeks (Galante, 2014). Training in the *Four Immeasurables* includes training in: a) loving-kindness, b) sympathetic joy, c) compassion, and d) equanimity. These practices may be viewed as a practice of altruistic motivation (Wallmark et al., 2012). The practice of *Tonglen*, which means to give and receive is considered an advanced form of compassion meditation. The training involves breathing in the suffering of all sentient beings on an in-breath, transforming the suffering to compassion and breathing out compassion for all sentient beings on the out-breath (Chödrön, 2001). Results suggested that KBM interventions were moderately effective in decreasing depression, and increasing self-compassion, compassion and mindfulness (Galante, 2014).

One year later, a systemic review on the impact of CM and LKM interventions for treatment of psychopathology was undertaken (Shonin et al., 2015). In this systematic review, RCTs and non-RCTs, child and adolescent populations, and studies published after March 2013 were included. Twenty studies included a LKM intervention, seven studies included a CM intervention and five studies included a mixed LKM and CM intervention (Shonin et al., 2015). The duration of all included studies was between four-eight-weeks. Fourteen of the studies used an RCT design, three used a non-randomized design and three trials did not have a control group. Eighteen of the studies included adult participants of healthy, subclinical or clinical diagnostic status, and two studies included adolescents at risk for psychopathology (Shonin et al., 2015). Taken together, results suggested that CM, LKM, or combined CM and LKM interventions were effective in treating an array of mental health issues. Improvement in psychological distress, levels of positive and negative affect, the frequency and intensity of positive thoughts and emotions, empathic accuracy, and interpersonal skills were seen. The conclusion was that the interventions may have applications as preventive interventions (Shonin et al., 2015).

In 2017 a systematic review and meta-analysis of the current state and knowledge of compassion-based interventions was published (Kirby et al., 2017). Here, all studies included had to be 1) interventions that purposefully sought to train compassion or self-compassion, 2) had to be longer than one session, 3) published in a peer-reviewed journal, 4) written in English, 5) an RCT, 6) only adults included and 7) had to have a self-report measure of compassion or self-compassion (Kirby et al., 2017). A total of 21 RCTs were included in the meta-analysis with five RCTs utilizing the Mindful Self-Compassion (MSC) program, six RCTs were based on combined LKM and CM practices, three RCTs were based on Compassion Focused Therapy (CFT), two RCTs were informed by the Mindfulness Based Cognitive Therapy (MBCT), two RCTs employed the Compassion Cultivation Training (CCT) program, and one RCT was based on the Cognitively-Based Compassion Training (CBCT) program (Kirby et al., 2017). The results of the meta-analysis suggested a moderate effects size for the compassion-based interventions on pre to post measures on mindfulness, compassion and self-compassion and decreased scores of depression, anxiety, and psychological distress. Significant moderate effects were also found for well-being (Kirby et al., 2017). The results of the systematic reviews and meta-analysis over the last ten years suggest that compassion-based training programs may

indeed be thought of as preventive interventions that may decrease psychological distress and increase overall wellbeing.

Manualized compassion-based interventions

Over the last decade a number of manualized compassion-based training programs have been developed and research has been conducted to understand the effectiveness of these programs on psychological distress and well-being. The first main program is Compassion Focused Therapy (CFT), developed by clinical psychologist Paul Gilbert. CFT is an individual therapeutic intervention aimed at strengthening self-compassion, compassion for others, receiving compassion from others and accessing affiliative feelings (Gilbert, 2009). CFT may be used in populations with chronic disabilities and complex psychiatric illnesses where shame and self-criticism are central to the disorder. The second main program is the manualized Mindfulness Self Compassion (MSC), program developed by researcher Kristen Neff and clinical psychologist Christopher Germer. The MCS program focuses on educating participants on self-compassion, on training self-compassion for their own suffering and to help participants develop their own self-compassionate voice (Kirby, 2017; Neff & Germer, 2013). The third main program is the Cognitively Based Compassion Training (CBCT). This is a manualized program and was developed by Lobsang Tenzin Negi, Charles Raison and colleagues at Emory University, to aid in developing emotional resilience to undergraduate students at the university (Kirby, 2017). Table 1 provides an overview of the research on the main compassion-based interventions excluding the Compassion Cultivation Training (CCT) program, which will be explained in more detail below.

Table 1. Manualized Compassion-based Interventions

Author	Intervention	Population	Follow-up	Results	Limitations
Neff et al., 2013	8-week MSC compared to waitlist control group	Healthy, primarily well-educated women with an established mediation practice (N=51)	6-and-12-months	Improvement on self-compassion, compassion, depression, mindfulness, life satisfaction, stress and avoidance. No improvements on connectedness or happiness	Only 15 out of 24 answered the 6-and-12 months follow-up No active control
Friis et al., 2016	8-week MSC compared to waitlist control group	Patients with type 1 or type 2 diabetes (N=63)	3-months	Improvements self-compassion, depression and diabetes distress	No active control group

				(HBA1c)	
Torrijos et al., 2021	8-week MSC compared to CBT	Chronic pain patients (N=123)		Improvements on pain interference, pain acceptance, self-compassion and anxiety	
Braehler et al., 2013	16-week CFT compared to treatment as usual	Psychosis (N=40)	None	Improvements on depression and marginalized increased, compassion	No active control group
Kelly et al., 2016	12-week CFT compared to treatment as usual	Eating disorder (N=22)	None	Improvements on self-compassion, fear of receiving compassion from others, and shame.	Small sample size
Sommers et al., 2018	9-week CFT Self-help book compared to waitlist control group	Women with low well-being (N=242)	3-and-9-months	Improvements on well-being	No active control group
Sadeghi et al., 2018	8-week CFT compared to Motivational Enhancement Therapy (MET)	Women suffering from breast cancer (N=30)	None	Decreased depression and anxiety	Small sample size
Daneshvar et al., 2020	8-week CFT compared to control group	Women with PTSD due to IPV (N=42)	None	Improvements on avoidance and meaning-with-life	No active control group
Desbordes, 2012	CBCT compared to Meditation Awareness Training (MAT) and a control group that received information and discussions on health	Non-clinical adult population (N=51)	None	Increased Amygdala activity in CBCT group Decreased depression in CBCT group Decreased amygdala activity in MAT group	
Dodson et al. 2015	CBCT compared to waitlist control group	Women with breast cancer (N=33)	4-months	Reduction in depression, avoidance and fear of relapse Increased vitality mindfulness, No change in cortisol and perceived stress	No active control
Mascaro, 2016	CBCT compared to waitlist control group	Medical students (N=32)	None	Increased compassion Decreased loneliness and depression	No active control

Gonzalez-Hernandez., 2018	CBCT compared to treatment as usual	Women with breast cancer (N=56)	6 -months	Reduced stress related to fear of relapse Increased self-kindness, common Humanity, self-compassion, mindful observation and acting with awareness, Results maintained at 6-month follow-up	
Poehlmann-Tynan, 2019	CBCT compared to waitlist control group	Parents of young children (4 months - 5 years) (N= 39)	None	Decreased cortisol in children and parenting stress	No active control group

MSC – Mindful Self-Compassion, CFT – Compassion Focused Therapy, CBCT – Cognitively Based Compassion Training Meditation Awareness Training, MET, Motivational Enhancement Therapy, PTSD – Post Traumatic Stress Disorder, IVP – Intimate Violent Partner

Compassion Cultivation Training (CCT) program

Compassion Cultivation Training (CCT) is a manualized program, developed by Geshe Thupten Jinpa and colleagues at Stanford University in 2009. The program focuses on practicing compassion towards self and others. It is developed to promote a person's ability to connect and feel kindness towards others by understanding both their own and others suffering (Jazaieri, 2012). Two previous RCTs have been conducted on the CCT intervention with populations from the general public. Preliminary research findings on CCT have yielded several results. In 2012 an RCT was conducted with 100 healthy adults randomized into either the CCT intervention group or a waitlist control group. Result of the eight week compassion training resulted in 1) significant decreases in fears of compassion for self and others and from receiving compassion from others, 2) changes in emotion experience such as increased positive affect, decreased negative affect and perceived distress, 3) significant changes in emotion regulation such as increased cognitive reappraisal and acceptance and decreased suppression of emotion, and 4) significant changes in cognitive regulations such as increased mindfulness skills, decreased negative rumination and mind-wandering (Goldin & Jazaieri, 2020; Jazaieri, 2012; Jazaieri et al., 2014; Jazaieri et al., 2018). Results further indicated that when participants had practiced a compassion meditation that same day, the probability of the participant having both an other-focused caring behavior and self-caring behavior increased substantially (Goldin, 2017).

In 2017, a pilot study with no control group sought to understand whether the CCT program could reduce burnout and increase mindfulness and self-compassion of healthcare workers employed at a hospital (Scarlet et al., 2017). Result of the pilot study indicated that the CCT program did not decrease burnout and interpersonal conflict, but did increase mindfulness, self-compassion, and job satisfaction (Scarlet et al., 2017).

In 2018, a RCT on the CCT program (Brito-Pons, 2018) was designed with two goals in mind: 1) to assess the impact of CCT compared to a waitlist control on several self-report measures of psychological well-being, and 2) to understand whether there is a difference when practicing compassion implicitly like in the Mindfulness-Based Stress Reduction (MBSR) program or explicitly as in the CCT program. Results related to the first part of the study found that participants in the CCT group, showed significant improvements on increased satisfaction with life, happiness, mindfulness, self-compassion and compassion. Further improvements were observed with a decrease in depression and stress. Results related to the second non-randomized part of the study (comparing the data from the RCT with data from a group of individuals who had received the MBSR program) observed that both the MBSR and CCT program were effective in enhancing psychological well-being and increasing mindfulness and compassion. Moreover, the CCT program had a greater impact on developing empathic concern and identification with all humanity (Brito-Pons, 2018).

Lastly, in 2019, a pilot study with a mixed-methods design and no control group, evaluated the impact of a CCT elective course for medical students' stress management skills, mindfulness, and compassion (Weingartner et al., 2019). Results on factors of mindfulness showed significant improvements in skills related to accepting without judgment and in observing. The qualitative data suggested that students found the CCT elective course rewarding. Students reported that they used mindfulness, meditation, and compassion skills outside the course and reported that the skills strengthened interpersonal interactions, including with their patients. The students also described how the training helped them address major personal, academic, and clinical stressors (Weingartner et al., 2019). This body of research suggests that the CCT program may benefit mental health by decreasing psychological distress and increasing overall well-being, yet knowledge regarding mediators of change of compassion-based training program is lacking.

Mediators of change of Mindfulness-Based Interventions (MBI's)

Only one study to date, has investigated the mediating variables of a compassion-based intervention. The intervention was a self-help book based on the compassion focused therapy (CFT) approach (Sommers-Spijkerman et al., 2018) (but not the actual CFT approach as it was developed for individual therapy (Gilbert, 2009). The study included a healthy population with low well-being scores. The results of the single mediation model showed that changes in well-being and psychological distress in the intervention compared to the control group, became significantly mediated by the improvements in self-reassurance and self-criticism. Moreover, changes in positive affect showed to be a significant mediator of the intervention effect on well-being and depressive symptoms. Changes in negative affect showed to be a significant mediator of the intervention effect on well-being and anxiety symptoms. In the multiple mediation model results showed that the effects of the intervention on well-being was only mediated through improvements in self-reassurance. Regarding the psychological distress outcome, the impact of anxiety symptoms between the intervention and waitlist group, were found to be simultaneously mediated by pre-post changes in self-reassurance and negative affect. Changes in positive affect was the sole significant mediator of the intervention effect on depressive symptoms. These results indicate that all four variables: self-reassurance, self-criticism and positive/negative affect, were mediators of the effectiveness of the intervention, though it seemed that the mechanisms that mattered most varied depending on the outcome (Sommers-Spijkerman et al., 2018).

As this was the only study, to our knowledge, looking at mediating variables for compassion-based programs with three timepoints, we also looked to research on mediators and mechanisms conducted on the eight-week Mindfulness Based Stress Reduction (MBSR) (Kabat-Zinn, 1982) program developed by Jon Kabat-Zinn in 1979 and the Mindfulness-Based Cognitive Therapy (MBCT) developed by Segal, Williams and Teasdale (Fresco et al., 2007). We choose these programs as they were of similar duration, format, and included meditation practices. While there are many similarities between mindfulness-based and compassion-based programs, one of the main differences is whether the explicit focus and training is on mindfulness or compassion (Brito-Pons, 2018)

Several systematic reviews (Alsubaie et al., 2017; Gu et al., 2015; van der Velden et al., 2015) have been conducted on the MBSR and MBCT program with an aim to understand what the underlying mediators and mechanism are. This, in order to better understand what leads to beneficial psychological outcomes in participants. In a systematic review of the mechanism of MBCT in RCT studies with people with major depressive disorder (MDD), results showed evidence supporting the mediating role of mindfulness, compassion, rumination, worry and meta-awareness (van der Velden et al., 2015). Another systematic review of mechanisms of the MBSR/MBCT programs on mental health and well-being outcomes, included RCT or quasi-experimental studies, and found strong evidence for cognitive and emotional reactivity, moderate evidence for mindfulness, worry, and rumination, and insufficient evidence for self-compassion and psychological flexibility (Gu et al., 2015) Results of a third systematic review on the mechanisms of 14 RCT and non-RCT MBSR/MBCT trials, showed that of all the different mechanisms proposed the most consistent finding was that greater self-reported changes in mindfulness mediated clinical outcomes in participants who had psychological problems (Alsubaie et al., 2017). However, a strong limitation of the studies included in the reviews and meta-analysis were that none of them fully met Kazdin's criteria for examining treatment mechanisms (Kazdin, 2007) namely, a clear association between change in the proposed mediator and the proposed outcome, and that change in the mediator precedes change in the outcome (Kazdin, 2007). The studies included some theory, wide variability in measures used, time assessments were not optimal to test mediators and all studies failed to assess that the changes in the mediators preceded changes in the outcomes.

Summery and limitation of the current literature

Research on the effects of informal caregiver interventions on decreasing psychological distress show little consistent evidence. Knowledge regarding which intervention modality and delivery format is most effective, and which intervention components are important in order to bring about change in caregiver psychological distress is lacking. Moreover, while research on compassion-based training programs have established that they are effective in decreasing psychological distress and increase overall well-being in healthy populations and in populations of people with physical and psychological difficulties, they have not investigated the effectiveness of such programs for a high-risk population such as informal caregivers of people with a mental illness. Lastly, while the investigation on mediators

of change has been undertaken on mindfulness-based interventions, there is a paucity of research on mediators of change of compassion-based training interventions and good methodology is lacking.

Current Study Design

Aim of thesis

To address these gaps in the literature, this Ph.D. project aimed to 1) conduct a systematic review and meta-analysis to gain a greater understanding of the evidence regarding interventions and their effect on psychological distress of informal caregivers of people with a mental illness, 2) conduct an effectiveness trial of an eight-week manualized compassion cultivation training (CCT) for informal caregivers of people with a mental illness in a randomized controlled trial and 3) investigate the potential mediators of the CCT program on symptoms of depression, anxiety, and stress.

Research methodology

In the first part of the Ph.D. project, we chose to use a systematic review and meta-analysis design as this design has been placed at the top of the evidence-based medicine pyramid and warrants the most confidence (Murad et al., 2016). While this being true there are several limitations to conducting systematic reviews and meta-analysis. A main limitation is related to the clinical, statistical and methodological heterogeneity of the included studies. This methodological limitation may result in uncertainty and error regarding the results of such systematic review and meta-analysis (Murad et al., 2016).

For the second paper we chose a randomized controlled trial (RCT) including a waitlist control group, which is a common design in evaluating interventions. Based on the evidence-based medicine pyramid, RCTs are right below systematic reviews and meta-analysis (Murad et al., 2016), and while using such a design may overestimate intervention effect, there are other reasons why employing such a design is useful. In using the waitlist control design, we increased the likelihood that participants in the control group would continue to participate in the research project and answer follow-up measurements. This allowed us to collect more data and decrease the chances of high drop-out rates. We also felt that utilizing this design, allowed us to address an ethical dilemma; all informal caregivers were offered the CCT course, the waitlist control groups just received the course later than the intervention group.

We chose self-report measures as it is a common way of collecting data from participants. The strengths of using self-report measures includes being a simple and cost-effective way of collecting data and sending the questionnaires via email allowed us to save time. There are several limitations to using self-report measures including reliability and validity of the measures. Reliability relates to whether the outcomes of the measurements are repeatable and validity relates to whether the instrument measures the variable it is intended to measure (I-Chant A; Chiang; Rajiv S. Jhangiani., 2013).

Self-report measures

Primary outcome measures

The primary outcome measure used was the Danish 42-item version of the Depression Anxiety Stress Scale (DASS) (Lovibond & Lovibond, 1995). The DASS-42 is a self report instrument designed to measure the three related negative emotional states of depression, anxiety and tension/stress. The DASS depression scale can be characterized by a loss of incentive and self-esteem and is also associated with the person perceiving that it is highly unlikely that he/she will reach his/her life goals. The DASS anxiety scale is characterised by a relatively consistent state of anxiety, a persons acute response to fear while also addressing situational anxiety. Lastly, the DASS stress/tension scale is measuring whether a person consistently is feeling overly aroused and also having a low tolerance for becoming frustrated and upset (Lovibond & Lovibond, 1995). Participants are asked to rate whether or not they have experienced the symptoms over the last week and the DASS uses a 4-point frequency scale (eg. “I couldn’t seem to experience any positive feelings all day”, “I found it difficult to relax”, “I felt that I was using a lot of nervous energy”). The DASS is scored by summing up the 14 items relevant for each subscale. The depression subscale score and interpretation is as follows: 0-9 = no evidence of depression, 10-13 = mild depression, 14-20 moderate depression, 21-27 = severe depression. The anxiety subscale score and interpretation is as follows: 0-7 = no anxiety, 8-9 = mild anxiety, 10-14 = moderate anxiety, 15-19 = severe anxiety. The stress subscale score is as follows: 0-14 = no stress, 15-18 = mild stress, 19-25 = moderate stress and 26-33 = severe stress (Gale, 2015). The internal consistency for each of the subscales is high: Depression scale, Chronbach’s α of 0.91, Anxiety scale 0.84, and for the Stress scale 0.90 (Lovibond & Lovibond, 1995).

Secondary outcome measures

The secondary outcome measures were the Perceived Stress Scale (PSS), which measures how stressful a person perceives an event or situation in their lives to be (Cohen et al., 1983). The PSS is a 10 item self-report questionnaire, which uses a 5 point-Likert scale ranging from 0 = never to 4 = very often (Cohen et al., 1983). Participants are asked how often they have felt a certain way in their lives within the last month (e.g. "In the last month, how often have you been upset because of something that happened unexpectedly?", "In the last month, how often have you felt nervous and stressed?", "In the last month, how often have you felt that things were going your way?". Scores can range from 0 to 40 with higher scores indicating higher perceived stress. Reliability measured by the coefficient α was .84 in sample 1, .85 in sample 2, and .86 in sample 3. The PSS is said to have adequate internal and test-retest reliability. We used the Danish version of the PSS-10 for this study. In a review of the psychometric evidence for the PSS, 14,10, and 4 by Lee (2012), the author concluded that "the psychometric properties of the PSS-10 are superior to those of the PSS-14. Therefore, it is recommended that the PSS-10 be used to measure perceived stress, both in practice and research" (pp.126).

Brief Resilience Scale (BRS) is a 6-item scale assessing the ability to bounce back or recover from stress (Smith et al., 2008). Participants answer on a 5-point Likert scale with 1 = strongly disagree to 5 = strongly agree. Questions include "*I have a hard time making it through stressful events" and "*I usually come through difficult times with little trouble. Cronbach's α ranged from .80–.91. We translated the BRS into Danish following the WHO-guidelines for translating measurements (WHO, 2020).

The World Health Organization Five Well-Being Index (Bech, 2012). The WHO-5 index is a short self-reported measure of current mental wellbeing that consists of five statements, which respondent's rate according to the 6-point Likert scale. Respondents' can receive a score between 0-100 and higher scores indicate higher levels of well-being. Questions include in the last two weeks "I have felt cheerful and in good spirits" and "My daily life has been filled with things that interest me". If the score is 50 or below the respondent is at risk of developing stress or depression and in Denmark the mean WHO-5 score is 70 (Topp et al., 2015). Internal consistency was α = .83 and a Danish version of the WHO-5 was used.

Secondary outcome measures and mediator measures

The Emotion Regulation Questionnaire (ERQ) is a 10-item scale designed to measure respondents' tendency to regulate their emotions in two ways: either Cognitive Reappraisal and/or Expressive Suppression (Gross & John, 2003). Respondents answer each item on a 7-point Likert-type scale. An example of cognitive reappraisal is "When I want to feel more *positive* emotion (such as joy or amusement), I *change what I'm thinking about*, and an example of an expressive suppression question is "I control my emotions by *not expressing them*". ERQ cognitive reappraisal (α = .89-.90) and expressive suppression (α = .76-.80) scores showed between acceptable to excellent levels of internal consistency reliability. A Danish version of the ERQ instrument was used.

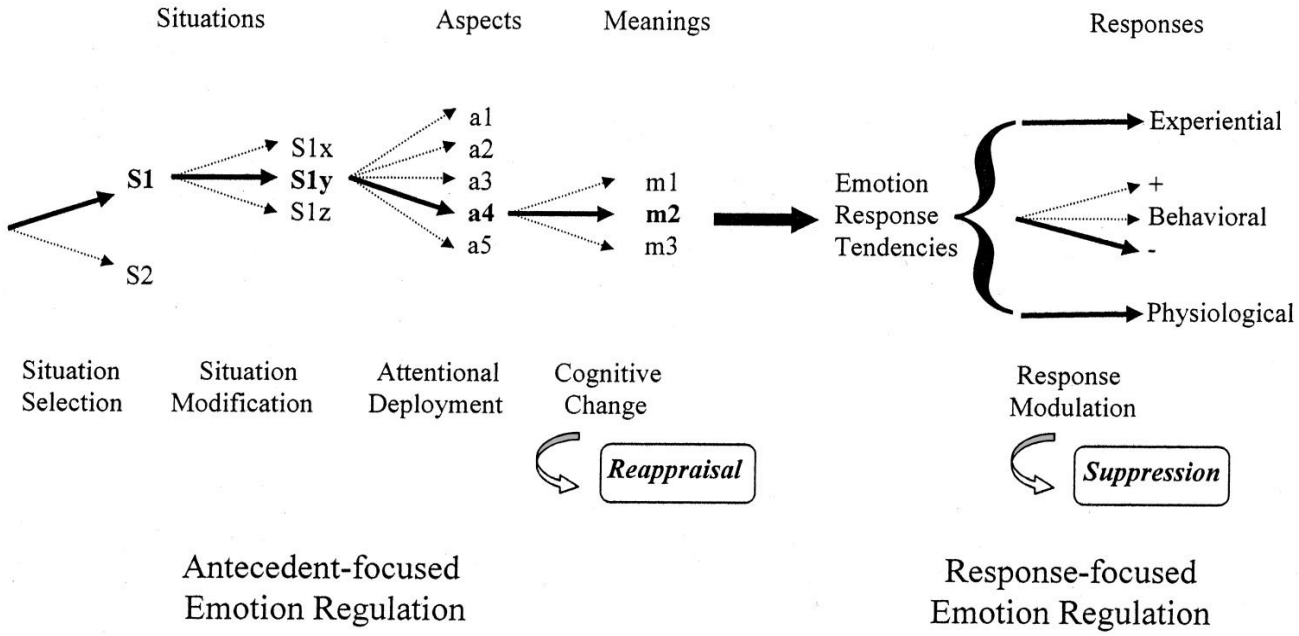
The Self-compassion Scale-SF is a 12-item scale designed to measure participants level of self-compassion (Raes et al., 2011). Respondents answer on a 5-point Likert scale ranging from 1 = almost never to 5 = almost always. Examples of questions include "I try to be understanding and patient towards those aspects of my personality I don't like", and "When I'm going through a very hard time, I give myself the caring and tenderness I need". Correlation r = 0.97 is very high between the SCS (26 items) and the SCS-SF (12) for a total score of self-compassion. The internal consistency between the subscales of the SCS and the subscales of the SCS-SF are not highly correlated and it is therefore recommended that when using the SCS-SF one only computes the total score as the subscale scores are less reliable (Raes et al., 2011). A Danish version of the SCS was used.

The Multidimensional Compassion Scale, is a scale that gives a general measure of compassion with four subscales and a total score. The four subscales are 1) cognitive, 2) affective, 3) intentional, and 4) motivational (H. Jazaieri, 2018). The scale is comprised of 16 questions and respondents answer on a 7-point Likert scale. The scale has excellent internal consistency with a Cronbach's $\alpha \geq .88$. Test-retest reliability over a 6-week time period was excellent (.93). Examples of questions include *"I experience strong emotions when I encounter suffering"* and "Suffering is everywhere". We translated the MCS scale into Danish following the WHO guidelines for translating measurements (WHO, 2020).

The Five Facet Mindfulness Scale (FFMQ-15) is a 15-item scale measuring mindfulness. Respondents answer on a 5-point Likert scale with 1 = never or very seldom true to 5 = very often or always true (Baer et al., 2006). The FFMQ includes five subscales and a total score. The five subscales are 1) observing, 2) describing, 3) acting with awareness, 4) non-judging of inner experience, and 5) non-reactivity to inner experience. Higher scores indicate higher levels of mindfulness. The internal consistency has been found to be adequate for the FFMQ-15 (Gu et al. 2016). Examples of questions include "*I'm good at finding words to describe my feelings*", and "*I tell myself that I shouldn't be feeling the way I am feeling*". A Danish version of the questionnaire was used.

Kazdin's framework for mediational analysis

For the third paper we wanted to investigate mediators of change of the CCT program on symptoms of depression, anxiety and stress and to address some of the methodological concerns when exploring mediators of change. Therefore, we followed Kazdin's framework for mediational analysis. First, we included an underlying theory. The theoretical model used was the Process Model of Emotion Regulation developed by Gross & John (2003). Underlying this model is a concept of an emotion-generating process. This concept considers that feelings start with an evaluation of emotion cues. When a person attends to and evaluates the emotion cue in different ways, the emotion cues then set in motion an organized set of responses including experiential, physiological and behavioral systems. When a person's response tendency arises, the feelings may be regulated in different ways (Gross & John, 2003).



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According to the model, feelings can be regulated at five different points: 1) selection of the situation, 2) modification of the situation, 3) deployment of attention, 4) change of cognitions, and 5) modulation of the experiential, physiological, and behavioral responses (Gross & John, 2003).

The first four responses are called *antecedent- focused:* These are the things we do before an emotion response habit or impulse has become fully activated and changed our behavior and physiological response. The fifth response is called *response-focused:* These are the things we do once an emotion is already in process and after the response habit or impulse have already been created (Gross & John, 2003). One response-focused strategy is called emotion suppression and can be used as an emotion regulation strategy when faced with difficult emotions.

In a study by Gross & John (2003), participants who suppressed their emotions, produced feelings of inauthenticity, masked their inner feelings and felt confused about what they were feeling. They were less successful at mood repair, viewed their emotions less favorably and accepting, experienced more

negative emotions and less positive emotions, were more reluctant to share how they felt with others and avoided close relationships (Pendry & Wright, 2016).

A main intention behind compassion-based interventions is to train the capacity to be with suffering in a skillful manner. Caregivers may not be able to change the fact that suffering is present daily, but they may change how they respond to the suffering. If caregivers learn to embrace their own feelings of inadequacy, hopelessness, powerlessness, fear, guilt and shame, and respond to these feelings with compassion, they may in turn be able to stay present with the suffering of their loved ones without responding in empathetic distress. Therefore, the thoughts behind the application of this theory to compassion-based training was that by increasing the informal caregivers' ability to regulate and accept difficult thoughts and emotions it would allow for less emotion suppression and greater acceptance of their own emotional responses, leading to a decrease in overall psychological distress.

Second, we included four potential mediators: 1) mindfulness, 2) self-compassion and 3) emotion regulation (cognitive reappraisal and emotion suppression). Third, we established a timeline by including four time-points. This allowed us to establish a clear association between changes in the proposed mediator and the proposed outcome, and that changes in the mediator preceded changes in the outcome (Kazdin, 2007). Fourth, by using a randomized controlled trial design that included four time point we were able to evaluate the mediators. Fifth, we were not able to examine consistencies across different types of studies as we were only able to identify one previous study that had investigated mediators of a compassion-based intervention, and the RCT had used different mediators than the current study. Sixth, we did not intervene to change the proposed mediator or mechanisms as this was beyond the scope of this study (Kazdin, 2007).

Research Papers

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The effect of mental health interventions on psychological distress for informal caregivers of people with mental illness on: A systematic review and meta-analysis (paper I)

The effect of mental health interventions on psychological distress for informal caregivers of people with mental illness on: A systematic review and meta-analysis.

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Abstract

Introduction: Informal caregivers of people with a mental illness are at increased risk for developing depression, anxiety and stress, and preventive interventions are needed.

Method: The review was reported in Prospero, Id: CRD42018094454. PsycINFO, PubMed, and Scopus databases were searched June 2019, and the Cochrane Risk of Bias and Jadad scale score was used to assess study quality. Inclusion criteria were: RCTs of informal caregiver interventions regardless of care-receiver mental illness and intervention modality. Interventions should be compared to a waitlist, treatment as usual or active control, taught in real-time by a mental health professional, and include an outcome measure on psychological distress, published in a peer reviewed journal article in English. RCTs were excluded if the intervention was given in dyads (caregiver + care-receiver), limited to the provision of respite care, where the patient sample included a mix of both physical and psychological illness, were unpublished, not peer reviewed, a study protocol, or a dissertation.

Results:
2148 studies were identified, of those forty-four RCT studies met inclusion criteria and thirty-two studies had sufficient data to conduct a meta-analysis including subgroup analysis (N=1899). The

systematic review showed that thirty-one out of forty-four RCTs had effect of the intervention on decreasing psychological distress. Results of the meta-analysis, which included informal caregiver interventions, compared to waitlist, treatment as usual, or active control, regardless of care-receiver mental illness, or intervention modality showed a small effect 0.34 (95% CI -0.55 to -0.13. Heterogeneity of the included studies was high (I^2 78). Subgroup analysis including manualized interventions lasting at least eight-weeks and subgroup analysis that included an active control showed a small effect and low heterogeneity. Lack of active control and long-term follow-up are limitations in most studies.

Conclusion: Evidence supports that several interventions improve mental health in caregivers. Manualized interventions, ≥ 8 weeks with active participation are most effective. Future RCT should improve methodology and research should investigate, which intervention modality is most effective for what kind of caregiver. Future research should clearly specify what the included interventions components are, use longer follow-up times and conduct mediational analyses to better understand what mediators create the effect of an intervention.

Introduction

Informal caregivers of people with a mental illness are at raised risk for mental health difficulties such as depression, stress and anxiety (Clark et al., 2014; Dharmawardene et al., 2016; Sorrell, 2014; Stansfeld et al., 2014). Caregivers become "hidden patients" who are struggling with their own psychological and physical health as well as providing care for someone with mental illness (Lancet, 2017; Lu & Wykle, 2007). Interventions that provide caregivers with the skills they need to take care of their own mental health is recommended (Sörensen et al., 2002).

There is a call for evidence-based interventions for caregivers (Northouse et al., 2010). Systematic and meta-analytic reviews of intervention programs for caregivers have found conflicting evidence for the effectiveness of interventions programs on psychological distress (Knight et al., 1993; Sörensen et al., 2002). Early reviews looked at different intervention modalities calling for more controlled evaluations of the different interventions. Others found little evidence of change when measures of effect on psychological distress were used or when the study design included a control group (Knight et al., 1993). Subsequent systematic reviews and meta-analysis tended to divide the effectiveness of interventions based on type of mental illness. Broadly there were two categories: 1) caregiver interventions for people with dementia/Alzheimer's disease, and 2) caregiver interventions for people with severe mental illness (usually including; psychosis, schizophrenia, psychosis, and bipolar

disorder).

Regarding the first broad category, a systematic review and meta-analysis included 78 RCTs and non RCTs showed a small to moderate effect on the effectiveness of informal caregiver interventions on depression and burden, with psychoeducational and psychotherapeutic interventions showing the most consistent results (Sörensen et al., 2002) Moreover, individual delivery format was more effective than group and number of sessions (approximately 7-9), moderated the observed effects (Sörensen et al., 2002). Results from a later updated meta-analysis included RCTs and non RCTs and suggested that intervention effects were small on burden and depression, and that psychoeducational interventions with active participation had the largest effect. In addition, structured and more intensive interventions showed greater effect than less structured interventions (Pinquart & Sörensen, 2006). The most recent systematic review, including 18 RCTs, investigated the effectiveness of psychoeducational interventions on outcomes such as burden, depression and anxiety. Results showed that technology-based psychoeducational interventions decreases burden, while group-based psychoeducational interventions decreased anxiety, burden and depression (Frias et al., 2020). Future directions include the use of RCTs, more methodological rigor, investigation on how complex interventions relate to treatment effects and investigating mediators of change (Frias et al., 2020; Pinquart & Sörensen, 2006; Sörensen et al., 2002).

The second broad group of caregiver intervention studies, were caregivers of people with severe mental illness (psychosis, schizophrenia spectrum and bipolar disorder). Two systematic reviews and one meta-analysis investigated the effects of caregiver interventions on decreased burden and emotional response, and intervention components such as; duration, delivery mode, structure and content (Lobban et al., 2013; Sin et al., 2017; Yesufu-Udechuku et al., 2015). Results showed that psychoeducation decreased psychological distress and subjective burden, (Sin et al., 2017; Yesufu-Udechuku et al., 2015), and support groups and bibliotherapy were also effective in decreasing psychological distress (Yesufu-Udechuku et al., 2015). No evidence was found to suggest that the presence or absence of different components rendered an intervention more or less effective (Lobban et al., 2013). In addition, the meta-analysis performed by Sin et al. turned out to be inconclusive (Sin et al., 2017) with no statistically significant results found for an association between intervention modality, duration and outcomes (Sin et al., 2017), and the quality of the evidence was rated low.

Limitations included small sample size, substantial heterogeneity, lack of reported data and intervention components. There is a call for better research methodology, including investigating which intervention modality is most effective in decreasing caregiver psychological distress, what intervention components are effective and associated with improved outcomes, greater consensus on the most relevant outcomes, and whether there is an optimal intervention duration (Lobban et al., 2013; Sin et al., 2017). In sum the literature is unclear about the evidence for caregiver interventions, and the literature is expanding requiring updated reviews regularly.

Therefore, our first aim was to update the literature by pooling all the different intervention modalities (e.g. psychoeducational, multicomponent, technology, psycho-social etc.), regardless of care-receiver´s mental illness, and investigate if they showed effect in reducing informal caregiver psychological distress compared to a waitlist, treatment as usual or active control group? Second aim was to address some of the gaps in the literature by conducting several subgroup meta-analyses. We aimed to: 1) investigate which intervention modality showed most effect in decreasing caregiver psychological distress, 2) investigate which type of delivery format showed (group/individual) most effect, 3) investigate intervention components such as; structure (manualized) and duration (≥ 8 weeks) and interventions including non-manualized interventions and ≤ 8 weeks showed most effect 4) investigate the effect of informal caregiver interventions when grouped into two main categories a) dementia/Alzheimer's disease and b) severe mental disorders.

Method

Eligibility Criteria

In conducting this systematic review and meta-analysis, we followed the PRISMA 2020 checklist (Prisma, 2020). We included any randomized controlled trial (RCT) that included any intervention for adult informal caregivers of people with a mental disorder included in the *Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition] [*DSM-5*](APA, 2013) that was real-time and taught by a mental health professional. We defined an informal caregiver as someone who was 18 years or older, and either a spouse, child, partner, parent, and/or other family member to a person with a mental illness. RCTs were included if they included an outcome measure on psychological distress, depression, anxiety, stress, satisfaction with life or emotion regulation. RCTs were included if the

control group was either waitlist, treatment as usual or active control. Lastly, RCTs were included if they were published in a peer reviewed journal article in English. We excluded RCTs where the intervention was given in dyads (caregiver + care-receiver), limited to the provision of respite care, and where the patient sample included a mix of both physical and psychological illness. Finally, RCTs were excluded if they were unpublished, not peer reviewed, or a study protocol.

Identification of studies

We performed a search using PubMed, PsycINFO, and Scopus databases for RCTs published from first available year through June 2019, which reported on interventions for informal caregivers of people with a mental illness. The search terms used were: caregiver* OR "carer" OR "informal caregiver*") AND (interventions* OR therapy OR "psycho-education" OR psychosocial* OR "skills training" OR multicomponent OR group OR internet-based OR "stress reduction" OR "mindfulness training" OR "cognitive behavioral therapy" OR "CBT" OR "acceptance and commitment therapy" OR "ACT" OR "dialectical behavioral therapy" OR "DBT" OR "compassion training" OR psychological OR "support groups" OR psychotherapy OR "One-day" OR "face-to-face") AND ("Mental illness" OR "mental disorders" OR schizophrenia OR "anxiety disorders" OR "bipolar disorders" OR "post-traumatic stress disorders" OR "PTSD" OR depression* OR "personality disorders" OR "mood disorders" OR "eating disorders" OR "obsessive compulsive disorders" OR "OCD" OR "attention deficit hyperactivity disorders" OR "ADHD" OR "autism spectrum disorders" OR Alzheimer's* OR dementia* OR "substance abuse disorders") AND (randomis* OR randomiz* OR "controlled trial") NOT ("literature review" OR interview OR "qualitative study" OR "meta-analysis" OR "systematic review" OR book*). The references of the selected papers were checked for additional eligible papers. The following criteria were applied for selection

Outcome and data collection

The primary outcome was psychological distress, which was measured using a multitude of self-report questionnaires. We chose the outcome that the study author had chosen as primary outcome. If a primary outcome did not measure psychological distress but a secondary outcome did, we included this one instead. If multiple primary or secondary outcomes had been used we chose the first one that the study author had written in the measurement section. If a study had used two different instruments to

measure an outcome (e.g. a self-report questionnaire and an interview instrument) we used the self-report questionnaire. If the study author had not reported which measure was primary and/or secondary, we chose the first one written in the measurement section.

Quality assessment of the included studies

We used Cochrane Risk of Bias (RoB) tool to assess the risk of bias of each study included. Two of the authors (NHH and KJ) completed the risk of bias assessment independently. Any issues that arose was resolved through discussion. Each of the following domains were rated high, low or unclear risk of bias. The domains that were rated included: 1) random sequence generation, 2) allocation concealment, 3) blinding of Participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting and 7) other sources of bias (see table 8 for risk of bias assessment). We also included the Jadad scale score, which rated the quality of each RCT on five domains: 1) was the study described as random, 2) was the randomization scheme described and appropriate, 3) was the study described as double-blind, 4) was the method of double blinding appropriate and 5) was there a description of dropouts and withdrawals. Scores ranged from 0-5, and RCTs with a score between 0-2 was rated low quality and RCTs with a score between 3-5 was rated high quality.

Data Extraction

Searches of the literature was conducted using the search strategy in the above specified databases. Titles and/or abstracts was placed in a database to eliminate the duplicates. Titles and/or abstracts that were not relevant were discarded and the remaining titles and/or abstracts were carefully reviewed to determine their relevance based on the inclusion and exclusion criteria's. Reference lists were also searched to determine if there were additional studies that had been overseen. Once the title and /or abstracts had been sorted, a full text of the studies was retrieved and assessed by two members of the review team (NHH & LB). When a study presented with insufficient data the authors attempted to contact the study authors; some answered right away, others did not respond to our request, while others had retired or passed away. The two authors reviewed the relevant articles independently and disagreements were discussed until a consensus was reached.

The following data was collected: intervention modality, mental illness, number of participants allocated, treatment duration, outcome measured, baseline, post and any follow-up mean value, standard deviations, outcome analyzed, and information for assessment of the risk of bias. Any missing data was requested from study authors.

Analysis Strategy

We extracted means and standard deviations from the included studies at baseline and the last follow-up measure in each study. We estimated within-group changes with standard error (SE) using STATA version 16. A few RCTs used self-report measures where an increase in the measurement indicated effect (e.g. quality of life). When this was the case, we reversed scored so that in all RCTs a reduction was in favor of intervention. We exported these data as well as participants totals (N) included in each group for each RCT into Review Manager 5.3 (RevMan 5.3) and estimated an overall standardized mean difference (SMD) with 95% confidence interval (CI) including all studies, and some subgroup analyses. We performed a random effects analysis as there was high heterogeneity between the studies (Higgins, 2011). We used the statistics I^2 to assess inconsistency. I^2 presents the percentage of the variability in effect estimates due to heterogeneity of intervention effects suggesting that the variation in effect estimates are beyond chance (Cochrane, 2021). To investigate if high heterogeneity was associated with the quality of included RCTs, we conducted a sensitivity analysis and excluded RCTs of poor quality (e.g. either unclear risk of bias on either sequence generation, allocation concealment, incomplete outcome data or selective outcome reporting).

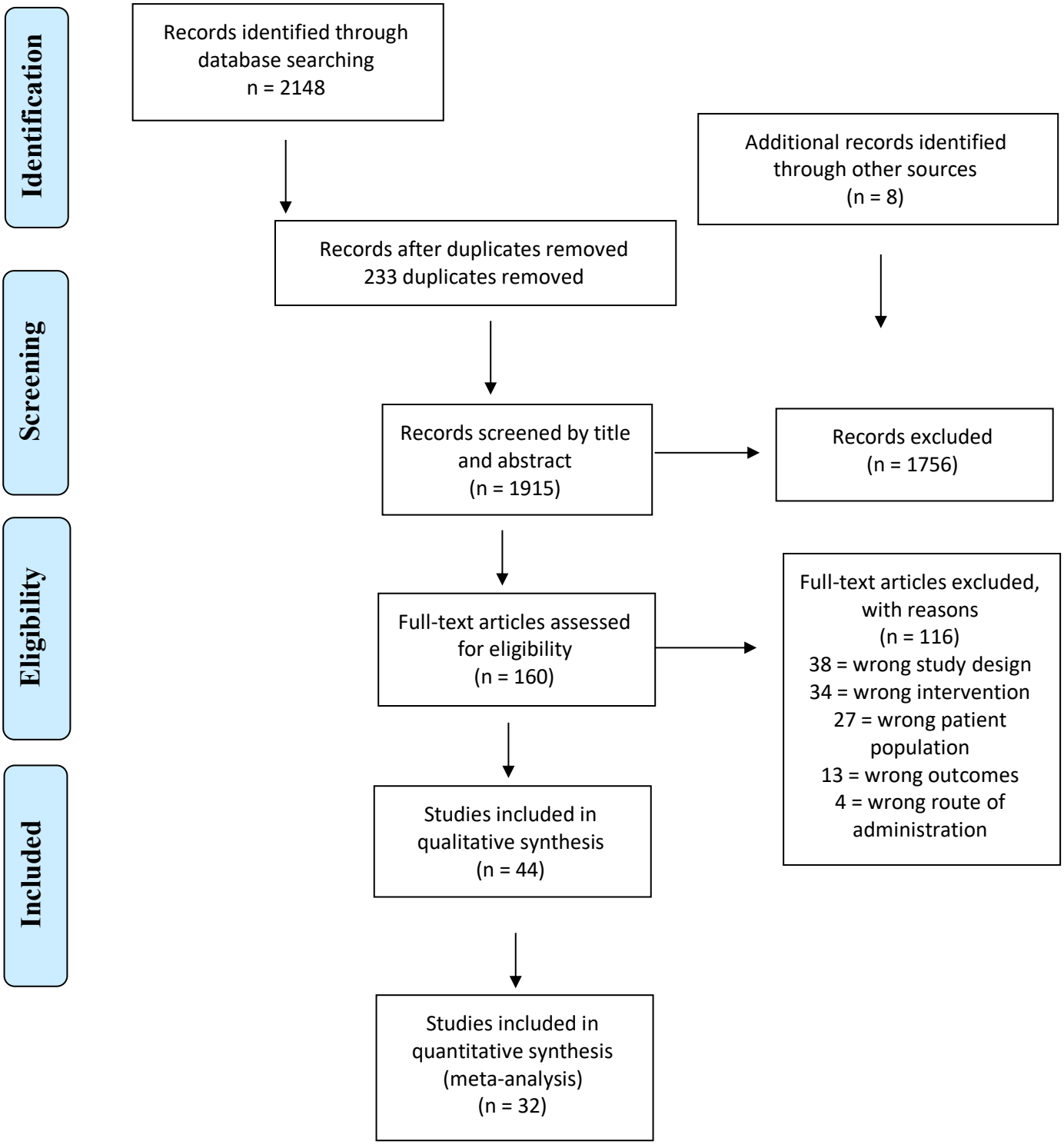
Results

Study selection

The search yielded a total of 2148 studies (Figure 1). There were 233 duplicates removed leaving a total of 1915 studies for title and abstract screening. We also went through reference pages of articles to make sure we had not left out any articles and found another eight articles, which we included. 1755 articles were excluded and 160 full-text articles were assessed for eligibility. A total of 116 were excluded for the following reasons: not meeting inclusion criteria; for study design (n=38); for intervention (n=34); for patient population (n=27); for outcome (n=13) and for route of administration (n=4) (Figure 1). Forty-four studies were considered relevant and included in this review (Table 1). All

forty-four papers were assessed for quantitative data to be used in the meta-analysis. Twelve studies could not be used due to insufficient data, leaving thirty-two studies to be included in the meta-analysis.

Figure 1. Prisma flow diagram



Overview

Overview of all included RCTs is presented in table 1. The intervention group significantly improved mental health compared to a waitlist, treatment as usual or active control group on at least one self-reported outcome in 31 of 44 included studies. Effect is seen of psychoeducation, psychosocial, multicomponent, cognitive behavioral therapy, mindfulness-based and support group interventions. The no effect studies are characterized by being of short duration, having a long-term follow-up period, or being a technology-based intervention.

Table 1. Overview of all included RCTs

Author	Study Population	Intervention	Control group	Measures	Follow-up	Reported conclusion
(Aakhus et al., 2009)	Informal caregivers of psycho-geriatric in-patients	5-hour non-manualized group psychoeducation N=16	Waitlist N=14	GHQ30, IES, GDS-30	End of intervention and 3-month follow-up	No group x time significant effect on self-reported psychological health
(Akkerman & Ostwald, 2004)	Informal caregivers of people with Alzheimer's disease	9-week manualized group cognitive behavioral therapy N=18	Waitlist N=17	HAMA, BAI	End of intervention and 6-week follow-up	Group x time significant effect on self-reported anxiety
(Ata & Doğan, 2018)	Informal caregivers of people with schizophrenia	7-week manualized individual cognitive behavioral stress management N=28	Waitlist N=33	ZCBS, COPE, GHQ-28, SIS	End of intervention	Group x time significant effect on self-reported burden
(Barnes & Markham, 2018)	Informal caregivers of people with dementia	3 sessions manualized individual talking sense intervention N=28	1-hour session N=27	HADS, ACQOL	3-month follow-up	No group x time significant effect on self-reported psychological health
(Brown et al., 2016)	Informal caregivers of people with Alzheimer's disease	8-week manualized mindfulness-based group intervention N=23	8- week manualized social support group N=15	PSS, POMS, SF-36, ZBI	End of intervention and 3-month follow-up	Group x time significant effect on self-reported stress at end of intervention
(Berwig et al., 2017)	Informal caregivers of people with Alzheimer's disease	6-month manualized individual multi-component intervention N=47	Treatment as usual N=45	ZBI, SF-12, RMBPC-24	End of intervention and 3 months follow-up	Group x time significant effect on self-reported burden
(Cheng & Chan, 2005)	Informal caregivers of people with schizophrenia	10-week manualized psychoeducation group intervention N=32	Treatment as usual N=32	FBIS	End of intervention	Group x time significant effect on self-reported burden
(Chou et al., 2002)	Informal caregivers of people with schizophrenia	8-week manualized support group intervention N=35	Waitlist N=35	CBI, BDI	End of intervention and 1-month follow-up	Group x time significant effect on self-reported burden
(Czaja et al., 2013)	Informal caregivers of people with Dementia	6-month manualized individual multi-component intervention N=38	1)Received information N=36 2) Attention control intervention (Received same amount of contact) N=36	RMBPC, CESD,	End of intervention	Group x time significant effect on self-reported subjective burden
(Danucalov et al., 2017)	Informal caregivers of people with Alzheimer's disease	8-week manualized group multicomponent intervention N=25	Waitlist N=21	WHOQOL-BREF, MAAS, SCS	End of intervention	Group x time significant effect on self-reported quality of life
(Davis et al., 2011)	Informal caregivers of people with Dementia	3-month manualized technology-based intervention N=24	Treatment as usual N=22	CES-D, ZBI, SF-36	End of intervention	No group x time significant effect on self-reported depression
(de Mamani & Suro, 2016)	Informal caregivers of people with schizophrenia	15-week manualized individual psychoeducation intervention N=64	3 sessions of psychoeducational intervention N=49	BAS	End of intervention	Group x time significant effect on self-reported subjective burden
(de Souza et al., 2016)	Informal caregivers of people with bipolar disorder	6-week non-manualized individual psychoeducational intervention N=25	Treatment as usual N=28	FBIS-BR, SF-36	End of intervention and 6- month follow-up	No group x time significant effect on self-reported subjective burden
(Eisdorfer et al., 2003)	Informal caregivers of people with Alzheimer's disease	1)12-month manualized individual psychosocial intervention N= 75 2) 12-month manualized individual psychosocial	12-month technology-based support intervention N=73	CES-D, RMBPC	6 months follow-up	Group x time significant effect on self-reported depression in the multicomponent intervention (2)

		intervention + technology support N= 73				
(Fung & Chien, 2002)	Informal caregivers of people with dementia	12-week manualized support group intervention N=26	Treatment as usual N=26	NPI, WHOQOL-BREF	End of intervention	Group x time significant effect on self-reported psychological health
(Gallagher-Thompson et al., 2007)	Informal caregivers of people with Dementia	4-month manualized individual psychoeducation intervention N=23	4-month manualized individual technology-based intervention N=22	CES-D-20, PSS, RMBPC-CB, SES	End of intervention	Group x time significant effect on self-reported depression
(Garand et al., 2014)	Informal caregivers of people with mild cognitive impairment and dementia	18-week manualized individual psychosocial intervention N=36	18-week manualized individual nutritional training N= 37	CES-D, STAI	End of intervention, 1-2-6- and-12-month follow-up.	Group x time significant effect on self-reported depression and anxiety
(Gendron et al., 1996)	Informal caregivers of people with dementia	8-week manualized group cognitive behavioral therapy N=18	8-week manualized information support group N=17	Hopkins Symptom Checklist, Scale, BIS	End of intervention 3-and-6-month follow-up	No group x time significant effect on self-reported psychological health
(Gerkensmeyer et al., 2013)	Informal caregivers of children with mental health problems	8-week manualized individual technology-based intervention N=30	Waitlist N=31	BDI-II, Parent Experience Scale	End of intervention 3- and 6-month follow-up	No group x time significant effect on self-reported depression
(Gonyea et al., 2016)	Informal caregivers of people with Alzheimer's disease	5-week manualized group cognitive behavioral therapy + telephone coaching N=33	5-week manualized group psycho-education + telephone coaching N=34	NPI-D, CES-D, STAI-S	End of intervention 3-month follow-up	Group x time significant effect on self-reported psychological health.
(Gonzalez et al., 2014)	Informal caregivers of people with Alzheimer's disease	6-week non-manualized group multicomponent intervention N=50	Treatment as usual N=52	STAI, CES-D	End of intervention 3-month follow-up	No group x time significant effect on self-reported on self-reported anxiety
(Gossink et al., 2018)	Informal caregivers of people with dementia	6-month, manualized support group intervention N=15	Treatment as usual N=15	ZBI, PSS, CES-D	End of intervention	No group x time significant effect on self-reported subjective burden
(Grover et al., 2011)	Caregivers of people with anorexia nervosa	8-week manualized individual technology-based intervention N=33	Treatment as usual N=30	HADS, ECI	End of intervention 4-and -6-month follow-up	Group x time significant effect on self-reported depression
(Gutierrez-Maldonado & Caqueo-Urizar, 2007)	Informal caregivers of people with schizophrenia	5-month manualized group psychosocial intervention N= 22	Treatment as usual N=34	ZCBS	End of intervention	Group x time significant effect on self-reported subjective burden
(Hubbard et al., 2016)	Informal caregivers of people with bipolar disorder	2-session non-manualized group psychoeducation intervention N=18	Waitlist N=14	DASS, BAS	End of intervention 1- month follow-up	No group x time significant effect on self-reported subjective burden
(Ji et al., 2014)	Informal caregivers of people with Autism Spectrum Disorder	8-week manualized group multicomponent intervention N= 22	Waitlist N=20	SF-36, CBI	End of intervention	Group x time significant effect on self-reported psychological health
(Fallahi Khoshknab et al., 2014)	Informal caregivers of people with Schizophrenia	4-week manualized group psychoeducation intervention N=36	Treatment as usual N=35	FBIS	End of intervention 1- month follow-up	Group x time significant effect on self-reported subjective burden
(Koolaee & Etemadi, 2010)	Informal caregivers of people with Schizophrenia	1) 12-week manualized group psychosocial intervention N=21	Treatment as usual N=20	FBIS	End of intervention 3-and 6-month follow-up	Group x time significant effect on self-reported subjective burden

		2) 12-week manualized group psycho-education intervention N=21				
(Lavretsky et al., 2013)	Informal caregivers of people with Dementia	8-week manualized group and individual multicomponent intervention N=23	8-week relaxation training N= 16	SF 36, HRSD	End of intervention	Group x time significant effect on self-reported psychological health
(Leach et al., 2015)	Informal caregivers of people with dementia	24-week manualized individual multicomponent intervention N=8	Waitlist N=9	HRQoL, WebNeuro	End of intervention and 3-month follow-up	No group x time significant effect on self-reported quality of life
(Livingston et al., 2013)	Informal caregivers of people with dementia	8-week manualized individual psychoeducation intervention N= 152	Treatment as usual N=77	HADS, ZBI, COPE	End of intervention 4-and 8-month follow-up	Group x time significant effect on self-reported psychological health at the end of treatment
(McCallion et al., 2004)	Informal caregivers of children with developmental disabilities and delays	6-session non-manualized support group intervention N= 49	Waitlist N=46	CES-D	3-month post intervention	Group x time significant effect on self-reported depression.
(Mittelman et al., 2007)	Informal caregivers of people with Alzheimer's disease	6-session non-manualized individual and group multicomponent intervention N= 199	Treatment as usual N=197	OARS	4-8-12-18-24-month follow-up	Group x time significant effect on self-reported mental health
(Mohide et al., 1990)	Informal caregivers of people with dementia	6-month non-manualized individual psychoeducation intervention N=30	Treatment as usual N=30	CES-D, STAI, CQLI	End of intervention	No group x time significant effect on self-reported depression
(Neece, 2014)	Informal caregivers of children with developmental delays	7-week manualized group mindfulness intervention	Waitlist N=21	CES-D, SWLS, MASS, SCS	End of intervention	Group x time significant effect on self-reported depression
(Oken et al., 2010)	Informal caregivers of people with Dementia	1) 7-week manualized group mindfulness intervention N=10 2) 7-weeks manualized group psychoeducation intervention N=11	Respite N=10	RMBPC, PSS, CES-D, MASS	End of intervention	Group x time significant effect on self-reported subjective burden in both interventions
(Polo-Lopez et al., 2015)	Informal caregivers of people with a mental disorder	10-week manualized individual cognitive behavioral therapy N=29	Waitlist N=20	SCL-90-R, STAI, BDI-II, SCQ	End of intervention and 6-month follow-up	Group x time significant effect on self-reported psychological health
(Reinares et al., 2004)	Informal caregivers of people with bipolar disorder	12-week manualized group psycho-education intervention N=30	Waitlist N=15	SBAS	End of intervention	Group x time significant effect on self-reported subjective burden
(Stolley et al., 2002)	Informal caregivers of people with Alzheimer's disease	4-hour non-manualized individual psycho-education intervention N=133	4- hour, non-manualized individual information intervention N=108	ZMBPC	3-6-and 12-month follow-up	Group x time significant effect on self-reported subjective burden
(Szmukler et al., 2003)	Informal caregivers of people with Psychosis	9-months non-manualized individual therapy	Treatment as usual N=23	CISR, ECI, COPI	End of intervention and 6-month follow-up	No group x time significant effect on

		N=26				self-reported psychological health
(Szmukler et al., 1996)	Informal caregivers of people with Schizophrenia	6-week manualized individual psychoeducation intervention N=32	1-hour information session N=31	GHQ-28, ECI, Ways of Coping WOC	3-and-6-month follow-up	No group x time significant effect on self-reported psychological health
(Tabeleão et al., 2018)	Informal caregivers of people with mental disorders	6-session manualized individual psycho-education intervention N=66	Treatment as usual N=64	ZBI, SRQ-20 BHS	End of intervention	Group x time significant effect on self-reported subjective burden
(Tonge et al., 2006)	Informal caregivers of children with Autism	20-week manualized group psychoeducation + behavior management intervention N=35	20-week manualized group psychoeducation + counseling intervention N=35	GHQ-28. Parenting Stress Thermometer	End of intervention and 6- month follow-up	Group x time significant effect on self-reported psychological health
(Whitebird et al., 2013)	Informal caregivers of people with dementia	8-week manualized mindfulness group intervention N=38	8-week manualized group psychoeducation + social support intervention N=40	PSS, CES-D, STAI, SF-12	End of intervention and 6- month follow-up	Group x time significant effect on self-reported stress at the end of intervention

Dementia or Alzheimer's disease

Twenty-three studies investigated the effectiveness of informal caregiver interventions of people with dementia or Alzheimer's disease and psychological distress decreased in 16 RCTs. Four out of the five individual psychoeducational interventions decreased psychological distress. All three mindfulness-based interventions decreased psychological distress. Five out of seven multicomponent interventions decreased psychological distress. Four out of six psychosocial or support group interventions deceased psychological distress, whereas neither individual therapy or a technology-based intervention deceased psychological distress.

Severe mental illness

Twenty-one RCTs were included in the category of interventions for informal caregivers of people with a severe mental illness and fifteen decreased psychological distress. Six out of ten psychoeducational interventions decreased psychological distress. All five psychosocial or support group interventions decreased psychological distress. One mindfulness intervention and one multicomponent intervention decreased psychological distress, where as one out of two individual therapy interventions and one technology-based intervention decreased psychological distress.

Included outcomes of psychological distress

Table 2 reflects the mean difference in change from baseline in all the specific outcome measures included in the RCTs and used in the meta-analysis. Some of the results in table 2 show a non-significant effect on the outcome measure, while the study author has reported a significant effect on the outcome measure. This discrepancy between the two results is most like due to different statistical models being used. We report here both the results found in the meta-analysis and the results reported by the study author. Therefore, two RCTs showed effect on depression (Gallagher-Thompson et al., 2007; McCallion et al., 2004), two RCTs showed effect on anxiety (Akkerman & Ostwald, 2004; Livingston et al., 2013), three RCTs showed effect on stress (Brown et al., 2016; Oken et al., 2010; Whitebird et al., 2013), four RCTs showed effect on quality of life (Danucalov et al., 2017; Ji et al., 2014; Lavretsky et al., 2013; Tonge et al., 2006), seven RCTs showed effect on subjective burden (Ata & Doğan, 2018; Berwig et al., 2017; Fallahi Khoshknab et al., 2014; Gutierrez-Maldonado & Caqueo-Urizar, 2007; Koolaee & Etemadi, 2010; Reinares et al., 2004; Tabeleão et al., 2018) and three RCTs showed effect on psychological distress (Fung & Chien, 2002; Gonyea et al., 2016; Polo-Lopez et al., 2015).

Table 2. Mean difference in change from baseline in the specific outcomes of psychological distress included in the meta-analysis

Outcome	RCT	Intervention	Control Group	Mean Difference in change from baseline with 95% CI
Depression	Davis et.al, 2011	Technology	Treatment as usual	CES-D 0.29 (-8.76, 9.34)
	*Gallagher-Thompsen et al., 2006	Psychoeducation	Technology	CES-D -5.40 (-13.95, 3.15)
	Hubbard et al., 2016	Psychoeducation	Waitlist	DASS 1.39 (-1.05, 3.83)
	*McCallion et al., 2004	Support Group	Waitlist	CES-D -4.80 (-10.61, 1.01)
	Mohide et al., 1990	Psychoeducation	Treatment as usual	CES-D -0.18 (95% CI -0.78 to 0.43)
Anxiety	Akkerman et al., 2004	Cognitive Behavioral Therapy	Waitlist	BAI -10.49 (-17.79, -3.19)
	Gonzales et al.,2014	Multicomponent	Treatment as usual	STAI 2.36 (-4.32, 9.04)
	*Livingston et al., 2013	Psychoeducation	Treatment as usual	HADS -0.69 (-3.59, 2.21)

Stress	*Brown et al., 2016	Mindfulness	Social Support	PSS 0.05 (-0.82, 0.92)
	*Whitebird et al., 2012	Mindfulness	Psychoeducation +Social Support	PSS -2.70 (-6.65, 1.25)
	*Oken et al., 2010	Mindfulness	1.Psychoeducation 2.Respite	RMBPC 4.20 (-9.52, 17.92)
Subjective burden	Ata et al.,2018	Cognitive behavioral stress management	Waitlist	ZCBS -15.16 (-25.45, -4.87)
	Berwig et al., 2017	Multicomponent	Treatment as usual	ZBI -5.43 (-9.78, -1.08)
	De Souza et al., 2016	Psychoeducation	Treatment as usual	FBIS 1.10 (-8.65, 10.85)
	Gossink et al., 2018	Support Group	Treatment as usual	ZBI -1.40 (-9.61, 6.81)
	Gutiérrez Maldonado et al., 2007	Psychosocial	Treatment as usual	ZCBS -32.19 (-43.66, -20.72)
	Khoshknab et al., 2013	Psychoeducation	Treatment as usual	FBIS -16.13 (-18.01, -14.25)
	Koolae et al., 2010	Psychosocial	Treatment as usual	FBIS -17.52 (-26.37, -8.67)
	*Reinares et al.,2004	Psychoeducation	Waitlist	SBAS -0.17 (-0.39, 0.05)
	*Tabeleáo et al., 2018	Psychoeducation	Treatment as usual	ZBI -2.90 (-9.97, 4.17)
Quality of life	Aakhus et al., 2009	Psychoeducation	Waitlist	GHQ 6.95 (0.03, 13.87)
	Danucalov et al., 2017	Multicomponent	Waitlist	WHOQOL- BREF -3.00 (-5.35, -0.65)
	*Ji et al., 2014	Multicomponent	Waitlist	SF-36 -3.01 (-13.32, 7.30)
	*Lavretsky et al., 2012	Multicomponent	Relaxation	SF-36 -2.10 (-4.77, 0.57)
	Leach et al., 2015	Multicomponent	Waitlist	AQoL-8D 0.03 (-0.10, 0.16)
	Szmukler et al., 1996	Psychoeducation	Information	GHQ-28 4.90 (-4.03, 13.83)
	*Tonge et al.,2006	Psychoeducation + behavior management	Psychoeducation + counseling	GHQ-28 -6.12 (-13.14, 0.90)
Psychological distress	*Fung et al.,2002	Support Group	Treatment as usual	NPI -5.02 (-13.90, 3.86)
	Gendron et al., 1996	Cognitive behavioral Therapy	Information Support	HSCL -0.40 (-5.94, 5.14)

	*Gonyea et al., 2014	Cognitive behavioral Therapy	Psychoeducation	NPI, -0.60 (-4.91, 3.71)
	*Polo-Lopez et al., 2015	Cognitive behavioral Therapy	Waitlist	SCL-90, -1.26 (-10.67, 8.15)
	Szmukler et al., 2003	Individual therapy	Treatment as usual	CISR -2.80 (-10.14, 4.54)

***Those RCTs where the study author reported significant effect of the outcome measure.**

BAI- Becks Anxiety Inventory (Beck At Fau - Epstein et al., 1988), **STAI**-State Trait Anxiety Inventory (Spielberger, 1983), **DASS**-Depression Anxiety Stress Scale (S. H. Lovibond, & Lovibond, P. F. , 1995), **RMBPC**-The Revised Memory and Behavior Problem Checklist (Teri et al., 1992), **BAS –** The Modified Burden Assessment Scale (Reinhard et al., 1994), **WHOQOL-BREF –** World health Organization Quality of Life Questionnaire (World Health Organization, 2012), **ZCBS**-Zarit Caregiver Burden Scale (Zarit, 1985), (MBPC) Zarit Memory and Behavior Problems Checklist (Zarit SH., 1983), **CISR –** Clinical Interview Schedule Revised (Lewis et al., 1992), **HSCL** - Hopkins Symptom Checklist (Derogatis Lr Fau - Lipman et al., 1974), **SCL-90** Symptom Check List-90 (Derogatis Lr Fau - Morrow et al., 1983), **AQoL-8D-** Assessment of Quality of Life 8-Dimension (Richardson et al., 2014)

Quality of included studies

According to Cochranes Risk of Bias, all forty-four studies included were of low quality (table 3). Twenty-eight RCTs had low and sixteen had unclear risk of bias on sequence generation. Thirty-two had low and twelve had unclear risk of bias on allocation concealment. Thirty-seven had high risk of bias, four unclear and three low on blinding of participants and personnel. Nineteen RCTs were unclear, eighteen low and seven high on blinding of outcome assessors. Thirty-nine had low, four had unclear and one had high risk of bias on incomplete data. Twenty-two had low and twenty-two had unclear risk of bias on selective outcome reporting. According to the Jadad quality score twenty-one of forty-four studies were of good quality (table 4).

Table 3. Cochranes Risk of Bias

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Author	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Overall quality
Aakhus et al., 2009	low	unclear	high	unclear	low	low	poor
Akkerman & Ostwald, 2004	unclear	unclear	high	low	low	unclear	poor
Ata & Dögan, 2018	unclear	unclear	high	unclear	low	low	poor
Barnes & Markham, 2018	low	low	high	high	low	unclear	poor
Berwig et al., 2017	low	low	high	high	low	low	poor
Brown, et al., 2016	unclear	unclear	high	low	low	unclear	poor
Cheng & Chan 2005	unclear	low	high	high	low	low	poor
Chou et al., 2022	low	low	high	high	unclear	low	poor
Czaja et al., 2013	low	low	high	low	low	low	poor
Danucalov et al., 2017	low	unclear	high	low	low	unclear	poor
Davis et al., 2011	low	low	low	unclear	low	unclear	poor
De Mamani & Suro, 2016	unclear	low	high	unclear	low	low	poor
De Souza et al., 2016	low	low	high	unclear	unclear	low	poor
Eisdorfer et al., 2003	low	low	high	unclear	low	low	poor
Fung & Chien, 2002	unclear	low	high	unclear	low	low	poor
Gallagher-Thompsen et al., 2006	unclear	low	high	high	low	low	poor
Garand et al., 2014	low	low	high	high	low	unclear	poor
Gendron et al., 1996	unclear	high	high	low	low	unclear	poor
Gerkensmeyer et al., 2013	low	low	low	high	low	unclear	poor
Gonyea et al., 2014	unclear	unclear	high	unclear	low	low	poor
Gonzalez et al., 2014	low	unclear	unclear	unclear	low	low	poor
Gossink et al., 2018	unclear	low	high	unclear	unclear	low	poor
Grover et al., 2011	low	low	high	low	low	low	poor
Gutiérrez- Maldonado & Urízar, 2007	unclear	low	high	low	low	unclear	poor
Hubbard et al.,	low	low	high	unclear	low	unclear	poor
Ji et al., 2014	unclear	unclear	high	low	low	unclear	poor
Khoshknab et al., 2013	low	low	high	low	low	unclear	poor
Koolaee & Etemadi, 2010	unclear	low	high	low	low	unclear	poor
Lavretsky et al., 2012	low	low	high	unclear	high	low	poor
Leach et al., 2015	low	low	high	low	low	low	poor
Livingston et al., 2013	low	low	high	low	low	low	poor
McCallion & Janicki, 2004	unclear	low	high	unclear	low	unclear	poor
Mittleman et al., 2007	low	low	high	unclear	low	unclear	poor
Mohide et al., 1990	low	low	low	unclear	low	unclear	poor
Neece, 2014	unclear	low	high	unclear	low	low	poor
Oken et al., 2010	low	low	high	low	low	unclear	poor
Polo-Lopez et al., 2015	low	unclear	high	unclear	unclear	low	poor
Reinares et al., 2004	low	low	high	low	low	low	poor
Stolley et al., 2002	unclear	low	unclear	low	low	unclear	poor
Szmukler et al., 2003	low	low	high	low	low	unclear	poor
Szmukler et al., 1996	unclear	unclear	unclear	unclear	low	unclear	poor
Tabeleáo et al., 2018	low	unclear	high	low	low	unclear	poor
Tonge et al., 2006	low	low	high	low	low	unclear	poor
Whitebird et al., 2012	low	low	unclear	unclear	low	low	poor

Table 4. Jadad quality score

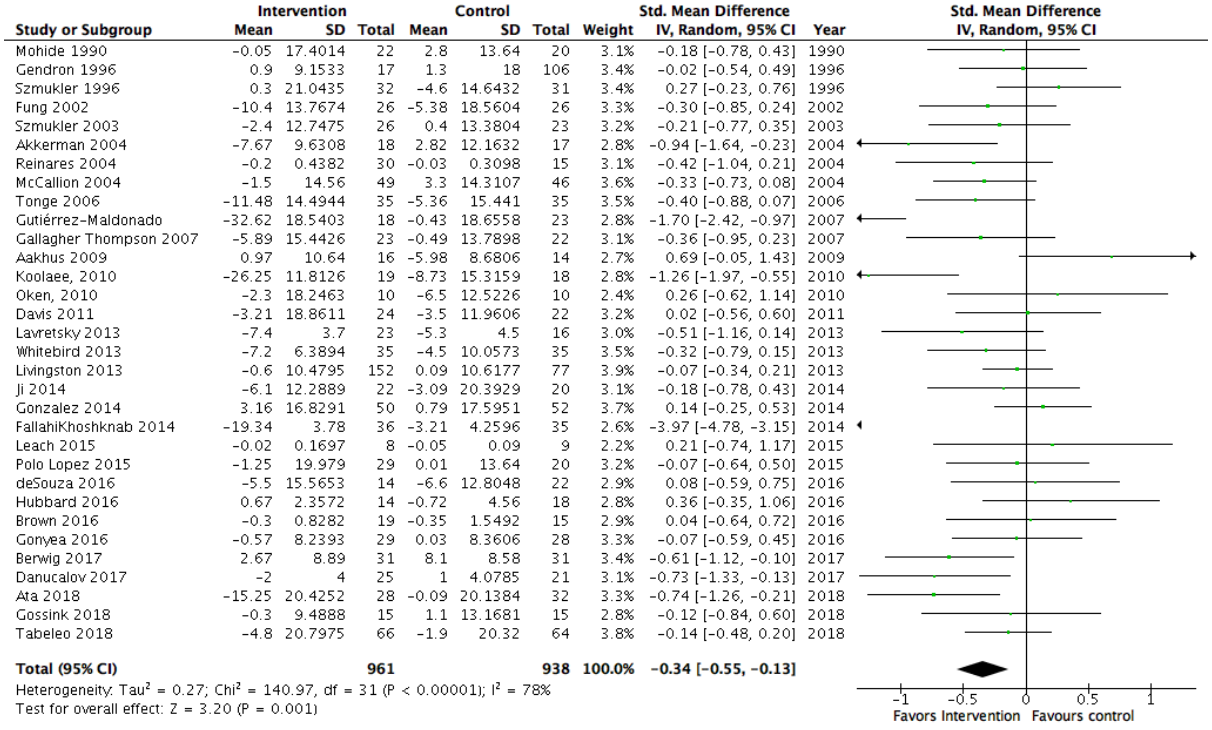
Author	Was the study described as random	Was the randomization scheme described and appropriate?	Was the study described as double-blind?	Was the method of double blinding appropriate?	Was there a description of dropouts and withdrawals?	Total Jadad score
Aakhus et al., 2009	1	1	0	0	1	3
Akkerman & Ostwald, 2004	1	0	0	0	1	2
Ata & Dögan, 2018	1	0	0	0	1	2
Barnes & Markham, 2018	1	1	0	0	1	3
Berwig et al., 2017	1	1	0	0	1	3
Brown, et al., 2016	1	0	0	0	1	2
Cheng & Chan 2005	1	0	0	0	1	2
Chou et al., 2022	1	1	0	0	0	2
Czaja et al., 2013	1	1	0	0	1	3
Danucalov et al., 2017	1	1	0	0	1	3
Davis et al., 2011	1	1	0	0	1	3
De Mamani & Suro, 2016	1	0	0	0	1	2
De Souza et al., 2016	1	1	0	0	0	2
Eisdorfer et al., 2003	1	1	0	0	1	3
Fung & Chien, 2002	1	0	0	0	1	2
Gallagher-Thompsen et al., 2006	1	0	0	0	1	2
Garand et al., 2014	1	1	0	0	1	3
Gendron et al., 1996	1	0	0	0	1	2
Gerkensmeyer et al., 2013	1	1	0	0	1	3
Gonyea et al., 2014	1	0	0	0	1	2
Gonzalez et al., 2014	1	1	0	0	1	3
Gossink et al., 2018	1	0	0	0	0	1
Grover et al., 2011	1	1	0	0	1	3
Gutiérrez-Maldonado & Urízar, 2007	1	0	0	0	1	2
Hubbard et al.,	1	1	0	0	1	3
Ji et al., 2014	1	0	0	0	1	2
Khoshknab et al., 2013	1	1	0	0	1	3
Koolaee & Etemadi, 2010	1	0	0	0	1	2
Lavretsky et al., 2012	1	1	0	0	1	3
Leach et al., 2015	1	1	0	0	1	3

Livingston et al., 2013	1	1	0	0	1	3
McCallion & Janicki, 2004	1	0	0	0	1	2
Mittleman et al., 2007	1	1	0	0	1	3
Mohide et al., 1990	1	1	0	0	1	3
Neece, 2014	1	0	0	0	1	2
Oken et al., 2010	1	1	0	0	1	3
Polo-Lopez et al., 2015	1	1	0	0	0	2
Reinares et al., 2004	1	1	0	0	1	3
Stolley et al., 2002	1	0	0	0	1	2
Szmukler et al., 2003	1	1	0	0	1	3
Szmukler et al., 1996	1	0	0	0	1	2
Tabeleáo et al., 2018	1	1	0	0	1	3
Tonge et al., 2006	1	1	0	0	1	3
Whitebird et al., 2012	1	1	0	0	1	3

Meta-analysis results

A total of thirty-two RCTs (N=1899) were included in the meta-analysis. We found a statistically significant pooled effect favoring the intervention over waitlist, treatment as usual, or active control: -0.34 (95% CI -0.55 to -0.13) (figure 2). I^2 was 78% suggesting substantial heterogeneity between the included RCTs. Sensitivity analysis with exclusion of RCTs with poor quality resulted in an I^2 of 89% suggesting even more substantial heterogeneity between the included RCTs (Supplemental figure 1). Ten RCTs were included in the sensitivity analysis. Five RCTs showed no effect and majority were characterized by short duration and being a technology-based, psychoeducational, multicomponent or transcendental meditation intervention.

Figure 2. All informal caregiver interventions included in the meta-analysis. Mean within-group changes and standardized mean differences.

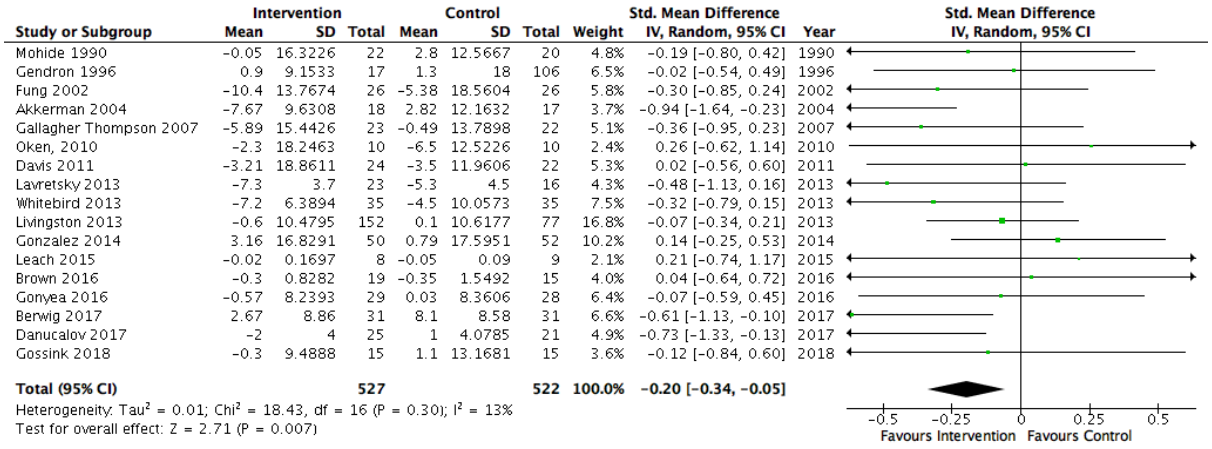


Subgroup analysis

Interventions for informal caregivers of people with Dementia/Alzheimer's disease

The subgroup analysis including interventions for informal caregivers of people with dementia/Alzheimer's disease (17 studies, N= 1049) did show a statistically significant pooled effect favoring interventions for informal caregivers of people with Dementia/Alzheimer's disease -0.20 (95% CI: -0.34 to -0.05) (figure 3). I^2 was 13% suggesting low heterogeneity between the included RCTs.

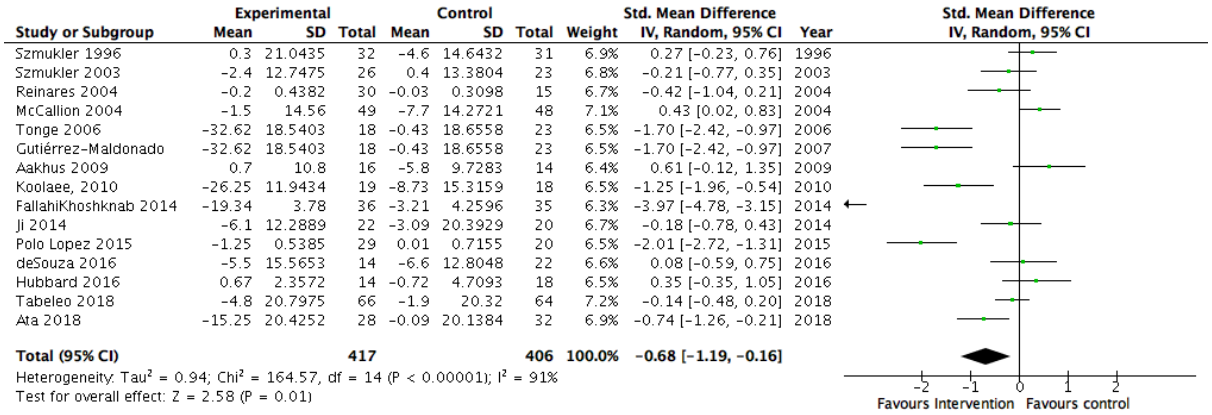
Figure 3. Subgroup analysis of interventions for informal caregivers of people with dementia/Alzheimer's disease, individual/group: All Studies. Mean within-group changes and standardized mean differences.



Interventions for caregivers of people with severe mental, group/individual

The subgroup analysis including all interventions for informal caregivers of people with severe mental illness (15 studies, N= 823) showed a statistically significant pooled effect favoring interventions for informal caregivers of people with a mental illness -0.68 (95% CI: -1.19 to -0.16) (figure 4). I^2 was 91% suggesting high heterogeneity between the included RCTs. Sensitivity analysis with exclusion of RCTs with poor quality resulted in an I^2 of 96% suggesting even more substantial heterogeneity between the included RCTs (Supplemental figure 1).

Figure 4. Subgroup analysis of interventions for informal caregivers of people with severe mental illness, group/individual: All studies. Mean within-group changes and standardized mean differences.

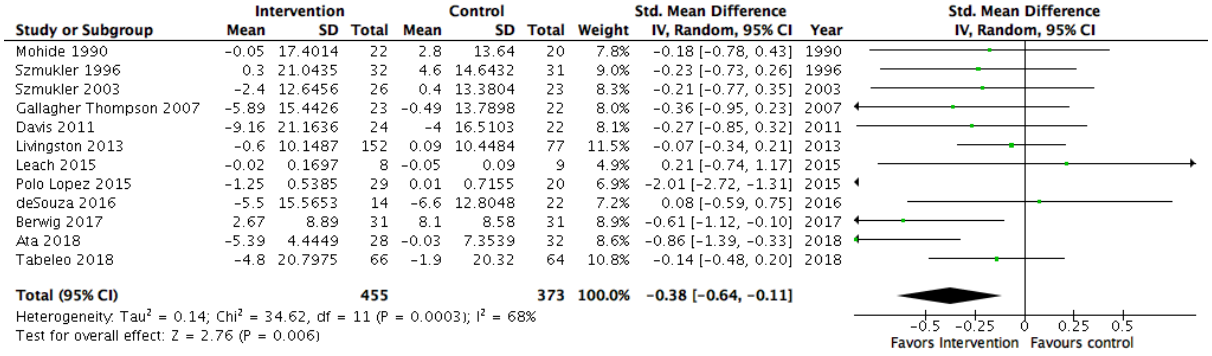


Subgroup analysis

Interventions with an individual delivery format

The subgroup analysis including all interventions with an individual delivery format (12 studies, N= 828) showed a statistically significant pooled effect favoring individual interventions -0.38 (95% CI: -0.64 to -0.11) (figure 5). I^2 was 68 % suggesting high heterogeneity between the included RCTs. Sensitivity analysis with exclusion of RCTs with poor quality resulted in an I^2 of 4% suggesting no heterogeneity between the included RCTs (Supplemental figure 1). Five RCTs were included in the sensitivity analysis. One RCT carried the main effect and was characterized by having a duration of 10 session, being an individual manualized multicomponent intervention, while one RCT was underpowered with a small sample size and consisted of a transcendental meditation program. Substantial heterogeneity was most likely due to the quality of included RCTs.

Figure 5. Subgroup analysis of interventions with an individual delivery format: All studies. Mean within-group changes and standardized mean differences.

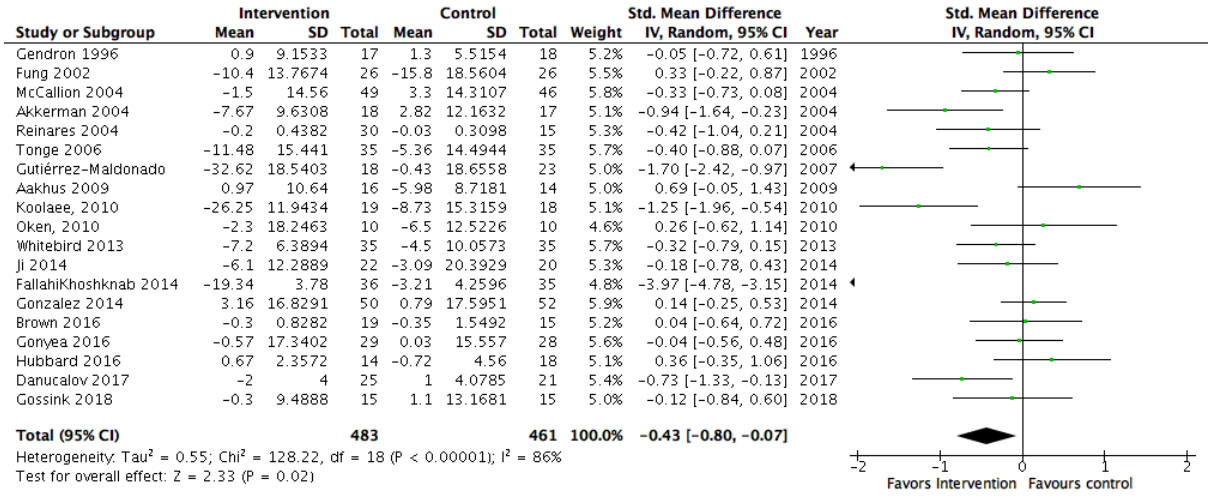


Subgroup analysis

Interventions with a group delivery format

The subgroup analysis including all interventions with a group delivery format (19 studies, N= 932) did show a statistically significant pooled effect favoring group interventions -0.43 (95% CI: -0.80 to -0.07) (figure 6). I^2 was 86% suggesting there was substantial heterogeneity between the included RCTs. Sensitivity analysis with exclusion of RCTs with poor quality resulted in an I^2 of 95% suggesting even more substantial heterogeneity between the included RCTs (Supplemental figure 1).

Figure 6. Subgroup analysis of group interventions: All studies. Mean within-group changes and standardized mean differences.

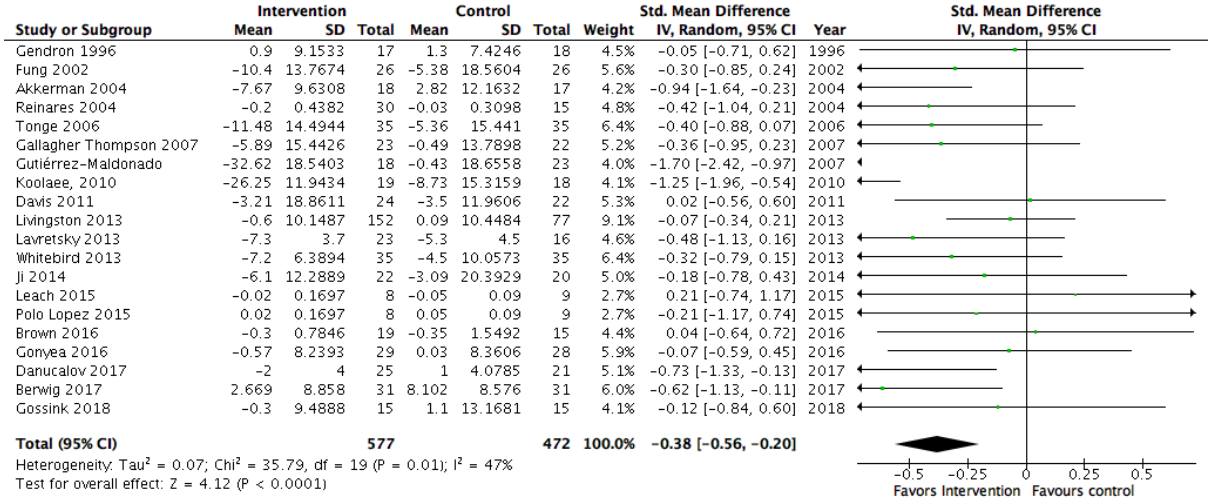


Subgroup analysis

Manualized interventions, ≥ 8 weeks *of duration, individual/group delivery format*

The subgroup analysis including all manualized interventions that were ≥ 8 weeks long and had either an individual or group delivery format (20 studies, N= 1049) showed a statistically significant pooled effect favoring interventions ≥ 8 weeks long and manualized -0.38 (95% CI: -0.56 to -0.20) (figure 7). I^2 was 47 % suggesting moderate heterogeneity between the included RCTs. Sensitivity analysis with exclusion of RCTs with poor quality resulted in an I^2 of 2% suggesting low heterogeneity between the included RCTs (Supplemental figure 1). Seven RCTs were included in the sensitivity analysis. Of those, two carried the main effect and were characterized by a group CBT and an individualized multicomponent intervention. The moderate heterogeneity may be due to the quality of the included RCTs.

Figure 7. Subgroup analysis of interventions that were manualized and ≥ 8 weeks duration, group/individual: All studies. Mean within-group changes and standardized mean differences.



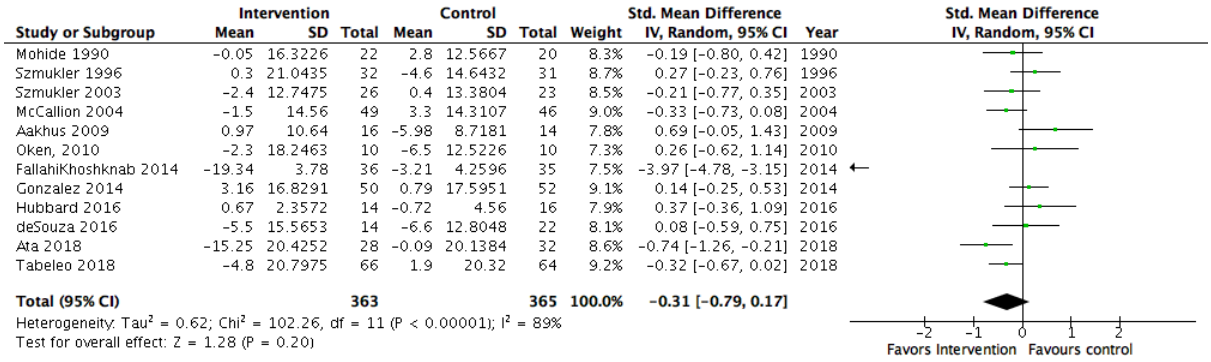
Subgroup analysis

Non-manualized interventions, ≤ 8 weeks *of duration, individual/group delivery format*

The subgroup analysis including all non-manualized interventions that were less than eight-weeks long and had either an individual or group delivery format (21 studies, N= 728) did not show a statistically significant pooled effect favoring interventions ≤ 8 weeks long and non-manualized -0.31 (95% CI: -0.79 to 0.17) (figure 8). I^2 was 89 % suggesting substantial heterogeneity between the included RCTs.

Sensitivity analysis with exclusion of RCTs with poor quality resulted in an I^2 of 96% suggesting even more substantial heterogeneity between the included RCTs (Supplemental figure 1).

Figure 8. Subgroup analysis of interventions that were non-manualized interventions, ≤ 8 weeks of duration, individual/group delivery format: All studies. Mean within-group changes and standardized mean differences.

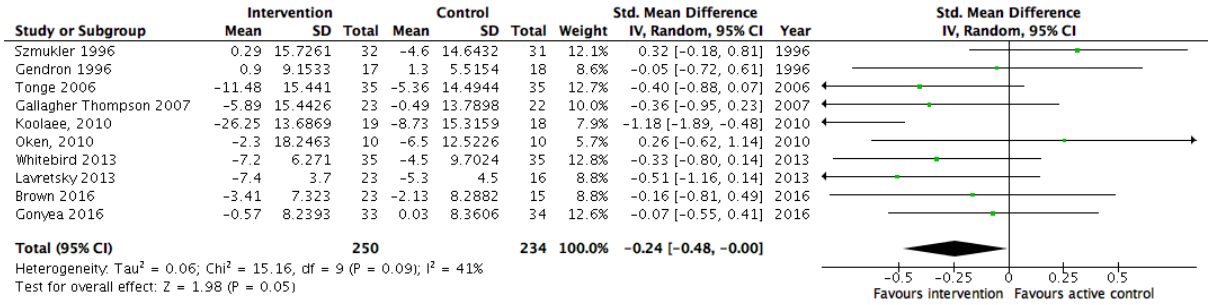


Interventions compared to an active control group

A total of ten RCTs were included in the meta-analysis with an active control group (10 studies, N=484). We found a statistically significant pooled effect estimate favoring the intervention compared to an active control group: -0.24 (95% CI: -0.48 to -0.00) (figure 9). I^2 was 41% suggesting moderate heterogeneity. In this analysis, three of the included RCTs compared Mindfulness-Based Interventions (MBI's) with psychoeducation, psychoeducation + support or social support, and results showed that two of the of the MBI's were more effective in decreasing psychological distress compared to the active intervention, and one MBI was as effective as a psychoeducation + support intervention. Two RCTs compared a psychosocial intervention with a technology-based and a psychoeducational intervention and found effect for the psychosocial intervention. Two RCTs found effect for a psychoeducational intervention compared to a technology-based or information intervention. Two RCTs found effect for a CBT intervention compared to either psychoeducation or information interventions, and one RCT found effect for a multicomponent intervention compared to a relaxation intervention. Sensitivity analysis with exclusion of RCTs with poor quality resulted in an I^2 of 0% suggesting no heterogeneity between the included RCTs (Supplemental figure 1). The sensitivity analysis included two RCTs characterized by being eight-week manualized group mindfulness and

yoga-and-compassion-based interventions. The moderate heterogeneity may have been due to the low quality of included RCTs.

Figure 9. Subgroup analysis of all informal caregiver interventions that included an active control group. Mean within-group changes and standardized mean differences.



Discussion

The systematic review showed that thirty-one out of forty-four RCTs showed effect of the intervention decreasing informal caregiver psychological distress. This was true for caregivers of people with dementia/Alzheimer's disease and caregivers of people with severe mental illness as well as for interventions delivered in individual and group format. Effect was seen for psychoeducation, psychosocial, multicomponent, cognitive behavioral therapy, mindfulness-based and support group interventions. The thirteen RCTs that did not show effect were characterized by being of short duration, including long-term follow-up and being technology-based interventions. All RCTs were of poor quality according to Cochranes RofB and twenty-one of the RCTs were of good quality according to the Jadad quality score.

Thirty-two studies had sufficient data to conduct a meta-analysis including subgroup analysis (N=1899). Of the RCTs that were included in the meta-analysis and that showed effect; two RCTs measured depression, two anxiety, three stress, four quality of life, seven subjective burden, and three measured psychological distress.

Results of the meta-analysis showed a small statistically significant effect (-0.32) of informal caregiver interventions on psychological distress compared to waitlist, treatment as usual or active control, regardless of care-receivers mental illness or intervention modality. Results suggest, that many different intervention modalities show effect in decreasing informal caregiver's psychological distress.

However, most studies only measured psychological distress by the end of intervention and there was high heterogeneity between RCTs, except for interventions that were for informal caregivers of people with dementia/Alzheimer's disease (I^2 = 13%), manualized, at least eight weeks duration, group/individual delivery format (I^2 = 43%) and RCTs that compared interventions with an active control group (I^2 = 41%).

Results of the two subgroup analyses, which included interventions for informal caregivers of people with dementia/Alzheimer's disease showed a small effect (-0.18), while the interventions for informal caregivers of people with severe mental illness showed a moderate effect (-0.68). Results of the subgroup analysis investigating interventions with an individual delivery format compared to waitlist, treatment as usual or active control showed a small effect (-0.38), and so did group delivery format (-0.43). Results of the subgroup analysis that included interventions that were manualized, at least eight weeks duration and had either an individual or group delivery format showed a small effect (-0.38), while results of the subgroup analysis that included RCTs with non-manualized interventions of less than eight weeks duration showed no effect. Sensitivity analysis of the meta-analysis including all RCTs, showed that when low quality studies were excluded heterogeneity increased. The same happened for the subgroup analysis; group delivery format, severe mental illness and non-manualized, less than eight weeks, individual/group. This suggest that the substantial heterogeneity was due to the different intervention modalities, duration and structure being pooled together. Sensitivity analysis for the subgroups; individual delivery format, manualized, eight weeks or more, group/individual, and active control showed that when low quality RCTs were excluded heterogeneity decreased.

Taken together, while the meta-analysis showed a small effect on informal caregiver psychological distress regardless of intervention modality, delivery format and care-receiver mental illness, the subgroup and sensitivity analysis suggest that only some interventions are effective. The effect seems to be carried by a few high quality RCTs characterized by being manualized, by duration and with active participation (e.g. mindfulness-based and cognitive-behavioral-based interventions). Thus, the intervention components, duration and structure (manual) are important in order to improve caregiver's mental health.

We overcame some limitations of previous reviews by only including RCTs and we replicated findings from three decades ago (Knight et al., 1993; Sörensen et al., 2002), showing a small effect of informal caregiver interventions on psychological distress. Moreover, as previous meta-analysis suggested, we found that structured (manual) interventions with active participation and a large number of sessions (≥8 weeks) had the best effect (Knight et al., 1993) . In line with more recent reviews, we were not able to investigate, which intervention modality showed most effect in decreasing caregiver psychological distress. This was due to difficulties with the classification of interventions based on the different components mixed together within interventions (Lobban et al., 2013; van Agteren et al., 2021). However, results of the subgroup analysis including interventions compared with an active control showed a small effect (-0.24). And when two interventions were directly compared, mindfulness-based interventions were superior to psychoeducation. Psychoeducation with active participation was superior to psychoeducation without active participation. Moreover, psychosocial and psychoeducational interventions were superior to technology-based interventions. CBT interventions were superior to both psychoeducational or informational interventions, and a multicomponent intervention was superior to a relaxation intervention.

We argue, that there is a great need, within the field, to have clearly defined intervention categories but also to clearly specify the different intervention components included. Psychoeducational interventions are characterized by having a structured program towards providing information about the care-receivers disease and how to respond effectively to the illness related problems, with support being secondary to the educational component (Pinquart & Sörensen, 2006; Sörensen et al., 2002). Supportive interventions are characterized by being either professionally or peer-led, unstructured, while building rapport and creating a safe place for caregivers to share their concerns. Multicomponent interventions are characterized by including a combination of support, psycho-therapy, and educational components (Sörensen et al., 2002), and psychosocial interventions have been defined as any intervention that emphasizes psychological or social factors (Forsman et al., 2011). While these categorizations appear to make sense, the literature is presenting a different picture.

One systematic review attempted to explore the relationship between intervention content and outcome. They categorizations included: 1) psychoeducation only, 2) psychoeducation plus mutual support, and

3) psychoeducation plus skills training. While results suggested that there was a positive effect of interventions on at least one outcome, there was no evidence that the presence or absence of any of the key components made an intervention more or less effective (Lobban et al., 2013). These issues point towards the fact that within informal caregiver intervention research, there is a lack of consensus as to what components go into the different intervention modalities and which intervention modality is the most effective in decreasing psychological distress. These inconsistencies are also in line with the results of a recent meta-analysis pointing to the lack of knowledge, as to what intervention modality is most helpful in decreasing informal caregiver distress (Sin et al., 2017; van Agteren et al., 2021),

While the meta-analysis and most of the subgroup analysis showed a small effect, a substantial amount of heterogeneity was present, majority of the included RCTs had small sample sizes, and there were many inconsistencies regarding outcome measures. These obstacles are known in the literature and have been reported elsewhere (Knight et al., 1993; Lobban et al., 2013; Sin et al., 2017). In the Prospero protocol we divided outcome measures into primary (psychological distress) and secondary outcomes (anxiety, depression and perceived stress, subjective well-being, and emotion regulation). While carefully reading the included studies, it became clear that the outcome measures used to measure psychological distress were not similar. This finding is also consistent with previous research in this field (Knight et al., 1993) and we therefore, decided to broadly define psychological distress to include depression, subjective burden, anxiety and perceived stress as has been done in a previous meta-analysis (Knight et al., 1993). It is possible that we would have seen different results had we conducted subgroup analysis based on interventions that used the same outcome measure (van Agteren et al., 2021), but we were not able to generate those analysis due to shortage of data. The field would benefit from RCTs using the same outcome measures, to include the data needed to conduct a meta-analysis and to have more consensus as to what constitutes psychological distress (Knight et al., 1993; Lobban et al., 2013; van Agteren et al., 2021)

The results suggesting that manual and duration may be important components of an intervention, are in line with results of previous reviews and meta-analysis that have suggested that structure and length are important components in the effectiveness of interventions on decreasing depression and burden in caregivers (Knight et al., 1993; Sörensen et al., 2002). Results of a recent meta-analysis suggested that

intensity was a moderator for increasing well-being and that singular or short-term interventions were not as effective (van Agteren et al., 2021). While our results may point towards these components being important for the effect of interventions on psychological distress, results of a previous systematic review and meta-analysis concluded that there was no association between the duration of the intervention and caregiver subjective burden (Sin et al., 2017)

Lastly, we found that individual and group delivery format showed effect when compared to waitlist, treatment as usual or active control. Previous reviews have suggested that an individual delivery format is more effective than group format (Sörensen et al., 2002), while others suggests there is no significant relationship between outcome effect and the mode of delivery (Sin et al., 2017). We posit that for some, group delivery format offers a unique opportunity for social connection and support, and for others it may not be either possible or suitable to meet in group. Delivery format (individual or group) may be important when thinking of the intention of the intervention (i.e. provide information about an illness, teach communication or emotion regulation skills, respite care etc.).
Knight et al., 1993 suggested that knowledge about an illness could not be correlated with caregiver distress. We therefore posit that intervention delivery format may not be as important, as the intention behind the intervention. Interventions developed to provide information to informal caregivers about an illness may not necessarily decrease either symptoms of depression, anxiety or stress, whereas interventions that are developed to train skills that allow for the informal caregiver to address, accept and regulate the difficult emotions experienced because of a loved one's mental illness, may decrease symptoms of caregiver depression, anxiety and stress.

To this point, a recent RCT showed that an eight-week manualized group compassion-based intervention given to informal caregivers of people with all types of mental illness (including, dementia, schizophrenia, bipolar, depression, autism etc.) decreased symptoms of depression, anxiety and stress and increased overall well-being (Hansen et al., 2021). The results lasted at six-month follow-up. The intention behind manualized compassion-based training programs is to increase a person's ability to be with and accept difficult emotions and feeling the motivation and wish to relieve the suffering. The results of the RCT suggest that the intention of the intervention (practice compassion for one's own and others suffering), the fact that the intervention is manualized, is at least eight-weeks

long, and includes psychoeducation along with active participation (psychosocial) is effective in decreasing informal caregiver psychological distress. These results are in line with the findings of this systematic review and meta-analysis and another current systematic review and meta-analysis investigating the effectiveness of psychological interventions. Results indicated that mental well-being was significantly improved when the intervention was either a mindfulness-based or a multicomponent intervention (van Agteren et al., 2021).

Based on the results found here, we find it appropriate to provide informal caregivers with interventions that aim to reduce psychological distress. However, our review can only provide information regarding the effect of informal caregiver interventions on psychological distress in general and not on any specific intervention modality. Our results indicate that a manualized intervention and duration of at least eight-weeks may be important components of an intervention in creating effect on informal caregiver psychological distress. Furthermore, our results showed that interventions for informal caregivers of people with dementia/Alzheimer's disease had a small effect, while interventions for informal caregivers of people with severe mental illness showed a moderate effect. It may be that age moderates the effect and should be investigated in the future. It may also reflect that the burden due to severe mental illness is more severe and leave more room for improvements. We should use caution when interpreting the results due to the substantial heterogeneity, small sample size and low quality of the included RCTs.

Implications

The number of informal caregivers is on the rise, and it is paramount that resources and efforts are put into preventing psychological distress in caregivers by conducting systematic intervention research of the continuing effectiveness of interventions and to implement these interventions into society. Intervention research would benefit from the use of similar outcome measures (Pinquart & Sörensen, 2006; Sörensen et al., 2002). Clear descriptions as to the structure and content of the intervention and reporting of means and standard deviations of primary and secondary outcomes may aid in the investigation of which intervention modality is most effective in decreasing caregiver psychological distress. Also, it may be helpful to investigate if duration, manual and outcome are important for caregiver interventions regardless of mental illness or whether there is a difference depending on the

type of mental illness. Lastly, we must understand the mediators that bring about the change in decreasing caregiver psychological distress. Program theory that describes key components and mechanisms may improve caregiver interventions and evidence.

Strengths and limitation

First, a main strength of this systematic review and meta-analysis is that we have updated the literature. In including RCTs of interventions for both broad categories; dementia/Alzheimer's disease and severe mental illness and conducting subgroup analysis of these categories we have managed to provide a good overview of the literature. Second, it was a strength that we calculated the SMD from the within group changes. In RCTs with small sample size, there is a greater probability of between-group differences in baseline values than in large RCTs. This may confound the effect estimates when only comparing the follow-up data. Third, this study was preregistered with a protocol in Prospero and we followed the PRISMA guidelines. Lastly, we had two independent reviewers assessing the quality of the RCTs and extracting quantitative data for the meta-analysis.

This review also had several limitations. First, it is limited by the quality of the included RCTs. Majority of the studies had small sample sizes limiting the generalizability of the treatment effect. Second, substantial statistically heterogeneity (I^2 = 50%-90%) was found for the main meta-analysis with interventions being compared with waitlist, treatment as usual or active control. Majority of the subgroup analysis had substantial heterogeneity and interpretation of these results must be taken with care, as the chi-squared test has low power in studies with low sample size and a small number of studies are included (Cochrane, 2021). We conducted sensitivity analysis in an attempt to understand what created the substantial heterogeneity. For some of the sensitivity analysis, the substantial heterogeneity came from poor quality RCTs and for others it was simply pooling to many RCTs with too many different intervention modalities, delivery method, duration and structure. One could even argue that it futile to conduct a meta-analysis when there is high heterogeneity among the included RCTs (Lobban et al., 2013).

Third, per the Prospero protocol, we wanted to conduct subgroup analysis on intervention modality to understand, which intervention modality showed effect in deceasing informal caregiver distress.

Unfortunately, we had to conclude that due to the different and inconsistent component descriptions we would not be able to conduct subgroup analysis on intervention modality, which is a common problem with in the literature (Lobban et al., 2013; van Agteren et al., 2021). Fourth, the RCTs used an array of different self-report questionnaires to measure psychological distress making it difficult to know whether the interventions were addressing the same construct, which is also a common problem within the intervention literature (Lobban et al., 2013; Sin et al., 2017). Fifth, it was often quite difficult to assess risk of bias, as authors often did not specifically report the different processes (e.g. randomization or allocation) in full, also a common issue within the field (van Agteren et al., 2021). Lastly, while some of the RCTs reported statistically significant effect of their outcome measure, we were not able to replicate the results in our analysis. We suggest that the discrepancy may be due to the use of different statistical models.

Conclusion

Evidence supports that several interventions improve mental health in caregivers. Manualized interventions, ≥ 8 weeks with active participation are most effective. Future RCT should improve methodology and future research should investigate, which intervention modality is most effective for what kind of caregiver, and clearly specify what the included interventions components are, use longer follow-up times and conduct mediational analyses to better understand what mediators create the effect of an intervention. This current systematic review and meta-analysis aid in highlighting how great this need truly is.

Figure of Legends

Figure 1. Prisma flow diagram

Table 1. Overview of all included RCTs

Table 2. Mean difference in change from baseline in the specific outcomes of psychological distress

included in the meta-analysis

Table 3. Cochranes Risk of Bias

Table 4. Jadad quality score

Figure 2. All informal caregiver interventions included in the meta-analysis. Mean within-group changes and standardized mean differences.

Figure 3. Subgroup analysis of interventions for informal caregivers of people with dementia/Alzheimer's disease, individual/group: All Studies. Mean within-group changes and standard

Figure 4. Subgroup analysis of interventions for informal caregivers of people with severe mental illness, group/individual: All studies. Mean within-group changes and standardized mean differences.

Figure 5. Subgroup analysis of interventions with an individual delivery format: All studies. Mean within-group changes and standardized mean differences.

Figure 6. Subgroup analysis of group interventions: All studies. Mean within-group changes and standardized mean differences.

Figure 7. Subgroup analysis of interventions that were manualized and ≥ 8 weeks duration, group/individual: All studies. Mean within-group changes and standardized mean differences.

Figure 8. Subgroup analysis of interventions that were non-manualized interventions, ≤ 8 weeks of duration, individual/group delivery format: All studies. Mean within-group changes and standardized mean differences.

Figure 9. Subgroup analysis of all informal caregiver interventions that included an active control group. Mean within-group changes and standardized mean differences.

Supplemental eFigure 1. Sensitivity analysis for meta-analysis and all subgroups

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Effect of a compassion cultivation training program for caregivers of people with mental illness in Denmark: A randomized clinical trial (paper II)

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Original Investigation | Psychiatry

Effect of a Compassion Cultivation Training Program for Caregivers of People With Mental Illness in Denmark
A Randomized Clinical Trial

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Abstract

IMPORTANCE Caregivers of people with mental illness are at increased risk of developing depression, anxiety, and stress.

OBJECTIVE To investigate the effect of a compassion cultivation training (CCT) program on decreasing caregiver psychological distress.

DESIGN, SETTING, AND PARTICIPANTS This waitlist-controlled randomized clinical trial was conducted in 2 different community settings in Denmark. Caregivers were excluded if they had a diagnosed and untreated mental illness, addiction, meditation practice, or current psychotherapeutic treatment. Enrollment occurred between May 2018 and March 2019. A repeated measurement model was used to examine the impact of the intervention. The primary analysis was based on the intention-to-treat principle. Data analysis was conducted from June 4 to July 7, 2020.

INTERVENTIONS Participants were randomized 1-to-1 to an 8-week CCT course or waitlist control. Block randomization was used with 40 participants in each block.

MAIN OUTCOMES AND MEASURES The main outcome was reduction in psychological distress, as measured by the Depression, Anxiety, Stress Scale (DASS). Baseline, postintervention, and 3- and 6-month follow-up measurements were collected.

RESULTS Among 192 participants assessed for eligibility, 161 participants were included in the study (mean [SD] age, 52.6 [12.5] years; 142 [88.2%] women), with 79 participants randomized to the CCT intervention and 82 participants in the waitlist control group. At baseline, the mean (SD) DASS scores for the intervention vs control groups were 10.89 (8.66) vs 10.80 (8.38) for depression, 6.89 (6.48) vs 6.68 (5.33) for anxiety, and 14.96 (7.90) vs 15.77 (7.40) for stress. The CCT group experienced statistically significant improvement in the primary outcome in mean change from baseline vs the control group at postintervention (adjusted mean difference: depression, −4.16 [95% CI, −6.75 to −1.58]; $P = .002$; anxiety, −2.24 [95% CI, −3.99 to −0.48]; $P = .01$; stress, −4.20 [95% CI, −6.73 to −1.67]; $P = .001$), the 3-month follow-up (adjusted mean difference: depression, −3.78 [95% CI, −6.40 to −1.17]; $P = .005$; anxiety, −2.50 [95% CI, −4.27 to −0.73]; $P = .006$; stress, −3.76 [95% CI, −6.32 to −1.21]; $P = .004$), and the 6-month follow-up (adjusted mean difference: depression: −4.24 [95% CI, −6.97 to −1.52]; $P = .002$; anxiety, −2.12 [95% CI, −3.96 to −0.29]; $P = .02$; stress: −3.79 [95% CI, −6.44 to −1.13]; $P = .005$).

CONCLUSIONS AND RELEVANCE These findings suggest that CCT was superior to the waitlist control in supporting caregivers' mental health. Statistically and clinically significant reductions in psychological distress were found and sustained at the 6-month follow-up. The improvements noted

(continued)

Key Points

Question Is a compassion cultivation training (CCT) intervention effective in decreasing psychological distress in informal caregivers of people with mental illness?

Findings In this randomized clinical trial including 161 caregivers randomized to a CCT program or waitlist group, caregivers who received CCT experienced significant improvements in depression, anxiety, and stress, and the improvements were maintained at 6-month follow-up.

Meaning Theses findings suggest that the CCT intervention was effective in decreasing psychological distress in caregivers of people with mental illness.

+ Supplemental content

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Abstract (continued)

in this randomized clinical trial could serve to encourage implementation of future evidence-based programs for caregivers.

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Introduction

Suffering related to psychiatric disorders is present in patients and caregivers. Compassion can be understood as the willingness to feel suffering and to relieve suffering. Compassion is a practice of turning toward suffering rather than away,[1] and it is a trainable skill.[2] Training in compassion may be especially beneficial for caregivers, as enhancing compassion may promote mental health and reduce suffering. Caregivers are at an increased risk for mental health difficulties.[3-7] Evidence-based programs to support caregivers' mental health are needed.

Approximately 1 in 4 people provide care to a loved one.[3] The economic contribution of informal care has been estimated as between 50% to 90% of the overall long-term cost of care in Europe,[3] and as many as half of family caregivers may be at risk of developing depression.[3,7]

In Denmark, psychiatric disorders make up the largest disease burden. A total of 38% of the adult population categorize themselves as caregivers of someone with a mental illness, and 61% of caregivers experience psychological distress.[8] It is estimated that the direct and indirect cost of poor mental health in Denmark is up to $9.17 billion.[9]

Compassion training has been found to be associated with decreased psychological distress and increased overall well-being.[10-13] However, evidence-based programs for the effectiveness in the prevention of psychological distress for informal caregivers of people with mental illness are lacking. Two systematic reviews demonstrated that compassion training may promote mental health.[11,12] However, the compassion interventions varied from 7 minutes to 8 weeks, with very few of the interventions being manualized, and not all included studies were randomized clinical trials (RCTs).[11,12]

A meta-analysis on compassion-based interventions with 21 RCTs,[13] including either healthy adults or adults with a physical or mental illness, suggested a moderate effect size on measures of mindfulness, compassion, and self-compassion and decreased depression, anxiety, and psychological distress scores. Significant moderate effects were also found for well-being.[13] However, there was great variability in the types of compassion-based interventions, their duration, and whether they were manualized or not.[13] In a meta-analysis from 2017, Kirby et al[13] concluded with suggestions for future research, including the use of larger samples sizes, an active control group, clinical samples, compassion-based questionnaires, and improved reporting and methods. This RCT sought to addresses some of these limitations by including a larger sample size, a high-risk population, 2 compassion-based self-report instruments (the 12-item Self-Compassion Scale-Short Form and Multidimensional Compassion Scale), and more rigorous methods by collecting repeated measurements at the 3- and 6-month follow-ups.

Compassion training programs may be thought of as preventive interventions that can decrease psychological distress and increase overall well-being. One such program is the manualized compassion cultivation training (CCT) program.[14] Two RCTs[15-19] including healthy adult participants have found significant increases in positive affect, cognitive reappraisal, acceptance, mindfulness skills, self-compassion, satisfaction with life, happiness, compassion, empathic concern, and identification with all humanity. Results of decreased negative affect, perceived distress, depression, suppression of emotion, negative rumination, and mind-wandering were also reported.[15-19]

Considering the potential for CCT to promote mental health and the lack of evidence-based programs for informal caregivers, our primary hypothesis was that the CCT program would decrease

psychological distress in caregivers (eg, sibling, parent, spouse, adult child) of people with mental illness (any kind of mental disorder; eg, depression, anxiety, schizophrenia, bipolar disorder). The secondary hypothesis was that the CCT program would increase overall well-being in caregivers.

Methods

Study Design and Participants

This RCT included an intervention group and a waitlist control group. The study was conducted in 2 different community settings in Denmark, specifically Copenhagen and a more rural area in Jutland. Ethical approval was obtained at the Central Denmark Region Committee of Health Research Ethics (De Videnskabsetiske Komitéer for Region Midtjylland). All participants provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for clinical trials. The detailed trial protocol is available in Supplement 1.

Participants were all adults from Denmark. Participants were recruited through primary care physicians and social media and through national associations for caregivers, ads in local newspapers, and local 1-hour informational meetings on the topic of compassion. A total of 192 informal caregivers were assessed for eligibility through a telephone interview. Inclusion criteria included caregivers who were the parent, spouse, adult child, or sibling of a person with mental illness (all mental illnesses were included as described in *Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition] [*DSM-5*][20]), aged 18 to 75 years, and Danish-speaking. The exclusion criteria included diagnosed and untreated mental illness, addiction, meditation practice, or current psychotherapeutic treatment. Of 192 assessed caregivers, 6 (3%) did not meet inclusion criteria, as they were either older than 75 years, they had an established meditation practice lasting more than 1 year, or they were receiving psychotherapy and did not feel they could manage without the help of a therapist.

Participants signed a written informed consent form before answering the demographic and baseline questionnaire and before randomization.

Randomization and Masking

Participants were randomized to CCT or a waitlist control (**Figure**) using a computer algorithm with predefined, concealed random numbers. The person creating the computer algorithm with predefined, concealed numbers was a university employee who administers the data software program, Redcap (Vanderbilt University), and was therefore blinded to study participants. We conducted block randomization with 40 participants in each block. The 40 participants in each block were all randomized at the same time, with 20 entering into the intervention group and 20 into the waitlist control group.

Participants enrolled in the trial received an email with a link to the questionnaires that they filled out online from their homes at postintervention and at the 3- and 6-month follow-ups. The data were collected in the RedCap secure university approved system. Once 6-month follow-up data were collected from the intervention and waitlist control groups, the waitlist control group received the CCT intervention.

Owing to the nature of the intervention, participants and the CCT instructor were aware of group allocation for the duration of the study. Data collection was remote, as participants answered the self-report questionnaires from their own homes via a link sent to them by email, and automatic, using the web-based Redcap software to ensure masking of outcome assessors. Everyone involved with the trial, except for the principle investigator and a research assistant, had no access to the data prior to analyzing the data.

Intervention

The CCT program is a structured and manualized compassion training program that was developed at Stanford University Medical School in 2009.[14] The program has a dual focus on training compassion and loving kindness for one's own suffering and the suffering of others. The focus within

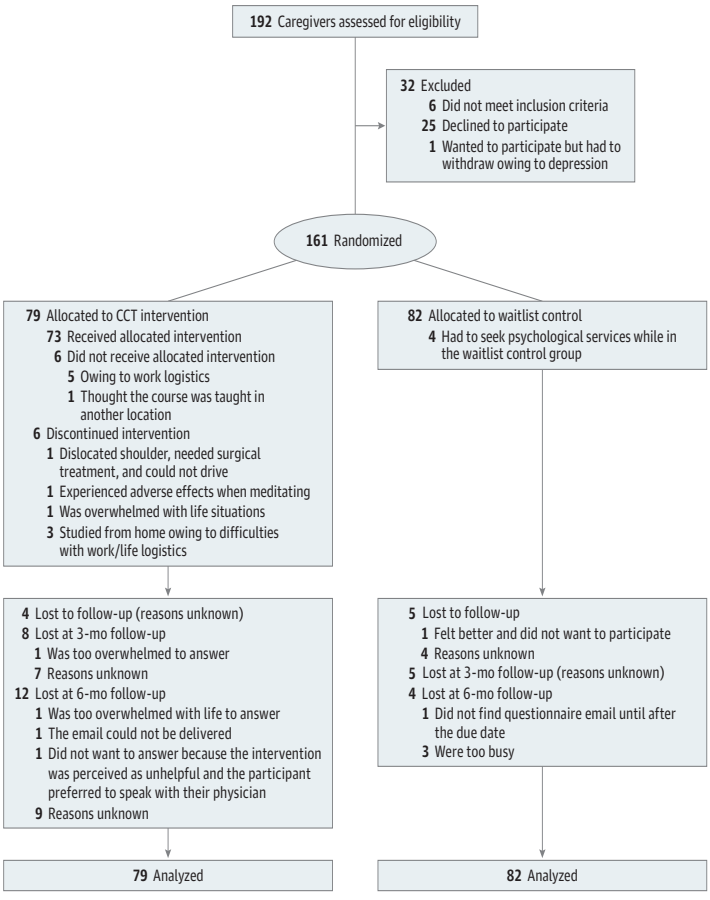
CCT is to notice and pay attention to the suffering within oneself or others thereby becoming motivated to relieve that suffering. The program trains a variety of skills and techniques for emotional and mental well-being and is designed to promote qualities of compassion and empathy, and to cultivate kindness toward self, strangers, difficult people, and all sentient beings.[19] The CCT program is a 8-week course (eTable 1 in Supplement 2). Participants meet for 2 hours each week, and the course incorporates practices of compassion, mindfulness, and meditation with scientific research on compassion and related topics in the fields of psychology and neuroscience along with contemplative thinking. Each week, participants engage in class discussions, formal meditations, and dyadic exercises. Participants are asked to meditate daily at home for 20 to 25 minutes using guided compassion meditations accessed through a website and engage in informal compassion practices, sent to the participants in an email each week. The CCT instructor adhered strictly to the CCT manual and received supervision on the teaching throughout the study by mindfulness and compassion practitioners with more than 20 years of experience.

Outcomes

The primary outcome measure used was the 42-item Depression Anxiety Stress Scale (DASS).[21] The DASS is scored by summing up the 14 items relevant for each subscale. Lower scores on each scale indicated less psychological distress.

There were 7 overall secondary outcome measures. We included the 10-item Perceived Stress Scale to measure how stressful a person perceives an event or situation in their life to be.[22] Scores

Figure. Flowchart of Participant Recruitment



CCT indicates compassion cultivation training.

range from 0 to 40, with higher scores indicating higher perceived stress. The Brief Resilience Scale was used to assess the ability to bounce back or recover from stress (range, 6-10, with higher scores indicating more resilience).[23] The World Health Organization 5-item Well-Being Index,[24] measured the participant's current mental well-being; scores range from 0 to 100, and higher scores indicate higher levels of well-being. A score of 50 or lower indicates a risk of developing stress or depression.[25] The Emotion Regulation Questionnaire measured respondents' tendency to regulate their emotions in 2 ways: either cognitive reappraisal or expressive suppression.[26] The 12-item Self-Compassion Scale-Short Form was used to measure participants' level of self-compassion.[27] The Multidimensional Compassion Scale was used to measure 4 dimensions of compassion (ie, cognitive, affective, intentional, and motivational) and a total score (H. Jazaieri, P. R. Goldin, E. Simon-Thomas, D. Keltner, and R. Mendoza-Denton, unpublished data, May 2018). The 15-item Five Facet Mindfulness Scale measured 5 dimensions of mindfulness (ie, observing, describing, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience) and a total score.[28,29] Higher scores indicate higher levels of mindfulness. All measures were Danish versions of the instruments, and the Brief Resilience Scale and Multidimensional Compassion Scale were translated into Danish using the World Health Organization guidelines for translating measurements.[30]

The CCT instructor assessed for safety and adverse events by informing participants that if any trauma resurfaced or other difficult emotions occurred during a session or at home when meditating, the participant should contact the CCT instructor (who is also a licensed psychologist). The participant and instructor would determine together the safest course of action.

Statistical Analysis

The sample size was calculated using effect sizes from related publications,[11,15-19] (respective η^2 values, and Cohen *d*) with G*Power statistical software version 3.1 (Heinrich-Heine-Universität Düsseldorf). The power analysis gave an approximate value of a minimum of 77 participants in both groups when we expected a medium effect size of $d = 0.5$ ($\alpha = .05$; power, 80%). A minimum of 77 participants per group allowed for an attrition rate of 20%, which gave us a minimum sample size of 64 participants each in the intervention and waiting list control groups.

Data were analyzed by a repeated measurement model with the systematic effect: age, sex, socioeconomic status, years as informal caretaker, schizophrenia (diagnosis of loved one), anxiety (diagnosis of loved one), time (4 time points), intervention, and interaction between time and intervention. We adjusted for schizophrenia, and anxiety as these 2 types of mental illness were overrepresented in the intervention or control group. The repeated measurement model is relatively robust to data missing at random, but we supplemented all analyses with sensitivity analyses representing 4 scenarios with data not missing at random. Missing outcomes were substituted with the model-based estimate, adding or subtracting 0.2 SD in the intervention or control group. We performed a loss to 6-month follow-up analysis for age, sex, educational level, income level, years of caretaking and baseline scores of DASS, Perceived Stress Scale, World Health Organization 5-item Well-Being Index, Brief Resilience Scale, and Emotion Regulation Questionnaire by *t* tests and χ^2 tests (eTables 2-4 in Supplement 2). *P* values were 2-sided, and statistical significance was set at $P = .05$. Data were analyzed from June 4 to July 7, 2020. Full details of the statistical analysis plan are in Supplement 1.

Results

Between May 18, 2018, to March 8, 2019, 192 caregivers were assessed for eligibility, and a total of 32 caregivers were excluded (6 for not meeting inclusion criteria, 25 declined to participate mainly owing to work/life balance, and 1 wanted to participate but became too depressed and withdrew). A total of 26 (14%) of the 187 caregivers eligible to participate in the study decided not to participate mainly due to logistical issues between work and home life. The final sample included 161 participants

(mean [SD] age, 52.6 [12.5] years; 142 [88.2%] women), with 79 participants randomized to the CCT intervention and 82 participants in the waitlist control group (Figure). Demographic characteristics were similar for both groups at baseline (**Table 1**), and also after conducting an analysis of loss to at the 6-month follow-up (Table 1). There were no observed differences between groups on outcomes measures at baseline (**Table 2**). In the intervention group, 73 participants (92%) received 2 or more sessions of 8 total sessions, 65 participants (88%) completed 5 sessions, and 54 participants (74%) completed 6 or more sessions. One participant in the intervention group experienced adverse effects to meditation (prior trauma resurfaced). It was deemed safest to terminate participation, and a referral to see a psychologist was offered, which the participant declined.

At baseline, the mean (SD) DASS scores for the intervention vs control groups were 10.89 (8.66) vs 10.80 (8.38) for depression, 6.89 (6.48) vs 6.68 (5.33) for anxiety, and 14.96 (7.90) vs 15.77 (7.40) for stress. We found statistically significant CCT group effect on the primary outcome (DASS) for all 3 subscales (depression, anxiety, stress) compared with the control group at postintervention, (adjusted mean difference: depression, −4.16 [95% CI, −6.75 to −1.58]; *P* = .002; anxiety, −2.24 [95%

Table 1. Demographic Characteristics of Caregivers at Baseline

Characteristic	No. (%)		
	Intervention group (n = 79)	Control group (n = 82)	Total (n = 161)
Sex			
Men	11 (14.1)	8 (9.7)	19 (11.8)
Women	68 (85.9)	74 (90.2)	142 (88.2)
Age, mean (SD), y	55.9 (13.3)	49.5 (10.8)	52.6 (12.5)
Educational level			
No high school	1 (1.3)	1 (1.2)	2 (1.2)
High school	4 (5.1)	2 (2.4)	6 (3.7)
Trade school	5 (6.3)	10 (12.2)	15 (9.2)
Short continuing education	8 (10.1)	3 (3.7)	11 (6.8)
Medium continuing education	43 (54.4)	25 (30.5)	68 (42.0)
Long continuing education	17 (21.5)	38 (46.3)	55 (34.0)
PhD	0	3 (3.7)	3 (1.9)
Other	1 (1.3)	0	1 (0.6)
Caretaking duration, y			
0-5	22 (28.2)	22 (27.1)	45 (28.1)
5-10	23 (29.5)	20 (24.7)	43 (26.9)
10-15	5 (6.5)	16 (19.8)	21 (13.1)
15-20	9 (11.5)	5 (6.2)	14 (8.8)
>20	19 (24.4)	18 (22.2)	37 (23.1)
Psychiatric disorder of person being cared for[a]			
Anxiety	18 (22.2)	35 (42.7)	53 (32.7)
ADHD	10 (12.7)	14 (17.1)	24 (14.8)
Autism	17 (21.5)	14 (17.1)	32 (19.8)
Bipolar disorder	9 (11.4)	12 (14.6)	21 (13.0)
OCD	6 (7.6)	12 (14.6)	18 (11.1)
Depression	19 (24.1)	21 (25.6)	40 (24.7)
Addiction	10 (12.7)	8 (9.8)	18 (11.1)
Personality disorder	8 (10.1)	13 (15.9)	21 (13.0)
PTSD	7 (8.7)	7 (8.5)	14 (8.6)
Schizophrenia	21 (26.6)	13 (15.9)	34 (21.0)
Eating disorder	7 (8.9)	3 (3.7)	10 (6.2)
Stress	6 (7.6)	9 (11.0)	16 (9.9)
Acquired brain injury	6 (7.6)	6 (7.3)	12 (7.4)
Other[b]	7 (8.7)	10 (12.2)	17 (10.5)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; OCD, obsessive compulsive disorder; PTSD, posttraumatic stress disorder.

[a] Caregivers often had loved ones with comorbid disorders; therefore, the percentages do not total 100.

[b] Includes disruptive behavior, bodily distress syndrome, intellectual disability, psychogenic nonepileptic seizures, Parkinson disease, schizotypal disorder, attachment disorder, Tourette syndrome, dementia.

Table 2. Effect of CCT on the Primary Outcome of Depression, Stress, and Anxiety in Informal Caregivers of People With Mental Illness at Postintervention and 3- and 6-Month Follow-up

Measure	CCT Intervention			Control			Between-group difference, mean (95% CI)[a]	*P* value	Cohen *d*
	Caregivers, No.	Score, mean (SD)	Within-group change from baseline, mean (95% CI)[a]	Caregivers, No.	Score, mean (SD)	Within-group change from baseline, mean (95% CI)[a]			
Depression[b]									
Baseline	76	10.89 (8.66)	NA	79	10.80 (8.38)	NA	NA	NA	NA
Postintervention	68	7.84 (8.30)	−3.60 (−5.47 to −1.73)	76	11.28 (9.53)	0.56 (−1.22 to 2.34)	−4.16 (−6.75 to −1.58)	.002	0.66
3 mo	63	7.02 (8.14)	−3.68 (−5.60 to −1.76)	76	11.09 (10.93)	0.11 (−1.67 to 1.88)	−3.78 (−6.40 to −1.17)	.005	0.56
6 mo	54	6.61 (8.27)	−3.93 (−5.96 to −1.90)	72	11.40 (10.67)	0.31 (−1.50 to 2.12)	−4.24 (−6.97 to −1.52)	.002	0.45
Anxiety[b]									
Baseline	74	6.89 (6.48)	NA	82	6.68 (5.33)	NA	NA	NA	NA
Postintervention	67	5.10 (5.33)	−2.03 (−3.32 to −0.75)	73	6.73 (7.00)	0.21 (−0.99 to 1.40)	−2.24 (−3.99 to −0.48)	.01	0.51
3 mo	62	4.95 (5.51)	−2.01 (−3.33 to −0.69)	76	7.05 (6.95)	0.49 (−0.70 to 1.67)	−2.50 (−4.27 to −0.73)	.006	0.56
6 mo	53	5.55 (5.94)	−1.18 (−2.57 to 0.21)	72	7.43 (7.85)	0.94 (−0.26 to 2.15)	−2.12 (−3.96 to −0.29)	.02	0.30
Stress[b]									
Baseline	77	14.96 (7.90)	NA	78	15.77 (7.40)	NA	NA	NA	NA
Postintervention	65	10.65 (7.11)	−4.15 (−6.00 to −2.30)	77	15.81 (8.81)	0.05 (−1.67 to 1.77)	−4.20 (−6.73 to −1.67)	.001	0.74
3 mo	63	10.75 (8.35)	−3.90 (−5.78 to −2.03)	76	15.68 (10.36)	−0.13 (−1.87 to 1.60)	−3.76 (−6.32 to −1.21)	.004	0.56
6 mo	54	10.39 (7.74)	−4.17 (−6.15 to −2.19)	71	15.38 (10.03)	−0.38 (−2.15 to 1.39)	−3.79 (−6.44 to −1.13)	.005	0.43

Abbreviations: CCT, compassion cultivation training; NA, not applicable.

[a] Adjusted for sex, age, educational level, years as informal caretaker, and diagnosis of schizophrenia or anxiety for patient.

[b] Measured using the Depression, Anxiety, Stress Scale. Each subscale has a range of 0 to 14, with higher scores indicating more psychological distress.

CI, −3.99 to −0.48]; *P* = .01; stress, −4.20 [95% CI, −6.73 to −1.67]; *P* = .001), the 3-month follow-up (adjusted mean difference: depression, −3.78 [95% CI, −6.40 to −1.17]; *P* = .005; anxiety, −2.50 [95% CI, −4.27 to −0.73]; *P* = .006; stress, −3.76 [95% CI, −6.32 to −1.21]; *P* = .004), and the 6-month follow-up (adjusted mean difference: depression: −4.24 [95% CI, −6.97 to −1.52]; *P* = .002; anxiety, −2.12 [95% CI, −3.96 to −0.29]; *P* = .02; stress: −3.79 [95% CI, −6.44 to −1.13]; *P* = .005) (Table 2). The results of the secondary outcome measures showed statistically significant positive effects of the CCT intervention compared with the control group at all time points on overall well-being, resilience, self-compassion, mindfulness, cognitive reappraisal (emotion regulation), and statistically significant reduction on perceived stress and emotion suppression (emotion regulation). No effect was found on the awareness subscale of the Five Facet Mindfulness Questionnaire and on the Multidimensional Compassion Scale measuring compassion as a multidimensional construct (**Table 3**). Results of the primary and secondary outcomes remained statistically significant after conducting the sensitivity analysis (eTable 5 and eTable 6 in Supplement 2).

Discussion

This randomized clinical trial found that the CCT intervention decreased symptoms of depression, anxiety, and stress in caregivers of people with mental illness. The effects remained at the 6-month follow-up. Positive effects of CCT compared with the control group were observed on overall well-being, resilience, self-compassion, and cognitive reappraisal, an emotion regulation strategy. Perceived stress was reduced as well as emotion suppression, another emotion regulation strategy. Of the 5 facets of mindfulness, 4 facets either increased, such as observing and describing, or decreased, such as nonjudging and nonreacting. No significant results were observed on the facet of awareness and on the 4 dimensions or total score of the Multidimensional Compassion Scale. This may be associated with the fact that these dimensions of compassion require more time to cultivate. Furthermore, there is a lack of consensus on how to define and measure the compassion for others construct.[13]

Our findings that CCT decreased psychological distress and increased overall well-being are in line with previous RCTs on CCT.[15-19] Comparing the results of our study with previous caregiver intervention studies, the literature does not present a clear picture of what kind of intervention is most helpful for caregivers of people with mental illness. An 8-week manualized group intervention with psychoeducation,[31,32] a caregiver education and social support program,[33] a cognitive behavioral therapy group,[34,35] a mindfulness-based stress reduction program,[36,37] and a yoga and compassion meditation program[38] have shown improved mental health at the end of treatment, but have either not tested the effect at the 6-month follow-up or not found significant results. An individual therapy session intervention[39] with 6 months of follow-up has produced similar results as our CCT study.

Systematic reviews and meta-analyses of caregiver interventions and mental health have found different results based on the type of mental illness. Psychoeducational and group interventions may be most helpful to people with severe mental illness,[40] while individual in-home multicomponent or psychoeducational interventions may be most helpful to caregivers of people with dementia.[41] Therefore, there is a great need for structured and systematic trials that replicate trials like this study of a CCT program with an active control group to understand whether the results observed here continue to be superior when an active control group is included, and investigate what mechanisms are the most helpful in interventions for informal caregivers.

Strengths and Limitations

This study's strengths include a well-powered, rigorously conducted RCT with 6-month follow-up data, a high-risk population that included citizens with broad inclusion criteria from 2 different geographically settings in Denmark, which enhances the generalizability of the results to a broad target population. However, we did not perform subgroup or effect modification analysis to

Table 3. Effect of CCT on Secondary Outcome Measures in Informal Caregivers of People With Mental Illness at Postintervention and 3- and 6-Month Follow-ups

Measure	CCT intervention			Control			Between-group difference, mean (95% CI)[a]	*P* value	Cohen *d*
	Caregivers, No.	Score, mean (SD)	Within-group change from baseline, mean (95% CI)[a]	Caregivers, No.	Score, mean (SD)	Within-group change from baseline, mean (95% CI)[a]			
BRS									
Baseline	77	3.11 (0.78)	NA	81	2.95 (0.81)	NA	NA	NA	NA
Postintervention	69	3.35 (0.85)	0.28 (0.14 to 0.43)	77	2.94 (0.80)	0 (−0.13 to 0.14)	0.28 (0.08 to 0.48)	.006	0.48
3 mo	63	3.46 (0.67)	0.35 (0.20 to 0.50)	77	2.97 (0.81)	0.04 (−0.10 to 0.17)	0.32 (0.12 to 0.52)	.002	0.60
6 mo	54	3.50 (0.89)	0.35 (0.20 to 0.51)	73	2.97 (0.88)	0.03 (−0.11 to 0.17)	0.32 (0.11 to 0.53)	.002	0.36
WHO-5									
Baseline	77	46.81(20.85)	NA	81	43.46 (19.10)	NA	NA	NA	NA
Post	68	55.76(19.74)	9.01 (4.51 to 13.52)	78	42.10 (19.41)	−1.17 (−5.40 to 3.07)	10.18 (3.99 to 16.36)	.001	0.74
3 mo	63	57.84(19.34)	10.51 (5.90 to 15.13)	77	46.39 (19.97)	3.12 (−1.14 to 7.37)	7.40 (1.12 to 13.67)	.02	0.53
6 mo	54	56.96(21.57)	8.91 (4.02 to 13.80)	73	44.82 (21.52)	1.38 (−2.95 to 5.71)	7.53 (1.00 to 14.05)	.02	0.35
PSS									
Baseline	79	21.20 (6.06)	NA	81	22.70 (6.60)	NA	NA	NA	NA
Postintervention	68	17.03 (6.57)	−4.48 (−5.87 to −3.09)	75	22.25 (7.41)	−0.27 (−1.60 to 1.06)	−4.21 (−6.14 to −2.29)	< .001	0.85
3 mo	63	17.10 (6.48)	−3.82 (−5.25 to −2.39)	76	21.62 (7.22)	−0.97 (−2.29 to 0.36)	−2.85 (−4.80 to −0.90)	.004	0.59
6 mo	54	16.85 (6.68)	−3.81 (−5.32 to −2.30)	73	20.85 (6.95)	−1.82 (−3.17 to −0.48)	−1.99 (−4.01 to 0.03)	.05	0.29
ERQ									
Reappraisal									
Baseline	79	25.57 (7.23)	NA	81	24.54 (6.71)	NA	NA	NA	NA
Postintervention	68	29.71 (6.17)	4.06 (2.68 to 5.45)	75	24.32 (7.20)	−0.07 (−1.40 to 1.26)	4.13 (2.21 to 6.05)	< .001	0.87
3 mo	63	29.68 (6.24)	3.48 (2.06 to 4.91)	77	25.39 (6.74)	0.84 (−0.48 to 2.15)	2.65 (0.71 to 4.59)	.007	0.58
6 mo	54	29.41 (6.84)	3.30 (1.79 to 4.80)	72	25.90 (6.98)	1.27 (−0.07 to 2.61)	2.02 (0.01 to 4.04)	.049	0.29
Suppression									
Baseline	79	12.68 (5.18)	NA	80	12.1 (4.34)	NA	NA	NA	NA
Postintervention	67	11.37 (3.80)	−1.14 (−2.16 to −0.12)	78	12.38 (5.53)	0.26 (−0.70 to 1.23)	−1.40 (−2.81 to 0)	.05	0.42
3 mo	63	11.32 (4.54)	−1.43 (−2.47 to −0.38)	77	12.05 (4.90)	0 (−0.97 to 0.96)	−1.42 (−2.85 to 0)	.05	0.43
6 mo	54	11.39 (4.82)	−1.28 (−2.38 to −0.17)	73	12.52 (4.61)	0.37 (−0.61 to 1.36)	−1.65 (−3.13 to −0.17)	.03	0.35
FFMQ									
Observing									
Baseline	77	10.23 (2.42)	NA	80	10.65 (2.70)	NA	NA	NA	NA
Postintervention	69	10.94 (2.45)	1.07 (0.58 to 1.57)	77	9.91 (2.69)	0.40 (−0.08 to 0.87)	0.68 (−0.01 to 1.36)	.05	0.37
3 mo	63	11.35 (2.49)	1.49 (0.97 to 2.00)	77	9.71 (2.72)	0.10 (−0.37 to 0.57)	1.39 (0.69 to 2.09)	< .001	0.75
6 mo	54	11.15 (2.37)	1.27 (0.72 to 1.81)	72	9.69 (2.78)	0.07 (−0.41 to 0.55)	1.20 (0.47 to 1.93)	.001	0.65
Describing									
Baseline	79	9.87 (2.75)	NA	81	9.63 (2.77)	NA	NA	NA	NA
Postintervention	68	11.25 (2.34)	1.17 (0.70 to 1.63)	78	10.56 (2.69)	−0.70 (−0.51 to 0.37)	1.24 (0.60 to 1.88)	< .001	0.69

(continued)

Table 3. Effect of CCT on Secondary Outcome Measures in Informal Caregivers of People With Mental Illness at Postintervention and 3- and 6-Month Follow-ups (continued)

Measure	CCT intervention			Control			Between-group difference, mean (95% CI)[a]	*P* value	Cohen *d*
	Caregivers, No.	Score, mean (SD)	Within-group change from baseline, mean (95% CI)[a]	Caregivers, No.	Score, mean (SD)	Within-group change from baseline, mean (95% CI)[a]			
3 mo	63	11.65 (2.03)	1.52 (1.05 to 2.00)	77	10.74 (2.59)	0.09 (−0.35 to 0.53)	1.43 (0.78 to 2.08)	<.001	0.87
6 mo	54	11.74 (2.51)	1.49 (0.99 to 2.00)	73	10.27 (2.70)	−0.19 (−0.64 to 0.26)	1.69 (1.01 to 2.36)	<.001	0.91
Awareness									
Baseline	79	9.42 (2.50)	NA	82	9.28 (2.60)	NA	NA	NA	NA
Postintervention	67	10.21 (2.35)	0.79 (0.23 to 1.34)	77	9.60 (2.56)	0.28 (−0.24 to 0.80)	0.50 (−0.25 to 1.26)	.19	0.29
3 mo	63	10.57 (2.19)	1.10 (0.54 to 1.66)	76	9.78 (2.83)	0.51 (−0.01 to 1.03)	0.59 (−0.18 to 1.36)	.13	0.33
6 mo	54	10.26 (2.51)	0.76 (0.17 to 1.36)	72	9.19 (2.68)	0.02 (−0.51 to 0.55)	0.74 (−0.06 to 1.54)	.07	0.40
Nonjudging									
Baseline	79	10.06 (2.45)	NA	80	10.05 (2.70)	NA	NA	NA	NA
Postintervention	68	11.43 (2.13)	1.49 (0.92 to 2.07)	75	10.17 (2.99)	0.47 (−0.06 to 1.01)	1.36 (0.59 to 2.14)	.001	0.74
3 mo	63	11.56 (2.39)	1.66 (1.05 to 2.27)	76	10.62 (2.73)	0.20 (−0.34 to 0.74)	1.02 (0.24 to 1.81)	.01	0.56
6 mo	54	11.69 (2.37)	1.36 (0.59 to 2.14)	73	10.26 (2.74)	1.37 (0.81 to 1.93)	1.46 (0.64 to 2.27)	<.001	0.81
Nonreacting									
Baseline	79	7.61 (2.10)	NA	80	7.2 (2.80)	NA	NA	NA	NA
Postintervention	68	9.35 (1.88)	1.75 (1.21 to 2.29)	78	7.18 (2.62)	0.08 (−0.43 to 0.60)	1.67 (0.92 to 2.41)	<.001	1.04
3 mo	62	9.23 (2.38)	1.57 (1.01 to 2.13)	77	7.65 (2.90)	0.51 (−0.01 to 1.02)	1.06 (0.30 to 1.83)	.006	0.56
6 mo	54	9.5 (2.77)	1.78 (1.19 to 2.37)	73	7.66 (2.68)	0.52 (0 to 1.05)	1.26 (0.47 to 2.05)	.002	0.65
Total									
Baseline	79	37.32 (5.96)	NA	77	37.31 (7.37)	NA	NA	NA	NA
Postintervention	65	42.26 (6.32)	5.01 (3.62 to 6.40)	74	37.45 (7.63)	0.18 (-1.15 to 1.50)	4.83 (2.91 to 6.75)	<.001	0.97
3 mo	62	42.90 (6.30)	5.70 (4.29 to 7.12)	76	38.80 (8.25)	1.50 (0.18 to 2.81)	4.21 (2.28 to 6.14)	<.001	0.81
6 mo	54	43.19 (7.32)	5.70 (4.22 to 7.19)	72	37.31 (7.75)	0.52 (−0.82 to 1.86)	5.18 (3.18 to 7.18)	<.001	0.69
SCS									
Baseline	76	36.45 (7.20)	NA	80	34.9 (8.13)	NA	NA	NA	NA
Postintervention	67	41.52 (7.57)	5.21 (3.66 to 6.76)	76	35.5 (8.71)	0.70 (−0.75 to 2.14)	4.52 (2.40 to 6.63)	<.001	0.78
3 mo	63	43.06 (7.90)	6.36 (4.78 to 7.94)	75	34.97 (8.85)	0.28 (−1.17 to 1.72)	6.08 (3.94 to 8.22)	<.001	1.03
6 mo	54	42.19 (8.56)	5.31 (3.64 to 6.99)	73	35.51 (8.37)	1.03 (−0.43 to 2.50)	4.28 (2.05 to 6.50)	<.001	0.51
MCS									
Cognitive									
Baseline	78	2.12 (0.77)	NA	81	2.04 (0.76)	NA	NA	NA	NA
Postintervention	68	1.82 (0.85)	−0.31 (−0.49 to −0.12)	77	2.03 (0.66)	0.01 (−0.16 to 0.19)	−0.32 (−0.58 to −0.63)	.02	0.59
3 mo	63	1.90 (0.85)	−0.20 (−0.40 to −0.01)	77	2.02 (0.72)	−0.01 (−0.19 to 0.16)	−0.19 (−0.45 to 0.07)	.15	0.34
6 mo	54	1.82 (0.69)	−0.29 (−0.49 to −0.09)	73	1.97 (0.59)	−0.02 (−0.20 to 0.16)	−0.27 (−0.54 to 0)	.05	0.59
Affective									
Baseline	78	2.43 (0.95)	NA	81	2.27 (0.95)	NA	NA	NA	NA

(continued)

Table 3. Effect of CCT on Secondary Outcome Measures in Informal Caregivers of People With Mental Illness at Postintervention and 3- and 6-Month Follow-ups (continued)

Measure	CCT intervention			Control			Between-group difference, mean (95% CI)[a]	*P* value	Cohen *d*
	Caregivers, No.	Score, mean (SD)	Within-group change from baseline, mean (95% CI)[a]	Caregivers, No.	Score, mean (SD)	Within-group change from baseline, mean (95% CI)[a]			
Postintervention	67	2.57 (0.93)	0.17 (−0.02 to 0.34)	76	2.39 (1.06)	0.18 (0.01 to 0.36)	−0.01 (−0.27 to 0.24)	.91	0.01
3 mo	63	2.42 (0.92)	0.03 (−0.16 to 0.22)	76	2.31 (1.06)	0.03 (−0.14 to 0.21)	0 (−0.26 to 0.26)	>.99	0
6 mo	54	2.50 (0.98)	0.04 (−0.16 to 0.24)	73	2.33 (0.96)	0.04 (−0.13 to 0.22)	0 (−0.27 to 0.27)	.99	0
Intentional									
Baseline	78	2.40 (0.83)	NA	80	2.45 (0.85)	NA	NA	NA	NA
Postintervention	68	2.01 (0.74)	−0.23 (−0.41 to −0.06)	77	2.25 (0.89)	0 (−0.17 to 0.17)	−0.23 (−0.48 to 0.01)	.06	0.40
3 mo	62	2.10 (0.66)	−0.12 (−0.30 to 0.07)	77	2.28 (0.82)	0.05 (−0.12 to 0.25)	−0.17 (−0.41 to 0.08)	.19	0.32
6 mo	53	2.13 (0.72)	−0.14 (−0.33 to 0.06)	72	2.29 (0.76)	0.04 (−0.13 to 0.21)	−0.18 (−0.44 to 0.08)	.17	0.34
Motivational									
Baseline	78	2.26 (0.78)	NA	81	2.22 (0.80)	NA	NA	NA	NA
Postintervention	67	2.56 (0.81)	0.15 (−0.04 to 0.33)	77	2.56 (0.91)	0.07 (−0.10 to 0.25)	0.07 (−0.18 to 0.33)	.57	0.11
3 mo	62	2.44 (0.67)	0.08 (−0.12 to 0.27)	77	2.59 (0.97)	0.10 (−0.08 to 0.28)	−0.02 (−0.29 to 0.24)	.86	0.03
6 mo	54	2.49 (0.82)	0.07 (−0.13 to 0.27)	73	2.57 (0.79)	0.07 (−0.11 to 0.24)	0 (−0.27 to 0.27)	.98	0
Total									
Baseline	75	2.22 (0.59)	NA	77	2.16 (0.62)	NA	NA	NA	NA
Postintervention	63	2.17 (0.63)	−0.01 (−0.14 to 0.12)	72	2.22 (0.65)	0.07 (−0.06 to 0.19)	−0.08 (−0.26 to 0.11)	.41	0.17
3 mo	60	2.15 (0.59)	0 (−0.14 to 0.13)	76	2.23 (0.62)	0.06 (−0.07 to 0.18)	−0.06 (−0.24 to −0.12)	.54	0.14
6 mo	53	2.18 (0.59)	0.03 (−0.17 to 0.11)	72	2.20 (0.48)	0.02 (−0.10 to 0.15)	−0.05 (−0.24 to 0.13)	.57	0.09

Abbreviations: BRS, Brief Resilience Scale; CCT, compassion cultivation training; ERQ, Emotion Regulation Questionnaire; FFMQ, Five Facet Mindfulness Questionnaire; MCS, Multidimensional Compassion Scale; NA, not applicable; PSS, Perceived Stress Scale; SCS, Self Compassion Scale; WHO-5, World Health Organization 5-item Well-Being Index.

[a] Adjusted for sex, age, educational level, years as informal caretaker, and diagnosis of schizophrenia or anxiety for patient.

investigate whether the effect differed given some characteristics (eg, diagnosis of loved one). It was outside the scope of this RCT, and the RCT was not powered to do so. The CCT intervention is a manualized program, the psychologist was experienced in delivering the CCT program and was supervised.

This study also has some limitations, including differential loss to follow-up at 6 months, which could bias the results. To mitigate against this possibility, we conducted sensitivity analysis for the primary and secondary outcomes and observed that all results remained statistically significant. A waitlist design has the potential to overestimate intervention effects owing to issues of expectancy. Research has shown larger effects sizes in favor of this type of control group when compared with treatment as usual.[35] As the trial did not include an active control group, we are not able to determine whether the CCT program had a greater effect compared with another type of intervention. However, a waitlist comparator may be more reflective of what usually happens in the absence of an intervention like CCT. We cannot rule out the potential bias caused by the nonblinding of the intervention allocation, as expectations may have been influenced by their allocation. Another limitation was that 2 teams of caregivers (eg, 2 parents sharing caregiving for an adult child with mental illness) were included in the trial. There is a possibility that a cluster effect may exist. The parental team was randomized into the control group and the mother/daughter team was randomized into the intervention group. We used self-reported outcome measures, and cannot exclude the possibility that information bias is present, although all participants in the waitlist group, regardless of whether they answered the self-report questionnaires, were invited to participate in the CCT group after collecting 6-month follow-up data.

Conclusions

This RCT found that the CCT intervention improved the mental health of a mixed group of caregivers whose loved ones had a variety of mental illnesses, with lasting effect of 6 months. The results suggest that compassion is a trainable skill that promotes mental health and that CCT could be taught in a group format reducing societal cost. According to WHO, depression is the leading cause of disability worldwide, and perceived stress is an independent risk factor for increased illness and mortality.[42] Policy makers and health care professionals have few options in offering caregiver's evidence-based interventions that help improve their mental health.[43] Future research should replicate findings and compare the intervention with an active control. Furthermore, a potential mediating effect of the CCT intervention on compassion for self and mindfulness on psychological distress should be explored and future research should investigate whether there is a difference in the effect depending on caregiver status, type of mental disorder, and length of intervention.

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SUPPLEMENT 1.
Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
eTable 1. Steps of the Compassion Cultivation Training Program
eTable 2. Loss to 6-Month Follow-up Analysis of Included and Missing Participants in Both the CCT Intervention and Waitlist Control Groups at 6-Month Follow-up
eTable 3. Loss to 6-Month Follow-up Analysis of Included and Missing Participants in the CCT Intervention Group at 6-Month Follow-up
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eTable 5. Sensitivity Analysis of Primary Outcome of Psychological Distress
eTable 6. Sensitivity Analysis of Secondary Outcome of Overall Well-Being

SUPPLEMENT 3.
Data Sharing Statement

AARHUS UNIVERSITY

Mediators for the effect of compassion cultivating training: A longitudinal path analysis in a randomized controlled trial among caregivers of people with mental illness (paper III)

Mediators for the effect of compassion cultivating training: A longitudinal path analysis in a randomized controlled trial among caregivers of people with mental illness

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Abstract

Background There is a paucity of research on mediators of change, within compassion training programs. The aim was to investigate the mediators, of an eight-week compassion cultivation training (CCT) program, on the effect of psychological distress on caregivers of people with a mental illness

Method Longitudinal path models in a randomized controlled trial (RCT). 192 participants were assessed for eligibility and 161 participants were included into the trial and randomized. Main outcome was psychological distress measured by Depression, Anxiety and Stress Scale at 6 months. Mediators included Self-Compassion (SC), Mindfulness (FM), and Emotion Regulation (Emotion Suppression (ES) and Cognitive Reappraisal (CR). Baseline, post, 3-and 6-month follow-up measurements were collected.

Results Mediated effects for CCT; depression at 6 months: SC: -1.81 (95% CI:-3.31 to -0.31); FM: -1.98 (95% CI:-3.65 to -0.33); ER: -0.14 (95% CI:-1.31 to 1.02) ; anxiety at 6 months: SC: -0.71 (95% CI:-1.82 to 0.40); FM: -1.24 (95% CI:-2.39 to -0.09); ER: 0.18 (95% CI:-1.04 to 1.40); stress at 6 months: SC: -1.44 (95% CI:-2.84 to -0.05); FM: -2.17 (95% CI:-3.63 to -0.71); ER: -0.27 (95% CI:-1.51 to 0.98).

Conclusion Mindfulness and self-compassion are important components in reducing psychological distress experienced by caregivers of people with a mental illness. Results contribute to the knowledge about the underlying mechanisms of CCT.

Introduction

Poor mental health is on the rise (WHO, 2021), and there is a need for evidence-based interventions that decrease psychological distress and increase overall well-being. Compassion-based training programs may be one way to address this need (Kirby et al., 2017). Compassion can be understood as the willingness to feel the suffering of one self and others and to do something to relieve the suffering (Fischer, 2012). Compassion is essential in caregiving and can become a practice of turning toward suffering rather than away, and is a trainable skill (Weng et al., 2013).
Despite growing evidence, the processes underlying treatment response remain unclear (Jazaieri, 2012). In fact, there is a paucity of research on the mediators (an intervening variable that may statistically account for the relationship between the independent and dependent variable) of compassion training programs (Alsubaie et al., 2017; Sommers-Spijkerman et al., 2018). To our knowledge, only one randomised controlled trial (RCT) have investigated the mediating variables of a self-help book intervention that was based on the principles of a compassion-based therapy (Gilbert, 2009; Sommers-Spijkerman et al., 2018). Results showed that positive affect significantly mediated well-being and depressive symptoms, and negative affect significantly mediated well-being and anxiety symptoms (Sommers-Spijkerman et al., 2018).

Four RCT studies investigated mediators of an eight week Mindfulness-Based Stress Reduction (MBSR) program on anxiety disorders (Alsubaie et al., 2017). Results suggested that effects of the MBSR program were mediated by increases in positive self-views, decentering, and mindfulness Limitations included small sample size and only two time-points of measurement (Alsubaie et al., 2017). Systematic reviews (Alsubaie et al., 2017; Gu et al., 2015; van der Velden et al., 2015) investigating the mechanisms of Mindfulness-Based Interventions (MBI), found evidence supporting the mediating role of mindfulness and compassion (Gu et al., 2015), moderate evidence for mindfulness and insufficient evidence for self-compassion and psychological flexibility (van der Velden et al., 2015). Moreover, greater self-reported changes in mindfulness lead to greater mediated clinical outcomes (Alsubaie et al., 2017). An important limitation of all the studies included were that

none of them fully met Kazdin's criterias for examining treatment mechanisms (Kazdin, 2007), namely: 1) a clear association between change in the proposed mediator and the proposed outcome, and 2) that change in the mediator precedes change in the outcome (Kazdin, 2007). The studies included some theory, wide variability in measures used, time assessments were not optimal to test mediators and all studies failed to assess whether changes in the mediators preceded the changes in the outcomes (Alsubaie et al., 2017).

We recently published a trial showing effect on mental health of a CCT program in caregivers of people with a mental illness (Hansen et al., 2021). The RCT showed effect of CCT on outcomes as well as proposed mediators; mindfulness (FM), self-compassion (SC) and emotion regulation measures; cognitive reappraisal (ER) and emotion suppression (ES) (Hansen et al., 2021). However, whether it was the effect on the mediators that led to the effect in the outcomes is unknown and require further investigation.

Therefore, the expected link between intervention activities, mediators and outcomes can be depicted by use of a logic model (Fraser, 2009; Moore et al., 2015). It has been suggested to divide a logic model into two; an action theory and a conceptual theory (Gottfredson et al., 2015). The conceptual theory describes how the mediators are related to the outcome(s). The action theory describes, how the intervention is supposed to affect the mediators. Our effectiveness trial supported the action theory as it showed statistically significant effects of CCT on mindfulness, self-compassion and emotion regulation (Hansen et al., 2021). Our pre-defined conceptual theory, was based on the Process Model of Emotion Regulation developed by Gross and John (Gross & John, 2003) . Numerous studies have shown that cognitive reappraisal and expressive suppression are among the most common explicit cognitive emotion regulation strategies (Hu et al., 2014) and are considered to have an important impact and effect on mental health and overall well-being. Difficulties in emotion regulation is related to psychological problems, contributing to depression and anxiety (Hu et al., 2014).

We therefore hypothesized that training in mindfulness allowed for caregivers to become aware of what they were currently experiencing (Kabat-Zinn, 1982), and training in self-compassion allowed participants to turn towards their own suffering in a kind and caring manner (Neff & Germer, 2013).

This in turn allowed caregivers to increase cognitive reappraisal and decrease expressive suppression (Hu et al., 2014). Specifically: An increase in scores of self-compassion and mindfulness will mediate the effects of emotion regulation skills i.e. increase cognitive reappraisal and decrease expressive suppression, which will mediate the effects of psychological distress in informal caregivers. The aim of the current study was therefore, to estimate the mediating effects of mindfulness, self-compassion and emotion regulation for CCT on symptoms of depression, anxiety and stress at 6 months follow up, in caregivers of people suffering from a mental illness.

Methods

Study design and participants

The current study design is longitudinal path model in an RCT. This is a secondary mediation analysis of a published RCT (Hansen et al., 2021) comparing a CCT intervention to waitlist control group for informal caregivers of people with a mental illness. Details of the RCT and adherence to the Consolidated Standards of Reporting Rrials (CONSORT) reporting guidelines have been reported previously (Hansen et al., 2021). The trial was conducted in two different community settings in Denmark and ethical approval was obtained at the Central Denmark Region Committee of Health Research Ethics (De Videnskabsetiske Komitéer for Region Midtjylland) with approval 238/2017. The study was registered in ClinicalTrails.gov NCT03730155 before commencement. One-hundred and sixty-one caregivers of a relative with a mental disorder were included in the study.

A computer algorithm with predefined concealed random numbers was used for the block randomization with forty participants in each block all randomized at the same time. To be included in the RCT participants had to be an informal caregiver (e.g. a parent /spouse/adult child/sibling of a person suffering from a mental illness (all mental illnesses were included as described in *Diagnostic and Statistical Manual of Mental Disorders – 5 (DSM-5) (APA, 2013)*, between the age of 18 - 75 years and Danish speaking. Participants were excluded if they had a diagnosed and untreated mental illness, if they suffered from addictions, if they had a meditation practice, or received current psychotherapeutic treatment.

Data was collected between May 2018 - March 2019. Nineteen males and 142 females, with a mean age of 52.6. N=79 were randomized into the intervention group and N=82 were randomized into the

waitlist control group (Supplemental Efigure 1). Demographic measures were similar for both groups at baseline (Table 1). Measures were completed at four time points: baseline, two, three and six-month follow-up (Hansen et al., 2021).

Intervention

CCT is a eight-week manualized compassion training program, developed in 2009 at Stanford University (Brito-Pons, 2018; Jazaieri, 2012). The program has a dual focus on training compassion and loving kindness for one's own suffering and the suffering of others, and an implicit focus on mindfulness (for a more detailed description of the program format, please see Hansen et al., 2021). Participants meet weekly for 2 hours, and the group intervention was delivered face-to-face with 20 participants per group.

Blinding

Owing to the nature of the intervention, the participants and the CCT instructor were aware of treatment allocation and the researchers (NHH and LJ) were not blinded to group assignment when analyzing the data.

Outcome and Mediator Measures

We assessed the primary outcome of psychological distress using the 42-item Depression Anxiety Stress Scale (DASS), which measures symptoms of depression, anxiety and stress (S. H. Lovibond, & Lovibond, P.F., 1995). The internal consistency for each of the subscales is high: Depression scale, Chronbach's α of 0.91, Anxiety scale 0.84, and for the Stress scale 0.90 (S. H. Lovibond, & Lovibond, P.F., 1995). We assessed the mediators using the 12 item Self-Compassion Scale (SC) (Raes et al., 2011), designed to measure participants level of self-compassion with a correlation r = 0.97, which is very high between the SCS-26 and the SCS-12 for a total score of self-compassion. The 15-item Five Facet Mindfulness Questionnaire (FM) (Baer et al., 2006), is designed to measure five facets of mindfulness and the internal consistency has been found to be adequate for the FFMQ-15 (Gu et al., 2016). Lastly, the 10-item Emotion Regulation Questionnaire (ERQ), which measures two different emotion regulation strategies; Cognitive Reappraisal (ER) and Expressive Suppression (ES) (Gross & John, 2003). ERQ cognitive reappraisal (ER) (α = .89-.90) and expressive suppression (ES) (α = .76-

.80) scores showed between acceptable to excellent levels of internal consistency reliability (Gross & John, 2003). Danish versions of the instruments were used. The covariates were sex, age, educational level, years as informal caretaker, schizophrenia and anxiety (diagnosis of loved ones).

Statistical analysis

We analyzed the data using autoregressive models, with four time points of measurement, and contemporaneous and constant b paths (Goldsmith et al., 2018; MacKinnon, 2017) (Figure 1). The data were checked for normal distribution prior to analysis. For each outcome, we analyzed four models that included each mediator as single mediator. For each outcome, we analyzed a model that included all mediator variables, which had shown to be statistically significant mediators in the single mediator model at six-month follow up (Figure 2). The model with multiple mediators included direct paths from all mediators to the outcome (OC) and from FM and SC to ER. We fitted models in the structural equation model (SEM) framework in Stata 16 (Acock, 2013), using full information maximum likelihood and conditioning on covariates to account for missing data under the missing at random assumption.

We adjusted at baseline for the mediators and outcome values for the following covariates in the models: sex, age, educational level, years as informal caretaker, schizophrenia and anxiety (diagnosis of loved one). We allowed for correlations between baseline mediator and outcome measurements errors in order to prevent contamination of the b paths, and allowed for correlations of the errors of the mediator and outcome measurements over time. In the model with multiple mediators, we allowed for contemporaneous correlations between the errors of the mediator measurements.

In order to estimate the mediated effect of CCT on outcomes at six months in the model with single mediators, we first identified all paths that went from randomization to outcome at six months through any measure of the mediator and for each type of mediator. We multiplied the coefficients within each of these paths and added the path specific products to obtain the mediated effect.

In the model with multiple mediators, there were five types of mediated effects: mediated, only by FM, only by SC, only by ER, by FM and ER, and by SC and ER. For each of these we identified the relevant path and proceeded as above. The unmediated effect was estimated based on paths from randomization to outcome at 6 months not passing a mediator (all paths from randomization going to

outcomes at six months that started with a direct path for randomization to outcome at two months). The total effect was the combined effect via all paths from randomization to outcome (the sum of all the mediated effects and the unmediated effect).

We estimated the 95% CI´s of the results of the overall a paths, the mediated, the unmediated and the total effect, by use of 50 bootstrap replications. Goodness of fit of the models were tested by chi-squared test, the comparative fit index (CFI) and the root mean squared error of approximation (RMSEA). We used the following criteria to evaluate model fit; a CFI above 0.90 indicates a good model fit. A RMSEA below 0.08 indicates an acceptable model fit, and a RMSEA below 0.05 indicates good model fit (Acock, 2013; Goldsmith et al., 2018; Loehlin, 2017).

Results

DASS-depression

Results of the single mediation model showed that SC, FM, and ER all had statistically significant overall mediated effect for CCT on depression at six-months follow up (Supplemental Etable 1). Results of the model with ES as single mediator did not show statistically significant mediated effect (Supplemental Etable 1).

Results of the multiple mediator model including SC, FM and ER (Figure 2) showed that only SC and FM remained statistically significant mediators for the effect of CCT on symptoms for depression at six months: SC: -1.81 (95% CI -3.31 to -0.31), and FM: -1.98 (95% CI -3.65 to 0.33) (Table 2). The mediated effect of ER attenuated and was statistically insignificant: -0.14 (95% CI -1.31 to 1.02). Results suggested that both the overall a path and the b path were statistically insignificant when adjusted for the mediated effects of SC and FM (Table 2). Moreover, the mediated effects from SC and FM through ER were statistically insignificant: SC -> ER: 0.05 (95% CI -0.32 to 0.41); FM -> ER: 0.00 (95% CI -0.16 to 0.17) (Table 2). Goodness of fit tests in terms of RMSEA and CFI suggested acceptable model fits (Table 2).

DASS-anxiety

All the models with symptoms of anxiety as outcome did not show statistically significant total effects (Table 2 and Supplemental Etable 1). However, the single model with FM, SC and ER as mediators suggested statistically significant a and b paths and thereby also statistically significant mediated effects. The model with ES as single mediator did not show neither statistically significant a or b paths (Supplemental Etable 1). Results of the multiple mediator model including SC, FM and ER (Figure 2) suggested solely mediated effect of FM for CCT on symptoms on anxiety at 6 months follow up: FM: -0.12 (95% CI -0.20 to -0.03) (Table 2). Goodness of fit tests in terms of RMSEA and CFI suggested acceptable model fits (Table 2).

DASS-stress

Lastly, the single model with SC, FM and ER as mediators showed statistically significant mediated effects on symptoms of stress, and the total effects were statistically significant (Supplemental Etable 1). Results of ES in the single mediator model suggested that the mediated effect of ES for CCT on symptoms of stress at six months follow-up was statistically insignificant (Supplemental Etable 1) . Results of the multiple mediator model including SC, FM and ER (Figure 2) showed that the statistically significant mediated effects of SC and FM remained; SC: -1.44 (95% CI -2.83 to -0.05); FM: -2.17 (95% CI -3.63 to -0.71). However, the mediated effect of ER for CCT on stress attenuated and was statistically insignificant; -0.27 (95% CI -1.51 to 0.98). The results showed that both the overall a path and the b path estimate attenuated when adjusted for the mediated effects of self-compassion and mindfulness (Table 2). Goodness of fit tests in terms of RMSEA and CFI suggested acceptable model fits (Table 2).

Discussion

We found strong indications for mindfulness and self-compassion as mediators of the effect of CCT on symptoms of depression and stress at six-month follow up in caregivers of people with mental illness. Regarding symptoms of anxiety, we only found indication for mindfulness as mediator. We found no support for our hypothesis regarding emotion regulation (ER and ES) as mediators and mediation of emotion regulation through mindfulness or self-compassion was also not found.

A systematic review (Inwood & Ferrari, 2018), investigated the mechanisms of change in the relationship between self-compassion, emotion regulation and mental health (Inwood & Ferrari, 2018). All studies observed a significant negative relationship between self-compassion and emotion dysregulation. The findings were suggested to support the hypothesis that self-compassion work through emotion regulation to influence mental health outcomes. Limitations of the studies included small sample size and cross-sectional designs, thereby not obtaining temporal sequencing (Inwood & Ferrari, 2018).

Contrary to these findings, our study suggests that cognitive emotion regulation strategies are not mediating effects in decreasing psychological distress and that self-compassion and mindfulness are. Taken together, these results may suggest that self-compassion and mindfulness are not cognitive emotion regulating strategies but may be thought of as self-regulating or implicit emotion regulating strategies (Inwood & Ferrari, 2018).

David Vago and colleagues (Vago & Silbersweig, 2012) proposed a complex theory of the mechanisms of mind training. The framework focuses on self-processing and the underlying neural systems involved in self-awareness, -regulation, and -transcendence (S-ART). According to S-ART, perceptions, cognitions, and emotions related to our daily ordinary experiences may be biased, leading to unhealthy habits of mind with or without psychopathology (Vago & Silbersweig, 2012). Mind training, including the practice of mindfulness and compassion, leads to the development of: 1) self-awareness, 2) self-regulation, and 3) self-transcendence. Self-processing and self-regulation may therefore be heavily influenced through mind training and social interactions.

In the light of the above framework, caregivers are motivated to learn skills to take better care of their own mental health, with an intention to do so by completing an intervention. During the intervention they practice increasing and regulating attention and emotions towards kindness and compassion. This leads to a shift from external to internal awareness, and experiencing the benefits of mindfulness and compassion training from the inside. The educational component of compassion throughout the course, help caregivers understand that suffering is universal. Acknowledging and holding the suffering in a mindful and self-compassionate atmosphere may lead to the reduced symptoms of stress, anxiety and

depression. Furthermore, while biased cognition often directs a person to isolation, blame, and judgement, being in a group offers an opportunity for kindness and connection towards self and others. Therefore, as emotions are co-regulated through interactions, we suggest that learning in a group may also impact the caregivers' ability to reduce suffering.

Strengths and limitations

This is the first study to date that have investigated multiple mediators of the manualized CCT program, on symptoms of depression, anxiety, and stress. We investigated four potential mediators, established a timeline with four time points, and used a theory as an underlying guide. In addition, we analyzed the mediated and unmediated effects simultaneous by use of longitudinal path models in a RCT design inspired by Goldsmith et al., (2018). Including multiple mediators highlights the importance of adjusting for the effect of the most promising mediators. When analyzed in single mediation models, cognitive reappraisal seemed to be a statistically significant mediator. However, when adjusted for the mediating effects of mindfulness and self-compassion the effect disappeared.

We assumed the relationship between the mediater and outcome (conceptual theory) to be reasonably consistent over time. Hence, we made the b paths equal as constant b paths should provide more precise estimation (Goldsmith et al., 2018). We choose to use contemporaneous b paths (Kraemer et al., 2002), because we expected that changes in the mediators, as well as the outcomes, began during the CCT intervention, occurring before the first post randomization measurement (MacKinnon, 2017). Our results of the a paths and previously published total effects (Hansen et al., 2021) also showed that the CCT effects occurred primarily at the first post measurement point, but remained at 6 months follow up (Hansen et al., 2021) (Table 2, except for ER).

We did not find statistically significant total effects on anxiety at six months (Table 2). In our previously published effect analysis, we found statistically significant effect of CCT on anxiety at six months follow up: -2.12 (95% CI -3.96 to-0.29) (Hansen et al., 2021). The difference in results may be explained by use of different statistical models. Our previous analysis was conducted using a repeated measurement mixed effect model according to protocol (Hansen et al., 2021). The purpose of the

current path analysis was to investigate mediation. Kraemer et al., (2002) suggests that it makes sense to investigate mediating effects even without statistically significant total effects.

Unfortunately, it was not feasible to adjust for measurement error of latent variables as suggested by Goldsmith et al., (2018). As they only illustrated the application of the model on simulated data, their tutorials were not compatible with real data (Goldsmith et al., 2018). Hence, it is a limitation that our models only include observed measurements thereby including measurement error. However, our analysis addressed the limitations described in previous systematic reviews and meta-analysis (Alsubaie et al., 2017; Gu et al., 2015; van der Velden et al., 2015) and followed Kazdin's recommendations for research on mediators (Alsubaie et al., 2017; Kazdin, 2007).

Conclusion

Mindfulness and self-compassion are important components in reducing the psychological distress experienced by caregivers of people with a mental illness. These results contribute to the knowledge about the underlying mechanisms of a compassion cultivation training program.

Conflict of interest Disclosure: *The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

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Author Contributions

N.H. Hansen, L.O. Fjorback, M. Frydenberg and L. Juul developed the study concept and study design. Data collection was performed by N.H. Hansen and L. Juul and M. Frydenberg performed the data analysis and interpretation. N. H. Hansen drafted the manuscript, and L. Juul and L.O. Fjorback provided critical revisions. All authors approved the final version of the manuscript for submission.

Figure legends

Figure 1. Autoregressive model with a single mediator showing the a, b and c´paths. At baseline residual covariance between all mediators and outcome. For each mediator and the outcome residual covariance over time.

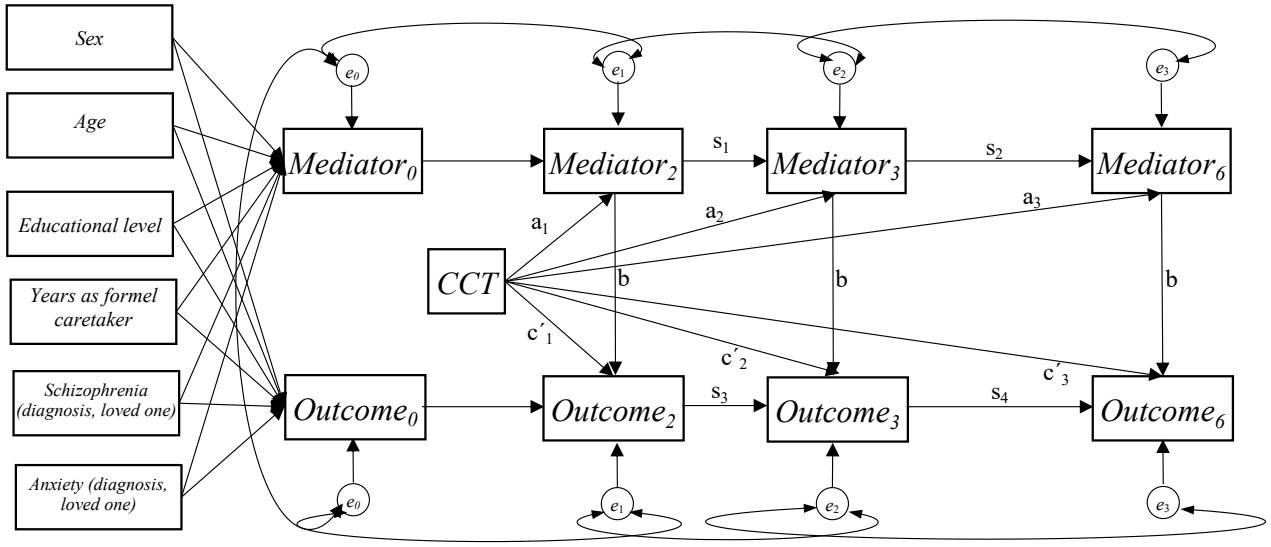

Figure 2. The paths in the main model including three mediators (Self-Compassion Scale-12, **SC**, Five Facet Mindfulness Questionnaire-15, **FM**, and Cognitive Reappraisal, The Emotion Regulation Questionnaire, **ER**.

Not shown in the figure: At baseline residual covariance between all mediators and outcome, **OC**. At each follow-up time residual covariance between all mediators. For each mediator and the outcome residual covariance over time.

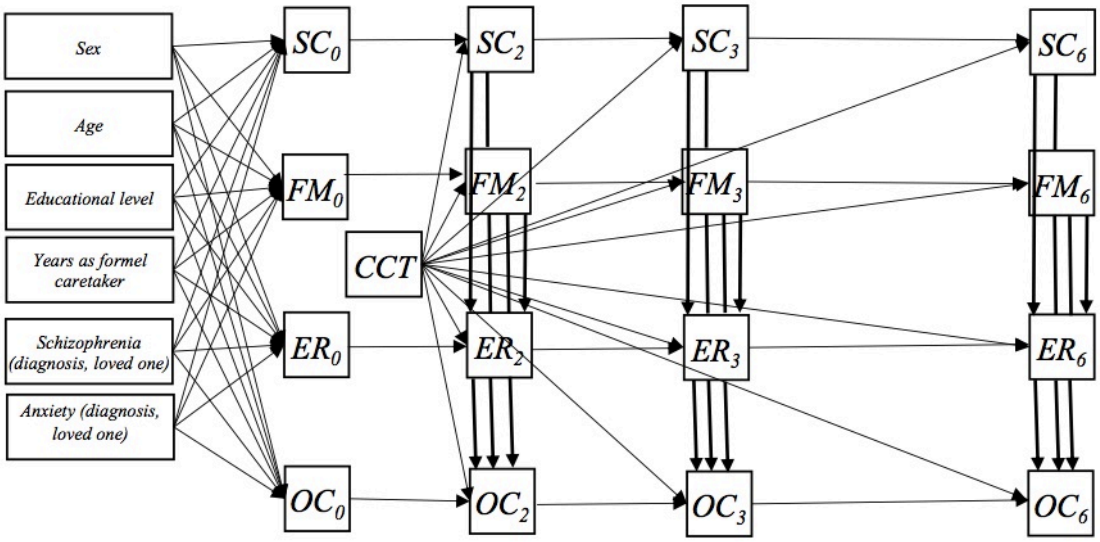

Table 1 Demographic Characteristics of Caregivers at Baseline

	Intervention Group N = 79	Control Group N = 82	Total N = 161
	N/%	N/%	N/%
Gender (n/%)			
Male	11 (14.1)	8 (9.7)	19 (11.8)
Female	68 (85.9)	74 (90.2)	142 (88.2)
Age (mean, sd)	55.9 (13.3)	49.5 (10.8)	52.6 (12.5)
Educational Level (n/%)			
No highschool	1 (1.3)	1 (1.2)	2 (1.2)
Highschool	4 (5.1)	2 (2.4)	6 (3.7)
Trade School	5 (6.3)	10 (12.2)	15 (9.2)
Short Continuing Education	8 (10.1)	3 (3.7)	11 (6.8)
Medium Continuing Education	43 (54.4)	25 (30.5)	68 (42.0)
Long Continuing Education	17 (21.5)	38 (46.3)	55 (34.0)
Ph.D.	0 (1.3)	1 (3.7)	4 (2.5)
Other	1 (0.0)	0 (0.0)	1 (0.6)
Years of Caretaking (n/%)			
0-5	22 (28.2)	22 (27.1)	45 (28.1)
5-10	23 (29.5)	20 (24.7)	43 (26.9)

10-15	5 (6.5)	16 (19.8)	21 (13.1)
15-20	9 (11.5)	5 (6.2)	14 (8.8)
> more than 20	19 (24.4)	18 (22.2)	37 (23.1)
Patient Psychiatric Disorders			
Anxiety	18 (22.2)	35 (42.7)	53 (32.7)
ADHD	10 (12.7)	14 (17.1)	24 (14.8)
Autism	17 (21.5)	14 (17.1)	32 (19.8)
Bipolar Disorder	9 (11.4)	12 (14.6)	21 (13.0)
OCD	6 (7.6)	12 (14.6)	18 (11.1)
Depression	19 (24.1)	21 (25.6)	40 (24.7)
Addiction	10 (12.7)	8 (9.8)	18 (11.1)
Personality Disorders	8 (10.1)	13 (15.9)	21 (13.0)
PTSD	7 (8.7)	7 (8.5)	14 (8.6)
Schizophrenia	21 (26.6)	13 (15.9)	34 (21.0)
Eating Disorder	7 (8.9)	3 (3.7)	10 (6.2)
Stress	6 (7.6)	9 (11.0)	16 (9.9)
Acquired Brain Injury	6 (7.6)	6 (7.3)	12 (7.4)
Other	7 (8.7)	10 (12.2)	17 (10.5)
Mediators at baseline (N, Mean, SD)			
SCS (C)	76 36.45 (7.20)	80 34.9 (8.13)	
FFMQ (F)	79 37.32 (5.96)	77 37.31 (7.37)	
ERQ (E-R)	79 25.57 (7.23)	81 24.54 (6.71)	
ERQ (E-S)	79 12.68 (5.18)	80 12.1 (4.34)	

Other included: disruptive behavior, Bodily Distress Syndrome (BDS), mental retardation, Psychogenic Non-Epileptic Seizures (PNES), Parkinson, schizotypal, attachment disorder, Tourette, dementia.
Caregivers often had loved ones with comorbid disorders, therefore the numbers do not total 100
Self-Compassion Scale-12 (SCS), Five Facet Mindfulness Questionnaire -15 (FFMQ), Emotion Regulation Questionnaire (ERQ)

Table 2. Mediated, Unmediated and Total effects for Compassion Cultivating Training (CCT) on symptoms of Depression, Anxiety and Stress (DASS) in Caregivers of People With Mental Illness at 6 -Months Follow-up in a longitudinal path model design with four repeated measurements in an RCT (n=161)[a]

	Depression	**Anxiety**	**Stress**
	estimate (95% CI)	estimate (95% CI)	estimate (95% CI)
	p-value[b]	p-value[b]	p-value[b]

Path coefficients				
a paths				
a^1	CCT->SC_2	5.49 (3.54 to 7.44) <0.001	5.43 (3.47 to 7.40) <0.001	5.50 (3.54 to 7.45) <0.001
a^2	CCT->SC_3	1.29 (-0.95 to 3.54) 0.26	1.36 (-0.88 to 3.60) 0.23	1.33 (-0.90 to 3.56) 0.24
a^3	CCT->SC_6	-1.40 (-3.62 to 0.82) 0.22	-1.42 (-3.64 to 0.81) 0.21	-1.41 (-3.64 to 0.82) 0.21
overall a	CCT->->SC_6	5.18 (3.20 to 7.16) <0.001	5.16 (3.18 to 7.14) <0.001	5.21 (3.25 to 7.17) <0.001
a^1	CCT->FM_2	4.39 (2.59 to 6.18) <0.001	4.34 (2.54 to 6.14) <0.001	4.34 (2.55 to 6.13) <0.001
a^2	CCT->FM_3	-0.77 (-2.60 to 1.06) 0.41	-0.76 (-2.60 to 1.07) 0.42	-0.79 (-2.62 to 1.05) 0.40
a^3	CCT->FM_6	1.21 (-0.62 to 3.03) 0.19	1.22 (-0.61 to 3.04) 0.19	1.22 (-0.61 to 3.04) 0.19
overall a	CCT->->FM_6	4.71 (2.79 to 6.63) <0.001	4.68 (2.71 to 6.64) <0.001	4.68 (2.77 to 6.58) <0.001
a^1	CCT->ER_2	5.00 (3.07 to 6.94) <0.001	5.02 (3.07 to 6.97) <0.001	5.05 (3.11 to 7.00) <0.001
a^2	CCT->ER_3	-1.48 (-3.66 to 0.70) 0.18	-1.46 (-3.66 to 0.74) 0.19	-1.50 (-3.70 to 0.69) 0.18
a^3	CCT->ER_6	0.36 (-2.69 to 1.98) 0.77	-0.38 (-2.73 to 1.97) 0.75	-0.38 (-2.72 to 1.97) 0.75
overall a	CCT->->ER_6	4.36 (-0.50 to 9.22) 0.08	4.47 (-0.12 to 9.07) 0.06	4.45 (-0.87 to 9.76) 0.10
mediator to mediator (constrained)				

	SC->ER	-0.11 (-0.22 to 0.01) 0.07	0.11 (-0.23 to 0.01) 0.07	-0.11 (-0.23 to 0.01) 0.07
	FM->ER	-0.00 (0.10 to 0.09) 0.93	-0.01 (-0.11 to 0.09) 0.87	-0.01 (-0.10 to 0.09) 0.92
b paths (constrained)				
	SC->OC	-0.15 (-0.26 to-0.04) 0.01	-0.05 (-0.12 to 0.03) 0.21	-0.15 (-0.27 to -0.04) 0.01
	FM->OC	-0.22 (-0.35 to -0.10) <0.001	-0.12 (-0.20 to -0.03) 0.01	-0.30 (-0.44 to -0.16) <0.001
	ER->OC	-0.02 (-0.13 to 0.09) 0.79	0.02 (-0.06 to 0.09) 0.68	-0.04 (-0.15 to 0.08) 0.55
Effects				
Mediated				
	CCT->SC->OC (all paths including ≥ 1 SC and not via ER)	-1.81 (-3.31 to -0.31) 0.02	-0.71 (-1.82 to 0.40) 0.21	-1.44 (-2.84 to -0.05) 0.04
	CCT->FM->OC (all paths including ≥ 1 FM and not via ER)	-1.98 (-3.65 to -0.33) 0.02	-1.24 (-2.39 to -0.09) 0.04	-2.17 (-3.63 to -0.71) <0.001
	CCT->ER->OC	-0.14 (-1.31 to 1.02) 0.81	0.18 (-1.04 to 1.40) 0.77	-0.27 (-1.51 to 0.98) 0.64

	(all paths including ≥ 1 ER)			
	CCT->SC->ER->OC (all paths including ≥ 1 SC and 1 ER)	0.05 (-0.32 to 0.41) 0.80	-0.06 (-0.45 to 0.34) 0.78	0.10 (-0.38 to 0.58) 0.69
	CCT->FM->ER->OC (all paths including ≥ 1 FM and 1 ER)	0.00 (-0.16 to 0.17) 0.99	-0.00 (-0.19 to 0.18) 0.97	0.00 (-0.21 to 0.22) 0.97
Unmediated	CCT->OR (all paths not via SC, FM or ER)	0.43 (-2.25 to 3.10) 0.76	0.44 (-1.69 to 2.58) 0.68	-0.03 (-3.20 to 3.14) 0.99
Total		-3.47 (-6.00 to -0.96) 0.01	-1.38 (-3.36 to 0.60) 0.17	-3.81 (-6.86 to -0.75) 0.02
Goodness of fit (degrees of freedom)=X^2, p		(188)=269, <0.001	(188)=247.3, <0.001	(188)=262, <0.001
RMSEA		0.07	0.06	0.07
CFI		0.94	0.95	0.94

Successful bootstrap out of 50	50	45	50

At baseline residual covariance between all mediators and outcome. At each follow-up time residual covariance between all mediators. For each mediator and the outcome residual covariance over time.

[a] According to figure 2. [b]Adjusted for sex, age, educational level, years as informal caretaker, schizophrenia (diagnosis, loved ones), anxiety
(diagnosis, loved ones).

SC Self-Compassion Scale-12, Neff

FM Five Facet Mindfulness Questionnaire-15

ER Cognitive Reappraisal, The Emotion Regulation Questionnaire

OC outcome

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Summary of Findings and General Discussion

This Ph.D. project aimed to understand the effect of interventions for informal caregivers on psychological distress by conducting a systematic review and meta-analysis. In addition, we investigated the effectiveness of an eight-week manualized compassion training (CCT) program on decreasing psychological distress for informal caregivers of people with a mental illness and lastly, we investigated the proposed mediators (self-compassion, mindfulness, and emotion regulation) of change of the CCT program on symptoms of depression, anxiety and stress.

Below, I briefly review the main findings and discuss their implications for future research.

Systematic Review and Meta-analysis on interventions for caregivers of people with a mental illness

Thirty-one out of forty-four RCTs showed effect of the intervention decreasing informal caregiver psychological distress. The RCTs, where no effect was found, were characterized by having long-term follow-up, being technology-based interventions and of short duration. Of the RCTs included in the meta-analysis, two showed effect on the outcome measure depression, two on anxiety, three on stress, four on quality of life, seven on subjective burden, and three showed effect on the outcome measure psychological distress. Twenty-one RCTs were of good quality according to the Jadad quality score, and according to Cochranes RofB all RCTs were of poor quality.

Results of the meta-analysis showed a small statistically significant effect (-0.32) of informal caregiver interventions on psychological distress, regardless of care-receivers mental illness or intervention modality compared to waitlist, treatment as usual or active control. However, most studies only measured psychological distress by the end of intervention and there was high heterogeneity between RCTs. The only subgroup analysis that had low heterogeneity were, interventions for informal caregivers of people with dementia/Alzheimer's disease (I^2 = 13%), interventions that were manualized, at least eight weeks duration, group/individual delivery format (I^2 = 43%) and RCTs that compared interventions with an active control group (I^2 = 41%).

Results of interventions for informal caregivers of people with dementia/Alzheimer's disease showed a small effect (-0.20), while the interventions for informal caregivers of people with severe mental illness showed a moderate effect (-0.68). Moreover, results of the subgroup analysis investigating interventions with an individual delivery format showed a small effect (-0.38), as well as interventions with a group delivery format (-0.43). Lastly, interventions that were manualized, at least eight weeks duration and had either an individual or group delivery format showed a small effect (-0.38), while RCTs with non-manualized interventions of less than eight weeks duration showed no effect.

We conducted sensitivity analysis for all groups. We excluded studies of low quality to investigate whether that would have an effect on the heterogeneity. Results of the sensitivity analysis for the meta-analysis showed that when low quality studies were excluded heterogeneity increased. Similar results emerged for; group delivery format, severe mental illness and non-manualized, less than eight weeks, individual/group. Conversely, results of the sensitivity analysis for the subgroups; individual delivery format, manualized, eight weeks or more, group/individual, and active control showed a decrease in heterogeneity.

Finally, results of the subgroup analysis that included interventions compared with an active control showed a small effect (-0.24). When interventions were directly compared, mindfulness-based interventions were superior to psychoeducation. Psychoeducation with active participation was superior to psychoeducation without active participation. Furthermore, psychoeducational interventions were superior to technology-based or informational interventions. CBT interventions were superior to both

psychoeducational or informational interventions, psychosocial interventions were superior to technology-based and psychoeducational interventions and lastly, a multicomponent intervention was superior to a relaxation intervention. In summary, the meta-analysis showed a small effect on informal caregiver psychological distress regardless of care-receiver mental illness, intervention modality, or delivery format. The subgroup and sensitivity analysis suggest that the aim of the intervention, duration and structure (manual) and intervention modality are important in order to improve caregiver's mental health.

Implications for future research

Systematic research is needed on informal caregiver interventions. First, RCTs with greater sample sizes are needed. Second, each published RCT should include means and standard deviations, so that there is enough data to conduct a meta-analysis. Third, a clear description as to what intervention components are included will aid in being able to place interventions into different broad categories, Fourth, a consensus in the literature of what constitutes psychological distress and which measures should be used when addressing this construct. Fifth, knowing what the intention of the intervention is would be helpful in choosing outcome measures that will address that intention. Sixth, RCTs that have included a mediational analysis investigating effective components of the intervention is lacking. Lastly, few RCTs have continued research on the effectiveness of the interventions using replication designs. In sum, implementation of methodological rigor, would aid in decreasing heterogeneity, thereby increase the validity of the results of systematic reviews and meta-analysis on informal caregiver interventions and psychological distress.

Effect of a Compassion Cultivation Training Program for Caregivers of People With Mental Illness in Denmark: A Randomized Clinical Trial

We conducted an RCT study with a waitlist control group to investigate the effectiveness of a compassion-based training intervention in decreasing psychological distress in informal caregivers of people with a mental illness. We specifically stated that our primary outcome was psychological distress, which we measured using the depression, anxiety and stress scale. Our results showed that an eight-week manualized CCT intervention significantly decreased symptoms of depression, anxiety and

stress and that these results stayed significant at 6-month follow-up. We also showed that the intervention increased overall well-being, mindfulness, self-compassion and emotion regulation strategies. Results were again significant at 6-month follow-up. We did not find an effect of the CCT intervention on compassion for others or the subscale awareness on the five facet mindfulness questionnaire.

Implications for future research

In addressing the implications for future research, we must highlight several limitations regarding these results. First, we do not know if the informal caregivers continued to meditate and practice compassion after the intervention? Begging the question: Were the results due to the eight-week intervention or the eight-week intervention plus continued practice? Second, the same instructor taught all the intervention groups and we cannot rule out whether the effects of the RCT were due to the CCT intervention or the instructor teaching the intervention. Third, we did not find any evidence showing that the eight-week CCT program (where three of the eight sessions are dedicated to practicing LKM and CM for strangers and all sentient being) significantly increased compassion for others. This begs the question: Is it possible for an eight-week compassion training program to cultivate compassion for others (loved ones, strangers, difficult people, and all sentient beings) in a way that is measurable and with the measures that are available thus far?

Future research should find ways to capture practice fidelity after the completion of an intervention. A replication trial using other instructors would possibly help us answer the question of whether the results were due to the intervention or the instructor. In addressing the third limitation, we must look towards previous RCTs. One RCT on the CCT program used the Compassion Scale to measure compassion for others, and concluded that the intervention increased scores on compassion for others (Brito-Pons, 2018). The wording of the Compassion Scale (Pommier et al., 2020) compared to the wording of the Multidimensional Compassion Scale (MCS) (used in this study) or the Sussex-Oxford Compassion Scale for Self and Other (SOCS-S and SOCS -O) (Gu et al., 2020) show differences in how compassion for others is presented in these outcome measures. For example, one of the questions measuring Common Humanity (or interconnectedness) on the Compassion Scale is worded: “it’s important to recognize that all people have weaknesses and no one is perfect” (Pommier et al., 2020).

Compare this with one of the questions on the MCS questionnaire "I am likely to respond in order to relieve suffering" or on the SOCS-O scale "When others are struggling, I try to do things that are helpful" (Gu et al., 2020). The inconsistencies of the wording of the different measures make it difficult to assess, whether we are measuring the same construct, and if such a construct as compassion for others can be measured using self-report questionnaires (Kirby et al., 2017; Strauss et al., 2016). Perhaps behavioral measures of prosocial behavior may be more useful in the future?

Another plausible explanation for why we did not observe any change in compassion for others is that many of the informal caregivers were not at a place in their lives where they were able to focus on the suffering of others/strangers, let alone the suffering of all sentient beings. Throughout the eight-week course they would say that it was too difficult to focus on others or they simply dismissed the practice, because they themselves were needing care and compassion. In sessions they voiced that they wanted to continue practicing compassion for themselves because they felt so depleted of self-care, warmth, and love and did not want to practice compassion for others (Hansen, 2018-2020). In the last session, when asked what they had learned, many caregivers stated that now they finally knew how to take care of their own mental health. They proceeded to explain how often a primary care physician would say at the end of a visit with their loved one "*Now remember to take good care of yourself*" whereto the caregiver would think to him or herself: "*Sure, but how? I don't know what to do*" (Hansen, 2018-2020)? Taken together, it may be the case that the greatest need of informal caregivers, is the need to learn skillful ways of taking care of their own difficult thoughts and feelings regarding their loved one. It may not be helpful for informal caregivers to practice compassion for strangers and all sentient beings.

In contrast many caregivers found great strength in practicing interconnectedness/common humanity. It seemed that their ability to align themselves with the idea that they were not alone in their suffering, and that countless other people knew what it was like to feel inadequate, hopeless, angry, shameful or sad was helpful. Moreover, many of the caregivers found great strength in the advanced Tonglen practice, practicing breathing in all their own and others suffering and transforming that suffering to compassion. For many caregivers this practice gave them something to do, made them feel more in control or more accepting when there was nothing else to do in a given situation (Hansen, 2018-2020).

Taken together, perhaps the most plausible reason for why we did not find any significant results regarding compassion for others is that we simply do not know how to capture this construct in a self-report questionnaire yet.

Mediators for the effect of Compassion Cultivating Training: A longitudinal path analysis in a randomized controlled trial among caregivers of people with mental illness.

Lastly, we conducted a secondary mediation analysis in order to investigate, which mediators of the CCT program were effective in decreasing depression, anxiety and stress. We had hypothesized that CCT effectively decreased symptoms of depression, anxiety and stress, by increasing self-compassion, mindfulness, and the emotion regulation skills cognitive reappraisal and decreasing the emotion regulation skill emotion suppression. We found that while self-compassion, mindfulness and the emotion regulation strategy cognitive reappraisal did mediate the effect of CCT on depression, anxiety and stress in a single mediation analysis, the same results did not hold true when we added the mediators into a multiple mediation analysis. Here results suggested that only self-compassion and mindfulness were mediators of change on depression and stress, and only mindfulness was a mediator of change on anxiety. The emotion regulation strategy of cognitive reappraisal and emotion suppression attenuated and became insignificant and and mediation of emotion regulation through mindfulness or self-compassion was also not found.. These results highlight the importance of adjusting for the effect of the most promising mediators.

Implications for future research

The third paper was a secondary mediation analysis, and is one of the few to date, that investigate the mediators of a compassion-based intervention, using an underlying theory, including multiple mediators, and including four time-points thereby establishing a timeline. Most of the mediation studies only use a single mediation analysis and two timepoints. Had we done the same, we would have concluded that our results showed that the emotion regulation strategy of cognitive reappraisal was a statistically significant mediator of CCT on reducing symptoms of depression, anxiety and stress. In using a multiple mediation analyses we found that the effects of the emotion regulation strategy, cognitive reappraisal and emotion suppression, attenuated and became statistically insignificant. This was a surprising finding as other studies had found that emotion regulation strategies such as cognitive

reappraisal and emotion suppression were effective in decreasing depression and stress (Inwood & Ferrari, 2018). Based on these findings, we therefore hypothesize that self-compassion and mindfulness skills are self-regulating in nature and do not involve a cognitive component per say. It may be that these skills self-regulate by downregulating the entire nervous system. This is important information as it provides us with a new understanding and could guide the development of new interventions. It also shows us why it is important to conduct mediation analysis. If we only stop after the effectiveness trial we do not get the full picture of which components are helpful in decreasing psychological distress for caregivers.

Methodological considerations

Strengths and limitations

The systematic review and meta-analysis showed a clear need for systematic and methodological rigor of intervention research, including larger sample size, reporting of data, clear description of intervention components and consensus regarding outcome measures. To date, we conducted one of the largest RCTs within the field of compassion-based training and informal caregiver interventions. Our study showed that compassion is a trainable skill and that it is effective in decreasing psychological distress and increase overall well-being at six month follow-up. We were able to show that while part of our hypothesis regarding mediators of the CCT program in symptoms of depression, anxiety and stress held true, we failed to show that emotion regulation strategies such as cognitive reappraisal and emotion suppression were mediators of change. This result leaves us with more questions regarding what active components are responsible for the effectiveness of compassion training in decreasing psychological distress?

There are several limitations to the Ph.D. project. First, many of the results of the systematic review and meta-analysis is fraught with substantial heterogeneity and we have to use caution when interpreting the results. Second, the review and meta-analysis is limited by the quality of included studies, such as RCTs with a small sample size limiting the generalizability of treatment effect. Third, all included RCTs used self-report questionnaires measuring psychological distress leaving an uncertainty as to whether the interventions addressed the same construct. Fourth, obtaining information

about the specific intervention components was also quite challenging making it difficult to categorize the intervention into groups that would enable subgroup analysis to investigate which intervention modality showed effect.

Limitations to the RCT included the lack of an active control group. As waitlist designed RCTs may overestimate the effects of an intervention, we are not able to say whether a different intervention is just as effective or even more effective than the CCT intervention. Using an active control group would have allowed us to investigate this. Another limitation, include the potential bias that may have been caused by the non-blinding of intervention allocation. Lastly, as we used self-reported questionnaires, the possibility that information bias is present cannot be excluded. Finally, limitations to the mediation analysis include the inability to show a statistically significant effect on symptoms of anxiety at 6 months, like we did in the RCT. We hypothesize that differences in the results may be due to the use of different statistical models. Moreover, we were not able to adjust for measurement error as our model only included observed measurements.

Moving beyond the scope of the Ph.D. Project

Adaptations to the CCT curriculum

Due to the extensive knowledge gained by teaching the CCT to one-hundred and sixty-one caregivers in eight groups, several adaptations to the CCT intervention has been undertaken and the Course in Compassion has been developed (table 2).

Learning point 1: In week two of the CCT program participants are asked to practice compassion and loving kindness for a loved one. Many of the informal caregivers, chose their loved one suffering from a mental illness, even though they were invited to choose a different person. The reason for inviting them to choose another person than their loved one with a mental illness, is that in choosing their loved one, they opened the door to their chronic grief too fast. It simply overwhelmed them.

Adaptation 1: We postpone practicing compassion for a loved one until participants have some experience with grounding the body. Therefore, the practice of compassion and loving kindness for a loved one has been moved to week three.

Learning point 2: When participants were asked to notice their bodily sensations, many simply did not know what that meant. When explaining to them that the body holds many emotions and much information, participants were only able to register the thoughts they were having but had no idea what their body was experiencing.

Adaptation 2: It is paramount that participants have experience with noticing and becoming aware of their bodies, as the information held by the body is informative for practicing compassion. Therefore, this practice is right after the first week where they have practice settling the mind by using the breath as an anchor.

Learning point 3: In week three of the CCT program, participants were asked to practice self-compassion. When practicing self-compassion, the participant would also notice how often they went into empathetic distress thereby becoming overwhelmed by their own suffering. The difference between empathetic distress and compassion is not something that is explicitly taught and practiced in CCT.

Adaptation 3: As understanding (both cognitively and somatically) the difference between empathetic distress and compassion is extremely important, a full week is dedicated to practice noticing and feeling the difference between when we engage with suffering by going into empathic distress and when we engage with suffering from a place of compassion.

Learning point 4: As mentioned, week 3 in CCT is the practice of self-compassion. For many of the caregivers, this practice came right after they had opened the door to their chronic grief and. As self-compassion is a practice that also has the potential to open the door to trauma and grief this practice was moved to week five.

Adaptation 4: We therefore moved learning to become one's own friend up in week four and moved the practice of self-compassion to week five. This allows for the participant to slowly ease into connecting with and accepting his/her own suffering.

Learning point 5: Training compassion for all sentient beings was not a priority for the informal caregivers and is an advanced skill.

Adaptation 5: We therefore removed practicing compassion for all sentient beings from the curriculum.

Table 2. Similarities and differences to the CCT program and the Compassion Course program

Week	Compassion Cultivation Training (CCT)	The Compassion Course
1	**Mindfulness:** I Introductions and learning to focus and settle the mind	**Compassion and Mindfulness: What you do matter** Introductions and investigation into the nature of our mind by using the breath as an anchor.
2	**Loving-kindness for a loved one:** Cultivating loving kindness and compassion for a loved one	**Bodily awareness: How does your heart feel?** We include awareness regarding the entire body, with a special focus on the heart. We investigate if it is possible to discover that compassion is all around.
3	**Self-compassion:** Training compassion for one's own suffering	**Empathic distress vs. Compassion: Giving to others make you happy.** Investigation of the difference between acting from empathic distress compared to compassion when a loved one is suffering
4	**Loving-kindness for your own suffering:** Training loving-kindness for one's own suffering	**Being your own best friend: Transform bad circumstances into learning.** What does it mean to be your own best friend? How do you practice loving-kindness for yourself?
5	**Interconnectedness:** Cultivating compassion towards others through embracing shared common humanity and appreciating the interconnectedness of all human beings	**Self-Compassion: Make practice your whole life**. How does it feel to have compassion for your own suffering and what are the barriers?
6	**Compassion for all sentient beings:** Training compassion towards all sentient beings	**Common Humanity: It could just as well be you.** Investigation into the possibility of sending compassion to strangers and difficult people. Are we more the same than we are different?
7	**Active Compassion:** Training active compassion using a Tonglen practice (it means to give and take) where participants imagine taking others' suffering away, and offering them all that is good in oneself	**Active Compassion: Relationships take discipline.** What does active compassion mean to you? What can we do to change societal structures and systems that are not skillful or helpful? Should we?
8	**Integrated compassion training:** Closure and training an integrated compassion practice	**Dedication: Live with ease in a crazy world** Closing: What have I learned, what am I taking with me and where do I start?

Instructor qualifications when teaching a compassion intervention to informal caregivers

Instructor qualifications are extremely important as difficult situations and emotions may arise when teaching the compassion intervention to informal caregivers. One aspect of great importance is the possibility of instructor burnout. Due to the chronic grief residing within caregivers and to the concept

of transference, the CCT instructor experienced physical fatigue following teaching the intervention. Curious (and concerned about burnout), this topic was highlighted in a weekly supervision group. Thanks to knowledgeable colleagues in the supervision group, the experience of the instructor was validated and future considerations should entail having two instructors teach the compassion-based intervention to minimize the risk of burnout.

Compassion Teacher Training Certification Program

We have developed a Compassion Teacher Training Certification program at Aarhus University, Department of Clinical Medicine, Danish Center for Mindfulness. We have done so for the following reasons. First, to be able to address the need for more than one compassion instructor when teaching the intervention to informal caregivers. Second, to be able to address one of the limitations of the current RCT, which was that only one instructor taught the intervention, therefore, a replication trial with several different instructors teaching the intervention, would address this limitation. Third, to address the great need to implement this type of intervention into other structures of society such as the healthcare system.

The program curriculum consists of three core courses that Lone Fjorback and I co-created: 1) Compassion and Science, 2) Compassion and Psychology and 3) Compassion, Ethics and Philosophy. Once these core classes have been taken, the participant may choose between three specializations: 1) Informal caregivers, 2) Healthcare and 3) Leadership, and content specifically tailored towards these specializations is taught in a workshop format. Once completed the participant teaches their own eight-week manualized compassion-based intervention while receiving supervision. Upon successful review of the teaching material the participant becomes a certified compassion instructor.

Replication trial

We are applying for funding for a replication trial in collaboration with Better Psychiatry (Bedre Psykiatri – a national association for informal caregivers of people with a mental illness). In this replication trial we would like to address some of the limitations of the current RCT. We are adding an active control group and a new primary outcome; a health-related quality of life outcome. The

questionnaire used provides us with the possibility of conducting a cost-effectiveness analysis in the future. This could potentially demonstrate that compassion-based training interventions for informal caregivers of people with a mental illness may be viewed and implemented as a preventive intervention. This would not only provide informal caregivers with skillful means in taking care of their own mental health, but may also benefit society in general. We will also be conducting a mediation analysis. We are keeping the two mediators of self-compassion and mindfulness but adding two new ones; mentalizing and decentering. This will allow us to investigate whether these components are mediators of change of a compassion-based intervention on symptoms of depression, anxiety and stress. In conducting a replication trial, we will be able to address many of the findings that emerged in our initial investigation. First, it will allow us to investigate whether we are able to show effectiveness once we have added an active control group. Second, we will have other instructors teaching the course. Third, we include the same and new mediators. In doing so we will attempt to replicate our initial findings while also generating new knowledge and add systematic research to the field of informal caregiver intervention research.

Conclusion

The field of informal caregiver intervention research lacks consensus. There may not be one simple answer and inconsistent results of systematic reviews and meta-analysis provide very little guidance as to what kind of intervention modality, delivery method, and what components bring about intervention effectiveness regarding informal caregiver psychological distress. Moreover, previous research on manualized compassion-based interventions have investigated the effects of such training primarily on populations with physiological and psychological conditions. Evidence as to the effectiveness of compassion-based training for a high-risk population, such as informal caregivers of people with a mental illness, has not been conducted. In addition, there is a paucity of research on mediators of change of compassion-based interventions, leaving the field with insufficient knowledge as to what active ingredients within the manualized programs bring about the change on psychological distress. This research project aimed to address these gaps by asking the following questions: 1) Does informal caregiver interventions, regardless of care-receiver illness, intervention modality and intervention delivery mode show effect in decreasing psychological distress? Will a manualized eight-week

compassion cultivation training (CCT) program be effective in decreasing informal caregiver psychological distress? Lastly, are self-compassion, mindfulness and emotion regulation mediators on the effect of the CCT program regarding symptoms of depression, anxiety and stress?

Based on the results of the systematic review and meta-analysis, we concluded that interventions, for informal caregivers of people with a mental illness, show a small effect in decreasing psychological distress. Results suggest that duration (at least eight weeks) and structure (manualized interventions) are important components on the effect of interventions in decreasing psychological distress. Results of the RCT suggests that an eight-week manualized CCT program is effective in decreasing informal caregiver's psychological distress and increase overall well-being, resilience, self-compassion, mindfulness, emotion regulation and decrease perceived stress with results lasting at six- month follow-up. Lastly, results of the mediation analysis, showed that self-compassion and mindfulness were mediators of the CCT intervention on symptoms of depression, anxiety and stress but not emotion regulation strategies such as cognitive reappraisal and emotion suppression.

This Ph.D. project has made a number of contributions to the field of intervention research. The systematic review and meta-analysis contribute by updating the current knowledge on the effect of informal caregiver interventions on decreasing psychological distress. Also, to our knowledge the RCT on the effectiveness of a compassion-based intervention for informal caregivers of people with a mental illness is the first of its kind in Denmark and internationally. The strengths of the study included an RCT design, a large sample size, two different locations, large age span, and inclusion of all care-receiver mental illness, thereby allowing for generalizability. Due to the paucity of knowledge and research on mediators of change of compassion-based interventions the mediation analysis has contributed by addressing a gap within the field and applying methodological rigor. In the investigation of mediators of change on the CCT program on depression, anxiety and stress, we used an underlying theory, established a timeline with four timepoints, and was able to investigate if there was a clear association between change in the proposed mediator and the proposed outcome, and that change in the mediator preceded change in the outcome. The mediation analysis also included four mediators in a single and multiple mediation analysis showing the importance of including more than one mediator and using a multiple mediator analysis.

There were several limitations in this Ph.D. project. First of all, one could argue that the PICO questions were too broad and that conducting a meta-analysis on so many different intervention modalities, care-receiver illness and duration is not helpful as the heterogeneity is too substantial. With substantial heterogeneity we must caution when interpreting our results. On the other hand, conducting the meta-analysis allowed us to investigate sub categories within the RCTs and allowed for more knowledge regarding the difficulties within the research of this field. Second of all, we did not include an active control in our RCT design. Therefore, we cannot say whether the CCT intervention is more effective than another type of intervention in decreasing caregiver psychological distress. It may also have been helpful to provide a prosocial measure to get a better understanding of whether the intervention would increase compassion for others, which we were not able to capture in the self-report measures. Third, a limitation regarding the mediation analysis was that we were not able to show a statistically significant effect on symptoms of anxiety at six-months, like we did in the RCT. Differences in the results may be due to the use different statistical models. We were also not able to adjust for measurement error as our model only included observed measurements.

In sum, we conclude that there is a great need for methodological rigor when conducting research on informal caregiver interventions and that interventions that are manualized, lasting at least eight weeks and have active participation may be most helpful in deceasing informal caregiver psychological distress. Moreover, compassion-based training programs for informal caregivers of people with a mental illness hold promise as a preventive intervention for informal caregiver mental health. Lastly, the practice of self-compassion and mindfulness are active components in decreasing informal caregiver psychological distress. Based on the knowledge acquired throughout the Ph.D. project the following future directions are suggested. There is a need to conduct systematic research on interventions for informal caregivers. This may be done by conducting replication trials, including an active control group, an outcome of health-related quality of life, and new proposed mediators of change. This in turn would heighten the quality of the research results. Ultimately, it would allow healthcare providers and policy-makers to feel more certain when choosing to implement preventive mental health interventions into society.

AARHUS UNIVERSITY

English Summery

Informal caregivers of people with a mental illness are at increased risk of developing depression, anxiety and stress. Informal caregiver interventions aiming to decrease psychological distress is needed and the research on the effectiveness of caregiver interventions is fraught with mixed results. Compassion-based interventions have showed promise in decreasing psychological distress and increasing overall well-being in the general public and people with psychological disorders and very little is known about mediators of change of compassion-based interventions. To address these gaps in the field of intervention and compassion research this Ph.D. project had three objectives: 1) conduct a systematic review and meta-analysis on the effect on informal caregiver interventions on decreasing psychological distress, 2) investigate, in a RCT, the effectiveness of an eight-week manualized Compassion Cultivation Training (CCT) program for informal caregivers of people with a mental illness on decreasing psychological distress and 3) investigate mediators of change of the CCT program on symptoms of depression, anxiety and stress. The four mediators were; mindfulness, self-compassion and emotion-regulation (cognitive reappraisal and emotion suppression). Results of the systematic review and meta-analysis showed a small statistically significant effect of informal caregiver interventions on decreasing psychological distress. Intervention components such as duration and structure may be effective components of an intervention and both individual and group delivery format showed effect. Lastly, interventions compared to an active control group showed a small effect. Results, of the RCT showed statistically significant results for the effectiveness of the CCT program on symptoms of depression, anxiety and stress. Moreover, results showed a statistically significant increase in general well-being, resilience, self-compassion, mindfulness, emotions regulation and decreased perceived stress. No effect was found for compassion for others and the awareness subscale. These results remained statistically significant at six-month follow-up. The results of the single mediation analysis showed that three mediators; self-compassion, mindfulness and emotion regulation

(cognitive reappraisal) mediated the effects of the CCT program on symptoms of depression, anxiety and stress. When including the mediators in a multiple mediation analysis results showed that self-compassion and mindfulness mediated the effect of CCT on symptoms of depression and stress but not anxiety. Mindfulness mediated the effect of CCT on symptoms of anxiety and the effects of emotion regulation (cognitive reappraisal and emotion suppression) attenuated.
Future directions include, systematic research on interventions for informal caregivers, replication trials with active control groups and continued investigation of mediators of change.

Dansk Resumé

Pårørende til mennesker med en psykisk lidelse har en øget risiko for at udvikle stress, angst og depression. Interventioner som nedsætter pårørendes psykiske lidelse er nødvendige. Forskningen omkring hvilke typer af interventioner, leveringsmetode, længe og struktur indenfor dette område er fyldt med modsatrettede resultater. Forskningen omkring Compassion interventioner har vist lovende resultater for at kunne nedsætte psykisk lidelse og øge trivsel i den generelle befolkning og hos folk med psykiske lidelser. Der eksisterer meget lidt viden omkring hvilke mediatorer skaber effekt i compassion interventioner. For at adressere disse huller i litteraturen havde dette Ph.d. projekt 3 mål: 1) lave en systematisk review og meta-analyse og undersøge effekten af hvorvidt pårørende interventioner nedsætter psykisk lidelse, 2) undersøge effekten af hvorvidt et otte-ugers Compassion Cultivation Training (CCT) program nedsættre psykisk lidelse hos pårørende til folk med en psykisk lidelse og 3) undersøge mediatorer af CCT programmet på symptomer af depression, angst og stress.

Indledningsvis blev en systematisk review og meta-analyse af interventioner til pårørende med en psykisk lidelse foretaget. Vi undersøgte om interventioner til pårørende til folk med en psykisk lidelse viste effekt i at nedsætte psykisk lidelse, uafhængigt af psykiatrisk diagnose, interventions modalitet, eller leveringsmetoden af intervention. Vi undersøgte også hvorvidt længde og struktur (manualiseret) var effektive komponenter af en intervention, hvorvidt leveringsmetode og mental sygdom betød noget. Derefter gennemførte vi et randomiseret kontrolleret studie der undersøgte effekten af et otte-ugers manualiseret Compassion Cultivation Training (CCT) program på pårørende med en psykiske lidelse.

Afslutningsvis undersøgte vi, hvilke mediatorer der er med til skabe effekten af CCT-programmet på symptomer af depression, angst og stress hos den pårørende.

Resultaterne af det systematiske review of meta-analyse viste en lille statistisk signifikant effekt af interventioner til pårørende, uafhængigt af psykiatrisk lidelse, interventions type eller leveringsmetoden af interventionen. Sub-gruppe analyser viste en statistisk signifikant effekt når leveringsmetoden var individuel og gruppe og når komponenter som længde (mindst otte uger) og struktur (manualiseret) var en del af interventionen. Vi fandt ingen statistisk signifikant effekt når interventionens længde var mindre end otte-uger og ikke manualiseret. Vi fandt en lille effekt når interventionen var målt imod en aktiv kontrol gruppe.

I det randomiserede kontrollerede studie blev det påvist, at et manualiseret Compassion Cultivation Training (CCT) program administreret til pårørende til folk med en psykisk lidelse, medførte en statistisk signifikant reduktion i de pårørendes symptomer på depression, angst og stress. Ydermere blev deres generelle trivsel, deres resiliens, compassion for selv, mindfulness, og følelses regulerende strategier forøget. De pårørendes opfattelse af stress i egen hverdag blev ligeledes nedsat. Disse resultater var statistisk signifikante og forblev statistisk signifikante ved 6 måneders opfølgning. Vi fandt ingen effekt på compassion for andre.

Mediationsanalysen inkluderede fire mediatorer: 1) compassion for selv, 2) mindfulness og 3) følelsesregulering (kognitiv vurdering) og 4) følelsesregulering (undertrykkelse af følelser). Analysen viste at ved hjælp af enkel mediationsanalyse, kunne vi påvise at tre: 1) compassion for selv, 2) mindfulness og 3) følelsesregulering (kognitive vurdering) medierede effekten af CCT-programmet på symptomer af depression, angst og stress. Mediationsanalyse, der inkluderede flere mediatorer, viste at compassion for selv medierede effekten af CCT-programmet på symptomer af depression og stress. Mindfulness medierede effekten af CCT-programmet på symptomer af angst. Effekten af følelsesregulering kognitiv vurdering påvist i single mediationsanalysen blev reduceret ved multiple mediationsanalyse.

Denne afhandling dokumenterer at interventioner for pårørende til folk med en psykisk lidelse viser en lille effekt i at nedsætte psykisk lidelse, og at længde og struktur af en intervention er mulige effektive komponenter. Der er i feltet en general mangel på analyse af og viden omkring, hvilke interventions-modaliteter, hvilken leveringsmetode og hvilke komponenter, der er effektive i at nedsætte psykisk lidelse hos pårørende til folk med en psykisk lidelse. Ydermere dokumenterer afhandlingen at et

manualiseret compassion trænings-program reducerer symptomer på depression, angst og stress og øger generel trivsel samt at compassion for selv og mindfulness er aktive komponenter af interventionen. Det anbefales at foretage mediationsanalyser i forbindelse med foretagelse af interventionsstudier til pårørende for at klarlægge sammenhængen mellem interventionerne og effekten.

Supplemental Materials

Supplemental Material Paper I

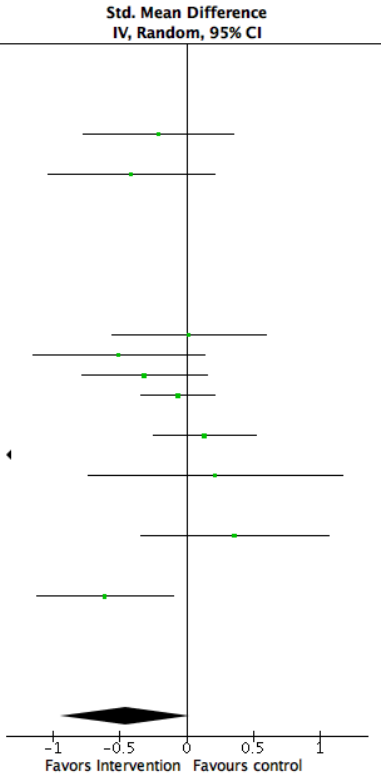
Hansen, N.H., Bjerrekær, L.A., Pallesen, K.J., *Juul, L., & *Fjorback, L.O. (2021). A Systematic Review and Meta-analysis on the effect of interventions on psychological distress for informal caregivers of people with a mental illness (ready for submission). (*shared last authorship)

eFigure 1. Sensitivity analysis for meta-analysis and all subgroups

Meta-analysis: all studies

	Intervention			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Mohide 1990	-0.05	17.4014	22	2.8	13.64	20	0.0%	-0.18 [-0.78, 0.43]	1990
Gendron 1996	0.9	9.1533	17	1.3	18	106	0.0%	-0.02 [-0.54, 0.49]	1996
Szmukler 1996	0.3	21.0435	32	-4.6	14.6432	31	0.0%	0.27 [-0.23, 0.76]	1996
Fung 2002	-10.4	13.7674	26	-5.38	18.5604	26	0.0%	-0.30 [-0.85, 0.24]	2002
Szmukler 2003	-2.4	12.7475	26	0.4	13.3804	23	9.3%	-0.21 [-0.77, 0.35]	2003
Akkerman 2004	-7.67	9.6308	18	2.82	12.1632	17	0.0%	-0.94 [-1.64, -0.23]	2004
Reinares 2004	-0.2	0.4382	30	-0.03	0.3098	15	9.0%	-0.42 [-1.04, 0.21]	2004
McCallion 2004	-1.5	14.56	49	3.3	14.3107	46	0.0%	-0.33 [-0.73, 0.08]	2004
Tonge 2006	-11.48	14.4944	35	-5.36	15.441	35	0.0%	-0.40 [-0.88, 0.07]	2006
Gutiérrez-Maldonado	-32.62	18.5403	18	-0.43	18.6558	23	0.0%	-1.70 [-2.42, -0.97]	2007
Gallagher Thompson 2007	-5.89	15.4426	23	-0.49	13.7898	22	0.0%	-0.36 [-0.95, 0.23]	2007
Aakhus 2009	0.97	10.64	16	-5.98	8.6806	14	0.0%	0.69 [-0.05, 1.43]	2009
Koolaee, 2010	-26.25	11.8126	19	-8.73	15.3159	18	0.0%	-1.26 [-1.97, -0.55]	2010
Oken, 2010	-2.3	18.2463	10	-6.5	12.5226	10	0.0%	0.26 [-0.62, 1.14]	2010
Davis 2011	-3.21	18.8611	24	-3.5	11.9606	22	9.2%	0.02 [-0.56, 0.60]	2011
Lavretsky 2013	-7.4	3.7	23	-5.3	4.5	16	8.9%	-0.51 [-1.16, 0.14]	2013
Whitebird 2013	-7.2	6.3894	35	-4.5	10.0573	35	9.6%	-0.32 [-0.79, 0.15]	2013
Livingston 2013	-0.6	10.4795	152	0.09	10.6177	77	10.3%	-0.07 [-0.34, 0.21]	2013
Ji 2014	-6.1	12.2889	22	-3.09	20.3929	20	0.0%	-0.18 [-0.78, 0.43]	2014
Gonzalez 2014	3.16	16.8291	50	0.79	17.5951	52	9.9%	0.14 [-0.25, 0.53]	2014
FallahiKhoshknab 2014	-19.34	3.78	36	-3.21	4.2596	35	8.1%	-3.97 [-4.78, -3.15]	2014
Leach 2015	-0.02	0.1697	8	-0.05	0.09	9	7.5%	0.21 [-0.74, 1.17]	2015
Polo Lopez 2015	-1.25	19.979	29	0.01	13.64	20	0.0%	-0.07 [-0.64, 0.50]	2015
deSouza 2016	-5.5	15.5653	14	-6.6	12.8048	22	0.0%	0.08 [-0.59, 0.75]	2016
Hubbard 2016	0.67	2.3572	14	-0.72	4.56	18	8.7%	0.36 [-0.35, 1.06]	2016
Brown 2016	-0.3	0.8282	19	-0.35	1.5492	15	0.0%	0.04 [-0.64, 0.72]	2016
Gonyea 2016	-0.57	8.2393	29	0.03	8.3606	28	0.0%	-0.07 [-0.59, 0.45]	2016
Berwig 2017	2.67	8.89	31	8.1	8.58	31	9.5%	-0.61 [-1.12, -0.10]	2017
Danucalov 2017	-2	4	25	1	4.0785	21	0.0%	-0.73 [-1.33, -0.13]	2017
Ata 2018	-15.25	20.4252	28	-0.09	20.1384	32	0.0%	-0.74 [-1.26, -0.21]	2018
Gossink 2018	-0.3	9.4888	15	1.1	13.1681	15	0.0%	-0.12 [-0.84, 0.60]	2018
Tabeleo 2018	-4.8	20.7975	66	-1.9	20.32	64	0.0%	-0.14 [-0.48, 0.20]	2018
Total (95% CI)			**429**			**333**	**100.0%**	**-0.46 [-0.94, 0.03]**	

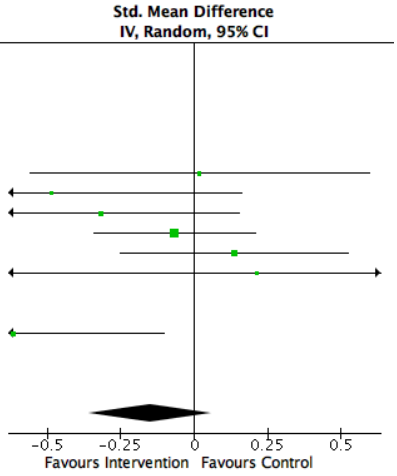
Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 92.56$, df = 10 (P < 0.00001); $I^2 = 89\%$
Test for overall effect: Z = 1.85 (P = 0.06)



Sensitivity analysis: Dementia/Alzheimer's disease

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Mohide 1990	-0.05	16.3226	22	2.8	12.5667	20	0.0%	-0.19 [-0.80, 0.42]	1990
Gendron 1996	0.9	9.1533	17	1.3	18	106	0.0%	-0.02 [-0.54, 0.49]	1996
Fung 2002	-10.4	13.7674	26	-5.38	18.5604	26	0.0%	-0.30 [-0.85, 0.24]	2002
Akkerman 2004	-7.67	9.6308	18	2.82	12.1632	17	0.0%	-0.94 [-1.64, -0.23]	2004
Gallagher Thompson 2007	-5.89	15.4426	23	-0.49	13.7898	22	0.0%	-0.36 [-0.95, 0.23]	2007
Oken, 2010	-2.3	18.2463	10	-6.5	12.5226	10	0.0%	0.26 [-0.62, 1.14]	2010
Davis 2011	-3.21	18.8611	24	-3.5	11.9606	22	10.6%	0.02 [-0.56, 0.60]	2011
Lavretsky 2013	-7.3	3.7	23	-5.3	4.5	16	8.8%	-0.48 [-1.13, 0.16]	2013
Whitebird 2013	-7.2	6.3894	35	-4.5	10.0573	35	14.7%	-0.32 [-0.79, 0.15]	2013
Livingston 2013	-0.6	10.4795	152	0.1	10.6177	77	29.2%	-0.07 [-0.34, 0.21]	2013
Gonzalez 2014	3.16	16.8291	50	0.79	17.5951	52	19.3%	0.14 [-0.25, 0.53]	2014
Leach 2015	-0.02	0.1697	8	-0.05	0.09	9	4.4%	0.21 [-0.74, 1.17]	2015
Brown 2016	-0.3	0.8282	19	-0.35	1.5492	15	0.0%	0.04 [-0.64, 0.72]	2016
Gonyea 2016	-0.57	8.2393	29	0.03	8.3606	28	0.0%	-0.07 [-0.59, 0.45]	2016
Berwig 2017	2.67	8.86	31	8.1	8.58	31	13.0%	-0.61 [-1.13, -0.10]	2017
Danucalov 2017	-2	4	25	1	4.0785	21	0.0%	-0.73 [-1.33, -0.13]	2017
Gossink 2018	-0.3	9.4888	15	1.1	13.1681	15	0.0%	-0.12 [-0.84, 0.60]	2018
Total (95% CI)			**323**			**242**	**100.0%**	**-0.15 [-0.36, 0.06]**	

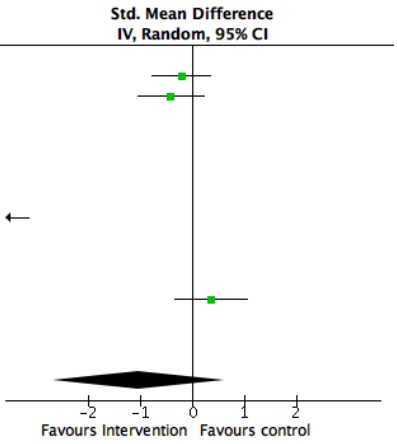
Heterogeneity: Tau² = 0.02; Chi² = 7.98, df = 6 (P = 0.24); I² = 25%
Test for overall effect: Z = 1.42 (P = 0.16)



Sensitivity analysis: Severe mental illness

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Szmukler 1996	0.3	21.0435	32	-4.6	14.6432	31	0.0%	0.27 [-0.23, 0.76]	1996
Szmukler 2003	-2.4	12.7475	26	0.4	13.3804	23	25.3%	-0.21 [-0.77, 0.35]	2003
Reinares 2004	-0.2	0.4382	30	-0.03	0.3098	15	25.2%	-0.42 [-1.04, 0.21]	2004
McCallion 2004	-1.5	14.56	49	-7.7	14.2721	48	0.0%	0.43 [0.02, 0.83]	2004
Tonge 2006	-32.62	18.5403	18	-0.43	18.6558	23	0.0%	-1.70 [-2.42, -0.97]	2006
Gutiérrez-Maldonado	-32.62	18.5403	18	-0.43	18.6558	23	0.0%	-1.70 [-2.42, -0.97]	2007
Aakhus 2009	0.7	10.8	16	-5.8	9.7283	14	0.0%	0.61 [-0.12, 1.35]	2009
Koolaee, 2010	-26.25	11.9434	19	-8.73	15.3159	18	0.0%	-1.25 [-1.96, -0.54]	2010
FallahiKhoshknab 2014	-19.34	3.78	36	-3.21	4.2596	35	24.5%	-3.97 [-4.78, -3.15]	2014
Ji 2014	-6.1	12.2889	22	-3.09	20.3929	20	0.0%	-0.18 [-0.78, 0.43]	2014
Polo Lopez 2015	-1.25	0.5385	29	0.01	0.7155	20	0.0%	-2.01 [-2.72, -1.31]	2015
deSouza 2016	-5.5	15.5653	14	-6.6	12.8048	22	0.0%	0.08 [-0.59, 0.75]	2016
Hubbard 2016	0.67	2.3572	14	-0.72	4.7093	18	24.9%	0.35 [-0.35, 1.05]	2016
Tabeleo 2018	-4.8	20.7975	66	-1.9	20.32	64	0.0%	-0.14 [-0.48, 0.20]	2018
Ata 2018	-15.25	20.4252	28	-0.09	20.1384	32	0.0%	-0.74 [-1.26, -0.21]	2018
Total (95% CI)			**106**			**91**	**100.0%**	**-1.04 [-2.70, 0.61]**	

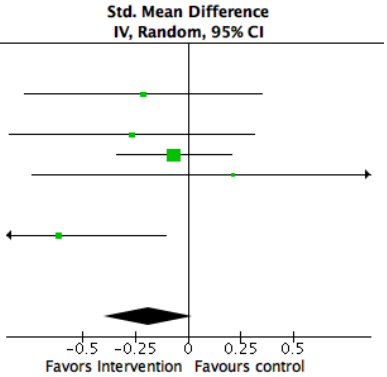
Heterogeneity: Tau² = 2.72; Chi² = 73.54, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.24 (P = 0.22)



Sensitivity analysis: Individual delivery format

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Mohide 1990	-0.05	17.4014	22	2.8	13.64	20	0.0%	-0.18 [-0.78, 0.43]	1990
Szmukler 1996	0.3	21.0435	32	4.6	14.6432	31	0.0%	-0.23 [-0.73, 0.26]	1996
Szmukler 2003	-2.4	12.6456	26	0.4	13.3804	23	13.7%	-0.21 [-0.77, 0.35]	2003
Gallagher Thompson 2007	-5.89	15.4426	23	-0.49	13.7898	22	0.0%	-0.36 [-0.95, 0.23]	2007
Davis 2011	-9.16	21.1636	24	-4	16.5103	22	12.9%	-0.27 [-0.85, 0.32]	2011
Livingston 2013	-0.6	10.1487	152	0.09	10.4484	77	52.0%	-0.07 [-0.34, 0.21]	2013
Leach 2015	-0.02	0.1697	8	-0.05	0.09	9	4.9%	0.21 [-0.74, 1.17]	2015
Polo Lopez 2015	-1.25	0.5385	29	0.01	0.7155	20	0.0%	-2.01 [-2.72, -1.31]	2015
deSouza 2016	-5.5	15.5653	14	-6.6	12.8048	22	0.0%	0.08 [-0.59, 0.75]	2016
Berwig 2017	2.67	8.89	31	8.1	8.58	31	16.5%	-0.61 [-1.12, -0.10]	2017
Ata 2018	-5.39	4.4449	28	-0.03	7.3539	32	0.0%	-0.86 [-1.39, -0.33]	2018
Tabeleo 2018	-4.8	20.7975	66	-1.9	20.32	64	0.0%	-0.14 [-0.48, 0.20]	2018
Total (95% CI)			**241**			**162**	**100.0%**	**-0.19 [-0.40, 0.02]**	

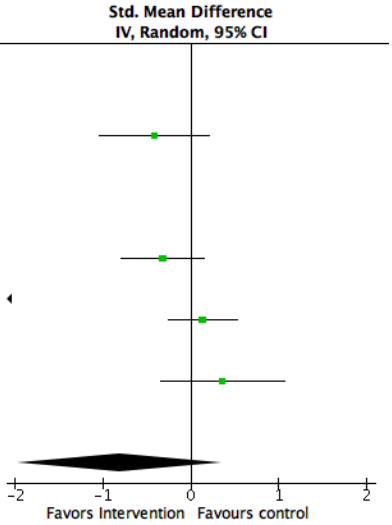
Heterogeneity: Tau² = 0.00; Chi² = 4.17, df = 4 (P = 0.38); I² = 4%
Test for overall effect: Z = 1.75 (P = 0.08)



Sensitivity analysis: Group delivery format

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Gendron 1996	0.9	9.1533	17	1.3	5.5154	18	0.0%	-0.05 [-0.72, 0.61]	1996
Fung 2002	-10.4	13.7674	26	-15.8	18.5604	26	0.0%	0.33 [-0.22, 0.87]	2002
McCallion 2004	-1.5	14.56	49	3.3	14.3107	46	0.0%	-0.33 [-0.73, 0.08]	2004
Akkerman 2004	-7.67	9.6308	18	2.82	12.1632	17	0.0%	-0.94 [-1.64, -0.23]	2004
Reinares 2004	-0.2	0.4382	30	-0.03	0.3098	15	20.0%	-0.42 [-1.04, 0.21]	2004
Tonge 2006	-11.48	15.441	35	-5.36	14.4944	35	0.0%	-0.40 [-0.88, 0.07]	2006
Gutiérrez-Maldonado	-32.62	18.5403	18	-0.43	18.6558	23	0.0%	-1.70 [-2.42, -0.97]	2007
Aakhus 2009	0.97	10.64	16	-5.98	8.7181	14	0.0%	0.69 [-0.05, 1.43]	2009
Koolaee, 2010	-26.25	11.9434	19	-8.73	15.3159	18	0.0%	-1.25 [-1.96, -0.54]	2010
Oken, 2010	-2.3	18.2463	10	-6.5	12.5226	10	0.0%	0.26 [-0.62, 1.14]	2010
Whitebird 2013	-7.2	6.3894	35	-4.5	10.0573	35	20.5%	-0.32 [-0.79, 0.15]	2013
Ji 2014	-6.1	12.2889	22	-3.09	20.3929	20	0.0%	-0.18 [-0.78, 0.43]	2014
FallahiKhoshknab 2014	-19.34	3.78	36	-3.21	4.2596	35	19.2%	-3.97 [-4.78, -3.15]	2014
Gonzalez 2014	3.16	16.8291	50	0.79	17.5951	52	20.7%	0.14 [-0.25, 0.53]	2014
Brown 2016	-0.3	0.8282	19	-0.35	1.5492	15	0.0%	0.04 [-0.64, 0.72]	2016
Gonyea 2016	-0.57	17.3402	29	0.03	15.557	28	0.0%	-0.04 [-0.56, 0.48]	2016
Hubbard 2016	0.67	2.3572	14	-0.72	4.56	18	19.7%	0.36 [-0.35, 1.06]	2016
Danucalov 2017	-2	4	25	1	4.0785	21	0.0%	-0.73 [-1.33, -0.13]	2017
Gossink 2018	-0.3	9.4888	15	1.1	13.1681	15	0.0%	-0.12 [-0.84, 0.60]	2018
Total (95% CI)			**165**			**155**	**100.0%**	**-0.81 [-1.97, 0.35]**	

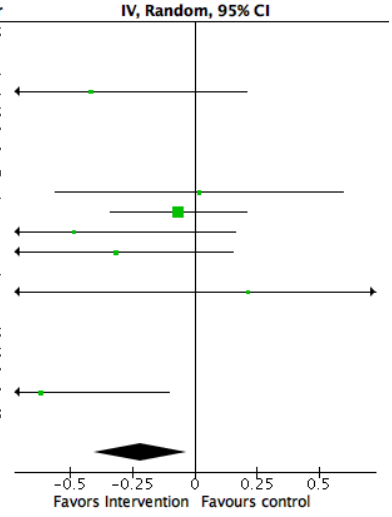
Heterogeneity: Tau² = 1.66; Chi² = 85.13, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.36 (P = 0.17)



Sensitivity analysis: Manualized, 8 weeks, group/individual

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Gendron 1996	0.9	9.1533	17	1.3	7.4246	18	0.0%	-0.05 [-0.71, 0.62]	1996
Fung 2002	-10.4	13.7674	26	-5.38	18.5604	26	0.0%	-0.30 [-0.85, 0.24]	2002
Akkerman 2004	-7.67	9.6308	18	2.82	12.1632	17	0.0%	-0.94 [-1.64, -0.23]	2004
Reinares 2004	-0.2	0.4382	30	-0.03	0.3098	15	8.5%	-0.42 [-1.04, 0.21]	2004
Tonge 2006	-11.48	14.4944	35	-5.36	15.441	35	0.0%	-0.40 [-0.88, 0.07]	2006
Gallagher Thompson 2007	-5.89	15.4426	23	-0.49	13.7898	22	0.0%	-0.36 [-0.95, 0.23]	2007
Gutiérrez-Maldonado	-32.62	18.5403	18	-0.43	18.6558	23	0.0%	-1.70 [-2.42, -0.97]	2007
Koolaee, 2010	-26.25	11.9434	19	-8.73	15.3159	18	0.0%	-1.25 [-1.96, -0.54]	2010
Davis 2011	-3.21	18.8611	24	-3.5	11.9606	22	10.0%	0.02 [-0.56, 0.60]	2011
Livingston 2013	-0.6	10.1487	152	0.09	10.4484	77	42.2%	-0.07 [-0.34, 0.21]	2013
Lavretsky 2013	-7.3	3.7	23	-5.3	4.5	16	8.0%	-0.48 [-1.13, 0.16]	2013
Whitebird 2013	-7.2	6.3894	35	-4.5	10.0573	35	14.9%	-0.32 [-0.79, 0.15]	2013
Ji 2014	-6.1	12.2889	22	-3.09	20.3929	20	0.0%	-0.18 [-0.78, 0.43]	2014
Leach 2015	-0.02	0.1697	8	-0.05	0.09	9	3.7%	0.21 [-0.74, 1.17]	2015
Polo Lopez 2015	0.02	0.1697	8	0.05	0.09	9	0.0%	-0.21 [-1.17, 0.74]	2015
Brown 2016	-0.3	0.7846	19	-0.35	1.5492	15	0.0%	0.04 [-0.64, 0.72]	2016
Gonyea 2016	-0.57	8.2393	29	0.03	8.3606	28	0.0%	-0.07 [-0.59, 0.45]	2016
Danucalov 2017	-2	4	25	1	4.0785	21	0.0%	-0.73 [-1.33, -0.13]	2017
Berwig 2017	2.669	8.858	31	8.102	8.576	31	12.8%	-0.62 [-1.13, -0.11]	2017
Gossink 2018	-0.3	9.4888	15	1.1	13.1681	15	0.0%	-0.12 [-0.84, 0.60]	2018
Total (95% CI)			**303**			**205**	**100.0%**	**-0.22 [-0.40, -0.03]**	

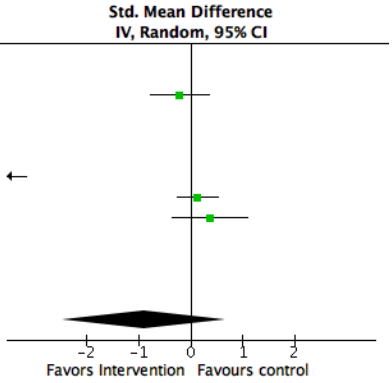
Heterogeneity: Tau² = 0.00; Chi² = 6.12, df = 6 (P = 0.41); I² = 2%
Test for overall effect: Z = 2.33 (P = 0.02)



Sensitivity analysis: Non-manualized, less than 8 weeks, group/individual

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Mohide 1990	-0.05	16.3226	22	2.8	12.5667	20	0.0%	-0.19 [-0.80, 0.42]	1990
Szmukler 1996	0.3	21.0435	32	-4.6	14.6432	31	0.0%	0.27 [-0.23, 0.76]	1996
Szmukler 2003	-2.4	12.7475	26	0.4	13.3804	23	25.2%	-0.21 [-0.77, 0.35]	2003
McCallion 2004	-1.5	14.56	49	3.3	14.3107	46	0.0%	-0.33 [-0.73, 0.08]	2004
Aakhus 2009	0.97	10.64	16	-5.98	8.7181	14	0.0%	0.69 [-0.05, 1.43]	2009
Oken, 2010	-2.3	18.2463	10	-6.5	12.5226	10	0.0%	0.26 [-0.62, 1.14]	2010
FallahiKhoshknab 2014	-19.34	3.78	36	-3.21	4.2596	35	24.4%	-3.97 [-4.78, -3.15]	2014
Gonzalez 2014	3.16	16.8291	50	0.79	17.5951	52	25.7%	0.14 [-0.25, 0.53]	2014
Hubbard 2016	0.67	2.3572	14	-0.72	4.56	16	24.7%	0.37 [-0.36, 1.09]	2016
deSouza 2016	-5.5	15.5653	14	-6.6	12.8048	22	0.0%	0.08 [-0.59, 0.75]	2016
Ata 2018	-15.25	20.4252	28	-0.09	20.1384	32	0.0%	-0.74 [-1.26, -0.21]	2018
Tabeleo 2018	-4.8	20.7975	66	1.9	20.32	64	0.0%	-0.32 [-0.67, 0.02]	2018
Total (95% CI)			**126**			**126**	**100.0%**	**-0.89 [-2.47, 0.68]**	

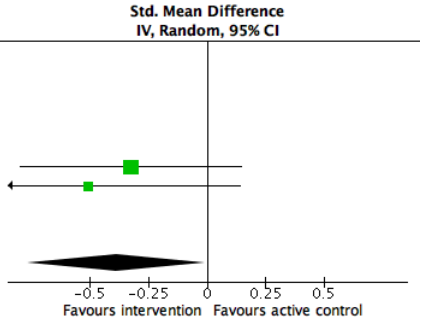
Heterogeneity: Tau² = 2.47; Chi² = 85.25, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.11 (P = 0.27)



Sensitivity analysis: Active control

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Szmukler 1996	0.29	15.7261	32	-4.6	14.6432	31	0.0%	0.32 [-0.18, 0.81]	1996
Gendron 1996	0.9	9.1533	17	1.3	5.5154	18	0.0%	-0.05 [-0.72, 0.61]	1996
Tonge 2006	-11.48	15.441	35	-5.36	14.4944	35	0.0%	-0.40 [-0.88, 0.07]	2006
Gallagher Thompson 2007	-5.89	15.4426	23	-0.49	13.7898	22	0.0%	-0.36 [-0.95, 0.23]	2007
Koolaee, 2010	-26.25	13.6869	19	-8.73	15.3159	18	0.0%	-1.18 [-1.89, -0.48]	2010
Oken, 2010	-2.3	18.2463	10	-6.5	12.5226	10	0.0%	0.26 [-0.62, 1.14]	2010
Whitebird 2013	-7.2	6.271	35	-4.5	9.7024	35	65.4%	-0.33 [-0.80, 0.14]	2013
Lavretsky 2013	-7.4	3.7	23	-5.3	4.5	16	34.6%	-0.51 [-1.16, 0.14]	2013
Brown 2016	-3.41	7.323	23	-2.13	8.2882	15	0.0%	-0.16 [-0.81, 0.49]	2016
Gonyea 2016	-0.57	8.2393	33	0.03	8.3606	34	0.0%	-0.07 [-0.55, 0.41]	2016
Total (95% CI)			**58**			**51**	**100.0%**	**-0.39 [-0.77, -0.01]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)



AARHUS UNIVERSITY

Supplemental Materials Paper II

Hansen, N. H., Juul, L., Pallesen, K. J., & Fjorback, L. O. (2021, Mar 1). Effect of a Compassion Cultivation Training Program for Caregivers of People With Mental Illness in Denmark: A Randomized Clinical Trial. *JAMA Netw Open, 4*(3), e211020. https://doi.org/10.1001/jamanetworkopen.2021.1020 (published)

eTable 1. Steps of the CCT program

Week 1	Introductions and learning to focus and settle the mind
Week 2	Cultivating loving kindness and compassion for a loved one
Week 3	Training compassion for one's own suffering
Week 4	Training loving-kindness for one's own suffering
Week 5	Cultivating compassion towards others through embracing shared common humanity and appreciating the interconnectedness of all human beings
Week 6	Training compassion towards all sentient beings
Week 7	Training active compassion using a Tonglen practice (it means to give and take) where participants imagine taking others' suffering away, and offering them all that is good in oneself
Week 8	Closure and training an integrated compassion practice

eTable 2. Loss to 6-month follow-up analysis of included and missing participants in both the CCT intervention and waitlist control (n=161) at 6-month follow-up.

	Included	**Missing**	**P-value**
Sex, n (%)	n = 116	n = 34	
Female	111 (88.10)	30 (88.24)	0.982
Male	15 (11.90)	4 (11.76)	
Age, mean (SD)	51.90 (11.65)	55.34 (15.13)	0.155
Educational level, n (%)			
No highschool	1 (0.79)	1 (2.86)	
Highschool	5 (3.97)	1 (2.86)	
Trade school	12 (9.52)	3 (8.57)	
Short continuing education	8 (6.35)	3 (8.57)	
Medium continuing education	54 (42.86)	14 (40.00)	
Long continuing education	44 (34.92)	11 (31.43)	
Ph.D.	2 (1.59)	1 (2.86)	
Other	0 (0.00)	1 (2.86)	0.630
Years of Caretaking			
0-5	32 (25.81)	12 (34.29)	
5-10	38 (30.65)	5 (14.29)	
10-15	17 (13.71)	4 (11.43)	
15-20	10 (8.06)	4 (11.43)	
> 20	27 (21.77)	10 (28.57)	0.353
DASS Depression, mean (SD)	10.90 (8.44)	10.64 (8.81)	0.874
DASS Anxiety, mean (SD)	6.90 (6.08)	6.35 (5.19)	0.632
DASS Stress, mean (SD)	15.79 (7.66)	13.88 (7.50)	0.200
PSS, mean (SD)	22.19 (6.45)	21.18 (6.07)	0.385

WHO-5, mean (SD)	44.84 (17.47)	45.94 (17.47)	0.776
BRS, mean (SD)	3.00 (.83)	3.14 (.68)	0.375
ERQ Reappraisal, mean (SD)	25.06 (7.00)	25.00 (6.96)	0.963
ERQ Emotion Suppression, mean (SD)	12.42 (4.67)	12.29 (5.18)	0.895

*Test of no difference between participants answering at 6 months follow-up and participants lost to follow-up. Pearson's χ^2 categorical variables, while t-test was used for continuing variables.
** Depression Anxiety Stress Scale (DASS), Perceived Stress Scale (PSS), World Health Organization (5) Well Being Index (WHO-5), Brief Resilience Scale (BRS), Emotion Regulation Questionnaire (ERQ)

eTable 3. Loss to 6-month follow-up analysis of included and missing participants in the CCT intervention (n=79) at 6-month follow-up.

	CCT		
	Included	**Missing**	**P-value**
Sex, n (%)			
Female	46 (85.19)	21 (87.50)	
Male	8 (14.81)	3 (12.50)	0.79
Age, mean (SD)	54.98 (11.62)	57.97 (16.68)	0.37
Educational level, n (%)			
No highschool	0 (0.00)	1 (4.00)	
Highschool	3 (5.56)	1 (4.00)	
Trade school	3 (5.56)	2 (8.00)	
Short continuing education	6 (11.11)	2 (8.00)	
Medium continuing education	31 (57.41)	12 (48.00)	
Long continuing education	11 (20.37)	6 (24.00)	
Ph.D.	0 (0.00)	0 (0.00)	
Other	0 (0.00)	1 (4.00)	0.53
Years of Caretaking			
0-5	13 (24.53)	9 (36.00)	
5-10	20 (37.74)	3 (12.00)	
10-15	3 (5.66)	2 (8.00)	
15-20	5 (9.43)	4 (16.00)	
> 20	12 (22.64)	7 (28.00)	0.23
DASS Depression, mean (SD)	10.46 (8.59)	11.83 (8.90)	0.52
DASS Anxiety, mean (SD)	7.12 (6.82)	6.42 (5.83)	0.67
DASS Stress, mean (SD)	15.50 (7.96)	13.84 (7.80)	0.39
PSS, mean (SD)	20.96 (6.37)	21.72 (5.44)	0.61
WHO-5, mean (SD)	47.00 (22.82)	46.40 (16.41)	0.91
BRS, mean (SD)	3.11 (.81)	3.13 (.73)	0.90
ERQ Reappraisal, mean (SD)	25.87 (7.04)	24.92 (7.75)	0.59
ERQ Emotion Suppression, mean (SD)	12.63 (4.50)	12.80 (5.65)	0.75

*Test of no difference between participants answering at 6 months follow-up and participants lost to follow-up. Pearson's χ^2 categorical variables, while t-test was used for continuing variables.
** Depression Anxiety Stress Scale (DASS), Perceived Stress Scale (PSS), World Health Organization (5) Well Being Index (WHO-5), Brief Resilience Scale (BRS), Emotion Regulation Questionnaire (ERQ)

eTable 4. Loss to 6-month follow-up analysis of included and missing participants in waitlist control (n=82) at 6-month follow-up.

	Control		
	Included	**Missing**	**P-value**
Sex, n (%)			
Female	65 (90.28)	9 (90.00)	
Male	7 (9.72)	1 (10.00)	0.98
Age, mean (SD)	49.59 (11.21)	49.04 (8.13)	0.88
Educational level, n (%)			
No highschool	1 (1.39)	0 (0.00)	
Highschool	2 (2.78)	1 (10.00)	
Trade school	9 (12.50)	1 (10.00)	
Short continuing education	2 (2.78)	2 (20.00)	
Medium continuing education	23 (31.94)	14 (40.00)	
Long continuing education	33 (45.83)	5 (50.00)	
Ph.D.	2 (2.78)	1 (10.00)	
Other	0 (0.00)	0 (0.00)	0.76
Years of Caretaking			
0-5	19 (26.76)	3 (30.00)	
5-10	18 (25.35)	2 (20.00)	
10-15	14 (19.72)	2 (20.00)	
15-20	5 (7.04)	0 (0.00)	
> 20	15 (21.13)	3 (30.00)	0.89
DASS Depression, mean (SD)	11.23 (8.37)	7.44 (8.16)	0.20
DASS Anxiety, mean (SD)	6.75 (5.55)	6.2 (3.43)	0.76
DASS Stress, mean (SD)	16.00 (7.47)	14.00 (7.04)	0.45
PSS, mean (SD)	23.11 (6.40)	19.44 (7.70)	0.12
WHO-5, mean (SD)	43.27 (19.09)	44.80 (20.81)	0.81
BRS, mean (SD)	2.92 (.83)	3.15 (.60)	0.40
ERQ Reappraisal, mean (SD)	24.46 (6.96)	25.22 (4.41)	0.75
ERQ Emotion Suppression, mean (SD)	12.25 (4.44)	10.89 (3.44)	0.38

*Test of no difference between participants answering at 6 months follow-up and participants lost to follow-up. Pearson's χ^2 categorical variables, while t-test was used for continuing variables.
** Depression Anxiety Stress Scale (DASS), Perceived Stress Scale (PSS), World Health Organization (5) Well Being Index (WHO-5), Brief Resilience Scale (BRS), Emotion Regulation Questionnaire (ERQ)

eTable 5. Sensitivity analysis of primary outcome of psychological distress.

	CCT			Control		
	Change score	CI 95%	p-value	Change score	CI 95%	p-value
			+ 0.2 SD			
DASS Depression						
Post	-3.52	-5.94 - -1.10	0.004	-3.78	-6.22 - -1.35	0.002
3 months	-4-04	-6.46 - -1.62	0.001	-4.43	-6.86 - -1.99	0.000
6 months	-4.26	-6.68 - -1.83	0.001	-4.95	-7.39 - -2.52	0.000
DASS Anxiety						
Post	-2.02	-3.66 - -.39	0.015	-2.26	-3.90 - -.63	0.007
3 months	-2.47	-4.11 - -.84	0.003	-2.75	-4.38 - -1.12	0.001
6 months	-2.08	-3.72 - -.45	0.012	-2.57	-4.21 - -.94	0.002
DASS Stress						
Post	-4.19	-6.59 - -1.79	0.001	-4.46	-6.87 - -2.06	0.000
3 months	-4.08	-6.48 - -1.69	0.001	-4.42	-6.83 - -2.02	0.000
6 months	-3.94	-6.34 - -1.55	0.001	- 4.60	-7.00 - -2.20	0.000
			-0.2 SD			
DASS Depression						
Post	-3.91	-6.34 - -1.47	0.002	-3.64	-6.06 - -1.22	0.003
3 months	-4.67	-7.11 - -2.24	0.000	-4.29	-6.71 - -1.87	0.001
6 months	-5.32	-7.76 - -2.89	0.000	-4.63	-7.05 - -2.21	0.000
DASS Anxiety						
Post	-2.22	-3.85 - -.59	0.008	-1.98	-3.61 - -.35	0.017
3 months	-2.84	-4.47 - -1.21	0.001	-2.56	-4.19 - -.93	0.002
6 months	-2.75	-4.38 - -1.12	0.001	-2.26	-3.89 - -.63	0.007
DASS Stress						
Post	-4.69	-7.11 - -2.28	0.000	-4.42	-6.82 - -2.02	0.000
3 months	-4.68	-7.09 - -2.26	0.000	-4.34	-6.74 - -1.93	0.000
6 months	-4.95	-7.37 - -2.54	0.000	-4.29	-6.70 - -1.89	0.000

* Missing outcomes were substituted with the model-based prediction adding or subtracting 0.2 SD in the intervention or control arm

** Depression Anxiety Stress Scale (DASS)

eTabel 6. Sensitivity analysis of secondary outcome of overall well-being.

	CCT			Control		
	Change score	CI 95%	p-value	Change score	CI 95%	p-value
			+ 0.2 SD			
WHO-5						
Post	10.81	5.04 – 16.57	0.000	10.16	4.42 – 15.91	0.001
3 months	8.95	3.18 – 14.71	0.002	7.98	2.24 – 13.72	0.006
6 months	9.80	4.03 – 15.56	0.001	8.14	2.39 – 13.98	0.005
BRS						
Post	.27	.08 - .46	0.005	.25	.06 - .43	0.009
3 months	.36	.17 - .55	0.000	.32	.14 - .51	0.001
6 months	.41	.22 - .59	0.000	.34	.16 - .53	0.000
PSS						
Post	-3.78	-5.51 - -1.91	0.000	-4.00	-5.81 - -2.19	0.000
3 months	-2.87	-4.67 - -1.07	0.002	-3.23	-5.04 - -1.42	0.000
6 months	-1.96	-3.76 - -.16	0.033	-2.54	-4.36 - - .73	0.006
ERQ-Reappraisal						
Post	4.44	2.61 – 6.27	0.000	4.15	2.34 – 5.97	0.000
3 months	3.31	1.48 – 5.14	0.000	2.96	1.15 – 4.76	0.001
6 months	2.80	.97 – 4.63	0.003	2.22	.41 – 4.03	0.016
ERQ-Suppression						
Post	-1.33	-2.65 - -.01	0.049	-1.48	-2.81 - -.16	0.028
3 months	-1.18	-2.50 - .14	0.081	-1.40	-2.72 - -.07	0.038
6 months	-1.41	-2.73 - -.09	0.036	-1.80	-3.11 - -.47	0.008
			-0.2 SD			
WHO-5						
Post	9.83	4.10 – 15.56	0.001	-3.64	-6.06 - -1.22	0.003
3 months	7.43	1.70 – 13.15	0.011	-4.29	-6.71 - -1.87	0.001
6 months	7.30	1.57 – 13.03	0.002	-4.63	-7.05 - -2.21	0.000
BRS						
Post	.24	.05 - .43	0.011	.26	.08 - .45	0.006
3 months	.30	.12 - .49	0.001	.34	.15 - .53	0.000
6 months	.21	.13 - .50	0.001	.38	.19 - .56	0.000
PSS						
Post	-4.08	-5.89 - -2.26	0.000	-3.79	-5.59 - - 1.98	0.000
3 months	-3.42	-5.24 - -1.61	0.000	-3.06	-4.96 - - 1.26	0.001
6 months	-2.85	-4.66 - -1.03	0.002	-2.26	-4.06 - -.46	0.014

ERQ-Reappraisal						
Post	4.07	2.26 – 5.89	0.000	4.36	2.54 – 6.19	0.000
3 months	2.76	.94 – 4.57	0.003	3.10	1.27 – 4.93	0.001
6 months	1.92	.10 – 3.73	0.038	2.50	.67 – 4.33	0.007
ERQ-Suppression						
Post	-1.60	-2.92 - -.28	0.018	-1.44	-2.75 - -.12	0.032
3 months	-1.55	-2.87 - -.23	0.022	-1.33	-2.64 - -.01	0.049
6 months	-2.00	-3.32 - -.68	0.003	-1.63	-2.94 - -.31	0.015

* Missing outcomes were substituted with the model-based prediction adding or subtracting 0.2 SD in the intervention or control arm

** World Health Organization (5) Well Being Index (WHO-5), Brief Resilience Scale (BRS), Perceived Stress Scale (PSS), Emotion Regulation Questionnaire (ERQ)

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Supplemental Materials Paper III

Hansen, N.H., Fjorback, L.O., Frydenberg, M., & Juul, L. (2021). Mediators for the effect of Compassion Cultivating Training: A longitudinal path analysis in a randomized controlled trial among caregivers of people with mental illness (submitted and accepted for publication in Frontiers in Psychiatry - Psychological Therapies).

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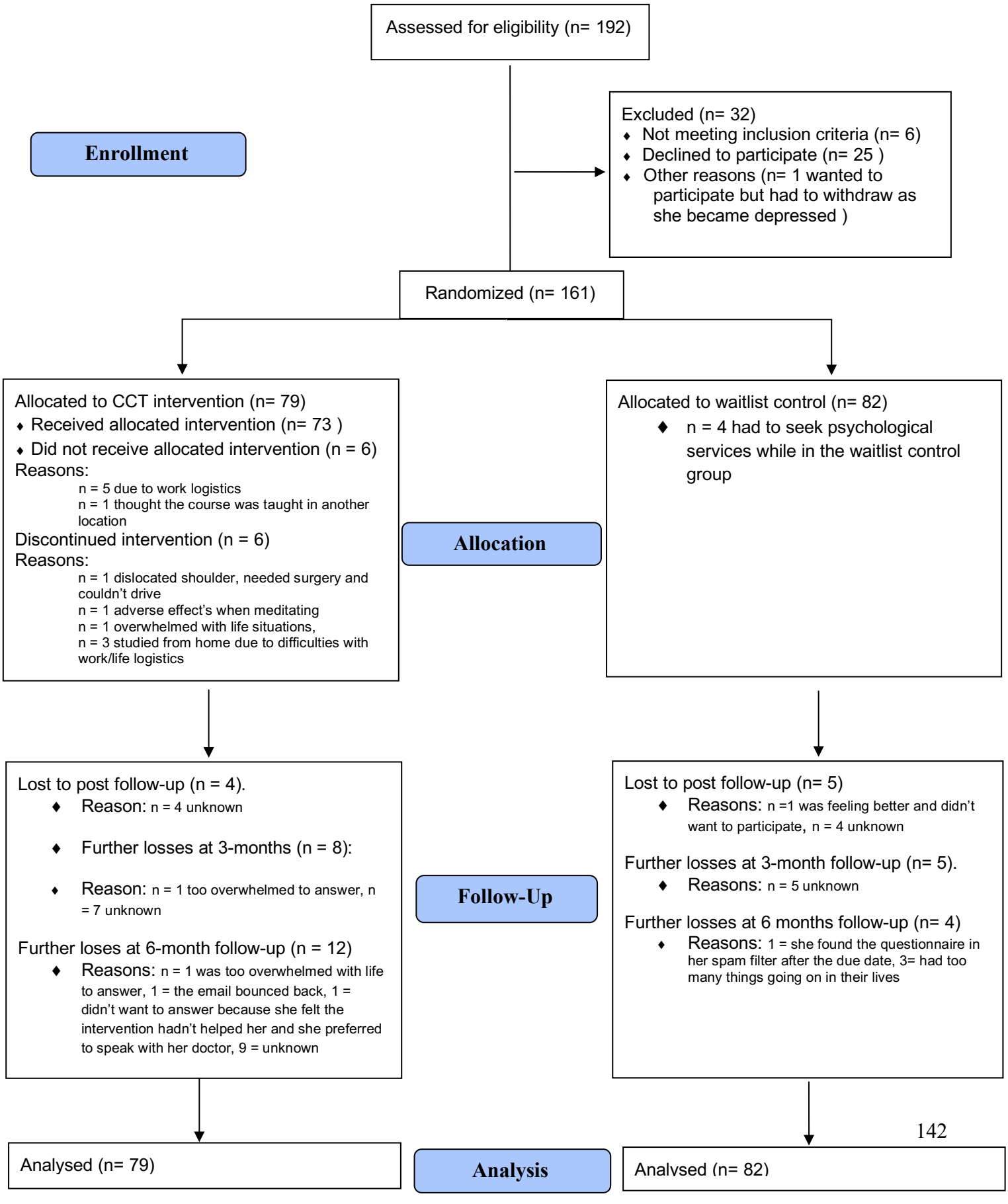
eFigure 1: Consort Flow Diagram of Participant Flow



eTable 1. Results of single mediator path models with four repeated measurements in an RCT: Mediated, Unmediated and Total effects for Compassion Cultivating Training (CCT) on symptoms of Depression, Anxiety and Stress (DASS) in Caregivers of People With Mental Illness at 6 -Months Follow-up (n=161)[a]

		Mediater			
		Self-Compassion Scale-12, Neff (SC) estimate (95% CI) p-valueb	**Five Facet Mindfulness Questionnaire-15 (FM)** estimate (95% CI) p-valueb	**Cognitive Reappraisal, The Emotion Regulation Questionnaire (ER)** estimate (95% CI) p-valueb	**Expressive Suppression, The Emotion Regulation Questionnaire (ES)** estimate (95% CI) p-valueb,c
Outcome (OC)					
Depression					
Path coefficients					
a path					
a1	CCT->mediator2	5.10 (3.15 to 7.06) <0.001	4.65 (2.81 to 6.49) <0.001	4.56 (2.78 to 6.34) <0.001	-1.22 (-2.46 to 0.02) 0.06
a2	CCT->mediator3	1.86 (-0.52 to 4.23) 0.13	-1.09 (-3.08 to 0.90) 0.29	-1.37 (-3.41 to 0.67) 0.19	-0.27 (-1.47 to 0.94) 0.66
a3	CCT->mediator6	-1.79 (-4.18 to 0.59) 0.14	1.45 (-0.38 to 3.29) 0.12	-0.73 (-3.01 to 1.55) 0.53	-0.49 (-1.78 to 0.81) 0.46
overall a	CCT->mediator6	4.90 (2.77 to 7.03) <0.001	5.05 (3.20 to 6.91) <0.001	2.42 (0.43 to 4.40) 0.02	-1.13 (-2.68 to 0.42) 0.15
b path	Mediator->OC	-0.26 (-0.36 to-0.16) <0.001	-0.34 (-0.45 to -0.23) <0.001	-0.21 (-0.31 to -0.12) <0.001	0.24 (0.10 to 0.38) <0.001
(constrained)					
Effects					
Mediated	CCT->mediator->OC (all paths including ≥ 1 mediator)	-3.30 (-5.70 to -0.90) <0.001	-3.41 (-4.89 to -1.93) <0.001	-1.74 (-2.92 to -0.56) <0.001	-0.59 (-1.34 to 0.16) 0.12
Unmediated	CCT->OC (all paths not via mediator)	0.03 (-3.17 to 3.22) 0.99	-0.46 (-3.19 to 2.27) 0.74	-1.86 (-4.09 to 0.38) 0.10	-3.80 (-6.91 to -0.69) 0.02
Total		-3.27 (-5.66 to -0.88) 0.01	-3.87 (-6.34 to -1.40) <0.001	-3.60 (-5.85 to -1.35) <0.001	-4.39 (-7.56 to -1.22) 0.01
Goodness of fit					
(degrees of freedom)=X2, p		(70)=70.0, 0.48	(70) =85.7, 0.10	(70)=70.4, <0.001	(34)=78.6, <0.001 0.09
RMSEA		<0.001	0.04	0.02	
CFI		1.00	0.98	0.99	0.92
Successful bootstrap out of 50		48	50	41	50
Anxiety					
Path coefficients					
a path					
a1	CCT->mediator2	5.01 (3.04 to 6.98) <0.001	4.78 (2.91 to 6.64) <0.001	4.67 (2.89 to 4.46) <0.001	-1.22 (-2.46 to 0.03) 0.06
a2	CCT->mediator3	2.09 (-0.26 to 4.45) 0.08	-1.07 (-3.07 to 0.93) 0.29	-1.31 (-3.32 to 0.71) 0.21	-0.28 (-1.48 to 0.93) 0.65
a3	CCT->mediator6	-1.90 (-4.30 0.51) 0.12	1.44 (-0.40 to 3.27) 0.13	-0.75 (-3.03 to 1.53) 0.52	-0.49 (-1.78 to 0.81) 0.46
overall a	CCT->mediator6	4.90 (2.85 to 6.95) <0.001	5.20 (3.04 to 7.35) <0.001	2.53 (0.57 to 4.49) 0.01	-1.13 (-2.67 to 0.41) 0.15
b path	Mediator->OC	-0.10 (-0.16 to -0.04) <0.001	-0.14 (-0.21 to -0.08) <0.001	-0.09 (-0.15 to -0.03) <0.001	0.05 (-0.04 to 0.14) 0.28
(constrained)					
Effects					
Mediated	CCT->mediator->OC (all paths including ≥ 1 mediator)	-1.48 (-2.53 to -0.41) 0.01	-1.74 (-2.73 to -0.73) <0.001	-0.84 (-1.48 to -0.19) 0.01	-0.14 (-0.44 to 0.16) 0.37
Unmediated	CCT->OC (all paths not via mediator)	0.26 (-1.94 to 2.46) 0.82	0.17 (-1.94 to 2.28) 0.88	-0.77 (-2.93 to 1.38) 0.48	-1.39 (-3.12 to 0.33) 0.11
Total		-1.21 (-3.09 to 0.68) 0.21	-1.56 (-3.59 to 0.47) 0.13	-1.61 (-3.70 to 0.48) 0.13	-1.53 (-3.29 to 0.22) 0.09
Goodness of fit					
(degrees of freedom)=X2, p		(70)=72.4, <0.001	(70)=83.0, <0.001	(70)=58.9, <0.001	(41)=63.7, 0.01
RMSEA		0.02	0.04	<0.001	0.07
CFI		1.00	0.98	1.00	0.94
Successful bootstrap out of 50		42	48	0	50
Stress					
Path coefficients					
a path					
a1	CCT->mediator2	5.24 (3.30 to 7.17) <0.001	4.61 (2.77 to 6.45) <0.001	4.49 (2.73 to 6.26) <0.001	-1.54 (-2.82 to -0.26) 0.02
a2	CCT->mediator3	1.94 (-0.41 to 4.29) 0.11	-1.17 (-3.18 to 0.85) 0.26	-1.32 (-3.35 to 0.72) 0.20	0.04 (-1.32 to 1.41) 0.95
a3	CCT->mediator6	-1.82 (-4.20 to 0.57) 0.14	1.46 (-0.37 to 3.30) 0.12	-0.74 (-3.02 to 1.54) 0.53	-0.29 (-1.63 to 1.05) 0.67
overall a	CCT->mediator6	5.06 (2.97 to 7.15) <0.001	5.03 (2.90 to 7.16) <0.001	2.40 (0.43 to 4.37) 0.02	-1.58 (-2.90 to -0.25) 0.02
b path	Mediator->OC	-0.27 (-0.38 to -0.16) <0.001	-0.40 (-0.53 to -0.27) <0.001	-0.21 (-0.32 to -0.10)<0.001	0.11 (-0.01 to 0.22) 0.08
(constrained)					
Effects					
Mediated	CCT->mediator->OC (all paths including ≥ 1 mediator)	-3.13 (-4.73 to -1.53) <0.001	-3.35 (-4.77 to -1.93) <0.001	-1.53 (-2.64 to -0.41) 0.01	-0.43 (-0.94 to 0.07) 0.09
Unmediated	CCT->OC (all paths not via mediator)	-0.30 (-3.33 to 2.72) 0.84	-0.77 (-3.81 to 2.27) 0.62	-2.31 (-5.11 to 0.50) 0.11	-3.97 (-6.86 to -1.08) 0.01
Total		-3.43 (-6.35 to -0.51) 0.02	-4.12 (-7.12 to -1.13) 0.01	-3.83 (-6.70 to -0.96) 0.01	-4.40 (-7.20 to -1.61) <0.001
Goodness of fit					
(degrees of freedom)=X2, p		**70)=72.5, 0.40**	(70) =98.1, 0.02	(70)=71.9, 0.42	(70)=58.0, 0.85
RMSEA		**0.02**	0.06	0.02	<0.001
CFI		**1.00**	0.95	1.00	1.00
Successful bootstrap out of 50		**50**	50	46	25

At baseline residual covariance between all mediators and outcome. For each mediator and the outcome residual covariance over time (except model with ES and depression and anxiety as outcome).

[a] According to figure 1. [b]Adjusted for sex, age, educational level, years as informal caretaker, schizophrenia (diagnosis, loved ones), anxiety (diagnosis, loved ones). [c]Adjusted for age, sex (in models with depression and anxiety as outcome). DASS Depression Anxiety Stress Scale

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Nanja Holland Hansen

This declaration concerns the following article/manuscript:

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Authors:	Hansen, N.H., Bjerrekær, L.A., Pallesen, K.J., L.Juul* & Fjorback, L.O*(*shared authorship)

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If published, state full reference:

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F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	A
Free text description of PhD student's contribution ***(mandatory)*** N.H.Hansen and L.O.Fjorback conceived of the design.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** N.H.Hansen, L. Bjerrekaer extracted quantitative data from each article. N.H.Hansen and K.J.Pallesen conducted Risk Of Bias assessment on each article. N.H.Hansen and L.Juul analyzed the data and N.H.Hansen, L.Juul and L.O.Fjorback interpreted the data.	
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Free text description of PhD student's contribution ***(mandatory)*** N.H.Hansen drafted the manuscript and critical revisions were conducted by L.Juul and L.O.Fjorback.	
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Full name of the PhD student: Nanja Holland Hansen

This declaration concerns the following article/manuscript:

Title:	Effect of a Compassion Cultivation Training Program for Caregivers of People With Mental Illness in Denmark: A Randomized Clinical Trial.
Authors:	Hansen, N. H., Juul, L., Pallesen, K. J., & Fjorback, L. O.

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Hansen, N. H., Juul, L., Pallesen, K. J., & Fjorback, L. O. (2021, Mar 1). Effect of a Compassion Cultivation Training Program for Caregivers of People With Mental Illness in Denmark: A Randomized Clinical Trial. JAMA Netw Open, 4(3), e211020. https://doi.org/10.1001/jamanetworkopen.2021.1020

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** N.H.Hansen and L.O.Fjorback conceived of the design for the study.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** N.H.Hansen and K.J.Pallesen completed the literature search. N.H.Hansen conducted the study with help from the rest of the authors. N.H.Hansen completed the data collection. L.Juul and N.H.Hansen completed the data analysis and the data interpretation.	
Drafting the manuscript:	B
Free text description of PhD student's contribution ***(mandatory)*** N.H.Hansen drafted the manuscript, with critical revisions from L.Juul and L.O.Fjorback. All authors agreed on the final draft before submitting the manuscript.	
Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
Submitted the manuscript and made changes to the manuscript based on peer-reviwers comments. Then resubmitted.

Signatures of first- and last author, and main supervisor

Date	Name	Signature
25.10.21	Nanja Holland Hansen	Nanja H. Hansen
25.10.21	Love Overby Fjorback	Love O Fjorback

Date: 29.10.2021

Nanja H. Hansen

Signature of the PhD student

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Nanja Holland Hansen

This declaration concerns the following article/manuscript:

Title:	Mediators for the effect of Compassion Cultivating Training: A longitudinal path analysis in a randomized controlled trial among caregivers of people with mental illness
Authors:	Hansen, N.H., Fjorback, L.O., Frydenberg, M., & Juul, L.

The article/manuscript is: Published ☐ Accepted ☒ Submitted ☐ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: Frontiers in Psychiatry - Psychological Therapies).

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

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E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	C
Free text description of PhD student's contribution ***(mandatory)*** N. H.Hansen, L.O. Fjorback, M. Frydenberg and L. Juul developed the study concept and study design.	
The acquisition, analysis, or interpretation of data:	D
Free text description of PhD student's contribution ***(mandatory)*** Data collection was performed by N.H. Hansen and L. Juul and M. Frydenberg performed the data analysis and interpretation.	
Drafting the manuscript:	C
Free text description of PhD student's contribution ***(mandatory)*** N. H. Hansen drafted the manuscript, and L. Juul and L.O. Fjorback provided critical revisions. All authors approved the final version of the manuscript for submission.	
Submission process including revisions:	B

Free text description of PhD student's contribution ***(mandatory)***
Submitted manuscript to journal for peer-review and resubmitted a final version of the manuscript based on peer-reviewers comments

Signatures of first- and last author, and main supervisor

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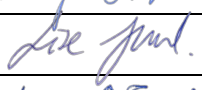
25.10.21	Nanja Holland Hansen	
25.10.21	Lise Juul	
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Signature of the PhD student