Anxiety in older adults: prevalence and low-threshold psychological interventions

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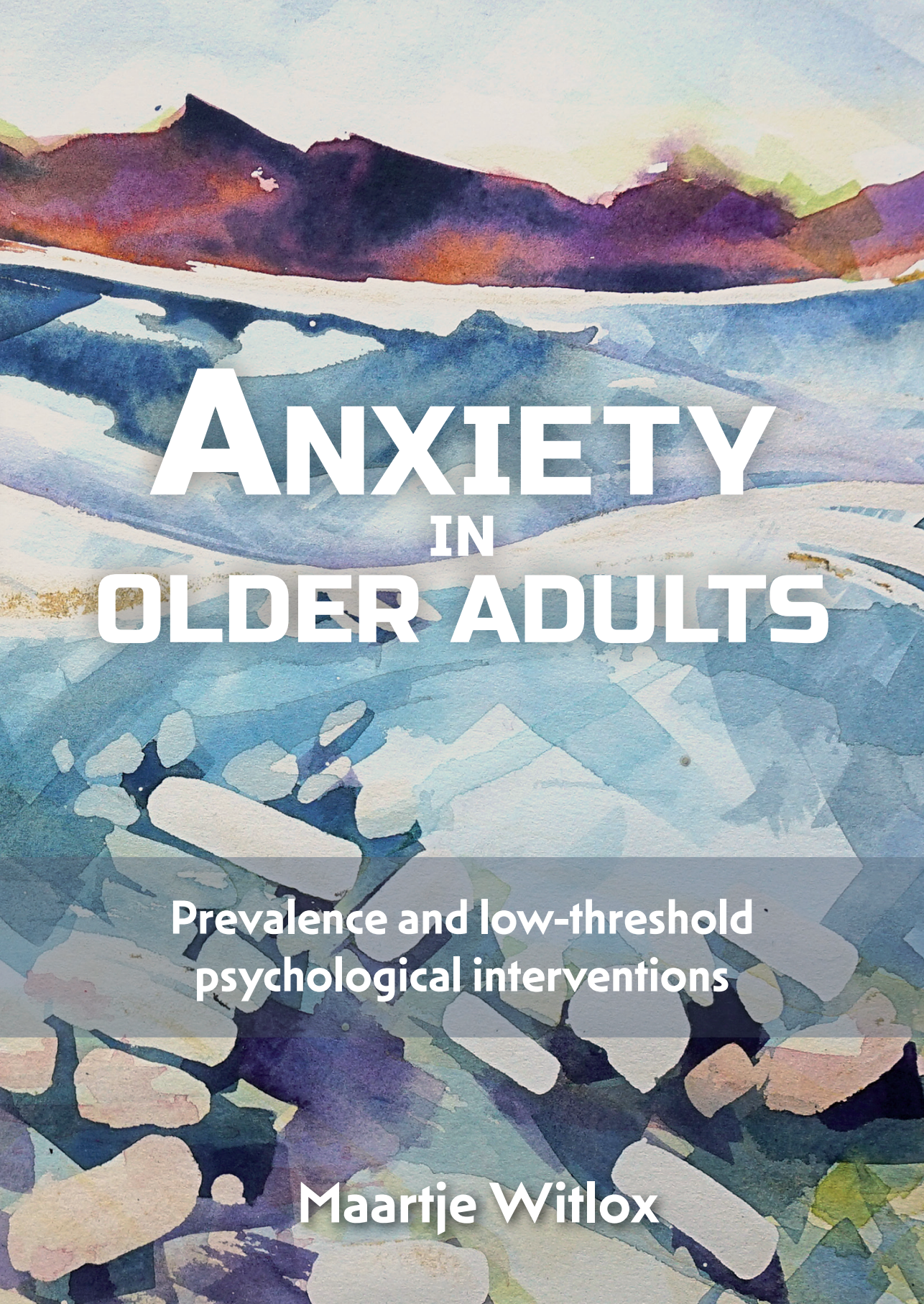
ANXIETY
IN
OLDER ADULTS
Prevalence and low-threshold psychological interventions
Maartje Witlox

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Voor Oma Bets

I've got a feeling
That this won't ever change
We're gonna keep on getting older
It's gonna keep on feeling strange
- Julia Jacklin

I have always imagined that Paradise will be a kind of a Library
- Jorge Luis Borges

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GENERAL INTRODUCTION

1. An unprecedented demographic shift

The global population is ageing at a rapid pace: in virtually all countries, the proportion of older adults and life expectancy are rising. In 2020, 18.5% of the world's population was aged 55 years and over. It is projected that by 2035, people aged 55 years and older will outnumber children under 15. Worldwide, life expectancy has increased from 66.8 years in 2000 to 73.4 years in 2019 [1]. In the Netherlands, the proportion of the population aged 55 years and over rose from 19% in 1970, to 22% in 1990 and 33% in 2019 [2]. Life expectancy in the Netherlands increased from 78 to 82 years between 2000 and 2019 [2].

The rapid increase in longevity and the proportion of older adults in the population impacts all facets of society. The key challenge for modern societies is to ensure that this demographic shift does not translate into an increased number of people facing extended periods of illness, disability and dependency, but instead to older people experiencing longer periods of health and well-being. To achieve this, it is important to understand the nature of growing old and the specific needs and abilities of older adults. We should recognize that older adults face particular challenges, not only related to their physical health but also related to their mental health and well-being.

In 2017, the World Health Organization stated that mental health in older adults is an under-identified and under-researched topic [3]. To understand the (future) requirements and challenges for society in general and mental health care practice in particular, research into the prevalence, nature, detection and treatment of mental health problems in the older population should be highly prioritized. This doctoral thesis aims to contribute to this endeavor by examining questions related to anxiety symptoms in later life. Anxiety is one of the most prevalent and disabling mental health conditions in older adults [4-7]. The current thesis has two aims. Firstly, it focuses on currently unresolved questions related to the prevalence of anxiety in later life. Secondly, it contains an elaborate comparative evaluation of two psychological interventions for older adults with anxiety symptoms.

1.1 How old is an 'older adult'?

Ageing is a continuous and gradual natural process. People do not become 'old' at any specific age. Age in years (also called chronological age) reflects only one dimension of ageing. Other dimensions are biological aging (related to declines in physical functioning), psychological/subjective ageing (how old or young one feels) and social ageing (changes in a person's roles and relationships) [3]. These different

aspects of ageing are not necessarily synchronous: some people who are 75 years old can feel and act much younger than some 55-year-olds.

Clearly, using a cut-off age to define 'old(er)' is always arbitrary to some extent. In the literature on (anxiety) in older adults, the cut-off for defining 'older' often differs between studies. Cut-offs of 55, 60 and 65 years old are the most common. In this doctoral thesis we use the cut-off of 55, as this low cut-off is most inclusive; it has less risk of excluding people based on their chronological age, who might be considered 'old(er)' on the other domains of ageing.

2. Prevalence of anxiety in later life

Epidemiological studies have repeatedly shown that although the prevalence of anxiety disorders (and most other mental health problems) declines with age, older adults still commonly suffer from anxiety disorders [4-9]. Prevalence estimates vary widely between studies, due to methodological differences: in their review article on anxiety disorders in older adults (defined as individuals aged 55 years and over), Wolitzky-Taylor and colleagues showed that reported prevalence estimates for anxiety disorders in older adults range from 3.2% to 14.2% [10].

Regarding the prevalence of specific anxiety disorders, a meta-analysis of prevalence studies in older adults in Western countries showed that specific phobia (SP) and generalized anxiety disorder (GAD) are most prevalent, with estimates of respectively 4.52% and 2.30% [11]. Pooled estimates for the other anxiety disorders were 1.68% for posttraumatic stress disorder (PTSD), 1.31% for social anxiety disorder (SAD), 0.90% for obsessive compulsive disorder (OCD), 0.88% for panic disorder and 0.53% for agoraphobia [11].

While the overall prevalence of anxiety disorders in older adults has been studied relatively frequently, epidemiological studies have not often focused on more complex and nuanced issues surrounding the prevalence of anxiety in later. Using a systematic review and meta-analysis of the literature, the current thesis aims to address two such issues: the prevalence of *subthreshold* anxiety in later life and differences in prevalence rates for anxiety disorders and subthreshold anxiety between different age groups of older adults.

2.1. Subthreshold anxiety in older adults

One of the most lively debates surrounding the topic of anxiety in older adults concerns the question whether adequate assessment of anxiety in later life requires

adapted/different diagnostic measures and methods. Clinical observations and empirical studies indicate that anxiety may manifest differently in older adults than in younger people and that common diagnostic assessments that have been developed with younger populations may therefore lack specificity in older adults [12, 13]. For example, compared to younger adults, older adults with either GAD or panic disorder tend to more strongly emphasize their physical complaints such as pain, tiredness, restlessness, lack of concentration, irritability, and sleep problems [14]. Diagnostic assessment is also complicated because older adults are more sensitive to stigma surrounding psychological symptoms and less accurate in identifying these symptoms [15-17]. This may lead to a reluctance and/or inability to adequately report on their mental health. Furthermore, impairment in work or social relationships (a criterion for the diagnosis of all DSM anxiety disorders) may not be readily apparent if an older person is retired and/or socially isolated [16,18]. Related to this, anxiety related avoidance behavior in older adults might be less noticeable or interpreted as less problematic, because as people get older, societal expectations regarding active living commonly decrease [19]. Lastly, both clinicians and older adults themselves might hold 'ageist' views that hinder the detection of anxiety. They might interpret anxiety symptoms as a part of the normal aging process or merely a byproduct of cognitive or physical conditions [13, 19].

All these factors can lead to a structural underdiagnosing of anxiety disorders in older adults. In support of this notion, Grenier et al. showed that the prevalence rate for anxiety problems in older adults was 26.2% when subthreshold anxiety was included, compared to 5.6% for DSM defined anxiety disorders only [20]. Subthreshold anxiety can be broadly defined as the presence of elevated levels of anxiety, without the symptomatology meeting all criteria for a full-blown anxiety disorder [21]. Findings like those from Grenier et al. suggest that anxiety in later life might mainly be a subthreshold phenomenon, and that a strict focus on DSM anxiety disorders does not do justice to the true prevalence and nature of the problem. The clinical relevance of subthreshold anxiety has also been demonstrated: studies found anxiety symptoms in later life to be associated with limited physical and social activities, decreased well-being, chronic physical problems, comorbid depressive complaints and increased health services utilization, irrespective of the anxiety symptoms meeting diagnostic criteria for an anxiety disorder or not [20, 22]. Clearly, to improve the understanding, assessment and treatment of anxiety in later life, the prevalence and nature of subthreshold anxiety should receive more attention.

2.2. Prevalence rates throughout later life

Another intricate and understudied issue related to anxiety in older adults concerns changes in the prevalence of anxiety throughout the later life span. Older adulthood can span over four decades, but we currently have a very limited understanding of how the prevalence of anxiety evolves throughout this period. Epidemiological studies commonly report a single prevalence estimate for a sample of older adults with an age range spanning over 30 years. Such an approach disregards differences between age groups of older adults, while it is plausible that the nature and prevalence of anxiety changes as people move throughout later life and undergo physical, cognitive and social changes. To truly comprehend the phenomenon of anxiety in later life, it is important to not consider older adults as a homogenous group. Instead, we should aim to unravel how prevalence rates of (different types of) anxiety vary between subgroups of older adults with different demographic and clinical characteristic. Such information can improve mental health care for older adults, by increasing clinician's awareness of factors that are relevant to anxiety in later life, thereby facilitating its detection and treatment.

2.3. This doctoral thesis

This thesis aims to address and answer two questions related to the prevalence of anxiety in later life, using a systematic review and meta-analysis of epidemiological studies in older adults. First, we will pool prevalence rates of subthreshold anxiety in older adults and see how these rates compare to the prevalence ratesof full-blown anxiety disorders in the older population. This comparison can provide insight into whether the current body of literature lends support to the claim that anxiety in later life is predominantly a subthreshold phenomenon. Secondly, we will examine how prevalence estimates for anxiety disorders and subthreshold anxiety differ between age groups of older adults. By systematically reviewing the currently available studies on the prevalence of anxiety in later life, we also aim to identify gaps and shortcomings in the literature and make recommendations for future research.

3. Psychological treatment of anxiety in later life

3.1. Previous research

Anxiety in older adults is a distressing, disabling and often chronic condition [23]. Also on a subthreshold level it is associated with an increased risk for multiple physical

conditions and cognitive decline, decreased subjective well-being and quality of life, and limitations in social functioning and self-care [24-30]. Unfortunately, currently a large proportion of anxious older adults do not receive adequate psychological care. There is clear evidence from multiple Western countries that older adults in general are less likely to seek, be referred for, and receive psychological treatment for mental health issues [31-33]. Given the increasing number of older adults with anxiety and the disabling nature of this mental health problem, rigorous evaluation and dissemination of evidence-based psychological treatment for later life anxiety should be a public health priority.

So far, most of the trials into psychological treatments for anxiety symptoms and disorders in later life have evaluated face-to-face cognitive behavioral therapy (CBT). Meta-analyses of these trials concluded that face-to-face CBT is effective in reducing the severity of anxiety symptoms in older adults [34-37] (N.B., these three meta-analyses used different age-cut-offs of respectively 55, 60 and 65 years). Multiple clinical guidelines have adopted these conclusions and recommend CBT as the first-choice psychological treatment of anxiety in older adults [e.g., 38-40]. However, caution is warranted in interpreting the meta-analytic findings, because the literature as a whole has several shortcomings: sample sizes are small, control groups are often absent or consist of wait-list conditions and long-term follow-up measurements are largely missing. Furthermore, the studies are rather homogeneous with regard to the specific type of anxiety they target (the majority focuses on the treatment of full-blown GAD) and with regard to the treatment setting (most are conducted in either an academic setting or a specialized mental health care setting). Also, meta-analyses showed that effect sizes in favor of CBT are small when CBT is compared to an active control condition and some evidence suggests that CBT might be less effective in older adults than in younger adults [41]. This indicates that it is worth investigating other treatment approaches. Another difficulty concerns the fact that traditional face-to-face CBT is relatively time and cost-intensive. Considering the high prevalence of anxiety symptoms in older adults and the rise in life expectancy, even affluent societies cannot easily afford to provide all anxious older adults with this type of treatment. It is therefore worth investigating the effectiveness of less expensive (e.g., briefer or with less therapist time) psychological interventions.

Concluding, while numerous important trials into the psychological treatment of anxiety in later life have been conducted over the last decades, there remains a significant amount of work to be done in this field of study. Clinical trials investigating

innovative, cost-reducing treatments, compared to proper active control conditions, in more diverse settings and in larger, more heterogeneous samples can move the field forward. In the following sections, we describe three ways of innovating evidence-based treatment for anxiety in later life, focusing respectively on treatment approach, treatment setting and treatment delivery format.

3.2. Treatment approach: Acceptance and Commitment Therapy

As stated, CBT is currently the dominant empirically validated psychological treatment for anxiety symptoms and disorders in later life, as it is for anxiety in general adult samples. In its broadest sense, CBT refers to a family of empirically evaluated psychological interventions that target cognitive and behavioral processes in order to ameliorate psychological distress [42]. The most widely used and investigated form of CBT is based on the cognitive model developed by Beck et al [43]. According to this model a successful CBT treatment for anxiety results in a new repertoire of functional thoughts and behaviors that compete with the dysfunctional anxiety-based network of cognitions and behavior [44].

Traditional CBT for anxiety encompasses a variety of therapeutic techniques, that are not necessarily all applied to each client: (a) psychoeducation; (b) monitoring/registering of symptoms; (c) relaxation/breathing training; (d) cognitive restructuring); (e) behavioral experiments, including exposure (imaginal or in vivo) and response prevention. Cognitive restructuring and behavioral experiments are thought to be the key elements of CBT for anxiety [44]. In cognitive restructuring, unrealistic and maladaptive negative thoughts are identified, critically examined and replaced with more adaptive cognitions. Behavioral experiments form a more direct method to disconfirm catastrophic expectations. By confronting previously avoided situations (or objects or bodily sensations) while not engaging in safety behaviors, corrective information is gathered and the link between the situation and anxiety is weakened [45].

While an impressive body of scientific literature supports the efficacy and effectiveness of traditional CBT for anxiety, clinical researchers have also been consistently interested in investigating other theoretically valid treatment alternatives. This is partly driven by a general desire to increase the number of evidence-based treatments for anxiety, thereby providing patients and clinicians with more flexibility in deciding on their preferred treatment. However, the search for evidence-based alternatives to traditional CBT also stems from findings that not all individuals with anxiety disorders can be equally successfully treated

with CBT (e.g., older adults seem to respond less favorably than younger adults), and both empirically and theoretically driven criticism on the key assumption of the cognitive model (that anxiety problems result from maladaptive cognitions and should therefore be treated by adapting these cognitions) [46-50].

An increasing amount of clinical and scientific interest has been dedicated to the so called third wave cognitive behavioral therapies. Instead of traditional CBT's focus on the content of a persons thoughts and emotions, third wave behavioral therapy approaches are mostly focused on the *context*, *processes*, and *functions* of how somebody relates to their internal experiences. Many of these third wave psychotherapies incorporate concepts such as acceptance, mindfulness, spirituality and metacognition. Within this family of therapies - Acceptance and Commitment Therapy (ACT) is one of the most theoretically strong and empirically evaluated treatment [50,51]. ACT is a transdiagnostic treatment approach that aims to foster psychological flexibility, which is defined as "the ability to be in contact with the private experiences that surface in the present moment without needing to avoid and/or escape from them, and to adjust one's behavior according to what the situation requires in order to pursue valued ends" [51]. Put differently, ACT focuses on two key principles: a) promoting an acceptance-based attitude towards internal experiences and b) clarification of personal values and engaging in actions that are in accordance with these values. ACT can be most clearly distinguished from traditional CBT in two ways. First, the treatments promote distinct strategies for handling maladaptive thoughts: traditional CBT aims to change the content of cognitions, while ACT aims to change how we relate and respond to cognitions. Second, their treatment goals differ: CBT mainly aims for symptom reduction, while ACT aims for a vital and valued life (with symptom reduction being a pleasant by product) [52,53].

ACT is commonly described in terms of six interrelated processes that stimulate psychological flexibility: a) acceptance, b) (cognitive) defusion, c) self as context, d) contact with the present moment, e) values, and f) committed action [51]. Acceptance refers to the process of stopping the struggle with painful internal experiences (emotions, thoughts, sensations, urges) and to instead open up and make room for these experiences. Defusion means 'untangling' from our thoughts. Instead of getting caught up in thoughts and being dictated by them, thoughts are seen for what they really are: words or pictures in our mind. Self-as-context (also sometimes called 'the observing self' or 'pure awareness') is the concept that we are not the content of our emotions and thoughts, but the consciousness that is experiencing those emotions and thoughts. Contact with the present moment consists of being psychologically present in the here and now; to connect and engage with whatever is happening in

the current moment. Values are desired qualities of ongoing action: they describe the kind of person we want to be and how we want to behave on an ongoing basis. Lastly, committed action refers to taking effective value-guided action: by behaving in a value-congruent manner, we can start building a rich, meaningful, vital life.

ACT has been found effective for a wide variety of patient populations, including adults with anxiety symptoms and disorders [54,55]. However, no high-quality trial into this treatment approach has yet been conducted in (anxious) older adults. The literature on ACT in older populations is currently limited to pilot studies and case studies which have concluded that ACT seems a promising treatment approach for anxious older adults that warrants a larger-scale investigation [56-58]. Although speculative at the moment, an argument could be made for why ACT may be especially acceptable and effective as a treatment for older adults. First, the ACT approach seems to align with age-related tendencies to behave in a more value-driven way, and to be more accepting towards (negative) internal experiences [59-61]. ACT may thus be especially beneficial for older adults, because it draws upon the psychological strengths commonly found in this age group [62,63]. A second reason why ACT might be a particularly befitting treatment for older adults is its transdiagnostic nature. Older adults often experience heterogeneous psychological problems, especially comorbid depression and anxiety [10]. Decreased levels of psychological flexibility have been linked to both anxiety and depressive symptoms, so stimulating psychological flexibility seems like a fruitful treatment approach in the older population [64].

3.3. Treatment setting: primary care

In 2008, the WHO published a report advocating for a global effort towards a better integration of mental health care services in primary care [65]. This is perceived to be the most efficient and affordable way of closing the treatment gap in people suffering from mental health problems. Services at the primary care level should consist of the prevention, detection and treatment of mental health problems and referral to more specialized institutions when required [66]. Studies in general adult samples have shown that treatment of (mild) psychological problems provided in primary care seems effective, easily accessible compared to treatment in specialized services and that it leads to satisfaction among patients and caregivers [67-69].

Improved integration of mental health services in primary care settings is thought to be especially beneficial for patient groups that commonly experience barriers in receiving appropriate mental health care in specialized settings. Older adults are one

of these groups. Research has shown that older adults are less likely to search for and receive professional help in specialized mental health care [33]. Older adults generally prefer to discuss and obtain help for their mental health problems in the more familiar and low-threshold setting of primary care, such as the general practice [70]. It is therefore important to conduct research into the effectiveness of primary care psychological interventions for older adults. To date, only a small number of studies have evaluated psychological treatments for older adults with anxiety in primary care. One study (n=31) compared a modular psychotherapy protocol to enhanced treatment-as-usual (in which healthcare providers were instructed to treat patients as they otherwise would, supplemented with a diagnostic assessment by the study staff and an appointment in which patients were informed by one of the researchers about their anxiety diagnosis) [71] and found that the modular protocol did not outperform the active control condition. However, in both conditions substantial improvements of anxiety and related clinical outcomes were observed. Another study (n=125) found that CBT for older patients with GAD in primary care was superior to enhanced usual care [72]. Lastly, a naturalistic study examined treatment outcomes in a group of 225 older patients in primary care receiving internet based CBT for depression or anxiety and concluded that it is an acceptable and effective treatment for this population [73].

Summarizing, psychological treatment in a primary care setting seems to align with older adult's treatment preferences and results regarding its effectiveness are promising. To improve the evidence-based practice in primary care mental health services, more pragmatic clinical trials, that evaluate psychological interventions for older adults in real-world primary care settings are required. In the Netherlands this translates to studies in which older adults receive short term treatment from mental health counselors working at a general practice (In Dutch such counselors are called Praktijkondersteuner Huisarts GGZ (POH-GGZ), which translates to *practice assistants mental health care*) [74]. The introduction of these mental health counselors in 2008 was one of the most important Dutch measures aimed at helping more patients with mental health problems in primary care [74]. The main tasks of these counselors are diagnostic assessment and short term psychological treatment for patients with non-complex mental health problems. Most clinicians in this occupation have an educational background in psychology, psychiatric nursing or social work [75]. Over the last decade, the number of Dutch general practices that employ a mental health counselor has grown steadily and these counselors play an increasingly important role in the Dutch mental health care system. A 2016 study found that 83% of Dutch general

practices employed a mental health counselor [75]. The number of patients seen by these counselors increased from 175.00 in 2013 to 571.000 in 2018 [76].

3.4. Treatment delivery format: internet-based treatment

To be able to provide a larger proportion of anxious older adults with adequate psychological treatment, it is important to study easily scalable, affordable, low-threshold interventions. Web-based psychological interventions are often mentioned as a promising way to decrease treatment costs, by reducing the therapist time per patient. Numerous controlled studies have been conducted into internet-based psychological treatment for a wide variety of mental health problems in general adult samples, including anxiety. The majority of these studies have examined CBT interventions [77]. Meta-analyses of these studies have shown that internet-based CBT forms an effective and promising alternative and complement to face-to-face treatment, especially if the internet-based help is guided by a clinician or coach (for example in the form of online feedback, e-mail contact or chat or telephone sessions) [78,79].

Older adults are underrepresented in studies into internet-based treatment. This might be the result of a common held conception that older adults often lack the willingness and/or ability to successfully work with internet-delivered services. However, as the computer literacy of older adults is steadily increasing each year, it is important to investigate the acceptability, effectiveness and uptake of internet based treatment for older adults [80]. So far, a small number of studies have examined the effectiveness of guided internet-delivered treatment for older adults with anxiety, all focusing on CBT interventions. All these studies conclude that internet delivered CBT with clinical guidance is (cost)effective in reducing anxiety symptom severity [81-84]. Furthermore, they did not report their older participants to experience significant obstacles or difficulties in working with the internet-based interventions. Internet-based psychological treatment thus seems promising for anxious older adults, although further research is still required.

Despite the promising results on the effectiveness of internet-based treatment for mental health problems, this type of treatment also has some disadvantages. Firstly, the lack of face-to-face contact does not match the treatment expectancies and preferences of a large group of patients that find ‘the talking aspect’ of psychological treatment particularly important. Furthermore, internet-based interventions often have a ‘one size fits all approach’, not allowing clinicians to tailor the intervention to the specific needs

of a client. Lastly, a purely online treatment setting might not suffice in crisis situations [85]. One way to partly overcome these barriers, is by combining face-to-face sessions with online treatment. This format is called 'blended treatment'. Blended treatment may combine the advantages of both face-to-face and internet-delivered treatment [85, 86]. The face-to-face contact enables clinicians to individualize the treatment and to adequately respond to crisis situations, while providing online modules between the face-to-face sessions could reduce therapist time and associated costs, increase patient self-management and stimulate the translation of treatment into daily life. No blended intervention has yet been evaluated in (anxious) older adults. However, adding face-to-face sessions to an internet-based intervention might be especially important in older populations, as research has shown that compared to younger adults, older adults put even more emphasis on talking and connecting with their therapist and consider this part of treatment to be the most important and helpful [87].

3.5. This doctoral thesis

To improve evidence-based treatment for older adults with anxiety it is important to broaden the scope of clinical trials in terms of therapeutic approach, treatment setting and treatment delivery format. ACT seems a promising treatment alternative to traditional CBT for older adults with anxiety, but strong empirical data to back up this claim are missing at the moment. To fill this gap in the literature, the current thesis will evaluate an ACT intervention in a large sample of older adults with anxiety symptoms. To properly investigate if the ACT intervention is a valuable treatment for anxiety in later life, the intervention will be compared to an enhanced treatment-as-usual condition consisting of a brief face-to-face traditional CBT intervention, as CBT is currently the gold standard psychological therapy for anxiety in later life. The ACT intervention under study is a blended intervention, as partly web-based interventions might play an invaluable role in providing treatment to the growing and currently underserved group of anxious older adults in a cost-effective way. We will conduct our study in the Netherlands, in the real-world setting of the general practice, where participants will receive short term treatment from a mental health counselor.

We will elaborately evaluate the blended ACT and CBT intervention: in addition to their clinical effectiveness, we will also examine their cost-effectiveness, moderators of treatment response to the interventions and potential mechanisms of change through which the interventions achieve their effects.

4. Aims and outline of this doctoral thesis

The first aim of this doctoral thesis is to provide an overview and integration of studies into the prevalence of anxiety in later life to answer two questions: how the prevalence of subthreshold anxiety compares to the prevalence of anxiety disorders in later life and how the prevalence of anxiety changes throughout the later life span. The second aim is to evaluate the (cost-)effectiveness of a brief blended ACT intervention compared to a brief CBT intervention. Additionally, we will investigate moderators and mediators of treatment effect. The content of the chapters of the doctoral thesis is shortly described below.

Chapter 2 contains a systematic review and meta-analysis that a) compares the prevalence rates of subthreshold anxiety and anxiety disorders in older adults and b) examines how prevalence rates change throughout the later life span.

Chapter 3 and 4 describe the study protocol and the main results of the randomized controlled trial (RCT) that evaluates the effectiveness of a brief blended ACT intervention for older adults with anxiety. The blended ACT intervention is compared to a brief face-to-face traditional CBT intervention. Effectiveness is evaluated in terms of anxiety symptom severity, depressive symptom severity, positive mental health, presence of anxiety disorder(s) and client satisfaction.

Chapter 5 describes a health economic evaluation of the interventions. The cost-effectiveness and cost-utility of the ACT intervention compared to the CBT intervention are assessed. Effects are presented in terms of long-term treatment response and QALY's.

Chapter 6 contains an explorative study into moderators and non-specific predictors of treatment response to the ACT and CBT intervention. This study provides insight into which variables differentially predict treatment response to the two treatments (moderators), and which variables are associated with better/worse treatment outcomes across both treatments (non-specific predictors).

Chapter 7 consists of a study into potential mechanisms of change of the ACT and the CBT intervention. We examine potential mechanisms related to the theoretical underpinnings of the treatment approaches, as well as variables assumed to drive change in psychotherapy in general.

Chapter 8 summarizes the results of the doctoral thesis and relates the findings to previous research. Strengths and limitations of the studies, recommendations for future research and implications for clinical practice are discussed.

PREVALENCE OF ANXIETY DISORDERS AND SUBTHRESHOLD ANXIETY THROUGHOUT LATER LIFE: SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

This systematic review and meta-analysis compared prevalence rates for subthreshold anxiety and anxiety disorders in adults aged 55+ and examined if these rates were associated with age. A systematic search and screening procedure resulted in 46 included articles. First, prevalence rates for subthreshold anxiety and anxiety disorders were statistically compared. Subthreshold panic, generalized anxiety and specific phobia were significantly more prevalent than the corresponding clinical disorders. In general, subthreshold anxiety appeared to be at least similarly prevalent to anxiety disorders, although firm conclusions are precluded due to the small number of samples that could be included in the analyses and the large heterogeneity between the reported prevalence rates. Second, using subgroup analyses, pooled prevalence rates for 4 age groups of older adults (55-64, 65-74, 75-84, 85+) were compared. For specific phobia, the 75-84 and 85+ groups had significantly lower prevalence rates than the 55-64 and 65-74 groups. Posttraumatic stress disorder was significantly more prevalent in the 55-64 group than in the other age groups, and lowest in the 85+ group. No other significant differences between age groups were found. The association between later life subthreshold anxiety and age could not be examined, due to a lack of reported information. The main limitation of this study is the small number of samples in the analyses, which limits their power and generalizability.

Keywords: older adults, anxiety disorders, subthreshold anxiety, prevalence, diagnostics, meta-analysis

Introduction

Epidemiological studies have repeatedly demonstrated that anxiety disorders are among the most common mental health issues in older adults, although prevalence rates are lower than those in younger adults [4-9]. While this general finding has been well-established, some issues regarding the prevalence of anxiety in later life remain unresolved. The current article aims to address two of these issues using a systematic review and meta-analysis.

First, although many studies have assessed the prevalence of anxiety disorders in older adults, little is known about the prevalence of subthreshold anxiety. Subthreshold anxiety can be defined as clinically significant anxiety symptomatology that does not meet all diagnostic criteria for an anxiety disorder [21]. While subthreshold depression in older adults has received considerable scientific attention, literature on subthreshold anxiety in later life is scarce. However, some evidence suggests that anxiety in later life might mostly be a subthreshold problem. For example, Grenier et al. [20] showed that the prevalence rate for anxiety problems was 26.2% when subthreshold anxiety was also considered, compared to 5.6% for DSM-defined anxiety disorders only

Research suggests that the decreased prevalence of anxiety disorders and relatively high prevalence of subthreshold anxiety in older adults might be a result of common diagnostic instruments and procedures being unsuitable for this age group. Most instruments have been developed for use in younger adult samples, but anxiety symptom expression and experience might be different in older adults [10]. Older adults are more likely to underreport their psychological symptoms [88], have more difficulty remembering symptoms and use other terms in describing them than younger adults [89]. Furthermore, due to the chronic nature of anxiety, some have lived with anxiety symptoms for so long, that they do not recognize them as highly problematic any longer [90]. Moreover, older adults might less often meet the functional impairment diagnostic criterion than younger adults as a result of age-related lower societal demands and expectations. For example, avoidance behavior might be less apparent or problematic in older adults, as they typically (are expected to) live less active lives in the first place [18,91]. Lastly, both clinicians and older adults themselves might interpret anxiety symptoms as a normal part of ageing [31] or a by-product of cognitive or physical conditions [13, 19]. All these factors could lead to the structural underdiagnosing of anxiety disorders in later life.

Studies found older adults with subthreshold anxiety to be similar to those with anxiety disorders in terms of limited physical and social activities, decreased

well-being, chronic physical problems, comorbid depressive complaints and health services utilization [20,22]. These findings support the notion that common diagnostic instruments do not adequately distinguish between 'healthy' and 'disordered' anxious older adults and indicate that a narrow focus on (DSM defined) anxiety disorders hinders a full understanding of later life anxiety. An overview of studies on the prevalence of subthreshold anxiety in older adults and how this compares to the prevalence of anxiety disorders in this population has not yet been published. The current article aims to fill this gap.

The second question this article aims to address is how the prevalence of anxiety disorders and subthreshold anxiety changes throughout later life. It is common for epidemiological studies to report one prevalence estimate for their sample of older adults, which often has a wide age range (e.g., 55+ or 65+). This ignores potential differences between age groups of older adults regarding the nature and prevalence of anxiety, which could arise from biological, psychological and social changes throughout the later life span. Findings from studies that examined the association between age and the prevalence of later life anxiety are conflicting. Two studies [8, 92] that compared 4 age categories of older adults (55–64, 65–74, 75–84, 85+), found a gradual decline with age for social phobia, panic disorder, specific phobia and posttraumatic stress disorder (PTSD). Their findings differed with regard to generalized anxiety disorder (GAD): Byers et al found a decline with age for this disorder too, while Reynolds et al. found GAD to be more prevalent in adults aged 85+ than in those aged 75-84 years. Another large epidemiological study [4] did not find significant differences between three age groups (55-64, 65-74, 75-85) regarding the prevalence of Obsessive Compulsive Disorder (OCD), GAD, panic disorder and phobic disorders (a category comprised of social phobia and specific phobia). Lastly, Baladon et al. [93] compared 3 age groups (65-74, 75-84, 85+) and observed a downward trend with age for the prevalence of agoraphobia, panic disorder, social phobia, specific phobia, GAD and OCD. However, when controlling for relevant demographic (gender, living situation, employment status) and clinical (somatic comorbidity, perceived social support, perceived disability) factors in a multivariate model, age group was not significantly associated with anxiety disorder prevalence. These conflicting findings might be partly explained by the methodological differences between the studies: they were conducted in different (western) countries, employed different diagnostic instruments and Beekman and colleagues used DSM-III criteria while the others used DSM-IV criteria. Combining data from multiple prevalence studies using meta-analysis could lead to more substantial conclusions about age

trends in the prevalence of anxiety disorders in later life. It could further provide for a more thorough understanding of the association between age and anxiety in older adults by exploring interactions between age and other relevant study- and participant characteristics (e.g., gender, somatic/cognitive comorbidity, diagnostic instruments/ criteria). With regard to subthreshold anxiety, to our knowledge no study has yet directly compared prevalence rates in different age groups of older adults. However, even in the absence of studies reporting separate prevalence rates for different age categories of older adults, a systematic search and integration of scientific literature could allow for a comparison of age groups, because the samples for which prevalence rates are reported might have non-overlapping age ranges.

Summarizing, the current article has two aims. First, to provide an overview and integration of articles that report prevalence rates for subthreshold anxiety in older adults and to see how these rates compare to those for anxiety disorders. Second, to examine the association between age and the prevalence of both later life anxiety disorders and subthreshold anxiety. This way, the current article will contribute to our understanding of later life anxiety, a topic of increasing relevance in light of the unprecedentedly large and steadily growing number and proportion of older adults worldwide [1].

Methods

Study selection

A first search was conducted in April 2018 using 4 databases (Psychinfo, PUBMED, Cochrane libraries, Web of Science). Reference lists of systematic reviews, meta-analyses and other relevant articles identified through the database search were also examined. Subsequent searches were conducted in November 2019 and April 2020, limited to articles that were published since the previous search. The full search strings can be found in Appendix 1. All articles were screened by authors M.W. and M.S. independently. Inclusion and exclusion decisions were cross-checked and disagreements were resolved by discussion. Studies were included if they (a) reported (12-month, 6-month, 1-month, current) prevalence rates for; (b) anxiety disorders or subthreshold manifestations of these disorders (panic disorder, agoraphobia, GAD, social anxiety disorder (SAD), OCD, PTSD and specific phobia); (c) in a community sample of adults aged 55 and over; (d) as established with a clinician-administered instrument using DSM-criteria (DSM-III, IV or V) or ICD-criteria. Articles had to be

written in English or Dutch and published in a peer-reviewed journal to be included. If a decision on exclusion/inclusion could not be reached due to missing information (e.g., the minimum age of the sample or the diagnostic instrument used was not reported) authors were sent an email with a request for additional information. If authors did not respond after two reminder emails, the study was excluded. Nine authors were sent an email of which 4 responded with the requested information. Although DSM-V does not classify OCD and PTSD as anxiety disorders, we decided on including these disorders in our analyses since most published prevalence studies used DSM-III or DSM-IV criteria (which do classify these two disorders as anxiety disorders) and because feelings of anxiety are a key feature of both disorders.

Multiplicity

If more than one article reported prevalence rates for the same anxiety disorder and/or subthreshold symptomatology in the same study sample (or subgroups of the sample), we included the article that presented rates for (most) different age groups. If none or all of the articles did this, the article that reported on the largest sample was included. In case of equal sample sizes, the article that provided the most descriptive information about the sample was included.

Coding

Author M.W. coded all articles. Author M.S. and two master levels clinical psychology students that were trained in the coding system independently coded one third of the articles each. Scorings between raters were cross-checked.

The following information was coded for every sample (if reported also for age based subsamples): publication year, country of data collection, setting (urban, suburban, rural), primary language(s) of participants, recruitment period, response rate, sample size, proportion of participants with somatic condition(s) (plus specification of the condition(s)), proportion with cognitive impairment (plus specification of assessment method), proportion that belongs to an ethnic/cultural minority (plus specification of the group), gender distribution, diagnostic instrument and diagnostic criteria used for classification, whether the instrument was adapted for use in an older population, whether hierarchical diagnostic rules were applied, interview mode, discipline of the interviewer, age range, mean age and standard deviation, prevalence rates of anxiety disorders/subthreshold anxiety for the sexes combined and (if reported) separately for men and women.

A review protocol was submitted to PROSPERO ((registration number: CRD42 018092953). The protocol can be assessed at https://www.crd.york.ac.uk/PROSPERO

Quality assessment

As there is no gold standard method for rating the quality of epidemiological studies, we constructed a 5-item scale adapted to the needs of this review. We based our rating system on the one used by Volkert et al. [11] in their meta-analysis on psychiatric disorders in older adults. Each included article was rated by authors M.W. and M.S. or one of the master level students independently on the following criteria: (a) sample size (low risk if sample size was equal or large than 1,000); (b) sample representativeness (low risk for random sampling method); (c) comparability between respondents and non-respondents (low risk if the response rate was 85% or more, or if a non-responder analysis indicated no relevant differences between responders and non-responders); (d) quality of diagnostic assessment method (low risk if psychometric qualities of the instrument were established); (e) quality of prevalence estimates (low risk if obtained from the total sample). Every criterion was scored '0' (high risk of bias/unclear risk of bias) or '1' (low risk of bias). Total quality scores were obtained by summing the 5 item ratings. Differences in quality ratings were resolved through discussion.

Statistical analyses

Analyses were conducted using the metafor package [94] and meta package [95] in the R programming software version 3.5 [96]. All analyses were performed separately for each of the 7 types of anxiety. Raw prevalence data were transformed to log its, to make the proportions normally distributed. Prevalence rates were weighted according to the sample size they were derived from, giving larger studies a greater impact on the pooled effect size. The logits were back-transformed after analysis and reported as percentages.

Pooled prevalence rates were calculated for both the clinical disorders and subthreshold symptomatologies. To compare the prevalence rates of anxiety disorders and subthreshold anxiety, relative risk ratios were calculated and pooled based on the articles that reported prevalence rates for both. The relative risk ratio represented the odds of older adults experiencing subthreshold anxiety compared to the odds of them fulfilling all diagnostic criteria for the anxiety disorder. A risk ratio larger than one indicated the odds of subthreshold anxiety to be higher than the odds of the anxiety disorder, while a risk ratio smaller than one indicated the opposite.

The association between age and the prevalence of anxiety disorders in later life was examined using mixed-effects subgroup analyses to compare prevalence rates for the following age categories: 55-64, 65-74, 75-84 and 85+. This categorization is common in large epidemiological studies [97]. Only articles reporting prevalence rates for (sub)sample(s) belonging to (one of) these age categories were included in the subgroup analyses. If the overall *Q*-test for moderation (i.e., the *Q*-between) was statistically significant, the subgroups were tested to examine differences among them. Interactions between age and other variables were tested by examining the *Q*-between value for the interaction term(s). If *Q*-between was significant, it was examined at what levels of the variables the interaction was present.

The Restricted Maximum Likelihood random effects method was used in all main analyses. *Q*-tests were conducted to test for heterogeneity across studies. Furthermore, heterogeneity was quantified using I^2 (values of 25%, 50% and 75%, representing cutoffs for low, medium and high heterogeneity, respectively), which indicates the proportion of between-study variance resulting from heterogeneity rather than from chance. 95% confidence intervals around I^2 were calculated. Tests with a p-value of less than .05 were interpreted as statistically significant. All p-values were two-sided. When more than two effect sizes were pooled, externally studentized residuals were inspected to identify outliers, which were defined as values over 2 [98].

No funnel plot inspection and formal tests for the detection of publication bias were performed. The results of the articles included in the current meta-analyses are non-comparative, and do not contain significance levels. Results from these studies are therefore not interpreted as 'negative/positive' or 'undesirable/desirable', which gives the size of the reported prevalence rate little influence in the publication process [99].

Results

Article search and selection

The database searches yielded 2209 articles, which dropped to 1825 after removal of duplicates. Examination of the reference lists of relevant articles identified through the database search resulted in an additional 162 articles. In total, titles and abstracts of 1987 articles were screened. Full-text screening was performed on 728 articles, of which 46 were included in the analyses. For a flowchart of the screening procedure and reasons for article exclusion see Figure 1. Table 1 and Table 2 list the articles that report prevalence rates for one or more anxiety disorders (all 46 included articles)

and types of subthreshold anxiety (6 articles), respectively. Articles were assigned an article ID to facilitate clear reporting.

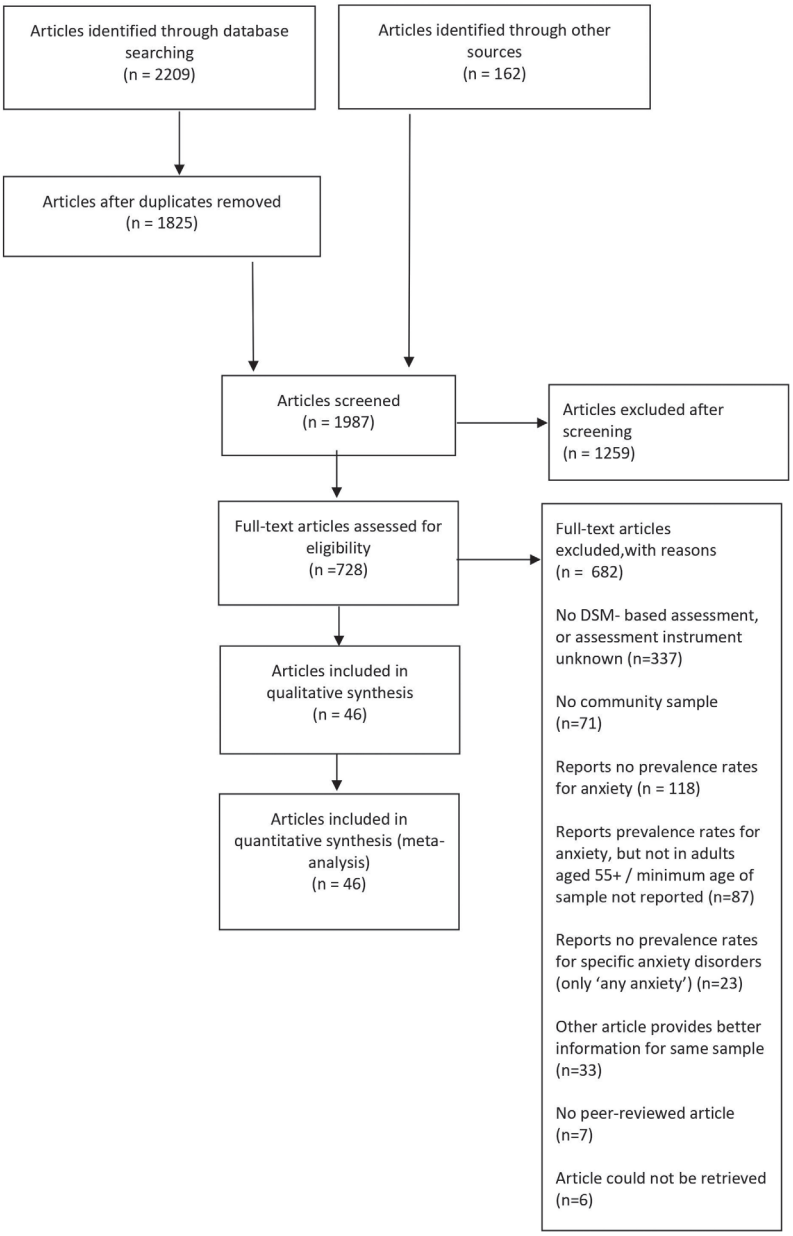


Figure 1. Flowchart of article inclusion and exclusion

Article description

The 46 included articles were published between 1984 and 2019 and reported prevalence rates for adults aged 55+ in 19 different countries across Europe, North- and South America, Asia and Australia. The most commonly used cutoffs to define old(er) were 65/66 years (n=17) and 55/56 years (n=10). The mean age of the sample was presented in 32 articles and ranged from 66.6 to 85.0 years, with a median of 72.9. Information on the gender composition of the sample was reported in 42 articles. Reported proportions of women ranged from 44.2% to 100%, with a median of 58.5%. The most frequently used diagnostic instruments were the Composite International Diagnostic Interview (CIDI, n=18) [138], the Mini-international Neuropsychiatric Interview (MINI, n=8) [139] and the Structured Clinical Interview for DSM Axis I Disorders (SCID, n=7) [140]. DSM-IV criteria were used in 33 articles, DSM-III criteria in 12 and DSM-V criteria in one. Twenty-five articles reported prevalence rates for GAD, 22 for panic disorder, 21 for SAD, 19 for agoraphobia, 14 for specific phobia, 15 for OCD and 12 for PTSD. Considering subthreshold anxiety, 3 articles reported prevalence rates for subthreshold social anxiety, 2 articles for subthreshold agoraphobia, generalized anxiety, specific phobia and posttraumatic stress and one article reported rates for subthreshold OCD. Subthreshold anxiety was operationalized differently across studies (see Table 2).

Quality assessment

Thirteen articles had a total quality score of 5, indicating that their risk of bias was low for all 5 criteria. Twenty articles had a total score of 4, 11 articles had a score of 3 and 2 articles scored 2. No articles had a total score of one or zero points. The most common risk of bias was the small sample size: 22 articles (47.8%) reported on sample sizes smaller than 1,000. Comparability of non-responders and responders was not sufficient or not investigated in 18 articles (39.1%). Quality of the diagnostic assessment method used was unknown for 4 articles: these articles reported to have used a DSM-based assessment method, but did not report a specific instrument. One article did not use a random sampling method. One article did not report prevalence rates based on the total study sample, but instead used subsample based extrapolation.

Prevalence of subthreshold anxiety and anxiety disorders

Table 3 shows the results of the meta-analyses on the prevalence of anxiety disorders and subthreshold anxiety. The following pooled prevalence rates were found for the

different types of subthreshold anxiety: 7.88% [6.98-8.89] for specific phobia; 5.01% [0.67-29.10] for posttraumatic stress; 2.96% [0.68-11.92] for social anxiety; 2.55% [2.05-3.18] for panic; 1.97% [0.34-10.59] for agoraphobia; 1.42% [1.12-1.79] for generalized anxiety. For subthreshold OCD, no pooled prevalence rate could be calculated, because only one study reported a prevalence rate for it (1.06%). Non-significant *Q*-values and I^2s below 50% (but with wide confidence intervals) indicated that reported prevalence rates for subthreshold generalized anxiety, panic and specific phobia were relatively homogeneous. Prevalence rates for subthreshold agoraphobia, PTSD and social anxiety were highly heterogeneous (i.e., statistically significant *Q*-values and I^2s over 75%).

The following pooled prevalence rates were found for anxiety disorders: 5.40% [3.55-8.14] for specific phobia; 2.32% [1.72-3.12] for GAD; 1.62% [0.93-2.81] for agoraphobia; 1.57% [1.13-2.18] for PTSD; 1.23% [0.90-1.67] for SAD; 0.89% [0.58-1.35] for OCD; 0.76% [0.50-1.16] for panic disorder. For all anxiety disorders, reported prevalence rates were highly heterogeneous as indicated by significant Q-values and large I^2s. With the exception of generalized anxiety, all pooled estimates were higher for subthreshold symptomatology than for the clinical disorder. However, panic was the only type of anxiety for which the confidence interval of the two pooled prevalence rates did not overlap.

The 6 articles that reported prevalence rates for subthreshold anxiety, also reported prevalence rates for anxiety disorders in their samples. For these samples, the prevalence rates for subthreshold anxiety and the clinical disorder were compared using risk ratios. These meta-analyses resulted in pooled risk ratios higher than one for every type of anxiety, which indicates that the odds of older adults experiencing subthreshold symptomatology is higher than the odds of older adults having an anxiety disorder. For generalized anxiety (RR=3.49 [1.90-6.43], $p<.001$), panic (RR=4.10 [2.71-6.21], $p<.001$) and specific phobia (RR=5.63 [2.05-15.46], $p<.001$), the estimates were statistically significant. With the exception of panic (I^2=0.00% [0.00-97.95]) and specific phobia (I^2=60.87% [00-99.76]), I^2 estimates for the pooled risk ratios were larger than 75%, indicating substantial unexplained heterogeneity between the estimates.

Prevalence rates in different age categories

Appendix 2 lists the studies that reported prevalence rates for anxiety disorders in one or more of the specified age categories (55-64, 65-74, 75-84, 85+). See Table 4 for the results of the subgroup analyses comparing prevalence rates of anxiety disorders between these age groups.

The test of moderation (Q-between) was significant for specific phobia (Q=10.31, p=.02) and PTSD (Q=60.82, p<.0001). Regarding specific phobia, both the 75-84 and 85+ group had lower pooled prevalence rates than the 55-64 (75-84: z=2.36, p=.02; 85+: z=2.48, p=.01) and 65-74 group (75-84: z=2.03, p=.04; 85+: z=2.16, p=.01). Regarding PTSD, the prevalence estimate in the 55-64 group was significantly higher than estimates for all 3 other age groups (65-74: z=6.00, p <.0001; 75-84: z=4.91, p<.0001; 85+: z=4.57, p<.0001). Furthermore, the estimate for the 85+ sample was lower than the pooled estimates for the 65-74 (z=2.11, p=.04) and 75-84 (z=2.18, p=.03) groups. No other significant differences between age groups were found. For all 7 anxiety disorders, subgroup analyses showed the 85+ group to have the lowest prevalence rate (although not significantly lower in most cases). No recurring pattern was apparent in the pooled prevalence rates for the other 3 age groups.

None of the subgroup analyses resulted in 4 groups with homogeneous prevalence rates. For all 85+ groups, I^2 estimates of 0.00% indicated low heterogeneity, but confidence intervals around the estimates were wide, ranging from 0% to values over 75%. I^2 estimates were also low (but with wide confidence intervals) for the 75-84 groups in the analyses on OCD, panic disorder, PTSD and specific phobia, the 65-74 group for PTSD and the 55-64 group for specific phobia.

The association between age and the prevalence of subthreshold anxiety could not be examined because no article reported prevalence rates for subthreshold anxiety in different age categories, nor did the samples for which prevalence rates were reported fall into different prespecified age categories.

Interactions of age and other participant/study characteristics

Separate prevalence rates for men and women in different age categories were available for GAD (65-74 and 75-84), OCD (all four age categories), panic disorder (55-64, 65-74, 85+) and SAD (65-74, 75-84, 85+). For none of these disorders, a significant interaction between age and sex was found (GAD: Q(1)=0.002, p=.96; OCD: Q(3)=1.67, p=.64; panic disorder: Q(2)=2.59, p=.28; SAD: Q(2)=0.05, p=.98). Interactions between age and the participant variables of physical impairment, cognitive impairment and ethnic/cultural background could not be examined, because no article provided information about these variables for one (or more) of the specified age categories.

The interaction between DSM-criteria (III vs. IV) and age could be examined for GAD (55-64, 65-74, 75-84), OCD (55-64, 65-74, 75-84) and panic disorder (55-64, 65-

74, 85+). Interaction terms were non-significant for all three disorders (GAD: $Q(2)=1.55$, $p=.46$; OCD: $Q(2)=3.63$, $p=.16$; panic disorder: $Q(2)=0.84$, $p=.66$). Interactions between age and the study characteristics of *use of hierarchical diagnostical rules* and *use of diagnostic instrument specifically adapted to older adults* could not be investigated, because they were not reported in any of the articles that reported prevalence estimates for (one or more of) the specified age categories. Interactions with interview mode, interviewer discipline, study country and study setting could also not be investigated because there was no variation in these variables among the age-specific samples.

Outliers

Outlying values were identified when pooling prevalence rates for agoraphobia (article ID 26), OCD (article IDs 23, 41), PTSD (article IDs 35, 41), panic disorder (article IDs 34, 43), SAD (article IDs 13, 41) and specific phobia (article ID 17). Regarding the pooled prevalence rates for the prespecified age categories, outliers were identified in the 55-64 group for GAD (article ID 43), the 65-74 group for OCD (article ID 1), the 55-64 and 65-74 group for panic disorder (article ID 43 for both groups) and the 55-64 (article ID 4) and 75-84 (article ID 22) group for SAD. The articles that reported the outlying values were inspected, but no factors were identified that could have structurally influenced the results, so it was not justified to exclude these articles from the main analyses.

Sensitivity analyses without the outliers resulted in the following pooled prevalence rates for anxiety disorders, which were only marginally different from the pooled estimates in the main analyses: 1.43% [0.85-2.39] for agoraphobia; 0.88% [0.58-1.35] for OCD; 1.67% [1.44–1.92] for PTSD; 0.81% [0.57-1.14] for panic disorder; 1.48% [1.18-1.85] for SAD; 5.94% [4.02-8.69] for specific phobia. For PTSD, heterogeneity between studies decreased after removing the outliers ($Q=4.23$, $p=.90$, $I^2=0.00$ [0.00-51.66]). For all other disorders heterogeneity was still large (i.e., p-values for $Q < .01$ and $I^2 > 80\%$).

See Appendix 3 for the results of the sensitivity subgroup analyses without outliers. For GAD, panic disorder and SAD, analyses without outliers had comparable results to the main analyses and did not show significant differences between the age groups. For OCD, results from the analysis without the outlier differed from those from the main analysis: the pooled prevalence rate for the 65-74 group of 2.58% [1.52–4.37] was significantly higher than those for the 55-64 groups(1.05% [0.53-2.04], $z=2.08$, $p=.04$) and 75-84 (0.55% [0.23-1.31], $z=2.99$, $p=.002$).

Table 1. Included studies reporting prevalence rates for anxiety disorders

Article ID	Authors (year of publication)	Study name	Country (recruit- ment period)	Total sample size	Mean age	Age range total sample	Separate prevalence rates for age categories (N)	Diagnostic instrument/ Diagnostic Criteria	Interviewer, interview mode	Women	Somatic disease	Cognitive impairment	Ethnic minority	Reported prevalence rates
1	Baladon et al. (2015) [93]	The Diagnostic and Assessment Study of Mental Disorders in Primary Care (DASMAP)	Spain (2005–2006)	1,192	74	65+	65–74 (707) 75–84 (434) 85+ (52)	SCID-I-Research Version and MINI for OCD/ DSM-IV,	Psychologist, Face-to-face	57.4%				AGO (3.0%); GAD (2.2%); OCD (0.18%); PD (1.4%); SAD (0.7%); SP (5.1%)
2	Beekman et al. (1998) [4]	The Longitudinal Aging Study Amsterdam (LASA)	Netherlands (1992-1993)	3,056	70.6	55-85	55-64 (964) 65–74 (954) 75-85 (1,138)	DIS/DSM-III	N.R., Face-to-face	51.6%	66.4%, one or more chronic illnesses (not specified)	15.5%, MMSE-score < 23		GAD (7.3%); OCD (0.6%); PD (1.0%)
3	Bland, Newman & Orn (1988) [100]	N.R	Canada (1983–1986)	721	N.R	N.R	55 – 64 (363) 65+ (358)	DIS/DSM-III	Trained lay interviewer Face-to-face	62.3%				OCD (0.7%); PD (1.8%)
4	Byers, Yaffe, Covinsky, Friedman & Bruce (2010) [92]	National Comorbidity Survey Replication (NCS-R)	USA (2001-2003)	2,575	68	55+	55-64 (1,114) 65-74 (813) 75-84 (526) 85+ (122)	World Mental Health-CIDI 3.0/ DSM-IV	Researcher, Face-to-face	59.1%			18.2%, non-white	AGO (0.8%); GAD (2.0%); PD (1.3%); SAD (3.5%); SP (6.5%)
5	Byrne & Pachana(2011) [101]	Longitudinal Assessment of Women (LAW) Study	Australia (2008-2009)	284	72.2	60– 87	N.R.	MINI-V/DSM-IV	Trained lay interviewer Face-to-face	100%				GAD (3.3%)
6	Byrne, Steele & Pachana (2015) [102]	Australian National Survey of Mental Health and Well-being (NSMHWB)	Australia (2007)	1,905	73.3	65-85	N.R.	World Mental Health-CIDI 3.0/ DSM-IV	Research Nurse, Face-to-face	52.6%		7.9%, MMSE-score ≤ 24		AGO (0.3%); OCD (0.7%); PD (0.5%); PTSD(1.5%); SAD (1.2%)
7	Cairney, Corna, Veldhuizen, Herrmann & Streiner (2008) [103]	Canadian Community Health Survey-Mental Health and Well-being (CCHS 1.2)	Canada (2002)	12,792	67.1	55-103	55–64 (5,056) 65–74 (4,113) 75-103 (3,623)	World Mental Health-CIDI 3.0/ DSM-IV	Trained lay interviewer Face-to-face	58.6%				AGO (0.6%); PD (0.8%); SAD (1.3%)

Table 1. Continued

Article ID	Authors (year of publication)	Study name	Country (recruit- ment period)	Total sample size	Mean age	Age range total sample	Separate prevalence rates for age categories (N)	Diagnostic instrument/ Diagnostic Criteria	Interviewer, interview mode	Women	Somatic disease	Cognitive impairment	Ethnic minority	Reported prevalence rates
8	Canuto et al., (2018) [5]	MentDis_ICF65+ study	Germany;Italy; England; Spain; Switzerland; Israel (N.R.)	3,142	73.7	65-84	N.R.	CIDI 65+/ DSM-IV	Mental health professionals or mental health graduate students, Face-to-face	51.7%				AGO (3.9%); GAD(3.1%); OCD (0.9%); PD (3.0%); PTSD (1.7%); SAD (1.1%)
9	De Bruijn et al. (2014) [104]	The Rotterdam Study	Netherlands (2002-2004)	3,069	75.5	57+	N.R.	Munich version of CIDI/ DSM-IV	Trained lay interviewer Face-to-face (computer assisted)	59.0%				PD (0.3%); SAD (0.9%); SP (1.7%)
10	Dehoust et al. (2017) [105]	MentDis_ICF65+ study	Germany; Italy; England; Spain; Switzerland; Israel (N.R.)	3,142	73.7	65-84	N.R.	CIDI 65+/ DSM-IV	Mental health professionals or mental health graduate students, Face-to-face (computer assisted)	51.7%				SP (8.9%)
11	Ford et al. (2007) [106]	The National Survey of American Life (NSAL)	USA	837	66.6	55-93	N.R.	World Mental Health-CIDI 3.0/ DSM-IV	N.R., Face-to-face	60.0%			100%, African-American	AGO (0.7%); GAD (0.7%); OCD (04%); PD (1.4%); PTSD (1.8%); SAD (2.3%)
12	Goncalves, Pachana & Byrne (2011) [107]	Australian National Survey of Mental Health and Well-being (NSMHWB)	Australia (2007)	3,035	68	55-85	55–64 (1,190) 65–74 (1,060) 74-85 (785)	World Mental Health-CIDI 3.0/ DSM-IV	Trained lay interviewer Face-to-face	52.0%				GAD (2.8%)

Table 1. Continued

Article ID	Authors (year of publication)	Study name	Country (recruit- ment period)	Total sample size	Mean age	Age range total sample	Separate prevalence rates for age categories (N)	Diagnostic instrument/ Diagnostic Criteria	Interviewer, interview mode	Women	Somatic disease	Cognitive impairment	Ethnic minority	Reported prevalence rates
13	Grenier et al. (2011) [20]	Enquête sur la Santé des Aînés (ESA)	Canada (2005–2006)	2,784	73.8	65+	N.R.	Adapted version of DIS and CIDI (ESA-Questionnaire)/ DSM-IV	Research nurse, Face-to-face	59.0%				AGO (0.3%) GAD (1.2%); OCD (1.5%); PD (0.6%); SAD (0.07%); SP (2.0%)
14	Grenier et al. (2019) [108]	Enquête sur la Santé des Aînés (ESA) Services Study	Canada (2011-2013)	1,193	N.R.	70+	N.R.	Adapted version of DIS and CIDI (ESA-Q)/ DSM-IV	Mental health professionals and graduate students, Face-to-face	57.8%				GAD (2.7%)
15	Guo, Li, Liu & Sun (2015) [109]	National Latino and Asian American Study of mental health (NLAAS)	USA (2002-2003)	616	69.6	60+	N.R.	World Mental Health-CIDI 3.0/ DSM-IV	Trained lay interviewer Face-to-face	56.9%			100% (41.6% Asian, 58.4% Latino)	AGO (1.0%); GAD (1.2%); PD (1.7%); PTSD (2.1%); SAD(1.2%)
16	Hek et al. (2011) [110]	The Rotterdam Study	The Netherla nds (2002-2005)	5,565	72.6	58-100	N.R	Munich version of CIDI/ DSM-IV	Trained lay interviewer Face-to-face (computer assisted)	58.1%				AGO (4.0%); GAD (2.2%)
17	Heun, Papassotiropoulus & Ptok (2000) [111]	N.R.	Germany (N.R.)	286	78.8	60+	N.R.	CIDI/DSM-III R	Student, Face-to-face	N.R.		12.94%, dementia (according to SIDAM)		AGO (1.0%); PD (0.3%); SAD (1.4%); SP (0.7%)
18	Husaini, Moore & Castor (1991) [112]	N.R.	USA (1987)	600	70.5	55-85	N.R.	DIS/DSM-III	N.R., Face-to-face	70.0%			100%, black	AGO (4.3%); SAD (1.7%); SP (13.8%)
19	Junginger, Phelan, Cherry & Levy (1993) [113]	N.R.	USA (N.R.)	50	N.R.	65+	N.R.	SCID/DSM-III R	Student, Face-to-face	76.7%			4%, non-white	AGO (2.0%); GAD (6.0%); OCD (2.0%); PD (2.0%); SAD (2.0%); SP (2.0%)

Table 1. Continued

Article ID	Authors (year of publication)	Study name	Country (recruit- ment period)	Total sample size	Mean age	Age range total sample	Separate prevalence rates for age categories (N)	Diagnostic instrument/ Diagnostic Criteria	Interviewer, interview mode	Women	Somatic disease	Cognitive impairment	Ethnic minority	Reported prevalence rates
20	Karam et al. (2016) [114]	Lebanese Evaluation of the Burden of Ailments and Needs of the Nation (LEBANON)	Lebanon (N.R.)	593	N.R.	60+	N.R.	World Mental Health-CIDI 3.0/ DSM-IV	Trained lay interviewer Face-to-face	51.6%				AGO (0.0%); GAD(1.3%); PD(0.4%); PTSD(2.5%); SAD(0.2%); SP(3.9%)
21	Karlsson et al. (2009) [115]	Prospective Population study of women and the H70 Birth cohort study	Sweden (2000)	914	74.6	70 92	70–70 (562) 78–92 (352)	MINI/DSM-IV	Research nurse, Face-to-face	75.5%		3.3%, hospital discharge diagnosis of dementia (assessment method not specified)		AGO(1.2%); SAD(1.9%)
22	Karlsson et al. (2016) [116]	H75 + H85 Birth cohort study	Sweden (N.R.)	1,200	78.6	75-85	75–75 (768) 85–85 (432)	MINI/DSM-IV	Research nurse, Face-to-face	61.7%				SAD(2.5%)
23	Kirmizioglu, Doğan, Kuğu & Akyüz (2009) [117]	N.R.	Turkey (N.R.)	462	N.R.	65+	65–69 (208) 70–74 (142) 75–79 (62) 80+ (50) [a]	SCID-I/DSM-IV	N.R., Face-to-face	51.3%	77.7%, one or more chronic illnesses (not specified)			GAD (6.9%); OCD (3.2%); PD (0.4%); PTSD (1.9%); SAD (2.8%); SP (11.5%)
24	Klenfeldt et al. (2014) [118]	Prospective Population study of women and the H70 Birth cohort study	Sweden (2000)	900	74.6	70–92	70–70 (559) 78–92 (341)	MINI + CPRS/ DSM-IV	Research nurse, Face-to-face	75.1%		3.3%, hospital discharge diagnosis of dementia (method not specified)		OCD (2.9%)
25	Kohn, Vicente, Saldivia, Rioseco & Torres (2008) [119]	Chile Psychiatric Prevalence Study (CPPS)	Chile (1992–1999)	352	N.R.	65+	65–74 (226) 75+ (126)	CIDI 1.0 and 1.1 + DIS for PTSD/ DSM-III Revised	Student, Face-to-face	58.5%				AGO (3.1%); GAD (0.4%); PD (0.0%); PTSD (1.5%)

Table 1. Continued

Article ID	Authors (year of publication)	Study name	Country (recruit- ment period)	Total sample size	Mean age	Age range total sample	Separate prevalence rates for age categories (N)	Diagnostic instrument/ Diagnostic Criteria	Interviewer, interview mode	Women	Somatic disease	Cognitive impairment	Ethnic minority	Reported prevalence rates
26	Lindesay & Banerjee (1993) [120]	N.R.	England (1990–1991)	168	N.R.	65+	N.R.	DSM-III criteria applied to information gathered with the GMS-AGECAT and Phobic disorders screen/ DSM-III	Psychiatrist Face-to-face	75.1%				AGO (6.5%); SAD (0.6%); SP(8.9%)
27	Lindesay, Briggs & Murphy (1989) [121]	Guy's Age Concern Survey	England (1986)	890	N.R.	65+	65–74 (542) 75+ (348)	Structured questions based on DSM-III criteria (not further specified)/ DSM-III	Trained lay interviewer Face-to-face	50.5%				PD (0.0%)
28	Miloyan, Byrne & Pachana (2014) [122]	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	USA (2001-2002)	13,420	68.9	55–98	N.R.	AUDADIS-IV/ DSM-IV	Trained lay interviewer Face-to-face	60.0%				GAD (1.5%)
29	Mohammadi et al. (2004) [123]	N.R.	Iran (2001)	3,591	N.R.	56+	56–65	SADS/DSM-IV	Psychologist, Face-to-face	44.2%				OCD (1.3%)
30	Myers et al. (1984) [124]	Epidemiologic Catchment Area Site	USA (1980 – 1984)	2,110[b]	N.R.	65+	N.R.	DIS/DSM-III	N.R., N.R.	61.2%				AGO (2.5%); SAD (1.5%); SP(5.6%)
31	Nilsson et al. (2012) [125]	N.R.	Sweden (2005–2006)	777	75	75–75	N.R.	MINI + CPRS/ DSM-IV	Research nurse, Face-to-Face	61.5%				GAD (4.1%)
32	Nilsson et al. (2018) [126]	H85 study	Sweden (2009)	433	85	85-85	N.R.	MINI + CPRS/ DSM-V	Research nurse, Face-to-Face	61.6%				GAD (3.3%)

Table 1. Continued

Article ID	Authors (year of publication)	Study name	Country (recruit- ment period)	Total sample size	Mean age	Age range total sample	Separate prevalence rates for age categories (N)	Diagnostic instrument/ Diagnostic Criteria	Interviewer, interview mode	Women	Somatic disease	Cognitive impairment	Ethnic minority	Reported prevalence rates
33	Préville (2014) [7]	Enquête sur la Santé des Aînés (ESA) Services Study	Canada (2011-2013)	1,765	73.2	65+	N.R.	N.R. /DSM-IV	Health professionals Face-to-face	57.3%				PTSD (1.8%)
34	Regier et al. (1988) [127]	Epidemiologic Catchment Area Site	USA (1980–1984)	5,702	N.R.	65+	N.R.	DIS/DSM-III	N.R., N.R.	N.R.		4.9% severe cognitive impairment ('low' score on MMSE)		OCD (0.8%); PD (0.1%)
35	Reynolds, Pietrzak, El-Gabalawy, Mackenzie & Sareen (2015) [8]	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	USA (2004–2005)	12,312	N.R.	55+	55–64 (5,135) 65–74 (3,634) 75–84 (2,673) 85+ (870)	AUDADIS-IV/ DSM-IV	Trained lay interviewer, Face-to-face	59.9%			34.0%, non-white	PD (1.5%); PTSD (3.9%); SAD (1.7%); SP (6.2%)
36	Ritchie et al. (2004) [9]	Etude Santé Psychologique Prévalence Risques et Traitement	France (1999–2001)	1,863	73	65–96	73	MINI/DSM-IV	Psychologists and nurses, Face-to-face	58.5%				GAD (4.6%); OCD (-0.5%); PD (0,3%); SAD (1.2%)
37	Ritchie, Norton,Mann & Carrière (2013) [128]	Etude Santé Psychologique Prévalence Risques et Traitement	France (1999–2001)	1,968	72.8	65+	84.9	MINI/DSM-IV	Psychologists and nurses, Face-to-face	58.2%				AGO(10.4%)
38	Schaub & Linden (2000) [129]	Berlin Aging Study	Germany (N.R.)	516	84.9	70-103	N.R.	N.R./DSM-III R	Psychiatrist, face-to-face	50.0%				AGO (0.6%); GAD (0.4%); OCD (0.2%); PD(0.2%)
39	Sigström et al. (2011) [130]	Prospective Population Study of Women (PPSW) and H70 Birth Cohort Study	Sweden (2000)	558	70	70–70	N.R.	MINI + CPRS/ DSM-IV	Research nurse or psychologist,Face-to-face	59.9%				SP (10.0%)

Table 1. Continued

Article ID	Authors (year of publication)	Study name	Country (recruit- ment period)	Total sample size	Mean age	Age range total sample	Separate prevalence rates for age categories (N)	Diagnostic instrument/ Diagnostic Criteria	Interviewer, interview mode	Women	Somatic disease	Cognitive impairment	Ethnic minority	Reported prevalence rates
40	Spitzer et al. (2008) [131]	Study of Health in Pomerania (SHIP)	Germany (2002-6)	851	72.8.	65+	N.R.	SCID-I/DSM-IV	Trained lay interviewer, Face-to-face	47.2%				PTSD (1.2%)
41	Trollor, Anderson, Sachdev, Brodaty & Andrews (2007) [132]	Australian National Mental Health and Well-being Survey of (NMHWS)	Australia (1997)	1,792	N.R.	65+	N.R.	CIDI 2.1./ DSM-IV	N.R., Face-to-face	54.5%		7.4%, MMSE-score < 24		GAD (0.9%); OCD (0.0%); PTSD (0.2%); SAD(0.2%)
42	van Zelst, de Beurs, Beekman, Deeg & van Dyck (2003) [133]	The Longitudinal Aging Study Amsterdam (LASA)	Netherlands (1998-1999)	422	72.4	61-95	N.R.	CIDI 2.1/ DSM-IV	Trained lay interviewer, Face-to-face	56.9%	81.6% presence of physical illness (not specified)	7.6%, MMSE-score < 24		PTSD (0.9%)
43	Wang, Berglund & Kessler (2000) [134]	Midlife Development in the United States (MIDUS)	USA (1996)	1,254	N.R.	55–74	55–64 (789) 65–74 (465)	World Health Organization-CIDI-Short Form/DSM-III R	N.R., N.R.,	N.R.				GAD (1.2%); PD (2.1%)
44	Wild et al. (2014) [135]	Epidemiologische Studie zu Chancen der Verhuetung, Frueherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung (ESTHER(	Germany (2010)	438	N.R.	58-82	58-64 (123) 65-74 (231) 75-82(84)	SCID/DSM-IV	Trained lay interviewer, Telephone	55.2%				GAD (6.2%)
45	Xavier et al. (2002) [136]	N.R.	Brasil (N.R.)	58	84	80-95	N.R.	SCID Research Version/ DSM-IV	Psychologist or geriatrician, Face-to-face	N.R.			100%, Italian descent	GAD (6.9%)

Table 1. Continued

Article ID	Authors (year of publication)	Study name	Country (recruit- ment period)	Total sample size	Mean age	Age range total sample	Separate prevalence rates for age categories (N)	Diagnostic instrument/ Diagnostic Criteria	Interviewer, interview mode	Women	Somatic disease	Cognitive impairment	Ethnic minority	Reported prevalence rates
46	Xiao et al. (2016) [137]	China Longitudinal Aging Study	China	1,068	72.8	57-97	57-85(972) 86–97 (94)	SCID Research Version/ DSM-IV	Psychologist or psychiatrist, N.R.	57.8%	33.5% Mild cognitive impairment dementia based on Petersen criteria and DSM-IV criteria			GAD (0.8%)

Note. N.R.= Not Reported, AUDADIS=Alcohol use Disorder and Associated Disabilities Interview Schedule, CIDI=Composite International Diagnostic Interview, CPRS=Comprehensive Psychopathological Rating Scale, DIS=Diagnostic Interview Schedule, GMS-AGECAT=Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy, MINI=Mini-International Neuropsychiatric Interview, MMSE=Mini-mental state examination, SADS=Schedule for Affective Disorders and Schizophrenia, SCAN=Schedules for Clinical Assessment in Neuropsychiatry, SCID=Structured Clinical Diagnostic Interview, SIDAM= Structured Interview for the Diagnosis of Alzheimer's Dementia, Multi-infarct dementia and dementias of other etiology. [a] For panic disorder the prevalence rates for the different age groups were not reported.

[b] Prevalence rates for social anxiety disorder based on smaller sample of 1187 participants.

Table 2. Included studies reporting prevalence rates for subthreshold anxiety

Article ID	Authors (year of publication)	Diagnostic instrument / Diagnostic Criteria	Definition	Prevalence
13	Grenier et al. [20]	Adapted version of DIS and CIDI (ESA-Q) / DSM-IV	AGO, GAD, OCD, PD, SAD, SP: Fulfilling DSM-IV symptom criteria for a specific anxiety disorder but reporting no significant disabilities in social functioning, or reporting symptoms of anxiety (e.g., anticipations, sweating, palpitations) not meeting symptom criteria for a disorder	AGO (4.2%) GAD (3.0%) OCD (1.6%) PD (2.6%) SAD (1.3%) SP (7.8%)
17	Heun, Papassotiropoulus & Ptok [111]	CIDI/DSM-III R	AGO: Unreasonable fear in places/situations from which it is difficult to leave; lack of avoidance or of symptoms of anxiety. PD: Presence of acute unexpected anxiety attacks, one to four physical symptoms. SAD: Persistent fear of situations in which the person is exposed to social interactions; lack of avoidance or social consequences. SP: Persistent fear of circumscribed stimulus, lack of avoidance or consequences.	AGO (0.7%) PD (1.7%) SAD (1.4%) SP (8.4%)
22	Karlsson et al. [115]	MINI / DSM-IV	SAD: Persistent fear of situations in which the person is exposed to social interactions (criterion A is fulfilled), The situations are avoided or endured with intense anxiety or distress (criterion D is fulfilled). The fear does not worsen functioning in social situations, nor does it cause considerable distress (criterion E is not fulfilled).	SAD (11.5%)
28	Miloyan, Byrne & Pachana (2014) [122]	AUDADIS-IV / DSM-IV	GAD: six or more months of worry, tension, or nervousness, without meeting criteria for a DSM anxiety disorder.	GAD (7.2%)
33	Préville (2014) [7]	N.R. / DSM-IV	PTSD: At least one symptom from each of the three DSM-IV symptom clusters for the last six months, with or without the presence of impairment in social functioning.	PTSD (1.8%)

Table 2. Continued

Article ID	Authors (year of publication)	Diagnostic instrument / Diagnostic Criteria	Definition	Prevalence
42	van Zelst, de Beurs, Beekman, Deeg & van Dyck [133]	CIDI 2.1 / DSM-IV	PTSD: A Self-Rating Inventory for Posttraumatic Stress Disorder (SRIP; scale is based on DSM-IV criteria) score of 39 or higher, without meeting all DSM-IV criteria.	PTSD (13.1%)

Note. AGO=Agoraphobia, GAD=Generalized Anxiety Disorder, OCD=Obsessive Compulsive Disorder, PD=Panic Disorder, PTSD=Posttraumatic Stress Disorder, SAD=Social Anxiety Disorder, SP=Specific Phobia, N.R.= Not reported, AUDADIS=Alcohol use Disorder and Associated Disabilities Interview Schedule, CIDI=Composite International Diagnostic Interview, DIS=Diagnostic Interview Schedule, MINI=Mini-International Neuropsychiatric Interview, SCAN=Schedules for Clinical Assessment in Neuropsychiatry.

Table 3. Pooled prevalence rates (percentages) and pooled risk ratios of anxiety disorders and subthreshold anxiety in adults aged 55 and older

	Subthreshold anxiety				Anxiety disorders				Comparison prevalence rates			
Disorder	**Number of studies *(N)***	**Pooled prevalence [95% CI]**	***I²* [95% CI]**	***Q***	**Number of studies *(N)***	**Pooled prevalence [95% CI]**	***I²* [95% CI]**	***Q***	**Number of studies *(N)***	**Pooled risk ratio [95% CI]** [a]	***I²***	***Q***
AGO	2 (3,070)	1.97% [0.34-10.59]	84.69 [23.06-99.74]	6.53** (0.01)	19 (38,965)	1.62% [0.93-2.81]	98.06% [96.42-99.20]	755.73**	2 (3,070)	3.29 [0.16-67.66]	94.22% [70.98-99.73]	17.31***
GAD	2 (16,204)	1.42% [1.12-1.79]	48.17 [0.00-99.95]	1.93	25 (47,355)	2.32% [1.72-3.12]	95.55 [92.68-98.23]	478.69**	2 (16,204)	3.49*** [1.90-6.43]	92.48% [62.20-99.99]	13.29***
OCD	1 (2,784)	1.06%[b]	-	-	15 (28,613)	0.89% [0.58-1.35]	89.29% [80.44–97.89]	87.79**	1 (2,784)	1.07[b] [0.79-1.45]	-	-
PD	2 (3,070)	2.55% [2.05-3.18]	0.00 [0.00–99.88]	0.79	22 (56,969)	0.76% [0.50-1.16]	94.65% [89.73-97.79]	294.06**	2 (3,070)	4.10*** [2.71-6.21]	0.00% [0.00-97.95]	0.05
PTSD	2 (2,187)	5.01% [0.67–29.10]	98.80% [93.96–99.97]	83.14**	12 (25,049)	1.57% [1.13-2.18]	87.63% [72.89–97.02]	132.15**	2 (2,187)	3.62 [0.29-45.77]	96.03% [80.06-99.87]	25.20***
SAD	3 (3,984)	2.96% [0.68-11.92]	98.00% [92.30-99.95]	143.28**	21 (50,651)	1.23% [0.90-1.67]	92.01% [86.32-97.61]	145.21**	3 (3,984)	4.72 [0.94-23.67]	89.86% [57.71-99.77]	14.95***
SP	2 (3,070)	7.88% [6.98-8.89]	0.00% [0.00-99.13]	0.11	14 (29,901)	5.40% [3.55-8.14]	98.34% [96.71-99.49]	332.93**	2 (3,070)	5.63*** [2.05-15.46]	60.87% [0.00-99.76]	2.56

Note. N = total sample size of the samples, AGO=Agoraphobia, GAD=Generalized Anxiety Disorder, OCD=Obsessive Compulsive Disorder, PD=Panic Disorder, PTSD=Posttraumatic Stress Disorder, SAD=Social Anxiety Disorder, SP=Specific Phobia.

[a] A value larger than one means the odds of having a subthreshold disorder is larger than the odds of a having threshold anxiety disorder.

[b] Not a summary effect size; estimate based on one sample.

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Table 4. Results of subgroup analyses comparing prevalence rates for anxiety disorders in four age categories of older adults

	Total group			*Subgroup results*								
Disorder	**Total pooled prevalence rate [95% CI]**	***Q***	***I²***	**Pooled prevalence 55–64 [95% CI]**	***I²* 55-64**	**Pooled prevalence 65-74 [95% CI]**	***I²* 65-74**	**Pooled prevalence 75–84 [95% CI]**	***I²* 75–84**	**Pooled prevalence 85+ [95% CI]**	***I²* 85+**	**Test of moderation *Q*-between (df)**
AGO	1.15% [0.62–2.11]	76.01**	88.67% [71.09-96.46]	1.06% [0.25-4.33]	75.62% [0.0-94.5]	1.16% [0.41-3.27]	93.31% [86.1-96.8]	1.44% [0.30-6.56]	89.33% [60.2-97.1]	0.62% [0.06–6.54]	0% [0.0-0.0]	0.35 (3)
GAD	2.98% [2.13–4.14]	248.77**	91.34% [84.39-96.24]	3.39% [1.67 – 6.76]	76.05% [41.5-90.2]	2.92% [1.62–5.20]	95.22% [92.6-96.9]	3.15% [1.68-5.82]	88.75% [79.3-93.9]	1.83% [0.61–5.40]	0% [0.0-84.2]	0.92 (3)
OCD	1.07% [0.58–1.99]	40.69**	83.53% [59.20-96.60]	0.93% [0.40 – 2.14]	72.00% [52.1-91.7]	2.15% [1.10–4.16]	75.32% [31.7-91.1]	0.57% [0.21–1.52]	0.00% [0.0-85.7]	0.001[a] [0.00-15.96]	-	5.46(2)
PD	1.29% [0.93–1.80]	150.11**	88.08% [76.80-95.42]	1.99% [1.18 – 3.36]	89.84% [80.6-94.7]	0.99% [0.58–1.69]	88.48% [79.6-93.5]	1.08% [0.48 – 2.41]	6.92% [0.0-90.3]	0.90% [0.29–2.72]	0% [0.0-0.0]	4.13 (3)
PTSD	2.90% [2.03-4.12]	62.33**	88.85% [63.84-97.38]	5.47[a] % [4.88-6.13]	-	2.89% [2.43-3.45]	0.00% [0.0-86.1]	3.00% [2.42–3.71]	0.00% [0.0-0.0]	1.61[a] % [0.96-2.70]	-	60.82*** (3)
SAD	1.71% [1.25–2.32]	125.53**	88.89% [75.53-95.51]	2.94% [1.70– 5.02]	94.11% [86.2-97.5]	1.66% [1.08-2.55]	83.83% [66.3-92.2]	1.38% [0.80-2.38]	70.45% [24.8-88.4]	0.81% [0.29 –2.19]	0% [0.0-81.4]	6.54(3)
SP	5.97% [4.73–7.51]	131.58**	91.33% [80.38-96.43]	8.59% [5.70-12.77]	0.00% [0.0-0.0]	7.13% [5.39-9.37]	91.02% [82.0-95.5]	4.43% [3.06–6.38]	0.00% [0.0-64.0]	3.72% [2.19-6.25]	0% [0.0-77.9]	10.31** (3)

Note. AGO=Agoraphobia, GAD=Generalized Anxiety Disorder, OCD=Obsessive Compulsive Disorder, PD=Panic Disorder, PTSD=Posttraumatic Stress Disorder, SAD=Social Anxiety Disorder, SP=Specific Phobia.

[a] These are not summary effect sizes; estimate based on one sample.

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Discussion

This article used a systematic review and meta-analyses to examine how prevalence rates of subthreshold anxiety compare to rates for anxiety disorders and if prevalence rates for later life anxiety differ between age groups of older adults.

Main findings

Statistical comparison of prevalence rates, using pooled risk ratios, showed that for generalized anxiety, panic and specific phobia, subthreshold symptomatology was significantly more prevalent than the corresponding clinical disorder. For the other types of anxiety, pooled risk ratios showed prevalence rates for subthreshold anxiety and anxiety disorders to not be significantly different. Although the results from this meta-analysis do not allow for strong conclusions due to the small number of included samples and large heterogeneity in the estimates, they do suggest that subthreshold anxiety is at least similarly prevalent to anxiety disorders. The combination of this finding with earlier studies showing subthreshold anxiety in older adults to be associated with decreased well-being, social functioning and physical health [20,22], indicates that subthreshold anxiety in later life is both a prevalent and clinically relevant phenomenon for which adequate detection and treatment is required. However, for a comprehensive understanding of subthreshold anxiety in older adults, more methodologically rigorous studies are needed. First and foremost, researchers and clinicians should work towards comprehensive definitions of the different types of subthreshold anxiety that can be used across studies. All studies on subthreshold anxiety included in this review used different definitions, which probably largely explains the substantial heterogeneity.

Regarding age trends in prevalence rates, for most anxiety disorders (agoraphobia, GAD, OCD, panic disorder and SAD) pooled prevalence rates did not significantly differ between age groups of older adults. The lack of statistical significance may be due to the low statistical power of the analyses caused by the small number of samples in the subgroups. Pooled prevalence rates for specific phobia and PTSD were found to differ significantly between age groups. For specific phobia, the 75-84 and 85+ groups had lower prevalence rates than both the 55-64 and 65-74 group. One explanation for the lower rates of specific phobia in the oldest groups is that diagnostic instruments do not adequately address fears typical to these age groups, most notably fear of falling. Prevalence estimates for fear of falling in older adults range between 21% and 85% and increase with age [141]. Other specific fears that may be relatively common in

the oldest groups are a fear of crime/aggression and the use of modern technology [142-144]. If diagnostic instruments would explicitly assess such age-related fears, prevalence estimates for specific phobia might be higher in the oldest groups. For PTSD, the prevalence rate for the 55-64 group was higher than that for all other age groups, while the 85+group had a significantly lower rate than the other groups. It could be speculated that an age-related decrease in PTSD prevalence partly reflects the natural course of recovery from trauma. Assuming that most traumatic events happen when people are younger adults, lower PTSD rates in the oldest adults could be reflective of a longer recovery time since the traumatic event [145,146].

Other explanations for an age-related decrease of specific phobia and PTSD are not disorder specific and could also account for the finding that prevalence rates were lowest in the 85+ group for all anxiety disorders (although not significantly lower in most cases). First, lower rates in the oldest groups of older adults could reflect a survivor effect, of older adults without anxiety generally living longer than their anxious peers [147]. Furthermore, it could be argued that age-related obstacles in adequately assessing anxiety disorders (i.e., overlap of anxiety symptoms and physical/cognitive conditions, underestimation of functional impairment due to lower societal expectations) increase with age and are therefore strongest in the oldest groups, leading to structural underdiagnosing. Third, community samples might not adequately represent the oldest adults, who are increasingly characterized by physical and neurodegenerative diseases and associated institutional care [1]. As community samples typically do not include institutionalized people, they might seriously underestimate the prevalence of anxiety disorders in the oldest groups. A systematic review of 18 studies on older adults in nursing homes and residential care facilities (mean age in the study samples ranged from 74.9 years to 86.2 years) indeed concluded that anxiety disorders appear to be more prevalent among old age care residents than community-dwelling older adults [148].

Sensitivity subgroup analyses without outliers replicated the results from the main analyses for most disorders, but for OCD, it resulted in a significant difference in pooled prevalence rates for OCD between age groups, with higher rates being reported for adults aged 65-74 than for those aged 55-64 and 75-84. More research into the prevalence of later life OCD is required to see if this finding replicates and -if so- to examine how a prevalence peak in the 65-74 years old could be explained.

For none of the anxiety disorders subgroup analyses resulted in 4 groups of homogeneous prevalence estimates, although for the 85+ and 75-84 groups hetero-

geneity was low in most cases. It is understandable that a categorization of samples based solely on their age range did not explain all heterogeneity in prevalence rates, as variation in reported rates is most likely caused by a combination of multiple study- and participant characteristics. Therefore, the current study set out to also explore interactions between age and other methodological/participant factors. Unfortunately, due to the limited amount of reported information in the included articles, interactions could not be explored extensively. The available information only allowed for the examination of interactions between age on the one hand, and sex and DSM-criteria on the other. These interactions were non-significant, which could be due to the lack of statistical power from the small number of included samples. To comprehensively investigate the association between age and the prevalence of anxiety disorders in later life, studies in older adults should consistently report descriptive information for different age groups within their sample.

Limitations

This study has several limitations. First, the small number of samples that could be used in answering our research questions influenced the confidence intervals and limits the statistical power of the analyses and generalizability of the results. For most types of anxiety, only 2 articles reported rates for both subthreshold symptomatology and the corresponding clinical disorder. Furthermore, no article reported prevalence rates for subthreshold anxiety in different age groups of older adults. For anxiety disorders, the age-based subgroups also consisted of a small number of samples, with the largest subgroup being comprised of eight samples. Importantly, only 5 articles reported prevalence rates for the 85+ group, which were mostly obtained in small sample. Large-scale epidemiological studies focused on the 85+ segment are required, especially since in many countries the oldest-old are the fastest growing part of the total population [1].

A second limitation concerns the subgroup analyses, in which subgroups were created based solely on the age of participants in the samples. This approach does not account for cohort effects, while these are likely to have also contributed to differences in reported prevalence estimates, as the included articles were published between 1984 and 2019. For a comprehensive understanding of the relation between age and prevalence rates of later life anxiety, age and cohort effects should be separated.

Third, we only included community samples, which limits the generalizability of the findings, especially with regard to the oldest-old.

Last, while 4 electronic databases were screened and an additional hand-search was conducted, it is possible that some relevant publications have not been included in the review and meta-analyses. For instance, publications in languages other than Dutch and English and non-peer reviewed articles were not included.

Conclusion and implications

This article provided an overview and integration of articles reporting prevalence rates for anxiety disorders and subthreshold anxiety in older adults and highlighted gaps and shortcomings in the literature. The findings from the meta-analyses suggest that subthreshold anxiety is similarly or more prevalent than anxiety disorders, although the small number of included samples and large heterogeneity between them precludes firm conclusions. As the currently available evidence suggests that subthreshold anxiety in older adults is both prevalent and clinically relevant, it should be studied more extensively. A first step is for researchers to work towards comprehensive definitions and operationalizations of subthreshold anxiety that can be used across studies.

Regarding the association between the prevalence of later life anxiety disorders and age, the subgroup analyses do not allow for strong conclusions due to the small number of included samples. Results suggest that specific phobia is more common in older adults aged 55-74 than in those aged 75 years and older. Furthermore, PTSD seems to be most prevalent in adults aged 55-64 and least prevalent in the 85+ group. We recommend future studies in older adults to consistently report information for different age categories. Furthermore, longitudinal studies following different cohorts of older adults are needed for a better understanding of the association between age and the prevalence of anxiety in later life. Such studies are time intensive and financially demanding, but as the number of older adults is steadily growing worldwide, high-quality studies into how people progress throughout later life are invaluable.

Appendix 1

Final search string Psychinfo

(DE “Anxiety” OR DE “Anxiety Disorders” OR DE “Generalized Anxiety Disorder” OR DE “Obsessive Compulsive Disorder” OR DE “Panic Disorder” OR DE “Post-Traumatic Stress” OR DE “Panic Attack” OR DE “Social Anxiety” OR DE “Social Phobia” OR DE “Agoraphobia”OR TI anxiety OR TI “anxiety disorder*” OR TI “anxiety symptom*” OR TI “subthreshold anxiety” OR TI “subsyndromal anxiety” OR TI “subclinical anxiety” OR TI “specific phobia” OR TI “simple phobia” OR TI “Phobic disorder*” OR TI “generalized anxiety disorder” OR TI agoraphobia OR TI “panic disorder” OR TI “panic attack* “ OR TI “social phobia” OR TI “social anxiety disorder” OR TI “obsessive compulsive disorder” OR TI “obsessive-compulsive disorder” OR TI “Posttraumatic Stress Disorder” OR TI “Post-traumatic Stress Disorder” OR TI “GAD” OR TI “OCD” OR TI “PTSD” OR TI panic OR TI worry OR AB anxiety OR AB “anxiety disorder*” OR AB “anxiety symptom*” OR AB “subthreshold anxiety” OR AB “subsyndromal anxiety” OR AB “subclinical anxiety” OR AB “specific phobia” OR AB “simple phobia” OR AB “Phobic disorder*” OR AB “generalized anxiety disorder” OR AB agoraphobia OR AB “panic disorder” OR AB “panic attack*” OR AB “social phobia” OR AB “social anxiety disorder” OR AB “obsessive compulsive disorder” OR AB “obsessive-compulsive disorder” OR AB “Posttraumatic Stress Disorder” OR AB “Post-traumatic Stress Disorder” OR AB “GAD” OR AB “OCD” OR AB “PTSD” OR AB panic OR AB worry OR KW anxiety OR KW “anxiety disorder*” OR KW “anxiety symptom*” OR KW “subthreshold anxiety” OR KW “subsyndromal anxiety” OR KW “subclinical anxiety” OR KW “specific phobia” OR KW “simple phobia” OR KW “Phobic disorder*” OR KW “generalized anxiety disorder” OR KW agoraphobia OR KW “panic disorder” OR KW “panic attack*” OR KW “social phobia” OR KW “social anxiety disorder” OR KW “obsessive compulsive disorder” OR KW “obsessive-compulsive disorder” OR KW “Posttraumatic Stress Disorder” OR KW “Post-traumatic Stress Disorder” or KW “GAD” OR KW “OCD” OR KW “PTSD” OR KW panic OR KW worry)

AND

(DE “epidemiology” OR TI prevalen* OR TI incidence OR TI occurrence OR TI epidemiology OR TI frequency OR AB epidemiology OR AB prevalen* OR AB incidence OR AB occurrence OR AB frequency OR KW epidemiology OR KW prevalen* OR KW incidence OR KW occurrence OR KW frequency)

AND

(TI “older adults” OR TI elder* OR TI senior* OR TI geriatric* OR TI aging OR TI “older people” OR TI “late* life” OR TI midlife OR AB “older adults” OR AB elder* OR

AB senior* OR AB geriatric* OR AB aging OR AB "older people" OR AB "late* life" OR AB midlife OR KW "older adults" OR KW elder* OR KW senior* OR KW geriatric* OR KW aging OR KW "older people" OR KW "late* life" or KW midlife)

Filters

- Publication year: 1952 – 2020
- Source types: Academic Journals
- Language: English
- Age: adulthood (18 yrs & older), aged (65 yrs & older), middle age (40-64 yrs), very old (85 yrs & older)

Final search string Cochrane

(Prevalence [mesh] OR incidence [mesh] OR epidemiology [mesh] OR prevalen* [ti,ab,kw] OR incidence [ti,ab,kw] OR epidemiology [ti,ab,kw] OR occurrence [ti,ab,kw] OR frequency [ti,ab,kw])

AND

(Anxiety [ti,ab,kw] OR "anxiety disorder*" [ti,ab,kw] OR "anxiety symptom*" [ti,ab,kw] OR "subclinical anxiety" [ti,ab,kw] OR "subthreshold anxiety" [ti,ab,kw] OR "subsyndromal anxiety" [ti,ab,kw] OR "specific phobia" [ti,ab,kw] OR "simple phobia" [ti,ab,kw] OR "phobic disorder*" [ti,ab,kw] OR "generalized anxiety disorder" [ti,ab,kw] OR "GAD" [ti,ab,kw] OR "agoraphobia" [ti,ab,kw] OR "panic disorder" [ti,ab,kw] OR "panic attack*" [ti,ab,kw] OR "social phobia' OR "social anxiety disorder" or OCD [ti,ab,kw] OR "obsessive-compulsive disorder" [ti,ab,kw] OR "Obsessive compulsive disorder" [ti,ab,kw] OR "Posttraumatic stress disorder" [ti,ab,kw] OR "Post-traumatic stress disorder" [ti,ab,kw] OR PTSD [ti,ab,kw] OR panic [ti,ab,kw] OR worry [ti,ab,kw] OR anxiety [mesh] OR anxiety disorders [mesh] OR Phobic disorders [mesh] OR Phobia, Social [mesh] OR Panic disorder [mesh] OR Agoraphobia [mesh] OR Obsessive-compulsive disorder [mesh] OR Panic [mesh] OR Stress Disorders, Post-traumatic [mesh])

AND

("older adults" [ti,ab,kw] OR elder* [ti,ab,kw] OR aging [ti,ab,kw] OR senior* [ti,ab,kw] OR geriatric* [ti,ab,kw] OR:"older people" [ti,ab,kw] OR "late* life" [ti,ab,kw] OR midlife [ti,ab,kw] OR OR Aged [mesh] OR Aging [mesh] OR Aged, 80 and over [mesh] OR Middle Aged [mesh])

Final search string Pubmed

"Anxiety"[Majr:NoExp]) OR "Anxiety Disorders"[Majr:NoExp]) OR "Phobic Disorders "[Majr:NoExp]) OR "Phobia, Social"[Majr:NoExp]) OR "Panic Disorder"[Majr:NoExp]) OR "Agoraphobia"[Majr:NoExp]) OR "Obsessive-Compulsive Disorder"[Majr:NoExp]) OR "Panic"[Majr:NoExp]) OR "Stress Disorders, Post-Traumatic"[Majr:NoExp])

anxiety[Title/Abstract] OR "anxiety disorder*"[Title/Abstract] OR "anxiety symptom* "[Title/Abstract] OR "subthreshold anxiety"[Title/Abstract] OR "subsyndromal anxiety" [Title/Abstract] OR "subclinical anxiety"[Title/Abstract] OR "specific phobia"[Title/ Abstract] OR "simple phobia"[Title/Abstract] OR "phobic disorder*"[Title/Abstract] OR "generalized anxiety disorder"[Title/Abstract] OR agoraphobia[Title/Abstract] OR "panic disorder"[Title/Abstract] OR "panic attack*"[Title/Abstract] OR "social phobia" [Title/Abstract] OR "social anxiety disorder"[Title/Abstract] OR "obsessive compulsive disorder"[Title/Abstract] OR "obsessive-compulsive disorder"[Title/Abstract] OR "Posttrau matic Stress Disorder"[Title/Abstract] OR "Post-traumatic Stress Disorder"[Title/ Abstract] OR "GAD "[Title/Abstract] OR "OCD"[Title/Abstract] OR "PTSD"[Title/Abstract] OR panic[Title/Abstract] OR worry[Title/Abstract]

"Prevalence"[Majr:NoExp]) OR "Incidence"[Majr:NoExp]) OR "Epidemiology" [Majr:NoExp])

Prevalen*[Title/Abstract] OR incidence[Title/Abstract] OR epidemiology[Title/ Abstract] OR occurrence[Title/Abstract] OR frequency[Title/Abstract]

"Aged"[Majr:NoExp]) OR ("Aging"[Majr:NoExp]) OR ("Aged, 80 and over"[Majr: NoExp]) OR "Middle aged"[Majr:NoExp])

"older adults"[Title/Abstract] OR elder*[Title/Abstract] OR senior*[Title/Abstract] OR geriatric*[Title/Abstract] OR "older people"[Title/Abstract] OR "late* life[Title/ Abstract] OR midlife[Title/Abstract] OR aging [Title/Abstract]

(#1 OR #2) AND (#3 OR #4) AND (#5 OR #6)

Filters

- Year of publication: 1952 – 2020
- Language: English
- Humans
- Age:
    - Adult: 19+ years
    - Adult: 19-44 years
    - Middle Aged + Aged: 45+ years

- Middle Aged: 45-64 years
- Aged: 65+ years
- 80 and over: 80+ years

Final search string Web of Science

1 TI= (anxiety OR “anxiety disorder*” OR “anxiety symptom*” OR “subthreshold anxiety” OR “subsyndromal anxiety” OR “subclinical anxiety” OR “specific phobia” OR “simple phobia” OR “Phobic Disorder*” OR “generalized anxiety disorder” OR “agoraphobia” OR “panic disorder” OR “panic attack*” OR “social phobia” OR “social anxiety disorder” OR “obsessive compulsive disorder” OR “obsessive-compulsive disorder” OR “Posttraumatic Stress Disorder” OR “Post-traumatic Stress Disorder” OR “GAD” OR “OCD” OR “PTSD” OR panic OR worry)

2 TS= (anxiety OR “anxiety disorder*” OR “anxiety symptom*” OR “subthreshold anxiety” OR “subsyndromal anxiety” OR “subclinical anxiety” OR “specific phobia” OR “simple phobia” OR “Phobic Disorder*” OR “generalized anxiety disorder” OR “agoraphobia” OR “panic disorder” OR “panic attack*” OR “social phobia” OR “social anxiety disorder” OR “obsessive compulsive disorder” OR “obsessive-compulsive disorder” OR “Posttraumatic Stress Disorder” OR “Post-traumatic Stress Disorder” OR “GAD” OR “OCD” OR “PTSD” OR panic OR worry)

3 TI=(“older adults” OR elder* OR senior* OR geriatric* OR aging OR “older people” OR “late* life” OR midlife)

4 TI=(prevalen* OR incidence OR epidemiology OR occurrence OR frequency)

(#1 OR #2) AND (#3) AND (#4)

Filters

- Language: English
- Document types: articles
- Year of publication: 1952-2020

Appendix 2

Table A1. Articles included in the subgroup analyses

Disorder	Articles (IDs*) reporting prevalence rates for age category 55-64 *(N)*	Articles (IDs) reporting prevalence rates for age category 65-74 (*N)*	Articles (IDs) reporting prevalence rates for age category 75-84*(N)*	Articles (IDs) reporting prevalence rates for age category 85+ *(N)*
AGO	4, 7 (6,170)	1, 4, 7, 24 (5,859)	1, 4 (960)	1,4 (174)
GAD	2, 4, 12, 43, 44 (4,180)	1, 2, 4, 12, 23, 25, 43, 44 (4,806)	1, 2, 4, 12, 23, 31, 44 (3,806)	1, 4, 32, 46 (701)
OCD	2, 3, 28 (3,259)	1, 2, 23, 24 (2,570)	1, 2, 23 (1,634)	1[a] (52)
PD	2, 3, 4, 5, 35, 43 (13,421)	1, 2, 4, 7, 25, 27, 35, 43, (11,454)	1, 4, 35 (3,633)	1, 3, 35 (1,044)
PTSD	35[a] (5,135)	23, 25, 34 (4,210)	23, 35 (2,735)	35[a] (870)
SAD	4, 7, 35 (11,305)	1, 4, 7, 21, 23, 35 (10,179)	1, 4, 22, 23, 35 (4,895)	1, 4, 35 (1,044)
SP	4, 35 (6,249)	1, 4, 23, 35, 39 (6,062)	1, 4, 23, 35 (3,695)	1, 4, 35 (1,044)

Note. AGO=Agoraphobia, GAD=Generalized Anxiety Disorder, OCD=Obsessive Compulsive Disorder,
PD=Panic Disorder, PTSD=Posttraumatic Stress Disorder, SAD=Social Anxiety Disorder, SP=Specific Phobia.

* See Table 1 (main text) for articles and their assigned ID number.

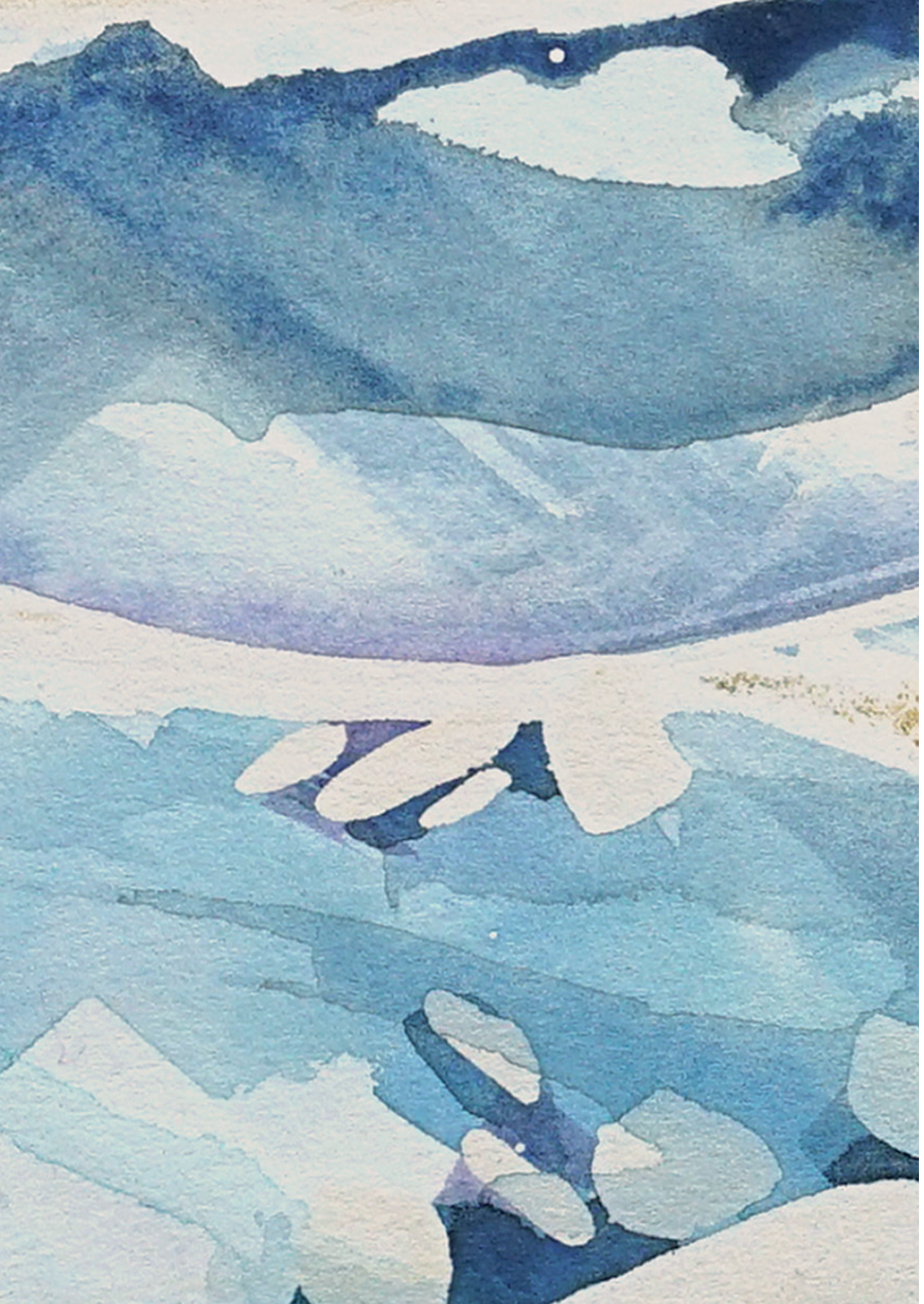
Table A1. Results of subgroup analyses of age categories without outliers

	Total group			*Subgroup results*								
Disorder	**Total pooled prevalence rate [95% CI]**	***Q***	***I²***	**Pooled prevalence 55–64 [95% CI]**	***I²* 55- 64**	**Pooled prevalence 65-74 [95% CI]**	***I²* 65-74**	**Pooled prevalence 75–84 [95% CI]**	***I²* 75 – 84**	**Pooled prevalence 85+ [95% CI]**	***I²* 85+**	**Test of moderation *Q*-between (df)**
GAD	3.09% [2.20–4.32]	230.26**	91.37% [84.29-96.43]	4.17% [1.92 – 8.84]	26.88% [0.0-72.5]	2.92% [1.63–5.18]	95.22% [92.6-96.9]	3.15% [1.69-5.80]	88.75% [79.3-93.9]	1.84% [0.61–5.38]	0.00% [0.0-84.2]	1.50(3)
OCD	1.22% [0.68–2.18]	35.59**	82.04% [53.42-96.00]	1.05% [0.53 – 2.04]	72.00% [52.1-91.7]	2.58% [1.52–4.37]	64.76% [0.00-89.9]	0.55% [0.23–1.31]	0.00% [0.0-85.7]	0.001% [a] [0.000-14.68]	-	10.34** (3)
PD	1.12% [0.84–1.49]	92.10**	79.69% [57.75-93.02]	1.68% [1.09 – 2.57]	82.62% [60.2-92.4]	0.80% [0.51–1.26]	79.54% [58.1-90.0]	1.07% [0.57–1.99]	6.92% [0.0-90.3]	0.90% [0.36–2.27]	0.00% [0.0-0.0]	5.73(3)
SAD	1.52% [1.14–2.02]	69.42**	82.73% [58.15-93.87]	2.24% [1.29– 3.88]	67.15% [0.0-92.6]	1.66% [1.15-2.41]	83.83% [66.3-92.2]	1.08% [0.60-1.93]	0.00% [0.0-71.7]	0.80% [0.31–2.01]	0% [0.0-81.4]	5.32(3)

Note. GAD=Generalized Anxiety Disorder, OCD=Obsessive Compulsive Disorder, PD=Panic Disorder, SAD=Social Anxiety Disorder.

[a] Not a summary effect size; based on one sample

**$p < 0.01$.



AN INTERNET-BASED ACCEPTANCE AND COMMITMENT THERAPY INTERVENTION FOR OLDER ADULTS WITH ANXIETY COMPLAINTS: STUDY PROTOCOL FOR A CLUSTER RANDOMIZED CONTROLLED TRIAL

Published as: Witlox M, Kraaij V, Garnefski N, de Waal MWM, Smit F, Hoencamp E, Gussekloo J, Bohlmeijer ET, Spinhoven P. An Internet-based Acceptance and Commitment Therapy intervention for older adults with anxiety complaints: study protocol for a cluster randomized controlled trial. Trials;2018;19(1):1-14.

Abstract

Background: Anxiety is among the most prevalent and disabling mental health problems in older adults. Few older adults with mild to moderately severe anxiety symptoms receive adequate interventions, putting them at risk for developing anxiety disorders, depression, and various somatic problems. Effective, low-threshold interventions should be developed. Blended care, in which a web-based intervention is combined with a limited amount of face-to-face contacts with a mental healthcare counselor at the general practice, is a promising option. The online self-help module "Living to the Full"—an Acceptance and Commitment Therapy (ACT) intervention—has been proven to reduce depression and anxiety in several patient groups, but has not yet been investigated in older adults. The aim of this study is to evaluate the (cost-)effectiveness of a blended form of "Living to the Full" in reducing anxiety symptoms in adults aged 55 to 75 years. Furthermore, moderators and mediators of the treatment effect are investigated.

Methods/design: The (cost-)effectiveness of the ACT intervention will be investigated in a cluster single-blind randomized controlled trial (RCT). The blended intervention will be compared to enhanced treatment-as-usual. Thirty-six mental health counselors working at general practices in the Netherlands will be randomized to deliver blended care or treatment-as-usual. A total of 240 participants (aged 55–75 years) with mild to moderately severe anxiety complaints (defined as a total score of 5–15 on the GAD-7) will be recruited. There are 4 measurements consisting of online questionnaires (primary outcome: GAD-7) and a telephone interview: before the start of the intervention; directly following the intervention (14 weeks after baseline); and six and twelve months after baseline. Possible mediator variables will be assessed multiple times basis during the intervention.

Discussion: This RCT will evaluate the effectiveness of a blended ACT intervention for older adults with anxiety symptoms. If the intervention is shown to be effective, it will be implemented, thereby improving the accessibility and quality of preventive interventions for older adults with anxiety problems.

Introduction

Anxiety problems form one of the most ubiquitous and disabling mental health conditions in older adults. Prevalence estimates of anxiety disorders in this age group are in the range of 1.2–14% [10,90]. Furthermore, prevalence studies on anxiety in older adults show that subclinical anxiety is even more widespread, with estimates in the range of 15–52.3% in community samples. These findings suggest that anxiety may mostly present as a sub-threshold disorder in elderly adults [10,90]. Unfortunately, anxiety symptoms (and anxiety disorders as well) frequently go unrecognized and untreated in older adults [10,90,149]. This is due to several characteristics of this age group such as a stronger belief in self-reliance, higher perceived stigma of mental health problems, a limited willingness to accept treatment for such problems, a tendency to minimize symptoms, mobility problems, use of different terms to describe psychological problems, and problems with remembering and recognizing symptoms [31, 87]. Also, it seems challenging for both clinicians and patients to differentiate between functional and pathological anxiety in older adults; anxiety in elderly adults is regularly considered to be an epiphenomenon of a physical condition or part of the normal aging process [31, 32].

The fact that only a small proportion of anxious older adults receive adequate treatment is alarming, since even on a subclinical level, anxiety in older adults is associated with diminished quality of life and wellbeing [22, 24], depressive symptoms, hypertension, urinary incontinence [25], cognitive decline [26, 27], functional disability [28], and an increased risk for stroke [29] and coronary heart disease [30]. Furthermore, anxiety symptoms tend to run a chronic course [22] and put people at risk for developing anxiety disorders [23]. To diminish the personal and societal impact of anxiety complaints in older adults, low-threshold, evidence-based interventions are needed [23, 150]. However, considering the high prevalence of anxiety symptoms in older adults and the rise in life expectancy, even existing healthcare systems in affluent societies cannot adequately address this need. Internet-based therapy (possibly combined with a limited amount of face-to-face contacts with a therapist, counselor, or coach) is a promising option to reduce the treatment gap in a cost-effective way. For older adults with anxiety symptoms, Internet-based therapy could lower some of the barriers that prevent them from seeking help (e.g., perceived stigma on seeing a therapist, mobility problems, strong belief in self-reliance with regard to mental health).

In younger adult populations, Internet-based therapy—predominantly cognitive behavioral interventions—have repeatedly been shown to form a (cost-)effective

treatment option for both anxiety disorders and subclinical anxiety [78,151-158]. Evidence so far suggests that a combination of an online self-help module and therapist support (either online, by telephone, or face-to-face) is the most effective form of Internet-based therapy [158].

To date, only one study has examined an online intervention for older adults with anxiety symptoms. This randomized controlled trial (RCT) found that Internet-delivered cognitive behavioral therapy (CBT) was an efficacious and cost-effective treatment for older adults with subclinical anxiety [84]. The vast majority of other trials in anxious older adults also focus on CBT but delivered as face-to-face therapy to patients with anxiety disorders. Several meta-analyses support the effectiveness of CBT for elderly adults with an anxiety disorder [34-37,159]. However, researchers suggest investigating other treatment approaches as well, since the effect sizes for CBT in anxious older adults are relatively small and several analyses suggest that older adults benefit less from CBT for anxiety than the younger adult population [10,32,35,3,160].

One treatment approach that might form a valuable alternative for CBT in older adults is Acceptance and Commitment Therapy (ACT), a so-called third-wave CBT [32, 52,59,60]. In contrast to CBT, ACT makes little to no use of content-oriented cognitive techniques. The goal of ACT is not to reduce the frequency or discomfort of negative internal experiences. Rather, ACT strives to reduce the struggle that arises when people try to suppress internal experiences and to stimulate people to engage in activities that are meaningful to them. Ultimately, ACT aims to promote psychological flexibility: the ability to fully and openly experience the present moment (including the negative or painful aspects); and to persist in or change behavior dependent on its accordance with personal goals and values [52,55,57]. Meta-analyses support the effectiveness of ACT in reducing various psychological problems, including anxiety disorders [54,55,161,162]. Internet interventions based on ACT have also been shown to be effective for adults with depressive and anxiety symptoms [163,164]. No large-scale, controlled trials have yet been conducted to evaluate ACT interventions for older adults.

However, it could be argued that the ACT approach might particularly resonate with older adults, as it concurs with the reorientation on important life values and associated value-directed behavior change in this life phase [59,60].

Furthermore, an acceptance-based coping style could be especially valuable for older adults, because age-related adversities such as loss of dear ones and declining health might be most effectively coped with through an acceptance-oriented style. Some

evidence suggests that in older adults, acceptance is associated with better emotional wellbeing and quality of life [60,61,165,166]. Another possible benefit of ACT is its transdiagnostic approach, since anxiety and depression are highly co-morbid in older adults [10,90,167]. Some evidence suggests that co-morbid depressive symptoms have a negative impact on treatment outcome in anxious older adults (when treated with CBT) [168]. Therefore, a transdiagnostic treatment that focuses on psychological factors that might underlie both anxiety and depression is highly valuable.

Considering the need for evidence-based interventions for older adults with subclinical anxiety and the plausible suitability of ACT for this group, the proposed study aims to evaluate the (cost-)effectiveness of an Internet-based ACT intervention for older adults with anxiety complaints in general practice. To promote compliance and reduce dropout, this intervention is combined with a limited amount of face-to-face contacts with the mental health counselor at the general practice. This intervention will be compared to optimized treatment-as-usual. In addition to the analysis of the (cost-) effectiveness, moderators and mediators of treatment effects will also be investigated in the study. The current paper describes the research protocol for this study.

Methods/design

Design

The proposed study is a pragmatic cluster single-blind RCT. In a clustered trial, the unit of randomization is not the individual participant, but a group of participants (e.g., patients from one general practice, students from the same school, family members). In this study, randomization takes place on the level of the mental health counselors at general practices, which creates clusters of participants that receive treatment from the same counselor. Cluster randomization is used in this study to reduce experimental contamination [169] and to minimize administrative burden and time spent on training the participating mental health counselors in the used treatment methods. Participating mental health counselors will be randomly assigned to one of the following two conditions: they will either treat all included patients in their practice(s) with the Internet-based ACT intervention or provide all their patients with optimized treatment-as-usual. In most cases, randomization of the mental health counselor will coincide with randomization of the practice(s) at which he/she is employed, but some practices employ multiple counselors. In these practices, a double randomization procedure will be used. First, the counselors are randomized. Second, when patients of this practice are included in the study, they are randomly allocated to one of the counselors in the practice.

The randomization table (containing 36 cells, block randomized into blocks of four cells) will be created by an independent researcher using R software [96]. Participants, mental health counselors, and the main researcher (who serves as the contact person for the mental health counselors) cannot be blind for allocation to conditions. However, participants are not informed on whether the treatment they receive is the experimental or active control intervention. They are told that the study aims to compare two treatment options for people with mild to moderate anxiety complaints. This is considered an ethically sound approach, since treatment-as-usual is delivered as optimized.

Each participant will complete 4 main measurements during the study: before the start of the intervention (and before participants are informed about which intervention they will receive) (T0); directly following the intervention (3 months after baseline; T1); and 6 (T2) and 12 months (T3) after baseline. All measurements consist mainly of online self-report questionnaires. T0, T1, and T3 also include a telephone interview conducted by a research assistant. The research assistant that conducts the telephone interviews will be unaware of treatment allocation of the participants. If for any reason this blinding is broken, another research assistant (that is blind to treatment condition of the participant) will take over the telephonic assessment.

The study is approved by the medical ethical committee of the Leiden University Medical Center (LUMC; no. P16.248).

Participants

A total of 240 participants will be included. In order for a person to be eligible to participate in the study, the following inclusion criteria have to be met: aged 55–75 years; presence of mild to moderate anxiety symptoms; access to Internet; mastery of the Dutch language; and the possibility and motivation to spend up to 30 min per day on the intervention. Potential individuals that meet any of the following exclusion criteria will be excluded from participation: Alzheimer's disease or other severe cognitive impairments; unstable severe medical condition(s); severe anxiety or few anxiety symptoms; severe depressive symptomatology; having received psychological or psychopharmacological treatment (with the exception of stable use of benzodiazepines or SSRIs) within the last 3 months; severe role impairment in at least 2 areas of role functioning; high suicide risk; substance use disorder or a lifetime diagnosis of bipolar disorder or schizophrenia. The main inclusion criterion—severity of anxiety symptoms—is measured with the GAD-7. This questionnaire uses well-established cut-

off points for mild, moderate, and severe anxiety symptoms [131]. These cut-offs point are used to identify our study population: people that score between 5 (cut-off point for mild anxiety) and 15 (cut-off point for severe anxiety) are considered to experience mild to moderately severe anxiety complaints. The information in the participants' medical record at the general practice is used to determine the presence of a severe unstable medical condition, severe cognitive impairment, and a lifetime diagnosis of bipolar disorder or schizophrenia.The PHQ-9 [170] is used to assess depressive symptomology (a score of $\geq$20 indicates severe symptoms and excludes people from participation). Role impairment is assessed with the Sheeran Disability Scale (SDS) [171]. A score of $\geq$8 on 2 of the 3 subscales is indicative of severe role impairment. Participants are screened for high suicide risk, substance use disorders, and a lifetime diagnosis of bipolar disorder or schizophrenia with the M.I.N.I.-Plus [139].

Sample size

Cluster randomization will be applied at the level of the participating mental health counselors. Assuming a mean cluster size of 5 patients per counselor, an intraclass correlation coefficient of 0.01 [172] and a coefficient of variation of 0.30 [173], 18 mental health counselors in each intervention arm and 90 participants per study arm are needed to detect a between group difference on the GAD-7 with a medium effect size (d=0.45) with an alpha of 0.05 (two-tailed) and a power of 0.80. Compensating for an anticipated dropout of 25% (based on trials similar to the proposed study with regard to either the treatment approach [163, 174] or the study population [84]), 240 participants will have to be included at baseline. In the most recent and comprehensive Cochrane meta-analysis of 101 studies of media-delivered CBT for anxiety disorders in adults, moderate-quality evidence showed medium effect sizes for CBT compared to control conditions (d=0.67; 95% confidence interval =0.55–0.80) [156]. These effects were somewhat smaller than those reported in other recent reviews [78,152-155] and also smaller than the large effect sizes for Internet-based ACT (0.80 and 0.87) in the study of Fledderus et al. [163] and for Internet-based CBT for anxiety complaints in older adults (1.43) in the study of Dear et al. [84]. These last 2 studies both compared active treatment to a waiting list control condition. Furthermore, Pots et al. reported an effect size of 0.41 for web-based ACT (with e-mail support) compared to an active control group (expressive writing) [164]. Based on these studies, a moderate effect size of d=0.45 is estimated for the difference between the ACT online intervention and optimized treatment-as-usual.

Recruitment of general practices

General practices will be recruited throughout the Netherlands, with a focus on the Leiden and the Hague area. Both general practitioners and the mental health counselors working at the general practices will receive a printed invitation to participate in the study, after which they will be contacted by email and phone to recommend participation. When a practice (both GP and mental health counselor) agrees to participate, the mental health counselor will be randomized. A total of 36 mental health counselors will be included. Randomization is performed by an independent researcher, who is informed by the main researcher when a group of 4 mental health counselors have been enrolled. The mental health counselors are informed about their group allocation by the main researcher and are invited to attend a training in the treatment method they will apply during the study.

Recruitment of participants

A data manager will visit the participating general practices to assist the general practitioner in the selection of patients aged 55–75 years that are eligible to receive an invitation letter for the study. Patients whose medical records mention a lifetime diagnosis of bipolar disorder or schizophrenia, a severe unstable medical condition, Alzheimer's disease, or other severe cognitive impairments will not receive an invitation. All other patients aged 55–75 years do receive an invitation letter. The invitation letter from the GP to the patients contains information about anxiety complaints and explains the aim, design, and procedure of the study. Furthermore, the letter refers to the study website. On this website, potential participants can read more extensive information about the study and indicate their interest to participate. After doing so, they will be asked to fill in the GAD-7 and PHQ-9 and to indicate whether they have received psychological treatment for emotional problems during the last 3 months, have Internet access, have sufficient time for treatment, are able to communicate in Dutch, and are aged 55–75 years. If based on these answers patients are still eligible to participate, they are asked if they are willing to be interviewed by phone to determine whether they fulfill all inclusion criteria. They are asked to fill in their telephone number and to indicate on which day they prefer to be called. Within 10 days they will be phoned by a research assistant, who will administer the SDS and M.I.N.I.-Plus. Furthermore, they will be asked about their medication use. Patients will also be given the opportunity to ask any remaining questions about the aim of the study and the study procedures. The interviewer will discuss his/her diagnostic findings from the M.I.N.I-Plus with a

senior clinical psychologist; subsequently the interviewee is informed by mail about inclusion or exclusion. When patients are eligible, they will receive a link to an online informed consent form and the baseline questionnaires (T0). Ineligible patients will be referred to their general practitioner in case they want help for their complaints. Once eligible patients have filled in the informed consent form and the baseline questionnaires, the mental health counselor at their general practice will be informed about study participation and they will be invited for a first appointment. In addition to the mass mailing, general practitioners and mental health counselors will recommend participation to patients aged 55–75 years that attend the practice with anxiety complaints during the inclusion period. They will inform these patients about the study and refer them to the study website if they want to participate. These patients then follow the screening and inclusion procedure as described above.

Procedure during study participation

During the intervention, participants will fill in a short questionnaire assessing potential mediator variables several times. At these moments they will also complete the GAD-2 [175] and PHQ-2 [176] to measure respectively anxiety and depression symptoms (the combination of PHQ-2 and GAD-2 is also known as the PHQ-4 [177]). They will also be asked whether they have had recurrent thoughts about death or hurting themselves in the past week, using an item of the PHQ-9 [170]. When participants have had suicidal thoughts in the past week, they will be recommended to discuss this with their mental health counselor at the general practice. Furthermore, their mental health counselor will be notified about the presence of suicidal thoughts by the researchers and are asked to contact the participant. Participants in the experimental condition complete this questionnaire at the end of every online lesson (9 times in total). Participants in the control condition, receive an email with a link to this questionnaire after every session with the mental health counselor (a total of 4 times).

Both interventions are delivered in a timespan of maximum 12 weeks, after which participants receive an e-mail with a link to the online self-report questionnaires of the post-treatment assessment (T1). T1 also includes a clinical interview by telephone conducted by a research assistant. The follow-up assessments take place 6 (T2) and 12 months (T3) after baseline. Both these assessments consist of self-report questionnaires and T3 also includes a clinical telephone interview. Figure 1 shows an overview of the patient flow through the phases of the study.

Prevention of attrition

Although available research shows that the effect of eHealth interventions does not depend on age and that older adults are even more adherent than younger adults [178], several precautions will be taken to reduce dropout and heighten compliance throughout this study. If participants fail to complete study assessments or intervention assessments, motivational reminders will be send repeatedly by email. If participants drop out or stop using the intervention, they will be asked for the reason(s) why they decided to quit the intervention and/or study.

Treatments

Experimental condition

The online intervention "Living to the Full" is an adaptation of the similarly titled ACT-based self-help book [179] (English version: [180]). The effectiveness of this web-based intervention (both with and without support from a counselor) in reducing depression and associated anxiety in adults has been established in RCTs [154,163,164,181]. A pilot study in which ten older adults worked through the online module, resulted in some age-matched adaptations of the layout and text of the intervention. The online module consists of 9 lessons that are ideally completed in a maximum of 12 weeks. The lessons are based on the 6 core processes of ACT that aim to promote psychological flexibility: acceptance; cognitive defusion; contact with the present moment; self as context; values; and committed action. Each lesson contains information in both text and video form about the relationship between the ACT processes and emotional wellbeing, experiential exercises, metaphors, and motivational exercises. Furthermore, participants are instructed to practice mindfulness for 10–15 min on a daily basis. The intervention provides them with audio files that guide them through the mindfulness exercises. Each week, participants receive 2 or 3 standardized motivational text messages, to increase motivation and adherence. In addition to the online self-help module, participants will have 4 face-to-face sessions with the mental health counselor at their general practice to increase motivation, evaluate their progress, and discuss problems. For these sessions, a protocol has been developed. To measure adherence to the protocol, mental health counselors will complete a short online questionnaire after every face-to-face session which asks them to give a brief summary of the session. The mental health counselors in this condition will receive training from an experienced clinical psychologist to get acquainted with ACT, the protocol, and the

online environment in which their patients will be working. During the study, the mental health counselors will have 2 supervision sessions from a clinical psychologist.

Control condition

Treatment-as-usual will be provided as optimized care-as-usual. Participants will be offered 4 face-to-face sessions with the mental health counselor at the general practice. The treatment is developed by the researchers and follows the traditional CBT principles. The treatment protocol consists of a manual that comprises 12 small interventions. Each intervention focuses on either a common form of anxiety (worrying, panic symptoms, social anxiety), cognitive or behavioral aspects typical of most anxiety complaints (catastrophic thinking, avoidance), or consequences of anxiety (sleeping problems, physical tension). All interventions consist of psycho-educative texts and exercises based on CBT. During the first session, the mental health counselor and participant make an overview of the psychological complaints of the participant. Based on this inventory, one or more of the small interventions are selected to form the basis of the next three sessions. In order to prevent treatment diffusion, the delivery of interventions resembling the web-based interventions (i.e., eHealth interventions in general and ACT and mindfulness-based interventions in particular) are not allowed. Mental health counselors will complete a short online questionnaire that measures treatment protocol adherence after every session. Mental health counselors in this condition will follow a training from an experienced clinical psychologist, to practice with the protocol. They will also be supervised during the study.

Assessments

Table 1 depicts an overview of the assessment instruments that will be used throughout the study. All questionnaires—except for the M.I.N.I.-Plus and SDS—will be conducted online. The M.I.N.I.-Plus and SDS are conducted by telephone.

Anxiety symptom severity

The primary outcome—severity of anxiety symptoms—will be assessed with the GAD-7 [131]. This questionnaire will be used to screen participants on anxiety symptoms and to measure change in these symptoms from baseline to post- and follow-up tests. The primary endpoint for this measure is the measurement 14 weeks after baseline (T1). The GAD-7 consists of seven items that are rated on a 4-point scale ranging from

0 (not at all) to 3 (nearly every day), e.g., “Over the last 2 weeks, how often have you been bothered by: feeling nervous, anxious or on edge.” Higher scores indicate more anxiety symptoms. Total scores are in the range of 0–21 and scores of 5, 10, and 15 are taken as the cut-off points for mild, moderate, and severe anxiety. Psychometric properties of the GAD-7 are adequate and the scale may also be used as a screener for panic disorder, social anxiety, and post-traumatic stress disorder [131,175,182]. The reliability and validity of a web-based Dutch translation of the GAD-7 have also been established [183].

Furthermore, during treatment, participants will fill in the GAD-2 [175] several times to measure anxiety symptom severity. The GAD-2 consists of the first 2 items of the GAD-7, which reflect core anxiety symptoms (“Feeling nervous, anxious, or on edge” and “Not being able to stop or control worrying”). Scores on the GAD-2 will be used in the mediation analyses. The GAD-2 is a reliable, valid, and sufficiently sensitive and specific instrument [175,183,184].

Depression symptom severity

Depression symptoms will be measured with the PHQ-9 [170]. This questionnaire will be used as a screener for depressive symptoms and to measure change in depressive symptomology from baseline to post- and follow-up tests. The questionnaire consists of nine items and includes the DSM-IV criteria for a major depressive disorder. The items are rated on a 4-point scale ranging from 0 (not at all) to 3 (nearly every day). Scores are in the range of 0–27 and cut-off points of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe levels of depressive symptoms. The PHQ-9 is sensitive to change, has good sensitivity and specificity for detecting depressive disorders, and its psychometric properties are adequate [182,184,185]. In addition, depression symptoms will be measured with the PHQ-2 [176] at several times during treatment. The 2 items of the PHQ-2 (which correspond to the first two items of the PHQ-9) measure core depressive symptomology. The scores on these items will be used in the mediation analyses. The reliability, validity, and sensitivity to change of the PHQ-2 have been established [176,177,184].

Presence of psychiatric disorder

Presence of current and/or lifetime diagnosis of anxiety disorder (generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social phobia), obsessive-compulsive disorder, depressive disorder, post-traumatic stress disorder, and illness

anxiety disorder will be determined by the M.I.N.I.-Plus [139]. Current substance abuse disorder and suicide risk as well as a lifetime diagnosis of psychotic disorder and bipolar disorder will also be assessed. The M.I.N.I.-Plus is the most widely used psychiatric structured diagnostic interview instrument in the world and has been validated against the Structured Clinical Interview for DSM diagnoses (SCID-P) and the Composite International Diagnostic Interview for ICD-10 (CIDI) [139]. Trained research assistants who are blind to the randomization scheme will conduct the M.I.N.I-Plus by phone. The M.I.N.I.-Plus will be administered during the screening (T0). At T1 and T3, only the modules for current anxiety disorders, depressive disorder, post-traumatic stress disorder, obsessive-compulsive disorder, and illness anxiety will be conducted. Minor adjustments will be made to the M.I.N.I.-Plus, so it corresponds with the criteria of the DSM-V. When uncertain of a diagnosis, the interviewers will have the opportunity to consult a psychiatrist or senior clinical psychologist, who is also blind to randomization status of the participants.

Table 1. Overview of assessments during the study

Assessment	**Screening**	**T0: Baseline**	**During intervention**	**T1 Post-intervention (14 weeks after T0)**	**T2 Follow-up (26 weeks after T0)**	**T3 Follow-up (52 weeks after T0)**
GAD-7	X	X	-	X	X	X
PHQ-9	X	X	-	X	X	X
PHQ-4 (GAD-2 + PHQ-2)	-	-	X	-	-	
M.I.N.I.-Plus	X	-	-	X	-	X
SDS	X	-	-	X	-	X
CERQ	-	X	-	X	X	X
AAQ-II	-	X	-	X	X	X
MHC-SF	-	X	-	X	X	X
FFMQ-SF	-	X	-	X	X	X
EQ-5D-5L	-	X	-	X	X	X
TIC-P	-	X	-		X	X
CSQ-8	-	-	-	X	-	-
Self-esteem, Mastery and Support	-	X	-	-	-	-
Life-events	-	X	-	-	-	-
Somatic problems	-	X	-	-	-	-
Demographics and other information	-	X	-	-	-	-

Table 1. Continued

Assessment	Screening	T0: Baseline	During intervention	T1 Post-intervention (14 weeks after T0)	T2 Follow-up (26 weeks after T0)	T3 Follow-up (52 weeks after T0)
Treatment credibility and expectancy	-	-	X	-	-	-
Emotion Regulation	-	X	X	X	X	X
Behavioral avoidance	-	X	X	X	X	X
Treatment expectancy	-	-	X	-	-	-
Self-efficacy	-	-	X	-	-	-
SRS	-	-	X	-	-	-

GAD-7 General Anxiety Disorder 7, PHQ-9 Patient Health Questionnaire 9, PHQ-4 Patient Health Questionnaire 4,GAD-2 General Anxiety Disorder 2, PHQ-2 Patient Health Questionnaire 2, M.I.N.I.-PLUS, Mini-International Neuropsychiatric Interview-PLUS, SDS Sheehan Disability Scale, CERQ Cognitive Emotion Regulation Questionnaire, AAQ-II Acceptance and Action Questionnaire II, MHC-SF Mental Health Continuum Short Form, FFMQ-SF Five Facet Mindfulness Questionnaire Short Form, EQ-5D-5 L EuroQol 5 dimensions 5 levels questionnaire, TiC-P Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness, CSQ-8 Client Satisfaction Questionnaire 8, SRS Session Rating Scale

Functional impairment

The SDS [171] was developed to assess functional impairment in 3 inter-related domains: work/school; social life; and family life. The SDS measures the extent to which work/school, social life, and home life or family responsibilities are impaired by psychiatric symptoms on a 10-point visual analogue scale. The 3 items can be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). A psychometric analysis in a large sample of primary care patients demonstrated that the SDS has good psychometric qualities [171]. Research assistants that are blind to group allocation, will administer the SDS by telephone during the screening (T0) and at T1 and T3.

Cognitive emotion regulation

The subscales Rumination, Catastrophizing, Positive reappraisal, and Blaming yourself of the CERQ [186,187] will be used to measure the extent to which participants use these cognitive coping strategies when confronted with adversities. The choice for these subscales is based on several studies that have demonstrated the association between these strategies and anxiety and depression symptoms [187-189]. The subscales consist of 4 items each. Higher scores on a subscale indicate that this

cognitive coping strategy is more often used to regulate emotions. Psychometric properties of the Dutch CERQ are adequate [188,190].

Experiential avoidance

The Acceptance and Action Questionnaire (AAQ-II) [191,192] is a uni-dimensional measure [192,193] that assesses experiential avoidance: the unwillingness to remain in contact with aversive private experience and behaviors aimed at altering these experiences or the events that elicit them. The AAQ-II originally contained 10 items, but a study showed that a 7-item version has better psychometric qualities [192]. Items are scored on a 7-point scale ranging from 1 (never true) to 7 (always true). Higher scores reflect higher levels of experiential avoidance. The reliability and validity of a Dutch translation of the AAQ-II has been established in a sample of moderately depressed and anxious individuals [193].

Positive mental health

The Mental Health Continuum-Short Form (MHC-SF) [194] is a 14-item self-report questionnaire for positive mental health assessment. The questionnaire consists of 3 subscales, corresponding with the 3 dimensions of positive mental health: 3 items for emotional wellbeing; 6 items for psychological wellbeing; and 5 items for social wellbeing. Items are rated on a 6-point scale ranging from 0 (never) to 5 (every day). Confirmatory factor analysis (CFA) confirmed the 3-factor structure of a Dutch translation of the MHC-SF. Results from the same psychometric study also revealed high internal and moderate test–retest reliability for the Dutch MHC-SF [194].

Mindfulness

The Five Facet Mindfulness Questionnaire- Short Form (FFMQ-SF) [195] will be used to measure mindfulness, defined as the ability to bring one's attention to experiences in the present moment in a non-judgmental way [196]. The questionnaire contains 24 items that measure 5 facets of mindfulness: observing; describing; acting with awareness; non-judging; and non-reactivity. Items are scored on a 5-point scale ranging from 1 (never or very rarely true) to 5 (very often or always true). A psychometric study showed that the FFMQ-SF is a sensitive, reliable, and valid instrument. Furthermore, the 5-factor structure of the questionnaire was confirmed in this study [195].

Generic health status and quality of life

The EuroQol-5 Dimensions-5 Levels questionnaire (EQ-5D-5 L) measures general quality of life using five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [197]. Each dimension has 5 response categories, describing the severity of problems. A total of 3125 unique health states can be defined, by combining the responses for the 5 dimensions into a 5-digit number (ranging from "11111" meaning no problems at all to "55555" meaning extreme problems in all five dimensions) [198]. The EQ-5D-5 L is an adaption of the EQ-5D [199]. The EQ-5D consists of the same 5 dimensions but has only 3 response categories per dimension. Evidence suggests that the EQ-5D has limited responsiveness to changes in health, partly caused by ceiling and floor effects. Studies show that compared to the EQ-5D, the EQ-5D-5 L has smaller ceiling and floor effects, and improved reliability and discriminating ability [200,201].

Costs associated with psychiatric illness

For calculating the total direct medical costs, the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) [202] will be used. The TiC-P measures utilization of medical treatment, such as the number of contacts with the general practitioner and multiple other care providers (e.g., medical specialists and paramedics) during the last 4 weeks, as well as medication use and loss of productivity at (voluntary) work. The costs will be calculated using the Dutch guidelines for cost calculations in healthcare. Reference unit prices of the corresponding healthcare services will be applied. A psychometric study demonstrated that the Dutch version of the TIC-P is a feasible, reliable, and valid tool for assessing care consumption and productivity loss in patients with mild to moderate psychiatric problems [203].

Client satisfaction

The Client Satisfaction Questionnaire-8 (CSQ-8) [204] is an 8-item instrument that is designed to measure client satisfaction with services. The items for the CSQ-8 were selected based on mental health professionals' ratings of a number of items that could be related to client satisfaction and a subsequent factor analysis. The CSQ-8 is uni-dimensional, yielding a homogeneous estimate of general satisfaction with services. The questions are answered on a 4-point scale in the range of 1–4, but each question has different labels attached to these values. Higher scores indicate higher client satisfaction. The psychometric qualities of the Dutch translation of the CSQ are adequate [204,205].

Moderator variables

Self-esteem, mastery, and support

Starting from existing instruments, Bovier, Chamot, and Perneger used factor analyses to develop 4 brief scales for the assessment of self-esteem, affective social and confident/problem-solving social support [206]. All 12 items are answered on a 5-point Likert scale, with higher scores representing higher levels of the 4 measured constructs. All 4 scales have been found to demonstrate good internal and construct validity [206].

Life events

A self-developed questionnaire will be used to measure negative life events and associated distress. Participants are asked if they have experienced negative life events in the past 6 months and/or earlier in their life. If they indicate that they have experienced such (an) event(s), they are asked to rate them on an 11-point scale (ranging from 0 [not at all] to 10 [extremely]) to what extent these experiences currently still evoke strong negative feelings.

Co-morbid somatic problems

Co-morbid physical problems will be measured with a self-developed questionnaire listing 25 (chronic) conditions. This list is based on information from Statistics Netherlands. Participants will also be asked to rate to what extent their somatic problem(s) interferes with their current daily functioning on an 11-point scale ranging from 0 (not at all) to 10 (extremely).

Socio-demographics and other information

Using a self-developed questionnaire, the following socio-demographic information and additional information will be collected: age; gender; nationality; marital status; living conditions; education; work status; computer usage; and Internet usage.

Treatment credibility and expectancies

Participants' expectations of the treatment will be measured with a questionnaire derived from the Treatment Credibility Questionnaire (TCQ) from Borkovec and Nau [207]. In this study, the version as developed by De Jong et al. (Risk models for negative treatment

outcomes in psychiatric outpatients: predicting end state functioning and rate of change using classification and regression trees (CART) and multilevel modeling, unpublished) will be used. This version combines an adaptation of the TCQ [208] with one item ("How much improvement in your symptoms do you think will occur") from the Credibility Expectancy Questionnaire [209]. The questionnaire consists of 7 items that are scored on a 7-point rating scale, ranging from 1 (not at all) to 7 (extremely). The questionnaire consists of 2 factors: Expectancies and Credibility. The version that will be used in this study has an internal consistency of 0.89 for the Expectancies subscale and 0.84 for the Credibility subscale [210]. This questionnaire will be completed after participants have had the first session with the mental health counselor at the general practice.

Mediator variables

Emotion regulation

A self-developed questionnaire measures the use of the following emotion regulation strategies: distraction; reappraisal; acceptance; rumination/worry; and suppression. Adaptive strategies (distraction, reappraisal, acceptance) are consistently more strongly related with reduced negative affect and maladaptive strategies (rumination/worry and suppression) with enhanced negative affect in laboratory studies [211] and psychopathology in clinical studies [212]. Participants will report on the extent to which they have engaged in each of these emotion-regulation strategies on a 6-point scale ranging from 0 (never) to 5 (always).

Behavioral avoidance

Since both interventions stimulate participants to limit their avoidance behavior, this factor will be included in the mediation analyses. Behavioral avoidance is measured with one item (i.e., "In the past week my anxiety caused me to avoid situations and/or activities"), that participants rate on a 6-point-scale ranging from 0 (never) to 5 (always).

Treatment expectancy

Treatment expectancy is measured with one item: "How confident are you that the course will be helpful in reducing your anxiety complaints?" Participants rate this question on a 7-point scale ranging from 1 (not at all) to 7 (very confident). Several studies have shown the impact of client expectancies on treatment effect. Evidence suggests that eliciting hope and positive expectations about the effect of the treatment is a crucial factor in many psychotherapies [213-216].

Self-efficacy

Preliminary results suggest that the outcome of psychological interventions may be mediated by patient's self-efficacy with regard to the treatment (i.e., one's judgment of the capability to successfully participate in and complete the treatment) [217,218]. Self-efficacy with regard to therapy is measured with one item: "How confident are you that you will do what is required to successfully follow and complete this course?" Participants rate this question on a 7-point scale ranging from 1 (not at all) to 7 (very confident).

Session Rating Scale

The Session Rating Scale (SRS) [219] will be used to measure the working alliance between the participants and their mental health counselor. The items assess four aspects of the working alliance: the relational bond (the degree to which one feels heard, understood, and respected); the degree to which desired goals and topics of the individual were discussed; an evaluation of the therapist's approach or method that was used; and an evaluation of how the individual perceives the session overall. Instead of using a visual analogue scale, an 11-point scale will be used to answer each of the four items, with "0" depicting the most negative response and "10" depicting the most positive response. The SRS was shown to have high test–retest and internal consistency reliability, as well as acceptable validity [220, 221]. The SRS will be completed after every face-to-face session.

Statistical analysis

All analyses will use intention-to-treat principles and a two-tailed alpha of 0.05 for significance testing. Cluster randomization at the level of mental health counselors (instead of individual patients) results in a lack of independence for the outcomes of patients receiving treatment from the same counselor. If clustering and dependence of outcome are ignored, this could lead to underestimation of standard errors and regression coefficients [222]. Therefore, multilevel regression analysis will be used to examine the treatment effect on the primary and secondary outcome measures. Multilevel analysis allows modeling of the variability of the outcome measures within clusters and analysis of a repeated-measure design with missing data. In this cluster randomized RCT, three levels can be distinguished: (1) repeated measures within patients; (2) treatment allocation; and (3) mental health counselors. To evaluate the intervention effect, a twofold analysis will be conducted. First, using a mixed-model analysis with treatment as a dummy variable and the dependent variable on baseline

as covariate it will be examined whether conditions differ across time. In addition, a subsequent mixed-model analysis without the dependent variable at baseline as covariate will analyze at which particular time point conditions differ as indicated by the interaction effect of treatment × time. Missing data will be imputed using a model-based approach. Covariance will be estimated using an unstructured covariance matrix.

To examine moderators of the treatment outcome, longitudinal multi-level regression analysis will be performed. Interaction effects will be investigated (e.g., time × condition × potential moderator). Bivariate latent difference score models will be used for the mediation analysis. This type of analysis is recommended for repeated measurements and multiple mediators, because they allow for a more dynamic approach to mediation, by assessing changes in multiple variables and their interrelations over time [223-225]. Cost-effectiveness analyses will be conducted in agreement with the CHEERS statement [226] and will be determined by relating the difference in healthcare costs (measured with the TiC-P) to the between-group difference in reliable change on GAD-7 scores (cost-effectiveness analysis) and quality-adjusted life-years (QALYs) gained based on the EQ-5D-5 L using the Dutch tariffs (cost–utility analysis). Productivity losses in paid work will be included in the economic evaluation and measured by assessing work-loss days due to absenteeism and work cutback days (presenteeism) while at work but not feeling well. All cost prices will be indexed for the appropriate reference year (likely to be 2017) but not discounted because the study's time horizon does not exceed the period of a single year. Stochastic uncertainty in the incremental cost-effectiveness ratios (ICERs) will be handled using non-parametric bootstraps (2500 replications), plotted on the ICER plane and depicted in an ICER acceptability curve. Sensitivity analyses will focus on the friction cost versus human capital method and on main cost-drivers.

Discussion

The proposed study will evaluate the (cost-)effectiveness of the Internet-based ACT intervention 'Living to the Full' for older adults with anxiety complaints in a RCT. This study has several strengths. First, the trial is unique in this field of research. It differs from the majority of studies in older anxious adults with regard to therapy approach (ACT instead of CBT), the delivery of the investigated intervention (Internet-based instead of face-to-face) and the study population (people with anxiety complaints instead of anxiety disorders). The moderation and mediation analyses form a second strength. These analyses will provide insight into respectively the effect of personal characteristics on treatment outcome and

the processes through which the intervention achieves its effects. Including such analyses broadens the scope of the study. The trial is not merely focused on answering the question if “Living to the Full” is more or less effective than treatment-as-usual. Because of the optimized active control condition, it is plausible that both treatments will result in a significant reduction in symptomology and related measures. In this scenario, the moderation and mediation analyses will still be of value in exploring if certain subgroups of patients benefit from one of the interventions in particular and if the processes through which the treatments achieved their effects differ. This sort of knowledge can contribute to a more personalized treatment approach by taking into account moderating factors and an increased effectiveness of interventions by refining and intensifying those components that focus directly on the mediators [227]. Another strength of this study is related to the fact that treatment-as-usual is delivered as optimized care as usual. Because participants in the control condition will receive appropriate treatment, a 12-month follow-up is defendable, allowing to investigate the long-term (cost-)effectiveness of the “Living to the Full” intervention compared to treatment-as-usual. A final strength of this study is its recruitment method. All patients aged 55–75 years from participating general practices are actively invited to participate in the study and are able to register online. Compared to studies in which only patients that visit their general practitioner with certain complaints are informed about a study, this method reaches a wider population and lowers the threshold for registering for participation.

The study also has some limitations. First, the online nature of the screening procedure and intervention might limit the study sample. It excludes people that are not proficient with computers. These people might share certain characteristics (e.g., older age, lower education levels), which reduces the representativeness of the sample. Second, the study might encounter difficulties in recruiting enough participants. Recruiting older adults for study participation is challenging [228]. Furthermore, due to the cluster-randomized design, more participants are needed to obtain equivalent statistical power as compared to an individually randomized trial [169]. However, this study uses a mass mailing as the main recruitment method, which has proven to be one of the most successful strategies to recruit older adults [228].

To conclude, the proposed study will evaluate an ACT online self-help program combined with face-to-face contacts with the mental health counselor at the general practice for older adults with anxiety symptoms. Since subclinical anxiety is highly prevalent in this age group, (cost-)effective, low-threshold interventions are needed. The proposed study complies with this request. When “Living to the Full” proves to be effective for this patient group, implementation of the intervention in general practices in the Netherlands will follow.

4

BLENDED ACCEPTANCE AND COMMITMENT THERAPY VERSUS FACE-TO-FACE COGNITIVE BEHAVIORAL THERAPY FOR OLDER ADULTS WITH ANXIETY SYMPTOMS IN PRIMARY CARE: PRAGMATIC SINGLE-BLIND CLUSTER RANDOMIZED TRIAL

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Abstract

Background: Anxiety symptoms in older adults are prevalent and disabling but often go untreated. Most trials on psychological interventions for anxiety in later life have examined the effectiveness of face-to-face cognitive behavioral therapy (CBT). To bridge the current treatment gap, other treatment approaches and delivery formats should also be evaluated.

Objective: This study is the first to examine the effectiveness of a brief blended acceptance and commitment therapy (ACT) intervention for older adults with anxiety symptoms, compared with a face-to-face CBT intervention.

Methods: Adults aged between 55-75 years (n=314) with mild to moderately severe anxiety symptoms were recruited from general practices and cluster randomized to either blended ACT or face-to-face CBT. Assessments were performed at baseline (T0), posttreatment (T1), and at 6- and 12-month follow-ups (T2 and T3, respectively). The primary outcome was anxiety symptom severity (Generalized Anxiety Disorder-7). Secondary outcomes were positive mental health, depression symptom severity, functional impairment, presence of Diagnostic and Statistical Manual of Mental Disorders V anxiety disorders, and treatment satisfaction.

Results: Conditions did not differ significantly regarding changes in anxiety symptom severity during the study period (T0-T1: b=.18, p=.73; T1-T2: b=−.63, p=.26; T1-T3: b=−.33, p=.59). Large reductions in anxiety symptom severity (Cohen d≥0.96) were found in both conditions post treatment, and these were maintained at the 12-month follow-up. The rates of clinically significant changes in anxiety symptoms were also not different for the blended ACT group and CBT group ($\chi 2$1=0.2, p=.68). Regarding secondary outcomes, long-term effects on positive mental health were significantly stronger in the blended ACT group (b=.27, p=.03, Cohen d=0.29), and treatment satisfaction was significantly higher for blended ACT than CBT (b=3.19, p<.001, Cohen d=0.78). No other differences between the conditions were observed in the secondary outcomes.

Conclusions: The results show that blended ACT is a valuable treatment alternative to CBT for anxiety in later life.

Trial Registration: Netherlands Trial Register TRIAL NL6131 (NTR6270)

Introduction

Background

Anxiety is among the most common mental health problems in older adults, with prevalence estimates for anxiety disorders ranging up to 15% [10,11,90]. When also considering the presence of anxiety symptoms that do not meet the diagnostic criteria for a disorder (so-called subclinical or subthreshold anxiety), estimates range between 15% and 52% [10,90]. Both anxiety disorders and subclinical anxiety in older adults are associated with limited physical and social activities, impairments in self-care, decreased well-being, comorbid depressive symptomatology, somatic problems, and increased use of benzodiazepines [20,22,229]. Despite the repeatedly demonstrated negative impact of anxiety in later life, only a small proportion of anxious older adults receive adequate psychological help [31-33]. This treatment gap is worrying as untreated anxiety symptoms in older adults tend to be chronic and to aggravate over time [23].

The current scientific literature on psychological interventions for anxiety in later life is limited with regard to both the number of well-evaluated treatment approaches and the precise types of anxiety they target. The large majority of trials in anxious older adults have investigated face-to-face cognitive behavioral therapy (CBT) for Generalized Anxiety Disorder (GAD). In the most recent meta-analysis on CBT for anxiety disorders in older adults that concluded CBT to be an effective treatment, 7 of the 12 included studies focused on GAD [35]. In recent years, researchers' focus has shifted a little to web-based and blended CBT interventions as treatment for anxiety in later life. To date, studies in older adults with heterogeneous anxiety symptomatology have found web-based CBT modules combined with guidance from a clinician to be effective in reducing symptom severity [81-84]. These results are promising, as scalable (partly) web-based interventions might be invaluable in bridging the current treatment gap in a cost-effective way.

As CBT is the only treatment that has been systematically studied and most studies thus far confirm its effectiveness, many clinical guidelines refer to it as the preferred treatment for older adults with anxiety [38-40]. However, to move the field forward and improve treatment of anxiety in later life, alternative treatment options should also be evaluated, because in most studies with active control conditions, effect sizes favoring CBT were small [35], and some evidence suggests that older adults benefit less from CBT for anxiety than younger adults [35,41,160]. It has been

hypothesized that the cognitive aspects of challenging negative thoughts could be especially problematic for older adults [160]. Unfortunately, no high-quality studies on other treatment approaches have yet been published.

Acceptance and commitment therapy (ACT), a promising alternative to CBT, has been found to be effective in reducing anxiety symptoms in general adult samples, both in face-to-face and (partly) web-based formats [54,55]. Contrary to CBT, which focuses on re-evaluating cognitions and changing safety behavior and avoidance to achieve decreased levels of anxiety, ACT promotes acceptance-based emotion regulation and valued engagement in life [52]. ACT ultimately aims to increase psychological flexibility: the ability to fully and openly experience the present moment, including the negative aspects, and to behave in accordance with personal values [52]. It has been recognized as a treatment that explicitly aligns with the understanding of mental health as not only the absence of disease and illness but also the presence of the so-called positive mental health [230-232].

ACT might be especially suitable for older adults because its focus on stimulating acceptance and value-based action is consistent with age-related changes in emotion regulation and behavior. Reorientation on personal values and associated behavior change, present moment awareness, and willingness to experience and accept negative emotions have all been found to increase with age [59-61,233]. As some studies suggest that treatment is more effective when it draws upon a patient's strengths rather than remediating their shortcomings [62,63], ACT holds promise as a particularly suitable treatment approach for older adults. Another argument for ACT as a treatment option for anxiety in later life is its transdiagnostic focus on increasing psychological flexibility. Low levels of psychological flexibility have been related to both anxiety and depression symptoms [64], which often co-occur in older adults. Although ACT seems to be a promising treatment option for older adults with anxiety, so far only one pilot study that examined face-to-face ACT for late-life GAD has been published. None of the participants dropped out and worry and depression scores improved [50], leading the authors to conclude that ACT warrants a large-scale evaluation in anxious older adults.

Objectives

This trial aims to advance evidence-based treatment of anxiety in later life by evaluating the short- and long-term effectiveness of an ACT intervention in a large sample of older adults with anxiety symptoms. Specifically, we will evaluate a blended

ACT intervention, because scalable internet-based interventions could be crucial in bridging the treatment gap in anxious older adults and should therefore be thoroughly evaluated. Furthermore, the low-threshold nature and easy accessibility of internet-based interventions might be especially appealing to older adults, who are known to experience barriers in seeking and receiving regular psychological treatment [33]. The blended ACT intervention will be compared with a face-to-face CBT intervention, which can be considered treatment as usual in the study setting [38,234,235]. As the ACT approach aligns with age-related changes in emotion regulation and behavior, we expect the ACT intervention to be more effective than CBT. In addition to the effect on the primary outcome anxiety symptom severity, the effects of interventions on positive mental health, depressive symptoms, functional impairment, presence of anxiety disorders, and treatment satisfaction will be evaluated. As this study is the first large-scale trial into an ACT intervention for anxiety in later life, the results will offer valuable new insights into how the large and currently underserved group of older adults with anxiety symptoms can be treated.

Methods

Design

The study was registered in the Netherlands Trial Register (NL6131; NTR6270) and approved by the Medical Ethics Committee of Leiden University Medical Center (P16.248). A detailed description of the study protocol has been published [236]. The study was designed as a pragmatic, single-blind cluster, randomized controlled trial with measurements at baseline (T0) and follow-ups at 3, 6, and 12 months (T1, T2, T3, respectively) postbaseline. Randomization took place at the level of mental health counselors working in general practices, creating clusters of participants who received treatment from the same counselor. Power analysis showed that to detect a between-group difference on the Generalized Anxiety Disorder-7 (GAD-7) at posttreatment with a medium effect size (Cohen d=0.45), a 2-tailed α of .05, and a power of 0.80, posttreatment data of 180 participants were required. Anticipating a dropout rate of 25%, we aimed to include 240 participants (36 counselors) at baseline. The block-randomization table (blocks of 4) was created by an independent researcher using the R software [96] and was concealed from the main researcher. If 4 mental health counselors had registered for participation, the main researcher received their allocation from an independent researcher. After a mental health counselor was informed about

their randomization status and had received training in the treatment they were allocated to provide to study participants, recruitment of participants from the general practice that employed the counselor started. Research assistants (Master's students or graduates in clinical psychology) who conducted telephonic diagnostic interviews as part of the assessments were blinded to the participants' treatment assignments. The main researcher, mental health counselors, and participants were not blinded to treatment allocation. Study participants were not informed whether the intervention they received was the experimental or the active control condition. To prevent selection bias, potential participants were not informed about the randomization status of the mental health counselor in their general practice (i.e., the intervention they would receive if they participated in the study) until they had given their informed consent and completed the baseline assessment.

Study Setting: General Practices

The treatment was provided by mental health counselors working in general practices in the Netherlands. Since 2008, general practices in the Netherlands have employed mental health counselors in response to the increasing demand for psychological treatment and the limited capacity of mental health care institutions [234]. The counselors offer brief psychological interventions to patients with mild to moderately severe symptomatology in the easily accessible environment of general practices. General practices were recruited by sending information and invitation letters to practices in the networks of Leiden University and Leiden University Medical Centre. Furthermore, study information was distributed through messages in relevant newsletters and online forums. When a general practice agreed upon study participation, employees of the practice were asked to distribute the information among their professional networks. A total of 38 general practices were recruited. These practices were located in villages (n=10), towns (n=11), and cities (n=17) throughout the Netherlands, in 9 out of the 12 Dutch provinces. The practices employed a total of 40 mental health counselors, who were randomized to provide study participants with either blended ACT (n=20) or face-to-face CBT (n=20). In total, 36 practices employed one mental health counselor and 2 practices employed 2 counselors each. Regarding the counselors' educational background, most were psychologists (n=13), social psychiatric nurses (n=14), or social workers (n=5). Two counselors were trained as system therapists, and the other 6 had different educational backgrounds. The number of years of experience in providing individual psychological treatment ranged from 3 to 42, with a median of 16 years.

Participants

Individuals aged between 55-75 years with mild to moderately severe anxiety symptoms (GAD-7 between 5 and 15 [131]) were eligible for participation. Mastery of the Dutch language, internet access, and motivation to spend 2.5 h per week on the intervention were also required. Exclusion criteria were severe cognitive impairment or unstable severe medical conditions (according to the medical record at the general practice); very mild or severe anxiety symptoms (GAD-7 score 15 [131]); severe depressive symptomatology (Patient Health Questionnaire-9 [PHQ-9] score≥20 [170]), psychological or psychopharmacological treatment within the last 3 months, with the exception of stable benzodiazepine or selective serotonin reuptake inhibitor use; severe functional impairment (score≥8 on 2 or 3 Sheehan Disability Scale (SDS) domains [171]), high suicide risk (Mini-International Neuropsychiatric Interview Plus [M.I.N.I.-Plus]) [139]; substance use disorder (M.I.N.I.-Plus); lifetime diagnosis of bipolar disorder or schizophrenia (medical record or M.I.N.I.-Plus).

Procedure

Patients (aged between 55 and 75 years) from participating general practices were sent a letter containing information about anxiety symptoms, the aim and design of the study, and an invitation to participate. A data manager from the Leiden University Medical Center assisted general practitioners (GPs) in preparing and sending the letters in accordance with Dutch privacy legislation. Patients whose medical records mentioned a lifetime diagnosis of bipolar disorder or schizophrenia, severe unstable medical conditions, or severe cognitive impairment did not receive an invitation letter. GPs could also exclude patients from the mailing list for other reasons (e.g., social circumstances or language barriers) and had to give written approval of the final mailing list.

The information or invitation letters refer people to the study website for detailed information about the trial and to register for participation. After registration, they were screened using web-based questionnaires (assessing anxiety severity [GAD-7], depression severity [PHQ-9], mastery of Dutch, and motivation for treatment) and by a telephone interview (assessing medication use, functional impairment [SDS], and presence of psychiatric disorders [M.I.N.I.-Plus]). If excluded for the presence of severe symptomatology, people were referred to their GP to discuss other treatment options. Web-based informed consent was obtained from all eligible participants before

they completed the web-based baseline questionnaire. After this, the main researcher informed the included participants about the intervention they would receive and updated the general practice about the inclusion.

Participants completed 4 assessments (T0, T1, T2, and T3). Assessments mainly consisted of web-based self-report questionnaires. Assessments at T0, T1, and T3 were complemented by telephone interviews conducted by trained research assistants.

Treatments

Blended ACT

Participants in the blended ACT condition were given access to the web-based ACT-module *Living to the Full* and attended 4 face-to-face sessions with their mental health counselor at the general practice. The *Living to the Full* module consisted of 9 lessons to be completed in 9 to 12 weeks. This module (an adaptation of the similarly titled self-help book [179, 180]) was proven effective in reducing distress and depression in earlier studies [163,164]. The web-based module could be accessed using computers and mobile devices. To complete the lessons in time, the participants were required to spend 15 minutes to 30 minutes on the module each day. The module consisted of 3 phases, each comprising three lessons. In the first phase, participants explored the negative consequences of their attempts to control or reduce their unwanted feelings or thoughts and were introduced to the idea of shifting their attitude toward their internal experiences from controlling to accepting. The next 3 lessons provided them with tools to be more accepting of their (unwanted) internal experiences: exercises focused on noticing thoughts and feelings without judgment and conceptualizing the self as the consciousness that notices internal experiences, instead of the content of these experiences. The last phase of the module focused on identifying core values and taking the first step toward living in accordance with these.

The authors of *Living to the Full* developed a treatment protocol for the 4 face-to-face sessions with the mental health counselor at the general practice. In the first session, the participants' complaints were inventoried and a web-based program was introduced. After this session, the participants were emailed their log-in credentials and could access the web-based module. The subsequent 3 sessions each connected to one of the three phases in the module and served to repeat key exercises, increase motivation, evaluate progress, and discuss potential problems. Mental health counselors could monitor the progress of their clients in the web-based module: they could

see their answers to the exercises and the amount of time they spent on the module but could not provide web-based feedback.

Treatment-As-Usual: Face-to-face CBT

Participants in the treatment-as-usual group received a protocolized CBT intervention, consisting of 4 face-to-face sessions over a period of 9 to 12 weeks. In addition, participants were given homework exercises that required 15 to 30 min per day (i.e., a similar time investment as the blended ACT intervention). The treatment protocol was developed by NG, MW, VK, and PS. It consisted of a manual with twelve different worksheets containing psychoeducation and CBT exercises. The main worksheets focused on thinking errors and avoidance behaviors. Other worksheets addressed specific forms of anxiety (e.g., worrying, panic, social anxiety) or common consequences of anxiety (e.g., sleep disturbances, muscle tension). On the basis of the intake and goal formulation during the first session, counselors and participants agreed upon which worksheets to use. In the second and third sessions, the mental health counselor and participant discussed and repeated homework exercises, evaluated progress, and discussed potential problems, and the counselor aimed to increase the participants' motivation to continue with the intervention. The last session was dedicated to formulating a relapse prevention plan.

Mental health counselors in both conditions received a six-hour long in-person training on working with the treatment protocol for their allocated treatment.

Measures

Table 1 presents an overview of the instruments used per measurement moment. Anxiety symptom severity was assessed using the GAD-7 (total scores 0-21), with higher scores indicating higher symptom severity [131]. Positive mental health was measured using the Mental Health Continuum-Short Form (MHC-SF; total scores: (range 0-5) were obtained by averaging the sum scores of the 14 6-point items, with higher scores indicating higher levels of positive mental health [194]). Depressive symptoms were assessed using the PHQ-9 (total score 0-27; higher scores reflect higher symptom severity [170]). The SDS [171] assessed functional impairment in the domains of work, social life, and family life (scores in each domain range 0-10, higher scores reflecting more impairment). The presence of current GAD, panic disorder, agoraphobia, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and illness anxiety disorder according to DSM-V criteria

was assessed using the M.I.N.I.-Plus [139]. Treatment satisfaction was assessed using the Client Satisfaction Questionnaire-8 (total scores 0-32; higher scores indicate higher satisfaction [204]). To assess treatment integrity, mental health counselors, after every session, indicated how closely they had followed the treatment protocol on a checklist with all the elements the protocol prescribed for the sessions. Secondary outcomes not reported in this article were mindfulness, experiential avoidance, cognitive emotion regulation, medical costs, and quality of life. These outcomes will be used in subsequent moderator-, mediator-, and cost-effectiveness analyses.

Table 1. Instruments per measurement moment

	Screening	T0	T1 (3m)	T2 (6m)	T3 (12m)
Anxiety symptom severity (GAD-7)	x	x	x	x	x
Positive mental health (MHC-SF)		x	x	x	x
Depression symptom severity (PHQ-9)	x	x	x	x	x
Presence of psychiatric disorder(s)* (MINI-plus)	x	x	x		x
Functional impairment* (SDS)	x	x	x		x
Treatment satisfaction (CSQ-8)			x		

GAD-7=Generalized Anxiety Disorder – 7 ; PHQ-9 =Patient Health Questionnaire – 9; MHC-SF =Mental Health Continuum – Short form; SDS=Sheehan Disability Scale; CSQ-8=Client Satisfaction Questionnaire-8; MINI.=Mini International Neuropsychiatric Interview-Plus.

**assessed during telephone interviews by trained research assistants. Scores on these measures obtained during screening are analyzed as part of T0.*

Statistical Analyses

Statistical analyses were performed using the R software [96]. The differences between conditions over time on continuous outcomes were examined using linear mixed models. The time variable was recoded into three contrasts: T0-T1 (baseline to posttreatment), T1-T2 (posttreatment to 6-month follow-up), and T1-T3 (posttreatment to 12-month follow-up). Functional impairment was not assessed at T2; therefore, these analyses included two contrasts (T0-T1 and T1-T3). The condition variable was effect-coded (CBT=−0.5, ACT=0.5) to ensure that the coefficients for the time variables reflected true main effects. Time, condition, and their interaction were included as fixed effects. Random intercepts were included at the participant level and mental health counselor level. Random slopes for time were included for mental health counselors but not for participants, as this would result in more parameters than observations. Treatment satisfaction was only assessed at T1, so this model included no time effects

and only a random intercept at the counselor level. For this model, the condition was dummy coded (CBT=0, ACT=1).

Mixed effects logistic regression was used to examine if proportions of participants that changed from anxiety disorder to no anxiety disorder—and vice versa—differed between groups. A total of 4 separate models were created to examine the differences between the conditions at T1 and T3 for participants without an anxiety disorder. All mixed models were fitted to the data using maximum likelihood estimation. This method does not replace or impute missing values but uses all observed data to estimate the value of a population parameter by determining the value that maximizes the likelihood function [237].

Cohen d was used as the effect size for continuous outcomes and was calculated using mixed model estimated means and observed SD [238]. Cohen d values were interpreted as very small (<0.20), small (0.20-0.50), medium (0.50-0.80), or large (>0.80) [239]. Odds ratios were used as effect sizes for between-group differences on the binary outcome and were classified as small (1.49-3.45), medium (3.45-9), and large (>9) [52].

For participants with a GAD-7 posttreatment score, a reliable change index (RCI) was calculated by dividing the difference between baseline and posttreatment scores by the standard error of difference (SED) [240]. The test-retest reliability of the GAD-7 (0.83) was used to calculate the SED [131]. RCI values lower than −1.96 indicate reliable symptom improvement, and values over 1.96 denote deterioration [241]. Recovery was operationalized as a posttreatment score below the cut-off for moderately severe anxiety symptoms (GAD-7 < 10 [40]) for participants who scored above this cut-off at baseline. Participants with both reliable improvement and recovery met the criteria for clinically significant changes [241]. The proportions of participants with reliable improvement, deterioration, and clinically significant change in both groups were compared using the $\chi 2$ test.

In addition to intention-to-treat (ITT) analyses, per-protocol (PP) analyses were also conducted. For both groups, PP treatment was defined as attending 3 or 4 of the face-to-face sessions (75% or more of the allocated treatment).

Results

Participants

Figure 1 presents the flowchart of the participants. From November 2017 to March 2019, 35,820 invitation letters were sent. A total of 683 people were screened, of whom

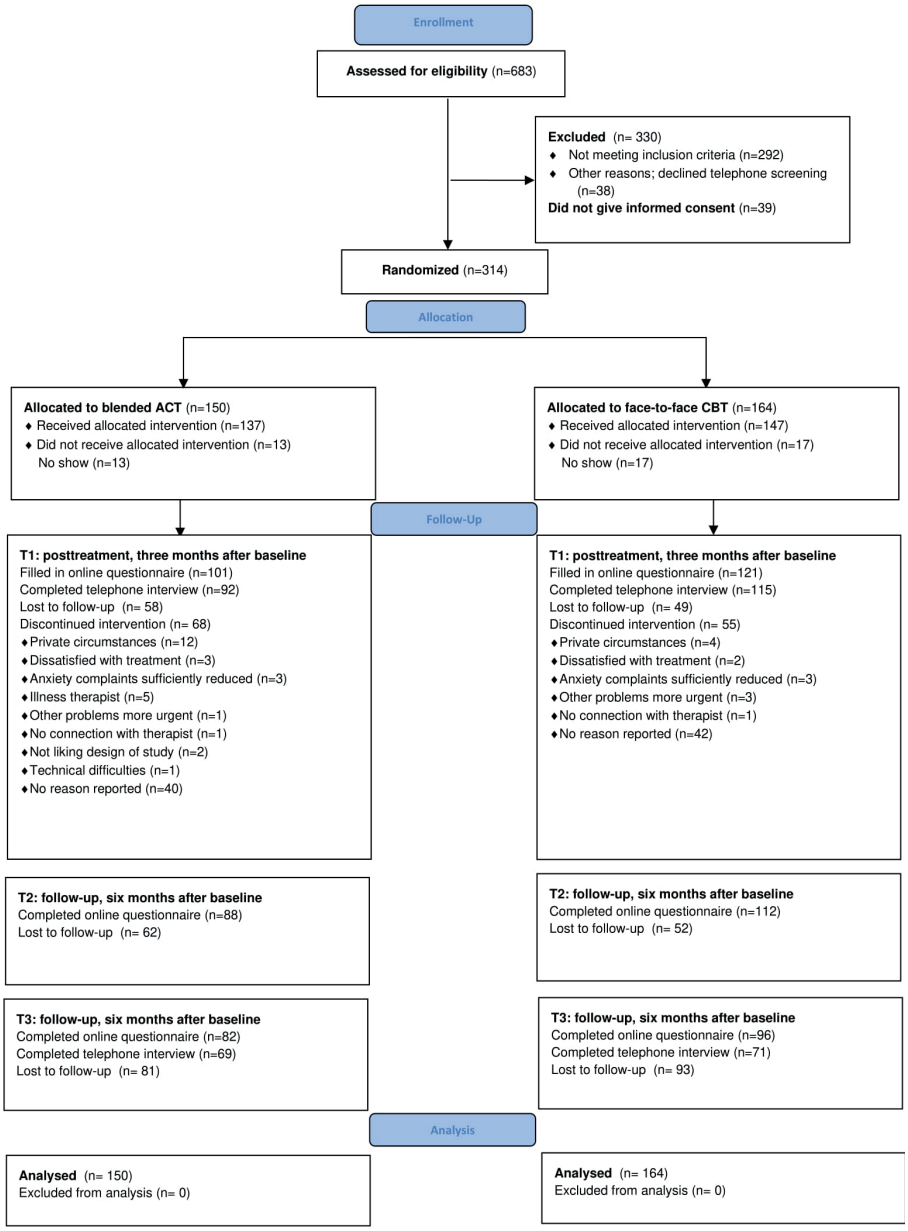

Figure 1. Flowchart of study participants

314 were included: 150 in the blended ACT group and 164 in the CBT group. Table 2 shows the demographic and clinical characteristics of the participants. A total of 13 participants in the ACT group and 17 in the CBT group did not start the treatment, as they did not show up for the first appointment and later indicated that they wanted to stop their participation or were not reachable by phone and email to discuss further participation. At T1, 70.7% (222/314) of the participants completed the web-based questionnaire (ACT 101/150, 67.3%, CBT 121/164, 73.8%); at T2, 63.7% (200/314; ACT 88/150, 58.6%, CBT 112/164, 68.3%), and at T3, 56.7% (178/314; ACT 82/150, 55%, CBT 96/164, 59%). Telephone interviews at T1 and T3 were completed by 66% (208/314; ACT 92/150, 61.3%, CBT 115/164, 70.1%) and 44.6% (140/314; ACT 69/150, 46.0%; CBT 71/164, 43.3%), respectively.

Table 2. Demographic characteristics of included participants at baseline

Characteristics	Blended ACT (*n*=150)	CBT (*n*=164)	Total sample (*n*=314)
Age (years), M (SD), [range]	62.75 (5.69) [55-75]	63.33 (5.71) [55-75]	63.06 (5.70) [55-75]
Sex, n (%)			
Female	100 (66.67)	92 (56.08)	192 (61.15)
Male	50 (33.33)	72 (43.92)	122 (38.85)
Nationality, n (%)			
Dutch	149 (99.33)	159 (96.96)	308 (98.01)
Dutch and other	0 (0.00)	5 (3.04)	5 (1.59)
Other	1 (0.77)	0 (0.00)	1 (0.40)
Education, n (%)			
Low	22 (14.67)	15 (9.15)	37 (11.78)
Middle	70 (44.67)	74 (45.12)	144 (45.86)
High	56 (37.33)	74 (45.12)	130 (41.40)
Unknown	2 (0.63)	1 (0.61)	3 (0.96)
Relational status, n (%)			
Married/in a romantic relationship	120 (80.00)	129 (78.66)	249 (79.30)
Not married/in a romantic relationship	30 (20.00)	35 (21.34)	65 (20.70)
Work status, n (%)			
Paid employment	77 (51.33)	76 (46.34)	153 (48.73)
Voluntary work	49 (32.67)	56 (34.15)	105 (33.44)
No work	53 (35.33)	59 (35.98)	112 (35.67)

Table 2. Continued

Characteristics	Blended ACT (*n*=150)	CBT (*n*=164)	Total sample (*n*=314)
Living situation, n (%)			
Alone	36 (24.00)	39 (23.78)	75 (23.89)
With partner	97 (64.67)	103 (62.80)	200 (63.69)
With children	11 (7.33)	13 (7.93)	24 (7.64)
With partner and children	6 (4.00)	8 (4.88)	14 (4.46)
Other	0 (0.00)	1 (0.61)	1 (0.32)
Community dwelling	150 (100)	164 (100)	314 (100)
Somatic comorbidity, n (%)			
No somatic problems	29 (19.33)	32 (19.51)	61 (19.43)
One or more somatic problems	121 (80.67)	132 (80.49)	253 (80.57)
Psychomedication use, n (%)			
SSRI	10 (6.67)	12 (7.32)	22 (7.01)
Benzodiazepine	19 (12.67)	15 (9.15)	34 (10.83)
No psychotropic medication	121 (80.67)	137 (83.54)	258 (82.17
Anxiety disorder, n (%)			
Panic disorder	10 (6.67)	7 (4.27)	17 (5.41)
Agoraphobia	5 (3.33)	5 (3.05)	10 (3.18)
Social phobia	5 (3.33)	8 (4.88)	13 (4.14)
Specific phobia	10 (6.67)	8 (4.88)	18 (5.73)
OCD	1 (0.67)	2 (1.22)	3 (0.96)
PTSD	2 (1.33)	1 (0.61)	3 (0.96)
Illness anxiety disorder	3 (2.00)	4 (2.44)	7 (2.23)
GAD	17 (11.33)	18 (10.98)	35 (11.15)
Any anxiety disorder	42 (28.00)	39 (23.78)	81 (25.80)
No anxiety disorder	108 (72.00)	125 (76.22)	233 (74.20)

Treatment Adherence and Study Dropout

Of the 314 participants, a total of 191 (60.8%) attended all 4 face-to-face sessions and 35 (11.1%) attended three sessions. Significantly more participants attended 3 or 4 sessions (i.e., received PP treatment) in the CBT group than in the ACT group (CBT: 126/164, 76.8%, ACT: 100/150, 66.7%, ($\chi^2(1)$=4.0, p=.045). A total of 41 participants reported their reason for dropping out of treatment (Figure 1). The proportion of participants who completed the T1 measurement did not differ between the groups ($\chi^2(1)$=1.6, p=.21). Baseline characteristics did not differ significantly between participants who completed

T1 and those who did not. Of the 222 participants who completed T1, 201 (90.5%) attended either three or four face-to-face sessions. There was no difference between the groups regarding the time participants at T1 reported to have spent on homework exercises or completing the web-based module ($F(1)$=1.24; p=.27).

Treatment Integrity

Mental health counselors in the ACT and CBT groups completed the treatment integrity checklist for 71.1% (315/443) and 82% (424/517) of the sessions, respectively. The ACT group indicated adherence to all the prescribed elements for 80% (252/315) of the sessions. For the CBT group, this was 85.8% (364/424) of the sessions.

Primary Outcomes

Tables 3 and 4 contain the results of the mixed models and the models' estimated mean scores. Figure 2 presents the estimated mean GAD-7 scores for all measurement moments for the 2 groups. Regardless of the condition, GAD-7 scores significantly decreased from T0 to T1 (b=−3.92, p<.001), increased significantly between T1 and T2 (b=.64, p=.02), and did not change significantly from T1 to T3 (b=−.23, p=.45). The within-group effect sizes for both conditions were large for the decreases from T0 to T1 (ACT: Cohen d=0.96; CBT: Cohen d=1.09) and small to very small for T1-T2 (ACT: Cohen d=0.10; CBT: Cohen d=0.28) and T1-T3 (ACT: Cohen d=0.11; CBT: Cohen d=0.02) changes. All time-by-condition interactions were statistically insignificant, indicating that changes in anxiety symptom severity over time did not differ between the groups.

Secondary Outcomes

The T1-T3 by condition interaction was significant for MHC-SF scores (b=.27, p=.03, Cohen d=0.29): from posttreatment to 12-month follow-up, MHC-SF scores decreased in the CBT group, whereas they increased in the ACT group. For the T0-T1 and T1-T2 intervals, no significant interactions with condition were found, but the significant main effects showed that positive mental health in both groups increased from baseline to posttreatment (b=.29, p<.001), and that these improvements were maintained at the month follow-up (b=.00, p=.99). Time-by-condition interactions for PHQ-9 depression and SDS functional impairment were statistically insignificant. Regardless of the

condition, depression severity decreased over time, as indicated by the significant main effects for all 3 time intervals. (T0-T1 b=−3.01, p<.001; T1-T2 b=−.65, p=.02; T1-T3 b=−.69, p=.04). Functional impairment in work (b=−1.87, p<.001), and family life (b=−1.93, p<.001) significantly decreased from baseline to posttreatment across groups. These decreases were maintained at the month follow-up (work: b=−.18, p=.57; social life: b=−.15, p=.59; family life: b=−.17, p=.51). In both conditions, within-group effect sizes for changes in the MHC-SF, PHQ-9, and SDS during the T0-T1 interval ranged from small to large; those for T1-T2 and T1-T3 were in the very small to small range.

Participants with anxiety disorders at baseline (n=81) had significantly higher baseline GAD-7 scores (M=10.07, SD=4.09) than participants without an anxiety disorder (M=1.95, SD=3.85; $F1$=16.72, p<.001). Among the participants with a baseline anxiety disorder, the odds of meeting the criteria for a disorder at T1 and T3 did not differ significantly between the conditions (T1: b=.38, p=.54; T3: b=−1.01, p=.35). The odds of participants without a baseline anxiety disorder meeting the criteria for a disorder at T1 and T3 were also not significantly different in the conditions (T1 b=1.28, p=.10; T3 b=.05, p=.94).

Treatment satisfaction was significantly higher in the ACT group than in the CBT group, and the effect size of the difference was large (b=3.19, p<.001, d=0.78). No adverse events were reported.

Improvement and Clinically Significant Change

The proportions of participants with reliable anxiety symptom improvement did not differ significantly between groups ($\chi^2(1)$=0.2, p=.66). In the ACT group, 43 of the 101 (42.6%) participants showed reliable improvement at T1. In the CBT group, this was the case for 48 of the 121 (39.7%) participants. In both groups, 2 participants deteriorated. In the ACT group, 22 of the 27 (81.5%) participants with an above-cut-off GAD-7 score at baseline showed clinically significant change, whereas in the CBT group, this was the case for 27 of the 35 (77.1%) participants. These proportions did not differ significantly ($\chi^2(1)$=0.2, p=.68).

PP Analyses

PP analyses included 226 participants (ACT: n=100; CBT: n=126). PP participants did not differ significantly from other participants in terms of baseline characteristics. PP analyses replicated all the findings from the ITT analyses.

Table 3. Mixed model analyses comparing the differences between the blended ACT- and CBT-group over time and between-group effect sizes

	b	SE	*t*	*p*	*d*
GAD-7					
T0-T1	-3.92	0.26	-15.01	<.001	
T1-T2	0.64	0.28	2.29	0.02	
T1-T3	-0.23	0.30	-0.78	0.45	
T0-T1* condition	0.18	0.52	0.35	0.73	0.02
T1-T2 * condition	-0.63	0.56	-1.13	0.26	0.15
T1-T3*condition	-0.33	0.60	-0.54	0.59	0.08
MHC-SF					
T0-T1	0.29	0.05	4.55	<.001	
T1-T2	0.00	0.06	0.01	0.99	
T1-T3	-0.06	0.06	-0.90	0.37	
T0-T1 * condition	-0.12	0.13	-0.94	0.36	0.06
T1-T2 * condition	0.03	0.12	0.24	0.82	0.03
T1-T3*condition	0.27	0.13	2.13	0.04	0.29
PHQ-9					
T0-T1	-3.01	0.26	-11.59	<.001	
T1-T2	-0.65	0.27	-2.37	0.02	
T1-T3	-0.69	0.33	-2.12	0.04	
T0-T1 * condition	0.31	0.52	0.59	0.56	0.03
T1-T2 * condition	-0.67	0.55	-1.21	0.23	0.16
T1-T3*condition	-0.53	0.66	-0.80	0.43	0.12
SDS work					
T0-T1	-1.87	0.27	-6.96	<.001	
T1-T3	-0.18	0.31	-0.58	0.57	
T0-T1 * condition	0.28	0.54	0.53	0.60	0.10
T1-T3*condition	0.64	0.62	1.03	0.31	0.23
SDS social life					
T0-T1	-1.78	0.26	-6.96	<.001	
T1-T3	-0.15	0.27	-0.55	0.59	
T0-T1 * condition	-0.18	0.51	-0.35	0.73	0.07
T1-T3*condition	0.08	0.55	0.15	0.88	0.03
SDS family life					
T0-T1	-1.93	0.22	-8.78	<.001	
T1-T3	-0.17	0.26	-0.66	0.51	
T0-T1 * condition	0.02	0.44	0.05	0.96	0.00
T1-T3*condition	-0.38	0.51	-0.74	0.46	0.11

Table 3. Continued

	b	SE	*t*	*p*	*d*
CSQ-8					
T1 Intercept	22.83	0.35	65.20	<.001	
T1 Condition	3.19	0.70	4.58	<.001	0.78
MINI-plus (for subgroup without anxiety disorder at baseline) *					
T1 Intercept	-3.47	0.96	-3.60	<.001	
T1 Condition	1.28	0.78	1.64	0.10	3.59
T3 Intercept	-2.38	0.47	-5.09	<.001	
T3 condition	0.05	0.70	0.07	0.941	1.05
MINI-plus (for subgroup with anxiety disorder at baseline) *					
T1 intercept	-1.34	0.46	-2.93	0.003	
T1 condition	0.38	0.62	0.61	0.54	1.46
T3 intercept	-1.39	0.79	-1.75	0.08	
T3 condition	-1.01	1.08	-0.94	0.35	2.75

Table 4. Mixed model estimated means for the outcomes and within-group effect sizes

	T0 [95% CI]	**T1 [95% CI]**	**T2 [95% CI]**	**T3 [95% CI]**	**ES T0-T1**	**ES T1-T2**	**ES T1-T3**
GAD-7							
Blended ACT	8.18 [7.49 – 8.88]	4.35 [3.59 – 5.12]	4.67 [3.86-5.49]	3.96 [3.09– 4.83]	0.96	0.10	0.11
CBT	8.78 [8.12 - 9.44]	4.76 [4.06– 5.47]	5.72 [4.99 – 6.45]	4.70 [3.89 – 5.50]	1.09	0.28	0.02
MHC-SF							
Blended ACT	2.73 [2.54-2.91]	2.96 [2.75 – 3.17]	2.98 [2.76 – 3.19]	3.04 [2.82 – 3.26]	0.24	0.02	0.09
CBT	2.57 [2.40-2.74]	2.92 [2.73-3.12]	2.91 [2.72-3.10]	2.73 [2.52-2.94]	0.38	0.01	0.20
PHQ-9							
Blended ACT	6.99 [6.28-7.71]	4.14 [3.30 – 5.00]	3.16 [2.35 – 3.97]	3.19 [2.31– 4.06]	0.70	0.26	0.27
CBT	7.92 [7.24-8.60]	4.76 [3.97- 5.55]	4.44 [3.71-5.18]	4.33 [3.52-5.14]	0.75	0.08	0.12
SDS work							
Blended ACT	3.52 [2.94-4.11]	1.80 [1.16-2.44]	-	1.94 [1.17-2.71]	0.67	-	0.06
CBT	3.76 [3.17-4.35]	1.75 [1.17-2.34]	-	1.25 [0.45-2.05]	0.82	-	0.24

Table 4. Continued

	T0 [95% CI]	T1 [95% CI]	T2 [95% CI]	T3 [95% CI]	ES T0-T1	ES T1-T2	ES T1-T3
SDS social life							
Blended ACT	4.02 [3.51-4.53]	2.16 [1.57-2.74]	-	2.05 [1.38-2.72]	0.75	-	0.04
CBT	4.08 [3.59-4.56]	2.39 [1.86-2.91]	-	2.20 [1.53-2.86]	0.63	-	0.07
SDS family/home							
Blended ACT	3.82 [3.30-4.33]	1.90 [1.34-2.45]	-	1.54 [0.84-2.23]	0.76	-	0.16
CBT	3.79 [3.30-4.28]	1.85 [1.35 – 2.35]	-	1.87 [1.19-2.55]	0.71	-	0.00
MINI-plus[1]							
Blended ACT	0	0.10 [0.02-0.30]	-	0.09 [0.03-0.21]	-	-	-
CBT	0	0.02 [0.00-0.17]	-	0.08 [0.03-0.19]	-	-	-
MINI-plus[2]			-				
Blended ACT	1	0.28 [0.14–0.46]		0.08 [0.02-0.28]	-	-	-
CBT	1	0.21 [0.10–0.39]	-	0.20 [0.05–0.54]	-	-	-

Note. GAD-7=Generalized Anxiety Disorder 7; PHQ-9=Patient Health Questionnaire 9; MHC-SF=Mental Health Continuum-Short Form; SDS=Sheehan Disability Scale; CSQ-8=Client Satisfaction Questionnaire 8.

[1] Probabilities of having an anxiety disorder for participants without anxiety disorder at baseline (n=233)

[2] Probabilities of having an anxiety disorder for participants with anxiety disorder at baseline (n=81)

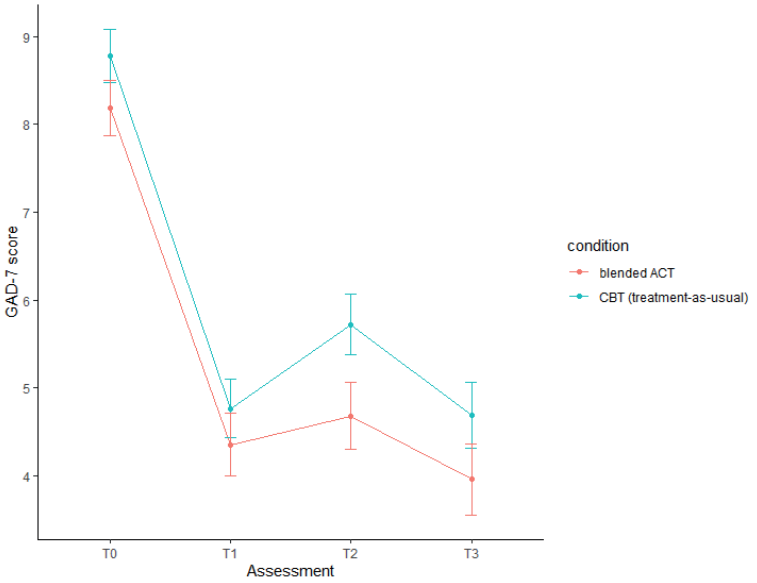

Figure 2. Mean GAD-7 scores at all assessments for both conditions

Discussion

This study evaluated the short- and long-term effectiveness of a blended ACT intervention for older adults with mild to moderately severe anxiety symptoms by comparing it with face-to-face CBT. Changes over time in anxiety symptom severity did not differ between the ACT group and CBT group. In both groups, anxiety scores significantly decreased from baseline to posttreatment, and the effect sizes for these decreases were large. At the 12-month follow-up, symptom reduction was maintained in both groups. Furthermore, rates of reliable improvement and clinically significant changes in anxiety symptoms did not differ between the groups. Analyses of secondary outcomes revealed two significant differences between the groups. First, improvements in positive mental health were better sustained in the long term in the ACT group. Second, treatment satisfaction was higher for the ACT intervention than for the CBT intervention. No other significant differences in secondary outcomes were found between the groups. Both groups showed significant improvements in depression severity, functional impairment, and positive mental status from baseline to posttreatment, which were mostly sustained or increased at follow-up. Finally, the proportion of participants who met the criteria for a DSM-V anxiety disorder at baseline

and no longer did so after treatment did not differ between the ACT group and CBT group.

This was the first large-scale trial to evaluate an ACT intervention for anxiety in later life, and the results therefore strongly contribute to the evidence-based treatment of this highly prevalent and undertreated problem. Overall, the results show that older adults with anxiety symptoms responded similarly to the blended ACT intervention and face-to-face CBT. The insignificant differences between the ACT group and CBT group regarding the majority of outcomes add to null findings from earlier studies comparing ACT and CBT in general adult samples with anxiety symptoms or disorders [243,244]. Therefore, studies thus far have indicated that for anxious adults within a wide age range, ACT and CBT interventions are equally effective. For a more thorough understanding of the (unique) clinical value of blended ACT and face-to-face CBT for anxiety in later life, in subsequent studies we will conduct a cost-effectiveness analysis, examine their working mechanisms (mediator analyses), and determine whether they differentially affect certain subgroups of patients (moderator analyses).

A significant difference between interventions was found for positive mental health: scores from posttreatment to 1-year follow-up decreased in the CBT group and slightly increased in the ACT group. Positive mental health is an important treatment outcome, as studies have shown that after correcting for psychopathology, low levels of positive mental health are associated with more somatic diseases, increased risk of developing a mental disorder, and decreased social and work-related functioning [244]. The significant interaction effect found in this study is in line with the fact that stimulating people toward value-based and engaged living is an explicit goal of ACT, whereas traditional CBT is primarily focused on alleviating psychopathology [230-232]. However, assuming that ACT directly targets positive mental health, it is unexpected that there was no difference in positive mental health between the groups directly after treatment. Furthermore, the p value for the interaction was just below the α level (p=.04), and the effect size was small (d=0.29). We should, therefore, be careful not to over-interpret this finding. Therefore, the main implication of this finding is that further research into the (long-term) effects of ACT and CBT on positive mental health is warranted.

We found that treatment satisfaction was significantly higher for the blended ACT intervention than for face-to-face CBT. A pilot study on ACT for older adults with anxiety and depressive symptoms found comparable satisfaction ratings [56]. These results suggest that ACT interventions constitute a positive treatment experience for older adults, which could be related to several aspects of the treatment that have been

theorized to be especially appealing to this age group [59]. However, these findings need to be interpreted with caution, as treatment satisfaction data were mainly derived from participants who attended all face-to-face sessions. As it is plausible that dropout was associated with lower treatment satisfaction and significantly more participants dropped out in the ACT group, the observed difference might, in part, be the result of selective attrition. We could not rule out this possibility because the data on reasons for dropout were incomplete.

This trial was designed to investigate the relative effectiveness of blended ACT and face-to-face CBT and does therefore not allow conclusions about the absolute effectiveness of the interventions. Still, the significant main effects of time and large within-group effect sizes for anxiety reduction from baseline to posttreatment suggest that both interventions succeeded in treating anxiety symptoms in this sample of older adults. Two earlier trials in anxious older adults found Cohen *d* values of 0.38 and 0.31 for anxiety symptom reduction (measured with the GAD-7) in waitlist conditions [81,82]. The pre-post within-group effect sizes of 0.96 (ACT) and 1.09 (CBT) in this study indicate that the symptom reduction in both conditions greatly surpassed improvements that could have been expected if participants had not received treatment.

The finding that the two brief, low-threshold interventions examined in this study were beneficial for a group that currently often goes untreated gives reason to be hopeful. However, to bridge the existing treatment gap, establishing the effectiveness of interventions for anxiety in later life will not suffice: efforts should also be made to increase the uptake of these interventions. In this light, it is promising that this study demonstrated a partial web-based intervention to be equally effective as face-to-face treatment, because scalable internet-based interventions might be crucial in bridging the treatment gap. As the proportion of older adults who successfully use the internet is steadily increasing [80], web-based psychological interventions seem feasible for this age group. However, it is important to note that studies have demonstrated socioeconomic disparities in internet use in older adults—higher education and income levels have been linked to more (successful) internet usage in later life [80]. This was also evident in the current trial, in which internet access and basic computer skills were required to participate: more than 85% of the participants had a middle or high level of education. Large-scale implementation of internet-based psychological interventions could therefore increase health inequalities by excluding older adults without internet access or skills from treatment [245]. To improve mental health care in an inclusive manner, studies into the effectiveness and acceptability of psychological interventions for older adults with lower socioeconomic status are needed.

This study has several limitations. First, treatment integrity was assessed suboptimally because it relied on therapists' self-reports. Second, of the 35,820 people who received the information letter, only 683 registered for study participation; this is a small number considering the high prevalence of anxiety in later life [10,11,90]. This group is likely to differ from the study population as a whole. For example, all participants were community-dwelling, 98% were of Dutch nationality, and most had middle to high education levels. The generalizability of the findings is also limited because the more severely (psychologically and/or physically) impaired older adults and those over the age of 75 years were excluded from participation. Finally, a considerable number of participants (although comparable with other studies on internet-based and low-threshold or low-intensity interventions in general [246,247]) dropped out before completing treatment, and only one-third of them reported their reason for dropout.

In conclusion, this study is an important advancement in the evidence-based treatment of anxiety in later life. We did not find differences between blended ACT and face-to-face CBT in their effects on anxiety symptom severity and several related clinical outcomes in a large sample of older adults. In both groups, anxiety symptoms improved significantly from baseline to posttreatment, and these improvements had large effect sizes. Regarding the long-term effects on positive mental health, ACT outperformed CBT. Therefore, these findings demonstrate that blended ACT is a valuable treatment alternative to CBT for anxiety in later life, providing patients and therapists with more flexibility in deciding on the preferred intervention with regard to both treatment approach and delivery format. We will follow up this study with examinations of the cost-effectiveness, treatment mediators, and moderators of blended ACT versus CBT. Furthermore, we recommend future research to go beyond the evaluation of psychological interventions for older adults with anxiety symptoms and to focus on increasing treatment uptake in this group.

5

COST-EFFECTIVENESS AND COST-UTILITY OF AN ACCEPTANCE AND COMMITMENT THERAPY INTERVENTION VS. A COGNITIVE BEHAVIORAL THERAPY INTERVENTION FOR OLDER ADULTS WITH ANXIETY SYMPTOMS: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: A previous randomized controlled trial in older adults with anxiety symptoms found no differences between a brief blended Acceptance and Commitment Therapy (ACT) intervention and brief face-to-face Cognitive Behavioral Therapy (CBT) regarding anxiety symptom severity at posttreatment and 12-month follow-up. A health-economic evaluation comparing these interventions has not yet been conducted.

Objective: This study examined the one-year cost-effectiveness and cost-utility of blended ACT compared to face-to-face CBT for older adults with anxiety symptoms.

Methods: The economic evaluation was embedded in a randomized controlled trial comparing blended ACT to CBT in 314 older adults with mild to moderately severe anxiety symptoms. Data were collected at baseline and 3, 6 and 12 months post baseline. For the cost-effectiveness analysis, treatment response was defined as a reliable improvement in anxiety symptom severity (measured with the Generalized Anxiety Disorder-7) between baseline and 12-month follow-up. To assess cost-utility, quality-adjusted life years (QALYs) were computed using EuroQol-5 Dimensions-5 Levels-5 utility scores. Analyses took the societal perspective, including both healthcare costs and productivity costs. Incremental cost-effectiveness ratios were calculated using 2500 bootstraps of seemingly unrelated regression equations of costs and effects. Sensitivity analyses were performed to assess the robustness of the findings.

Results: Differences between the blended ACT group and CBT group in treatment response and QALYs were statistically insignificant and clinically irrelevant. The ACT intervention was associated with an average per-participant cost reduction of €466 ($593) compared to CBT, which resulted from lower productivity costs in the blended ACT group. From a healthcare perspective, the ACT intervention was associated with higher costs (by €71 ($90)) than CBT.

Conclusions: The results do not indicate that from a health-economic perspective blended ACT should be preferred over CBT in the treatment of older adults with anxiety symptoms. The findings support a model of shared decision making, where clinicians and patients collaboratively decide on the preferred intervention, based on ethical-medical, practical and personal considerations.

Introduction

Anxiety symptoms are the most prevalent mental health problem in older adults (55 years and over) and have an adverse impact on subjective well-being, quality of life, physical health and everyday functioning [10,11,20,22,229]. In addition, anxiety symptoms are associated with increased costs stemming from healthcare utilization and productivity losses [248,249]. Reducing the personal and societal burden of anxiety in later life should therefore be a public health priority, especially in light of the unprecedented growth of the proportion of older adults worldwide that will confront mental health care institutions with an increasing number of older patients [1]. To advance the evidence-based treatment of anxiety in later life, psychological interventions should be rigorously evaluated in older study samples.

So far, most trials in anxious older adults have focused on face-to-face cognitive behavioral therapy (CBT) [35] and multiple clinical guidelines refer to CBT as the preferred treatment option for older adults with anxiety symptoms [38-40]. Recently, studies have indicated that online and blended CBT interventions are also effective at reducing anxiety symptom severity in older adults, which is promising as scalable internet-based interventions are likely to become crucial in providing this large patient population with adequate psychological treatment [81-84]. Although clinical trials so far confirm the effectiveness of CBT interventions for anxiety in later life, it is important to also examine other treatment approaches for anxious older adults. First, when compared to active control conditions, effect sizes favoring CBT are small in samples of older adults with anxiety symptoms and/or disorders [41]. Furthermore, some evidence suggests that CBT is less effective in older adults than in younger samples [41,160].

A promising treatment alternative is Acceptance and Commitment Therapy (ACT), a so called third-wave cognitive behavioral therapy. ACT is a transdiagnostic treatment that focuses on increasing acceptance-based emotion regulation and the identification and prioritization of intrinsic values and related behavior change [52]. The main goal of ACT is not to merely reduce psychological symptoms, but rather to stimulate people to start living a more meaningful, fulfilling life. ACT might be especially suitable for older patient populations because it aligns with age-related tendencies to be more accepting towards (negative) emotions and reevaluate personal values [61,233].

The present study evaluates the cost-effectiveness and cost-utility of a brief blended ACT intervention (a combination of an online self-help module with face-to-face sessions with a mental health counselor) compared to brief face-to-face CBT for older adults with anxiety symptoms. The cost-effectiveness analysis (CEA) presents effects

in terms of treatment response (i.e., long-term anxiety symptom improvement) and the cost-utility analysis (CUA) in terms of quality adjusted life years (QALYs). This health economic evaluation was embedded in a randomized controlled trial (RCT) that found no difference between these two interventions regarding anxiety symptom improvement at posttreatment and 12-month follow-up. On a within-group level, participants in both conditions showed significant reductions in anxiety symptom severity from baseline to posttreatment that were sustained at the 6- and 12-month follow-ups [250]. This RCT was the first large-scale study to evaluate an ACT intervention for older adults with anxiety symptoms. The results are promising and suggest that blended ACT is at par with CBT.

The cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) in the current study can add valuable insights into the comparative effects of blended ACT and CBT for older adults with anxiety symptoms. First, as the cost-utility analysis considers treatment effects in terms of quality of life, this study provides insight into the broader, transdiagnostic effects of the interventions. Second, the analyses will shed light on how the two interventions affect healthcare utilization and work productivity. Lastly, the integration of data on treatment effects and associated costs may inform policy making as it could indicate if the ACT intervention is likely to achieve its effects at similar or lower societal costs than CBT, which is currently the gold standard treatment for anxiety in later life [9-12]. This study will be the first health-economic evaluation of an ACT intervention for older adults. Furthermore, to the best of our knowledge, it will also be the first such evaluation of ACT compared to CBT in any patient population.

Methods

Research Design

The health-economic evaluation was embedded in a study into the effectiveness of a brief blended ACT intervention compared to brief face-to-face CBT for older adults with anxiety symptoms. This study was a pragmatic cluster-randomized, controlled, single-blind trial, comparing the relative merits of both interventions over a period of 12 months.

Randomization took place at the level of mental health counselors working at general practitioner's (also sometimes called primary care physician) offices. This created clusters of participants that all received the same treatment from the same counselor.

Assuming a mean cluster size of 5 participants per mental health counselor at posttreatment, an intraclass correlation of 0.01 and a coefficient of variation of 0.30, 18 mental health counselors (or 90 participants) were required in each of the two study arms to detect a between-group difference on the Generalized Anxiety Disorder-7 (GAD-7) at posttreatment with a medium effect size (Cohen *d*=0.45), a 2-tailed α of .05, and a power of 0.80 [236]. Anticipating a dropout rate of 25%, we aimed to include 240 participants at baseline.

Participating mental health counselors were randomized to either blended ACT or face-to-face CBT using a block-randomization table (blocks of four) that was created by an independent researcher. This table was concealed from the other researchers. The randomization table was created by randomizing the 6 different possible sequences of two conditions in blocks of 4.

Each time 4 new mental health counselors had registered for participation, the independent researcher informed the main researcher about the randomization allocation of these 4 counselors (N.B., the main researcher received the allocation status of the 4 counselors in a block at the same time. If randomization status would have been disclosed separately for each new counselor that registered for participation, the main researcher would have been able to predict the status of each third and or/ fourth counselor within a block). Consequently, the main researcher contacted the counselors to inform them about their allocation.

The main researcher, mental health counselors, and participants were not blind for treatment allocation. However, participants were not informed about whether the intervention they were provided with was the experimental condition (blended ACT) or active control condition (CBT).

The study was registered in the Netherlands Trial Register (NL6131) and approved by the medical ethics committee of Leiden University Medical Center (LUMC; P16.248). The study protocol that describes the methods in detail has been published elsewhere [236].

Participants and procedure

From November 2017 to March 2019 participants were recruited in 38 general practices located in the Netherlands (the last 12-month follow-up assessment was completed in March 2020). The practices employed (one or more) mental health counselor(s) that provided treatment to the study participants. Patients aged 55-75 years from the participating general practices were sent an information and invitation letter and could

register for participation on a study website, after which they entered a screening procedure consisting of both self-report online questionnaires and a telephone interview conducted by trained research assistants. The following inclusion criteria were used: age 55–75 years, presence of mild to moderately severe anxiety symptoms as measured with the Generalized Anxiety Disorder-7 (GAD-7; scores between 5 and 15 [131]); mastery of the Dutch language, internet access and motivation to spend 2.5 hours per week on the intervention. Exclusion criteria were: severe cognitive impairment or unstable severe medical condition(s); very mild or severe anxiety symptoms ((GAD-7) score $< 5 / > 15$ [131]); severe depressive symptomatology (Patient Health Questionnaire-9 (PHQ-9) score $\geq$ 20 ([170]); psychological or psychopharmacological treatment within the last 3 months, with the exception of stable benzodiazepine or SSRI use (assessed during the telephone interview); severe functional impairment (score $\geq$8 on 2 or 3 Sheehan Disability Scale (SDS) domains [171]; assessed during the telephone interview); high suicide risk (M.I.N.I.-Plus [139]); substance use disorder (M.I.N.I.-Plus; assessed during the telephone interview); lifetime diagnosis of bipolar disorder or schizophrenia (medical record or M.I.N.I.-Plus (conducted during telephone interview).

Eligible participants were informed about their treatment allocation by the main researcher after they had given online informed consent and completed the baseline assessment. Participants completed 4 main assessments: baseline (T0), posttreatment (T1; 3 months after baseline), 6 months after baseline (T2) and 12 months after baseline (T3). These assessments consisted predominantly of online self-report questionnaires. T0, T1 and T3 additionally included a telephone interview, conducted by trained and supervised research assistants that were blind to randomization status of the participants.

Interventions

Blended Acceptance and Commitment Therapy

Participants in the blended ACT condition received a combination of 4 face-to-face sessions with the mental health counselor at their general practice and internet self-help in the form of the online module “Living to the Full” [180], which was proven to be effective in reducing psychological distress in adults [163,164]. The module is comprised of 9 lessons that revolve around the 6 core processes of ACT: acceptance, cognitive defusion, contact with the present moment, self-as-context, values and committed action. Completing the lessons in time required the participants to spend 15 to 30 minutes on the module each day. During the face-to-face sessions (which lasted 30 to 40 minutes), the mental health counselors followed a treatment protocol that was

developed by the authors of “Living to the Full”. The intervention was delivered in a period of 9 to 12 weeks (e.g., the allowed period between the first and last face-to-face session was nine to twelve weeks).

Brief face-to-face Cognitive Behavioral Therapy

Participants received protocolized CBT, consisting of 4 face-to-face sessions (30 to 40 minutes; period between first and last session ranged between 9 and 12 weeks) and homework exercises that required between 15 and 30 minutes on a daily basis. The protocol contained 12 different worksheets that mainly focused on identifying thinking errors and reducing anxiety-related avoidance behavior. Most of the worksheets were focused on specific types of anxiety (panic, worrying, social anxiety). Some focused on common side effects of anxiety (sleeping problems, physical tension). After the intake session, the counselor and participant set treatment goals and homework exercises were planned and prepared. In the second and third session, homework exercises were evaluated and key exercises/information repeated. The last session was dedicated to evaluating progress and formulating a relapse prevention plan.

Therapists

Treatment was provided by 40 mental health counselors working at general practices, who were randomized to either provide participants with blended ACT (n=20) or with CBT (n=20). Since approximately 2008, general practices in the Netherlands have employed mental health counselors that provide treatment to patients with mild to moderately severe psychological problems, preventing these patients from being referred to (specialized) mental health care institutions, which often have long waiting lists [234]. This position is fulfilled by mental health professionals from diverse educational and professional backgrounds. In the current study, most counselors were psychologists (n=13), social psychiatric nurses (n=14) or social workers (n=5). Mental health counselors received a 6 hour in-person training in working with the treatment protocol for the treatment they were allocated.

Outcome Measures

Cost-effectiveness: Treatment response

Health benefit in the CEA was measured in terms of anxiety symptom improvement over 12 months.

Anxiety symptom severity was measured with the GAD-7, a widely used 7-item anxiety screener with well-established psychometric qualities (total scores 0-21, higher scores indicating greater symptom severity)[131]. For the CEA, long-term treatment response was operationalized as reliable improvement of anxiety symptom severity between baseline and the 12-month follow-up. For each participant, a so-called reliable change index (RCI) was computed by dividing the difference between GAD-7 scores at baseline and 12-month follow-up by the standard error of difference (the error variance in a set of scores resulting from the unreliability of the used scale) [240]. RCIs lower than -1.96 indicate reliable symptom improvement [241]. Using the RCIs, we created the final binary treatment response variable (0=no treatment response (i.e., RCI > -1.96); 1=treatment response (i.e., RCI < -1.96)).

Cost-utility: Quality of life

For the CUA, QALYs were computed from participants' responses on the 5-level EQ-5D (EQ-5D-5L) questionnaire [197] at baseline and 3-, 6- and 12-month follow-up. The EQ-5D-5L assesses self-reported quality of life at the day of assessment using 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Severity of problems in each domain can be scored from 1 to 5. A total of 3125 unique health states can be defined, by combining the responses for the five domains into a 5-digit number (ranging from '11111' meaning no problems at all to '55555' meaning extreme problems in all five dimensions) [187]. These 5-digit numbers can be translated into preference-based utility scores (using the Dutch social tariff [198]), anchored between 0 (health state equivalent to being dead) and 1 (full health). The utility scores at the 4 measurement points were then used to calculate QALY gains using the area under the curve method, which assumes that change in the utility scores occurs linearly in the periods between the assessments. This method weighs the 12-month study period according to the utility scores at each measurement point.

Costs

For each participant, healthcare costs and costs stemming from productivity losses over the preceding 4 weeks were collected at baseline and 6- and 12-month follow-up with the Trimbos Institute and Institute of Medical Technology Assessment Questionnaire for Costs Associated with Psychiatric Illness (TiC-P) [202]. Appendix 1 lists all the assessed health care services. For each service, participants indicated if they had used it during the preceding four weeks, and if so, how many times they

used it. They were also asked how many days they had used prescribed medication for depression, anxiety, pain and sleeping problems. To assess productivity losses, both absenteeism ("How many days did you not work due to health problems") and presenteeism ("How many days did you work while not feeling well?") were assessed in relation to paid work, voluntary work and informal care. The TiC-P is the most widely used health service receipt interview in the Netherlands and its reliability in assessing information on health care utilization and productivity losses in patients with mild to moderate mental health conditions has been established [203]. Cumulative costs over the total 12-month study period were calculated using interpolation, assuming a linear trend in costs during the periods between the measurement points.

Direct medical costs (healthcare utilization)

Costs associated with healthcare utilization were computed by multiplying health service units (e.g., visits, consults) with their standard unit cost price [251] according to the Dutch manual for economic evaluations in healthcare (see Appendix 1). Standard unit cost prices reported in this manual were calculated using various sources, including bottom-up micro costing studies, and top-down studies using information from national databases [251]. Medication costs were calculated as the average cost price per standard daily dose (using prices of the 5 most frequently prescribed medications in each of the 4 categories), as reported in the Dutch Pharmaceutical Compass [252], multiplied by the number of prescription days, plus pharmacists' dispensing costs per monthly prescription.

Direct non-medical costs (travel costs)

Travel costs incurred in the context of visiting health services were calculated as the average distance of a return-trip to and from a health service (according to the Dutch manual for economic evaluations in healthcare [251]) multiplied by the costs per kilometer (€0.19; as stated in the same manual [38]) (See Appendix 2).

Indirect costs (productivity losses)

Productivity losses at paid work, voluntary work and informal care due to absenteeism and presenteeism were assessed. Productivity loss due to presenteeism was computed by multiplying the number of workhours for which the participant reported reduced productivity with a fraction reflecting the reported level of inefficiency during those hours. Total costs due to productivity losses were calculated by multiplying the

amount of work hours lost by the standard economic cost prices for paid work (€37.11) and unpaid work (€14.95) as reported in the Dutch manual for economic evaluations in healthcare [251] (see Appendix 1).

Intervention costs

Participants in both conditions had 4 sessions with the mental health counselor (total costs €73). The additional per-participant costs of the online ACT module were €49, based on the market price of the module as determined by the current provider.

Statistical Analysis

Analyses were conducted using R statistical Software [96] and Stata, version 13.1 [253].

Imputation

All analyses followed the intention-to-treat principle, which required imputing missing values. Missing data were imputed using multiply imputed chained equations (MICE), with the predictive mean matching procedure, where the missing outcome for a non-respondent (so called '*recipient*') is imputed with the observed outcome from a respondent ('*donor*') with a comparable predicted mean outcome [237]. This procedure ensures that the imputed data have plausible values. In the current study this meant that imputed costs were not negative and imputed utility scores fell between 0 and 1. We included the following baseline variables into the imputation, because they were predictive of missingness and/or associated with the outcome variable(s): sex, education level, age, depression symptom severity, presence of DSM-V anxiety disorder.

Cost-effectiveness and cost-utility analyses

To examine between-group differences in treatment response, we calculated a risk difference using a linear probability model that accounted for the clustered structure of the data (i.e., clusters of participants receiving treatment from the same therapist). Cumulative QALY gains and costs in both conditions were compared using linear regression, also accounting for the clustering in the data. We do not report a p value for the between-group costs differences, because cost data usually have a high variance and therefore require very large sample sizes to detect a statistically significant difference, for which this trial was not powered. Costs in euros were converted to US dollars using purchasing power parities (PPP) as reported by the Organisation for Economic Co-operation and Development (OECD) for the reference year 2019 [254].

PPPs take into account both the currency exchange rate and the differences in buying power between the two countries in that year.

The CEA and CUA were conducted from the societal perspective, which means that both medical costs and costs stemming from productivity losses were included in the cost calculations. In both analyses, incremental cost-effectiveness ratios (ICERs) were calculated as the between-group cost difference divided by the between-group effect difference. The ICER reflects the additional costs associated with blended ACT per additional unit of effect gained. Cost- and effect differences between the conditions were obtained simultaneously from seemingly unrelated regression equations (which allows the residuals of the two equations to be correlated, thereby producing more efficient estimates). To capture the stochastic uncertainty in the ICERs due to sample error, the seemingly unrelated regression equations models were bootstrapped 2500 times and the mean ICER of each bootstrap step was plotted on a cost-effectiveness plane. This produces estimates of the probability that 1) compared to CBT, blended ACT results in better health for more costs (northeast quadrant); 2) blended ACT is dominated by CBT because it is associated with less health gains and higher costs (northwest quadrant); 3) compared to CBT, blended ACT produces less health gains for lower costs (southwest quadrant); 4) blended ACT is the dominant intervention, because compared to CBT better outcomes for lower costs are obtained (southeast quadrant). Besides the arrhythmic means of the bootstrapped cost-differences and effect-differences, the median cost- and effect differences were also calculated to better reflect that the underlying cost and effect data may not be normally distributed.

Acceptability curves were created to visualize the probability that blended ACT is cost-effective compared to CBT, for a range of willingness-to-pay (WTP) thresholds per gained health unit. As there are no established willingness-to-pay ceilings available for the outcome in the CEA, curves were only created for the CUA. Research in the Netherlands has showed that people are willing to pay €53,000/QALY for another person, which rises to €83,000/QALY if it concerns themselves or a relative. Therefore, we used threshold values of €50,000 and €80,000 per QALY [255].

To test the robustness of the results, we conducted three sensitivity analyses. First, we repeated the analyses on a dataset imputed with the expectation maximization (EM) method, to assess the influence of imputation method on the results. Second, we conducted per-protocol analyses, in which we only included participants that attended either 3 or 4 face-to-face sessions (ACT n=100, CBT n=126). Lastly, we performed a cost-effectiveness and cost-utility analysis from a healthcare perspective, which only included healthcare costs.

Results

A total of 40 mental health counselors participated in the study and were randomized to provide participants with either blended ACT (n=20) or face-to-face CBT (n=20). Mean cluster size (i.e., average number of participants treated by the same mental health counselor) at baseline was 7.85 (*SD*=4.28, range 0-18). At posttreatment, mean cluster size was 5.55 (*SD*=2.91 range 0-11).

A total of 314 participants gave informed consent and completed the baseline assessment: 150 were allocated to blended ACT condition, 164 to CBT. The difference in sample size between the two conditions stems from the cluster-randomized design; fourteen more participants were recruited from the general practices that employed mental health counselors who were randomized to the face-to-face CBT condition. Table 1 presents baseline demographic and clinical characteristics for the participants in the two conditions and the total study sample. We did not observe any clinically relevant differences between the conditions at baseline, suggesting that there was no baseline imbalance between the conditions. At first follow-up, T1, 71% (n=222) of the participants completed the assessment (ACT 67%, CBT 74%); at T2, 64% (n=200; ACT 59%, CBT 68%), and at T3, 57% (n=178; ACT 55%, CBT 59%). The proportion of participants who did not complete one or more of the follow-up assessments did not differ between the conditions ($\chi^2(1)$= 1.2, p=.27). Loss to follow-up was associated with gender: 55.74% of male participants did not complete one or more assessments, compared to 44.27% of female participants ($\chi^2(1)$=3.9, p= .048). No adverse events were reported by any of the participants.

Table 1. Baseline characteristics of study sample

Characteristics	Blended ACT (*n*=150)	CBT (*n*=164)	Total sample (*n*=314)
Age (years), M (SD), [range]	62.75 (5.69) [55-75]	63.33 (5.71) [55-75]	63.06 (5.70) [55-75]
Sex, n (%)			
Female	100 (66.67)	92 (56.08)	192 (61.15)
Male	50 (33.33)	72 (43.92)	122 (38.85)
Nationality, n (%)			
Dutch	149 (99.33)	159 (96.96)	308 (98.01)
Dutch and other	0 (0.00)	5 (3.04)	5 (1.59)
Other	1 (0.77)	0 (0.00)	1 (0.40)
Education[a], n (%)			
Low	22 (14.67)	15 (9.15)	37 (11.78)
Middle	70 (44.67)	74 (45.12)	144 (45.86)
High	56 (37.33)	74 (45.12)	130 (41.40)
Unknown	2 (0.63)	1 (0.61)	3 (0.96)

Table 1. Continued

Characteristics	Blended ACT (*n*=150)	CBT (*n*=164)	Total sample (*n*=314)
Relational status, n (%)			
Married/in a romantic relationship	120 (80.00)	129 (78.66)	249 (79.30)
Not married/in a romantic relationship	30 (20.00)	35 (21.34)	65 (20.70)
Work status, n (%)			
Paid employment	77 (51.33)	76 (46.34)	153 (48.73)
Voluntary work	49 (32.67)	56 (34.15)	105 (33.44)
No work	53 (35.33)	59 (35.98)	112 (35.67)
Living situation, n (%)			
Alone	36 (24.00)	39 (23.78)	75 (23.89)
With partner	97 (64.67)	103 (62.80)	200 (63.69)
With children	11 (7.33)	13 (7.93)	24 (7.64)
With partner and children	6 (4.00)	8 (4.88)	14 (4.46)
Other	0 (0.00)	1 (0.61)	1 (0.32)
Community dwelling	150 (100)	164 (100)	314 (100)
Somatic comorbidity, n (%)			
No somatic problems	29 (19.33)	32 (19.51)	61 (19.43)
One or more somatic problems	121 (80.67)	132 (80.49)	253 (80.57)
Medication use, n (%)			
Antidepressants	15 (9.15)	12 (8.00)	27 (8.60)
Anxiolytics	12 (7.32)	19 (12,67)	31 (9.87)
Sleeping medication	23 (14.02)	17 (11.33)	40 (12.74)
Pain medication	21 (12.80)	17 (11.33)	38 (12.10)
Anxiety disorder[b], n (%)			
Any anxiety disorder	42 (28.00)	39 (23.78)	81 (25.80)
No anxiety disorder	108 (72.00)	125 (76.22)	233 (74.20)

Note. [a] High education level includes completed higher vocational education or university education. Middle education level includes a completed secondary school or intermediate vocational education. Low education level includes completion of primary school and/or secondary school. [b] Anxiety disorder diagnoses were established with the M.I.N.I.-PLUS during a telephone diagnostic interview conducted by trained research assistants.

Effects and costs

In Appendix 4, reported units of healthcare utilization and reported days of absenteeism and presenteeism are presented. Table 2 contains the mean healthcare-, productivity- and total societal costs and mean anxiety symptom severity and utility values at the different measurement points for both treatment conditions.

Table 2. Mean costs and outcomes by condition over assessments

Costs and outcomes	Baseline		Posttreatment (3 months)		Follow-up (6 months)		Follow-up (12 months)	
	ACT	CBT	ACT	CBT	ACT	CBT	ACT	CBT
Costs, mean (SD)								
Healthcare costs	€100 (186)	€88 (123)	-	-	€92 (169)	€106 (136)	€108 (225)	€87 (129)
Productivity costs	€106 (256)	€179 (483)	-	-	€69 (197)	€125 (503)	€134 (470)	€130 719)
Total societal costs	€206 (329)	€267 (502)	-	-	€161(277)	€231 (526)	€242 (520)	€218 765)
Outcomes, mean (SD)								
Anxiety symptom severity	8.2 (4.1)	8.8 (4.2)	4.3 (3.7)	4.5 (3.5)	4.8 (3.2)	5.7 (3.6)	4.5 (4.0)	4.8 (3.6)
Utility value	.75 (.15)	.75 (.16)	.79 (.20)	.78 (.20)	.82 (.14)	.81 (.15)	.82 (16)	.81 (15)

Note. Costs were measured with the Trimbos Institute and Institute of Medical Technology Assessment Questionnaire for Costs Associated with Psychiatric Illness (TiC-P), on which participants reported their healthcare utilization and work productivity losses during the four weeks prior to the assessment. Anxiety symptom severity was measured with the Generalized Anxiety Disorder-7, a self-report measure that assesses anxiety symptoms during the preceding two weeks (range 0 – 21). Utility values were assessed with the EQ-5D-5L, which measures self-reported quality of life at the day of assessment.

Treatment response

In the blended ACT group 54 out of 150 (36%) participants were considered treatment responders, as they showed reliable improvement of anxiety symptoms between baseline and the 12-month follow-up. In the CBT group this was the case for 70 out of 164 (43%) participants. The between-group risk difference (i.e., the incremental effect) was 0.36 – 0.43= -0.07 [95% CI: -0.17 to 0.04], which was not statistically significant (*SE*=0.06, *z*=1.13, *p* =.26).

Quality of life

Average quality of life utility values in the blended ACT group were .75 at baseline, .79 at 3-month follow-up, .81 6-month follow-up and .82 at 12-month follow-up. In the CBT group average scores were .75 at baseline, .78 at 3-month follow-up, .81 at 6-month follow-up and .81 at 12-month follow-up. This shows that health-related quality of life increased over time in both conditions. Cumulative QALYs were 0.797 in the CBT-group and 0.804 in the ACT-group. The 0.007 [95% CI: -0.22 to 0.04] between-group difference in cumulative QALYs was statistically nonsignificant (*SE*=.02, *t*=-0.46, *p* =.65) and fell below the established threshold for the minimal clinically relevant difference for the EQ-5D of 0.074 [256].

Healthcare Costs

In the blended ACT group, the average per-participant healthcare costs were €100 at baseline, €92 at 6-month follow-up and €108 at 12-month follow-up. The average healthcare costs per participant in the CBT group were €88 at baseline, €105 at 6-month follow-up and €87 at 12-month follow-up. Cumulative healthcare costs as incurred over the 12-month follow-up (including intervention costs of €73 for CBT and €112 for ACT) were €1300 in the ACT group and €1233 in the CBT group. The between-group difference (i.e., incremental costs) in total cumulative costs was €67 [95% CI: -€278 to €412] ($85).

Costs Stemming from Productivity Losses

In the blended ACT group, average costs stemming from productivity losses were €106 at baseline, €69 at 6-month follow-up and €134 at 12-month follow-up. For the CBT group average costs were €179 at baseline, €125 at 6-month follow-up and €130 at 12-month follow-up. Cumulative costs per participant between baseline and 12-month follow-up were €1133 in the blended ACT group and €1681 in the CBT

group. Cumulative costs over the study period were €548 [95% CI: -€1160 to €64] (-$698) lower in the ACT condition.

Total Costs from the Societal Perspective

The average cumulative costs per participant from a societal perspective were €2433 in the blended ACT group and €2914 in the CBT group. Cumulative societal costs were thus lower in the ACT group, by €480 [95% CI: -€1190 to €229] (-$611).

Cost-effectiveness and cost-utility

Table 3 summarizes the results of the main cost-effectiveness and cost-utility analyses and the sensitivity analyses: the mean incremental costs and effects from the 2500 bootstraps and the distribution of the bootstrapped ICERs over the quadrants of the cost-effectiveness plane. Additionally, in Appendix 4 we present the median of the bootstrapped incremental costs and effects. The cost-effectiveness planes and acceptability curves of the sensitivity analyses are presented in Appendix 5.

Table 3. Result of the main analyses (cost-effectiveness and cost-utility) and sensitivity analyses

				Distribution of ICERs over the quadrants, %			
Analysis	**Incr. Cost (ACT-CBT)**	**Incr. Effect (ACT-CBT)**	**ICER**	**NE**	**NW**	**SW**	**SE[2]**
Base case CEA	-€466 (-$593)	-0.06	€7767 ($9988)	2	12	75	11
Sens 1: expectation maximization	-€429 (-$546)	-0.04	€10725 ($13653)	4	13	66	18
Sens 2: per-protocol	-€321 (-$409)	-0.08	€4013 ($5109)	4	25	64	8
Sens 3: healthcare perspective	€71 ($90)	-0.06	dominated[1]	8	55	33	4
Base case CUA	-€466 (-$593)	0.007	dominant[2]	8	6	26	60
Sens 1: expectation maximization	-€429 (-$546)	0.005	dominant[2]	8	8	27	56
Sens 2: per-protocol	-€323 (-$409)	-0.006	€53833 ($68532)	8	21	43	28
Sens 3: health care perspective	€71 ($90)	0.007	€10143($12913)	38	26	6	30

Note. Incr. Cost=Incremental costs, i.e. $Cost_{ACT}$ - $CostC_{BT}$; Incr. Effect=Incremental effects, i.e. $Effect_{ACT}$ - $EffectC_{BT}$; ICER= Incremental Cost Effectiveness Ratio; CEA=Cost-effectiveness analysis; CUA=Cost-utility analysis; NE=northeast quadrant with higher cost for better effects; NW=northwest quadrant with higher cost for less effect (=dominated); SW=southwest quadrant with less cost for less effect; SE=southeast quadrant with less costs for better effects (=dominant). [1] "Dominated", because ACT costs more and is less effective than CBT, hence reject ACT as a cost-effective alternative for CBT [2] "Dominant", because ACT costs less than CBT and has better effectiveness than CBT, hence accept ACT as the more cost-effective alternative treatment option compared to CBT.

Cost-effectiveness

In the base case cost-effectiveness analysis, the mean incremental costs and effects (treatment responders) from the 2500 bootstrapped samples were -€466 (-$593) and -0.06, which translates to an ICER of €7767. This ICER means that every treatment responder gained by offering CBT instead of blended ACT costs €7767. The incremental cost-effectiveness plane in Figure 1 shows that the large majority (75%) of the 2500 bootstrapped ICERs fell in the south-west quadrant, indicating lower costs associated with ACT compared to CBT, but also a lower treatment response rate.

The EM-imputation and per-protocol sensitivity analyses confirmed the finding from the base case analysis that compared to CBT, blended ACT generates a lower treatment response rate albeit for lower costs per treatment responder. In the cost-effectiveness planes this was reflected by a majority of 66%, respectively 64% of the bootstrapped ICERs falling into the south-west quadrant.

In the analysis from the healthcare perspective, a majority of 55% of the bootstrapped ICERs fell in the northwest quadrant, indicating that from this perspective blended ACT is dominated by face-to-face CBT because it is associated with a lower treatment response rate and higher healthcare costs.

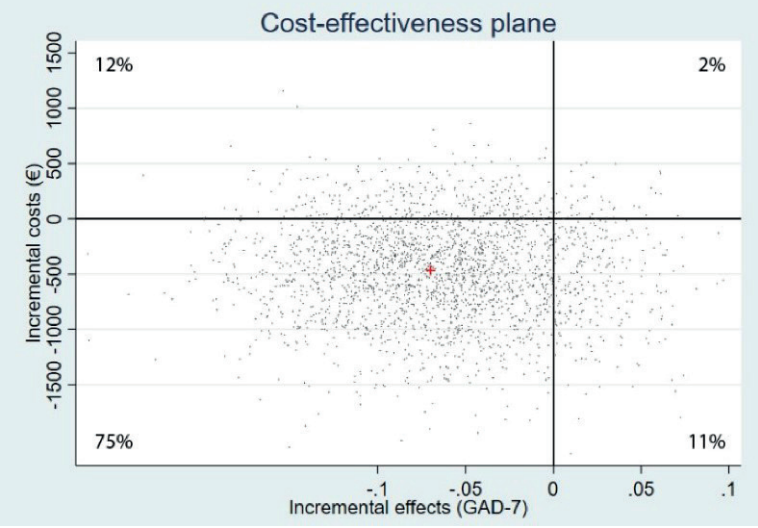

Figure 1. Cost-effectiveness plane reflecting the probability that blended ACT is cost-effective compared to CBT in terms of treatment responders

Cost-utility

In the base case cost-utility analysis ACT cost €466 ($593) less than CBT over the 12-month time period, and was associated with a QALY gain of 0.007. As can be seen in the incremental cost-effectiveness plane in Figure 2, the majority (60%) of bootstrapped ICERs fell in the south-east quadrant, indicating that in terms of cost-utility blended ACT is likely to be the dominant treatment, with lower costs and larger QALY gains compared to CBT. At the WTP ceilings of €50,000 and €80,000 per QALY the probability of ACT being cost-effective was respectively 81% and 78%, as can be seen in Figure 3.

The sensitivity analysis on the EM-imputed dataset had roughly similar results as the base case analyses, with 56% of the bootstrapped ICERs located in the south-east quadrant of the cost-effectiveness plane. The probability of ACT being cost-effective compared to CBT at WTP thresholds of €50,000 and €80,000 was 77% and 73%, respectively.

Contrary to the base case analyses, the per protocol analysis indicated less QALY gains in the ACT group than the CBT group. A fraction of 43% of the bootstrapped ICERs fell in the southwest quadrant, indicating lower costs associated with blended ACT, but also health losses. The probability of ACT being cost-effective compared to CBT at WTP ceilings of €50,000 and €80,000 was 50% and 46%, respectively.

Analysis from the healthcare perspective resulted in a total of 38% of the bootstrapped ICERs in the northeast quadrant, indicating that compared to CBT, blended ACT results in better health but for more healthcare costs. The probability of ACT being cost-effective compared to CBT was 63% at the WTP of €50,000 and 65% at the ceiling of €80,000.

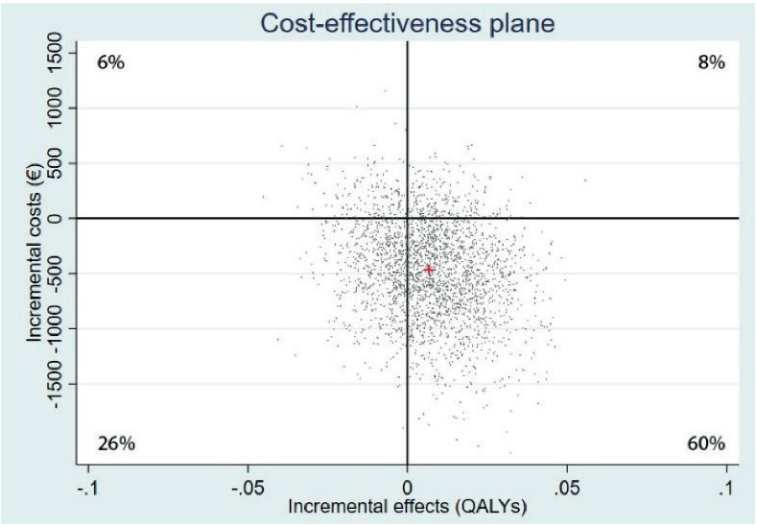

Figure 2. Cost-effectiveness plane reflecting the probability that blended ACT is cost-effective compared to CBT in terms of QALYs (cost-utility)

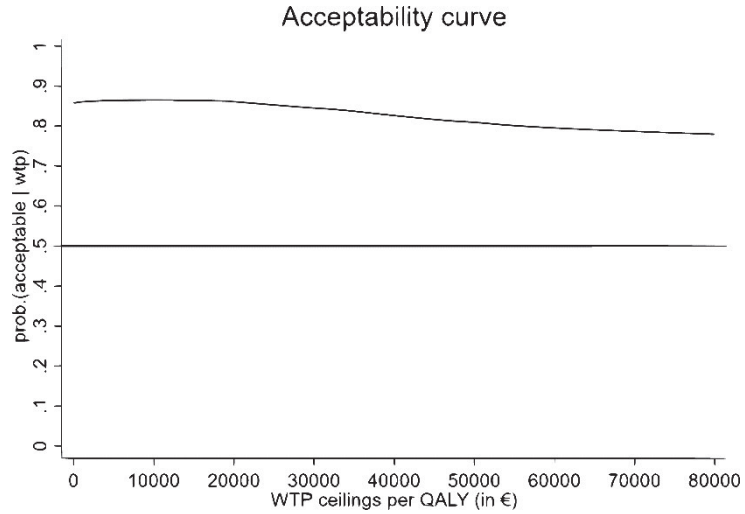

Figure 3. Acceptability curve reflecting the probability that blended ACT is cost-effective compared to CBT in terms of QALYs (cost-utility) at different willingness-to-pay ceilings

Discussion

The present study evaluated the cost-effectiveness and cost-utility of a brief blended ACT intervention compared to brief face-to-face CBT for older adults with anxiety symptoms. This health economic evaluation was conducted alongside an RCT which previously demonstrated that there were no statistically significant differences between the interventions in terms of anxiety symptom improvement at posttreatment and 12-month follow-up [250].

The results from the current study confirm the comparable effects of these interventions and do not indicate a clear preference for either the blended ACT intervention or the CBT intervention from a clinical perspective: ACT was associated with slightly fewer treatment responders on the GAD-7 and tiny QALY gains compared to CBT. The general impression therefore is that both treatments are equally effective, because the differences, if any, were statistically insignificant and clinically irrelevant. Assuming that there are virtually no clinically relevant effect differences between the interventions, blended ACT might be preferred over CBT from a strictly economic point of view. In all analyses from the societal perspective, the blended ACT intervention was associated with somewhat lower costs than CBT. In the base case analyses, 86% of the bootstrapped ICERS were indicative of lower costs and the mean per-participant societal cost reduction associated with blended ACT compared to CBT was €466

($593). The observed costs reduction stemmed completely from the lower productivity costs in the blended ACT group and disappeared when the analyses were conducted from a healthcare perspective. When only considering healthcare costs, blended ACT was even slightly more expensive (by €71 ($90)) than CBT.

In the cost-effectiveness analyses, blended ACT was associated with slight health losses compared to CBT, but also with lower costs. The ICER of €7767 means that each treatment responder gained by offering CBT instead of blended ACT, would cost €7767. Put differently, each treatment responder lost by offering blended ACT instead of CBT would save €7767. Since there are no established willingness-to-pay thresholds for the outcome measure used in the current CEA analysis, it is not possible to tell whether this would be considered a reasonable tradeoff between health gains and costs. In terms of cost-utility, the small QALY gains combined with societal cost reductions in the ACT condition translated into a 81% and 78% probability of blended ACT being cost-effective compared to CBT at willingness-to-pay ceilings of €50,000/QALY and €80,000/QALY respectively. However, sensitivity analyses did not confirm these findings: in the per protocol analyses, the CBT group had larger QALY gains than the ACT group. It is therefore premature to conclude that blended ACT is cost-effective compared to CBT in terms of QALY's.

The results of the current study do not allow for a decisive conclusion that from a health-economic perspective blended ACT should be preferred over CBT in the treatment of older adults with anxiety symptoms. The findings do suggest that blended ACT is associated with lower productivity costs, which is a factor that could be taken into account by healthcare providers and policy makers. For patients with an occupation (either paid or unpaid), the blended ACT intervention might be preferred over the CBT intervention as it is likely to be associated with less costs related to productivity losses. However, in practice, clinical (policy) decisions are not and should not be solely guided by economic considerations. Looking at the clinical equivalency of blended ACT and CBT for anxiety in later life, both interventions should be covered by insurance and the choice between these treatments should for now be predominantly guided by practical and medical-ethical considerations and preferences of both patient and therapist. Such a model of shared decision making, which promotes patient autonomy, can lead to improved treatment adherence and outcomes by increasing the alignment of the treatment with a patient's preferences and values [257,258].

The current study was the first to assess the cost-effectiveness and cost-utility of an ACT intervention compared to a CBT intervention in any patient population.

Therefore, we cannot compare the current findings with previous research. Health economic evaluations of ACT and other third-wave cognitive behavioral therapies are remarkably scarce given the growing body of evidence in support of their clinical effectiveness [259]. This was also the main conclusion of a recent meta-analysis into the economic impact of third-wave cognitive behavioral therapies, which only included eleven trials, of which three were focused on ACT [259]. To bring ACT to the next stage of clinical trial testing, health economic evaluations in which ACT interventions are compared to other active treatments would be welcome.

Some limitations of the current study need to be addressed. First, a substantial number of participants dropped out of the RCT and did not complete the posttreatment and/or follow-up measurements. This resulted in a considerable amount of missing data. However, we imputed missing data using predictive mean matching and expectation maximization—two well-established imputation methods [237]—and sensitivity analyses based on both imputation techniques led to very similar results. Another limitation concerns the fact that the TIC-P only assessed participants' healthcare use and work productivity during the 4 weeks preceding each measurement moment. We used linear interpolation to estimate the costs between the measurement points at months 0, 6 and 12 to obtain the cumulative costs over the full 12-month study period, but we cannot ascertain whether the assumption of linear change between the measurement points is valid. Lastly, all measures are based on self-report, which can be vulnerable to recall bias. Medication and other healthcare use is often underestimated in self-reports [260]. However, medication use was asked over a short period of 2 weeks retrospectively and if any bias would have occurred, then most likely in equal measure across both conditions.

Overall, the results of this health-economic evaluation in a sample of older adults with anxiety symptoms suggest that the ACT intervention and CBT intervention do not differ in terms of treatment responders and QALY gains over a one year period. The analyses indicate that, from a societal perspective, the blended ACT intervention has a small economic advantage over the CBT-intervention, because it is associated with less productivity costs. Combined with earlier findings about the comparability of the effectiveness of both interventions on multiple clinical outcomes, the current findings imply that both interventions should be covered by insurance and that -following the principles of shared decision making- clinicians and patients should collaboratively decide on which intervention they prefer, guided by personal, ethical and practical considerations.

Appendix 1

Table A1. Prices health care units and productivity losses

Health care unit	Price*
Consult general practitioner	€35.24
Home visit general practitioner	€53.40
Telephone consult general practitioner	€18.16
Consult mental health counselor at general practitioner	€18.16
Consult psychotherapist/psychiatrist	€104.66
Consult fysiotherapist/ergotherapist	€35.24
Consult social worker	€69.42
Consult company doctor	€35.24
Consult medical specialist	€97.19
Consult alternative medicine	€14.95
Meeting selfhelp group	€14.95
Visit home care service	€22.96
Pharmacist dispensing costs	€6.41
Daily dose medication depression	€0.13
Daily dose medication anxiety/stress	€0.08
Daily dose sleep medication	€0.09
Daily dose pain medication	€0.67
Hour paid work	€37.11
Hour voluntary work / informal care	€14.95

*prices were calculated using standard economic prices as reported for the year 2015, indexed for the year 2019.

Appendix 2.

Table A1. Indirect medical costs (travel costs)

Health care service	Price (kilometers return trip)
General practice / pharmacy	€0.38 (2 km)
Mental health care institution	€5.70 (30 km)
Hospital	€2.66 (14 km)
Fysiotherapist/ergotherapist	€0.84 (4.4 km)
Alternative medicine / self-help group	€3.80 (20 km)

Appendix 3

Table A3. Total reported units of healthcare utilization and total reported days of absenteeism and presenteeism in the ACT-group and CBT-group at over assessments

	Baseline		Follow-up (6 months)		Follow-up (12 months)	
Resource use	**ACT (n=150)**	**CBT (n=164)**	**ACT (n=88)**	**CBT (n=112)**	**ACT (n=86)**	**CBT (n=96)**
Consult GP	73	59	36	45	28	27
Home visit GP	2	2	1	1	1	1
Telephone consult GP	19	18	5	12	2	5
Consult GP's mental health counselor	19	19	11	21	11	14
Consult psychotherapist/psychiatrist	1	3	7	11	7	8
Consult fysiotherapist/ergotherapist	107	84	63	72	51	48
Consult social worker	4	0	1	2	1	0
Consult company doctor	6	6	1	2	4	6
Consult medical specialist	45	56	19	34	23	20
Consult alternative medicine	15	25	10	9	9	7
Meeting selfhelp group	0	3	3	0	0	1
Visit home care service	92	26	71	29	101	20
Use of antidepressant	168	196	118	133	93	142
Use of anxiolytics	197	134	20	89	65	94
Used medication for sleep	97	164	25	113	35	91
Used medication for pain	150	169	80	88	73	56
Absenteeism work	48	39	17	33	37	39
Presenteeism work	147	202	29	40	55	59
Absenteeism informal care	39	4	0	2	0	3
Presenteeism informal care	30	15	1	17	7	12
Absenteeism voluntary work	43	5	6	9	0	24
Presenteeism voluntary work	18	22	14	14	10	8

Appendix 4

Table A4. Mean and median incremental costs and effects of the 2,500 bootstraps

Analysis	**M Incr. Cost**	**Mdn Incr. costs**	**M Incr. Effect**	**Mdn Incr. costs**
Base case CEA	-€466	-€452	-0.06	-0.06
Sens 1: EM imputation	-€429	-€424	-0.04	-0.04
Sens 2: per-protocol	-€321	-€304	-0.08	-0.08
Sens 3: healthcare	€71	€61	-0.06	-0.07
Base case CUA	-€466	-€451	0.007	0.007
Sens 1: EM Imputation	-€429	-€424	0.005	0.005
Sens 2: per-protocol	-€323	-€304	-0.006	-0.006
Sens 3: health care	€71	€59	0.007	0.007

*Note.*Incr. Cost=Incremental costs, i.e. $Cost_{ACT}$ - $CostC_{BT}$; Incr. Effect=Incremental effects, i.e. $Effect_{ACT}$ - $EffectC_{BT}$

Appendix 5. Cost-effectiveness planes of the sensitivity analyses

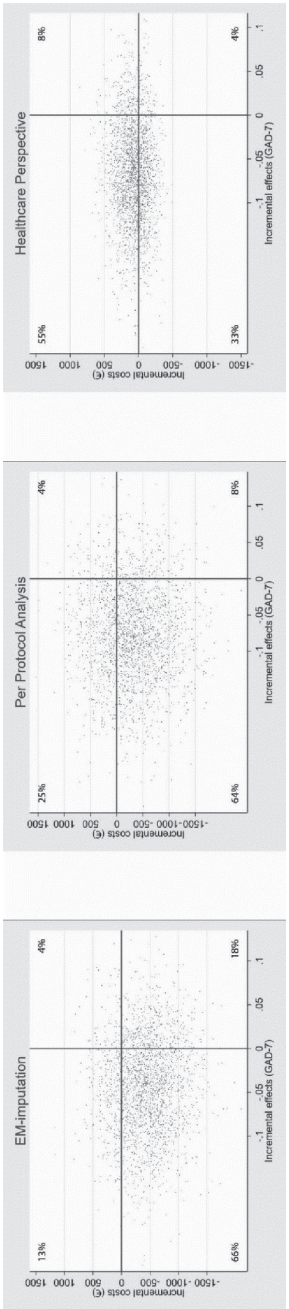

Figure A1. Cost-effectiveness planes reflecting the distribution of the bootstrapped ICERs from the sensitivity cost-effectiveness analyses

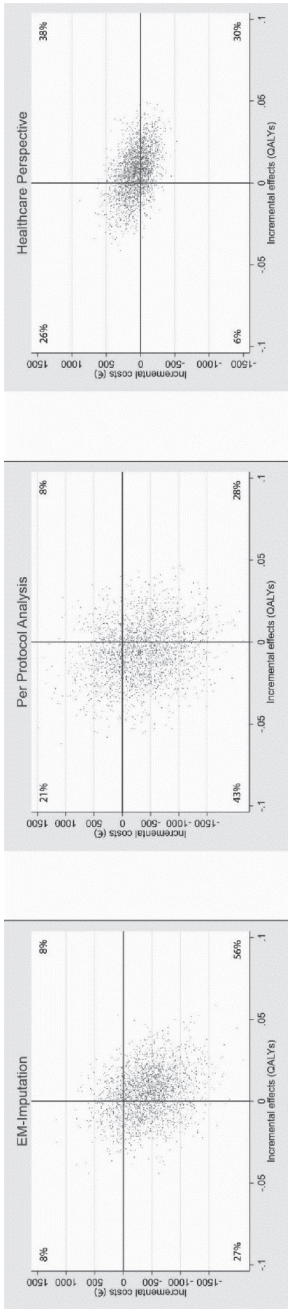

Figure A2. Cost-effectiveness planes reflecting the distribution of the bootstrapped ICERs from the sensitivity cost-utility analyses

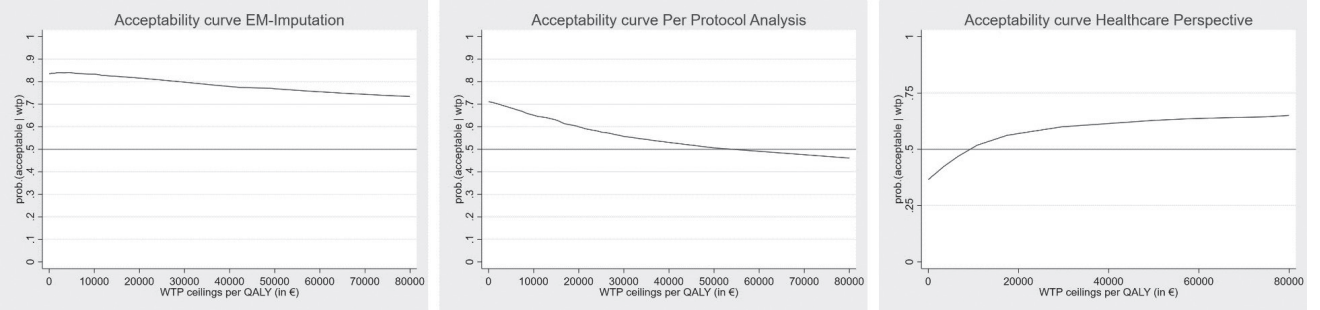

Figure A3. Acceptability curves from the sensitivity cost-utility analyses reflecting the probability that blended ACT is cost-effective compared to at different willingness-to-pay ceilings

PREDICTORS OF TREATMENT RESPONSE TO ACCEPTANCE AND COMMITMENT THERAPY AND COGNITIVE BEHAVIORAL THERAPY IN OLDER ADULTS WITH ANXIETY SYMPTOMS

Manuscript under revision: Witlox M, Kraaij V, Garnefski N, Dusseldorp E, Bohlmeijer ET, Spinhoven P. Predictors of treatment response to Acceptance and Commitment Therapy and Cognitive Behavioral Therapy in older adults with anxiety symptoms.

Abstract

Background: A recent trial in older adults with anxiety symptoms found no differences between an ACT intervention and a CBT intervention regarding their effect on anxiety symptom severity.

Objective: To follow up these earlier findings, the current study aimed to identify moderator variables, that predict differential treatment response to these two interventions. Secondary, the study aimed to identify non-specific predictors, that predict treatment response in both conditions.

Methods: The sample consisted of 314 older adults with anxiety symptoms, randomized to ACT or CBT. The following baseline characteristics were examined: 1) demographics (sex, age, education, work hours, relationship status, negative life events); 2) (psycho) pathology (anxiety severity, depression severity, presence anxiety disorder, medication use, somatic comorbidity); 3) social support (problem solving support, affective support); 4) psychological processes (self-esteem, mastery, experiential avoidance, mindfulness, emotion regulation). Anxiety symptom severity (measured with the GAD-7) was the outcome variable.

Results: No moderator variables were identified. Two non-specific predictors were identified: more severe depression symptoms predicted worse short-term (b=0.20, p=.02) and long-term (b=0.25, p=.002) response to ACT and CBT, and higher levels of mastery predicted better short-term treatment response (b=-0.17, p=.03) in both conditions.

Conclusions: Since no moderator variables were identified, both the ACT and CBT intervention can for now be offered to all older adults with anxiety symptomatology. The prognostic effects of depression symptom severity and mastery may hold implications regarding treatment enhancement strategies.

Introduction

Anxiety disorders and symptoms are one of the most prevalent mental health issues in older adults and are associated with considerable distress and impairment [11,20,229]. Although anxiety in later life has received an increasing amount of scientific attention over the last decades, the literature on psychological treatment for older adults with anxiety symptoms is still limited and mainly focused on the evaluation of face-to-face cognitive behavioral therapy (CBT) [35]. To broaden the scope of this field of research and advance treatment of anxiety symptoms in later life, we conducted a randomized controlled trial (RCT) to evaluate the short- and long term effectiveness of a blended Acceptance and Commitment Therapy (ACT) intervention in a sample of older adults with anxiety symptoms. ACT is a behavior therapy that promotes an acceptance-based attitude towards (negative) feelings and thoughts, and stimulates people to (re)connect with their core values and act in accordance with these [52]. In the RCT, the blended ACT intervention was compared to face-to-face CBT, which could be considered optimized treatment-as-usual in the study setting. We found no differences in effectiveness of ACT and CBT on anxiety symptom severity at posttreatment and one-year follow-up. Looking at the within-group effect sizes, both groups showed a large and significant decline in anxiety symptom severity from baseline to posttreatment. This decrease was sustained one year after baseline in both conditions [250].

Findings like those from our RCT, namely that two (or more) active treatments appear equally effective for a certain patient population, are common in the field of clinical psychology [261]. Notwithstanding the importance of such findings, they do present a challenge for evidence-based clinical practice, as they do not provide information about how individual patients are likely to respond to (a) particular treatment(s) [261]. Therefore, the goal of the current study is to examine predictors of short- and long term anxiety symptom improvement in ACT and CBT for anxiety symptoms in later life. There are two types of predictors of treatment response: non-specific predictors and moderators. Non-specific predictors are variables that are predictive of treatment response, irrespective of treatment type. Such variables provide *prognostic* information by clarifying which subgroups of patients are likely to benefit more or less from treatment in general. Moderators, on the other hand, are baseline characteristics that differentially predict response to two or more interventions in a patient population [7]. Moderators thus provide *prescriptive* information about treatment selection, as they indicate subgroups of patients who respond differentially to different types of treatment. Compared to non-specific predictors, the clinical implications of

findings on treatment moderators are therefore more profound: ultimately, information about moderators could be used to transform mental health care into *'precision mental health care'*, where patients are provided with the intervention that is likely to be most effective for them based on their pretreatment characteristics, thereby improving treatment outcomes.

To our knowledge, two studies so far have examined moderators and non-specific predictors of treatment response to ACT and CBT for anxiety, both using data from a trial that compared face-to-face ACT and CBT in a sample of 121 adults (maximum age of 60 years, mean age of 37.93 years (*SD*=11.79)) with mixed principal anxiety disorder diagnoses [262,263]). The first study [262] examined multiple demographic and psychological variables and found ACT to be the optimal treatment (in terms of anxiety symptom improvement) for patients with a comorbid mood disorder at baseline, while CBT outperformed ACT among patients without a comorbid mood disorder. Furthermore, it was found that among the participants with moderate baseline levels of anxiety sensitivity, CBT outperformed ACT. Neuroticism was identified as a non-specific predictor, with higher baseline levels being associated with poorer outcomes in both ACT and CBT. In the other study, Davies et al. [263] focused on physiological and behavioral indices of emotion dysregulation as potential moderators and found that patients with higher behavioral avoidance (operationalized as the unwillingness to endure physical sensations caused by a hyperventilation task) benefitted more from ACT than CBT. Heartrate variability emerged as a non-specific predictor, with higher variability being predictive of overall poorer treatment outcome.

Both Wolitzky-Taylor et al. [262] and Davies et al. [263] used a statistical approach that is common in studies concerned with the identification of treatment moderators: in a series of regression analyses they tested for statistical interaction between baseline person characteristics and treatment type, examining each person characteristic in isolation. In other words, the effect of each putative moderator variable was investigated with a separate regression model. Results from such analyses offer little guidance to clinicians, as it is unclear how the information about the moderators should be combined when deciding upon the optimal treatment for a specific patient [264], especially when findings on different individual moderators lead to conflicting treatment recommendations. For example, the results from the study by Wolitzky-Taylor et al. [262] pose a problem for a therapist who has to select the optimal treatment for a patient with an anxiety disorder, moderate anxiety severity (related to superior outcomes for CBT) and a comorbid mood disorder (related to superior outcomes for ACT).

Clearly, for findings on moderator variables to inform clinical practice in a meaningful way, they should be integrated and translated into treatment recommendations for individual patients. This was also recognized by DeRubeis et al. [265], who developed a statistical procedure in which data from clinical trials are used to create a model that predicts treatment outcomes for the different interventions for each trial participant, based on their pattern of pretreatment characteristics. The method builds upon classical moderated regression analysis, but goes beyond the approach of examining each putative moderator in isolation by combining the information from the univariate analyses into one prediction model. Such a model can be used for individualized treatment selection, by providing patients with the treatment they are predicted to respond to optimally based on their pretreatment characteristics. Previous studies have shown that this method indeed holds promise as a tool for individualized treatment assignment [266-268].

In sum, in the current study we will examine moderators of short term and long term treatment response to blended ACT and face-to-face CBT for older adults with anxiety symptoms. Secondary, we are also interested in non-specific predictors of treatment response to the two interventions. Since there is no solid body of scientific literature to inform hypotheses about putative moderators and non-specific predictors of treatment response to ACT and CBT for anxiety symptoms in later life, we will use an exploratory approach and include a selection of demographic and clinical baseline variables. Furthermore, if the analyses will identify multiple moderator variables, we will follow the statistical procedure from DeRubeis et al. [265] to create an algorithm that uses the identified moderator(s) to predict (optimal) treatment outcomes for individual trial participants.

Methods

This study used data from a cluster-randomized single blind controlled trial that was conducted in the Netherlands. The trial evaluated the effectiveness of a brief blended ACT intervention compared to brief face-to-face CBT over a period of 12 months. Randomization took place at the level of the therapists that participated in the study (n=40), who consequently either only provided blended ACT (n=20) or only CBT (n=20) to study participants. Details about the study design and methods have been published elsewhere [236]. The trial was registered in the Netherlands Trial Register and approved by the medical ethics committee.

Participants and procedure

Between November 2017 and March 2019, participants were recruited in 38 general practices in the Netherlands. Patients (aged 55-75) from the participating general practices were sent a letter that contained information about the study and an invitation to participate. Those interested in participation could register on a study website, after which they entered a screening procedure. Inclusion criteria were: age between 55 and 75 years, presence of mild to moderate anxiety symptoms (Generalized Anxiety Disorder-7 [131] score between 5 and 15), mastery of the Dutch language, internet access and the possibility to spend up to 30 min per day on the intervention. Exclusion criteria were: unstable severe medical condition(s); severe cognitive impairment; very high or low anxiety symptom severity (GAD-7 score < 5 / > 15); severe depressive symptoms (PHQ-9 [170] score ≥ 20); psychological or psychopharmacological treatment (stable benzodiazepine or SSRI use excepted) within the last 3 months; severe role impairment in at least 2 life areas (score of ≥ 8 on two or three items of the Sheehan Disability Scale (SDS) [171]); high suicide risk (M.I.N.I.-Plus [139]); substance use disorder (M.I.N.I.-Plus); lifetime diagnosis of bipolar disorder or schizophrenia (medical record and M.I.N.I.-Plus).

Eligible participants signed an online informed consent form and completed the baseline assessment, after which they were informed about their treatment allocation. Participants completed 4 main assessments: at baseline (T0), posttreatment (T1; 3 months after baseline), 6 months after baseline (T2) and 12 months after baseline (T3). In the current study, we will use data from T0, T1 and T3. The assessments consisted of online self-report questionnaires and a telephone interview conducted by trained and supervised research assistants that were blind to randomization.

Interventions

Therapists

Treatment was provided by mental health counselors working in general practices in the Netherlands. Around 2008, general practices in the Netherlands started employing mental health counselors in response to the increasing demand for treatment of psychological problems and the high costs and limited capacity of mental health care institutions [234]. The counselors provide short term psychological treatment to patients with mild to moderately severe psychological complaints. The occupation is fulfilled by mental health professionals with different educational backgrounds. Most counselors participating in the study were master graduates in psychology (n=13), social psychiatric nurses (n=14) or social workers (n=5). Their years of experience

with providing individual psychological treatment ranged from 3 to 42, with a median of 16 years.

Blended Acceptance and Commitment therapy

Participants in the Blended ACT condition completed the online ACT-module 'Living to the Full' [179,180] and attended 4 face-to-face sessions with the mental health counselor at their general practice. The module consists of 9 lessons that revolve around the 6 core processes of ACT: acceptance, cognitive defusion, contact with the present moment, self as context, personal values and committed action. Participants completed the module in 9 to 12 weeks. The 4 face-to-face sessions with the mental health counselor followed a protocol developed by the authors of Living to the Full and served to increase motivation, repeat key exercises and discuss problems that arose while working with the module.

Cognitive Behavioral Therapy

Participants in the CBT condition attended 4 face-to-face sessions and completed homework exercises. The sessions took place in a timespan between 9 to 12 weeks. A treatment protocol was developed that focused on identifying and challenging negative cognitions and reducing anxiety-related avoidance behavior. Furthermore, it contained information and exercises related to specific types of anxiety (panic, worrying, social anxiety) and common side effects of anxiety (sleeping problems, physical tension). After the intake session, the counselor and client collaboratively set treatment goals. In the second and third session, homework was evaluated, key exercises/information repeated and the counselor and participant agreed on a planning regarding homework exercises for the succeeding weeks. The last session was dedicated to an evaluation of the progress of the client and the formulation of a relapse prevention plan.

Measurements: outcome variable

Anxiety symptom severity

Anxiety symptom severity at T1 and T3 was assessed with the GAD-7, a widely-used seven-item anxiety screener with good psychometric properties [171]. Total scores range from 0 to 21, with higher scores reflecting more severe anxiety symptoms in the last two weeks. Values for Cronbach's alpha for the GAD-7 in the current study sample at T1 and T3 were α= 0.86 and α=0.87, respectively.

Measurements: predictor variables

All predictor variables were assessed during the baseline measurement.

Demographic variables

Age, gender, romantic relationship status, education level and weekly work hours (both paid and voluntary work) were assessed with a self-developed questionnaire.

Recent negative life events

Recent negative life-events were assessed with a self-developed yes/no question: "In the past 6 months, did you experience one or more major negative events?". Participants that responded yes, could describe the event in a textbox.

Somatic problems

Physical problems in the previous year were assessed with a self-developed checklist, listing the 25 most common (chronic) medical conditions, according to Statistic Netherlands. Participants could also report somatic problems they experienced that were not included in the checklist.

Psychiatric medication use

Participants completed a yes/no question to indicate if they had used benzodiazepines and/or SSRIs during the preceding 3 months.

Presence of anxiety disorder

Trained research assistants conducted The Mini-International Neuropsychiatric Interview [139] by phone to assess the presence of generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder and illness anxiety disorder.

Depression symptom severity

Depression symptom severity was measured with the PHQ-9 [170], a nine item self-report questionnaire with good psychometric properties. Total scores range from 0 to 27 with higher scores indicating higher symptom severity in the previous two weeks. Cronbach's alpha for the PHQ-9 in the current sample was $\alpha = 0.73$.

Self-esteem, mastery and social support

Bovier, Chamot and Perneger [206] developed a 14-item questionnaire to measure social support and psychological resources. The questionnaire consists of 4 scales, measuring self-esteem (defined as one's overall sense of worthiness as a person; 4 items), mastery (people's belief that their life's course is under their own control in contrast to being fatalistically ruled; 4 items), affective social support (the availability of people who express emotional involvement with and care for the participant during challenging situations; 2 items) and problem solving social support (the availability of people one can confide in and receive advice from when challenging situations occur; 4 items). Items are answered on a scale ranging from 0 to 4 and higher scores on each subscale represent higher levels of the measured construct. All four scales have proper psychometric properties [206]. In the current study sample, Cronbach's alpha values were: α= 0.76 for self-esteem, α= 0.78 for mastery, α= 0.87 for affective social support and α= 0.83 for problem solving social support.

Experiential Avoidance

The Acceptance and Action Questionnaire-II (AAQ-II) is a validated unidimensional measure [191] that assesses experiential avoidance. Experiential avoidance is a key concept in ACT and refers to the unwillingness to remain in contact with aversive private experience and the behaviors aimed at altering these experiences or the events that elicit them [191]. AAQ items are scored on a 7-point scale and total scores range from 7 to 49 with higher scores reflecting higher levels of experiential avoidance. Cronbach's alpha for the AAQ-II at T0 in the current study sample was α= 0.87.

Mindfulness

The Five Facet Mindfulness Questionnaire-Short Form (FFMQ-SF) was used to assess mindfulness, defined as the ability to bring one's attention to experiences in the present moment in a nonjudgmental manner [195]. The questionnaire is comprised of 24 6-point items (ranging from 0 to 5) that measure five facets of mindfulness: observing (4 items), describing (5 items), acting with awareness (5 items), non-judging (5 items) and non-reactivity (5 items). The sum score of all items reflects the level of mindfulness, with higher scores indicative of higher levels. The questionnaire has good psychometric properties [195]. Cronbach's alpha for the FFMQ-SF at T0 in the current study sample was α= 0.69.

Cognitive Emotion Regulation Strategies

Participant completed the subscales self-blame, rumination, positive reappraisal and catastrophizing. of the Cognitive Emotion Regulation Questionnaire (CERQ) [188]. The subscales consist of four 5-point items each, with total scores for each scale ranging between 0 and 16. Higher scores on a subscale indicate that this cognitive coping strategy is more often used to regulate emotions. The CERQ has good psychometric qualities [188]. Cronbach's alpha values for the four scales in the current study sample were: α=0.79 for self-blame, α= 0.77 for rumination, α= 0.86 for positive reappraisal and α= 0.82 for catastrophizing.

Anxiety symptom severity at baseline

Anxiety symptom severity at T0 was measured with the GAD-7 [131]. Cronbach's alpha for the GAD-7 at T0 in the current study sample was α= 0.78.

Statistical analysis

All analyses were performed using the R statistical software environment [96]. Analyses followed the intention-to-treat principle, which required missing data imputation. We used Multiple Imputation by Chained Equations (MICE), with the predictive mean matching procedure, in which the missing outcome of a participant is imputed with the observed outcome from another participant with a comparable predicted mean outcome. This procedure ensures that the imputed data have plausible values [237]. A total of 100 imputed datasets were analyzed and their results pooled to arrive at the presented estimates.

Analyses were conducted separately for short term (T0-T1) and long term (T0-T3) treatment response. To identify moderators and non-specific predictors, we used a domain approach similar to the one outlined by Fournier et al. [269] and more recently by Huibers et al. [265]. Continuous variables were standardized and categorical variables were effect coded. First, we grouped the predictors in 4 domains (Table 1). To prevent excessive multiple testing, we conducted omnibus tests to compare the fits of three nested models within each domain: a simple model (regressing GAD-7 end-score on baseline GAD-7 score and treatment condition), an additive model (adding main effects of all the predictors in the domain) and a full prediction model (also adding interaction terms between treatment condition and each predictor in the domain). Using the Wald test, we tested whether the full prediction model fit the data significantly

(α=0.05) better than both the simple model and the additive model. If the omnibus tests indicated that the full domain model had a superior fit, we used a stepwise procedure to identify the prescriptive and prognostic variables within that domain. In step 1, the full prediction model was inspected and variables that were significant at a threshold of α=0.2 were selected and combined into a new model. If an interaction between a predictor variable and the treatment variable fell below the significance threshold, the main effect of the predictor was carried through to the next step, irrespective of it being significant itself (maintaining the principle of marginality). The main effects of baseline anxiety symptom severity and treatment condition were always carried through to the next step, irrespective of their statistical significance. In step 2, the second model was examined and a same process was applied using a stricter threshold value of α=0.1. In Step 3, the same process was repeated, but with a threshold of α=0.05.

In domains where the full prediction model did not provide the superior fit, but the additive fit the data better than the simple model, we used the same procedure, but only aimed at identifying non-specific predictors.

We build a final prediction model combining the variables from all the domains that were significant at the 0.05 level in the third step of the domain specific analyses. The variables that remained significant at the 0.05 level in this final model, were considered moderators and/or non-specific predictors

If multiple moderators were identified, we followed the guidelines from DeRubeis et al. [265] to predict the optimal treatment for each individual participant with a model that regressed GAD-7 end-scores on the identified moderators and non-specific predictors. Outcome estimates for each participant were calculated with a leave-one-out cross-validation procedure, where the estimates for an individual participant are derived from a prediction model based on the data from all other participants. For each participant, a 'factual' prediction (predicted outcome for the intervention the participant was assigned to in the RCT) was calculated by entering their observed values on the independent variables in the model. The counterfactual prediction (predicted outcome for the intervention the participant was not assigned to in the RCT) was then calculated by changing the value of the treatment variable to reflect the intervention they had not received during the RCT. The factual and counterfactual predictions were compared to see which intervention was expected to be optimal for each participant (e.g., predicted to lead to the lowest GAD-7 score at T1/T3).

Table 1. Domains of baseline variables

Domain 1: Demographics
Sex (male=0, female=1)
Age
Education level (0=low, 1=middle, 2=high)
Weekly workhours
Relationship status (0=married or in a relationship, 1=not married or in a relationship)
Recent negative life events (0=no recent event, 1=recent event)
Domain 2: (Psycho)pathology
Anxiety symptom severity (GAD-7)[1]
Depression symptom severity (PHQ-9)
Presence of anxiety disorder(s) (MINI-Plus)
Psychiatric medication use (0=no medication use, 1=medication use)
Somatic comorbidity (continuous variable, reflecting the number of somatic problems during the previous year)
Domain 3: Social Support
Problem solving social support (Questionnaire developed by Bovier, Chamot & Perneger)
Affective social support (Questionnaire developed by Bovier, Chamot & Perneger)
Domain 4: Psychological processes
Self-esteem (Brief scale developed by Bovier, Chamot & Perneger)
Mastery (Brief scale developed by Bovier, Chamot & Perneger)
Experiential avoidance (AAQ-II)
Mindfulness (FFMQ-SF)
Self-blame (CERQ)
Rumination (CERQ)
Positive reappraisal (CERQ)
Catastrophizing (CERQ)

[1] baseline anxiety severity was only examined as potential moderator of treatment effect and not as a potential non-specific predictor, as the main effect of baseline anxiety severity was included as a control variable in all analyses.

Results

A total of 35,820 older adults (all living independently) received an information/invitation letter, of which 683 were screened after they registered for study participation. 314 people were included; 150 in the blended ACT group, 164 in the CBT-group. Table 2 presents the baseline characteristics of the sample. The T1 measurement was completed by 222 participants: 101 participants (67%) in the blended ACT-group and 121 participants (74%) in the CBT-group. The T3 measurement was completed by 178 participants: 82 (55%) in the blended ACT-group and 96 (59%) in the CBT-group.

Table 2. Baseline characteristics of the study sample

Characteristics	Blended ACT (*n*=150)	CBT (*n*=164)	Total sample (*n*=314)
Age (years), M (SD), [range]	62.75 (5.69) [55-75]	63.33 (5.71) [55-75]	63.06 (5.70) [55-75]
Sex, n (%)			
Female	100 (66.67)	92 (56.08)	192 (61.15)
Male	50 (33.33)	72 (43.92)	122 (38.85)
Nationality, n (%)			
Dutch	149 (99.33)	159 (96.96)	308 (98.01)
Dutch and other	0 (0.00)	5 (3.04)	5 (1.59)
Other	1 (0.77)	0 (0.00)	1 (0.40)
Education, n (%)			
Low	22 (14.67)	15 (9.15)	37 (11.78)
Middle	70 (44.67)	74 (45.12)	144 (45.86)
High	56 (37.33)	74 (45.12)	130 (41.40)
Unknown	2 (0.63)	1 (0.61)	3 (0.96)
Relational status, n (%)			
Married/in a romantic relationship	120 (80.00)	129 (78.66)	249 (79.30)
Not married/in a romantic relationship	30 (20.00)	35 (21.34)	65 (20.70)
Work status, n (%)			
Paid employment	77 (51.33)	76 (46.34)	153 (48.73)
Voluntary work	49 (32.67)	56 (34.15)	105 (33.44)
No work	53 (35.33)	59 (35.98)	112 (35.67)
Living situation, n (%)			
Alone	36 (24.00)	39 (23.78)	75 (23.89)
With partner	97 (64.67)	103 (62.80)	200 (63.69)
With children	11 (7.33)	13 (7.93)	24 (7.64)
With partner and children	6 (4.00)	8 (4.88)	14 (4.46)
Other	0 (0.00)	1 (0.61)	1 (0.32)
Somatic comorbidity, n (%)			
No somatic problems	29 (19.33)	32 (19.51)	61 (19.43)
One or more somatic problems	121 (80.67)	132 (80.49)	253 (80.57)
Psychiatric medication use, n (%)			
SSRI	10 (6.67)	12 (7.32)	22 (7.01)
Benzodiazepine	19 (12.67)	15 (9.15)	34 (10.83)
No psychotropic medication	121 (80.67)	137 (83.54)	258 (82.17
Anxiety disorder, n (%)			
Any anxiety disorder	42 (28.00)	39 (23.78)	81 (25.80)
No anxiety disorder	108 (72.00)	125 (76.22)	233 (74.20)

Moderators

None of the full prediction models provided a superior fit to the data (see Table 3). Thus, no moderators were identified for short term or long term treatment response to blended ACT and CBT.

Table 3. Results of the omnibus tests comparing domain specific simple, additive and full prediction models

	Short term					Long term				
Model comparison	***DF1***	***DF2***	***ΔR²***	***f***	***p***	***DF1***	***DF2***	***ΔR²***	***f***	***p***
Demographic domain										
Additive vs. simple	7	208.03	0.04	1.52	0.16	7	282.28	0.03	1.25	0.28
Full vs. additive	7	287.20	0.04	0.70	0.67	7	165.04	0.04	0.47	0.85
Psychopathology domain										
Additive vs. simple	4	285.48	0.06	4.18	.003*	4	269.24	0.06	2.73	0.03*
Full vs. additive	5	287.78	0.01	0.38	0.86	5	278.49	0.01	0.34	0.89
Support domain										
Additive vs. simple	2	278.09	0.02	2.93	0.06	2	235.46	0.02	1.53	0.22
Full vs. additive	2	276.88	0.00	0.52	0.60	2	257.24	0.00	0.25	0.78
Psychological processes domain										
Additive vs. simple	8	290.64	0.08	2.61	.009*	8	281.85	0.06	1.14	0.34
Full vs. additive	8	285.87	0.03	0.74	0.66	8	280.08	0.02	0.32	0.96

Note. All statistics are derived from pooling the results of 100 imputed datasets. R^2 of the simple model predicting short term treatment response was 0.12, the R^2 of the long term simple model 0.13.
*p<.05

Non-specific predictors

Short term treatment response

Of the additive models predicting short term treatment response, the psychopathology domain model (F(4, 285.48)=4.18, p=.003) and psychological processes domain model (F(8, 290.64)=2.61, p=.009) fit the data significantly better than the simple model (see Table 3). See Table 4 and 5 for the results of the stepwise inspection of the predictors in these domains. In the psychopathology domain, depression symptom severity (b=0.26, p < .001) was a significant predictor of treatment outcome: more severe symptoms of depression at baseline were associated with worse treatment outcomes, regardless of treatment condition. In the psychological processes domain, mastery (b=-0.19, p=.006) significantly predicted short term treatment response: higher baseline levels were related to better treatment outcome, irrespective of the treatment being blended ACT or CBT.

In the final prediction model (see Table 6), both depression symptom severity (*b*=0.20, *p*=.02) and mastery (*b*=-0.17, *p*=.03) were significantly associated with anxiety symptom severity at T1. Therefore, depression symptom severity and mastery were considered non-specific predictors of short term treatment response to the blended ACT and CBT intervention. The R^2 of the final model (that contained condition and baseline anxiety symptom severity as control variables, and baseline depressive symptom severity and mastery as predictors) was 0.19 [95% CI: 0.10 to 0.28].

Table 4. Stepwise inspection of non-specific predictors of short term treatment response: (psycho) pathology domain

Predictors	*b*	Std. error	*t*	*p*
Model 1				
Condition	-0.03	0.12	-0.21	.84
Anxiety symptom severity	0.16	0.07	2.16	.03***
Depression symptom severity	0.24	0.08	3.08	.00***
Anxiety disorder	0.22	0.14	1.55	.12*
Psychiatric medication	0.17	0.17	1.01	.32
Somatic comorbidity	0.07	0.06	1.04	.30
Model 2 (retained effects at p < .20)				
Condition	-0.03	0.13	-0.22	.83
Anxiety symptom severity	0.15	0.07	2.06	.04***
Depression symptom severity	0.27	0.08	3.53	<.001***
Anxiety disorder	0.23	0.14	1.59	.12
Model 3 (retained effects at p < .10)				
Condition	-0.02	0.13	-0.13	.90
Anxiety symptom severity	0.18	0.07	2.50	.01***
Depression symptom severity	0.26	0.08	3.42	<.001***

Note. All statistics are derived from pooling the results of 100 imputed datasets. The regression coefficients for anxiety symptom severity and depression symptom are standardized coefficients, because the variables were standardized before entering the model. *= p<.20; *** p<.05

Table 5. Stepwise inspection of non-specific predictors of short term treatment response: psychological processes domain

Predictors	*b*	Std. error	*t*	*p*
Model 1				
Condition	-0.05	0.12	-0.40	.69
Anxiety symptom severity	0.20	0.08	2.64	.00***
Self-esteem	-0.04	0.06	-0.59	.56
Mastery	-0.19	0.08	-2.53	.01***
Mindfulness	-0.15	0.08	-1.91	.06**
Experiential avoidance	0.12	0.09	1.36	.17*
Self-blame	-0.11	0.08	-1.49	.14*
Rumination	0.02	0.08	0.25	.81

Table 4. Continued

Predictors	*b*	Std. error	*t*	*p*
Positive reappraisal	0.06	0.07	0.89	.38
Catastrophizing	-0.09	0.07	-1.30	.20*[1]
Model 2 (retained effects at p < .20)				
Condition	-0.05	0.12	-0.38	.71
Anxiety symptom severity	0.21	0.07	2.88	.01***
Mastery	-0.18	0.07	-2.49	.01***
Mindfulness	-0.13	0.08	-1.69	.09**
Experiential Avoidance	0.12	0.09	1.35	.18
Self-blame	-0.09	0.07	-1.33	.19
Catastrophizing	-0.08	0.07	-1.26	.21
Model 3 (retained effects at p <.10)				
Condition	-0.06	0.12	-0.50	.62
Anxiety symptom severity	0.21	0.07	3.00	.00***
Mastery	-0.19	0.07	-2.76	.01***
Mindfulness	-0.14	0.07	-1.92	.06

Note. All statistics are derived from pooling the results of 100 imputed datasets. All regression coefficients are standardized coefficients, because continuous variables were standardized before entering the model All regression. [1] =rounded up to 0.20, original value was 0.196. *= p<.20; ** p<.10; *** p<.05

Table 6. Final prediction model short term treatment response

Predictors	*b*	Std. error	*t*	*p*
Condition	-0.04	0.12	-0.29	.77
Anxiety symptom severity	0.16	0.07	2.28	.02***
Depression symptom severity	0.20	0.08	2.32	.02***
Mastery	-0.17	0.07	-2.26	.03***

Note. All statistics are derived from pooling the results of 100 imputed datasets. All regression coefficients are standardized coefficients, because continuous variables were standardized before entering the model All regression *** p<.05

Long term treatment response

Of the additive models predicting long term treatment response, only the psychopathology domain model fit the data significantly better than the simple model (F(4, 269.24)=2.73, p=.03) (see Table 3). Stepwise inspection of the variables in the domain indicated that -similar to the short term analysis- baseline depression symptom severity (b=0.25, p=.002) was a non-specific predictor of long term treatment outcome (see Table 7): participants with higher depression symptom severity at baseline had more severe anxiety symptoms at the twelve month follow-up, irrespective of treatment condition. The R^2 of the final model (that contained condition and baseline anxiety

symptom severity as control variables, and baseline depressive symptom severity as predictor) was 0.18 [95% CI: 0.08 to 0.28].

Table 7. Stepwise inspection of non-specific predictors of long term treatment response: (psycho) pathology domain

Predictors	***b***	**Std. error**	***t***	***p***
Model 1				
Condition	-0.07	0.13	-0.54	.59
Anxiety symptom severity	0.21	0.08	2.55	.01***
Depression symptom severity	0.23	0.08	2.81	.01***
Anxiety disorder	0.04	0.16	0.27	.79
Psychiatric medication	0.09	0.18	0.52	.60
Somatic comorbidity	0.07	0.07	1.06	.29
Model 2 (retained effects at p < .20)				
Condition	-0.07	0.13	-0.57	.57
Anxiety symptom severity	0.20	0.08	2.57	.01***
Depression symptom severity	0.25	0.08	3.15	.00***

Note. All statistics are derived from pooling the results of 100 imputed datasets. The regression coefficients for anxiety symptom severity and depression symptom are standardized coefficients, because continuous variables were standardized before entering the model. *= p<.20; ** p<.10; *** p<.05

Optimal treatment prediction

Since we did not identify any moderators of treatment response, we could not conduct the planned second step of the analyses in which a prediction model would be built to predict optimal treatment (outcome) for individual participants.

Discussion

This study examined predictors of short term and long term treatment response to a blended ACT intervention vs. a face-to-face CBT intervention in older adults with anxiety symptoms. These two brief interventions were previously found to be equally effective for this patient population [5]. We were primarily interested in identifying moderator variables, as insight into how ACT and CBT differentially affect certain subgroups of patients could inform evidence-based personalized treatment assignment. With this study, we wanted to go beyond the common approach of only examining putative moderators in isolation and aimed to integrate the results from the moderator analyses into a model for assigning treatment to individual patients based on their pattern of pretreatment characteristics. We did not identify any moderators of treatment response

to the blended ACT intervention and CBT intervention. This precluded the development of a treatment assignment model following the procedure from DeRubeis et al [265].

The secondary aim of this study was to identify non-specific predictors of treatment response. These predictors provide prognostic information about which subgroups of anxious older adults are likely to respond more or less favorably to treatment, irrespective of the treatment being the ACT or the CBT intervention. Two non-specific predictors were identified. First, more severe depression symptoms at baseline were found to be predictive of poorer short term and long term treatment response to both the ACT and CBT intervention. Second, baseline mastery levels were predictive of short term treatment response, with higher levels being associated with more favorable responses in both treatment conditions.

Regarding baseline depression symptom severity, earlier studies into the prescriptive and prognostic effects of comorbid depression on treatment response in anxious patients present mixed findings. Some studies found comorbid baseline depression to be associated with worse anxiety outcomes across different treatments [270-273], while others found that it did not predict posttreatment anxiety severity [274-277]. In the study from Wolitzky-Taylor and colleagues [8], depressive comorbidity was found to be a moderator of treatment response. Patients with a comorbid depressive disorder responded better to ACT than CBT, which the authors ascribed to ACT being a more transdiagnostic treatment that targets psychological constructs related to both anxiety and depression. Considering the mixed findings so far, more research into how comorbid depressive symptoms are associated with treatment response in anxious patients is indicated. Ultimately, these studies could inform clinical practice on whether and how the subgroup of anxious patients with comorbid depression (symptoms) could benefit from additional/adapted treatments.

Mastery, the other prognostic variable identified in this study, is part of a set of closely connected psychological constructs (a.o., locus of control, self-efficacy) that are all related to one's perceived control over situations or events [278]. Perceived control variables have been examined in the context of psychological treatment and higher baseline values of different measures have repeatedly been demonstrated to be related to more favorable treatment outcomes across a wide spectrum of psychological conditions (including anxiety) and treatments [279-282]. People with higher levels of perceived control show increased task motivation and stronger intentions to complete planned behaviors and also demonstrate more effort and persistence when faced with obstacles or adversity [283,284]. In a psychotherapy setting, this might translate

into an increased ability and motivation to actively engage with the treatment, thereby improving treatment outcomes. The current finding implies that patients with lower levels of mastery at the outset of treatment might benefit from additional therapeutic strategies to enhance their mastery. Further research is needed to establish if and how mastery can be directly targeted, and whether such treatment enhancement strategies indeed lead to more favorable treatment outcomes.

Some limitations of the current study have to be discussed. First, like most studies into treatment moderators, the current study was a post-hoc analysis of RCT-data, which was not primarily designed to test for treatment moderators, and might therefore be underpowered to detect multiple modest interaction effects [285]. To truly advance evidence-based personalized treatment assignment in mental health care, moderator analyses should be conducted in larger study samples. This could also be achieved by combining participant level data from multiple studies using individual patient data (IPD) meta-analyses. Furthermore, studies specifically designed to confirm variables' moderating effects are essential for the development of decision tools for personalized treatment assignment, but these are lacking at the moment [286]. A second limitation is the absence of a non-active control condition. Because of this, we cannot ascertain whether the identified prognostic effects truly reflect a difference in *treatment response* between participants, or if individuals scoring higher on mastery and lower on depression severity would have also shown relatively larger symptom improvement without (active) treatment. Third, a substantial number of participants did not complete the posttreatment and/or follow-up measurements, which resulted in a considerable amount of missing data. However, we aimed to handle this problem optimally by imputing data using predictive mean matching, which is a well-established imputation method [237]. Fourth, generalizability of the results is limited by the fact that several exclusion criteria were used during participant recruitment for the RCT. Most importantly, people over 75 years and those with more severe psychological and/or physical conditions were excluded from participation. This reduces the heterogeneity and representability of the study sample. Last, we did not examine interactions between predictor variables, as we already conducted a large number of statistical tests. Therefore, we do not know if the prognostic effects we observed vary as a function of other predictor variables. Examining these more complicated relations between predictor variables is an important task for future studies.

Despite these limitations, the current study adds to the scientific literature, as it was the first to examine moderators and non-specific predictors of treatment response

to an ACT and CBT intervention in older adults with anxiety symptoms. We did not identify any moderators of short term or long term treatment response. These results indicate that, for now, the choice between blended ACT and face-to-face CBT for anxiety symptoms in later life can be guided by client- and therapist preferences and practical considerations. Regarding non-specific predictors, we found that higher levels of baseline depression symptom severity predicted poorer treatment response across the interventions on both the short and long term. Furthermore, higher baseline levels of mastery were predictive of more favorable short term treatment response in both the ACT and CBT intervention. Before these preliminary findings can be translated into clinical recommendations, they should be replicated and elaborated upon in future research, preferably in studies primarily designed to investigate prescriptive and non-specific predictors of treatment outcomes in anxious patients.

MEDIATORS AND PREDICTORS OF CHANGE IN COGNITIVE BEHAVIORAL THERAPY AND ACCEPTANCE AND COMMITMENT THERAPY FOR ANXIETY SYMPTOMS

Manuscript under review: Witlox M, Kraaij V, Garnefski N, Bohlmeijer ET, Spinhoven P. Mediators and predictors of change in Cognitive Behavioral Therapy and Acceptance and Commitment Therapy for anxiety symptoms.

Abstract

Background: Research suggests that Cognitive Behavioral Therapy (CBT) and Acceptance and Commitment Therapy (ACT) are equally effective in the treatment of anxiety symptomatology. So far, little empirical evidence is available on the working mechanisms of both treatments.

Objective**:** This study examined multiple candidate mechanisms of change in CBT and ACT for anxiety in terms of their prospective and/or mediational role. It was hypothesized that reappraisal mediated change in anxiety symptom severity in CBT. Acceptance, rumination, distraction and suppression were hypothesized to be ACT-specific mediators. Furthermore, behavioral avoidance, therapeutic alliance and treatment expectancies were hypothesized to be prospectively predictive of anxiety symptom severity in both treatments.

Methods: Data were collected as part of a randomized controlled trial comparing the effects of CBT and ACT in a sample of 314 older adults (aged 55-75 years) with anxiety symptomatology. Participants filled in self-report questionnaires assessing anxiety symptom severity (Generalized Anxiety Disorder-2) and the candidate mechanisms a total of five times over the course of treatment. Random intercept-cross lagged panel models were used to model the hypothesized prospective and mediational relationship on the within-person level.

Results: None of the candidate mechanisms were found to be mediators or prospective predictors of anxiety symptom severity over the course of the CBT and ACT intervention.

Conclusions**:** The examined candidate mechanisms were not found to be predictors or mediators of anxiety symptom change in CBT and ACT. The discrepancy with previous positive findings may be attributed to earlier studies not using a longitudinal design and analysis on the within-person level.

Introduction

Anxiety disorders and symptoms form the most common class of adult psychological problems [287,288]. Over the past decades, Cognitive Behavioral Therapy (CBT) has become the most empirically supported psychological treatment for anxiety [289-291]. More recent studies have demonstrated that Acceptance and Commitment Therapy (ACT) has similar effects as CBT in the treatment of anxiety symptoms in adults [53,243,292]. Our research team recently conducted the first large-scale randomized controlled trial (RCT) comparing CBT and ACT in a large sample of *older* adults with anxiety symptomatology [250] and also found no important differences between the two interventions regarding their effects on anxiety symptom severity and related clinical outcomes. Significant reductions of anxiety symptom severity (effect sizes d $\geq$.96) were observed in both the CBT and the ACT condition between baseline and posttreatment and were sustained at the one year follow up. Research so far thus suggests that CBT and ACT do not differ regarding their effectiveness in treating adults with anxiety.

Although the effectiveness of CBT and ACT for anxiety has been demonstrated, relatively little research has been conducted into the mechanisms through which these treatments lead to anxiety symptom change. Investigating the mechanisms that might be responsible for psychotherapeutic change will lead to a better understanding of the theoretical underpinnings of the treatments and provide directions for treatment augmentation strategies [227]. Convincingly demonstrating *the causal role* of proposed mechanisms of change is complicated and requires a series of studies and experiments. An important first step in understanding mechanisms of change in psychotherapy is the identification of treatment mediators: variables that statistically account for the relationship between treatment and treatment outcome [227].

One of the most common shortcomings of studies into treatment mediators is that they lack the establishment of a timeline that shows that the candidate mediator precedes the outcome, which is a necessary (but not sufficient) condition for mediation [227, 293]. Most studies into treatment mediation only assess the putative mediator(s) and outcome variable(s) at baseline and after treatment. Such studies cannot distinguish whether change in the putative mediator indeed *precedes* symptom change, *co-occurs* with symptom change, or *follows* symptom change. Rigorous examination of treatment mediators requires a study design in which the proposed mechanism of change and the outcome variable are repeatedly assessed during treatment. That is why in the current study we used data from multiple timepoints during treatment to

examine the temporal relationships between candidate mechanisms of change and anxiety symptom improvement in a brief CBT intervention and a brief ACT intervention for older adults with anxiety symptoms.

Theories of change in CBT and ACT

Both CBT and ACT are developed with an explicit theoretical notion of how the treatment leads to change. The two treatments can be most clearly distinguished by how they proposedly influence cognitive emotion regulation strategies. On the one hand, CBT aims to reduce the frequency and intensity of anxiety symptoms by identifying and adapting anxiety related cognitions. Through a process of reappraisal, unrealistic negative thoughts concerning the threat posed by certain situations, events or bodily sensations are replaced with more nuanced and adaptive thoughts [44]. Meta-analyses concluded that CBT for anxiety disorders indeed leads to improvements in threat reappraisal [294] and that these improvements are associated with reductions in anxiety symptom severity [295], but that there is not enough evidence yet to conclude that changes in threat reappraisal *cause* symptom improvement in CBT

Contrary to CBT, ACT does not directly focus on changing or reducing anxious feelings and thoughts, but instead stimulates active acceptance of all internal experiences, including those we tend to label as 'negative', 'unwanted' or 'harmful'. A more accepting stance towards internal experiences is theorized to lead and to less use of cognitive and behavioral strategies aimed at changing or controlling emotions or thoughts, that actually sustain or exaggerate anxiety (e.g., rumination, distraction, suppression, behavioral avoidance) [296]. Two review articles on the working mechanisms of ACT concluded that changes in constructs related to the acceptance of inner experiences seem to occur prior to changes in psychological symptoms, but strong causal evidence is lacking [64,297].

So far, three studies have directly compared cognitive emotion regulation strategies as mediators in CBT and ACT for anxiety, using session-by-session data [298-300]. These studies present mixed findings: on the one hand, they confirmed that ACT achieved its effect specifically through an increased acceptance of feelings, while change in CBT was mediated by increased use of strategies to change feelings [300]. On the other hand, the studies indicated that treatment outcomes in ACT and CBT were equally associated with changes in negative and dysfunctional thinking (expected to be CBT-specific mediators) and cognitive defusion (the process of distancing oneself from the literal meaning of anxiety-related cognitions; expected to be an ACT specific

mediator) [298,299]. Taken together, these results suggest that CBT and ACT may have both similar and distinct cognitive mechanisms of change.

While CBT and ACT differ regarding the cognitive emotion regulation strategies they assumedly promote, they also share an important theorized mechanism of change in the treatment of anxiety: both treatments aim to reduce anxiety related avoidance behavior through exposure. Although the rationale behind exposure differs between CBT and ACT, it can be expected that reductions in behavioral avoidance contribute to anxiety symptom improvement in both interventions. To date only Forman et al. [300] have examined the role of (self-reported) behavioral avoidance in ACT and CBT in a sample of students with an anxiety or mood disorder. This study indeed found that reductions in self-reported behavioral avoidance was associated with improvement of treatment outcome, irrespective of treatment group.

Common factors

Contrary or supplementary to the idea that treatments exert their effects through (specific) theorized mechanisms is the idea that treatments work through so called common factors: mechanisms of change that most or all psychotherapies share. One of the most well-known and well-developed common factor theories is the contextual model [301,302]. This model states that psychotherapies achieve their effects through two common pathways: 1) the therapeutic relationship and 2) creating positive expectations/hope. First, an empathic, genuine and caring connection between the client and therapist is assumed to be beneficial in itself, especially for those patients that do not have such connections in their everyday lives. Second, the model states that psychotherapies elicit positive expectancies in the clients by providing them with an explanation about their psychological problems and how the treatment will help them in reducing these problems. Clients' expectancies regarding their ability to successfully complete the treatment –also called treatment self-efficacy- are also stimulated. The clients thus come to believe that completing the treatment will help them in coping with their problems and are provided with a sense of control over their own distress, as they contribute their therapeutic progress to their own efforts.

Looking at the empirical evidence for the common factors in the contextual model, a recent review article that included studies that accounted for temporality through the use of repeated assessments during treatment, concluded that improvement of the therapeutic alliance may indeed precede symptom reduction, which might point to a causal role of this common factor [303]. Considering client expectations, a large meta-

analysis including studies into different patient populations and treatment approaches found a small but statistically significant association between more optimistic early-therapy treatment expectancies and more favorable therapeutic outcomes [304]. Treatment expectancy is thus an empirically validated *correlate* of treatment outcome, but it is not clear if it should be considered a mechanism of action or merely a proxy of therapeutic improvement. Regarding evidence for a mechanistic function of this common factor, one elegant study found that changes in treatment expectancy during CBT for generalized anxiety disorder (GAD) mediated the relationship between baseline GAD severity and reliable change in this outcome at posttreatment [305].

The current study

The current study used data collected at multiple assessments during treatment to examine candidate mechanisms of change in a brief CBT and brief ACT intervention for older adults with anxiety symptomatology. The candidate mechanisms were divided into mechanisms related to the theoretical underpinnings of CBT and ACT and mechanisms assumed to drive change in psychotherapy in general (common factors). We hypothesized that increased use of cognitive reappraisal mediated treatment outcome in CBT. Furthermore, we expected that treatment outcome in ACT was mediated by an increase in the non-judgmental acceptance of feelings, decreased dwelling upon feelings (rumination) and decreased use of strategies aimed at avoidance of internal experiences (suppression, distraction). Lastly, we expected behavioral avoidance to be equally associated with anxiety symptom severity in the ACT and CBT group. Behavioral avoidance was thus not studied as a mediator in the strict sense of the term in the current study, as the study did not include a control condition in which behavioral avoidance was not targeted. Since behavioral avoidance was hypothesized to be a mechanism of change in both ACT and CBT, statistical analyses concerning the role of behavioral avoidance did not include treatment condition as an independent variable. Regarding common mechanisms, we followed the contextual model and hypothesized the therapeutic alliance and treatment expectancies (treatment outcome expectancy and treatment self-efficacy expectancy) to be associated with anxiety symptom severity across both treatments. Similarly to behavioral avoidance, these three factors could not be studied as mediators and were only expected to prospectively predict change in anxiety symptom severity during treatment across both conditions.

Methods

This study uses data collected in a cluster-randomized single blind controlled trial in the Netherlands. The trial evaluated the effectiveness of face-to-face CBT compared to a blended ACT intervention over a period of 12 months. The study was powered to detect a difference between the conditions on the primary outcome anxiety symptom severity as measured with the Generalized Anxiety Disorder-7 (GAD-7) [131]. Randomization took place at the level of the mental health counselors that provided the interventions (n=40). The mental health counselors were randomized to either provide only CBT (n=20) or only ACT (n=20) to study participants. Details about the study design and methods have been published [236]. The trial was registered in the Netherlands Trial Register (NL6131 (NTR6270)) and approved by the medical ethics committee of Leiden University Medical Center (LUMC; no. P16.248).

Participants and procedure

Participants were recruited from 38 general practices in the Netherlands between November 2017 and March 2019. Patients (aged 55 – 75) from the participating general practices were sent a letter containing information about the study and an invitation to participate. If people were interested in participation, they could register on a study website, after which they entered the screening procedure which consisted of an online questionnaire and a telephone interview. Inclusion criteria were: age between 55 and 75 years, presence of mild to moderate anxiety symptoms (GAD-7 score between 5 and 15 [131]), mastery of the Dutch language, internet access and the possibility to spend up to 30 min per day on the intervention. Exclusion criteria were: unstable severe medical condition(s); severe cognitive impairment; very high or low anxiety symptom severity (GAD-7 score < 5 / > 15 [131]); severe depressive symptoms (PHQ-9 [170] score $\geq$ 20); psychological or psychopharmacological treatment (stable benzodiazepine or SSRI use excepted) within the last 3 months; severe role impairment in at least 2 life areas (score of $\geq$8 on two or three items of the Sheehan Disability Scale (SDS) [171]; high suicide risk (M.I.N.I.-Plus [139]); substance use disorder (M.I.N.I.-Plus); lifetime diagnosis of bipolar disorder or schizophrenia (medical record and M.I.N.I.-Plus).

Eligible participants signed an online informed consent form and subsequently completed the baseline assessment, after which they were informed about their treatment allocation. Participants completed 4 main assessments: at baseline, posttreatment

(three months after baseline), 6 months after baseline and 12 months after baseline. In the current study, data from the 6- and 12-month follow up are not used in the analysis.

During treatment, participants were asked to complete a short questionnaire assessing anxiety symptom severity and potential mechanisms of change multiple times. Participants in the CBT group were sent the questionnaire after every session with their mental health counselor (4 times). Participants in the blended ACT group were asked to fill in the questionnaire at the beginning of each lesson of the online module (9 times). In order to compare the hypothesized temporal and mediational pathways in both groups, in the current study we did not include the data of all the 9 assessments in the ACT group, but only those completed after each face-to-face session. Furthermore, for both the CBT and ACT group, we excluded the data collected after the fourth (final) face to face session: only 62 participants completed this assessment and of these a majority of 37 did so one day prior or on the same day as the posttreatment assessment. Summarizing, in the current study we used data collected at baseline (T0), during treatment (T1-T3) and posttreatment (T4). To study the common factors we only used data collected during treatment (T1-T3), because participants could not rate the therapeutic alliance and expectations regarding treatment before having been introduced to their mental health counselor and the treatment approach in the first session. The data used for analyses in the current study were all collected using online self-report questionnaires.

Interventions

Therapists

Treatment was provided by mental health counselors working in general practices in the Netherlands. The counselors provide short term psychological treatment to patients with mild to moderately severe psychological complaints. The occupation is fulfilled by mental health professionals with varying educational backgrounds. Of the counselors participating in this study, most were graduates in psychology (n=13), social psychiatric nurses (n=14) or social workers (n=5). Years of experience with providing individual psychological treatment in the sample of mental health counselors ranged from 3 to 42, with a median of 16 years.

Cognitive Behavioral Therapy

Participants in the CBT condition attended 4 face-to-face sessions with the mental health counselor and completed homework exercises in between the sessions. The sessions took place in a timespan between 9 to 12 weeks. The sessions followed a

protocol (developed by authors N.G., M.W., V.K. and P.S.) that focused on identifying and challenging negative cognitions and reducing anxiety-related avoidance behavior. The protocol mainly consisted of worksheets and exercises related to specific types of anxiety (e.g., panic, worrying, social anxiety). Additionally, some worksheets/exercises focused on common side effects of anxiety (e.g., sleeping problems, physical tension). After the first session, which served as an intake, the counselor and client collaboratively set treatment goals. In the second and third session, homework was evaluated and prepared and key exercises/information were repeated. The last session focused on evaluating the progress of the client and formulating a relapse prevention plan.

Blended Acceptance and Commitment therapy

Participants in the Blended ACT condition were provided with the online ACT-module 'Living to the Full' [180,181] and 4 face-to-face sessions with the mental health counselor at their general practice. The online module contains 9 lessons that revolve around the 6 core processes of ACT: acceptance, cognitive defusion, contact with the present moment, self as context, personal values and committed action. Participants completed the module in 9 to 12 weeks, which required them to dedicate 15-30 minutes to the program on a daily basis. The 4 face-to-face sessions with the mental health counselor followed a protocol developed by the authors of Living to the Full and focused on increasing motivation, repeating key exercises, and discussing potential problems the client faced in working with the online module.

Measurements: outcome variable

Anxiety symptom severity

Anxiety symptom severity at baseline, during treatment and at posttreatment was measured with the Generalized Anxiety Disorder-2 [183]. The GAD-2 consists of the first two items of the Generalized Anxiety Disorder-7 ("Feeling nervous, anxious, or on edge" and "Not being able to stop or control worrying"). The GAD-2 is a reliable, valid, and sufficiently sensitive and specific instrument [183].

Measurements: candidate mechanisms of change

Cognitive emotion regulation strategies

The cognitive emotion regulation strategies reappraisal, acceptance, rumination, distraction, suppression and were each measured with one self-developed item. See

Table 1 for the items. Participants were asked to rate how often they used the strategy during the preceding week on a scale ranging from 0 (never) to 5 ((almost) always).

Behavioral avoidance

Behavioral avoidance was assessed with a self-developed item that is presented in Table 1. Participants indicated how often they avoided situations/activities due to their anxiety in the preceding week on a 0-5 scale.

Common factors

The Session Rating Scale (SRS) [219] was used to measure participant's rating of the therapeutic relationship. The SRS assesses 4 aspects of the working alliance during a therapeutic session, using one item per aspect: the relational bond, the degree to which desired goals and topics of the individual were discussed, the therapist's approach or working style, and an overall evaluation of the session. Items were answered on an 11-point, with '0' reflecting the most negative evaluation and '10' the most positive response. A sum score of the 4 items was calculated, with higher scores reflecting a better alliance according to the client. The SRS has high test-retest and internal consistency reliability, as well as acceptable validity [220, 221]. Treatment outcome expectancy was measured with one item, that was answered on a scale ranging from 1 (not at all) to 7 (very much). The item comes from the Treatment Credibility Questionnaire [207]. Treatment self-efficacy was assessed with one self-developed item, that used the same 7-point scale as the treatment outcome expectancy question. See Table 1 for the items.

Table 1. Overview of the examined candidate mechanisms of change and related hypotheses

Candidate mechanism	Measure	Hypothesis
Reappraisal	I tried to change how I think about the cause of my feelings	Mediates reduction of anxiety symptom severity in CBT
Acceptance	I tried to accept my feelings without judging them	Mediates reduction of anxiety symptom severity in ACT
Rumination	I could not stop thinking about my feelings	Mediates reduction of anxiety symptom severity in ACT
Distraction	I tried to distract myself from my feelings	Mediates reduction of anxiety symptom severity in ACT
Suppression	I tried to suppress my feelings	Mediates reduction of anxiety symptom severity in ACT
Behavioral avoidance	My anxiety made me avoid situations and/or activities	Prospectively predicts changes in anxiety symptom severity across CBT and ACT

Table 1. Continued

Candidate mechanism	Measure	Hypothesis
Therapeutic alliance	SRS	Prospectively predicts changes in anxiety symptom severity across CBT and ACT
Treatment outcome expectancy	How confident are you that the intervention will be helpful in reducing your anxiety complaints	Prospectively predicts changes in anxiety symptom severity across CBT and ACT
Treatment self-efficacy	How confident are you that you will do what is required to successfully follow and complete this intervention?"	Prospectively predicts changes in anxiety symptom severity across CBT and ACT

Statistical Analysis

Descriptive statistics were calculated in SPSS 25.0 [306]. All other statistical procedures were performed using Mplus v 6.11 [307]. To test whether the candidate mechanisms of change predicted anxiety symptoms over the course of treatment, Random Intercept Cross Lagged Panel Models (RI-CLPM) were used. A separate model was created for each candidate mechanism. RI-CLPM is an extension of the traditional Cross Lagged Panel Model that accounts for time-invariant, trait-like stability in the modelled variables by the inclusion of random intercepts [308]. Traditional CLPM assumes no stable intra-individual differences in the studied variables. This assumption is often untrue, as many psychological variables are trait-like to a certain extent. In RI-CLPM the variance of the observed score is divided into variance due to a between-person stable invariant trait (by adding a random intercept) and variance due to within-person fluctuation. By separating within-person variance from between-person variance, RI-CLPM allows for statements regarding within–person processes, which are more likely to reflect causal effects than between-person associations [308,309].

Prior to the RI-CLPM analyses, we calculated intra-class correlations (ICC) for all variables. ICC can be defined as the proportion of the variance explained by differences between subjects. Consequently, the RI-CLPM was created, by first regressing the observed scores for anxiety symptom severity and the candidate mechanism on their own latent factor (loading fixed to 1). Residual variances of the observed variables were set to zero, so that the latent factor structure captured the within- and between-person variance.

Next, two random intercepts (one for anxiety symptom severity, one for the candidate mechanism) were added to the model, with factor loadings constrained at one. These random intercepts reflect an individual's time-invariant deviation

from the grand means and therefore represent stable trait-like differences between participants with regard to the modelled variables. The correlation between the random intercepts represents the association between stable between-person differences in the candidate mechanism variable and stable between-person differences in anxiety symptom severity.

The latent factors were used to model autoregressive paths, cross-sectional paths and cross-lagged paths. Autoregressive paths are interpreted as the extent to which deviations from expected scores (based on the grand mean and random intercept) at one wave predicted deviations from expected scores for the same variable at the next assessment wave. The cross-sectional paths reflect the association between deviations from the expected scores on anxiety symptom severity and deviations from the expected scores on the candidate mechanism variable at each assessment wave. To test the hypotheses concerning the temporal precedence of the candidate mechanisms, the cross-lagged paths are of interest. These paths reflect the bidirectional relationship between anxiety symptom severity and the candidate mechanism. They indicate to what extent deviations from expected scores on the candidate mechanism variable are associated with deviations from expected anxiety symptom severity at the next measurement moment, and vice versa.

Lastly, for the subset of candidate mechanisms that we hypothesized to be treatment mediators (reappraisal, acceptance, rumination, distraction, suppression), we estimated the indirect effect of the intervention condition (CBT=0, ACT=1) on anxiety symptoms severity at assessment wave *t* via the hypothesized mediating variables at *t-1* using a bootstrapping procedure (n=5000). This resulted in 3 indirect effects in each mediation model (anxiety symptom severity at T4 via mediator at T3; anxiety symptom severity at T3 via mediator at T2; anxiety symptom severity T2 via mediator at T1). The mediation test required that we also added the direct effects of intervention condition on scores at all assessment waves after baseline to these models.

Analyses were performed on the basis of the intention-to-treat principle, including all randomized participants with baseline assessments. Full information maximum likelihood (FIML) estimations were used to handle missing data. We used 4 model fit indices to evaluate the fit of the models: the Root Mean Square Error of Approximation (RMSEA), the Standardized Root Mean squared residual (SRMR), the Comparative Fit Index (CFI) and the Tucker–Lewis index (TLI). For the RMSEA and SRMR values smaller than 0.08 and 0.05 were considered indicators of respectively acceptable and good model fit [42, 43]. For the CFI and TFI model fit was considered adequate for values higher than 0.90 and good for values higher than 0.95 [310,311].

Results

Assessments were completed by 314 participants at baseline (T0) (CBT n=164; ACT n=150), 238 after session 1 (T1) (CBT n=131; ACT n=107), 204 after session 2 (T2) (CBT n=102; ACT n=102), 153 after session 3 (T3), (CBT n=91; ACT n=62) and 222 at posttreatment (T4) (CBT n=121 ACT n=101). See Table 2 for the means and standard deviations of the observed scores for the total sample and two treatment conditions at each assessment wave. ICC's for the examined variables varied from 0.15 (reappraisal) to 0.41 (therapeutic alliance); all other ICC values fell in a range of 0.21 to 0.32. This indicates that for most variables between 21% and 32% of variance could be explained by differences *between* participants, while the rest (i.e., most) variance could be explained by fluctuations *within* participants.

Outcomes of the RI-CLPM are presented in Table 3 and in Figure 1-9 in Appendix 1. Model fit was acceptable or good for all RI-CLPM's (RMSEA: 0.00 – 0.04; SRMR: 0.02 – 0.05; CFI: 0.96 – 1.00; TLI: 0.90 – 1.00). At the between-person level, we found statistically significant associations between the random intercept of anxiety on the one hand and the random intercepts of the variables rumination, distraction, suppression and behavioral avoidance on the other hand. This indicates that participants who had higher anxiety symptom severity scores across the 5 measurement waves (i.e., higher trait-like anxiety) also reported higher levels of rumination, distraction, suppression and behavioral avoidance across the assessments. The random intercepts of the other predictor variables were not significantly associated with the random intercept of anxiety symptom severity.

Most auto-regressive paths were not statistically significant, indicating no consistent relation between within-person fluctuations at successive assessment waves. Regarding cross-sectional associations, reappraisal, rumination and behavioral avoidance showed a consistent positive relationship with anxiety symptom severity on a within-person level. This indicates that within-person change in anxiety symptom severity was related to within-person change in reappraisal, rumination and behavioral avoidance at the same assessment wave. Suppression scores were positively associated with anxiety symptom severity at the first three assessment waves, and distraction scores only at the third assessment. No other cross-sectional paths were statistically significant.

The mediation hypotheses regarding the variables of reappraisal, acceptance, rumination, distraction and suppression were not confirmed: none of the modelled indirect paths were statistically significant. Results did indicate some statistically significant direct

effects: during treatment participants in the ACT group showed larger deviations from expected scores (based on the grand mean and random intercept) on the hypothesized ACT-mechanisms than participants in the CBT group. At T2 scores from participants in the ACT group scored showed larger deviations (in the expected direction) than participants in the CBT group on acceptance (t=3.45, p=.00), rumination (t=-2.33, p=.02), suppression (t=-2.80, p=.01) and distraction (t=-3.37, p=.02). At T3 this was still the case for suppression (t=-4.55, p=.00) and distraction (t=-2.74, p=.01). Furthermore, at T2 the c-path (from the independent variable to the dependent variable) was significant, with participants in the ACT group showing larger downward deviations from their expected anxiety symptom severity than participants in the CBT group (t=-2.99, p=.00).

Lastly, contrary to our hypotheses, none of the within-person cross-lagged paths from behavioral avoidance, therapeutic alliance, treatment outcome expectancy and treatment self-efficacy to anxiety symptom severity were statistically significant. This means that none of these variables prospectively predicted anxiety symptom severity over the course of the treatments.

Table 2. Mean scores and standard deviations for both conditions on all measurement waves

Variable	Condition	T0 (baseline), M (SD)	T1, M (SD)	T2, M (SD)	T3, M (SD)	T4 (posttreatment), M (SD)
Anxiety	CBT	2.40 (1.62)	2.33 (1.61)	2.22 (1.42)	1.65 (1.51)	1.48 (1.23)
	ACT	2.24 (1.52)	2.40 (1.51)	1.67 (1.19)	1.29 (0.98)	1.48 (1.21)
	Total	2.33 (1.57)	2.37 (1.55)	1.94 (1.33)	1.50 (1.33)	1.48 (1.22)
Reappraisal	CBT	1.44 (1.03)	1.68 (1.04)	2.05 (1.08)	2.30 (1.40)	2.38 (1.40)
	ACT	1.58 (1.11)	1.97 (0.99)	2.28 (1.20)	2.76 (1.35)	2.57 (1.43)
	Total	1.51 (1.07)	1.84 (1.02)	2.16 (1.14)	2.48 (1.30)	2.47 (1.41)
Acceptance	CBT	2.29 (1.22)	2.28 (1.20)	2.24 (1.28)	2.69 (1.25)	2.65 (1.36)
	ACT	2.23 (1.32)	2.24 (1.01)	2.83 (1.31)	3.05 (1.49)	2.80 (1.51)
	Total	2.26 (1.27)	2.26 (1.09)	2.53 (1.32)	2.84 (1.36)	2.72 (1.43)
Rumination	CBT	2.27 (1.26)	2.70 (1.36)	2.07 (1.32)	1.65 (1.16)	1.67 (1.31)
	ACT	2.06 (1.29)	2.61 (1.27)	1.69 (1.18)	1.36 (1.26)	1.42 (1.21)
	Total	2.12 (1.27)	2.65 (1.31)	1.88 (1.26)	1.53 (1.20)	1.56 (1.27)
Distraction	CBT	2.41 (1.11)	2.78 (1.17)	2.40 (1.19)	2.33 (1.24)	1.98 (1.30)
	ACT	2.40 (1.24)	2.70 (1.04)	1.99 (1.22)	1.53 (1.18)	1.76 (1.27)
	Total	2.41 (1.17)	2.74 (1.10)	2.20 (1.22)	2.01 (1.27)	1.88 (1.29)
Suppression	CBT	2.38 (1.16)	2.58 (1.25)	2.17 (1.28)	2.08 (1.17)	1.77 (1.28)
	ACT	2.29 (1.19)	2.60 (1.08)	1.66 (1.12)	1.11 (1.12)	1.30 (1.15)
	Total	2.33 (1.18)	2.59 (1.15)	1.92 (1.23)	1.69 (1.24)	1.56 (1.24)
Behavioral Avoidance	CBT	1.83 (1.15)	2.19 (1.30)	1.69 (1.29)	1.50 (1.11)	1.31 (1.22)
	ACT	1.77 (1.17)	2.21 (1.12)	1.36 (1.06)	0.79 (0.87)	1.02 (1.11)
	Total	1.80 (1.16)	2.20 (1.20)	1.52 (1.19)	1.21 (1.07)	1.18 (1.18)
Treatment expectancy	CBT	-	4.59 (1.19)	3.68 (1.00)	3.77 (1.19)	-
	ACT	-	4.69 (1.02)	3.86 (1.10)	4.3 (1.11)	-
	Total	-	4.64 (1.09)	3.77 (1.05)	3.99 (1.19)	-
Treatment self-efficacy	CBT	-	5.45 (1.36)	4.47 (0.98)	4.41 (1.28)	-
	ACT	-	5.41 (1.09)	4.46 (1.24)	4.55 (1.24)	-
	Total	-	5.43 (1.22)	4.46 (1.03)	4.46 (1.26)	-
Therapeutic Alliance	CBT	-	32.41 (6.06)	32.81 (6.89)	35.02 (5.77)	-
	ACT	-	31.81 (6.28)	32.54 (6.55)	35.15 (4.43)	-
	Total	-	32.08 (6.18)	32.68 (6.71)	35.07 (5.25)	-

Table 3. Outcomes of the random intercept cross-lagged panel models examining the temporal and mediational relationships of the candidate mechanisms of change and anxiety symptom severity

	Reappraisal	Acceptance	Rumination	Distraction	Suppression	Behavioral avoidance	Therapeutic alliance	Treatment expectancy	Treatment self-efficacy
Model fit									
RMSEA	0.04	0.03	0.00	0.02	0.03	0.02	0.00	0.03	0.01
CFI	0.96	0.98	1.00	1.00	0.99	1.00	1.00	1.00	1.00
TLI	0.90	0.96	1.00	0.99	0.97	1.00	1.01	0.97	1.00
SRMR	0.05	0.04	0.03	0.05	0.05	0.03	0.02	0.03	0.02
Random intercepts									
Variance RI anx	0.59 (0.12)***	0.56 (0.11)***	0.56 (0.11)***	0.58 (0.11) ***	0.59 (0.11)***	0.62 (0.11)***	0.45 (0.29)	0.46 (0.30)	0.51 (0.28)
Variance RI m	0.13 (0.06)*	0.29 (0.08)***	0.42 (0.08)***	0.36 (0.07)***	0.41 (0.06)***	0.42 (0.08)***	12.87 (3.8)**	0.43 (0.15)**	0.57 (0.21)**
RI anx with RI m	0.08 (0.06)	-0.07 (0.06)	0.35 (0.08)***	0.36 (0.07)***	0.37 (0.07)***	0.36 (0.07)***	0.53 (0.75)	-0.18 (0.13)	-0.12 (0.17)
Autoregressive paths									
anx1 on anx0	0.28 (0.08)***	0.26 (0.08)***	0.24 (0.08)**	0.25 (0.08)***	0.26 (0.08)**	0.28 (0.08)***	-	-	-
anx2 on anx1	0.14 (0.07)	0.14 (0.07)	0.12 (0.08)	0.10 (0.08)	0.11 (0.08)	0.12 (0.07)	0.19 (0.13)	0.16 (0.14)	0.20 (0.30)
anx3 on anx2	0.19 (0.12)	0.17 (0.14)	0.22 (0.13)	0.22 (0.13)	0.16 (0.13)	0.06 (0.13)	0.22 (0.19)	0.19 (0.21)	0.24 (0.19)
anx4 on anx3	0.15 (0.11)	0.13(0.11)	0.27 (0.10)**	0.19 (0.10)	0.17 (0.11)	0.14 (0.12)	-	-	-
m1 on m0	0.04 (0.08)	0.13 (0.08)	0.04 (0.08)	0.10 (0.08)	0.11 (0.08)	0.16 (0.09)	-	-	-
m2 on m1	0.15 (0.11)	0.04 (0.08)	-0.04 (0.10)	-0.03 (0.10)	-0.09 (0.11)	0.10 (0.09)	-0.16 (0.27)	-0.09 (0.30)	0.15 (0.16)
m3 on m2	0.23 (0.10)*	-0.02 (0.12)	0.27 (0.10)**	0.05 (0.10)	0.29 (0.10)**	0.35 (0.10)***	0.47 (0.13)***	0.60 (0.17)***	0.23 (0.11)
m4 on m3	0.49 (0.08)***	-0.09 (0.12)	0.23 (0.10)*	0.17 (0.11)	0.41 (0.10)***	0.25 (0.14)	-	-	-
Cross-sectional paths									
anx0 with m0	0.21 (0.10)*	-0.06 (0.11)	0.31 (0.11)*	0.12 (0.10)	0.21 (0.10)*	0.21 (0.10)*	-	-	-
anx1 with m1	0.34 (0.11)**	-0.05 (0.10)	0.34 (0.11)**	0.04 (0.10)	0.20 (0.10)*	0.34 (0.11)**	0.25 (0.83)	0.16 (0.16)	0.25 (0.18)
anx2 with m2	0.38 (0.09)***	-0.10 (0.10)	0.48 (0.10)***	0.10 (0.10)	0.20 (0.10)*	0.38 (0.09)***	-0.45 (0.76)	0.02 (0.15)	-0.00 (0.18)
anx3 with m3	0.42 (0.09)***	-0.10 (0.13)	0.42 (0.12)**	0.44 (0.12)***	0.16 (0.11)	0.42 (0.09)***	-0.49 (0.56)	-0.09 (0.10)	-0.13 (0.10)
anx4 with m4	0.29 (0.08)***	0.03 (0.09)	0.21 (0.09)*	0.09 (0.09)	0.14 (0.09)	0.29 (0.08)***	-	-	-

Table 3. Continued

	Reappraisal	Acceptance	Rumination	Distraction	Suppression	Behavioral avoidance	Therapeutic alliance	Treatment expectancy	Treatment self-efficacy
Cross-lagged paths									
anx1 on m0	-0.14 (0.10)	-0.03 (0.09)	0.06 (0.09)	0.07 (0.10)	-0.05 (0.10)	-0.09 (0.11)	-	-	-
anx2 on m1	-0.07 (0.10)	-0.15 (0.10)	0.01 (0.09)	-0.09 (0.10)	-0.01 (0.10)	0.04 (0.10)	0.00 (0.03)	-0.05 (0.19)	0.05 (0.21)
anx3 on m2	-0.19 (0.10)	-0.06 (0.09)	0.04 (0.12)	-0.08 (0.12)	-0.17 (0.12)	0.25 (0.13)	0.00 (0.03)	-0.03 (0.17)	-0.30 (0.24)
anx4 on m3	-0.08 (0.09)	-0.11 (0.08)	0.11 (0.11)	-0.18 (0.10)	-0.18 (0.12)	0.01 (0.15)	-	-	-
m1 on anx0	-0.03 (0.06)	-0.02 (0.06)	0.17 (0.07) ***	0.12 (0.06)*	0.14 (0.06)*	0.06 (0.06)	-	-	-
m2 on anx1	-0.08 (0.07)	-0.00 (0.07)	0.19 (0.07)**	0.04 (0.07)	0.05 (0.07)	0.14 (0.06)	-0.25 (0.44)	0.18 (0.10)	0.10 (0.12)
m3 on anx2	-0.23 (0.12)	-0.17 (0.12)	0.10 (0.13)	0.05 (0.10)	0.01 (0.11)	0.03 (0.09)	-0.87 (0.63)	-0.03 (0.11)	0.06 (0.11)
m4 on anx3	-0.11 (0.12)	-0.10 (0.11)	0.24 (0.11)*	-0.13 (0.10)	-0.05 (0.09)	0.16 (0.11)	-	-	-
Mediational paths									
cond to anx2 via m1	-0.02 (0.03)	0.01 (0.03)	0.00 (0.02)	0.00 (0.02)	0.00 (0.02)	-	-	-	
cond to anx3 via m2	-0.05 (0.04)	-0.04 (0.06)	-0.01 (0.05)	0.03 (0.05)	0.08 (0.07)	-	-	-	-
cond to anx4 via m3	-0.02 (0.03)	-0.01 (0.03)	0.03 (0.05)	0.11 (0.10)	0.15 (0.14)	-	-	-	-
cond to m2 via anx1	-0.01 (0.02)	0.00 (0.02)	0.03 (0.04)	0.01 (0.02)	0.01 (0.02)	-	-	-	-
cond to m3 via anx2	0.11 (0.08)	0.09 (0.07)	-0.05 (0.07)	-0.02 (0.08)	-0.01 (0.07)	-	-	-	-

Discussion

This study examined potential mechanisms of change in a brief CBT and a brief ACT intervention for adults aged 55-75 years with mild to moderately severe anxiety symptoms. These interventions were previously found to result in comparable reductions of anxiety symptom severity [8]. Data were collected at multiple assessments during treatment, which enabled the examination of the relationships between the candidate mechanisms and the outcome variable anxiety symptom severity on the within-person level.

Contrary to our hypotheses based on the theories of change in CBT and ACT, we did not find evidence that the treatments exert their effects on anxiety symptom severity through different cognitive emotion regulation strategies. The relationship between treatment condition and anxiety symptom severity during treatment was not mediated by previous levels of reappraisal, acceptance, rumination, distraction or suppression. Moreover, none of these variables prospectively predicted anxiety symptom severity during treatment across the two treatment conditions. We did find that after the second session participants in the ACT group on average scored higher (on the within-person level) on acceptance and lower on rumination, distraction and suppression than participants in the CBT group. For distraction and suppression this difference was also significant after the third session. At posttreatment however, the conditions did not differ on these variables. These findings may indicate that the ACT has a more direct impact on these cognitive processes than CBT, affecting them earlier during treatment. Lastly, behavioral avoidance did also not prospectively predict anxiety symptom severity over the course of treatment. The current results do therefore not indicate that the examined cognitive emotion regulation strategies and behavioral avoidance were mechanisms of action in the CBT and ACT intervention. This contradicts earlier studies testing the theories of change in CBT and ACT for anxiety. Those studies concluded that cognitive strategies aimed at changing thoughts mediate outcomes in CBT, that acceptance is an ACT-specific mediator [299,300] and that reductions in negative thinking, cognitive fusion and behavioral avoidance are equally associated with treatment outcome in CBT and ACT [298-300]. Importantly, these studies focused on (slightly) different variables and employed different statistical analyses than the current study, which hinders a straightforward comparison with the current findings.

Our hypotheses regarding the common factors were also not confirmed: ratings of the therapeutic alliance and treatment expectancies did not prospectively predict anxiety symptom severity over the course of the CBT and ACT intervention. The null-

finding regarding therapeutic alliance runs counter to earlier studies that found that within-person changes in the patient-rated alliance precede symptom reduction during treatment [303]. The most evident difference between the majority of those studies and the current one is the measurement of the therapeutic alliance. In the current study the Session Rating Scale (SRS) was used, while most other studies employed the Working Alliance Inventory (WAI) [303]. Psychometric evaluations of the SRS found that its concurrent validity with the WAI is moderate (r = .57–.65), which is lower than expected as both instruments aim to measure the working alliance in therapy [221,312]. The two scales might thus measure slightly different concepts, which may explain the discrepancy between the current findings and those from studies that used the WAI. A comprehensive discussion of the null-findings regarding treatment expectancy is precluded because rigorous studies into treatment expectancy as a mechanism of change in psychotherapy are largely lacking at the moment. Most previous studies have operationalized expectancy as a static construct and only assessed it once at the beginning of treatment [304]. To elucidate the role of treatment expectancy in psychological treatment, more studies are needed that –similar to the current study- consider expectancy as dynamic and malleable and measure it multiple times during treatment.

As is clear, we cannot easily compare the current findings to results from earlier studies, due to differences in research design, measurement and statistical procedure. Two features that have already been touched upon that most clearly distinguish the current study from many previous studies are its longitudinal design and the disentanglement of within- and between-person variance. These two features are important strengths of the current study, because they increase its weight in terms of potential causal inferences. Using data from multiple assessments during treatment enabled the establishment of a timeline, which is a requisite for inferring mediation or a causal relation. Furthermore, separating between-person and within-person variance is crucial in ascertaining whether associations reflect relatively stable differences *between* people (that can often be explained away by time-invariant third variables) or if they point to processes that occur over time *within* people and thus to possibly causal processes that might be useful targets for treatment augmentation strategies [313]. Unfortunately, the majority of studies into the mechanisms of psychotherapeutic change (of CBT and ACT) did not establish temporal precedence and/or did not separate within- and between-person variance in their analysis [64,294,295,297-300,303,304]. These studies have therefore mostly established cross-sectional

associations between candidate mechanisms and outcome variables on the between-person level. We replicated these findings and found that on the between-person level rumination, distraction, suppression and behavioral avoidance are indeed associated with anxiety symptom severity. However, such between-person associations do not allow for conclusions about a mechanistic role of the studied variables. To improve the examination and understanding of psychotherapeutic change, we prompt future research to use longitudinal designs and statistical procedures that separate between- and within-person variability. Only with such studies can we begin to elucidate whether hypothesized mechanisms of change indeed seem to play a causal role, or if they are merely correlates of treatment outcome [303].

However, even with optimal research designs it remains highly challenging to understand psychotherapeutic change. Psychotherapy is a complex and multi-level process that is likely to work through a complex chain of changes: different mechanisms of change (at either the physiological, cognitive, behavioral or affective level or on multiple levels) occur at different time points and rates during treatment and certain changes might occur suddenly instead of gradually [314]. Furthermore, it may be the case that treatment components and the mechanisms of action associated with them work differently at different points of treatment and that their workings differ between subgroups of people receiving treatment. Therefore, we may never be able to explain psychotherapeutic change using the relatively simplistic (causal) models of change and associated research designs that psychological science has relied upon so far.

This study has some limitations that are important to discuss. First, although the use of longitudinal data is an important advantage of this study, it is plausible that the data (based on 5 measurement moments) was not sufficiently fine-grained to accurately model mechanisms of therapeutic change. The current null-findings might have resulted from the measurement waves being too far apart to adequately capture changes in the measured constructs during treatment. Future studies should therefore focus on establishing a more fine-grained analysis of the shape of therapeutic change. Experience Sampling Methods (ESM) are promising in this regard [315]. Second, like most studies in this field of research, all data in the current study came from self-report instruments. Self-report relies on people's ability to identify and remember their own mental processes – an ability that might be far from perfect [316]. A combination and integration of data collected with different types of measurement instruments (e.g., clinician rating scales, physiological measures, behavioral tasks, neuroimaging) is preferable over relying upon one assessment method [317]. A third shortcoming is

that we used self-developed one item assessments for most candidate mechanisms. We opted for this type of measurement to avoid placing too large a burden on the participants, because too many demands for data can lead to measurement artefacts as a result of study drop-out or unreliable completion of the measurements. Although we used straight-forward items mostly based on questions from validated instruments, we cannot be certain that the self-developed items reliably measure the intended constructs and are sufficiently sensitive to change. Fifth, the generalizability of our findings might be limited because we tested our hypotheses in a sample of adults aged 55-75 years. The findings may not generalize to younger adult samples, although there is currently no strong theoretically or empirically valid reason to assume that CBT and ACT might work through different processes in older patient populations.

Summarizing, the current study examined multiple putative mechanisms of change of a CBT intervention and an ACT intervention for older adults with anxiety symptoms. The cognitive emotion regulation strategies reappraisal, acceptance, rumination, distraction and suppression were expected to mediate treatment outcome, but hypotheses were not confirmed. Furthermore, contrary to our hypotheses, behavioral avoidance, therapeutic alliance and treatment expectancies did not prospectively predict anxiety symptom severity during treatment. The current study positively distinguishes itself from many previous studies in the field, because it used data collected at multiple time points during treatment and a statistical approach that examined the hypothesized relationships on the within-person level. Future studies are encouraged to use longitudinal designs that allow for a more fine-grained analyses of therapeutic change and to analyze the associations between potential mechanisms of change and treatment outcome on the within-person level.

Appendix 1

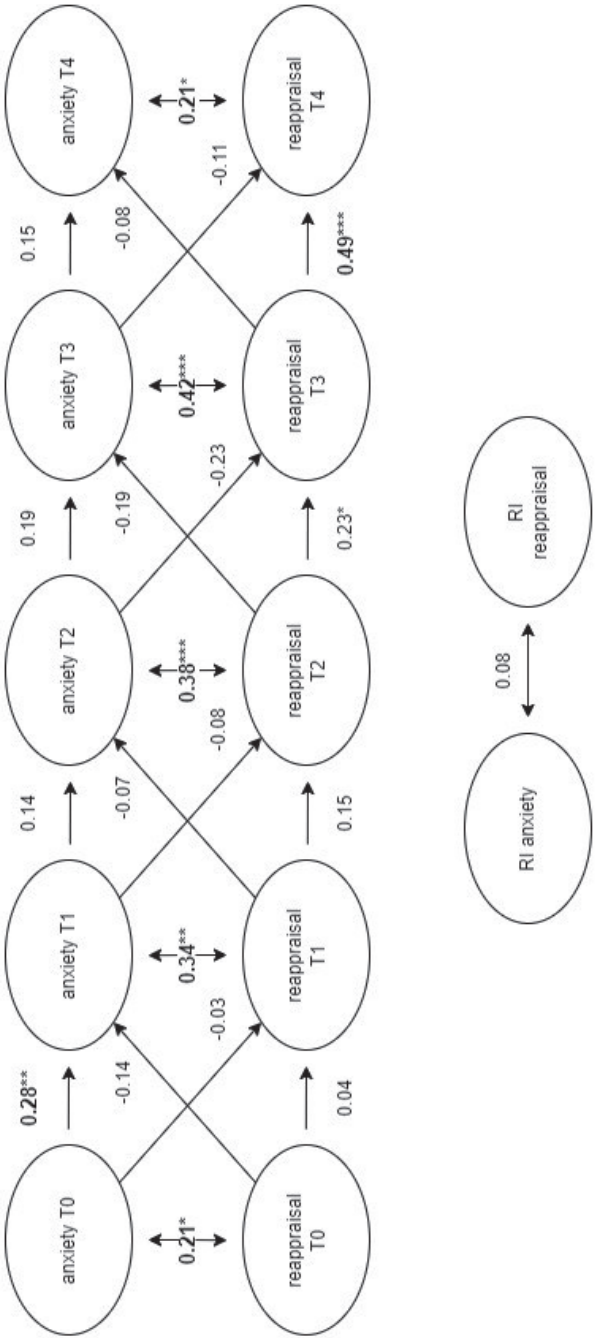

Figure A1. RI-CLPM reappraisal

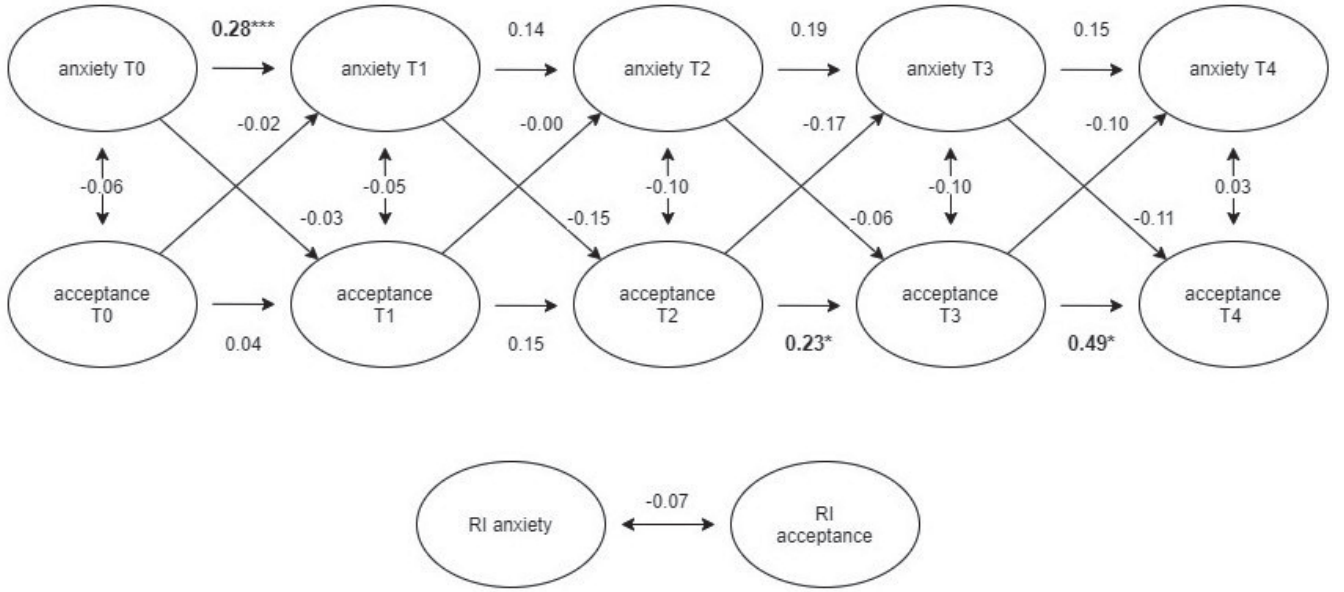

Figure A2. RI-CLPM acceptance

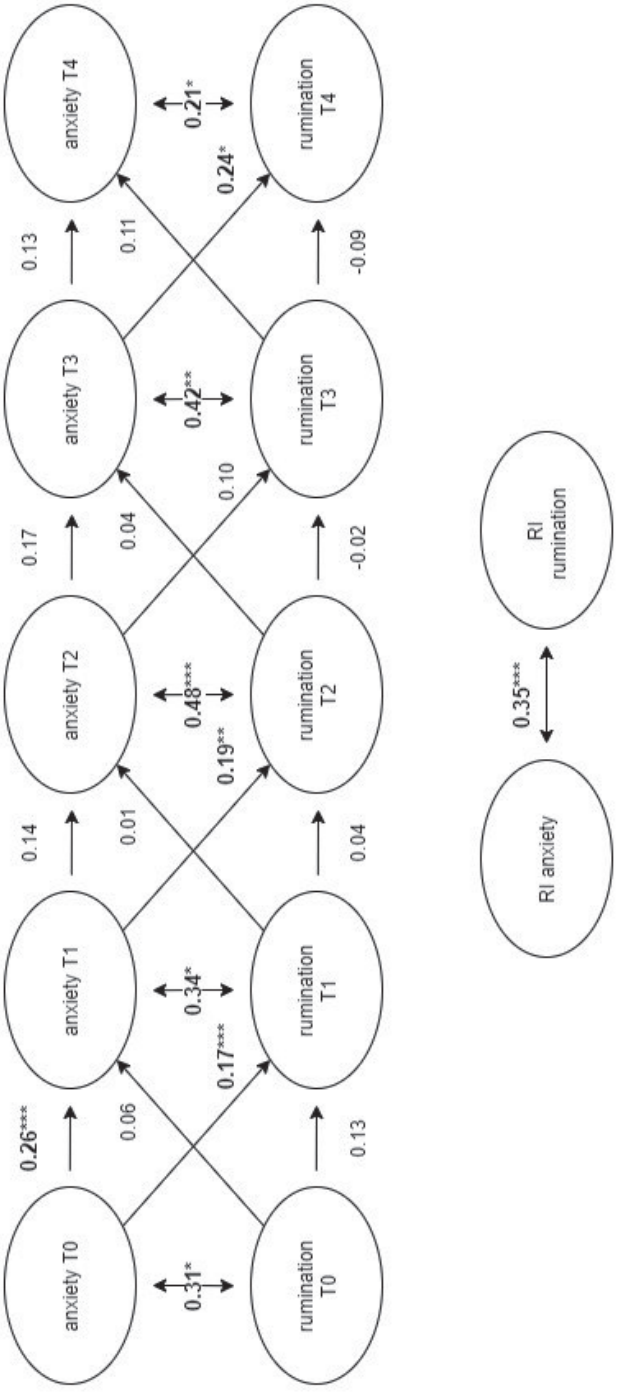

Figure A3. RI-CLPM rumination

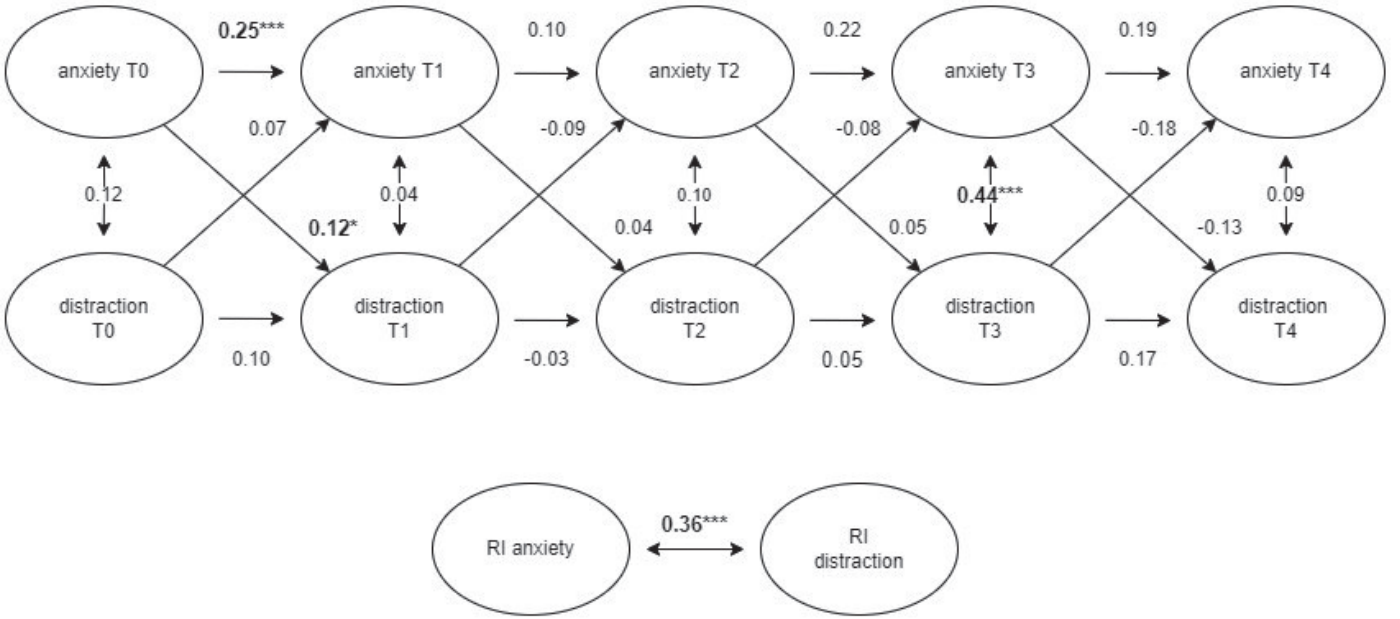

Figure A4. RI-CLPM distraction

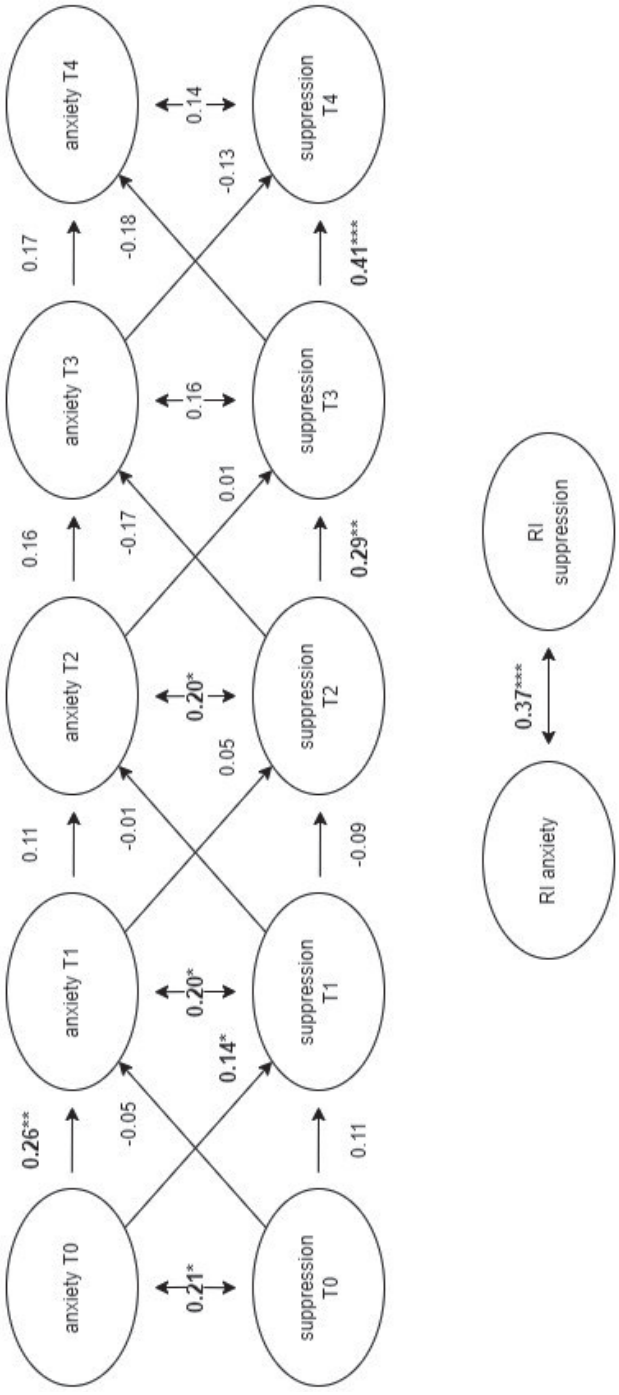

Figure A5. RI-CLPM suppression

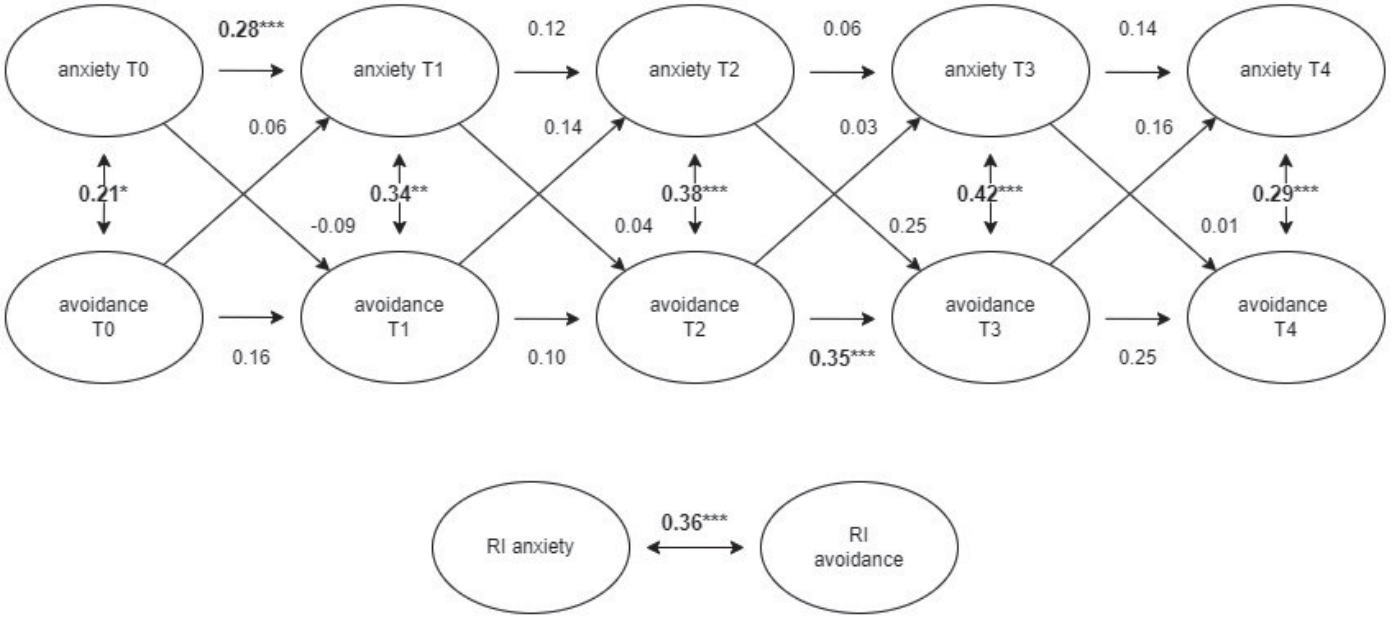

Figure A6. RI-CLPM avoidance

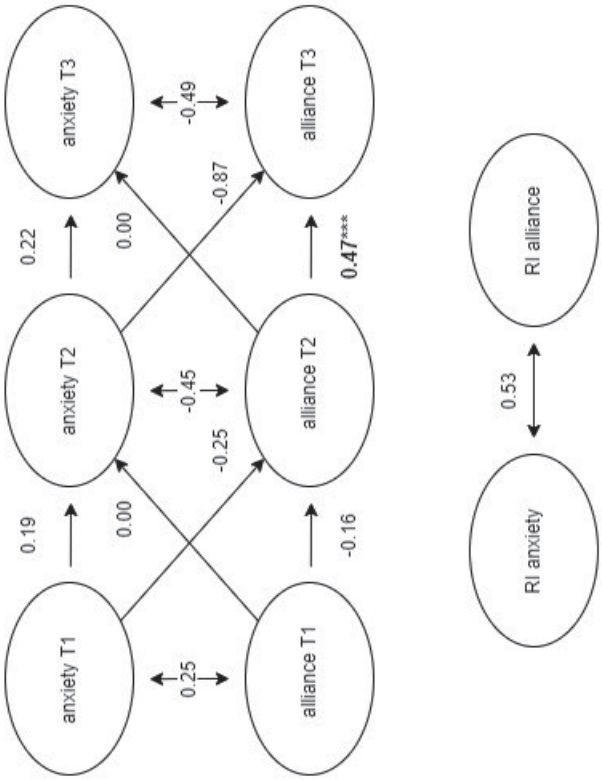

Figure A7. RI-CLPM therapeutic alliance

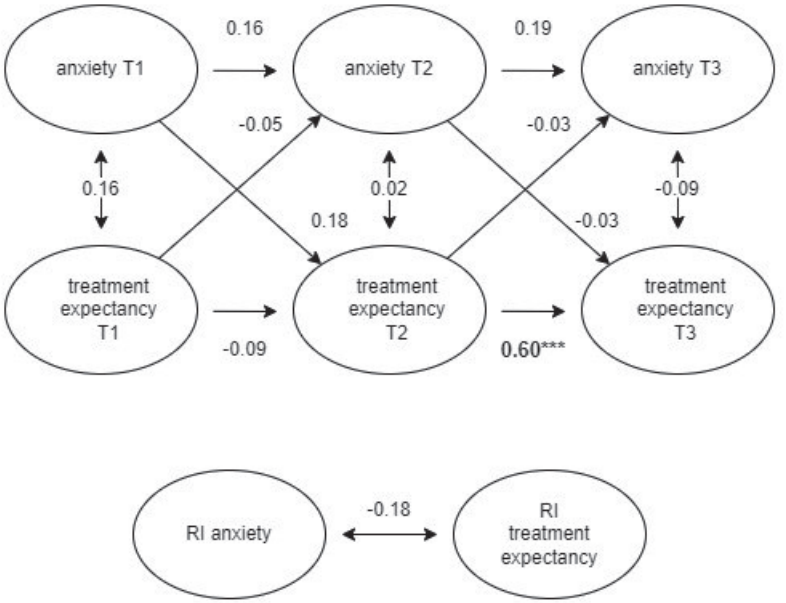

Figure A8. RI-CLPM treatment expectancy.

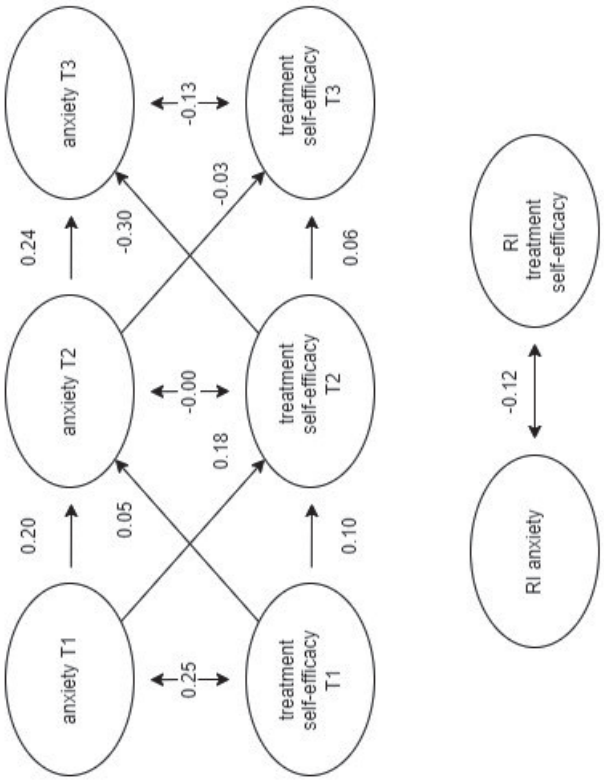

Figure A9. RI-CLPM treatment self-efficacy

SUMMARY AND GENERAL DISCUSSION

This doctoral thesis aimed to contribute to the understanding of anxiety in later life by examining questions related to its prevalence and psychological treatment. This chapter summarizes and discusses the main findings. We will also address the strengths and limitations of the studies and discuss their implications for future research and clinical practice.

1. Prevalence of anxiety in later life

1.1. Summary

Chapter 2 contained a systematic review and meta-analysis of studies into the prevalence of anxiety in older adults. The study had a two-fold aim: 1) to compare prevalence rates for subthreshold anxiety and anxiety disorders in adults aged 55 years and over and 2) to examine if prevalence rates varied between different age groups of older adults. Statistical comparisons of the prevalence rates for subthreshold anxiety and anxiety disorders indicated that subthreshold panic, generalized anxiety and specific phobia were significantly more prevalent than the corresponding full-blown disorders. For the other types of anxiety, no statistically significant difference was found between the rates for subthreshold symptoms and the full-blown disorders. To examine if and how prevalence rates for anxiety disorders change throughout the later life span, pooled prevalence rates for four age groups of older adults (55– 64, 65–74, 75– 84, 85+) were compared. For specific phobia, the 75-84 and 85+ groups had significantly lower prevalence rates than the 55-64 and 65-74 groups. We also found that posttraumatic stress disorder was significantly more prevalent in the 55-64 group than in the other age groups, and significantly lower in the 85+ group. No other significant differences between age groups were found. Importantly, only a small number of studies could be included in the statistical analyses and heterogeneity between the reported prevalence rates was large.

1.2. Discussion

Based on the currently available scientific literature on the topic, it can be concluded that subthreshold anxiety in older adults is a subject worthy of scientific and clinical attention. First, as indicated by the meta-analysis in chapter 2, subthreshold forms of anxiety appear to be at least similarly prevalent to full-blown anxiety disorders in older adults. Second, subthreshold anxiety can be clinically relevant, because it is comparable to full-blown anxiety disorders in terms of its associations with multiple

negative health outcomes [22]. It is clear that considering anxiety in later life only in terms of DSM anxiety disorders hinders a comprehensive understanding of the phenomenon and may result in the underdetection and undertreatment of a large group of older adults with clinically significant anxiety symptoms.

The high heterogeneity of the studies that reported prevalence rates for subthreshold anxiety is probably largely due to the fact that none of the studies operationalized subthreshold anxiety in the same way. However, establishing an empirically based consensus on the operationalization of subthreshold anxiety might be challenging. When attempting to define subthreshold anxiety, one runs into the so called 'double threshold problem' [318]. As stated before, the problem with the current diagnostic threshold for full-blown clinical disorders is that it excludes a large group of older adults with subthreshold but clinically relevant conditions. However, an undifferentiated lowering of the threshold could result in a medicalization of everyday life, an enormous increase in health care costs and less resources for seriously ill individuals. Thus, a second empirically defined threshold is required: one that defines normal mental health in older adults. Subthreshold anxiety would then refer to anxiety that is more severe than 'normal everyday anxiety', while not meeting the criteria for an anxiety disorder.

A seemingly straightforward way of separating subthreshold anxiety from normal anxiety states in older adults might be a clinical relevance criterion. Most anxiety disorders described in the DSM contain a 'clinical significance criterion', which implies that symptoms must cause distress or impairment in social, occupational, or other important areas of functioning. It has repeatedly been argued -especially in relation to subthreshold depression- that the clinical significance criterion does not have much added value in discriminating full-blown disorders from normality, because the severity and number of symptoms required for a diagnosis often already imply a considerable level of impairment and/or distress. However, subthreshold anxiety can consist of less severe symptomatology and/or a less strictly defined number of symptoms. Therefore, to separate individuals with clinically relevant subthreshold anxiety from people with normal anxiety states, the distress and/or impairment criterion could be used [318]. Subthreshold anxiety would then refer to functionally impairing anxiety symptoms that do not meet all symptom criteria for a full-blown disorder. Interestingly, some of the studies included in the meta-analysis in chapter 2 defined subthreshold anxiety as the presence of one or more of the symptom criteria of an anxiety disorder, without it meeting the distress or impairment criterion. Such definitions might result in an overestimation of the number of older adults with clinically relevant anxiety symptoms.

Of course, determining whether somebody is functionally impaired as a result of anxiety symptoms is also not perfectly clear-cut. Clinicians should be aware of older adults being less likely to describe themselves as disabled by psychological problems than younger adults [90]. Furthermore, 'functional impairment' may mean something different for people in different age categories [90]. Determining whether anxiety symptoms in later life are clinically relevant and in need of treatment requires a careful assessment. In any case, clinicians and researchers should not consider anxiety in later life as an all-or nothing phenomenon, but instead as consisting on a continuum regarding the number of symptoms, duration of symptoms, severity of symptoms, and impairment.

Regarding the second aim of the review and meta-analysis, we found that for specific phobia and PTSD prevalence rates decreased with age and that for most anxiety disorders the lowest rates were observed in the oldest-old groups (85+). Age thus seems to be related to anxiety disorder prevalence, but we can not draw firm conclusions about this association because we could not distinguish the effect of chronological age from the influence of other important factors (cohort effects, methodological differences between studies, sample differences). As expected, heterogeneity of reported prevalence rates was not adequately explained by age-category only. That is why we aimed to explore interactions between age and other relevant study- and participant factors, which was unfortunately precluded by the limited amount of reported information in the included articles. We therefore encourage future epidemiological studies in older adults to more elaborately describe their study sample, as this will foster the identification of factors associated with anxiety in later life. Such knowledge enriches the clinical portrait of older adults with anxiety and might improve diagnostic procedures. Variables that have so far been consistently linked to higher rates of anxiety disorders are female sex, non-married status, and having a medical condition [167]. To better understand the role of age, studies should more consistently report separate prevalence rates for different age groups. Moreover, longitudinal studies following different cohorts of older adults are necessary to disentangle age effects from cohort effects.

1.3. Limitations and strengths

An important limitation of the systematic review and meta-analysis is the limited generalizability and power of the findings as a result of the small number of studies that could be included in our analyses. Furthermore, we could not examine the association between prevalence rates of subthreshold anxiety and age, and the interaction effects

between age and other relevant characteristics, because very little to no studies were suited to answer these questions. This underscores that most studies into the prevalence of anxiety in later life have not focused on the more nuanced questions related to this topic and that much work remains to be done in this field of study.

The findings of the meta-analysis should be interpreted with caution, and do not allow for firm conclusions due to the high heterogeneity between included studies. While it could be argued that no meta-analysis should be conducted in the presence of large heterogeneity, we think that an integration of available information on a topic should still be preferred over leaving clinicians and scientists to make their own estimation of pooled effect sizes. Our elaborate search procedure resulted in the description and integration of a large number of studies into the prevalence of anxiety in older adults conducted over the last decades. Chapter 2 therefore provides a good overview of this field of study, the shortcomings and gaps in the currently available literature, and topics requiring further scientific attention.

2. Psychological treatment of anxiety in later life

2.1. Effectiveness of the interventions

2.1.1. Summary

Chapter 3 contained the study protocol for the Randomized Controlled Trial (RCT) that compared the effectiveness of a brief blended Acceptance and Commitment Therapy (ACT) intervention to a brief Cognitive Behavioral Therapy (CBT) intervention. The two interventions were provided by mental health counselors working at the general practice. The study was a cluster-randomized trial, which means that randomization took place on the level of the mental health counselor: each participating mental health counselor was randomized to either only provide the Blended ACT intervention or the CBT intervention to participants from their practice. Both interventions consisted of 4 face-to-face sessions that were provided over a timespan of 9 to 12 weeks. In between the sessions, participants in the ACT-condition worked with the online module 'Living to the Full', while participants in the CBT-intervention were given their homework assignments on paper. Adults aged 55-75 years with mild to moderately severe anxiety symptomatology could participate in the study. The RCT included 4 main assessments, consisting of online self-report questionnaires and telephone interviews conducted by trained research assistants: a baseline assessment (before treatment), a posttreatment assessment (3 months after baseline) and two follow-ups

(6 and 12 months after baseline). Furthermore, participants were asked to complete a short online questionnaire multiple times during the intervention. Chapters 4 to 7 reported on the results of this RCT.

Chapter 4 reported on the comparative clinical effectiveness of the blended ACT and CBT intervention. A total of 314 older adults with mild to moderately severe anxiety symptoms participated in the study, of which 150 were allocated to the ACT intervention and 164 to the CBT intervention. Participants were recruited from 38 general practices across the Netherlands, which employed a total of 40 mental health counselors that were randomized to the ACT (n=20) or CBT (n=20) condition. We did not find a statistically significant difference between the conditions in terms of the primary outcome, anxiety symptom severity as measured with the Generalized Anxiety Disorder-7 (GAD-7). Participants in both conditions showed large reductions in anxiety symptom severity from baseline to posttreatment. At the 6-month and 12-month follow-up, the conditions did also not differ: the reduction in anxiety symptom severity was sustained in both interventions. The trajectories of the secondary outcomes of depression symptom severity and the presence/absence of an anxiety disorder did not differ between the two groups: both groups showed medium to large improvements from baseline to posttreatment, that had sustained at the 12-month follow-up. Two statistically significant differences were found, both in favor of the blended ACT intervention. First, from posttreatment to 1-year follow-up, positive mental health decreased in the CBT group, but increased in the ACT group. Second, posttreatment treatment satisfaction ratings were higher in the ACT group than in the CBT group, a result that likely resulted from selective attrition.

The cost-effectiveness and cost-utility analyses described in **chapter 5** mainly confirmed the absence of major differences between the blended ACT and the CBT intervention. In these analyses, health benefits were expressed in terms of reliable change on the GAD-7 between baseline and the twelve-month follow-up (cost-effectiveness) and in Quality Adjusted Life Years (QALYs) calculated over the study period (cost-utility). The differences between the conditions on these outcomes were minimal and not statistically significant. The economic evaluation was conducted from a societal perspective, which means that it included both healthcare costs and non-health care costs (e.g., losses in work (voluntary) work and informal care productivity. Regarding societal costs, the analyses pointed to a possible benefit of blended ACT: compared to the CBT intervention, the ACT intervention was associated with reduced costs, as participants in the ACT group reported less health-problem related

absenteeism and presenteeism at (voluntary) work. Overall, the results did not indicate a clear preference for either blended ACT or CBT from a health-economic perspective.

2.1.2. Discussion

First, for the sake of completeness, it is important to note that chapter 4 does not report on all the assessed clinical outcome variables. As can be seen in the study protocol in chapter 3, we also assessed several cognitive coping strategies (e.g., blaming yourself, rumination, reappraisal and catastrophizing), mindfulness and experiential avoidance. Appendix 1 contains the results from the statistical analyses of these variables (which were conducted following the same procedure as described in Chapter 4), which also indicate no differences between the conditions.

The current findings on the non-significant differences between blended ACT and CBT add to earlier studies in general adult samples with anxiety, which also did not indicate major differences between the two approaches [242,243]. These accumulating findings thus suggest that adult anxiety symptoms can be effectively treated with both ACT and CBT. For clinicians, this offers greater flexibility in the delivery of psychological interventions to patients with anxiety. Still, since the RCT described in this doctoral thesis was the first large-scale trial into an ACT intervention for older adults with anxiety, establishing the clinical value of ACT for this population will require more research that replicates and elaborates upon this first trial.

Strictly speaking, the null findings in our study do not allow for the conclusion that ACT and CBT are equally effective. First, the study did not have a waitlist condition, which precludes conclusions about the absolute effectiveness of the studied interventions. However, when we compare the effect sizes in our study (d=0.96 (ACT); d=1.09 (CBT)) to those found in waitlist groups of older adults with anxiety symptoms (Cohen d values of 0.38 and 0.31 [81,82]), it seems safe to conclude that the improvements in both conditions can mainly be ascribed to the participants receiving an intervention. Second, it may be that our study was underpowered to detect small but relevant differences in effectiveness. Furthermore, the interventions might have different effects on clinical outcomes that were not assessed in the current RCT. Another possible reason for the lack of a significant difference between the groups is that the mental health counselors in the study were on average more experienced in providing CBT than ACT, as CBT is the most commonly used treatment approach for anxiety and the gold-standard treatment in psychotherapy in general. This prior experience may have inflated the effect size for the CBT intervention, although findings on the effect of prior therapist

experience with a specific treatment approach and clinical outcomes are mixed [319]. On the other hand, many of the mental health counselors that participated in the study did so out of an interest or affinity with the ACT-approach. Since treatment allegiance has been shown to increase effect sizes, one could also argue that effect sizes for ACT were inflated in the current RCT [319]. We unfortunately did not properly assess mental health counselors' prior experience with the treatment approaches and their treatment allegiance. For future studies that compare two active treatments, it is important to assess therapist experience and therapist allegiance and examine how these factors are associated with treatment outcomes.

Although the general picture that arises from our findings is one of no important differences between the ACT and CBT intervention regarding their clinical effectiveness, it is worth elaborating upon the differences that did emerge. First, the significant (but small) difference between the ACT and CBT intervention regarding the long-term effects on positive mental health is an interesting finding, because it concurs with the fact that ACT explicitly aims to increase positive mental health while this is not the case for traditional CBT. In ACT, symptom reduction is not the main goal of treatment but considered a byproduct of engaging with life in personally meaningful ways and an increased acceptance of (negative) internal experiences [51]. This conceptualization of mental health as a positive state of well-being and not the absence of illness or symptoms, aligns with the WHO definition of health: "a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community" [320]. Empirical research has also confirmed that mental health can best be conceptualized as consisting of two related but distinct dimensions: positive mental health and psychopathology [321]. Furthermore, interventions that are effective in promoting positive mental health are not always effective in reducing psychopathology, and vice versa, although a moderate correlation exists between these effects [322]. So, although the idea that psychological treatment should not only be evaluated in terms of symptomatic change can hardly be called controversial, a large majority of clinical trials still exclusively focus on symptom change as treatment outcome, even when the theoretical underpinnings of the evaluated treatment do not align with this view [323]. For example, we are not aware of other studies comparing ACT to other active treatments in terms of positive mental health. To fully understand the functions and benefits of psychological interventions, clinical trials should more systematically evaluate treatments in terms of positive mental health and related outcomes.

In the economic evaluation in Chapter 5 we found that although the ACT and CBT interventions did not differ regarding reported anxiety symptoms and overall health, participants in the ACT-group did report less interference of their (mental) health problems with their work productivity. Although not a statistically significant difference (cost data have a high variance and it would therefore require a very large sample size to detect a statistically significant difference), it is an interesting result, which could possibly also be understood as stemming from the specific therapy aims of ACT. ACT aims to increase acceptance-based emotion regulation and value-oriented behavior. People are stimulated to live a vital and active life, also in the presence of physical problems or psychological pain. The finding in chapter 5 may reflect this: maybe the participants in the ACT condition were able to live a more active and vital life (including (voluntary) work), even when faced with comparable physical or mental health problems as participants in the CBT group. Of course, this finding is only preliminary and the interpretation is speculative. Our study was the first economic evaluation of an ACT intervention vs. a CBT intervention in any patient population. In anticipation of more studies into the cost-effectiveness of ACT interventions vs. CBT interventions, the choice between ACT and CBT for anxious older adults should for now be guided by ethical, personal and practical considerations of both clinicians and patients.

The last statistically significant difference between the two conditions concerned treatment satisfaction: at posttreatment average treatment satisfaction was higher in the ACT group than the CBT group. This finding does however not justify the conclusion that ACT leads to higher patient treatment satisfaction. Data on treatment satisfaction were predominantly derived from participants who attended all the face-to-face sessions, and more participants in the ACT than the CBT group dropped out of treatment before having attended all sessions. As treatment dissatisfaction can be a reason for treatment drop-out, it is possible that the difference in treatment satisfaction is the result of selective attrition. Therefore, this result for now mostly invites us to take a closer look at the drop-out rates in our study.

Drop-out is commonly thought of as an adverse treatment outcome, being perceived as a sign that the treatment is too demanding, ineffective or not tailored to the wishes of the client [324]. However, people can also drop out for reasons not directly related to treatment. People regularly drop-out before the first therapy session, due to low motivation or the timing for treatment not being optimal in their view. Furthermore, external difficulties such as transport problems, moving house/job and family circumstances are commonly reported as a reason to discontinue treatment

[324]. Lastly, patients can also prematurely quit treatment if they feel that they have already sufficiently improved [18]. In those cases, drop-out could even be thought of as a favorable outcome.

If we define drop-out in our study as participants not attending all four face-to-face sessions after being included in the study, 45% (n=68) of the participants in the ACT group and 34% (n=55) of participants in the CBT group would be considered drop-outs. However, these rates include 13 participants in the ACT group and 17 participants in the CBT group that did not show up for the first session. As these participants never started treatment, this type of drop-out does not reflect dissatisfaction with the intervention. Of the included participants who started treatment (e.g., attended the first session), 40% (55/137) in the ACT group and 26% (38/147)in the CBT group dropped-out before attending all four sessions. These participants were asked for their reason for dropping out, but data are unfortunately incomplete. For five participants in the ACT group the reason for not completing the intervention was that their mental health counselor became severely ill and stopped working. This reflects another instance in which drop-out should not be interpreted as reflecting poorly on the intervention. Among the other participants that reported their reason for dropping out, 16 participants terminated treatment due to private circumstances, 6 reported that they felt their anxiety symptoms had sufficiently improved and 7 reported treatment/therapist dissatisfaction as their reason for drop-out. Although we can not draw any firm conclusions, from these data it appears that in our study drop-out was not an adverse outcome per se. The above furthermore illustrates that drop-out is a somewhat elusive outcome, which can be defined in multiple different ways, with the definitions varying in terms of their relevance for evaluating an intervention.

A last important finding from the RCT is that none of the participants reported any adverse events or side-effects related to the interventions during the study period. This mainly indicates that psychological interventions may be preferable over treatment with benzodiazepines or antidepressants, which are often prescribed to older adults with anxiety [325,326]. Long-term use of these types of psychotropic drugs by older adults has been linked to increased risks for falling, fractures, cognitive impairment and abuse of or dependence on the drug. Especially benzodiazepines are known to be highly addictive [327]. Over the last decade benzodiazepine prescriptions have been decreasing in the Netherlands at a rate of approximately 2% per year. However, benzodiazepines are still one of the most prescribed classes of psychotropic drugs in primary care, and among the group of long-term benzodiazepine users older adults are

still overrepresented [328]. Looking at the sample of our RCT, 17.8% of the participants used a stable dose of either benzodiazepines or SSRI's for at least 3 months. We decided to not exclude people with stabilized benzodiazepine or SSRI use, because general practitioners in our advisory committee warned us that this would lead to the exclusion of a large group of older adults with anxiety and drastically limit the generalizability of the study. The statistics on psychotropic drug use among older adults with anxiety underline the importance of general practitioners becoming more aware of the availability of effective short-term psychological interventions. To help older adults with anxiety in a constructive way, such interventions are more valuable than psychotropic drugs.

2.1.3.Clinical implications

Concluding, the studies described in chapter 4 and chapter 5 did not find major differences between the blended ACT intervention and the CBT intervention. Blended ACT appears to be a valuable treatment alternative to face-to-face CBT. The differences between the conditions that did emerge were small and/or might have resulted from bias. They should therefore be interpreted with caution and should mainly be considered as indicators of viable areas for further research. The findings from chapter 4 and 5 stem hopeful as they indicate that the currently underserved patient population of older adults with anxiety symptoms can be successfully treated in a primary care setting with low-threshold, brief psychological interventions. The fact that a partly web-based intervention does not differ from a face-to-face intervention in terms of effectiveness is important: easily scalable web-based interventions might be invaluable in providing this growing patient population with adequate psychological treatment.

To fully realize the potential of these interventions and to do justice to the time and resources spend on their evaluation, we want to follow-up our study with proper dissemination and implementation. In terms of implementation of the treatments, blended ACT interventions are already available to many mental health counselors working in general practices in the Netherlands, because most general practices use e-health portals that contain an ACT-module. Furthermore, CBT is the most widely taught and used psychological intervention in the Netherlands, so we can assume that most mental health counselors working for general practitioners are trained in working with this approach. We therefore feel that our efforts at dissemination should not be primarily focused on increasing the availability of the specific interventions that were evaluated in our RCT. Rather, we want to bring across the message that the specific

population of older adults with anxiety symptomatology (which is a large group) can benefit from brief, low-intensity ACT and CBT. We want to inform both older adults and mental health professionals about the fact that anxiety symptoms are highly prevalent in later life and that they can be successfully treated in the general practice, using either low-intensity blended ACT or CBT. Our experiences during the recruitment phase of our RCT underscore the importance of this message. Multiple general practitioners and mental health counselors that collaborated in the RCT reported that they were surprised by the number of patients that registered for participation. For a subgroup of participants, it was not known at the practice that they struggled with anxiety (even in cases where the anxiety was quite severe and/or long lasting) before they registered for study participation. Multiple participants, on the other hand, reported that before receiving the study invitation they were unaware of the possibility to receive psychological treatment for their anxiety symptoms at their general practice. This underscores the importance of actively disseminating information about mental health problems and available treatment options. Evidence-based interventions are of limited value as long as a large part of the patient population and many health care providers are unaware of their availability and effectivity.

In terms of dissemination we have so far created information videos in both Dutch and English about the prevalence and nature of anxiety in later life and the effective blended ACT and CBT intervention. We created one video targeted at older adults and one at clinicians. These videos have been published on several online media outlets. See Appendix 2 for the hyperlinks to the videos. Furthermore, with financial support from a ZonMw implementation fund we will collaborate on a project with which we aim to increase the awareness of the low-threshold psychological help that is available at the general practice among groups that currently make relatively little use of this service, such as people with low social economic status, people with limited mastery of the Dutch language and older people.

Lastly, it is important to note that findings like those presented in chapter 4 and 5, that indicate no major differences in effectiveness between two different psychological interventions, are common. So far, RCTs and meta-analyses have not demonstrated consistent differences in the average effect sizes of psychological treatments [302,329]. Moreover, despite the accumulation of evidence-based psychological treatments, overall effectiveness of psychotherapy has not increased over recent decades and there is still substantial room for improvement [302]. It is clear that increasing the effectiveness of mental health care will require more than developing new treatments

and performing clinical trials to evaluate their effectiveness. The studies in chapter 6 and 7 reflect two approaches towards improving the effectiveness of psychological care.

2.2. Moderators and mechanisms of change

2.2.1. Summary

Chapter 6 described an explorative study into treatment moderation. We used the data collected during the RCT to examine moderator variables, which are baseline patient characteristics that are predictive of differential treatment response to the ACT intervention and the CBT intervention. We included a variety of demographic and clinical variables in our exploratory analyses. As a secondary goal, we set out to identify non-specific predictor variables, which are variables associated with treatment response in both the ACT and the CBT intervention. The following baseline characteristics were examined as potential moderators/non-specific predictors: 1) demographics (sex, age, education, work hours, relationship status, negative life events); 2) (psycho)pathology (anxiety severity, depression severity, presence anxiety disorder, medication use, somatic comorbidity); 3) social support (problem solving support, affective support); 4) psychological processes (self-esteem, mastery, experiential avoidance, mindfulness, emotion regulation). Anxiety symptom severity (measured with the GAD-7) was the outcome variable. Analyses did not identify any moderator variables, which means that based on the examined baseline variables we could not distinguish subgroups of participants that responded better/worse to the ACT and the CBT intervention. Two non-specific predictors were identified: more severe depression symptoms predicted worse short-term and long-term response to ACT and CBT, and higher levels of mastery predicted better short-term treatment response in both conditions.

With the study in **Chapter 7** we aimed to gain more insight into possible mechanisms of change in the ACT and CBT intervention. We categorized the examined candidate mechanisms into those directly related to the theories underlying ACT and CBT (cognitive reappraisal, acceptance, rumination, distraction, suppression, behavioral avoidance) and so called 'common factors'- mechanisms that proposedly drive change in most psychological treatments (therapeutic alliance, treatment expectancy and treatment self-efficacy). We hypothesized that acceptance, rumination, suppression and distraction were ACT-specific mediators, while cognitive reappraisal was expected to mediate treatment outcome in CBT. Furthermore, we hypothesized that behavioral avoidance, client-rated therapeutic alliance and treatment expectancies

would be equally predictive of changes in anxiety symptom severity in both the ACT and CBT group. To test the hypotheses, we used data collected at multiple assessment waves during treatment, and a statistical procedure which allowed us to examine the hypothesized associations on the within-person level. We did not find support for our hypotheses. The candidate mechanisms did not prospectively predict anxiety symptom change and the hypothesized mediational pathways were also not statistically significant. The results do therefore not lend support to the theories of change in ACT and CBT and the common factor theory.

2.2.2. Discussion

The study in chapter 6 fits into a tradition of scientific efforts to increase the effectiveness of psychological treatment through personalized treatment selection. Personalized treatment selection means that instead of providing one treatment to all patients, each individual patient is provided with the intervention that is most likely to be optimal for him or her [264]. This requires the identification of subgroups of patients that seem to respond most favorably to a specific type of treatment. Two earlier studies comparing ACT and CBT for anxiety suggested that anxiety treatment approaches resonate better with patients when they draw upon a patient's strengths rather than remediating their shortcomings. Specifically, people with a greater ability and desire to reduce/control anxiety may be more receptive to CBT and people with a greater willingness to experience anxiety may be more responsive to ACT [30,31]. This was not replicated by the study in chapter 6, as measures related to acceptance (e.g., experiential avoidance, mindfulness) did not predict better outcomes in ACT. The findings in chapter 6 suggest that based on the included predictor variables, no subgroups of older adults with anxiety can be distinguished that respond more or less favorably to either ACT or CBT. This indicates that for now all older adults with anxiety symptoms can be offered either blended ACT or face-to-face CBT: the choice can be guided by client- and therapist preferences and practical considerations.

The lack of statistically significant moderators precluded the development of a personalized treatment assignment tool, which was one aim of our study. The model would combine information from multiple moderator variables to predict which treatment is optimal for each individual patient. Such models have earlier been deemed promising for personalized mental health care [264]. However, it is important to note that despite the often-emphasized promise of personalization tools, research into personalized mental health care is still in its infancy. For example, there have only been

a handful of studies that tested personalized treatment assignment models outside of the sample in which they were developed, and the results were disappointing [332]. Moreover, considering personalized treatment assignment for people with anxiety specifically, research so far has not yet identified consistent moderators of treatment response to different therapies [333]. Much work is still required before personalization tools can become part of clinical decision making in mental health care. First, findings on moderator variables need to be replicated across multiple studies. Subsequently, findings on consistent moderators can be translated into personalization tools that need to be thoroughly evaluated in terms of their feasibility, acceptability, and effectiveness. These tools should only be implemented in mental health care if they will prove to outperform current clinical decision making.

The study in chapter 7 reflects another approach towards improving treatment effectiveness: the identification of the mechanisms of change of psychotherapies. Understanding how a treatment achieves its effects can translate into treatment augmentation strategies, by optimizing those aspects of the treatment that directly target the processes responsible for change and minimizing or eliminating those that do not [227]. With our study we did not find evidence that cognitive emotion regulation strategies prospectively mediated change in anxiety symptom severity during the ACT and CBT intervention. Furthermore, we did also not find evidence that behavioral avoidance, therapeutic alliance and treatment expectancies predicted anxiety symptom severity over the course of the two interventions.

The null findings from chapter 7 can not easily be compared to earlier literature, because of profound methodological differences between our study and earlier research. The study in chapter 7 of this doctoral thesis sets itself apart from much previous research in terms of its potential to infer causality. First, we established a timeline, that allowed to examine if the candidate mechanisms *preceded* treatment outcome. Second, we separated within-person variance from between-person variance in our statistical analyses. This allowed us to report on the associations between the examined candidate mechanisms and anxiety symptom severity on the within-person level. An association on the within-person level is more likely to point to a causal process than an association on the between-person level [313]. Most previous studies into the mechanisms of change of ACT and CBT (and other psychotherapies) have only demonstrated correlations between putative mechanisms and treatment outcome. Such studies do not allow for any causal inferences, while demonstrating that a factor is likely to play a causal role is exactly what research into

treatment mechanisms should aim for [227]. We therefore prompt future studies into mechanisms of psychotherapeutic change to use longitudinal design and statistical analyses that allow for statements about within-person processes.

Here it is also important to note that establishing temporality and disentangling within- and between-person variance are necessary but not sufficient to identify mechanisms of psychotherapeutic change. Establishing that a factor is indeed a mechanism of action in psychotherapy requires multiple research strategies, including direct experimental manipulation of the candidate mechanism, studies demonstrating a dose–response association between proposed mechanisms and treatment outcome, and studies establishing that there is no third variable that is responsible for changes in the mediator and the outcome [227]. In sum, considering the examination of mechanisms of change of psychotherapy, we can draw a similar conclusion to the one we made in relation to personalized treatment selection: there is still a long way to go. It will take many individual studies and a great collaborative effort to elucidate the working mechanisms of psychological treatment.

2.3. Limitations and strengths

The main limitation of the studies in chapter 4-7 concerns the generalizability of the findings. Generalizability is limited because people that were severely impaired by their psychological, cognitive or physical problems were excluded from participation in the trial, as were adults over 75 years of age. Furthermore, to be included people had to register online, which required internet access and some skills in working with computers. This resulted in a sample that is not representative for the study population: all participants were community-dwelling, 98% were of Dutch nationality, and most had middle to high education levels.

Second, an inherent limitation of defining a research sample in terms of chronological age, is that this does not account for cohort effects. This means that the generalizability of the findings is limited because the current 55-75 year olds differ from the 55-75 year olds of the (near) future in multiple potentially clinically important ways. For example, during the writing of the grant proposal for the RCT that chapters 4-7 report on (this was around 2015), it was decided to exclude adults over 75 years from participation, because digital literacy was generally still low in this group and this could introduce bias to the data [334]. However, from 2015 to 2020 the percentage of adults aged 75 years and over that used the internet on a daily basis increased from 30 to 49 percent, so it plausible that currently the majority of this age group is used to

working with computers and the internet [334]. Of course, digital literacy is only one of many factors on which future 55-75 year- olds may differ from the adults that are currently in this age range.

Another important limitation that was already touched upon is the absence of an inactive control condition, which precludes direct conclusions about the effectiveness of the studies interventions in absolute terms.

Considering strengths, the studies in chapter 4 -7 constitute the first large-scale and comprehensive clinical evaluation of an ACT intervention vs. a CBT intervention for older adults with anxiety symptoms. Besides an evaluation in terms of clinical effectiveness (chapter 4), we also conducted an economic evaluation (chapter 5), an explorative moderator analyses (chapter 6) and an examination of potential mechanisms of change of the two interventions (chapter 7). Together, these studies form a thorough clinical evaluation and comparison of the blended ACT and the face-to-face CBT intervention for older adults with anxiety symptomatology. To our knowledge the sample size of 314 is larger than that of any other study into the psychological treatment for anxiety in older adults. Furthermore, we compared the effectiveness of the interventions over a period of 12-months, thereby also gaining insight into the longer-term effects of the treatments.

3. Overall conclusion

With this doctoral thesis we aimed to improve the understanding of the prevalence and treatment of anxiety in later life. Our systematic review and meta-analysis of prevalence studies suggests that subthreshold anxiety might be at least equally prevalent to full-blown anxiety disorders in later life, and that for some types of anxiety prevalence rates seem to decrease throughout the later life span. The review article also highlights that little is still known about the ways in which age is associated with the prevalence and manifestation of anxiety. As earlier studies have indicated that anxiety is among the most common mental health problem in later life, it is important that future research focuses on answering more delicate questions regarding the presentation and prevalence of anxiety in older adults.

Considering the psychological treatment of anxiety in later life, we found that a brief blended ACT intervention and a brief CBT intervention did not differ regarding their effects on anxiety symptom severity and related clinical outcomes. In both treatment conditions, large reductions of anxiety symptom severity were observed. Also, in terms of cost-effectiveness and cost-utility, there is no clear preference for

one of the two interventions. Furthermore, we explored whether baseline participant characteristics moderated treatment response to the two interventions. We did not identify moderator variables, which indicates that there are no specific subgroups of patients that benefitted more from one of the two treatments. Lastly, we examined potential working mechanisms of the two interventions, but did not found evidence that the examined candidate mechanisms were related to anxiety symptom change during the ACT and CBT intervention.

The results are promising, because they show that older adults with mild to moderately anxiety symptomatology can be effectively treated in a primary care setting with two low-threshold, brief psychological interventions. Mental health counselors and clients can together decide on their preferred treatment approach. These psychological interventions form a more constructive alternative to psychotropic drugs, which are still often prescribed to older adults with anxiety. Low-intensity psychological interventions for anxiety in later life have not previously been studied on such a large scale. This doctoral thesis therefore makes a timely and important contribution to the evidence-based treatment of the highly prevalent problem of anxiety in older adults. Hopefully our research will inspire more scientific and clinical attention for anxiety symptoms in later life. Ultimately, we hope that successful implementation and an increased uptake of evidence-based psychological interventions will improve the mental well-being and quality of life of older adults.

Appendix 1

Table A1. Mixed model analyses comparing the differences between the blended acceptance and commitment therapy and cognitive behavioral therapy group over time

Outcome	b	SE	t	p
Blaming yourself				
T0-T1	-0.93	0.26	-3.54	< 0.001
T1-T2	-0.90	0.29	-3.08	0.002
T1-T3	-0.95	0.30	-3.15	0.002
T0-T1 * condition	-0.05	0.53		0.93
T1-T2 * condition	-0.22	0.59	-0.09	0.71
T1-T3*condition	-0.23	0.60	0.37	0.70
Rumination				
T0-T1	-1.10	0.27	-4.09	< 0.001
T1-T2	-0.97	0.30	-3.22	0.001
T1-T3	-0.93	0.31	-3.01	0.003
T0-T1 * condition	0.40	0.54	0.74	0.46
T1-T2 * condition	-0.64	0.60	-1.07	0.28
T1-T3*condition	-1.18	0.62	-1.91	0.06
Reappraisal				
T0-T1	0.09	0.33	0.27	0.79
T1-T2	-0.93	0.37	-2.50	0.01
T1-T3	-1.04	0.38	-2.74	0.001
T0-T1 * condition	0.73	0.67	2,00	0.27
T1-T2 * condition	-0.31	0.74	-0.42	0.67
T1-T3*condition	-0.24	0.76	-0.31	0.76
Catastrophizing				
T0-T1	-0.68	0.21	-3.31	<0.001
T1-T2	-0.30	0.23	-1.29	0.20
T1-T3	-0.35	0.24	-1.47	0.14
T0-T1 * condition	0.34	0.42	0.83	0.41
T1-T2 * condition	-0.60	0.46	-1.32	0.19
T1-T3*condition	-0.52	0.47	-1.10	0.27
Mindfulness				
T0-T1	3.80	0.93	4.08	< 0.001
T1-T2	0.90	1.04	0.86	0.39
T1-T3	1.86	1.07	1.75	0.08
T0-T1 * condition	1.41	1.86	0.76	0.45
T1-T2 * condition	0.27	2.08	0.13	0.90
T1-T3*condition	2.00	2.13	0.94	0.35
Experiential avoidance				
T0-T1	-2.79	0.67	-4.13	< 0.001
T1-T2	-2.68	0.75	3.57	< 0.001
T1-T3	-3.02	0.77	-3.93	< 0.001
T0-T1 * condition	2.77	1.35	2.06	0.06
T1-T2 * condition	-2.10	1.50	-1.40	0.16
T1-T3*condition	-2.48	1.54	-1.61	0.11

Appendix 2

Supplementary material 1. Links to videos created for older adults

Dutch

https://www.youtube.com/watch?v=QCcDCvt9N5E

English

https://www.youtube.com/watch?v=HlBp_5oUeMw

Supplementary material 2. Links to videos created for clinicians

Dutch

https://www.youtube.com/watch?v=4zUTpkXTR1c

English

https://www.youtube.com/watch?v=d4BMGtrHTi0

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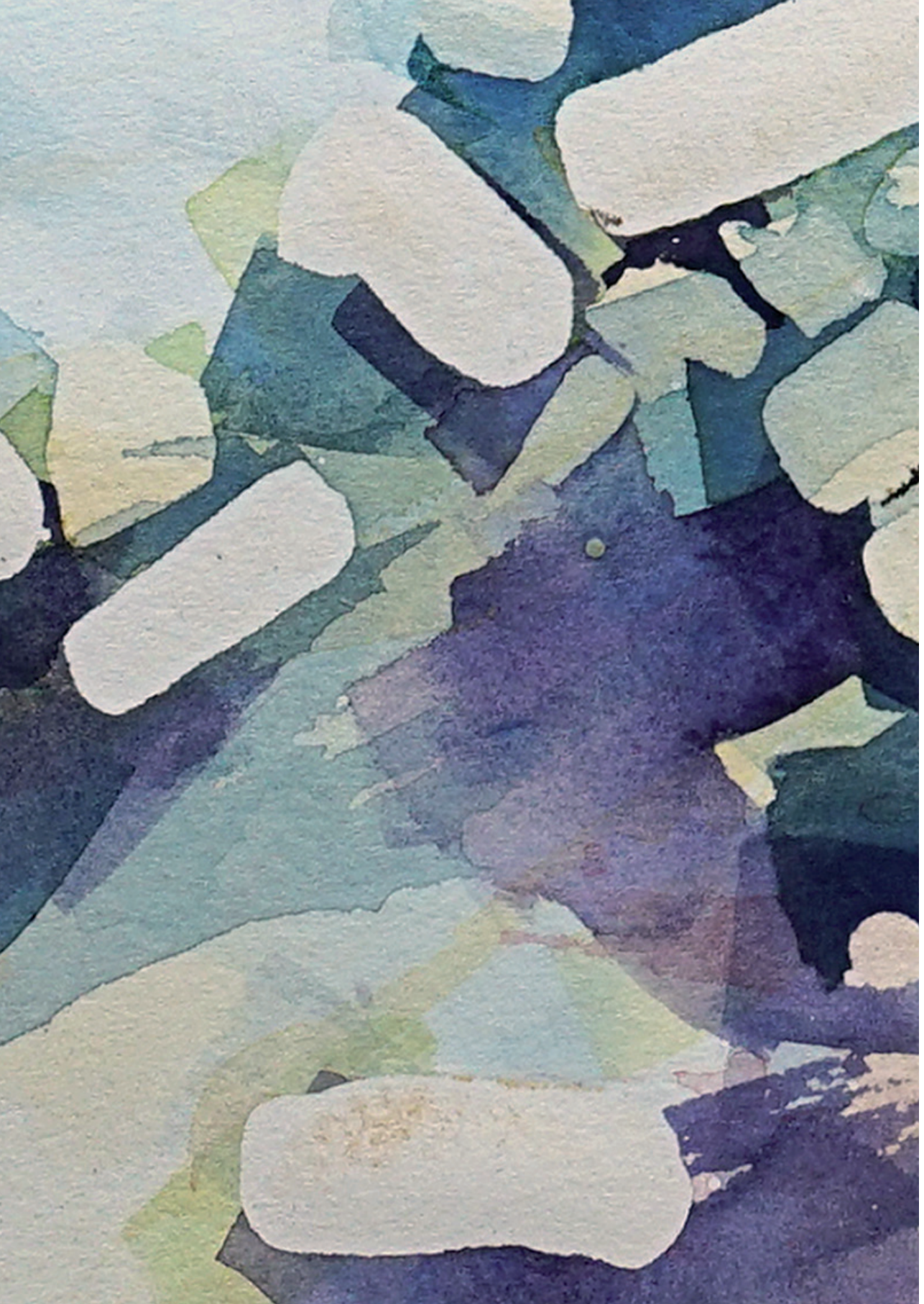

Nederlandse samenvatting

De afgelopen decennia is wereldwijd het absolute en relatieve aantal oudere volwassenen sterk toegenomen. In Nederland groeide het percentage 55-plussers van 19% in 1970 naar 22% in 1990 en 33% in 2019. Deze veroudering van de bevolking heeft invloed op alle facetten van de samenleving, inclusief de geestelijke gezondheidszorg. Met dit proefschrift hoopten wij bij te dragen aan het begrip van mentale gezondheid bij oudere volwassenen. We richtten ons daarbij specifiek op angstklachten, aangezien angstklachten een van de meest voorkomende psychologische klachten zijn onder oudere volwassenen. Dit proefschrift had twee doelen. Ten eerste poogde het middels een systematische review en meta-analyse antwoord te geven op vragen gerelateerd aan de prevalentie van angst op latere leeftijd. Ten tweede beschreef het de uitkomsten van een grootschalig gecontroleerd gerandomiseerd onderzoek (randomized controlled trial, RCT) waarin twee kortdurende psychologische behandelingen voor oudere volwassenen met angstsymptomen met elkaar vergeleken werden.

1. De prevalentie van angst bij oudere volwassenen

Tientallen studies hebben de prevalentie van angststoornissen bij ouderen onderzocht. Prevalentie schattingen variëren tussen de 3.2% en 14.2%. Er is echter nog weinig onderzoek gepubliceerd dat zich bezighoudt met de meer complexe vragen omtrent de prevalentie van angst in de latere levensfasen. Met een systematische review en meta-analyse hebben we in dit proefschrift data uit de reeds bestaande wetenschappelijke literatuur geïntegreerd om antwoord proberen te geven op twee onderzoeksvragen die doorgaans niet de focus zijn van prevalentie onderzoek.

Ten eerste wilden we met onze systematische review en meta-analyse onderzoeken hoe de prevalentie van zogenoemde subklinische angst zich verhoudt tot de prevalentie van angststoornissen. Met subklinische angst bedoelen we angstklachten die niet voldoen aan de diagnostische criteria voor een angststoornis. Onderzoek laat zien dat er een vrij grote groep oudere volwassenen is met (sterk) verhoogde angstniveaus, die niet voldoen aan alle diagnostische criteria voor een angststoornis. Zo heeft een eerdere studie aangetoond dat 5.6% van de oudere volwassenen in de steekproef voldeed aan de criteria voor een angststoornis, terwijl 26.2% verhoogde angstniveaus rapporteerde. Verder blijkt uit onderzoek dat angstklachten het dagelijks functioneren en de kwaliteit van leven van oudere volwassenen sterk negatief kunnen beïnvloeden, ook wanneer niet aan alle diagnostische criteria voor een stoornis wordt

voldaan. Subklinische angst bij oudere volwassenen lijkt dus zowel vaak voor te komen als klinisch relevant. Mogelijk komt subklinische angst veel voor onder ouderen omdat de gangbare diagnostische procedures en instrumenten voor het vaststellen van angststoornissen niet voldoende toegesneden zijn op oudere leeftijdsgroepen, wat kan leiden tot onderdiagnosticering. Om angst op latere leeftijd goed te begrijpen, lijkt het belangrijk om niet enkel op gediagnosticeerde angststoornissen te focussen, omdat hiermee een grote groep oudere volwassenen met relevante angstklachten over het hoofd wordt gezien. Met onze systematische review en meta-analyse probeerden we antwoord te geven op de vraag hoe groot de groep oudere volwassenen met subklinische angst is.

De tweede vraag die we poogden te beantwoorden is of er een verschil bestaat in de prevalentie van angststoornissen tussen verschillende leeftijdsgroepen van oudere volwassenen. Veel epidemiologisch onderzoek rapporteert een enkel prevalentiecijfer voor de groep 'oudere volwassenen' waarbij deze groep vaak een leeftijdsspanne van 30 tot 40 jaar beslaat (bijv. 55-plussers, 60-plussers of 65-plussers). Het is echter aannemelijk dat de vele sociale, fysieke en cognitieve veranderingen die mensen doormaken gedurende de latere leeftijdsfasen invloed hebben op de aard en prevalentie van angstklachten in verschillende leeftijdsgroepen van oudere volwassenen. Voor een goed begrip van de prevalentie van angst op latere leeftijd dienen we oudere volwassenen niet als een homogene groep te zien, maar proberen te begrijpen hoe verschillende demografische en klinische variabelen invloed hebben op de aanwezigheid van angstklachten op latere leeftijd. In onze meta-analyse vergeleken we daarom gerapporteerde prevalentie cijfers voor verschillende leeftijdsgroepen van oudere volwassenen (namelijk 55-64 jarigen, 65-74 jarigen, 75-84 jarigen en 85-plussers). Ook onderzochten we of er sprake is van interactie-effecten tussen leeftijd en andere methodologische, demografische of klinische kenmerken (bijv. het diagnostisch instrument dat gebruikt is in het onderzoek, geslacht, nationaliteit, woonsituatie).

In **Hoofdstuk 2** beschreven we de resultaten van de systematische literatuur review en meta-analyse. Na een systematische literatuur screening werden er 46 publicaties geïncludeerd. Om de gerapporteerde prevalentie cijfers voor subklinische angst en angststoornissen te vergelijken, berekenden we per type angststoornis een relatief risico (risk ratio) dat uitdrukte hoe vaak de subklinische manifestaties voorkwamen ten opzichte van de corresponderende angststoornissen. Een relatief risico groter dan 1 betekent dat subklinische angst vaker voorkomt dan de angststoornis

en een relatief risico kleiner dan 1 betekent het omgekeerde. Een vergelijking van de gerapporteerde prevalentiecijfers voor subklinische angst en angststoornissen liet zien dat subklinische angst minstens evenveel lijkt voor te komen als angststoornissen. Alle relatieve risico's waren groter dan 1. Voor een aantal typen angst (gegeneraliseerde angst (RR=3.49 [1.90-6.43], $p<.001$), paniek (RR=4.10 [2.71-6.21], $p<.001$) en specifieke fobie (RR=5.63 [2.05-15.46], $p<.001$)) bleken subklinische manifestaties ervan significant vaker voor te komen dan de corresponderende angststoornissen zelf. De statistische power van onze bevindingen is laag vanwege het kleine aantal artikelen dat we in onze analyses konden gebruiken, dus we kunnen op basis van deze meta-analyse geen harde conclusies trekken over de prevalentie van subklinische angst bij oudere volwassenen. Wat opvalt in de literatuur is het ontbreken van een eenduidige definitie van subklinische angst. Het is ingewikkeld om tot een valide en werkbare definitie te komen, maar dit is wel belangrijk om het onderzoek naar en de klinische aandacht voor subklinische angst bij oudere volwassenen te bevorderen.

De vergelijking van prevalentiecijfers in de vier onderscheiden leeftijdsgroepen van oudere volwassenen toonde aan dat specifieke fobie vaker voorkwam in de 55-64 (8.59%, [5.70-12.77]) en 65-74 (7.13%, [5.39-9.37]) groep dan in de 75-84 (4.43%, [3.06–6.38]) en 85+ groep (3.72%, [2.19-6.25]). Posttraumatische stress stoornis kwam het meest voor in de 55-64 groep (5.47%, [4.88-6.13]) en het minst in de 85+ groep (1.61%, [0.96-2.70]). Voor de andere angststoornissen vonden we geen significante verschillen tussen de leeftijdsgroepen. De interacties tussen leeftijd en andere variabelen konden beperkt worden onderzocht, omdat slechts een klein aantal van de geïncludeerde publicaties informatie rapporteerde die hiervoor gebruikt kon worden. Geen van de onderzochte interacties bleek significant in het voorspellen van de prevalentie van angststoornissen. Ook voor deze analyses geldt dat de statistische power laag was vanwege het kleine aantal artikelen dat informatie rapporteerde voor verschillende leeftijdsgroepen. Om beter te begrijpen hoe de prevalentie van angst verandert gedurende de latere volwassenheid is het belangrijk dat studies consistenter informatie rapporteren voor verschillende leeftijdsgroepen. Daarnaast is longitudinaal onderzoek waarin verschillende cohorten van oudere volwassenen langdurig gevolgd worden noodzakelijk om leeftijdseffecten van cohorteffecten te kunnen onderscheiden.

2. Psychologische behandeling van oudere volwassenen met angst

Angstklachten komen veel voor onder oudere volwassenen en kunnen flink belemmerend zijn. Als mensen lange tijd met deze klachten rond blijven lopen, kunnen de klachten verergeren. Daarom is het belangrijk dat er op tijd passende hulp wordt geboden. Behandelaren en wetenschappers zullen bestaande interventies (die vaak zijn ontwikkeld voor en onderzocht bij jongere volwassenen) kritisch moeten evalueren op hun geschiktheid voor oudere patiëntenpopulaties. Er is al vrij veel onderzoek gedaan naar de psychologische behandeling van angst bij oudere volwassenen, maar het onderzoek is erg homogeen wat betreft de onderzochte behandeling (cognitieve gedragstherapie (CGT)) en de doelgroep (oudere volwassenen met een gegeneraliseerde angststoornis). Er is daarom behoefte aan meer variatie in het behandelonderzoek. De RCT die we in hoofdstuk 3 tot en met 7 van dit proefschrift beschreven, verschilt op drie cruciale punten van de meerderheid van de eerdere onderzoeken naar psychologische behandelingen voor angstklachten bij oudere volwassenen. Ten eerste wat betreft de onderzochte behandelaanpak, ten tweede qua behandelformat en ten derde qua behandelsetting.

Wat betreft behandelaanpak, vergeleken we in onze studie kortdurende traditionele CGT met kortdurende Acceptance & Commitment Therapy (ACT). CGT is op dit moment de meest onderzochte en meest toegepaste behandelvorm voor angst bij oudere volwassenen. Kort gezegd is traditionele CGT gericht op het verkrijgen van inzicht in en het veranderen van de gedachten- en gedragspatronen die samenhangen met angstgevoelens. Cognitief herstructureren en gedragsexperimenten vormen vaak de kern van de behandeling. Bij cognitief herstructureren worden onrealistische en onbehulpzame negatieve gedachten opgespoord die samenhangen met de angst. Deze gedachten worden vervolgens kritisch onderzocht en vervangen door meer functionele/genuanceerde gedachten. Gedragsexperimenten worden daarbij ingezet als directere manier om de angstige interpretaties of voorspellingen van mensen te testen. Mensen worden aangemoedigd om situaties op te zoeken die zij eerder vanuit hun angst vermeden, om zo direct te ondervinden dat hun angstige gedachten vaak niet realistisch zijn.

ACT is een behandelvorm die de afgelopen decennia veel klinische en wetenschappelijke aandacht heeft gekregen. ACT wordt gerekend tot de 'derde golf van cognitieve gedragstherapieën'. De therapieën in deze stroming verschillen van traditionele CGT omdat ze zich niet richten op de *inhoud* van wat iemand denkt en voelt, maar *op hoe iemand zich verhoudt* tot deze innerlijke ervaringen. ACT is gericht

op het vergroten van 'psychologische flexibiliteit'. Psychologische flexibiliteit is het vermogen om flexibel om te kunnen gaan met situaties, gedachten en gevoelens, ook als ze moeilijk of pijnlijk zijn - en tegelijkertijd betekenisvolle keuzes (m.a.w. keuzes vanuit je eigen intrinsieke waarden) in het leven te kunnen maken. Anders gezegd, ACT richt zich op het vergroten van acceptatie van (negatieve) gevoelens en gedachten en op het stimuleren van een meer waardengericht leven. Onderzoeken hebben aangetoond dat ACT effectief is als behandeling voor een grote variëteit aan mentale klachten, inclusief angst. Echter, tot op heden zijn er geen grootschalige onderzoeken uitgevoerd naar ACT-behandelingen voor oudere volwassenen.

Er zijn verschillende redenen waarom ACT een geschikte behandeling zou kunnen zijn voor oudere volwassenen met angstklachten. Ten eerste sluit de focus op waardengericht leven aan bij de natuurlijke neiging van mensen in deze levensfase om te (her)evalueren wat daadwerkelijk belangrijk voor hen is. Ten tweede kan het ontwikkelen van een acceptatiegeoriënteerde coping stijl belangrijk zijn voor oudere volwassenen, omdat dit mogelijk de meest passende manier van omgaan is met de vaak onvermijdelijke leeftijd gerelateerde veranderingen waarmee zij te maken krijgen, zoals rolverandering, gezondheidsproblemen en verlies van naasten. Tot slot is de transdiagnostische benadering van ACT een belangrijk voordeel. De comorbiditeit van angst- en depressieklachten is bij oudere volwassenen nog hoger dan bij jongere volwassenen. Door de transdiagnostische focus op het vergroten van de psychologische flexibiliteit, richt ACT zich gelijktijdig op beide typen klachten.

Wat betreft behandelformat: de ACT interventie die wij hebben onderzocht is een blended behandeling. Dit betekent dat het face-to-face gesprekken met een hulpverlener combineert met een online zelfhulp module. Onderzoek naar internet interventies laat zien dat gedeeltelijk online behandelingen effectief en kostenbesparend kunnen zijn in het behandelen van veel voorkomende mentale klachten zoals angst en depressie. Onder oudere volwassenen is nog niet veel onderzoek gedaan naar dit type interventies, mogelijk vanwege het idee dat ouderen minder graag en/of goed werken met computers en internet. Er is echter een klein aantal studies dat laat zien dat online interventies ook effectief kunnen zijn in het verminderen van angstsymptomen bij oudere volwassenen.

De behandelsetting van ons onderzoek was de huisartspraktijk, waar deelnemers behandeling kregen van praktijkondersteuners-geestelijke gezondheidszorg (POH-GGZ). We hebben voor deze setting gekozen omdat het meeste eerdere onderzoek naar de behandeling van angstklachten bij ouderen plaats vond in specialistische

behandelsettings. Echter, in de dagelijkse praktijk zoeken oudere volwassenen minder snel specialistische hulp en worden ze hier ook minder snel naar verwezen dan jongere volwassenen. De huisartspraktijk kan vanwege de laagdrempeligheid en bekendheid voor veel oudere volwassenen met milde tot matig ernstige angstklachten de meest geschikte en aansprekende behandelsetting zijn. Daarom hebben wij ons onderzoek uitgevoerd in deze realistische behandelsetting.

Aard van de behandelingen

In **Hoofdstuk 3** beschreven we het studieprotocol van de RCT waarin een korte blended ACT behandeling werd vergeleken met een korte traditionele face-to-face CGT behandeling. Beide behandelingen werden door de POH-GGZ uitgevoerd in de huisartspraktijk van de deelnemers. We verwachtten dat de blended ACT interventie effectiever zou zijn dan de CGT interventie, omdat ACT meer lijkt aan te sluiten bij het psychologisch profiel van oudere volwassenen. De blended ACT-interventie maakte gebruik van de *Voluit Leven* module, een eerder onderzocht en effectief gebleken online zelfhulp programma. Deze online module werd gecombineerd met 4 gesprekken bij de POH-GGZ. De CGT-interventie bestond ook uit 4 gesprekken met de POH-GGZ, gecombineerd met huiswerkopdrachten aan de hand van werkbladen. De behandelingen dienden te worden afgerond in een tijdspanne van 9 tot 12 weken. Oudere volwassenen konden deelnemen aan het onderzoek als ze 55–75 jaar oud waren en last hadden van milde tot matig ernstige angstklachten. Mensen bij wie er sprake was van zeer ernstige óf zeer milde angstklachten of ernstige lichamelijke, cognitieve of psychische aandoeningen konden niet deelnemen aan het onderzoek. Deelnemers aan het onderzoek vulden op 4 momenten vragenlijsten in: vóór de behandeling (de baseline meting), direct na de behandeling (3 maanden na baseline) en 6 en 12 maanden na de baseline meting. De meeste vragenlijsten konden door deelnemers online worden ingevuld. Een deel van de lijsten werd telefonisch afgenomen door masterstudenten klinische psychologie.

Effectiviteit van de behandelingen

In **Hoofdstuk 4** presenteerden we de bevindingen over de klinische effectiviteit van de twee behandelingen. Werving van deelnemers vond plaats in 38 huisartspraktijken verspreid over Nederland. Volwassenen tussen de 55 en 75 jaar die ingeschreven stonden bij deze praktijken ontvingen een informatie- en uitnodigingsbrief over het

onderzoek. In totaal werden er 35.820 brieven verstuurd en meldden 683 mensen zich aan voor deelname aan het onderzoek. Na de screening en het invullen van de voormeting werden er 314 oudere volwassen met angstsymptomen geïncludeerd in het onderzoek. De behandelingen werden uitgevoerd door een totaal van 40 POH's-GGZ. Randomisatie over de CGT-interventie en ACT-interventie vond plaats op het niveau van de POH's-GGZ. Dit betekent dat 20 POH's-GGZ alleen maar CGT behandelingen uitvoerden in het kader van het onderzoek en de 20 andere POH's-GGZ enkel ACT behandelingen. De CGT-interventie werd gevolgd door 164 deelnemers, de ACT-interventie door 150. Uit de intention to treat analyses bleken geen statistisch significante verschillen tussen de twee behandelingen wat betreft hun korte- en lange termijneffect op angstklachten. Direct na het afronden van de interventies was in beide behandelgroepen een sterke afname van angstklachten te zien in vergelijking met de baseline meting. Deze afname was nog steeds zichtbaar tijdens de follow-up metingen 6 en 12 maanden na de baseline meting. Ook op de andere uitkomstmaten bleek de effectiviteit van de twee interventies weinig te verschillen. Wel bestond er een significant verschil tussen de condities wat betreft hun effect op positieve mentale gezondheid: in de ACT-groep nam positieve mentale gezondheid toe tussen de 3-maanden meting (direct na de behandeling) en de 12-maanden follow-up meting, terwijl positieve gezondheid in die periode afnam in de CGT-groep. Verder was na afloop van de behandeling de gerapporteerde tevredenheid met de interventie significant hoger in de ACT-groep dan de CGT-groep. Deze bevinding is echter mogelijk veroorzaakt doordat er ook meer deelnemers vroegtijdig stopten met de ACT-interventie, wat ertoe geleid kan hebben dat vooral de meest tevreden deelnemers de evaluatie van de interventie invulden.

Hoofdstuk 5 bevat een kosteneffectiviteitsanalyse en een kostenutiliteitsanalyse van de blended ACT-interventie vergeleken met de CGT-interventie. Uitkomstmaat in de kosteneffectiviteitsanalyse was de lange termijn (12 maanden na baseline) effectiviteit van de interventies op het angstniveau van de deelnemers. In de kostenutiliteitsanalyse werd kwaliteit van leven gemeten als voor kwaliteit gecorrigeerde levensjaren (Quality Adjusted Life Years, QALYs) gedurende de 12 maanden van het onderzoek. Beide analyses werden uitgevoerd vanuit een maatschappelijk perspectief en omvatten interventiekosten, medische kosten en niet-medische kosten (bijvoorbeeld productiviteitsverlies op werk) gedurende 12 maanden. Deze analyses bevestigden het beeld uit **Hoofdstuk 4** dat er geen belangrijke verschillen bestaan in de klinische effectiviteit van de ACT-interventie en de CGT-interventie. Wel leek ACT gepaard te gaan met minder niet-medische kosten dan CGT. Vanuit gezondheids-economisch

perspectief is er op basis van onze bevindingen echter geen duidelijke voorkeur uit te spreken voor een van de twee interventies.

De belangrijkste conclusie uit **Hoofdstuk 4** en **Hoofdstuk 5** was dat de twee kortdurende interventies beide effectief lijken te zijn in het behandelen van angstklachten bij oudere volwassenen. Dit komt overeen met resultaten uit eerdere onderzoeken die ACT en CGT voor angst vergeleken in steekproeven van jongere volwassenen. De bevinding dat oudere volwassenen met angstklachten goed geholpen kunnen worden met laagdrempelige en kortdurende interventies in de huisartspraktijk is hoopgevend. Het is belangrijk deze bevindingen onder de aandacht te brengen bij oudere volwassenen en bij hulpverleners. Dit kan er toe leiden dat meer oudere volwassenen die worstelen met angst psychologische hulp ontvangen, in plaats van dat ze rond blijven lopen met hun klachten of kalmerende medicatie met (soms gevaarlijke) bijwerkingen voorgeschreven krijgen. Een van de manieren waarop we onze onderzoeksbevindingen hebben verspreid is aan de hand van korte animaties die op verschillende media zijn gepubliceerd (zie de QR-codes onder deze tekst voor de links naar deze videos). Ook zijn we betrokken bij een ZonMW implementatie project dat de bekendheid met de POH-GGZ wil vergroten onder verschillende demografische groepen–waaronder oudere volwassenen- die momenteel relatief weinig gebruik maken van deze vorm van psychologische hulpverlening.

Uit de analyses kwam een klein aantal verschillen naar voren, allen in het voordeel van de ACT-interventie. Deze verschillen waren echter klein en/of mogelijk het gevolg van bias en dienen vooral opgevat te worden als aanwijzingen voor mogelijk interessant vervolgonderzoek.

Een limitatie van ons onderzoek is dat de generaliseerbaarheid van onze bevindingen beperkt is, omdat de deelnemers met name hoogopgeleide, zelfstandig thuiswonende ouderen met een Nederlandse achtergrond waren. Mensen met ernstige psychische of fysieke problemen konden ook niet deelnemen aan het onderzoek. Een andere beperking van het onderzoek is dat de twee interventies niet vergeleken werden met een controle conditie (zoals een aandachtscontrole conditie of een wachtlijst). Hierdoor konden we op basis van ons onderzoek geen conclusies trekken over de absolute effectiviteit van de interventies. Echter, de effectgrootte van de afname van angstklachten in beide condities (d=0.96 (ACT); d=1.09 (CBT)) was aanzienlijk groter dan gerapporteerde effectgroottes van wachtlijstcondities in andere trials bij oudere volwassenen met angst (d waarden van rond de 0.30).

De bevinding dat twee interventies niet verschillen wat betreft hun effectiviteit is vrij gebruikelijk in psychologisch onderzoek. De afgelopen decennia is er veel

behandelonderzoek gedaan waaruit blijkt dat de meeste psychologische behandelingen ongeveer even effectief zijn. Ondanks de vele bewezen effectieve behandelingen is de algehele effectiviteit van psychologische behandeling weinig toegenomen in de afgelopen decennia: er is nog steeds een grote groep mensen die niet of weinig profiteert van therapie. Het is duidelijk dat de bevindingen van enkel RCT's niet genoeg zijn om de effectiviteit van de mentale gezondheidszorg te verbeteren. Om psychologische behandeling te optimaliseren houden onderzoekers zich daarom steeds meer bezig met de vraag welke behandeling voor welke patiënt het meest geschikt is (*wat werkt voor wie?*) en proberen ze te identificeren wat de werkzame mechanismen van psychologische behandeling zijn (*hoé werkt het*)? In **Hoofdstuk 6** en **Hoofdstuk 7** van dit proefschrift probeerden we deze twee vragen te beantwoordden in relatie tot de onderzochte ACT-interventie en CGT-interventie.

Moderatoren en mogelijke mechanismen van de behandeleffecten

In **Hoofdstuk 6** omschreven we een exploratieve studie naar moderatoren en non-specifieke predictoren van het behandeleffect van de ACT-interventie en de CGT-interventie. Om dit te onderzoeken analyseerden we de relatie van verschillende baseline kenmerken van deelnemers met de uitkomst van de behandelingen. We onderzochten de volgende kenmerken: 1) demografische kenmerken (geslacht, leeftijd, opleidingsniveau, werkstatus, relaties tatus, negatieve levensgebeurtenissen); 2) (psycho)pathologie kenmerken (ernst van angstklachten, ernst van depressieve klachten, de aanwezigheid van een angststoornis, medicatie gebruik, somatische klachten); 3) sociale steun (zowel praktische als emotionele steun); 4) psychologische processen (eigenwaarde, mastery, experiëntiele vermijding, mindfulness, emotieregulatie). Een variabele is een moderator wanneer mensen die hoger/lager of wel/niet scoren op de variabele beter reageren op de ACT-interventie dan de CGT-interventie, of andersom. Non-specifieke predictoren zijn kenmerken die geassocieerd zijn met betere behandeluitkomsten, ongeacht welke behandeling werd aangeboden. We vonden geen moderatoren van het behandeleffect, wat betekent dat er op basis van de onderzochte variabelen geen subgroepen van deelnemers konden worden onderscheiden die beter op de ACT- of CGT-interventie reageerden. Wel vonden we twee non-specifieke predictoren. Ernstigere depressieve klachten bij aanvang van de behandeling voorspelden een slechtere behandelrespons op zowel de korte als lange termijn in beide behandelcondities. Verder voorspelden hogere baseline scores op mastery (de mate waarin mensen het idee hebben dat zij zelf invloed hebben op

de situaties en gebeurtenissen in hun leven) een betere behandelrespons op beide behandelingen op de korte termijn.

In **Hoofdstuk 7** presenteerden we de resultaten van analyses waarmee we poogden variabelen te identificeren die verwijzen naar mogelijke werkzame mechanismen van verandering tijdens de ACT-interventie en de CGT-interventie. We probeerden dus antwoord te geven op de vraag welke mechanismen ertoe leidden dat de angstklachten van de deelnemers verminderd waren na de behandelingen. We onderzochten twee typen mechanismen. Ten eerste keken we naar mechanismen waarvan we verwachtten dat ze kenmerkend waren voor specifiek ACT of specifiek CGT, gebaseerd op de theorieën achter de beide behandelingen. We verwachtten dat variabelen gerelateerd aan het accepteren van innerlijke ervaringen ACT-specifieke mediatoren zouden zijn en dat cognitieve herwaardering een mediator zou zijn in de CGT-groep. Ten tweede keken we naar variabelen waarvan we verwachtten dat deze in beide behandelingen voorspellend zouden zijn voor verbetering van angst, te weten gedragsmatige vermijding, behandelverwachtingen van de deelnemer en de therapeutische relatie. Omdat we een causaal verband tussen de veronderstelde mediatoren en de behandeluitkomst wilden aantonen, gebruikten we data die we verzameld hadden op meerdere momenten tijdens de behandeling (zodat we konden nagaan of verandering in de mediatoren *vooraf ging aan* verandering van het angstniveau). Geen van de onderzochte variabelen bleek van invloed te zijn op veranderingen in angstniveaus gedurende de behandelingen.

We hebben derhalve geen moderatoren en mediatoren van het behandeleffect van de ACT-interventie en de CGT-interventie kunnen identificeren. We kunnen op basis van ons onderzoek dus geen aanbevelingen doen over welke behandeling aan welke patiënt aangeboden dient te worden om de kans op succes zo groot mogelijk te maken. Ook ondersteunen onze bevindingen de theorieën over de werkingsmechanismen van ACT en CGT niet. Het is belangrijk om te noemen dat onderzoek naar moderatoren en mediatoren nog in de kinderschoenen staat; er zijn nog weinig moderatoren en mediatoren herhaaldelijk aangetoond. Ook verschillen onderzoeken sterk wat betreft onderzoeksdesign en statistische analyses, waardoor resultaten van verschillende onderzoeken lastig met elkaar te vergelijken zijn. Verder zijn er weinig studies die als primair doel hebben om moderatoren of mediatoren op te sporen. Ook ons onderzoek was primair ontworpen om de effectiviteit van de twee interventies met elkaar te vergelijken. Hierdoor konden wij de moderatie en mediatie analyse niet optimaal uitvoeren. Er is nog een lange weg te gaan voordat bevindingen uit onderzoek naar moderatoren en mediatoren stevig genoeg zijn om vertaald te kunnen worden naar de klinische praktijk.

Conclusie

Dit proefschrift richtte zich op het beantwoorden van vragen omtrent de prevalentie en de psychologische behandeling van angstklachten bij oudere volwassenen. Met een systematische review en meta-analyse hebben we de wetenschappelijke literatuur over de prevalentie van subklinische angst en de prevalentie van angststoornissen in verschillende leeftijdscategorieën van oudere volwassenen samengevat en geïntegreerd. We vonden aanwijzingen dat subklinische angst minstens even veel lijkt voor te komen onder oudere volwassenen als angststoornissen en dat de prevalentie van specifieke fobie en posttraumatische stressstoornis lager is in de oudere leeftijdsgroepen van oudere volwassenen dan in de jongere groepen. Het grootste deel van het proefschrift beschreef de resultaten van een RCT waarin we een blended ACT-interventie vergeleken met een CGT- interventie in een grote groep oudere volwassenen met angstklachten. We richtten ons op het analyseren van de klinische effectiviteit en kosteneffectiviteit van de interventies en op mogelijke moderatoren en mediatoren van de behandeleffecten. We vonden geen duidelijke verschillen tussen de ACT-interventie en CGT-interventie wat betreft hun effectiviteit op korte en lange termijn. Ook vonden we geen moderatoren en mediatoren van het behandeleffect. Beide interventies leidden tot een sterke afname van angstklachten. Dit betekent dat oudere volwassenen met angstklachten goed geholpen kunnen worden met laagdrempelige en korte behandelingen in de huisartspraktijk. Meer onderzoek naar de prevalentie, aard, diagnostiek en behandeling van mentale klachten bij oudere volwassenen is van groot belang om de juiste professionele psychologische hulp te kunnen aanbieden aan een toenemend oudere bevolking.

Video voor oudere volwassenen

Video voor hulpverleners

Publications

Witlox M, Kraaij V, Garnefski N, Bohlmeijer ET, Spinhoven P. (under review) Mediators and predictors of change in Cognitive Behavioral Therapy and Acceptance and Commitment Therapy for anxiety symptoms.

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Curriculum Vitae

Maartje Witlox was born on the 13th of April 1992 in Breda. In 2015 she obtained her Master's degree in Clinical Psychology from Utrecht University. After graduating she worked at the Altrecht Academic Anxiety Centre (AAA), where she combined research activities with clinical work. In 2017 Maartje started with her PhD project at the department of Clinical Psychology at Leiden University. In 2021 and 2022 she worked as a mental health counselor (POH-GGZ) at gezondheidscentrum de Bosrand in Driebergen. Currently she is working as a lecturer at the Clinical Psychology department at Leiden University and at psychology practice LEV in The Hague where she will start her postmaster training (GZ-opleiding).

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