Sylvia van Beugen

PSYCHODERMATOLOGY 2.0

Towards Improved Assessment and Effective Internet-based Interventions

Psychodermatology 2.0
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CHAPTER 1

General Introduction

PSYCHODERMATOLOGY

Chronic skin conditions are very common and are reported to be one of the leading causes of nonfatal disease burden [1–4]. As there is no permanent cure, patients have to cope with the consequences of their chronic skin condition for the rest of their lives. Chronic inflammatory skin conditions such as acne, atopic dermatitis, and psoriasis are known for their large impact on daily life, and lowered levels of physical and psychological functioning [2, 5, 6]. One of the most common chronic inflammatory skin conditions is psoriasis, with an estimated prevalence of 1.6% in the Netherlands [4], and worldwide prevalence rates ranging from 0.5% to 11.4% [7]. Psoriasis is a chronic, immune-mediated inflammatory skin condition typically characterized by red and scaly plaques on the skin [8]. Its severity can range from just a few marks to plaques covering almost the entire body surface. One of the most frequent complaints in psoriasis is itch, which is experienced by an estimated 60-80% of patients [9–11]. Other frequently occurring symptoms include fatigue, experienced by over half of all patients [10], and pain, experienced by 25-43% of patients [10, 12]. The condition can occur at any age, and its cause is still not fully understood. While psoriasis used to be viewed as a condition limited to the skin and joints, accumulating evidence shows that psoriasis is a systemic condition associated with increased risk for comorbidity such as cardiovascular conditions, stroke, and diabetes mellitus [13–15]. Moreover, the psychosocial impact of chronic skin conditions is substantial.

Psychodermatology refers to the field of research and medicine that involves the complex interaction between psychological factors and the skin [16]. Although the field has been in existence for several decades [e.g., 17], research to date has been relatively limited and psychodermatology is still considered 'upcoming' [18]. One of the most frequent topics that psychodermatological research has focused on to date is the increased risk for psychological problems in patients with chronic skin conditions. Given that the skin is the largest organ of the body and one of the first things we notice about another person, having a visible skin condition such as psoriasis can have a major impact on psychological and social functioning. Aspects of the psychosocial burden of chronic skin conditions include impairments in psychological functioning [5, 19], social functioning [20], quality of life [21, 22], work productivity [23, 24], body image [25], sleep quality [14, 26], sexual functioning [27], and perceived stigmatization [28–31]. An estimated 30-40% of patients with chronic skin conditions are at risk for long-term adjustment problems, such as symptoms of anxiety or depression [32, 33]. For example, in a recent large-scale study across 13 European countries, a significantly higher prevalence for clinical depression, anxiety, and suicidal ideation was found in patients with psoriasis than in controls [5]. The burden of the condition is often not limited to the patients themselves, but may also affect their significant others. In one study, relatives of patients reported social

disruptions (55%) limitations to holiday plans and leisure activities such as sports and evenings out (44%), and negatively affected close relationships (37%) [34].

The psychosocial impact of chronic skin conditions, and particularly psychosocial distress, are not only *consequences* of living with a chronic skin condition such as psoriasis; they also play a significant role in its *exacerbation*. Psychosocial distress has been indicated as a trigger in various inflammatory skin conditions, including psoriasis [35–38], atopic dermatitis [39], and acne vulgaris [40, 41]. This relationship between distress and disease exacerbation has been demonstrated in prospective studies, which showed that peak levels of psychological distress could predict increased disease severity a month later [35–38]. Individual cognitive and behavioral reactivity factors may play a role in the impact of psychosocial distress on disease severity, as patients with high levels of worrying and scratching seem particularly vulnerable to the influence of daily stressors at moments of high stress [37]. Similarly, excessive worrying has been related to impaired dermatological treatment success [42]. The mechanisms underlying the influence of distress on inflammatory disease processes in chronic skin conditions such as psoriasis remain largely unknown, but are likely to involve an altered functioning of the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Sympathetic Adrenal Medullary (SAM) system, combined with the release of nerve-related factors from peripheral sensory nerves [43]. The typically symmetrical pattern of psoriasis lesions provide further indications that the nervous system may be involved [44]. There may also be behavioral pathways contributing to disease severity. For example, psychological factors such as depressed mood have been found to be related to impaired dermatological treatment adherence [45] and unhealthy lifestyle behavior [46, 47]. Given that patients with psoriasis are already at increased risk for unhealthy lifestyle behavior such as excessive drinking, smoking, and overeating [48–50], psychological distress may additionally enhance these behavioral patterns and negatively impact patients' overall health.

To summarize, having a visible chronic skin condition such as psoriasis may result in significant distress and psychosocial burden for patients, and this distress and burden in itself may be an exacerbating factor in chronic inflammatory skin conditions, increasing flare-ups and the length of time until disease clearance. This process can over time become a vicious, self-perpetuating cycle. In order to help break this cycle, it is important to advance research in the field of dermatology by examining new concepts of relevance to disease management of these conditions, by developing new methods to assess relevant aspects of the psychosocial impact of chronic skin conditions, and by examining the (cost-)effectiveness of new treatments to reduce the impact of chronic skin conditions on daily life.

PSYCHODERMATOLOGY 2.0: TOWARDS BREAKING THE VICIOUS CYCLE

There are several areas that have remained relatively unexplored in previous research in psychodermatology. First, new concepts of relevance to disease management should be examined. Disease management, such as dermatological treatment adherence, is generally suboptimal in chronic skin conditions [51–53], despite the fact that adequate adherence and self-care is of utmost importance to ensure that patients benefit optimally from their treatment. Therefore, in **Part I** of this thesis, we will examine new concepts in psychodermatology that may play a role in patients' adherence and self-care behavior, namely aspects of body awareness. Second, new assessment methods in psychodermatology are needed to examine relatively unexplored implicit aspects of the psychosocial impact of chronic skin conditions, such as perceived stigmatization. Therefore, in **Part II** of this thesis, both direct and indirect assessment methods will be used to assess stigmatization-related implicit bias, as well as predictors of perceived stigmatization, in patients with chronic skin conditions. Third, new evidence-based interventions are needed to target the overall impact of chronic skin conditions in daily life. This is important not only to improve patients' psychological functioning, but also to prevent disease exacerbation, as illustrated above. Therefore, in **Part III** of this thesis, the effectiveness and cost-effectiveness of therapist-guided internet-based cognitive behavioral treatment (ICBT) will be examined in patients with psoriasis.

CONCEPTS 2.0: THE ROLE OF BODY AWARENESS IN CHRONIC SKIN CONDITIONS

Disease management of chronic skin conditions such as psoriasis often relies heavily on self-care, as the majority of patients have to apply topical treatments on a regular basis to prevent deterioration of their skin lesions. This can take up a considerable amount of patients' time each day [54, 55] and can have a substantial impact on their daily lives [56]. While adherence to dermatological treatment and adequate self-care behavior (e.g., applying topical treatments) is essential for effective disease management, adherence is often found to be poor [51–53]. A prerequisite for adequate self-care may be that the patient is sufficiently aware of bodily signals (e.g., dry or itchy skin) that indicate that self-care is required. Therefore the concept of body awareness, which can be defined as an attentional focus on, and awareness of, bodily signals [57], may be especially relevant in patients with psoriasis. Theoretically, a distinction needs to be made between body awareness and concepts such as somatosensory amplification, in which individuals show a hypervigilance toward bodily signals, and a catastrophizing interpretation of these signals [58]. This concept differs from body awareness with regard to the focusing style involved: body awareness encompasses a non-evaluative focusing style, while

somatosensory amplification clearly has an evaluative (typically negative) component consisting of attributing threatening characteristics to regular bodily signals [58, 59]. In contrast to somatosensory amplification, body awareness is considered to be an adaptive characteristic (e.g., enhancing alertness and recognition of bodily signals that are relevant for disease management in chronic skin conditions).

Despite the potential relevance of body awareness for chronic skin conditions, no studies to date have assessed body awareness in a dermatological population, nor have its associations with physical and psychological functioning been examined in this group. Given that body awareness may be an important prerequisite for adequate self-care, patients who show impaired body awareness (such as not recognizing bodily signals, or ignoring them) may be at risk for impaired physical and psychological functioning. For this reason, the assessment of aspects of body awareness in chronic skin conditions, and their associations with physical and psychological functioning, are studied in **Part I** of this thesis.

METHODS 2.0: EXPLICIT AND IMPLICIT MEASURES OF PERCEIVED STIGMATIZATION

An important aspect that differentiates the psychosocial impact of skin conditions from that of many other chronic somatic conditions is the effect that skin conditions can have on patients' appearance. A chronic skin condition such as psoriasis, for instance, can cause thick, red, scaly marks, and the visibility of these lesions can have a profound effect on the way patients experience social interactions. Patients with skin conditions commonly report negative social experiences, for example people staring at them, making negative remarks, avoiding contact with them, or even requesting them to leave public places [29, 60, 61]. These accounts are examples of stigmatization, which can be defined as an awareness of social disapproval, discrediting, or devaluation based on an attribute or physical mark [62]. These experiences likely originate from common misconceptions and negative prejudices due to a lack of knowledge about the condition, such as believing that the condition is contagious [63]. A recent study demonstrated that 50% of participants from the general population reported discriminatory behavior towards people with the chronic skin condition psoriasis, including a reluctance to shake hands or kiss on the cheek in greetings, to maintain friendships or to have sexual relations with individuals with the condition [63]. Perceived stigmatization is increasingly recognized as a common and disabling disease-related stressor in chronic skin conditions. Stigmatizing experiences, or the anticipation of such experiences, can lead to feelings of shame, social anxiety, and avoidance of social situations [31, 64–67]. Furthermore, stigmatization has been found to have a substantial impact on patients' daily lives and to contribute significantly to disability and depression [31, 65, 68]. Although research is

accumulating, little is known about vulnerability factors for stigmatization in patients with chronic skin conditions. More knowledge about the intra-individual characteristics associated with higher levels of perceived stigmatization could provide important input for the development of screening and intervention procedures.

Another topic that warrants further attention is whether the stigmatization experience is also reflected in implicit processes, and how these potential stigmatization-related implicit biases may be assessed in patients with chronic skin conditions. Perceived stigmatization is traditionally measured using self-report questionnaires. When patients fill out a questionnaire to self-assess perceived stigmatization, this is a conscious, direct, and reflective process: patients have an idea of what is being assessed and provide answers based on their conscious experiences. Although this type of direct assessment can provide valuable information about patients' experiences, it can also lead to socially desirable responses [69]. Furthermore, there may be aspects of the stigmatization experience that cannot be assessed by questionnaires, such as more or less automatic reactions that occur reflexively. Such automatic reactions can be assessed by indirect tasks that provide implicit measures of stigmatization-related bias. Dual-process models and related research in other conditions suggest that these automatic reactions influence information processing and social behavior at least as strongly as conscious and reflective processes [70]. Furthermore, previous studies have shown that implicit biases can be found in various physical conditions [71–73], and retraining these biases may be a promising way to enhance the effectiveness of current psychological interventions [73–76].

Although research on implicit processes in chronic skin conditions is scarce, there are indications that patients with psoriasis show an attentional bias to words related to skin symptoms and social threat [77]. Similarly, increased attentional focus on skin symptoms has been found in people with acne: an eye tracking study showed that, when presented with pictures of faces with acne lesions, people with acne gazed more at these lesions than did healthy controls [78]. A skin-related behavioral bias has also been found in people suffering from chronic skin picking: they displayed greater distraction and avoidance of pictures of skin irregularities than did controls [79]. Indications of biases for stimuli related to social threat and disgust have also been found, for example in a previous study demonstrating an attentional bias to social threat in patients with psoriasis [77]. Furthermore, a functional magnetic resonance imaging (fMRI) study showed that patients with psoriasis had diminished insular cortex activity in response to pictures of disgusted faces, possibly due to an avoidance-based coping mechanism [80]. Taken together, these preliminary findings of skin-related and social threat-related biases suggest that the impact of having a skin condition may be reflected in reflexive, more or less automatic, cognitive and behavioral reactions.

Studies examining methods for assessing implicit biases in chronic skin conditions can establish whether implicit biases in chronic skin conditions are present. These

methods that assess stigmatization-related cognitive and behavioral bias in chronic skin conditions may also provide promising starting points for innovative interventions that comprehensively target the problem from different angles by incorporating both explicit and implicit aspects of stigmatization. Furthermore, examining implicit biases in several chronic skin conditions will enable us to compare potential differences and similarities in implicit biases across conditions. Lastly, chronic skin conditions may also have a substantial impact on the lives of patients' significant others [34], and the stigma of chronic skin conditions may extend to these significant others due to a process called courtesy stigma [62, 81], making it worthwhile to examine whether implicit stigmatization-related biases are also present in patients' significant others.

Part II of this thesis will examine the concept of perceived stigmatization using both explicit and implicit measures. First, we study predictors of perceived stigmatization; such predictors can assist in screening and in developing interventions. Second, we examine whether implicit stigmatization-related biases are present in patients with chronic skin conditions. To enable us to compare differences and similarities in implicit stigmatization-related biases across conditions, we performed this study in two groups of patients with chronic skin conditions, patients with psoriasis and patients with alopecia, and compared both groups with healthy controls. Furthermore, significant others of both patient groups also participated in the study, allowing us to examine whether stigmatization-related biases can also be identified in patients' significant others.

TREATMENT 2.0: INTERNET-BASED COGNITIVE BEHAVIORAL TREATMENT

Although previous research in psychodermatology clearly underlines the substantial psychosocial impact and increased risk for psychological problems in patients with chronic skin conditions, there is still a relative lack of studies on the effectiveness of psychological interventions to target these problems. The studies that have been conducted show that there is currently very limited evidence for the effectiveness of purely educational interventions in patients with chronic skin conditions [82]. Psychological interventions with components of cognitive behavioral therapy (CBT) and habit reversal seem more promising, as in a meta-analysis of psychological interventions for chronic skin conditions the largest effects were found for these types of interventions. In this meta-analysis, based on relatively few studies, overall moderate effects were found for the impact of psychological interventions on disease severity, itching/scratching, and psychosocial outcomes [83]. When we examine the evidence specifically for psoriasis, CBT-based interventions currently show the most promising effects on psychosocial functioning and disease severity [84, 85].

In order to increase access to CBT-based interventions and potentially decrease societal costs, interventions are increasingly being offered online (internet-based CBT; ICBT). There are several potential benefits to these online treatments, for patients as well as for care providers. For patients, ICBT may offer advantages in terms of flexibility and time/cost reductions: there is no need to travel for face-to-face consultations, which saves both time and costs, and no need for face-to-face consultations during working hours: patients can determine for themselves when and where they would like to invest time in their treatment [86–88]. In addition, it may be easier for patients to implement what they have learned from ICBT in their own environment, considering that the intervention already takes place in their own personal environment and not in a doctor's office. Furthermore, some patients may find it easier to share personal matters from the comfort of their home as a safe environment [89]. Last, ICBT may save a considerable amount of therapist time. Therapist guidance in ICBT is often less time-intensive than in face-to-face consultations [86–88], and therapists can be more flexible in the way they allocate their time, which makes it a promising treatment in terms of cost-effectiveness.

While systematic reviews and meta-analyses have shown the effectiveness of ICBT in patients with chronic somatic conditions [90–93], there is a lack of a disease-transcending overview and meta-analysis of the overall effects of ICBT on different relevant outcomes in patients with chronic somatic conditions. Furthermore, to date no studies have been published on the effects of therapist-guided ICBT in patients with chronic skin conditions. To our knowledge only one randomized controlled trial has examined the effects of unguided ICBT in psoriasis, with promising effects on anxiety and quality of life [94].

Therapist guidance and personalized care have both been shown to be possibly relevant to optimize ICBT treatment effects. Previous research has shown that increased therapist guidance is associated with increased effects and decreased dropout rates [95–97]. The effects of tailoring ICBT interventions are currently less established, although initial studies are promising [98–101]. Internet-based interventions have often adopted a standardized 'one-size-fits-all' approach, in which all participants receive the same intervention, usually based largely on self-help and including minimal therapist support [87]. These types of interventions may serve well for patients with relatively minor complaints and have advantages from a societal perspective, as they can be disseminated to large numbers of people at relatively low cost. However, the effects of these programs are often quite modest and adherence can be low [e.g., 102]. Furthermore, they may not be suitable for patients with more complex complaints and co-morbidity.

In order to offer each patient the best fitting care, internet-based interventions could be organized in a stepped care model, offering less intensive self-help interventions to patients with minimal adjustment problems or for prevention of future problems [103]. For patients with more moderate to severe adjustment problems, offering tailored in-

terventions with therapist guidance could increase intervention effectiveness by taking into account the large inter-individual differences in disease characteristics, personal characteristics, and psychological comorbidity [103]. Furthermore, internet-based interventions may be a cost-effective approach from a societal perspective; they have previously been shown to be cost-effective for a range of conditions, when compared with, for example, wait-list, care as usual, unguided interventions, and face to face CBT [104]. However, the effectiveness and cost-effectiveness of internet-based therapist-guided ICBT for patients with chronic skin conditions have not been examined to date for patients with chronic skin conditions. Therefore, in **Part III** of this thesis, we examine the overall effectiveness of guided ICBT for patients with chronic somatic conditions, as well as the effectiveness and cost-effectiveness of an individually tailored and therapist-guided ICBT approach in patients with psoriasis.

AIMS AND OUTLINE OF THE THESIS

To summarize, this thesis aims to expand the current literature in psychodermatology, by examining 1) new concepts in psychodermatology, specifically aspects of body awareness that may be related to physical and psychological functioning; 2) new methods in psychodermatology, specifically both explicit and implicit methods to assess the stigmatization experience; and 3) new psychological treatment methods in psychodermatology, specifically the (cost-)effectiveness of ICBT for patients with psoriasis.

In **Part I** (Concepts 2.0), we examine the assessment of aspects of body awareness in patients with psoriasis, as well as the relationship between impairments in body awareness and reduced physical and psychological functioning (**Chapter 2**).

In **Part II** (Methods 2.0), we investigate predictors of self-reported perceived stigmatization in a large cross-sectional study in patients with psoriasis in **Chapter 3**. Furthermore, in **Chapter 4**, we examine the use of implicit measures to assess attentional and behavioral bias to stigmatization-related stimuli in patients with psoriasis and alopecia, as well as in their significant others.

In **Part III** (Treatment 2.0), we assess the effectiveness of internet-based interventions in reducing the impact of chronic conditions in daily life. First, we establish the state of the art in guided internet-based cognitive behavioral treatment (ICBT) for patients with chronic somatic conditions by conducting a meta-analytic review of randomized controlled trials (**Chapter 5**). Next, we present the results of a randomized controlled trial on the effectiveness, for patients with psoriasis, of individually tailored therapist-guided ICBT in comparison with regular dermatological care (**Chapter 6**). Last, we undertake a cost-effectiveness analysis to examine whether the clinical benefits of this intervention outweigh the costs to society (**Chapter 7)**.

To conclude this thesis, a summary of results is provided in **Chapter 8**, and the theoretical and clinical implications of our findings and directions for future research are discussed in the context of current knowledge in **Chapter 9**.

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PART I

Concepts 2.0: The Role of Body Awareness in Chronic Skin Conditions

CHAPTER 2

Body Attention, Ignorance and Awareness Scale: assessing relevant concepts for physical and psychological functioning in psoriasis

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ABSTRACT

A certain level of attention to bodily signals may be adaptive in the management of chronic skin conditions, as a lack of attention may lead to inadequate self-care behavior and, consequently, may affect functioning and treatment outcomes. The purpose of this study was to develop a body awareness questionnaire and to investigate its psychometric properties and physical and psychological correlates in a cross-sectional study in patients with psoriasis (n = 475). The 16-item Body Attention, Ignorance and Awareness Scale demonstrated a 3-factor structure that could be interpreted as body ignorance, body attention, and body awareness (Cronbach's α of .73, .74, and .68, respectively). Higher body ignorance was significantly related to more physical symptoms and worse psychological functioning. Body attention and body awareness showed small significant correlations with coping and personality. Given the negative influence of impaired psychological functioning on treatment outcomes, it may be clinically important to screen for these constructs of body awareness in chronic skin conditions.

INTRODUCTION

Having a chronic skin condition can have negative consequences for physical as well as psychological wellbeing [1–4]. One of the major problems that patients have to cope with is itch, which accompanies the majority of dermatological diseases [5–10]. The prevalence of itch ranges from 50% up to 92% in patients with chronic skin conditions [6–10]. Physical symptoms such as itch are known to significantly affect patients' quality of life [5–7] and are associated with emotional distress [5, 7, 9, 10]. In order to manage their chronic skin condition, patients are often required to take an active role in their treatment; the majority of patients need to use topical treatments on a regular basis to prevent deterioration. As better treatment adherence generally results in greater improvement, adequate self-care behavior is very relevant in these patients [11]. In order to respond to symptoms of the skin condition with appropriate self-care behavior, patients should be aware of the bodily signals that indicate that self-care is required. Thus, the way in which people pay attention to and interpret bodily signals, which is an important aspects of body awareness, may be relevant, especially in patients with chronic skin conditions.

Body awareness can be defined as an attentional focus on, and awareness of, body sensations [12]. In previous research, heightened body awareness has been viewed mainly as a mechanism that may be detrimental to health and wellbeing [13, 14] as it may lead to excessive worrying about physical symptoms and somatizing thoughts. These findings originated partly from findings regarding health anxiety [excessive concern about one's health; 15] and hypervigilance [heightened attention; e.g., 16] to bodily symptoms, both of which are associated with an increased attention to bodily signals, high levels of symptom reporting, and negative health outcomes [e.g., 17]. Recently, however, an alternative view has emerged that perceives body awareness as an adaptive process that may be useful in the management of chronic conditions, as long as body awareness involves mindful attentiveness to the present moment and not excessive worrying about symptoms [12, 13, 18, 19].

Even though they are different constructs, both alexithymia, which is characterized by the inability to identify and verbalize emotions [20], and body awareness show similarities, in the sense that they share a focus on internal awareness processes. Previous research has found moderately negative associations between alexithymia and body awareness [21–23], suggesting that a lack of ability to identify and verbalize emotions may be related to a lack of awareness of physical sensations.

In samples of dermatological patients, a certain level of body awareness may lead to patients paying adequate attention to bodily symptoms such as dry skin and, resultantly, to taking appropriate action, such as using moisturizing ointments. Subsequently, the lack of body awareness, especially, could be detrimental for patients with a chronic

skin condition. For instance, patients who do not pick up subtle bodily signals, such as dry skin or itch, may not take care of their skin accordingly and thus are less able to control their skin condition through adequate skin care. Finally, there are some indirect indications that body awareness interventions may have positive effects on wellbeing for chronic skin conditions. For instance mindful awareness, which includes elements of body awareness, may be of relevance for chronic skin conditions; a brief attention intervention focusing on mindful meditation has shown to accelerate the rate of clearance in psoriasis patients undergoing photo(chemo)therapy [24, 25]. Although these results are based on a small study in need of replication, they indicate that (mindful) aspects of body awareness may play a role in alleviating physical symptoms in chronic skin conditions such as psoriasis.

A systematic review examined existing self-report measures for body awareness and concluded that they often lacked adequate psychometric properties and were often unidimensional, leaving out key aspects of body awareness [12]. The authors of this review recently constructed a new, relatively elaborate measure of body awareness consisting of 8 subscales as an alternative [18, 26]. However, this measure does not include items regarding a specific lack of attention to, or ignorance of, bodily signals, which is hypothesized to be important in dermatological patient samples. The current study aims to: (i) assess a conceptualization of body awareness including ignorance of bodily signals in psoriasis patients by means of a new brief scale suitable for dermatological patient groups; and (ii) examine its psychometric properties and correlations with measures of physical and psychological functioning, personality characteristics, coping, and illness cognitions.

MATERIALS AND METHODS

Participants and procedure

In order to prevent selection bias, patients were recruited from both academic (Radboud university medical center, Nijmegen, the Netherlands) and non-academic (Canisius-Wilhelmina Hospital, Nijmegen; Rijnstate Hospital, Velp; Ziekenhuis Groep Twente, Almelo, the Netherlands) hospitals, as well as from the Dutch Psoriasis Association. Inclusion criteria were: a minimum age of 18 years and a dermatologist-confirmed psoriasis diagnosis. Exclusion criteria were: illiteracy, pregnancy, presence of other physical conditions that had a larger perceived impact on the daily life than psoriasis, presence of psychiatric comorbidity [according to the Diagnostic and Statistical Manual of Mental Disorders; 27] and/or current psychological treatment. The study protocol was approved by the regional medical ethics committee and written informed consent was obtained from each participant. The current study was part of a larger study examining

the effectiveness of E-health cognitive behavioral therapy for patients with psoriasis, and made use of questionnaires that were assessed as part of the screening procedure. All participants who completed questionnaires in the period March 2010 - May 2013 were included. The resulting sample size of 475 can be considered (highly) sufficient according to often-cited sample size guidelines for factor analysis [28]. Sociodemographic characteristics of participants are shown in Table 1. Participants' mean ± SD age was 52 ± 13 years and gender was approximately evenly distributed (56% male). Disease severity was mild to moderate [29]. Approximately half of our sample (46%) reported medical conditions in addition to psoriasis, of which 32% indicated more than one other medical condition. Most commonly reported conditions were: rheumatic disease (100 of 220 patients; 45%), high blood pressure (*n* = 27; 12%), heart disease (*n* = 28; 13%), lung disease (*n* = 26; 12%), diabetes (*n* = 26; 12%), chronic back/muscle/tendon pain (*n* = 21; 9.5%), skin disease besides psoriasis (*n* = 20; 9%), and thyroid disease (*n* = 14; 6%).

Table 1. Sociodemographic characteristics of the study population (*n* = 475)

Characteristics	
Sex, *n* (%)	
Male	266 (56)
Female	209 (44)
Age, (years), mean ± SD (range)	52.08 ± 13.06 (18-84)
Marital status, *n* (%)	
Single	56 (12)
Married/ living together	380 (80)
Divorced	22 (5)
Widowed	17 (4)
Educational level, *n* (%)	
Primary education	72 (15)
Secondary education	226 (48)
Tertiary education	175 (37)
Missing	2 (0.4)
Disease severity (SAPASI), mean ± SD (range)	5.12 ± 4.03 (0-33)
Disease duration (years), mean ± SD (range)	16.00 ± 14.95 (0-64)

Note. SAPASI = Self-Administered Psoriasis Area and Severity Index.

Item generation and scale construction

Based on a review of the literature, an item pool was generated with (adjusted) items of the following questionnaires: Bermond-Vorst Alexithymia Questionnaire [BVAQ; 20], Toronto Alexithymia Scale [TAS-20; 30], Body Awareness Questionnaire [BAQ; 31], Kentucky Inventory of Mindfulness Skills [KIMS; 32], Mindful Attention Awareness Scale [MAAS; 33] and Amplification Questionnaire [APQ; 34]. Items were adjusted to suit the

revised conceptualization of body attention and ignorance [12]. For instance, suitable items from the identifying, analyzing, and verbalizing dimensions of the alexithymia questionnaires were rephrased to reflect (a lack of) body awareness instead of a lack of emotional awareness (e.g., "I don't know what's going on inside my body" instead of "I don't know what's going on inside me" [TAS-20]). In four cases, original items were used. Initial item selection was conducted by three medical psychologists with a research and/or clinical focus on psychodermatology. The resulting item pool was sent to five other clinicians and researchers involved in the field of psychodermatology and to three patients involved in patient participation for dermatological research, with the instruction to evaluate the items on relevance, clarity and readability. This process led

Table 2. Rotated factor loadings of the 3-factor solution for the Body Attention, Ignorance and Awareness Scale (BAIAS)

Items		Body Ignorance	Body Attention	Body Awareness
Factor I				
1.	I do not know what is happening inside my body[a]	**0.68**	-0.05	0.00
2.	When I am not feeling well physically, I do not know the reason[b]	**0.64**	0.17	0.10
3.	I have physical sensations that I can't quite identify[a]	**0.63**	-0.22	0.02
4.	I do not know what is going on in my body[b]	**0.62**	0.16	-0.16
5.	I am often confused about what I observe in my body[a]	**0.62**	-0.11	-0.14
6.	I find it difficult to describe my physical sensations[b]	**0.59**	0.23	0.09
7.	I tend not to notice feelings of physical tension or discomfort until they really grab my attention[c]	**0.55**	0.19	0.17
Factor II				
8.	I notice changes in my body, such as whether my breathing slows down or speeds up[d]	-0.04	**0.72**	0.12
9.	I notice when my physical sensations are beginning to change[d]	0.17	**0.69**	0.17
10.	I pay attention to whether my muscles are tensed or relaxed[d]	0.03	**0.67**	0.19
11.	I know in advance when I am getting the flu[e]	0.02	**0.66**	0.10
12.	I know I am running a fever without taking my temperature[e]	0.08	**0.65**	0.09
Factor III				
13.	I think that you should pay attention to your body[b]	0.01	0.05	**0.76**
14.	When my body feels tense, I want to know where this feeling comes from[b]	-0.11	0.08	**0.68**
15.	In general I pay attention to my physical sensations[d]	0.21	0.31	**0.68**
16.	It is important that you are aware of your body[a]	0.01	0.28	**0.64**
% of variance explained		**23.0**	**16.0**	**8.4**

Note. Item adapted from: [a]TAS-20 (Toronto Alexithymia Scale), [b]BVAQ (Bermond-Vorst Alexithymia Questionnaire), [c]MAAS (Mindful Attention Awareness Scale), [d]KIMS-obs (Kentucky Inventory of Mindfulness Skills – observe subscale), [e]BAQ (Body Awareness Questionnaire). Factor loadings ≥ 0.55 printed in bold.

to a 23-item scale comprising 14 indicative (positively formulated) and nine contra-indicative (negatively formulated) items (Table 2). Respondents were asked to indicate on a 4-point Likert scale to what extent they agree with each statement (1 = not at all, 2 = somewhat, 3 = to a large extent, 4 = completely).

Measures of physical and psychological functioning

The following commonly-used and well-validated self-report questionnaires were used to examine correlations of body awareness with physical and psychological functioning and provide first indications of construct validity:

Physical and psychological wellbeing

The Impact of Chronic Skin Disease on Daily Life [ISDL; 35] was used to measure physical functioning (itch, pain, and scratching behavior). Symptoms of itch were assessed by means of a 4-item subscale measuring the intensity and duration of itch during the past 4 weeks (Cronbach's α in current study = .92). The answers are indicated on a 4-point Likert scale (ranging from "not at all" to "completely") and higher scores indicate higher levels of itch. Pain was assessed on a 10-point VAS scale (0 = no pain, 10 = worst pain ever experienced). Scratching behavior was assessed with 2 subscales: a 3-item conscious scratching subscale that assesses the frequency and duration of scratching behavior (Cronbach's α = .79) and a 3-item automatic scratching subscale that evaluates scratching behavior to non-itching stimuli and scratching in the absence of itch or without being aware of it (Cronbach's α = .71). In both scales, higher scores reflect more scratching behavior.

The 8-item fatigue subscale of the Checklist Individual Strength [CIS; 36] was used to assess fatigue. The subscale consists of 8 items that are responded to on a 7-point Likert scale (ranging from "yes, that is true" to "no, that is not true"), with higher scores reflecting more fatigue (Cronbach's α = .94).

The Self-Administered Psoriasis Area and Severity Index [SAPASI; 37] was used to assess disease severity. On anterior and posterior silhouettes, patients mark the areas that are currently affected by psoriasis. Below the silhouettes, patients can note the redness, thickness, and scaliness of their psoriasis on 3 analogue scales. Scores on the SAPASI can range from 0 (complete remission) to 72 (most severe psoriasis). The SAPASI has shown good reliability and validity [37, 38].

The Dermatology Life Quality Index [DLQI; 39] is a dermatology-specific instrument used to measure quality of life. The questionnaire assesses the impact of chronic skin conditions on several physical, psychological, and social aspects of daily life. It consists of 10 items that are responded to on a 4-point scale (ranging from "very much" to "not at all"). Higher scores reflect poorer quality of life (Cronbach's α = .85).

The Hospital Anxiety and Depression Scale [HADS; 40] was used to assess anxiety (7 items; Cronbach's α = .82) and depression (7 items; Cronbach's α = .80). The questions refer to the mood in the last week and they are responded to on a 4-point scale. Higher scores reflect higher levels of anxiety and depression.

Coping

Two subscales of the Utrecht Coping List [UCL; 41] were used to assess active coping (problem-focused coping, 7 items, Cronbach's α = .83) and passive coping (avoidance strategies, 8 items, Cronbach's α = .71) related to handling everyday stressful events. Respondents answer on a 4-point Likert scale (from "seldom or almost never" to "very often/ frequently"). Higher scores reflect a stronger tendency to use that specific coping strategy.

Illness cognitions

The Illness Cognition Questionnaire [ICQ; 42] was used to measure illness cognitions related to chronic diseases: helplessness (concentration on aversive aspects of the disease), acceptance (positive adaptation to chronic illness with emphasis on decreasing its negative aspects), and perceived benefits (assigning positive meaning to illness). Each subscale consists of 6 statements answered on a 4-point Likert scale (from "not at all" to "completely"), with higher scores indicating higher levels of the illness cognition. The ICQ was found to be highly reliable in the current sample (Cronbach's α = .88 for each scale).

Personality traits

The Eysenck Personality Questionnaire [EPQ; 43] was used to evaluate the personality traits neuroticism (Cronbach's α = .92) and extraversion (Cronbach's α = .87). It consists of 41 items with a dichotomous response format (yes/no), with higher scores reflecting higher levels of the personality trait.

Statistical analysis

Exploratory factor analysis (EFA) with Varimax rotation and Kaiser normalization was performed to assess the underlying structure of the new questionnaire [44]. Selection of the number of factors for the most optimal solution was based on conjunctive criteria requiring the eigenvalue of a factor being at least 1.0 and a clear bend in Cattell's scree test [45]. To assess the reliability of the new questionnaire, Cronbach's α were computed for the three scales. To examine associations between body awareness and measures of physical and psychological functioning and sociodemographic characteristics, Pearson correlation coefficients were computed for measures of physical and psychological wellbeing, personality characteristics, coping, illness cognitions, and sociodemographic

characteristics. Statistical significance was accepted at $p < .05$ in two-tailed tests. All analyses were performed using Statistical Packages for the Social Sciences version 20.0 [46].

RESULTS

The newly developed 23-item questionnaire was sent to 682 psoriasis patients, 475 of whom returned the questionnaire (70% response rate). Missing values on this questionnaire were present in 1% of data and were randomly distributed. Missing values were present in 1.6% of data in the entire dataset of included questionnaires (excluding the DLQI, as this scale was not distributed to the entire sample). Due to their low percentage and random distribution, the impact of these missing values is considered to be negligible. No cases with extreme values on one or more variables were observed; all values were within 3 standard deviations of the mean and all variables were normally distributed (skewness and kurtosis < 1.1).

Exploratory factor analysis of the Body Attention, Ignorance and Awareness Scale

The 23 items of the original questionnaire were reduced to 16, based on examination of item loadings and cross-loadings (i.e. primary factor loadings > 0.50 and at least 0.20 difference in cross-loadings; six items removed based on these criteria), meaningfulness and usefulness for the corresponding factor (one additional item removed). Based on these 16 items, three factors were extracted, explaining a total of 47.4% of the variance. The resulting questionnaire was termed the Body Attention, Ignorance and Awareness Scale (BAIAS). The first component, "Body Ignorance" (not recognizing and/or ignoring bodily signals), explained 23.0% of the variance, the second component, "Body Attention" (being aware of and paying mindful attention to bodily signals), added 16.0% and the third component, "Body Awareness" (self-perceived importance of and general attitude towards body awareness), added 8.4%.

Body Attention, Ignorance and Awareness scale: means and associations with sociodemographic variables

Based on the above-mentioned components, mean scores on the three scales were calculated by adding the scores of the items and dividing them by the total number of items of that scale. If more than one-third of the items on one particular scale were missing, the mean score of the scale was not calculated. Mean scores on BAIAS scales for the total sample, and stratified by age, gender, educational level, and marital status are shown in Table 3. Women scored slightly higher than men on Body Awareness ($t(469)$

= −2.61, $p < .01$), no gender differences were found for the other 2 scales. Patients with a higher educational level scored lower on Body Ignorance ($F(2,452) = 13.98$, $p < .001$) and higher on Body Attention ($F(2,452) = 8.78$, $p < .001$) and Body Awareness ($F(2,453) = 3.78$, $p = .02$). No differences according to age group or marital status were found for any of the three scales, nor were the subscales of the BAIAS significantly correlated with age (continuous scores; p-values ≥ .36).

Table 3. Mean scores on the Body Attention, Ignorance and Awareness Scale (BAIAS), stratified by age, gender, education, and marital status

	Body Ignorance (mean ± SD)	**Body Attention** (mean ± SD)	**Body Awareness** (mean ± SD)
Total sample	13.59 ± 3.51 (n = 470)	12.32 ± 3.31 (n = 470)	11.61 ± 2.26 (n = 471)
Stratified by age			
18-44	13.40 ± 3.45 (n = 127)	12.02 ± 3.35 (n = 127)	11.67 ± 2.17 (n = 126)
45-64	13.49 ± 3.61 (n = 261)	12.52 ± 3.31 (n = 260)	11.54 ± 2.30 (n = 262)
65-84	14.18 ± 3.27 (n = 82)	12.15 ± 3.23 (n = 83)	11.74 ± 2.28 (n = 83)
Stratified by gender			
Male	13.76 ± 3.67 (n = 262)	12.35 ± 3.28 (n = 261)	11.37 ± 2.24** (n = 263)
Female	13.37 ± 3.30 (n = 208)	12.28 ± 3.35 (n = 209)	11.91 ± 2.25** (n = 208)
Stratified by education			
Primary	15.00 ± 2.93*** (n = 71)	10.85 ± 3.42*** (n = 72)	10.93 ± 2.43* (n = 72)
Secondary	13.82 ± 3.32*** (n = 219)	12.61 ± 3.26*** (n = 218)	11.69 ± 2.29* (n = 219)
Tertiary	12.59 ± 3.61*** (n = 165)	12.58 ± 3.16*** (n = 165)	11.75 ± 2.13* (n = 165)
Stratified by marital status			
Married /long-term relationship	13.51± 3.53 (n = 398)	12.24 ± 3.21 (n = 399)	11.61 ± 2.22 (n = 400)
Single	14.07 ± 3.42 (n = 71)	12.67 ± 3.79 (n = 70)	11.61 ± 2.52 (n = 70)

$^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Reliability and intercorrelations of the Body Attention, Ignorance and Awareness Scale

The internal consistency was satisfactory for the Body Ignorance (α = .73), Body Attention (α = .74) and Body Awareness (α = .68) scales of the BAIAS. The subscale Body Attention showed a moderate correlation with the subscale Body Awareness ($r = .43$, $p < .001$),

and the Body Ignorance and Body Attention subscales were slightly, but significantly, negatively correlated ($r = –.16$, $p < .001$). No significant correlation was found between the Body Awareness and Body Ignorance subscales ($r = –.08$, $p = .09$).

As reported in Table 4, higher levels of Body Ignorance were associated with higher levels of itch, pain, and fatigue, more scratching, a decreased quality of life, higher levels of anxious and depressive symptoms, more avoidant coping, less active coping, higher levels of neuroticism and helplessness, and lower levels of extraversion and acceptance. Correlations between the Body Attention subscale and measures of physical and psychological wellbeing were mostly non-significant, with the exception of small correlations of higher Body Attention with higher levels of active coping, acceptance, and extraversion. Similarly, small correlations were found for higher Body Awareness, with higher levels of active coping and higher levels of anxiety, neuroticism and extraversion.

Table 4. Correlations between the Body Attention, Ignorance and Awareness Scale (BAIAS) and measures of physical and psychological functioning

Measure	Body Ignorance		Body Attention		Body Awareness	
	r	*n*	*r*	*n*	*r*	*n*
Physical and psychological wellbeing						
Itch	0.20***	466	0.00	465	0.06	466
Pain	0.24***	461	-0.05	461	0.03	462
Fatigue	0.32***	468	0.04	468	0.01	469
Conscious scratching	0.18***	451	-0.05	451	0.03	452
Automatic scratching	0.12*	451	-0.05	451	0.06	451
Quality of life	0.25***	362[a]	0.02	362[a]	0.03	362[a]
Disease severity	0.06	448	0.00	449	0.05	449
Depression	0.33***	467	-0.04	467	-0.07	469
Anxiety	0.34***	468	0.01	468	0.11*	469
Coping						
Active	-0.24***	465	0.27***	465	0.18***	466
Passive	0.29***	466	-0.07	466	-0.06	467
Illness cognitions						
Helplessness	0.30***	467	0.04	466	0.02	467
Acceptance	-0.24***	467	0.10*	466	0.02	467
Perceived benefits	0.10*	464	0.07	463	0.07	464
Personality traits						
Neuroticism	0.33***	469	-0.05	469	0.12**	470
Extraversion	-0.23***	468	0.12**	468	0.14**	469

Note. [a]Quality of life was not assessed in the whole study sample.
*$p < .05$ **$p < .01$ ***$p < .001$.

DISCUSSION

The aims of the current study were to develop a measure to assess body awareness and to examine its physical and psychological correlates in patients with psoriasis. The results showed that body awareness can be measured adequately in patients with psoriasis by means of the BAIAS. In addition, body ignorance and, to a lesser extent, body awareness and attention were related to physical and psychological functioning. In particular, patients who do not recognize and/or ignore their bodily signals experience lower levels of physical and psychological wellbeing.

The BAIAS showed a 3-factor structure, with three reliable scales: body ignorance (not recognizing and/or ignoring bodily signals), body attention (being aware of and paying mindful attention to specific internal bodily signals) and body awareness (self-perceived importance of and general attitude towards body awareness). In line with our hypothesis, the aspect of the BAIAS reflecting a low level of body awareness demonstrated associations with poorer physical and psychological wellbeing. Higher levels of body attention and body awareness were not related to physical and psychological wellbeing, but slightly to aspects of coping and personality that are generally perceived as adaptive (active coping and extraversion). We explicitly added items in the BAIAS that assess the failure to recognize bodily signals, which was shown to be only slightly negatively correlated with body attention. Results suggest that body awareness is not a unidimensional construct, but rather consists of multiple aspects that may be independently associated with physical and psychological functioning.

The concepts of body awareness and body ignorance seem to have inherently different meanings. While body awareness refers to the general tendency to be aware of and pay attention to bodily signals, body ignorance is related more to not recognizing or to actively ignoring bodily signals. Several mechanisms can be suggested to play a role in both concepts. For example, parallels can be drawn between body ignorance and the emotion regulation strategies of avoidance and suppression, which were found to be related to psychopathology in meta-analysis with moderate to large effect sizes [47]. Body ignorance may also be related to the maladaptive emotion regulation construct of "experiental avoidance"; the suppression or avoidance of a broader range of psychological experiences, including bodily signals, but also, for instance, cognitions, emotions, memories and sensations [48, 49]. Body ignorance might be related to problems with adherence; bodily signals often have a certain threat value due to signals of disease, and are therefore potentially avoided or ignored in patients who score high on body ignorance. In contrast, the construct body attention is hypothesized and operationalized to be more related to mindfulness and perhaps a broad awareness of, or sensitivity to, signals in general. When this sensitivity is accompanied by excessive worrying about bodily signals, this process may become maladaptive, as in health anxiety [15]. Future research should examine these hypotheses and constructs further.

The body ignorance subscale was found to be associated with more physical symptoms of itch, pain, and fatigue, as well as more scratching behavior. Because treatment of chronic skin conditions relies heavily on adequate self-care behavior and treatment compliance [11], being aware of bodily sensations and taking appropriate action may be especially important in this population. In addition, not being conscious of bodily sensations such as itch could also lead to unaware, automatic ways of dealing with these sensations, for instance through more frequent automatic scratching behavior. Scratching may cause further damage to the skin and lead to more itch, a process called the itch-scratch cycle.

Body ignorance was also found to be correlated with psychological wellbeing; patients who do not recognize or ignore bodily signals were found to be more anxious and depressed. In addition, they scored higher on generally maladaptive personality traits and coping styles. These findings may suggest that patients who do not recognize or pay attention to their bodily signals may be at risk for psychological problems. This may be relevant not only for patient wellbeing, but also for dermatological treatment outcomes, as it is known that psychological distress plays a significant role in the exacerbation of psoriasis [50]. An alternative explanation could be that patients with high levels of psychological distress may be less aware of their bodily signals as they are focused on exaggerated worries of, for example, health anxiety. Further research is needed on the association between body awareness in its current conceptualization and these distress-related constructs of health anxiety and hypervigilance, which are known to be associated with both increased symptom reporting and increased attention to bodily signals [e.g., 17].

The BAIAS was also found to be correlated with sociodemographic variables; women scored slightly higher than men on the body awareness subscale, and a higher educational level was slightly associated with lower levels of body ignorance and higher levels of body attention and awareness. These results correspond with the notion that women [51] and individuals with a higher educational level [52] have also been found to score lower on the related emotion regulation construct alexithymia.

The findings of this study should be considered in light of its limitations, which may be addressed in future research. Firstly, as this is the first study on this newly developed questionnaire, the BAIAS should be further validated based on these results. Also, this study was conducted in a sample of psoriasis patients with relatively mild to moderate disease severity from various hospitals, which raises the issue of representativeness and possible floor effects in the development of the questionnaire. However, all three body awareness subscales showed a normal distribution and few participants scored the highest or lowest possible values, indicating that floor effects were not likely to be a problem. Moreover, none of the three body awareness scales correlated with disease severity. In addition, disease severity in psoriasis is known to be, on average, mild to moderate in

general practice [e.g., 6, 53]. However, in order to generalize beyond this group, studies need to be conducted that replicate these results in patients with more severe disease activity, other chronic conditions, such as atopic dermatitis, and healthy participants. The developed questionnaire should also be administered to other independent samples to confirm its factor structure and further test its psychometric properties, such as test-retest reliability and sensitivity to change. In addition, it would be informative to perform a qualitative assessment on comprehension of the scale for respondents with diverse educational levels and cultural backgrounds, in order to examine whether the scale is equally comprehensible for all respondents.

Secondly, a substantial part of our sample had a comorbid medical condition. As research clearly suggests that psoriasis patients are at an increased risk for several other chronic somatic conditions, such as diabetes and cardiovascular conditions [see for an overview: 54], excluding these patients would leave us with a sample that would probably not be very clinically representative. However, this leaves the possibility that differences in body awareness according to medical conditions may have influenced our results. For example, diabetics are taught to be attuned to physiological sensations as they need to detect possible hypoglycemia in an early stage. Even though in the current study no differences in body awareness between patients with and without these medical conditions were observed, future studies should shed more light on this matter.

Thirdly, while correlations between the body ignorance scale and psychological and physical functioning were consistently in the same direction, the magnitude of the correlations was generally small to moderate. This corresponds with the knowledge that a multitude of factors can contribute to poor physical and psychological wellbeing, with body awareness being one of these factors. Lastly, the cross-sectional nature of this study precludes causal conclusions. While it could be hypothesized that a low awareness of bodily signals leads to poorer self-care behavior and, therefore, poorer skin status and lower physical and psychological wellbeing, alternative hypotheses cannot be ruled out. Future prospective studies should disentangle the causal pathways between body awareness and wellbeing.

In conclusion, the current study provided new insights into the potential relevance of body ignorance, body attention, and body awareness, which can be reliably measured with the BAIAS. Body ignorance was found to be associated with worse physical and psychological functioning. If it is proven that body ignorance is predictive of worse functioning in longitudinal studies, the BAIAS may be useful in assessment and screening for body ignorance in patients with psoriasis. Subsequently, psychological interventions, such as mindfulness or body awareness training, may be helpful in reducing body ignorance and improving body attention and awareness in an adequate manner [55–59].

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PART II

Methods 2.0: Explicit and Implicit Measures of Perceived Stigmatization

CHAPTER 3

Predictors of perceived stigmatization in patients with psoriasis

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ABSTRACT

Background: The physical appearance of psoriasis can be cosmetically disfiguring, resulting in a substantial social burden for patients. An important aspect of this burden is the experience of stigmatization. While stigmatization is known to be disabling and stressful for patients, little is known about its correlates and effective interventions are lacking.

Objectives: To examine predictor variables for perceived stigmatization in psoriasis.

Methods: Questionnaires were administered to 514 patients with psoriasis in a cross-sectional study. Zero-order correlation and multiple regression analyses were conducted including sociodemographic, disease-related, personality, illness cognitions, and social support predictor variables.

Results: Stigmatization was experienced by 73% of patients to some degree, and correlated with all five categories of predictor variables. In multiple regression analyses, stigmatization was associated with higher impact on daily life; lower education; higher disease visibility, severity, and duration; higher levels of social inhibition; having a type D personality; and not having a partner.

Conclusions: Results indicate that perceived stigmatization is common in psoriasis, and can be predicted by sociodemographic, disease-related, and personality variables. These predictor variables provide indications on which patients are especially vulnerable regarding perceived stigmatization, which might be used in treatment.

INTRODUCTION

It has long been theorized that humans have a fundamental need to be accepted by others and included in social interactions [1]. Social relationships are important for health and wellbeing, and social rejection can lead to physical, behavioral, and emotional problems [1]. Social rejection is central to the experience of stigmatization, which can be defined as an awareness of social disapproval, discrediting, or devaluation based on an attribute or physical mark [2–3].

In psoriasis, a chronic skin condition characterized by red plaques on the skin [4], the experience of stigmatization is commonly mentioned as one of its more troubling characteristics [5–9]. Patients often experience felt or perceived stigma, referring to the negative attitudes and responses that they perceive to be present in society and the sense of shame and fear of being discriminated against because of being 'flawed' due to their illness [10–11]. Actual experiences of stigmatization (i.e. enacted stigma) are also reported, for instance reactions of disgust or aversion, negative comments, or avoidance of contact [7, 9]. Stigmatization contributes considerably to disability, depression, and reduced quality of life in psoriasis [12–14], and can be considered a stressor. As distress can be a trigger for psoriasis exacerbation, this can become a vicious self-perpetuating cycle [15–17].

Despite these detrimental consequences, relatively few studies have studied interventions targeting stigmatization-related problems, and thus far no compelling evidence has been found for any type of intervention [18–19]. Firstly, it is important to recognize that stigmatization is a societal problem, and therefore societal educational interventions including contact between patients and the general population are called for to alter the public view [20]. Furthermore, interventions with a more inter- and intrapersonal focus are needed to improve patients' ability to cope with perceived stigmatization. In order to aid intervention development, a broad understanding of associated risk factors is needed, to be able to identify risk populations and focus points for interventions.

The literature suggests several potential sociodemographic predictors of perceived stigmatization in psoriasis, such as lower age [7], being female [5], and lower education [7]. Secondly, disease-related variables such as higher disease severity, longer disease duration, greater cosmetic involvement, and greater impact of the condition on daily life may be relevant [7–9, 13, 21, 22]. General ways in which patients deal with a chronic condition, such as heightened helplessness regarding the disease and its consequences, and lower disease acceptance have also been found to be predictive [7]. Additionally, social support and a large social network may serve a protective function against experiences of stigmatization [7].

While several studies have examined the abovementioned variables as predictors, the role of personality has hardly been studied [7, 9]. A possibly relevant personality

construct is type D, which is defined as a tendency to inhibit the expression of emotions or behavior to avoid negative reactions of others (social inhibition; SI), in combination with the stable tendency to experience negative affect (negative affectivity; NA [23]). Type D personality has been associated with increased risk of cardiovascular morbidity and mortality [24] and impaired health behavior [25], which are both frequently reported in psoriasis [26, 27]. The two main features – SI and NA – may both increase the impact of perceived stigmatization. Being socially inhibited implies being sensitive to negative reactions of others, which may cause stigmatization experiences to be especially detrimental. Additionally, having a stable tendency to experience negative affect may worsen psychological distress, which in turn may increase disease severity and resultantly visibility [15–17], and thereby vulnerability to stigmatization experiences. Furthermore, individuals with high levels of NA may be more likely to perceive social interactions as negative, due to the associated cognitive bias to negative information [28]. The specific combination of heightened SI and NA, type D, has mainly been related to adverse outcomes in cardiovascular patients [24, 29–31], but also to poorer physical, psychological and social functioning in other healthy and patient samples [32, 33], including two studies in psoriasis [34, 35].

This study aims to examine the relative contributions of a broad range of concepts, including never examined variables such as type D personality, to perceived stigmatization in a large sample of patients with psoriasis. It was hypothesized that perceived stigmatization would be related to the sociodemographic variables age, educational level, and being single; the disease-related variables severity, duration, visibility, and impact; type D personality; the illness cognitions acceptance and helplessness; and social support. This broad approach may provide indications for screening and interventions for reducing stigmatization-related problems.

MATERIALS AND METHODS

Participants

Psoriasis patients were recruited from one academic and three non-academic hospitals, and the Dutch Psoriasis Association. Inclusion criteria were a minimum age of 18 years and a dermatologist-confirmed psoriasis diagnosis. Exclusion criteria were illiteracy, pregnancy, and severe physical and mental comorbid conditions. This study made use of questionnaires that were administered between 2010 and 2013 to determine participant eligibility for a study on the effectiveness of internet-based cognitive behavioral treatment for psoriasis [36]. Parts of these data have been used in a previous paper [37]. All questionnaires were assessed prior to the intervention. The study was approved by

the regional medical ethics committee and carried out in accordance with the declaration of Helsinki [38]. All participants provided informed consent.

Measures

Perceived stigmatization was measured with a six-item subscale of the Impact of Chronic Skin Disease on Daily Life questionnaire (ISDL [39]; Cronbach's α in this study = .88). This assesses to what extent the patient feels stigmatized as a result of the skin condition. Items are assessed on a four-point Likert scale, with higher scores reflecting higher levels of perceived stigmatization (theoretical range 6-24). Example items are "others feel uncomfortable touching me due to my skin disease" or "other people sometimes make annoying comments about my skin disease".

Measures used for assessment of predictor variables

Sociodemographic variables

Sociodemographic variables were assessed with a general checklist that assessed patients' sex, age, educational level and marital status. Educational level was categorized into primary (i.e. lower education, elementary school), secondary (i.e. middle school and high school, including vocational training) and tertiary (i.e. higher professional education and university-level education).

Disease-related variables

Self-assessed disease severity was measured with the Self-Administered Psoriasis Area and Severity Index (SAPASI [40, 41], theoretical range 0-72). Self-assessed disease visibility was measured with a four-item ISDL subscale [39] asking about the extent of involvement of the face, scalp, neck, and hands (theoretical range 4-16). Disease duration was assessed by asking how old the patient was when diagnosed, and subtracting this number from their current age (range 0-64 years). Impact of the disease on daily life was assessed with a 10-item ISDL subscale [39], assessing the extent that the skin condition affects daily life activities (theoretical range 10-40, α = .89).

Personality

The Type D scale 14 [23] was used to assess type D personality. It consist of two seven-item subscales: SI (α = .88, example item: "I often feel inhibited in social interactions", theoretical range 0-28) and NA (α = .89, example item: "I often feel unhappy", theoretical range 0-28). A cutoff score of ≥ 10 on both scales is used to classify type D personality. Using these cutoff scores, one in four participants in this study (25.1%) had a type D personality. As previous studies indicate that type D is best represented as a continuous

variable [42, 43] the interaction term between the NA and SI subscales was used as a measure of type D.

Illness cognitions

The Illness Cognition Questionnaire [44] was used to measure two illness cognitions: acceptance, assessing the extent of positive adaptation to chronic illness with emphasis on decreasing its negative aspects (six items, α = .88, theoretical range 6-24) and helplessness, assessing the extent to which patients concentrate on aversive aspects of the disease (six items, α = .88, theoretical range 6-24).

Social support

Social support was assessed with a five-item ISDL subscale [39], assessing the qualitative aspect of social support (α = .86, theoretical range 5-20), and the quantitative aspect, asking patients about the actual size of their social network (range 0-25). This score was categorized according to norm groups [39].

Statistical analysis

All variables were checked for outliers, normality and normal distribution of residuals, and logarithmic transformations were successfully applied in case of non-normal distribution of variables (i.e. perceived stigmatization, helplessness and disease severity). Winsorizing was applied in outlying SAPASI scores prior to log-transformation, limiting the influence of extreme values. Zero-order correlations between perceived stigmatization and predictor variables were examined by Pearson correlation coefficients for continuous variables, and t-tests and ANOVAs for categorical variables. Zero-order correlations were interpreted as small (r = .10 - .29), moderate (r = .30 - .49), or large ($r \geq$ .50) [45]. Only study variables showing significant zero-order correlations with perceived stigmatization were entered in regression analyses. To study the relative contribution of five categories of variables (sociodemographic, disease-related, personality, illness cognitions, and social support), each category was entered in a consecutive step with perceived stigmatization as the dependent variable. Only statistically significant individual predictor variables ($p < .05$) were retained in further models. For type D personality, the main effects of mean-centered NA and SI were first examined and in a second block their interaction term was added. All regression analyses were conducted with SPSS 21.0 (IBM, Armonk, NY, USA) on a dataset without missing values (n = 433).

RESULTS

Sample characteristics

The sociodemographic characteristics of the study sample (n = 514) and means and SDs of the study variables can be found in Tables 1 and 2. Disease severity was generally mild to moderate, with 6.7% of patients having severe psoriasis (SAPASI >10) [46]. The mean values of perceived stigmatization, impact on daily life, social support and illness cognitions were similar to those found in previous research in psoriasis [39], and scores on type D personality were comparable with those found in the general population [33, 47].

Table 1. Sociodemographic characteristics of study sample (n = 514)

Patient characteristics		
Age (years), mean ± SD; range	52.21 ± 13.0; 18-84	
Sex		
Male	286	(55.6)
Female	228	(44.4)
Marital status		
Unmarried	62	(12.1)
Married/living together	410	(79.8)
Divorced	24	(4.7)
Widowed	18	(3.5)
Educational status		
Primary	16	(3.1)
Secondary	306	(59.5)
Tertiary	190	(37.0)
Missing	2	(0.4)

Note. Values are n (%) unless stated otherwise.

Perceived stigmatization

Seventy-three percent of our sample perceived at least some stigmatization, as indicated by a positive score on at least one of the six items, as reported in previous studies [7, 8]. The feeling of being stared at was reported most often (in 61.9% of patients), followed by other people thinking their condition was contageous (44.9%), finding them unattractive because of their skin condition (38.1%), avoiding to touch them (32.3%), and making negative comments (27.7%).

Table 2. Means and standard deviations of study variables

Characteristic	Mean ± SD	Range
Perceived stigmatization	9.02 ± 3.48	6-24
Disease-related		
Disease severity[a]	5.09 ± 4.02	0-33
Disease visibility	1.85 ± 0.57	1.0-3.5
Disease duration (years)[b]	15.72 ± 14.75	0-62
Impact on daily life	16.06 ± 6.06	10-40
Type D, (*n, %*)	129 (25.1)	
Negative affectivity (NA)	8.45 ± 6.02	0-26
Social inhibition (SI)	9.13 ± 6.01	0-27
Illness cognitions		
Helplessness	9.38 ± 3.74	6-24
Acceptance	17.19 ± 4.46	6-24
Social support		
Perceived support	15.80 ± 3.60	5-20
Actual support	8.12 ± 5.33	0-25

Note.[a]$n = 489$, [b]$n = 498$.

Individual associations with perceived stigmatization

Zero-order correlations of study variables are reported in Table 3. Higher perceived stigmatization showed a large correlation with a greater impact of the skin condition on daily life; moderate correlations with higher disease severity, helplessness, NA, and lower levels of acceptance; and small correlations with lower age, longer disease duration, greater visibility, higher levels of SI, and less perceived social support. Furthermore, higher perceived stigmatization scores were associated with a smaller social network ($p = 0.001$), not having a partner ($p < 0.001$), and a lower educational level ($p = 0.01$), but not with sex ($p = 1.00$).

Table 3. Zero-order correlation matrix of continuous study variables

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. Stigmatization	-										
2. Age	-.28***	-									
3. Disease severity	.34***	-.14**	-								
4. Disease visibility	.26***	-.12**	.29***	-							
5. Disease duration	.13**	.22***	.11*	-.03	-						
6. Disease impact	.61***	-.17***	.32***	.26***	.11*	-					
7. Type D: NA	.30***	-.23***	.20***	.12*	-.05	.36***	-				
8. Type D: SI	.22***	-.11*	.05	.07	-.03	.17***	.41***	-			
9. Helplessness	.49***	-.09#	.28***	.19***	.10*	.67***	.39***	.17***	-		
10. Acceptance	-.34***	.10*	-.19***	-.23***	.10*	-.48***	-.42***	-.20***	-.52***	-	
11. Perceived support	-.16***	-.02	.02	.00	.00	-.18***	-.36***	-.27***	-.17***	.26***	-

Note. NA = Negative Affectivity; SI = Social Inhibition.
*$p < .05$ **$p < .01$ ***$p < .001$ #$p < .10$.

Relative impact on perceived stigmatization

Table 4 presents the results of multiple regression analyses that were performed to examine the relative impact of predictors on perceived stigmatization.

Table 4. Predictors of stigmatization: multiple regression analyses

Predictors	Standardized regression coefficients (β)				
	Block 1	Block 2	Block 3	Block 4	Block 5
Sociodemographic					
Age	-.27***	-.19***	-.19***	-.19***	-.18***
Education (primary[a])	.06	.03	.03	.03	.02
Education (secondary[a])	.15**	.12***	.12**	.11**	.11**
Married / With partner[b]	-.13**	-.07*	-.07#	-.07#	-.06
Disease-related					
Disease severity		.10**	.10**	.10*	.11**
Disease visibility		.12**	.12**	.12**	.12**
Disease duration		.11**	.11**	.11**	.09*
Impact on daily life		.51***	.50***	.46***	.50***
Personality					
Negative affectivity (NA)			.00	-.01	-.02
Social inhibition (SI)			.10**	.10*	.09*
Type D personality (interaction NA*SI)			.08*	.08*	.07*
Illness cognitions					
Helplessness				.05	
Acceptance				-.01	
Social support					
Perceived support					-.03
Actual support (1-4[c])					-.15
Actual support (5-14[c])					-.17
Actual support (15-25[c])					-.13
***F*-change**	16.78***	76.16***	4.31**	0.44	0.63
R^2	.12	.48	.50	.50	.50

Note. [a]Reference group = tertiary education, [b]Reference group = no partner, [c]Number of friends, reference group = no friends.
***$p < .001$, **$p < .01$, *$p < .05$, #$p < .10$.

In block 1, sociodemographic variables explained 11.9% of the variance in perceived stigmatization, with lower age, lower education, and being singe being predictive of higher levels of perceived stigmatization. In block 2, adding the disease-related variables explained a total of 48.3% of the variance, with greater disease severity and visibility, longer disease duration, and a higher disease impact predicting more perceived

stigmatization. In block 3, adding the personality variables resulted in a total of 49.7% explained variance, with the main effect of SI (but not NA) and the type D interaction effect being predictive of perceived stigmatization. Patients scoring both high on SI and NA, indicating a type D personality, had higher levels of perceived stigmatization (Figure 1). In blocks 4 and 5, illness cognitions of helplessness and acceptance, and perceived and actual social support did not significantly add to the model.

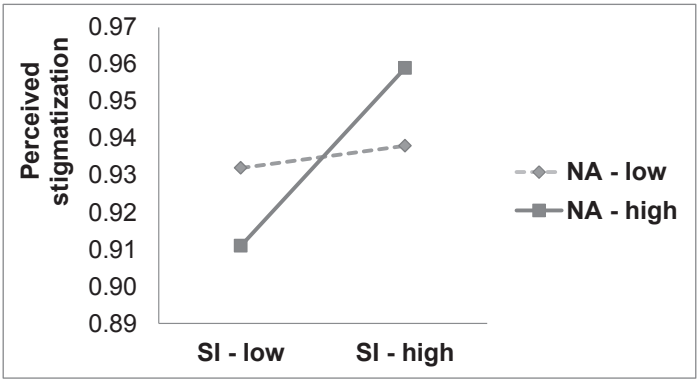

Figure 1. Interaction effect of negative affectivity (NA) and social inhibition (SI) on perceived stigmatization. Predicted values of perceived stigmatization are displayed for high and low levels of NA and SI (i.e. 1 SD above/below the mean). For all other variables included in the model, mean scores were used to calculate the regression outcome. In this figure, the degree of SI was not associated with perceived stigmatization when patients had low NA. For patients high on NA, specifically the combination with high SI, indicating a type D personality, was related to higher levels of perceived stigmatization.

The final model, including only the significant predictors, explained a total of 49.7% of the variance in perceived stigmatization (Table 5). Predictors, from highest to lowest standardized regression coefficients, were higher disease impact, lower age, lower education and greater disease visibility, longer disease duration, higher disease severity and higher levels of SI, having a type D personality, and being single. A model excluding multivariate outliers (n = 16; critical Mahalanobis Distance value = 32.91, degrees of freedom = 12, p = .001) yielded similar results, with the exception of two predictors that became marginally significant (type D personality, p = .08) or non-significant (marital status, p = .11).

Table 5. Predictors of stigmatization: final model

Predictors	β	B	SE
Sociodemographic			
Age	-.19***	-.00***	(.00)
Married / With partner[a]	-.07#	-.02#	(.01)
Education (primary)[b]	.04	.03	(.03)
Education (secondary)[b]	.12**	.03**	(.01)
Disease-related			
Disease severity	.10*	.02*	(.01)
Disease visibility	.12**	.03**	(.01)
Disease duration	.11**	.00**	(.00)
Impact on daily life	.50***	.01***	(.00)
Personality			
Negative affectivity	.00	.00	(.01)
Social inhibition	.10**	.01**	(.00)
Type D	.08*	.01*	(.00)
***F*-change**		37.80***	
R^2		.50	

Note. β = standardized coefficients, B = unstandardized coefficients, SE = standard error of B.
[a]Reference group = no partner, [b]Reference group = tertiary education.
***$p < .001$, **$p < .01$, *$p < .05$, #$p < .10$.

DISCUSSION

This study examined perceived stigmatization and its potential sociodemographic, disease-related, and psychosocial predictors in a large sample of patients with psoriasis. The vast majority of our sample experienced perceived stigmatization to some degree, corresponding with previous studies [7, 8]. Higher levels of perceived stigmatization were found to be correlated with sociodemographic and disease-related variables, personality, illness cognitions and social support. Perceived stigmatization was found to be particularly predicted by disease impact, as well as by lower age, lower education, greater disease visibility and lower education, longer disease duration, greater disease severity and higher levels of SI, having a type D personality, and being single.

Greater severity and visibility and longer disease duration were predictive of perceived stigmatization, underlining the importance of early dermatological treatment; patients whose psoriasis is not adequately controlled may be more affected by stigmatization. However, the impact of the condition was a much stronger predictor, corresponding with the notion that the subjective experience of impact is generally more important than disease severity [48, 49]. In contrast with an earlier study [7], the impact of the

condition was also a stronger predictor than the illness cognition of helplessness. The relative and different contribution of both variables may be explained by the high correlation between these variables in the current study and in previous research [48]. It seems likely that patients with psoriasis who are prone to feelings of helplessness regarding the disease may also experience a larger impact of psoriasis and magnify negative reactions of others.

Type D personality and its subcomponent SI were found to be significant predictors of perceived stigmatization. The fear of disapproval that leads individuals to inhibit emotions or behavior in SI [23] may explain its relation to perceived stigmatization; socially inhibited individuals may be more sensitive to the reactions of others and may therefore perceive themselves to be stigmatized more readily. Not only SI in itself, but also the combination of higher levels of SI and NA (type D personality) was a significant predictor of perceived stigmatization. This corresponds with studies suggesting that type D is associated with social impairments [50, 51]. These results extend preliminary evidence indicating that type D may be a risk factor for worse outcomes in psoriasis [34, 35], by showing for the first time that it is associated with increased perceived stigmatization. However, these results should be replicated in further research, as the effect of type D became marginally significant when excluding multivariate outliers. In the current study, NA was not a significant predictor of perceived stigmatization. It seems that, while the shared variance with NA can also be explained by other variables, SI contains more unique information relevant for perceived stigmatization.

Regarding sociodemographic variables, the significant predictors lower age, lower educational level and being single were in line with previous research indicating that the negative psychosocial influence of psoriasis is particularly strong in younger patients [7, 52].

To develop a comprehensive model of factors influencing perceived stigmatization, both potential risk factors (e.g., social fears and inhibition) and protective factors (e.g., social support) need to be taken into account. While the current study provides evidence for the former, results of the latter (social support) were inconsistent with previous research [7], possibly due to the inclusion of predictor variables not previously studied. Furthermore, while the current study examined self-perceived support, a more objective measure may lead to different results. Nonetheless, current results suggest that it is not so much the experienced social support that plays a significant role in perceived stigmatization, but more the extent to which patients may experience social anxiety and want to avoid negative reactions, as captured in SI. Future research should further explore the role of protective factors in perceived stigmatization.

Strengths of the current study include the large sample size, simultaneous assessment of relevant variables to control for shared variance, including personality variables never before studied, and inclusion of patients from a variety of settings. Limitations include

the cross-sectional design, precluding conclusions about cause and effect, and the relatively mild disease severity of our sample, which may limit generalizability. In addition, self-report measures were used to assess disease severity. However, self-assessed PASI scores correlate reasonably well with clinician-assessed PASI scores [40, 53] and modest relationships with stigmatization have also been found in studies using the clinician-assessed PASI [54, 55]. Lastly, some predictor variables showed high intercorrelations, but none of them were above the multicollinearity cutoff point of .80 [56].

In conclusion, perceived stigmatization was found to be common in patients with psoriasis and was predicted by specific sociodemographic, disease-related, and personality variables. This provides several possible focus points for individual screening and interventions, in addition to the societal interventions that are needed to target the overarching problem. Firstly, the predictors found in this study provide clinicians with an understanding of which patients may be especially vulnerable to stigmatization-related problems, which may warrant special attention during consultations. Type D and especially its social inhibition component may be screened for, when further evidence confirms our preliminary results indicating that individuals with this personality subtype are especially vulnerable to stigmatization-related problems. Stigmatization-related problems may be screened using validated instruments [39], followed by targeted interventions that may focus on the impact of the condition on daily life, considering that this was the largest predictor. Cognitive behavioral treatment, including social skills training, seems promising as an intervention framework. Previous research indicates that it can decrease perceived stigmatization in skin conditions [57], improve psychological and disease-related outcomes in psoriasis [58, 59], and decrease helplessness, which shows high correlations with disease impact [60–62]. In order to target the social inhibition aspect of type D personality, social skills training and evidence-based interventions for social fears, such as cognitive behavioral therapy and/or exposure therapy, may be an additional treatment approach [63, 64].

The current study provides a framework of characteristics of patients who are at greater risk to perceive stigmatization, which has been shown to have detrimental psychological consequences in psoriasis. Future research should expand upon these findings in order to examine interplays between predictors in prospective studies. Further development of screening and intervention procedures are needed in order to facilitate implementation of tailored evidence-based treatment to reduce the psychosocial burden of chronic skin conditions.

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CHAPTER 4

Implicit stigmatization-related biases in individuals with skin conditions and their significant others

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ABSTRACT

Objective: Stigmatization is common in people with chronic skin conditions and may also affect their significant others (SOs). The fast and implicit processing of stigmatization-related stimuli has received little attention in these populations; however, such knowledge may offer indications for new treatment methods. This study aimed to investigate implicit processing of stigmatization-related stimuli in people with skin conditions and their SOs.

Method: A modified Stroop task and 2 approach-avoidance tasks were administered to participants with chronic skin conditions (alopecia: $n = 50$ and psoriasis: $n = 50$); their significant others (alopecia SOs: $n = 47$ and psoriasis SOs: $n = 50$); and controls ($n = 50$). The aim was to examine attentional and behavioral biases toward disease-related and social threat-related stigmatization stimuli.

Results: An attentional bias to disease-related stimuli was found in participants with alopecia and their SOs, compared with controls ($p < .001$). This effect was not found for participants with psoriasis and their SOs. Increased behavioral avoidance of disgusted faces was found in participants with psoriasis and their SOs, compared with controls ($p = .047$). This effect was not found in participants with alopecia and their SOs.

Conclusions: These results provide support for the idea that individuals with skin conditions and their SOs are characterized by a stigmatization-related stimulus bias regarding implicit cognitive and behavioral reactions, in comparison to healthy individuals. Furthermore, preliminary results suggest that these processes may differ across skin conditions, with people with psoriasis being more affected by social reactions (i.e. disgusted faces) and people with alopecia by disease-related cues possibly related to internalized self-stigma.

INTRODUCTION

The visible marks of a skin condition can have substantial social consequences. In alopecia, people experience hair loss, ranging from minor patches to loss of all scalp and body hair. This may have negative consequences for social interactions, body image, and self-esteem [e.g., 1]. Psoriasis is characterized by red patches of skin covered with silvery scales, that may be unjustly viewed as "unclean" and likely to be contagious [e.g., 2, 3], resulting in negative social reactions. People with chronic skin conditions frequently experience stigmatization [e.g., 4], which can be defined as an awareness of social disapproval, discrediting, or devaluation based on an attribute or physical mark [5]. In self-stigma, stigmatization becomes internalized, as the stigmatized individual endorses stereotypes about the discreditable attribute that he or she has and applies them to him/herself [6]. Self-stigma has been associated with negative psychological and physical health outcomes [e.g., 7, 8].

Stigmatization and self-stigma are usually assessed by questionnaires [9]. However, dual-process models suggest that information processing and behavior are influenced not only by the relatively slow, reflective processes assessed by questionnaires, but perhaps even more by the fast, reflexive reactions assessed by indirect tasks [10]. The experience of stigmatization in people with skin conditions may also be reflected in these implicit processes. Biases could then be expected regarding (a) social threat-related stimuli (perceived stigma) and (b) disease-related stimuli to assess the individual's response to his or her own condition (self-stigma). While disease-related and social threat-related attentional biases were previously found in individuals with psoriasis [11], it is unknown whether they also occur on a behavioral level (e.g., in avoidance responses) and/or in other skin conditions.

As theorized in disease-avoidance models [12], visible cues of disease, such as skin lesions, may activate disgust reactions and motivate behavioral avoidance. Disgust-related brain regions were found to be activated in healthy participants when they were shown pictures of stigmatized groups [e.g., 13]. Given that people with skin conditions may experience and/or anticipate these disgust reactions, they may develop a behavioral avoidance bias to social threat-related information (e.g., disgusted faces), similar to the biases seen in social anxiety [e.g., 14]. In line with this, a reduced ability to identify disgusted faces, and diminished associated brain activity, was found in psoriasis; this suggests an avoidance-based coping mechanism [15]. In addition to social threat-related stimuli, biases may also be present for disease-related stimuli. An eye-tracking study showed that people with acne automatically gazed more at acne lesions than did controls, which suggests an attentional bias [16]. Also, in pathological skin picking, greater behavioral avoidance of pictures of skin irregularities was found compared to controls [17].

Social threat-related and disease-related biases may also occur in significant others (SOs), because they often experience increased distress and a substantial burden because of the chronic skin condition [e.g., 18]. No research has yet focused on these biases in significant others of individuals with chronic skin conditions. However, indications of a larger implicit preference for clear skin were found in people from the general population who knew someone with a skin condition than in people who did not. The authors explained this finding by suggesting that these individuals attempted to suppress their stereotypical reaction, which required cognitive effort [19]. The current study explores whether social threat-related and disease-related biases also occur in SOs.

This study examines attentional bias and approach-avoidance tendencies in relation to disease-related and social threat-related stigmatization stimuli using reaction time (RT) tasks, to gain new insights into the concept of stigmatization, which has previously only been examined using questionnaires. It was hypothesized that, compared with controls, people with chronic skin conditions and their SOs would show an attentional bias and an increased avoidance reaction toward both stimulus categories. The two skin conditions were exploratively compared, with the expectation that both conditions would show similar biases.

METHODS

This section provides a condensed summary of the methods used. For detailed information, we refer to the supplemental material. This study included 247 participants: people with chronic skin conditions, their SOs, and controls from the general population (see Table S1, supplemental material). Attentional bias to disease-related and social threat-related words was assessed with a modified Stroop task ([20]; Table S3). Approach-avoidance tendencies regarding disease-related and social threat-related pictures were assessed with two approach-avoidance tasks (AATs; [21]). Last, questionnaires were administered regarding disease severity, self-perceived visibility, psychological distress, social anxiety, and fear of negative evaluation. For all picture (AATs) or word (modified Stroop task) categories, repeated-measures ANOVAs were conducted to compare the RTs of individuals with each chronic skin condition and their SOs with those of controls.

RESULTS

This section summarizes the main results. For more details, see supplemental material.

Attentional bias: modified Stroop task

Mean RTs for the modified Stroop task are presented in Figure 1 and Table S4. People with alopecia, their SOs, and controls differed in their RTs to specific word categories (p = .002), η_p^2 = .09): people with alopecia and their SOs were slower than controls to name colors of hair-related words compared with neutral words (p = .001, $\eta_p^2 \geq .10$). No differences were found between people with psoriasis, their SOs, and controls regarding the RTs for skin-related words compared with neutral words (p = .43). Last, no differences were found between individuals with either chronic skin condition, their SOs, and controls regarding social threat-related words ($p \geq .40$).

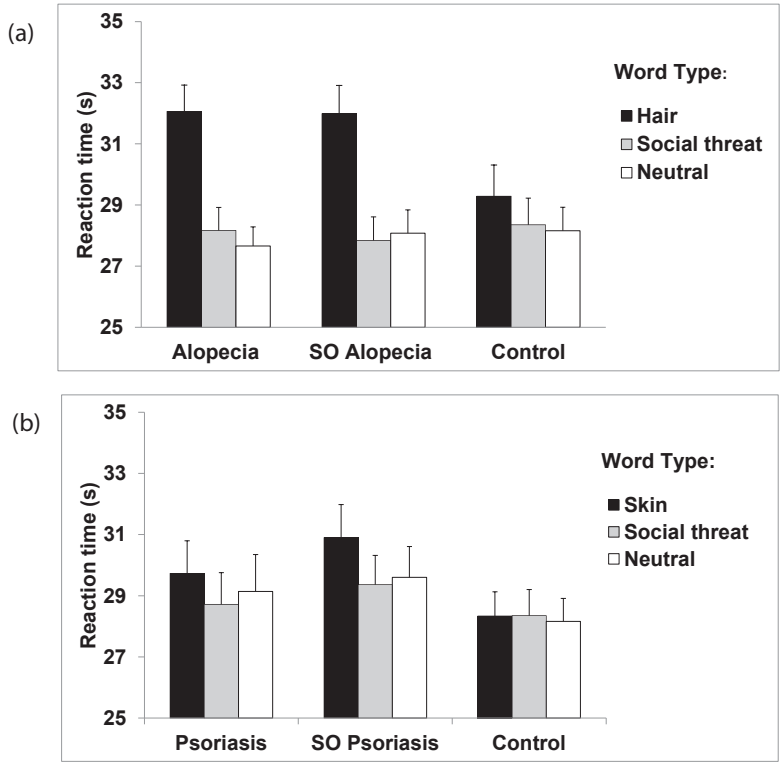

Figure 1. Modified Stroop task: average color-naming reaction times in seconds (±SEM) for (a) alopecia, significant others, and controls, and (b) psoriasis, significant others, and controls. *Note.* SO = significant others.

Behavioral bias: approach-avoidance tasks

Mean RTs and AAT-effects for the disease-related and social threat-related AATs can be found in Figure 2 and Tables S5 and S6, respectively. In the disease-related AAT, people with psoriasis and their SOs did not differ from controls regarding their approach-avoidance reactions to psoriasis-related and neutral pictures ($p \leq .73$). In the social

threat-related AAT, people with alopecia and their SOs did not differ from controls regarding their approach-avoidance reactions to emotional faces ($p \leq .68$). Similarly, no differences in approach-avoidance reactions to emotional faces were found between people with psoriasis, their SOs, and controls ($p \leq .46$). In the case of disgusted faces, specifically, participants with psoriasis and their SOs were quicker than controls to avoid than approach disgusted faces ($p = .047$, $\eta_p^2 = .03$), while participants with alopecia and their SOs did not differ from controls ($p = .71$).

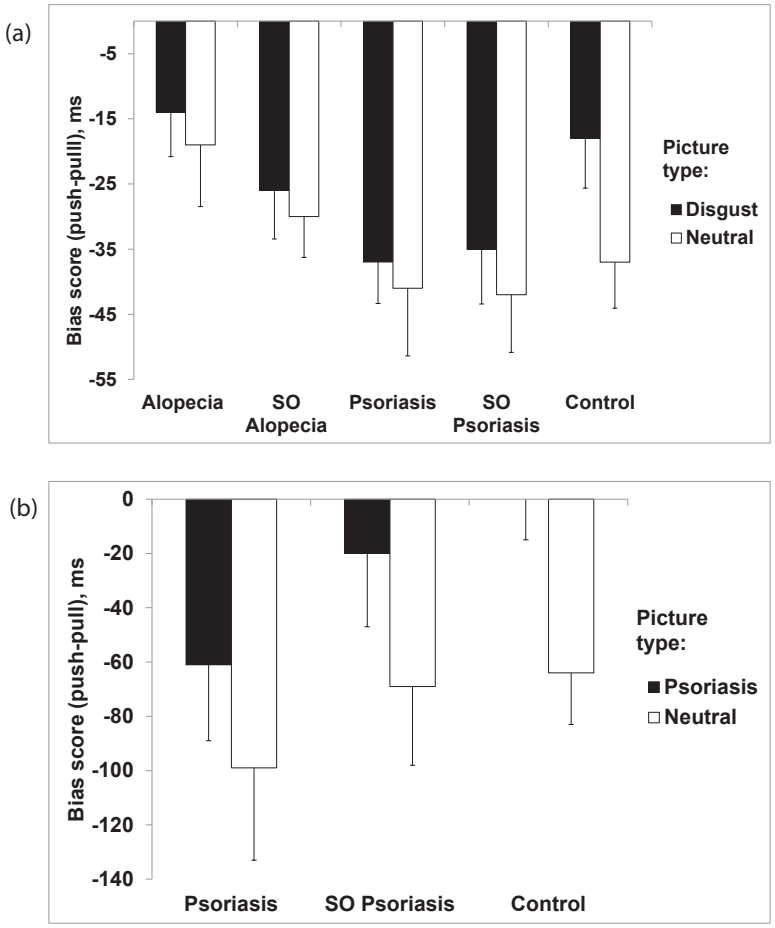

Figure 2. Approach-Avoidance Tasks: average approach-avoidance task (AAT) effects (push-pull) in milliseconds (±SEM), depending on group and picture type, for (a) social threat-related AAT, and (b) disease-related AAT. *Note.* SO = significant others.

DISCUSSION

This study examined implicit bias to social threat-related and disease-related stimuli in relation to two chronic skin conditions. In people with alopecia and their SOs, compared with controls, an attentional bias to disease-related words was found, but no behavioral avoidance bias for social threat-related pictures. The opposite was found in people with psoriasis and their SOs (again compared with controls): no attentional bias, but indications of a behavioral avoidance bias. These results provide preliminary support for the idea that people with skin conditions and their significant others differ from healthy controls regarding their implicit reactions to stigmatization-related stimuli. Furthermore, in contrast to what was initially expected, these processes may differ between specific skin conditions.

In contrast to a previous study [11], an attentional bias was found in individuals with alopecia, but not with psoriasis. This may be because of the relatively mild disease severity and lower levels of fear of negative evaluation (FNE) in psoriasis compared with alopecia, and the lower levels of disease severity, anxiety, and depression among participants than in the previous study [11]. It may also be because of inherent differences between the two skin conditions. Skin lesions in psoriasis may provoke social avoidance responses because of these being viewed as "unclean" or "contagious" [3]. In contrast, hair loss in alopecia may provoke fewer direct social responses, as the majority of patients tend to hide their condition. However, the significant disease-related distress and illness-related cognitive preoccupation reported in this patient group suggest that alopecia patients are psychologically affected by their condition [22], and these psychological effects may be reflected in an attentional bias to disease-related words. The markedly higher levels of FNE further underline the concerns that these people have about being unfavorably evaluated by others, which may be the result of their "hidden stigma". No attentional biases to social threat-related words were found for any of the groups. In a pilot validation study, these words were selected based on their high ratings of stigmatization combined with their negative emotional valence. However, as words were not specifically selected on ratings of individual threat, they may have been insufficiently threatening in comparison to words used in previous research [11].

Behavioral avoidance bias was examined using social threat-related and disease-related stimuli. In the disease-related AAT, no differences were found between people with psoriasis, their SOs, and controls. Instead, for people with psoriasis, the stigmatization experience seems to be better captured by their fear and avoidance of disgust reactions of others. Indications toward a social threat-related bias were found in psoriasis, but not in alopecia. This is in line with the idea that disgust reactions are more relevant in psoriasis and with the finding that the neural response of people with psoriasis to disgusted faces is consistent with an avoidance-based coping mechanism [15]. The fact

that biases were also observed in SOs corresponds with a study showing increased bias to skin irregularities in people who knew someone with a skin condition [2]. Equally, however, this could reflect the burden of chronic conditions on SOs [18].

Limitations of this study include the differences between groups in certain sociodemographic and psychological characteristics; this limits the comparability of the groups and calls for a cautious interpretation of results. In contrast with previous research [e.g., 23], relatively low distress levels were found in participants with chronic skin conditions. As this study was the first of its kind, further studies are needed to examine the psychometric properties of the implicit measures used. While the reliability of the AATs was good, the validity of these and other implicit measures should be further established [e.g., 24]. Another possible limitation was that this study used several stimulus categories in each task. As responses on each stimulus may influence subsequent responses, we cannot exclude the possibility that this confounded the results. A simpler design, for instance only including disgusted and neutral faces in an AAT, could perhaps be considered to examine specific hypotheses in future research.

To conclude, an attentional bias for disease-related stimuli was found in people with alopecia and their SOs, while indications of a behavioral avoidance bias for disgusted faces were found in people with psoriasis and their SOs. These results provide preliminary support for the idea that, compared with healthy individuals, people with chronic skin conditions show different implicit cognitive and behavioral reactions to stigmatization-provoking stimuli. Furthermore, these processes may differ between skin conditions, with people with psoriasis being more affected by reactions of others, and those with alopecia being more affected by disease-related cues relating to self-stigma. Future research should focus on extending these results in other samples (e.g., people with other skin conditions, other somatic conditions, or elevated levels of social anxiety), to help unravel the underlying mechanisms and to examine their clinical relevance.

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SUPPLEMENTAL MATERIAL: SUPPLEMENTAL METHODS

Participant recruitment and inclusion criteria

People with skin conditions were recruited through two patient associations, the Dutch Alopecia Association and the Dutch Psoriasis Association, and by contacting participants from previous studies on alopecia and psoriasis who had given permission to be approached for future studies. People with alopecia and psoriasis were asked to invite a significant other (partner, family member, or friend) to participate. Study participants from the general population were recruited by contacting a subsample of the Nijmegen Biomedical Study, a population-based survey (www.nijmegenbiomedischestudie.nl). Inclusion criteria for patients were a diagnosis of alopecia or psoriasis, age ≥ 18 years, and a sufficient understanding of the Dutch language. Exclusion criteria for patients were psychiatric conditions, current psychological treatment, and co-morbid medical conditions that had a larger self-perceived impact on patients' daily lives than their skin condition. Exclusion criteria for SOs and controls were having a chronic skin condition. All participants had normal or corrected-to-normal vision. The regional medical ethics committee indicated that the study did not need formal approval due to its non-invasive nature. Written informed consent was obtained from each participant.

Materials & procedure

In this study, several implicit tasks and self-report questionnaires were administered in a laboratory setting. Table S2 shows the order in which the tasks and questionnaires were administered.

Attentional bias: modified Stroop task

To assess attentional bias for word stimuli, a modified Stroop task [20] was used. Participants are instructed to name aloud the print color of the words presented, as quickly and accurately as possible. The assumption of the task is that the saliency of words interferes with the color-naming task and results in longer response latencies, indicating an attentional bias. In the current modified Stroop task, disease-related words (i.e. hair-related words for alopecia and skin-related words for psoriasis) and social threat-related stigmatization words were administered, along with three word categories taken from the Dutch Emotional Word list [25]. The aim was to assess processing of words without emotional or disease-related content (neutral), threatening emotional words (negative), and non-threatening emotional words (positive; see Table S3). Disease-related words were chosen as self-stigma stimuli as they most closely relate to the participants' skin conditions. The individual's reaction times to these stimuli are therefore indicative of the individual's implicit reaction to skin conditions. People with skin conditions may show longer reaction times to disease-related words, which would indicate an implicit

emotional reaction. This 'negative reaction to the self' closely relates to the concept of self-stigma, in which an individual endorses stereotypes about a discreditable attribute (e.g., damaged or flawed skin) that he or she has and applies these stereotypes to him/herself.

Disease-related and social threat-related stigmatization words were validated in a pilot study consisting of 43 people with skin conditions, healthy individuals, and medical psychology professionals. The pilot study examined both the extent to which stimuli reflected the underlying constructs and their emotional valence. Words were presented against a black background, in random order, in a blocked design: 1 screen per word category, containing 8 words repeated 5 times. The distribution of word colors was the same for each category. The experimenter, who was blind to word category, recorded response latencies (automated via mouse click at start and end of category), and number of errors (hand-scored) per category.

Behavioral bias: approach-avoidance tasks

To assess approach-avoidance tendencies regarding disease-related and social threat-related stimuli, two irrelevant-feature zooming approach-avoidance tasks (AATs) were used [21]. Disease-related pictures were chosen as self-stigma stimuli. The reasoning behind this was similar to that for disease-related words, as presented above (see 'Attentional bias: modified Stroop task'). Social threat-related pictures showed disgusted faces (for rationale, see 'Introduction'). For these tasks, participants were seated behind a 19-inch computer screen (resolution: 1024x786 pixels) and instructed to respond to each picture on the screen, as quickly and accurately as possible, with a joystick that was tightly fastened to the table. Depending on an irrelevant stimulus feature, participants had to either push the joystick away (avoidance, picture size decreases) or pull it towards them (approach, picture size increases). Whether participants had to push or pull in response to the irrelevant feature was determined randomly. If the participant responded correctly, the picture disappeared when the joystick was pushed or pulled by approximately 30 degrees.

For the disease-related AAT, stimuli were pictures of psoriasis and neutral control pictures of structured fabric resembling skin. The pictures of psoriasis had been previously validated in the pilot study described above; the neutral control pictures had been used in previous research [17]. Participants had to respond with push or pull according to whether the picture was tilted to the left or to the right. The task was introduced by 10 practice trials (pictures of empty frames), followed by 200 experimental trials distributed across two blocks. The reliability of each picture category and the response direction of the disease-related AAT was found to be good (Cronbach's alpha = .88 - .91). Due to the specific nature of the picture stimuli, this AAT was only administered to people with psoriasis, their SOs, and controls.

For the social threat-related AAT, the stimuli were pictures of emotional facial expressions: disgusted (main hypothesis), sad (bias to other negative emotional stimuli), smiling (bias to positive emotional stimuli), and neutral faces (as comparison). The pictures were selected from the Radboud Faces Database [26]. Participants now had to respond with push or pull according to whether the picture color was grey or sepia. The task was introduced by 10 practice trials (checkerboard pictures), followed by 324 experimental trials distributed across two blocks. The reliability of each picture category and the response direction of the social threat-related AAT was found to be good (Cronbach's alpha = .85-.91).

Questionnaires

Self-reported questionnaires were administered regarding disease severity, self-perceived visibility, psychological distress, social anxiety, and fear of negative evaluation. In addition, a general checklist was used to assess participants' gender, age, educational level, and marital status.

People with alopecia indicated their degree of *hair loss* as alopecia areata (circular patches of hair loss), androgenetica (female pattern baldness), totalis (total loss of hair on scalp), or universalis (total loss of hair on scalp and body). Disease severity in psoriasis was assessed with the commonly-used, valid, and reliable *Self-Administered Psoriasis Area and Severity Index* [SAPASI; 27]. This consists of an anterior and posterior silhouette on which people mark their affected areas, and three scales on which patients score the redness, thickness, and scaliness of their affected areas (range = 0 [complete remission] - 72 [most severe psoriasis]). *Self-perceived visibility* was assessed verbally, by asking: "To what extent do you think that your condition is generally visible to other people?" (range = 0 [never] - 4 [almost always]). To assess psychological distress, social anxiety, and fear of negative evaluation, three questionnaires were administered: the *Hospital Anxiety and Depression Scale*, the *Liebowitz Social Anxiety Scale*, and the *Fear of Negative Evaluation Scale*. The *Hospital Anxiety and Depression Scale* [HADS; 28] contains seven items measuring anxious symptoms and seven measuring depressive symptoms, rated on a 4-point scale. The total HADS score (range = 0-42, $\alpha = .80$ in the current study) was used as a global measure of psychological distress, with higher scores reflecting higher distress. Previous research indicates that the HADS is valid and reliable [e.g., 29] The *Liebowitz Social Anxiety Scale* [LSAS; 30] is a measure of social anxiety that assesses fear and avoidance across different social situations. On a 4-point scale, participants rate their levels of anxiety (from none to severe) and avoidance (from never to always) of 24 social situations. The total LSAS score (range = 0 - 144, $\alpha = .94$) was used, with higher scores indicating higher levels of social anxiety. The brief version of the *Fear of Negative Evaluation scale* [BFNE; 31, 32] is a 12-item questionnaire that assesses fear of negative

evaluation (FNE) on a scale from 0 to 4, with higher scores reflecting higher levels of FNE (range = 0 - 48, α = .89). Research supports its validity and reliability [33].

Data preparation

In the *preparation of Stroop data*, data of one participant in the Alopecia SO group were excluded as an extreme outlier (participants' mean reaction time [RT] across Stroop categories was 83.4 seconds, compared to the group mean RT of 28.8 ± 4.9). All other participants were included in the analyses, to provide the most accurate description of unaltered data. Repeating analyses on log-transformed variables, and on log-transformed variables in which outlying cases were given the value of the next-highest score, did not alter levels of significance. In the *preparation of AAT data*, individual trials with extreme RTs (< 300ms or > 2000ms, < 2% of trials) were removed before aggregating the data, in line with previous studies [e.g., 34]. Participants' median RTs were then calculated for all categories, to prevent outlier effects, and the mean of these median RTs (dependent variable) was calculated for each group [e.g., 21]. In addition, AAT-effects were calculated by subtracting participants' pull RTs (approach) from their push RTs (avoidance) for each picture category; a positive AAT-effect indicated relatively stronger approach than avoidance, while a negative AAT-effect indicated relatively stronger avoidance than approach [e.g., 21]. In the *psychological questionnaires*, one person with alopecia showed outlying scores on two of the questionnaires (mean LSAS score = 129, HADS = 31, > 4 SD from group mean). These results were reported unaltered to provide an accurate description of the sample used for analyses. The same individual did not show outlying scores in Stroop or AAT data, and excluding this person from between-group analyses on questionnaire data did not alter levels of significance.

Statistical analysis

To examine whether people with chronic skin conditions and their SOs showed implicit biases as compared with controls, repeated-measures ANOVAs were conducted. These compared the reaction times (RTs) of the chronic skin condition groups and their SOs with those of controls with regard to all picture categories (AATs) or word categories (modified Stroop task). In the modified Stroop task, if the participants with chronic skin conditions and their SOs showed a slower reaction time to hair-related or stigmatization-relation words than to neutral words, as compared with controls (i.e. a significant word category*group effect, followed by post-hoc analyses showing slower reaction times to hair-related and/or stigmatization-related words than to neutral words in these groups), this was taken as indicative of larger attentional bias in these groups. In the two AATs, significant picture category*response direction*group interactions, with quicker avoidance reactions to disease-related or disgust-related pictures in chronic skin conditions and SOs compared with controls, were taken as indicative of larger behavioral bias in

those groups. If significant effects emerged, post-hoc tests were conducted to examine for which specific groups and/or conditions the effects were significant. In the case of significant between-group differences on sociodemographic variables or self-report questionnaires regarding psychological variables, these variables were controlled for in secondary analyses.

SUPPLEMENTAL MATERIAL: SUPPLEMENTAL RESULTS

Sample characteristics

Table S1 shows further details on the characteristics of the sample. Of the people with alopecia, 54% had alopecia universalis, 18% alopecia totalis, 26% alopecia areata, and 2% alopecia androgenetica. People with psoriasis had a relatively mild disease severity (SAPASI mean ± SD = 4.56 ± 2.31). More females were present in the alopecia group than in the alopecia SO, psoriasis, and control groups ($p \leq .04$), and the alopecia group scored higher on FNE than the control group ($p = .001$). Furthermore, the psoriasis group was less highly educated than the alopecia group and the healthy controls ($p \leq .008$).

Attentional bias: modified Stroop task

Mean reaction times for the modified Stroop task are presented in Table S4. In people with alopecia, groups differed in their RTs to specific word categories ($F(8,262) = 3.13$, $p = .002$, $\eta^2_p = .09$). Both people with alopecia ($F(1,97) = 13.24$, $p < .001$, $\eta^2_p = .12$) and their SOs ($F(1,86) = 9.73$, $p < .001$, $\eta^2_p = .10$) were slower than controls to name colors of hair-related words compared to neutral words, while people with alopecia and their SOs did not differ from one another ($p = .61$). A main effect of word category ($F(4,131) = 20.02$, $p < .001$, $\eta^2_p = .38$) indicated that RTs differed across word categories, with participants overall being slower on hair-related words ($F(1,134) = 74.88$, $p < .001$, $\eta^2_p = .36$) and negative words ($F(1,134) = 5.04$, $p = .03$, $\eta^2_p = .04$) than on neutral words.

In people with psoriasis, groups differed in their RTs across word types ($F(8,280) = 2.21$, $p = .03$, $\eta^2_p = .06$); people with psoriasis were significantly faster to name the colors of negative words than of neutral words, compared with both SOs and controls ($F(2,143) = 3.67$, $p = .03$, $\eta^2_p = .05$), but no differences were found for skin-related words ($p = .43$). In addition, RTs tended to differ between word categories across groups ($F(4,140) = 2.23$, $p = .07$, $\eta^2_p = .06$), with marginally slower RTs on skin-related words than on neutral words ($p = .054$).

No differences were found regarding social threat-related stigmatization words for participants with either skin condition, SOs, or controls ($p \geq .40$).

Behavioral bias: approach-avoidance tasks

Mean RTs and AAT-effects for the disease-related and social threat-related AAT can be found in Tables S5 and S6, respectively.

Disease-related behavioral bias

When people with psoriasis, their SOs, and controls were compared, the groups did not differ regarding their approach-avoidance reactions to psoriasis-related and neutral pictures ($p \leq .73$). Participants' RTs were generally slower on psoriasis-related pictures than on neutral pictures ($F(1,145) = 25.78$, $p < .001$, $\eta^2_p = .15$), and quicker to push (avoid) pictures than to pull (approach) them ($F(1,145) = 14.79$, $p < .001$, $\eta^2_p = .09$). AAT-effects (i.e. pull RTs - push RTs) were less pronounced in psoriasis-related than in neutral pictures, possibly due to the near-zero AAT-effect in controls ($F(1,145) = 14.64$, $p < .001$, $\eta^2_p = .09$). Due to the specific nature of the picture stimuli, this skin-related AAT was not administered to people with alopecia and their SOs.

Social threat-related behavioral bias

When people with alopecia, their SOs, and controls were compared, the groups did not differ in their approach-avoidance reactions to pictures of emotional faces ($p \leq .68$). Participants were generally slower to respond to neutral faces than to the other faces ($F(3,140) = 13.88$, $p < .001$, $\eta^2_p = .23$), and quicker to push (avoid) pictures than to pull (approach) them ($F(1,142) = 26.59$, $p < .001$, $\eta^2_p = .16$), with this effect being statistically significant for disgusted, smiling, and neutral faces (all p-values < .001), but not for sad faces ($p = .89$). The push/pull response differed across picture categories ($F(3,140) = 12.16$, $p < .001$, $\eta^2_p = .21$); the avoidance tendency towards disgusted faces was more pronounced than towards sad faces ($p < .001$), less pronounced than towards neutral faces ($p = .04$), and did not differ from smiling faces ($p = .25$).

When people with psoriasis, their SOs, and controls were compared, groups did not differ in their approach-avoidance reactions to pictures of emotional faces ($p \leq .46$). Similarly to the alopecia group, participants were generally slower to respond to neutral faces than to other faces ($F(3,142) = 11.21$, $p < .001$, $\eta^2_p = .19$), and quicker to push (avoid) pictures than to pull (approach) them ($F(1,144) = 50.13$, $p < .001$, $\eta^2_p = .26$). Participants showed relatively more avoidance of disgusted and neutral faces than of sad and smiling faces ($F(3,142) = 12.77$, $p < .001$, $\eta^2_p = .21$).

Regarding the specific hypothesis for disgusted faces, explorative tests were performed specifically comparing people with skin conditions and their SOs to controls with regard to their RTs in pushing and pulling disgusted faces. In line with the hypothesis, people with psoriasis and their SOs were found to be quicker to avoid (push) than to approach (pull) pictures of disgusted faces, compared with controls ($F(1,146) = 4.01$, $p =$

.047, η^2_p = .03). People with alopecia and their SOs did not differ from controls (F(1,142) = 0.14, p = .71).

Confounder analyses

In the *modified Stroop task*, the significantly slower RTs to hair-related words than neutral words in people with alopecia and their SOs, compared with controls, remained significant when controlling for gender, education, and fear of negative evaluation. In the *social threat-related AAT*, the significantly faster avoidance than approach of pictures of disgusted faces in people with psoriasis and their SOs, compared with controls, remained significant when controlling for fear of negative evaluation (p = .04), and became marginally significant when controlling for gender (p = .051) and education (p = .06).

SUPPLEMENTAL MATERIAL: SUPPLEMENTAL TABLES

Table S1. Sociodemographic and psychological characteristics

Characteristic	Group				
	Alopecia (n = 50)	SOs Alopecia (n = 47)	Psoriasis (n = 50)	SOs Psoriasis (n = 50)	Control (n = 50)
Age (M (SD))	52.20 (14.25)	49.66 (15.55)	56.88 (12.91)	53.28 (15.47)	56.84 (12.08)
Gender (f (%))	42 (84)	31 (66)	23 (46)	27 (54)	23 (46)
Education (n (%))					
Primary	0 (0)[a]	1 (2)	1 (2)[a]	1 (2)	0 (0)[a]
Secondary	22 (44)[a]	16 (34)	36 (72)[a]	29 (58)	18 (36)[a]
Tertiary	28 (56)[a]	29 (62)	12 (24)[a]	20 (40)	29 (58)[a]
Missing	0 (0)[a]	1 (2)	1 (2)[a]	0 (0)	3 (6)[a]
Disease duration	20 (16)	*n.a.*	22 (16)	*n.a.*	*n.a.*
Disease visibility	1.69 (1.58)[b]	*n.a.*	2.48 (1.29)[b]	*n.a.*	*n.a.*
HADS (M (SD))	7.53 (5.70)	8.26 (4.15)	7.33 (4.96)	8.71 (4.17)	6.73 (4.56)
LSAS (M (SD))	28.10 (21.57)	28.00 (14.95)	21.50 (16.06)	24.42 (14.58)	21.26 (13.19)
BFNE (M (SD))	22.54 (11.69)[c]	19.56 (8.37)	16.80 (7.69)[c]	17.48 (7.70)[c]	16.20 (6.91)[c]

Note. f = number of females, BFNE = Fear of Negative Evaluation scale - brief version, HADS = Hospital Anxiety and Depression Scale, LSAS = Liebowitz Social Anxiety Scale, M = mean, SD = standard deviation, SOs = significant others.

[a]Lower educational level in psoriasis than in alopecia and healthy controls, $p \leq .008$

[b]Greater visibility in psoriasis than in alopecia, $p < .01$

[c]Higher BFNE scores in alopecia than in all other groups, except for SOs alopecia, $p \leq .01$.

Table S2. Order of administering tasks and questionnaires

Alopecia, SOs Alopecia	Psoriasis, SOs Psoriasis, Control
Social threat-related AAT[a]	Disease-related or Social threat-related AAT (random)[a]
Name Letter Task (NLT)[a,b]	Name Letter Task (NLT)[a,b]
Implicit Association Test (IAT)[a,c]	Disease-related or Social threat-related AAT (random)[a]
Modified Stroop task[1]	Modified Stroop task[a]
Questionnaires	Questionnaires

Note. AAT = approach-avoidance task, SOs = significant others.
[a]The NLT, IAT, two additional categories of words in the modified Stroop task (acceptance-related and itch-related), and four additional picture categories in the AATs (pictures of itch, ambiguous skin conditions, and empty frames in disease-related AAT, checkerboards in social threat-related AAT) were administered for research questions unrelated to this paper.
[b] [35], [c] [19].

Table S3. English translation of the word stimuli used in the modified Stroop task

Social threat	Hair[a]	Skin[b]	Negative	Positive	Neutral
Insecure	Alopecia	Skin disorder	Bombs	Good-humored	Mug
Shame	Hair loss	Rash	War	Friendly	Kettle
Inferior	Downy hair	Scaling	Fight	Honest	Nutcracker
Bullying	Hair growth	Eczema	Grenade	Helpful	Refrigerator
Unhappy	Scalp hair	Flaking	Pistol	Funny	Kitchen
Secluded	Baldness	Psoriasis	Murder	Polite	Tablecloth
Not understood	Hair falling out	Blisters	Violent	Nice	Light bulb
Vulnerable	Wig	Bumps	Explosion	Cheerful	Doorknob

Note. All words were single words in Dutch and matched in length between categories.
[a]This category was not administered to people with psoriasis and their significant others.
[b]This category was not administered to people with alopecia and their significant others.

Table S4. Modified Stroop task: average color-naming reaction times in seconds (with standard deviations) for each group and word category

Word category	Group				
	Alopecia	SOs Alopecia	Psoriasis	SOs Psoriasis	Control
Social threat	28.17 (5.32)	27.84 (4.82)	28.72 (7.17)	29.36 (6.63)	28.35 (6.04)
Hair	32.06 (6.10)	31.99 (5.74)	*n.a.*	*n.a.*	29.29 (7.05)
Skin	*n.a.*	*n.a.*	29.73 (7.40)	30.90 (7.49)	28.34 (5.58)
Neutral	27.66 (4.40)	28.08 (4.76)	29.14 (8.39)	29.60 (6.99)	28.16 (5.32)
Negative	28.57 (5.73)	28.69 (4.67)	28.10 (6.97)	30.33 (8.82)	28.47 (5.87)
Positive	28.18 (4.50)	28.95 (4.98)	29.27 (7.72)	30.41 (7.19)	27.84 (5.52)

Note. SOs = significant others, *n.a.* = not applicable.

Table S5. Disease-related AAT: Means of median reaction times (and standard deviations) in milliseconds depending on group, picture type, and response direction, including AAT-effects

Picture type	Response Direction	Group		
		Psoriasis	SOs Psoriasis	Control
Psoriasis-related	Pull	971 (448)	975 (391)	872 (244)
	Push	910 (344)	955 (388)	871 (279)
	AAT-effect	**-61 (196)**	**-20 (189)**	**0 (108)**
Neutral	Pull	946 (404)	908 (300)	861 (251)
	Push	847 (313)	840 (276)	797 (199)
	AAT-effect	**-99 (237)**	**-69 (204)**	**-64 (136)**

Note. AAT-effects were calculated by subtracting participants' pull RTs from their push RTs for each picture category, with a negative AAT-effect indicating relatively stronger avoidance than approach. AAT = approach-avoidance task; SOs = significant others.

Table S6. Social threat-related AAT: Means of median reaction times (and standard deviations) in milliseconds depending on group, picture type, and response direction, including AAT-effects

Picture type	Response Direction	Group				
		Alopecia	SOs Alopecia	Psoriasis	SOs Psoriasis	Control
Sad	Pull	700 (135)	699 (120)	687 (109)	721 (151)	713 (94)
	Push	703 (135)	699 (122)	682 (96)	697 (118)	708 (102)
	AAT-effect	**3 (45)**	**1 (41)**	**-5 (50)**	**-24 (70)**	**-5 (52)**
Disgusted	Pull	705 (143)	704 (118)	702 (107)	720 (142)	717 (92)
	Push	691 (150)	678 (119)	667 (100)	685 (126)	699 (109)
	AAT-effect	**-14 (48)**	**-26 (50)**	**-37 (44)**	**-35 (59)**	**-18 (54)**
Smiling	Pull	708 (142)	702 (126)	700 (111)	719 (139)	716 (90)
	Push	692 (130)	689 (117)	680 (103)	699 (126)	702 (100)
	AAT-effect	**-16 (51)**	**-13 (42)**	**-20 (44)**	**-20 (44)**	**-14 (44)**
Neutral	Pull	723 (139)	716 (124)	714 (112)	734 (144)	737 (90)
	Push	704 (159)	686 (118)	680 (101)	692 (133)	701 (103)
	AAT-effect	**-19 (67)**	**-30 (42)**	**-41 (72)**	**-42 (62)**	**-37 (50)**

Note. AAT-effects were calculated by subtracting participants' pull RTs from their push RTs for each picture category, with a negative AAT-effect indicating relatively stronger avoidance than approach. AAT = approach-avoidance task; SOs = significant others.

PART III

Treatment 2.0: Internet-based Cognitive Behavioral Treatment

CHAPTER 5

Internet-based cognitive behavioral therapy for patients with chronic somatic conditions: a meta-analytic review

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ABSTRACT

Background: Patients with chronic somatic conditions face unique challenges accessing mental health care outside of their homes due to symptoms and physical limitations. Internet-based cognitive behavioral therapy (ICBT) has shown to be effective for various psychological conditions. The increasing number of recent trials needs to be systematically evaluated and quantitatively analyzed to determine whether ICBT is also effective for chronic somatic conditions and to gain insight into the types of problems that could be targeted.

Objective: Our goal was to describe and evaluate the effectiveness of guided ICBT interventions for chronic somatic conditions on general psychological outcomes, disease-related physical outcomes, and disease-related impact on daily life outcomes. The role of treatment length was also examined.

Methods: PubMed, PsycINFO, and Embase were searched from inception until February 2012, by combining search terms indicative of effect studies, internet, and cognitive behavioral therapy. Studies were included if they fulfilled the following six criteria: (1) randomized controlled trial, (2) internet-based interventions, (3) based on cognitive behavioral therapy, (4) therapist-guided, (5) adult (≥ 18 years old) patients with an existing chronic somatic condition, and (6) published in English. Twenty-three randomized controlled trials of guided ICBT were selected by two independent raters after reviewing 4848 abstracts. Demographic, clinical, and methodological variables were extracted. Standardized mean differences were calculated between intervention and control conditions for each outcome and pooled using random effects models when appropriate.

Results: Guided ICBT was shown to improve all outcome categories with small effect sizes for general psychological outcomes (effect size range 0.17 to 0.21) and occasionally larger effects for disease-specific physical outcomes (effect size range -0.04 to 1.19) and disease-related impact outcomes (effect size range 0.17 to 1.11). Interventions with a longer treatment duration (> 6 weeks) led to more consistent effects on depression.

Conclusions: Guided ICBT appears to be a promising and effective treatment for chronic somatic conditions to improve psychological and physical functioning and reduce disease-related impact. The most consistent improvements were found for disease-specific outcomes, which supports the possible relevance of tailoring interventions to specific patient groups. Explorative analyses revealed that longer treatment length holds the promise of larger treatment effects for the specific outcome of depression. While the current meta-analysis focused on several chronic somatic conditions, future meta-analyses for separate chronic somatic conditions can further consolidate these results, also in terms of cost-effectiveness.

INTRODUCTION

Cognitive behavioral therapy (CBT) focuses on challenging cognitive distortions and dysfunctional underlying beliefs, and on teaching coping and problem solving skills [1]. A variety of techniques are combined to achieve this, including cognitive restructuring, relaxation, problem solving, and stress management. The central idea of CBT is that the way people make sense of their environment affects their feelings and behavior. CBT is an extensively researched and widely used form of treatment for a variety of psychological conditions [1] and is increasingly used to help a growing number of patients suffering from chronic somatic conditions cope with the consequences of their condition [1–5]. CBT models can, for instance, be applied to improve patients' adjustment to receiving a diagnosis of a chronic somatic condition and coping with it, to improve comorbid mood problems such as anxiety and depression, to alter disease-specific beliefs and attitudes, and to teach pain/symptom management strategies [6, 7].

Although studies indicate that CBT may be an effective treatment for chronic somatic conditions, it has not been implemented on a large scale, partly due to the lack of CBT therapists specializing in patients with chronic somatic conditions. Furthermore, chronically ill patients may have physical limitations that make it difficult to travel to a clinic for face-to-face CBT. A possible solution is to offer CBT online: Internet-based cognitive behavioral therapy (ICBT). Generally, ICBT takes the form of an online self-help program, guided by a therapist who gives feedback and answers questions [8]. Advantages of ICBT over offline computerized CBT and over bibliotherapy include the possibility of the patient connecting with a therapist or with peers who cope with similar problems, and the ability to log on and use the intervention anytime and anywhere they would like. ICBT may be beneficial to both patients and therapists: it is more convenient, flexible, and reduces traveling time, costs, and waiting lists, enabling more patients to be reached and treated [9]. In addition, providing CBT online may reduce the stigma of needing psychological help. Recently, first indications have been reported for the cost-effectiveness of ICBT [10–12].

Internet interventions are generally found to be effective for a variety of psychological conditions [13–16]. Preliminary evidence is also emerging for its effect on psychological and physical outcomes in various health problems [17–21] and in promoting health behavior change [22, 23]. In order to determine whether ICBT is effective for chronic somatic conditions, the results of the increasing number of recent randomized controlled trials (RCTs) need to be systematically evaluated and quantitatively analyzed. Moreover, knowledge of which types of outcomes are specifically improved by ICBT will provide insight into the types of problems that could be targeted with ICBT.

An additional focus on which elements of interventions are effective for which patients at what disease stage will aid development of effective tailored interventions. Scarce

evidence suggests that the amount of therapist contact is related to effectiveness [16]. An aspect of ICBT that has not been examined is whether the duration of ICBT influences treatment outcomes. For traditional face-to-face CBT for chronic somatic conditions, an average treatment of 12–16 sessions given once a week is suggested [24]. Although there are indications in patients with depressive symptoms that a longer ICBT treatment duration yields better outcomes [25], the role of treatment duration has not yet been examined for chronic somatic conditions.

The current review aims to describe and evaluate the effectiveness of guided ICBT interventions in randomized controlled trials, for three specific outcome categories –general psychological outcomes, disease-related physical outcomes, and disease-related impact outcomes– and to explore the role of treatment duration. The review focused on guided ICBT interventions, in order to optimize comparability with face-to-face CBT and decrease heterogeneity, as it is known that guided ICBT interventions generally lead to different (larger) effects than non-guided self-help interventions [16]. This review has a broad focus, including a large population of chronic somatic conditions. Because the literature on ICBT in different chronic somatic conditions is rather limited at this time, it is not yet possible to meaningfully summarize the evidence for efficacy of ICBT for these separate categories of chronic somatic conditions. Because the main elements of CBT are generic in scope and can be applied to a large variety of problems, combining these different chronic somatic conditions in this meta-analysis provides a first overall indication of the efficacy of ICBT interventions in the large population of chronic somatic conditions. In addition, the separate outcomes for different somatic conditions can also be deduced from the paper.

METHODS

Search strategy and inclusion criteria

PubMed, PsycINFO, and Embase were searched from inception until February 2012, by combining index terms indicative of effect studies, internet, and cognitive behavior therapy, and including the following Medical Subject Heading (MeSH) terms: internet, electronic mail, behavior therapy, psychotherapy, rehabilitation, counseling, and self-care (see Multimedia Appendix 1 for search strategies). Only studies investigating guided ICBT, which is comparable to face-to-face CBT, were included. All retrieved references were loaded into Endnote, and two raters (SvB, MSc Psychology, HvM, PhD Psychology) independently screened titles and abstracts without blinding to authorship or journal. The full text of potentially relevant studies was examined. Discrepancies between reviewers were resolved by discussion. The kappa statistic was calculated to determine consistency among raters. Inclusion criteria were (1) RCT or equivalence trial, (2) therapy

provided with the internet (not face-to-face, telephone, onsite computerized therapy, videoconferencing, or personal digital assistants) as the main way of communication (e.g., patient spends > 50% of total intervention time spent on an Internet-based intervention), (3) therapy based on CBT principles (in which at least some forms of cognitive and behavioral techniques are used), (4) therapy guided by contact with a therapist, with at least one episode of personalized patient contact (either through asynchronous messages, telephone, or another mode of contact), and (5) adult study sample (age ≥ 18 years) with an existing chronic somatic condition (i.e. a condition expected to last a year or longer, limit what a patient can do, and/or may require ongoing medical care) [26]. Aetiology was not an inclusion criterion; both functional and structural disorders were included. Conditions that may have physical consequences but do not have physical illness as its primary feature, such as eating disorders, insomnia, addiction problems, fertility problems, and sexual dysfunction, were also excluded. Papers not published in English were also excluded. Studies were excluded when the main focus of the intervention was focused on lifestyle change, such as increasing levels of exercise or improving diet. Publications of the same intervention were included if each study was based on a new patient sample. Papers were excluded based on a hierarchical approach, in which articles were not further assessed for remaining reasons if they were excluded based on a previous reason. The hierarchy of reasons for exclusion were that (1) the study does not examine ICBT for chronic somatic conditions, (2) the study is not an RCT, (3) the ICBT intervention is not guided by a therapist, and (4) the study does not examine adult patient populations (see Figure 1).

Data extraction

The following information was gathered per study: publication year, chronic somatic condition, country of data collection, number of patients included, completers, dropouts, dropout reasons, age, gender, type of CBT intervention, therapist contact, control condition, outcome measures, intervention length, completer or intent-to-treat analyses, post-treatment results, and follow-up results. A large variety of outcome measures were reported across studies. To enable general conclusions, these were grouped together into three main outcome categories that are of relevance to patients with chronic somatic conditions: (1) general psychological outcomes of depression, anxiety, and distress, (2) disease-related physical outcomes related to symptom severity, such as pain, fatigue, and headache, and (3) disease-related outcomes concerning the impact of a chronic somatic condition on daily life (i.e. disease-specific distress and disease-specific quality of life) (see Multimedia Appendix 2). To improve homogeneity and narrow the scope of the review, outcome measures that did not fit these categories (e.g., coping or behavior) or that were not suitable for pooling in meta-analysis (i.e. because of being assessed infrequently (e.g., general quality of life) or by means of different measures

(e.g., disability) were excluded. When more than one outcome was used to measure the same construct, results for the outcome that was most generic (e.g., total scale score versus subscale scores), most validated (e.g., Beck Depression Inventory (BDI [27]) versus Modified Beck Depression Inventory (mBDI [28]), or most comparable to other studies (e.g., visual analogue scale [VAS] of distress versus therapist-rated distress) was used, to prevent separate studies having too much influence on the analysis.

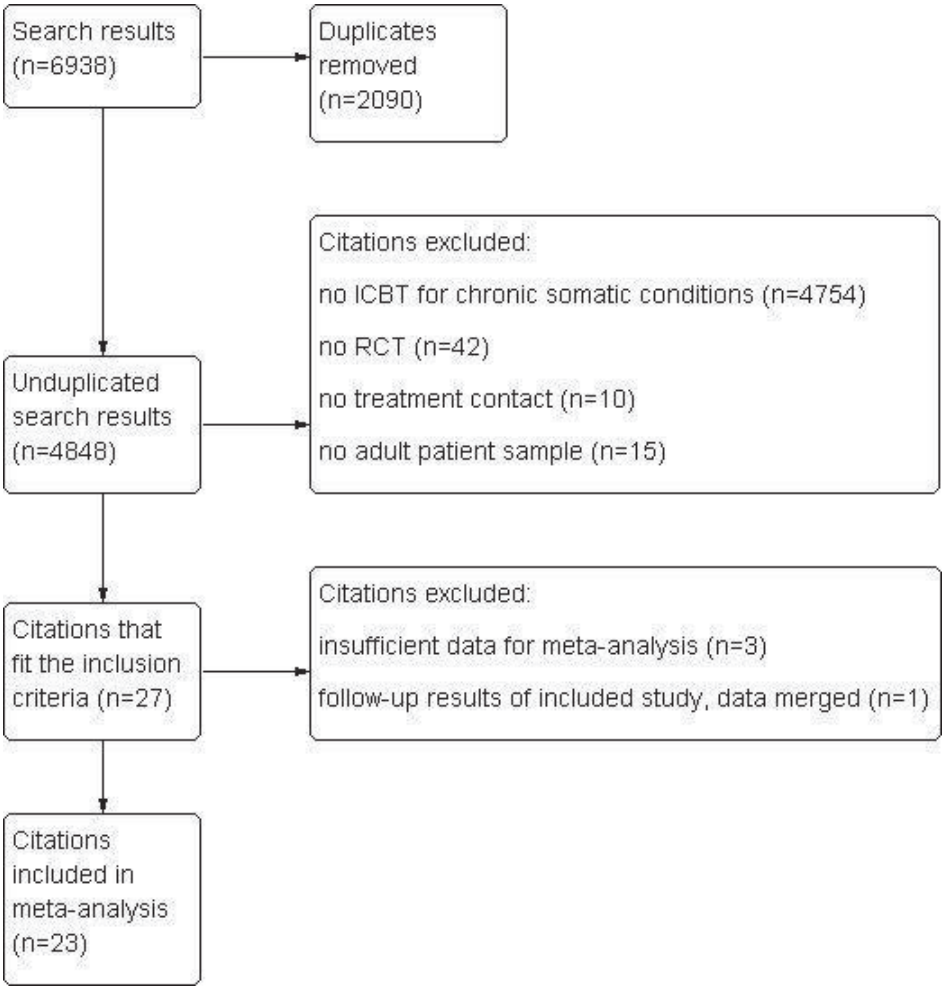

Figure 1. PRISMA flow diagram of study selection.

Assessment of risk of bias in included studies

Two independent authors (SvB, MSc Psychology; MF, MSc Psychology) assessed each study using the Cochrane risk of bias tool, including selection bias (randomization pro-

cess), performance bias (blinding of subjects and personnel), detection bias (blinding of outcome assessment), reporting bias (handling of missing data), and attrition bias (reasons for withdrawal in all conditions) [29]. A third rater (MR, professor of evidence-based surgery) was consulted to reach consensus when two raters were in disagreement. Risk of bias was assessed based on the information of original publications and on trial registrations on the ClinicalTrials website.

Reporting study results

Only between-group results were taken into account to examine the effect of ICBT as compared to a passive control condition. Passive control conditions were defined as conditions in which participants do not receive a therapeutic program and instead are placed on a waiting list, or receive only treatment as usual or treatment that is theorized to not lead to changes in therapeutic outcomes (e.g., patient education) (see Multimedia Appendix 2). For equivalence trials, in which patients receive an intervention that is theorized to lead to clinically relevant changes in outcomes as an active comparison condition, and for studies with a three-arm design, both between-group effects and main effects are reported (see Multimedia Appendices 3 and 4). Intent-to-treat analyses (ITT), in which all randomized patients are analyzed regardless of adherence to study protocol [30], were used wherever possible. When two active ICBT interventions were compared to a passive control condition in a three-arm RCT design, both comparisons are reported. Two types of dropout rates were calculated: (1) intervention dropouts by dividing the number of patients reported to have stopped the intervention (or did not return post-intervention questionnaires) by the number randomized to the intervention group, and (2) measurement dropouts by dividing the number of patients from both the intervention and control groups who did not return post-intervention questionnaires by the total number of patients randomized. As between-group follow-up results were not consistently and uniformly reported across studies, pooling was not feasible. Therefore, only post-intervention study results are reported and the number of studies that included follow-up results is briefly summarized.

Data analyses and synthesis

Standardized mean difference of effect sizes (SMDs) were calculated by subtracting the difference in means in the ICBT group from the difference in means in the control group and dividing the outcome by their pooled standard deviation [31]. Effect sizes of 0.2, 0.5, and 0.8 can be considered as small, moderate, and large, respectively [32]. When a study contained multiple eligible ICBT treatment groups, these were combined in a single pairwise comparison, according to recommendations and calculation methods from the Cochrane handbook [29]. If mean values and SDs were not reported, authors were contacted to obtain original trial data. When not provided, alternative methods

were used (i.e. using reported mean change scores and associated SDs). To decide whether meta-analytic pooling of data was justified, we computed I^2, which describes the percentage of total variation between studies due to heterogeneity rather than chance [33]. An I^2 of 25%, 50%, and 75% can tentatively be considered as low, moderate, and high heterogeneity, respectively [33]. High heterogeneity indicates that the effects are not the same for all studies and that there may be other variables that explain this heterogeneity. As significant heterogeneity is to be expected, SMDs were calculated in random effects models, using Cochrane Collaboration software Review Manager, version 5.1. These models assume that there is no one 'true effect size', but rather the effect sizes are sampled from a population of varying effect sizes [34]. Subgroup differences in intervention duration were analyzed using the chi-square test, with $p < .05$ indicating statistically significant differences.

RESULTS

Search results and study characteristics

The literature search identified 4848 unique studies, 23 of which met the inclusion criteria (see Figure 1) [35–57]. Interrater reliability of study selection was kappa = .805. The included studies involved 4340 subjects (2299 ICBT and 2041 control); 59% of subjects participated in three large studies by Lorig and colleagues [52–54].

In 74% (17/23) of studies, subjects were randomized to one of two conditions, 15 of which compared ICBT with a passive control condition: waiting-list (12 studies), care-as-usual (2 studies), and information-based psycho-education (1 study) (Multimedia Appendix 2). Three studies compared ICBT with an active CBT control condition: face-to-face group therapy, online stress management without CBT, and ICBT with added telephone contact (Multimedia Appendix 3). Five studies used a three-arm design, two of which reported results of the two joint intervention groups compared to a passive control condition (Multimedia Appendix 2), and three compared each of the three conditions (Multimedia Appendix 4).

A total of 70% (16/23) of studies were published between 2008 and 2011, and 52% (12/23) were carried out in Sweden. Eleven studies (48%) used intent-to-treat (ITT) analyses. The majority of these studies (6/11) used the last observation carried forward (LOCF) method, in which a participant's missing values after dropout are replaced with the last available measurement [58]. Four of the 11 studies used mixed models approaches [59], and one used multiple imputation by chained equations [60]. 74% (17/23) included some form of follow-up assessment ranging from 1-18 months: 10 (43%) used a between-group follow-up and 7 (30%) included a within-group or completers-only follow-up, ranging from 2 months to 1 year. Dropout rates differed widely but were over-

all relatively high (median 18%, range 2-57%), particularly in the intervention groups (median 29%, range 1-72%) (Multimedia Appendix 2). Of the 5 studies that reported reasons for dropout, the most common reason mentioned was lack of time.

Patient populations

Patient populations included chronic pain (5/23 studies, 21%), headache or migraine (4/23 studies, 17%), tinnitus (4/23 studies, 17%), irritable bowel syndrome (IBS, 4/23 studies, 17%), diabetes (2/23 studies, 8%), breast cancer (1/23 studies, 4%), epilepsy (1/23 studies, 4%), fatigue in patients with chronic neurological disorders (1/23 studies, 4%), and a heterogeneous patient population (1/23 studies, 4%) (Multimedia Appendix 2). Twenty studies of 23 (87%) involved community-based samples. The mean age range of subjects within studies varied between 34 and 66 years; most studies included more female than male subjects.

Intervention content and duration

Interventions consisted of a variety of generic CBT-based techniques, often supplemented with specific approaches appropriate for the chronic condition under study. Interventions focusing on relaxation and psycho-education were included only when combined with other CBT techniques, that is, some form of cognitive reappraisal or restructuring [61]. Treatment content was categorized into well-known CBT elements such as cognitive therapy, behavioral therapy, applied relaxation, and psycho-education (see Multimedia Appendix 2). The vast majority of studies described the interventions as self-help programs with structured modules, which were typically completed in a rate of one module per week, with minimal therapist guidance. The most commonly mentioned intervention components were cognitive therapy techniques, (applied) relaxation, psycho-education, and improving coping skills. These components were mentioned in 74-100% of interventions. Stress management and behavioral therapy techniques were also mentioned in over half of included interventions. Other therapy components, incorporated in 26-35% of interventions, were problem solving techniques, mindfulness-based techniques, exposure, and physical exercise. The majority of interventions were labelled as CBT and/or self-management interventions, while some interventions were based on acceptance and commitment therapy (ACT) [46], exposure-based treatment in combination with mindfulness techniques [49–51], or mindfulness-based cognitive therapy (MBCT) [56].

Interventions were generally broad and multifaceted, targeting various aspects of chronic somatic conditions within one intervention (e.g., comorbid mental health problems, coping with the chronic somatic condition, and reducing physical symptoms). Incidentally, studies indicated that there was a specific primary aim, for example, to reduce depressive symptoms [56–57], distress associated with the condition [35, 37],

or severity of the chronic somatic condition [41, 43, 50]. However, also in the interventions with a more specific aim, components were generally included to fit other aims as well. Therefore, it was not possible to meaningfully categorize interventions according to the intervention aim (e.g., physical, mental, prevention). When analysing the results, the SMDs in each meta-analysis generally did not meaningfully differ from one another, indicating that there are no differences in SMDs according to intervention aim.

Therapist contact and peer contact

All studies incorporated treatment-related contact options, usually in the form of (weekly) email contact with (psychology master students supervised by) licensed clinical psychologists. One study was based solely on therapist-patient contact via email without additional treatment components. Most studies did not report, or not in detail, the average time therapists spent on patients. The main mode of therapist contact was through asynchronous (email) messages, but in three of 23 studies (13%) telephone was the main contact option. Five studies (22%) used online group formats. A total of 43% (10/23) of studies included a bulletin board that enabled patients to interact with each other, as an addition to individual treatment tools.

Risk of bias in included studies

The authors' judgments about risk of bias for each included study and presented as percentages across all included studies can be found in Figures 2 and 3. While the majority of studies (14/23, 61%) reported adequate methods of randomization, 35% (8/23) of studies did not report randomization methods, and 4% (1/23) reported inadequate methods. The study with inadequate methods (e.g., randomization based on order of enrolment [47]) was excluded from primary analyses, as a randomized design was one of the inclusion criteria for this study. To be complete, we also report the results including this study, in a secondary analysis. In eight studies of the 23 (35%), allocation of participants was adequately concealed, while allocation concealment remained unclear in ten of 23 studies (43%) and was at risk for inadequate concealment in 22% (5/23); for example, tossing a coin, picking a piece of paper, or throwing dice. None of the included studies reported blinding of participants, personnel, and outcome assessments, which led to an unclear risk of bias in 43% of studies (10/23; no information on blinding) or a high risk of bias in 57% of studies (13/23; information indicating that blinding did not take place). Over half of all studies had incomplete outcome data that led to a high risk of bias, which was mainly due to a lack of intent-to-treat analyses in 48% (11/23) of studies. The risk of selective reporting bias remained largely unclear, mainly because only 26% (6/23) were registered with the ClinicalTrials site and registration often took place after study completion.

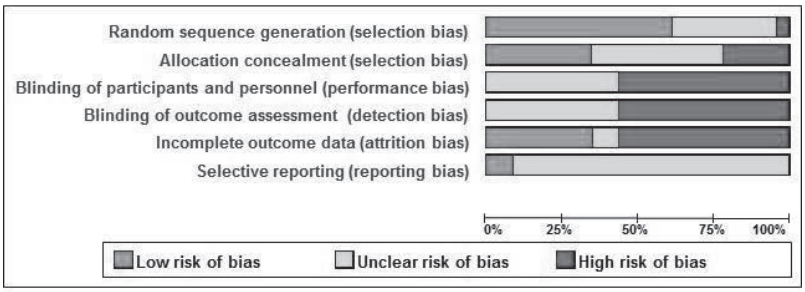

Figure 2. Risk of bias graph.

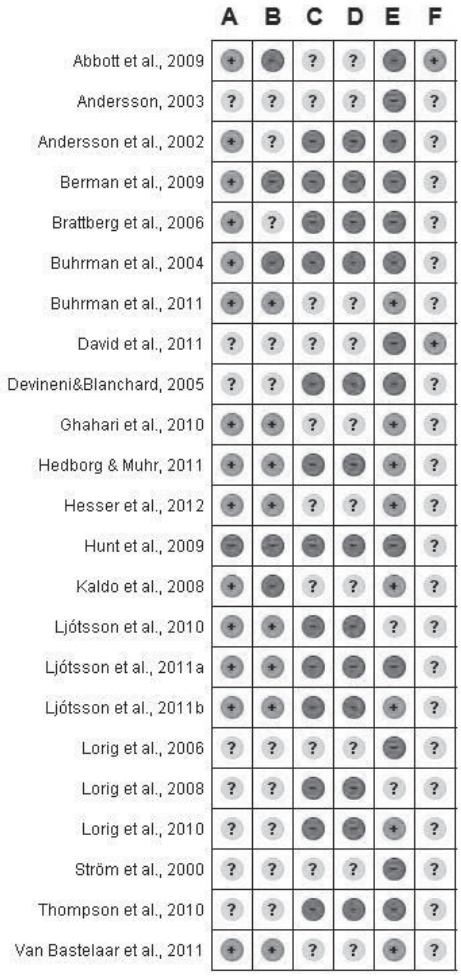

Figure 3. Risk of bias summary: review authors judgements for each included study about each risk of bias item. A = random sequence generation (selection bias); B = Allocation concealment (selection bias); C = Blinding of participants and personnel (performance bias); D = Blinding of outcome assessment (detection bias); E = Incomplete outcome data (attrition bias); F = Selective reporting (reporting bias).

Effectiveness of ICBT interventions

SMDs for the included outcomes are reported in Multimedia Appendix 2 for the 17 studies with a passive control condition, Multimedia Appendix 3 for the 3 studies with an active control condition, and Multimedia Appendix 4 for the 3 studies with a three-arm design. Pooled SMDs for the three outcome categories can be found in Table 1.

Table 1. Pooled SMDs for ICBT versus passive control conditions

Outcome category	k^a	SMD[b]	95% CI	*z*	*p*	I^2 (%)
General psychological outcomes						
Depressive symptoms	15	0.21	0.08-0.34	3.18	.001	29
Anxious symptoms	10	0.17	0.01-0.32	2.14	.03	0
General distress	6	0.21	0.00-0.41	1.98	.05	0
Disease-related physical outcomes						
IBS symptoms	2	1.19	0.82-1.57	6.25	<.001	0
Headache	3	0.49	0.21-0.77	3.41	<.001	0
Sleep quality	3	0.25	-0.02 to 0.53	1.80	.07	0
Pain	6	0.18	0.08-0.28	3.61	<.001	0
Fatigue	2	0.15	0.05-0.26	2.87	<.01	0
Tinnitus loudness	2	-0.04	-0.40 to 0.32	0.24	.81	0
Glycemic control	2	0.07	-0.17 to 0.30	0.54	.59	62
Disease-related impact outcomes						
Disease-specific quality of life	3	1.11	0.79-1.44	6.73	<.001	0
Disease-specific distress	6	0.17	0.03-0.31	2.41	.02	57

Note. IBS = irritable bowel syndrome.
[a]*k* = number of comparisons, [b] SMD =standardized mean difference.

General psychological outcomes

Sixteen of 17 studies comparing ICBT with a passive control condition included general psychological outcomes, 5 of which (31%) found greater improvements in the ICBT condition on at least one outcome (see Multimedia Appendices 2 and 4). ICBT had similar effects as active treatment control conditions (see Multimedia Appendices 3 and 4). Pooled SMDs for depressive symptoms, anxious symptoms, and general distress yielded small but generally statistically significant effects (see Table 1 and Figures 4 to 6). For depressive symptoms, results of a sensitivity analysis excluding one outlier with a very large effect on depression [SMD 4.34; 56] are reported; if included, the SMD would be 0.32 (k = 16, 95% CI 0.09 -0.55, p = .005, I^2 = 78%).

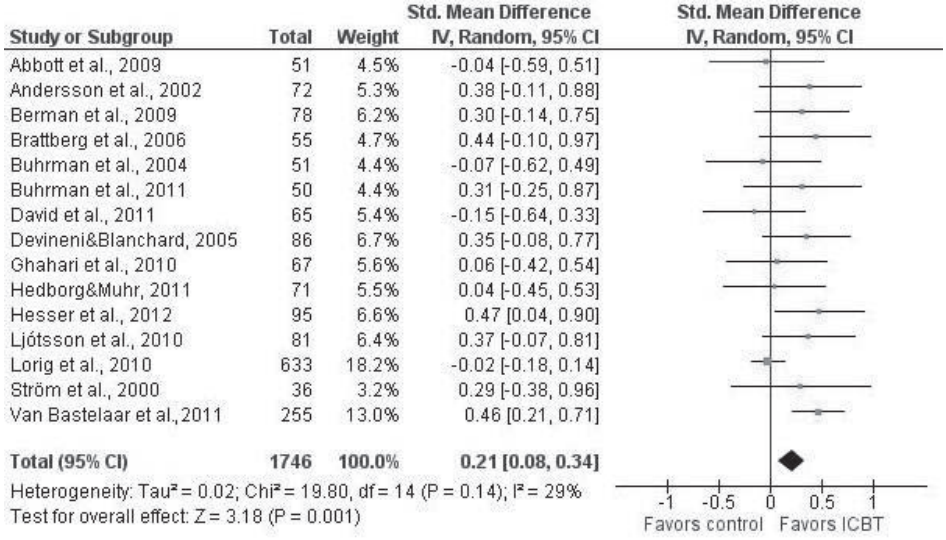

Figure 4. Forest plot of standardized mean differences of the effect on depression of Internet-based cognitive behavioral therapy compared with a passive control condition.

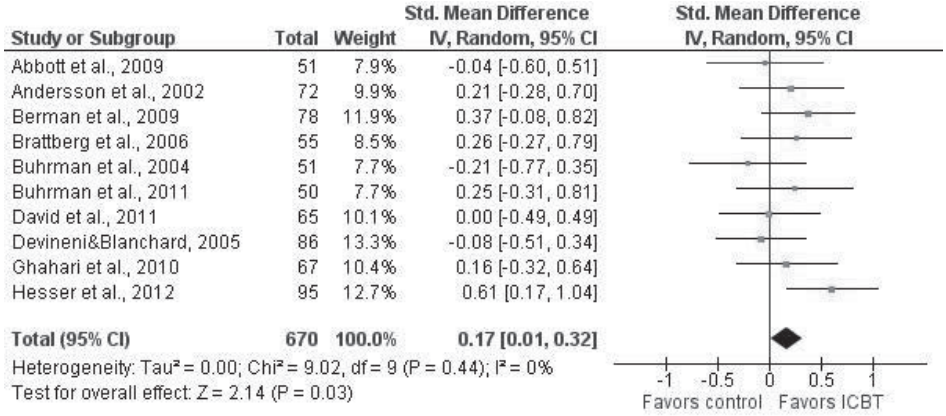

Figure 5. Forest plot of standardized mean differences of the effect on anxiety of Internet-based cognitive behavioral therapy compared with a passive control condition.

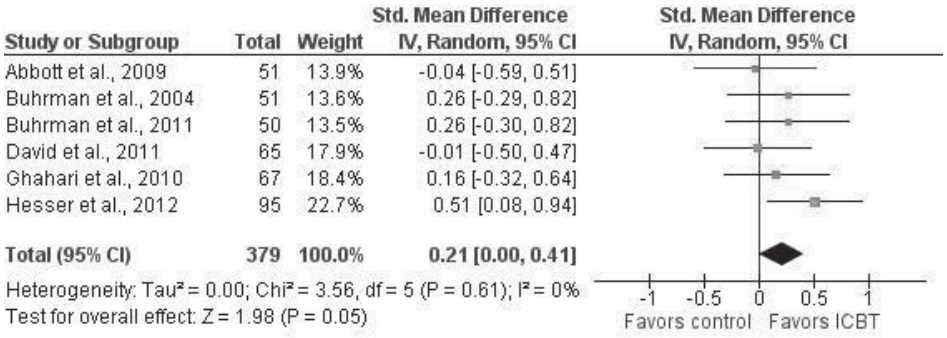

Figure 6. Forest plot of standardized mean differences of the effect on general distress of Internet-based cognitive behavioral therapy compared with a passive control condition.

Disease-related physical outcomes

Seventeen studies comparing ICBT with a passive control condition included disease-related physical outcomes, with 59% (10/17) finding effects in favor of the ICBT condition on at least one outcome (see Multimedia Appendices 2 and 4). Pooled SMDs for physical outcomes yielded varying results. Large effects were found for IBS symptoms, moderate effects for headache, small effects for pain and fatigue, and non-significant effects were found for tinnitus loudness, sleep quality, and glycaemic control (see Table 1). In the case of IBS symptoms, one study was excluded based on inadequate randomization procedures. A secondary sensitivity analysis including this study led to very similar results as the primary analysis (pooled SMD 1.14, 95% CI 0.81-1.48, $p < .001$, $I^2 = 0\%$, $k = 3$). Studies with an active control condition were not pooled due to a limited number of studies and comparable outcomes (see Multimedia Appendices 3 and 4 for the results of individual studies).

Disease-related impact on daily life

Nine studies with a passive control condition included measures of disease-related distress or quality of life, of which seven (78%) found effects in favor of the ICBT condition on at least one outcome (see Multimedia Appendices 2 and 4). Small but significant effects were found on disease-related distress, and large effects were found on disease-specific quality of life (see Table 1 and Figures 7 and 8). In the case of disease-specific quality of life, one study was excluded based on inadequate randomization procedures. A secondary sensitivity analysis including this study led to very similar results as the primary analysis (pooled SMD 1.09, 95% CI 0.80-1.39, $p < .001$, $I^2 = 0\%$, $k = 4$). Results from studies with an active control condition were not pooled due to a limited number of studies and outcomes. Individual study results can be found in Multimedia Appendices 3 and 4.

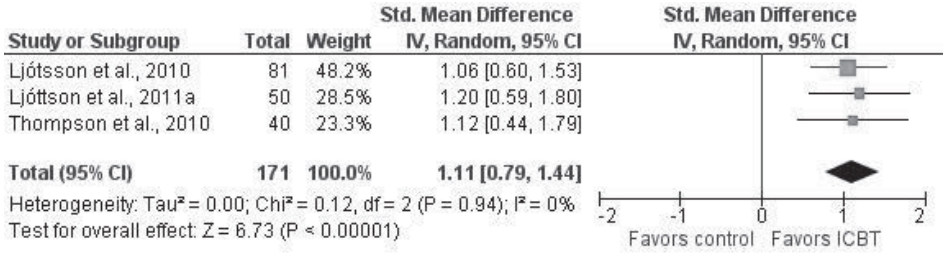

Figure 7. Forest plot of standardized mean differences of the effect on disease-specific quality of life of Internet-based cognitive behavioral therapy compared with a passive control condition.

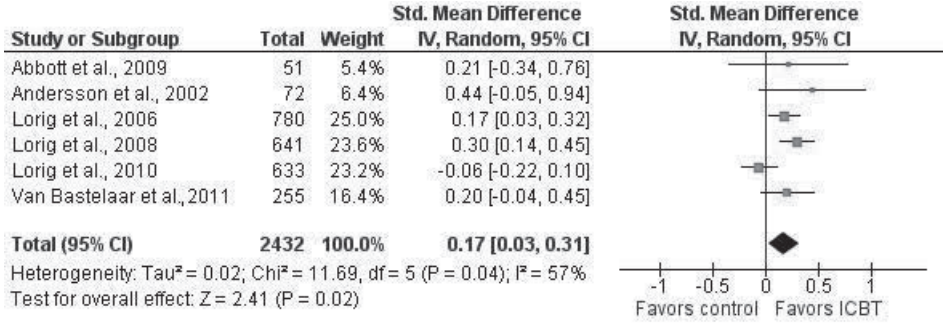

Figure 8. Forest plot of standardized mean differences of the effect on disease-specific distress of Internet-based cognitive behavioral therapy compared with a passive control condition.

Role of treatment duration in intervention effectiveness

Most interventions were relatively short, with little variability in treatment duration: 4% (1/23) of the interventions lasted 4 weeks, 48% (11/23) lasted 6 weeks, and 48% (11/23) lasted 7-24 weeks (see Multimedia Appendix 2). Consequently, outcomes of the studies in which the intervention lasted ≤ 6 weeks and > 6 weeks were compared. Of the 5 studies finding a between-group effect on depression, 4 (80%) had an intervention duration of > 6 weeks. Effect sizes of the longer interventions (n = 8; SMD 0.29; 95% CI 0.13-0.46) were larger than those in the shorter interventions, with marginal statistical significance (n = 7; SMD 0.08; 95% CI -0.05 to 0.22) (χ^2_1=3.91, p=.05). Intervention duration did not influence effectiveness for other outcomes.

DISCUSSION

Principal findings

Our meta-analysis indicates that ICBT is effective for chronic somatic conditions regarding both general psychological outcomes and disease-specific outcomes. Effect sizes

were generally small to moderate, with larger effect sizes occasionally found for disease-related outcomes, such as self-reported headache and IBS symptoms, and for disease-specific quality of life. These findings of larger effects on disease-specific outcomes may on the one hand reflect the larger sensitivity to change of these measures [62, 63] and on the other hand support the idea of tailoring interventions to the needs of specific patient groups, as disease-specific measures are likely the measures that respond well to more tailored, disease-specific approaches [64–67].

The three included studies that compared ICBT with an active treatment condition showed that ICBT can be as effective as group-based face-to-face CBT, for example. However, two studies also found that ICBT and an informational website without CBT content were similarly effective. These results indicate a need for studies in which the effects of specific components of ICBT are more closely investigated. The role of one such component of ICBT was examined in this meta-analysis –intervention length– suggesting that interventions lasting longer than 6 weeks result in greater improvements in depression.

Overall, results of this review extend previous reviews and meta-analyses, which concluded that ICBT may be a promising adjuvant treatment for psychological outcomes [13–16] and for patients with health problems [17–23]. Meta-analyses have typically reported small [18] to moderate [14, 16] pooled effect sizes for Internet-based psychotherapeutic interventions. The results are also comparable to meta-analyses of face-to-face CBT, which typically find small to moderate effect sizes on a variety of outcomes [1, 68–70], with sometimes larger disease-specific than more general mood-related effects [69]. Our review adds to previous findings by including all available studies in chronic somatic populations and by identifying differences in effectiveness for specific categories of outcome. With this approach, it was shown for the first time that guided ICBT is effective for various psychological and physical outcomes, with most promising results for disease-related outcomes, and that intervention duration might be a determinant of the effectiveness of ICBT for depression. These results underline the potential benefit of ICBT for patients with chronic somatic conditions in helping them cope with the consequences of their condition.

Limitations

Some potential limitations should be discussed. First, there are still a limited number of studies on ICBT in chronic somatic conditions, and sometimes only one study was available for a specific condition, which precludes drawing reliable conclusions about specific patient groups and generalizing across conditions. Over half of the studies were performed in Sweden by the same authors, but post-hoc analyses did not find differences in outcomes between the Swedish and other studies (data not shown). Women constituted a large proportion of most study populations, reflecting the often unequal

gender distribution of different chronic somatic conditions. Second, studies were found to be of variable methodological quality, which may influence both individual study results and overall outcomes in meta-analysis. Although all studies had unclear or high risk of blinding bias, this is often unfeasible or very difficult to achieve in non-pharmacological behavioral interventions and thus may not be a valid indicator of study quality [71]. In many studies, inadequate descriptions resulted in unclear risk of bias. This may be resolved by using guidelines for reporting RCTs [72]. Third, the appropriateness of pooling studies of ICBT for various patient populations can be discussed, as pooling is intended for more or less homogeneous populations and outcomes. The current review included a relatively diverse range of chronic somatic conditions, and outcomes were often assessed with various different questionnaires. However, similar effects and low heterogeneity were found for most outcomes, supporting the idea that the included studies were comparable regarding their outcomes. Including these various studies in this meta-analytic overview provides the reader with a first indication of the overall effectiveness of ICBT for chronic somatic conditions and increases the generalizability of findings [73, 74]. As more trials become available in the future, meta-analyses should be performed for separate chronic somatic conditions. Fourth, long-term between-group follow-up measurements were often lacking, precluding a reliable long-term estimate. Fifth, there was substantial variation in description of treatment content, therapist contact, and dropout. For instance, not all therapist contact was with a trained therapist but could also include "expert" patients, nurses, physicians, occupational therapists, or research assistants. Dropout rates were not always adequately described and generally high, which is a common problem with internet interventions [75]. Sixth, publication bias cannot be precluded. The current review was limited to published studies, as it was unfeasible to obtain a complete and unbiased overview of all unpublished grey literature on this subject. This may have led to an overestimation of effectiveness, as published studies are generally more likely to include statistically significant results [76]. However, several studies that did not find an effect were included in the current review, indicating that not only studies with significant results are published on this topic.

Finally, we used the pooled standard deviation based on pre- and post-intervention measurements in our meta-analysis. When using change scores in meta-analysis, the most appropriate measure would have been the standard deviation of changes. However, the included studies did not report sufficient information to calculate these standard deviations [29], which has been recognised as a common problem when using change scores. Our approach can, however, be considered as a conservative approach since the calculated standard deviations will be slightly larger than the standard deviations of changes would have been. Another alternative would have been to perform the meta-analysis based on post-intervention measurements, but such an approach does not take into account possible differences in baseline measurements. Nevertheless, we

also performed a meta-analysis based on post-intervention measurements results. The results of this meta-analysis were very similar to the change score results reported in our study (data not shown), and would have led to similar conclusions.

Future research

Results from this review suggest several areas for future research, related to study methodology and intervention design. More studies with adequate sample sizes focusing on a wider range of chronic somatic conditions with between-group long-term follow-up are needed. Only one study involved older patients [38], yet older patients are often affected by chronic conditions. As dropout is common with ICBT, ways to promote engagement and improve adherence should be investigated. Preliminary research suggests that tailoring interventions may be an effective strategy to promote engagement and adherence [77–79]. Strategies found to be predictive for adherence include increased therapist contact, more frequent website updates, and more frequent intended usage [80]. Also, future research is needed to examine the effects of ICBT on outcomes such as work-related outcomes, health behaviors, and cost-effectiveness, which were not evaluated in this meta-analysis in order to narrow its scope. Last, the "active ingredients" of interventions need to be identified, in order to develop effective interventions for specific problems. Additional control conditions including "sham" treatment websites should be included to assess the specific value of ICBT [81]. Analyses on computer-generated data about how subjects access the website may also be a worthwhile approach to examine engagement, usability, and active ingredients [82].

Conclusions

The current review indicates that ICBT interventions improve both psychological and disease-related physical outcomes in patients with chronic somatic conditions, with small-to-medium effect sizes. Larger improvements are occasionally found for disease-specific outcomes related to daily-life impact of the illness, which underlines the importance of tailoring interventions to specific (patient) groups. Our results also indicate that interventions of longer duration may be more effective for psychological outcomes such as depression, which implies that tailoring the duration of interventions to specific problems may be appropriate.

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MULTIMEDIA APPENDIX 1

SEARCH STRATEGIES

Pubmed search strategy

("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR random*[tiab] OR non-inferiority[tiab] OR equivalen*[tiab] OR rct[tiab] OR single blind[tiab] OR double blind[tiab] OR t r iple blind[tiab]) AND ("Internet"[Mesh] OR internet*[tiab] OR web*[tiab] OR online[tiab] OR "Therapy, Computer-Assisted"[Mesh] OR ehealth[tiab] OR e-health[tiab] OR "electronic mail"[MeSH Terms] OR "electronic mail"[tiab] OR "e mail"[tiab] OR email[tiab] OR cyber*[tiab] OR icbt[tiab] OR i-cbt[tiab] OR wcbt[tiab] OR w-cbt[tiab]) AND ("Behavior Therapy"[Mesh] OR psychotherapy[mesh] OR "rehabilitation"[Subheading] OR "rehabilitation"[tiab] OR "rehabilitation"[MeSH Terms] OR psychoeducational[tiab] OR psychoeducation[tiab] OR psycho-educational[tiab] OR psycho-education[tiab] OR "Counseling"[Mesh] OR counselling[tiab] OR counseling[tiab] OR ((therapy[tiab] OR therapies[tiab] OR treatment*[tiab]) AND (cognitive[tiab] OR behavior[tiab] OR behavioral[tiab] OR behaviour[tiab] OR behavioural[tiab] OR conditioning[tiab] OR cognition[tiab])) OR "Behavior Therapy"[Mesh] OR behavior modification[tiab] OR behaviour modification[tiab] OR conditioning therapy[tiab] OR conditioning therapies[tiab] OR conditioning treatment[tiab] OR cognition therapy[tiab] OR cognition therapies[tiab] OR cognitive psychotherapy[tiab] OR cognitive psychotherapies[tiab] OR cognitive t reatment[tiab] OR "Self Care"[Mesh] OR self care[tiab] OR self help[tiab] OR self management[tiab])

PsycINFO search strategy

((internet* or web* or online* or computer* or electronic* telemedicine or websites or ehealth or e-health or e-mail or email or electronic mail or cyber* or icbt or i-cbt or wcbt). ti,ab. or (internet or online therapy or telemedicine or computer assisted therapy or computer mediated communication).sh.) AND ((random* or non-inferiority or equivalen* or rct or single blind or double blind or triple blind).ti,ab. OR (("quantitative study" or "empirical study" or follow up study or "treatment outcome/clinical trial").md. AND random*.af) OR exp evidence based practice/ or clinical trials/ or treatment effectiveness evaluation/) AND (exp cognitive behavior therapy/ or exp behavior modification/ or exp behavior therapy/ or exp cognitive restructuring/ or exp cognitive therapy/ or exp dialectical behavior therapy/ or (rehabilitation or psychoeducational or psychoeducation or psycho-educational or psycho-education or counselling or counseling or ((therapy or therapies or treatment*) and (cognitive or behavior or behavioral or behaviour or behavioural or conditioning or cognition)) or behavior modification or behaviour modi-

fication or conditioning therapy or conditioning therapies or conditioning treatment or cognition therapy or cognition therapies or cognitive psychotherapy or cognitive psychotherapies or cognitive treatment or self care or self help or self management). ti,ab. or self management/ or exp cognitive therapy/ or exp self monitoring/)

Embase search strategy

((internet* or web* or online* or computer* or electronic* telemedicine or websites or ehealth or e-health or e-mail or email or electronic mail or cyber* or icbt or i-cbt or wcbt). ti,ab. or (internet or exp telehealth/ or computer assisted therapy or computer assisted therapy).sh.) AND ((random* or non-inferiority or equivalen* or rct or single blind or double blind or t r iple blind).ti,ab. or (randomized controlled trial or evidence based practice).sh. or (therapy effect.sh. and random*.af.)) AND (exp cognitive therapy/ or exp behavior modification/ or exp behavior therapy/ or exp self care/ or exp self monitoring/ or (rehabilitation or psychoeducational or psychoeducation or psychoeducational or psycho-education or counselling or counseling or ((therapy or therapies or treatment*) and (cognitive or behavior or behavioral or behaviour or behavioural or conditioning or cognition)) or behavior modification or behaviour modification or conditioning therapy or conditioning therapies or conditioning treatment or cognition therapy or cognition therapies or cognitive psychotherapy or cognitive psychotherapies or cognitive treatment or self care or self help or self management).ti,ab.)

Multimedia appendix 2. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with a passive control condition

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Abbott et al, 2009 [35]	ICBT, 32	Intervention 23/32 (72%)	**ICBT (6 wks)**	**General psychological**		ITT
			-applied relaxation	depression	DASS-D	0
(tinnitus)			-cognitive therapy	anxiety	DASS-A	0
	Online psychoeducation, 24	Measurement 32/56 (57%)	-behavioral therapy	stress	DASS-S	0
			-psychoeducation	**Disease-related physical**		
			-improving coping skills	tinnitus loudness	VAS	0
				quality of sleep	VAS	0
				Disease-related impact		
				tinnitus-related distress and annoyance	TRQ	0
Andersson et al, 2002 [37]	ICBT, 53	Intervention 26/53 (49%)	**ICBT (6 wks)**	**General psychological**		Non-ITT
			-applied relaxation	depression	HADS-D	–[e]
(tinnitus)			-cognitive therapy	anxiety	HADS-A	–[e]
			-behavioral therapy	**Disease-related physical**		
	Waiting list, 64	Measurement 45/117 (38%)	-mindfulness & acceptance-based techniques	tinnitus loudness	VAS	–[d]
			-psychoeducation	quality of sleep	VAS	0[c]
			-improving coping skills	**Disease-related impact**		
				tinnitus-related distress and annoyance	TRQ	–[e]
van Bastelaar et al, 2011 [57]	ICBT, 125	Intervention 72/125 (58%)	**ICBT (8 wks)**	**General psychological**		ITT
			-cognitive therapy	depression	CES-D	–[f]
(type 1 and 2 diabetes)			-applied relaxation	**Disease-related physical**		
	Waiting list, 130	Measurement 88/255 (35%)	-behavioral therapy	glycemic control	HbA1c	*n.r.*
			-stress management	**Disease-related impact**		
			-improving coping skills	diabetes-specific emotional distress	PAID	–[f]

Multimedia appendix 2. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with a passive control condition (continued)

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Berman et al, 2009 [38]	ICBT, 52	Intervention 10/52 (19%)	**ICBT (6 wks)**	**General psychological**		Non-ITT
	Waiting list, 37	Measurement 11/89 (12%)	-applied relaxation -cognitive therapy (group) -psychoeducation	depression	CES-D	0
(chronic pain)				anxiety	STAI-6	0
				Disease-related physical		
				pain intensity	BPI	0
				Disease-related impact		
				–	–	–
Brattberg, 2006 [39]	ICBT, 30	Intervention 3/30 (10%)	**ICBT (20 wks)**	**General psychological**		Non-ITT
	Waiting list, 30	Measurement 5/60 (8%)	-cognitive therapy (group) -psychoeducation	depression	HADS-D	– [d]
(chronic pain and/or burnout)				anxiety	HADS-A	0
				Disease-related physical		
				bodily pain	SF-36	– [d]
				Disease-related impact		
				–	–	–
Burhman et al, 2004 [40]	ICBT, 22[g]	Intervention *n.r.*	**ICBT (6 wks)**	**General psychological**		Non-ITT
			-improving coping skills -applied relaxation -stress management -cognitive therapy -physical exercise -psychoeducation	depression	HADS-D	0
(chronic back pain)	Waiting list, 29[g]	Measurement 5/56 (9%)		anxiety	HADS-A	0
				affective distress	MPI	0
				Disease-related physical		
				average pain intensity	Diary	0
				pain severity	MPI	0
				Disease-related impact		
				–	–	–

Multimedia appendix 2. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with a passive control condition (continued)

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Burhman et al, 2011 [41]	ICBT, 26	Intervention 3/26 (12%)	**ICBT (8 wks)**	**General psychological**		ITT
			-applied relaxation	depression	HADS-D	0
(chronic back pain)			-cognitive therapy	anxiety	HADS-A	0
			-stress management	affective distress	MPI	0
			-improving coping skills	**Disease-related physical**		
	Waiting list, 28	Measurement 4/54 (7%)	-mindfulness	pain severity	MPI	0
			-physical exercise	**Disease-related impact**		
			-psychoeducation	–	–	–
David et al, 2011 [42]	ICBT, 69	Intervention 37/69 (54%)	**ICBT (8 wks)**	**General psychological**		Non-ITT
			-psychoeducation	depression	BSI	0
(breast cancer)			-cognitive therapy	anxiety	BSI	0
			-behavioral therapy	psychological distress	BSI-GSI	0
			-stress management	**Disease-related physical**		
	Waiting list, 64	Measurement 63/133 (47%)	-improving coping skills	–	–	–
			-problem solving	**Disease–related impact**		
				–	–	–
Devineni and Blanchard, 2005 [43]	ICBT, 39[g]	Intervention *n.r.*	**ICBT (4 wks)**	**General psychological**		Non-ITT
	Waiting list, 47[g]	Measurement 53/139 (38%)	-applied relaxation	depression	CES-D	0
			-cognitive therapy	anxiety	STAI-T	0
(chronic headache)			-stress management	**Disease-related physical**		
			-improving coping skills	headache index	Diary	–[f]
			-biofeedback	**Disease-related impact**		
				–	–	–

Multimedia appendix 2. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with a passive control condition (continued)

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Hunt et al, 2009 [47]	ICBT, 28	Intervention 15/28 (54%)	**ICBT (6 wks)**	**General psychological**		Non-ITT
			-applied relaxation	–	–	–
(irritable bowel syndrome)	Waiting list (+self-monitoring), 26	Measurement 23/54 (43%)	-stress management -improving coping skills -cognitive therapy -behavioral therapy -exposure -psychoeducation	**Disease-related physical**		
				gastrointestinal symptom severity	GSRS	–[e]
				Disease-related impact		
				disease-specific quality of life	IBS-QOL	+[d]
Ljótsson et al, 2010 [50]	ICBT, 43	Intervention 13/43 (30%)	**ICBT (10 wks)**	**General psychological**		ITT
			-exposure	depression	MADRS-S	0[h]
(irritable bowel syndrome)	Waiting list + discussion forum, 43	Measurement 5/86 (6%)	-mindfulness & acceptance-based techniques -cognitive therapy -behavioral therapy -psychoeducation	**Disease-related physical**		
				IBS symptom severity	GSRS-IBS	–[f]
				Disease-related impact		
				disease-specific quality of life	IBS-QOL	+[f]
Ljótsson et al, 2011a [49]	ICBT, 30	Intervention 7/30 (23%)	**ICBT (10 wks)**	**General psychological**		ITT
			-exposure	–	–	–
(irritable bowel syndrome)	Waiting list + discussion forum, 31	Measurement 11/61 (18%)	-mindfulness & acceptance-based techniques -cognitive therapy -behavioral therapy -psychoeducation	**Disease-related physical**		
				IBS symptom severity	GSRS-IBS	–[f]
				Disease-related impact		
				disease-specific quality of life	IBS-QOL	+[f]

Multimedia appendix 2. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with a passive control condition (continued)

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Lorig et al, 2006 [53] (heterogeneous)	ICBT, 457 CAU, 501	Intervention 104/457 (23%) Measurement 175/958 (18%)	**ICBT (6 wks)** -psychoeducation -physical exercise -cognitive therapy -stress management -improving coping skills -relaxation -problem solving	**General psychological**		Non-ITT
				–	–	–
				Disease-related physical		
				pain	VNS	–[e]
				fatigue	VNS	–[d]
				Disease-related impact		
				health distress	HDS	–[d]
Lorig et al, 2008 [54] (arthritis or fibromyalgia)	ICBT, 433 CAU, 422	Intervention 123/433 (28%) Measurement 214/855 (25%)	**ICBT (6 wks)** -psychoeducation -physical exercise -cognitive therapy -applied relaxation -stress management -improving coping skills -problem solving	**General psychological**		ITT
				–	–	–
				Disease-related physical		
				pain	VNS	–[f]
				fatigue	VNS	0[c]
				Disease-related impact		
				health distress	HDS	–[f]
Lorig et al, 2010 [52] (type 2 diabetes)	ICBT, 259 ICBT + email reinforcement, 232 CAU, 270	Intervention 96/491 (20%) Measurement 116/761 (15%)	**ICBT (6 wks)** -stress management -improving coping skills -physical exercise -applied relaxation -problem solving -cognitive therapy -psychoeducation	**General psychological**		ITT
				depression	PHQ	0
				Disease-related physical		
				glycemic control	A1c	0[c]
				Disease-related impact		
				health distress	HDS	0

Multimedia appendix 2. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with a passive control condition (continued)

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Between group effects[b]
Ström et al, 2000 [55]	ICBT, 20[g]	Intervention *n.r.*	**ICBT (6 wks)** -applied relaxation -problem solving -improving coping skills	**General psychological**		Non-ITT
				depression	BDI	0
(recurrent headache)	Waiting list, 25[g]	Measurement 57/102 (56%)		**Disease-related physical**		
				headache index	Diary	–[d]
				Disease-related impact		
				–	–	–
Thompson et al, 2010 [56]	ICBT, 13	Intervention 7/26 (27%)	**ICBT (8 wks)** -cognitive therapy -mindfulness & acceptance based techniques -psychoeducation -applied relaxation	**General psychological**		Non-ITT
				depression	BDI	–[f]
(epilepsy)	MBCT delivered by phone, 12	Measurement 13/52 (25%)		**Disease-related physical**		
				–	–	–
	CAU waiting list, 27			**Disease-related impact**		
				physical health quality of life	BRFSS	0

Note.[a]BDI=Beck Depression Inventory; BPI=Brief Pain Inventory; BRFSS=Behavioral Risk Factor Surveillance System; BSI=Brief Symptom Inventory; BSI-GSI=Brief Symptom Inventory - Global Severity Index; CAU=Care as usual; CES-D=Centre for Epidemiologic Studies – Depression; DASS-A=Depression Anxiety Distress Scales - Anxiety; DASS-D=Depression Anxiety Distress Scales - Depression; DASS-S=Depression Anxiety Distress Scales - Stress; GSRS=Gastrointestinal Symptom Rating Scale; GSRS-IBS=Gastrointestinal Symptom Rating Scale - Irritable Bowel Syndrome; HADS-A=Hospital Anxiety and Depression Scale - Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; HbA1C=Hemoglobin A1C; HDS=Health Distress Scale; IBS=irritable bowel syndrome; IBS-QOL=Irritable Bowel Syndrome Quality of Life Instrument; ICBT=Internet-based cognitive therapy; ITT=intent-to-treat analysis; MADRS-S=Montgomery-Åsberg Depression Rating Scale self-rating; MPI=Multidimensional Pain Inventory; PAID=Problem Areas in Diabetes; PHQ=Patient Health Questionnaire; SF-36=Short Form Health Survey-36; STAI-S=State Trait Anxiety Inventory - State Anxiety; STAI-T=State Trait Anxiety Inventory - Trait Anxiety; TRQ=Tinnitus Reaction Questionnaire; VAS=Visual Analogue Scale; VNS=Visual Numeric Scale, [b]0 = no statistically significant effects, – = statistically significant effect indicating a reduction in the outcome, + = statistically significant effect showing an increase in the outcome, [c]$p \leq .1$, [d]$p < .05$, [e]$p \leq .01$, [f]$p \leq .001$, [g]after dropout, pre-dropout sample size not reported, [h]Per-protocol means and SDs are reported in the article (ITT did not affect results, except for non-significance of effect on MADRS-S).

Multimedia appendix 3. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with an active comparison condition

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Main effects ICBT[b]	Between group effects[b]
Andersson et al, 2003 [36]	ICBT + phone, 24	Intervention 7/24 (29%)	**ICBT (6 wks)** -applied relaxation -problem solving -cognitive therapy -psychoeducation -improving coping skills	**General psychological**		Non-ITT	
				depression	HADS-D	– [c]	0
(recurrent headache)				anxiety	HADS-A	0	0
				self-perceived stress	PSS	– [d]	0
	ICBT - phone, 20	Measurement 20/44 (45%)		**Disease-related physical**			
				headache index	Diary	0	0
				Disease-related impact			
				–	–	–	–
Kaldo et al, 2008 [48]	ICBT, 26	Intervention 10/26 (38%)	**ICBT (6 wks)** -applied relaxation -cognitive therapy -behavioral therapy -exposure -stress management -improving coping skills -psychoeducation -problem solving	**General psychological**		ITT	
				depression	HADS-D	– [g]	0
(tinnitus)				anxiety	HADS-A	– [h]	0
	Group-based CBT, 25	Measurement 2/51 (4%)		perceived stress	VAS	0	0
				Disease-related physical			
				tinnitus loudness	VAS	– [h]	0
				quality of sleep	ISI	+ [h]	0
				Disease-related impact			
				tinnitus-related distress and annoyance	TRQ	– [h]	0

Multimedia appendix 3. Study characteristics and post-intervention effects of ICBT for chronic somatic conditions: two-armed studies with an active comparison condition (continued)

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Main effects ICBT[b]	Between group effects[b]
Ljótsson et al, 2011b [51] (irritable bowel syndrome)	ICBT, 98	Intervention1/98 (1%)	**ICBT (10 wks)** -mindfulness & acceptance-based techniques -exposure -behavioral therapy -cognitive therapy	**General psychological**		ITT	
				depression	HADS-D	– [e]	0
				anxiety	HADS-A	– [e]	0
				self-perceived stress	PSS	– [c]	0
	Internet stress management (no exposure content), 97	Measurement 4/195 (2%)	**Stress Management (10 wks)** -stress management -improving coping skills -problem solving -psychoeducation	**Disease-related physical**			
				IBS symptom severity	GSRS-IBS	– [e]	– [e,f]
				Disease-related impact			
				disease-specific quality of life	IBS-QOL	+ [e]	– [e,f]

Note. [a]GSRS-IBS=Gastrointestinal Symptom Rating Scale – Irritable Bowel Syndrome; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; IBS-QOL=Irritable Bowel Syndrome Quality of Life Instrument; ICBT = internet-based cognitive behavioral therapy; ISI=Insomnia Severity Index; ITT=intent-to-treat analysis; PSS=Perceived Stress Scale; TRQ=Tinnitus Reaction Questionnaire; VAS=Visual Analogue Scale, [b]0 =no statistically significant effects, – =statistically significant effect indicating a reduction in the outcome, + =statistically significant effect showing an increase in the outcome, [c]$p < .05$, [d]$p \leq .01$, [e]$p \leq .001$, [f]Favoring ICBT, [g]Only for the Internet condition, [h]*p*-value not reported.

Multimedia appendix 4. Study characteristics and between-group post-intervention effects of ICBT for chronic somatic conditions: three-armed studies with two active treatment conditions and one passive control condition

Author, year (population)	Condition, *N*	Dropout *n* (%)	Treatment content (duration)	Outcome	Outcome measure[a]	Comparison	Between group effects[b]
Ghahari et al, 2010 [44]	ICBT, 34	Intervention 10/34 (29%)	**ICBT (7 wks)**	**General psychological**			ITT
			-stress management			ICBT - control	0
(fatigued patients with neurological conditions)	Online self-management, 28		-improving coping skills	depression	DASS-D	Info only - control	0
			-psychoeducation			ICBT - info only	0
	Care as usual, 33		-cognitive therapy			ICBT - control	0
				anxiety	DASS-A	Info only - control	0
						ICBT - info only	0
		Measurement 10/95 (11%)	**Online self-management (7 wks)**			ICBT - control	0
			-stress management	stress	DASS-S	Info only - control	0
			-improving coping skills			ICBT - info only	0
			-psychoeducation	**Disease-related physical**			
				–	–	–	–
				Disease-related impact			
				–	–	–	–
Hedborg & Muhr, 2011 [45]	ICBT, 28	Intervention 6/55 (11%)	**ICBT (6 months)**	**General psychological**			ITT
			-stress management			ICBT[+] - control	0
(migraine)	ICBT + massage, 27		-improving coping skills	depression	MADRS-S	ICBT - control	0
			-applied relaxation			ICBT[+] - ICBT	0
	Control, 28		-cognitive therapy	**Disease-related physical**			
			-physical exercise			ICBT[+] - control	– [c]
		Measurement 7/83 (8%)	-behavioral therapy	migraine frequency	Diary	ICBT - control	– [c]
			-psychoeducation			ICBT[+] - ICBT	0
	Disease-related impact						
	–			–	–	–	

Hesser et al, 2012 [46]	ICBT, 32	Intervention 10/67 (15%)	**ICBT (8 wks)**	**General psychological**			ITT
			-applied relaxation			ICBT - control	0
(tinnitus)			-cognitive therapy	depression	HADS-D	IACT - control	– [d]
			-behavioral therapy			ICBT - IACT	0
	IACT, 35		-exposure			ICBT - control	– [d]
			-stress management	anxiety	HADS-A	IACT - control	– [c]
			-improving coping skills			ICBT - IACT	0
			-psychoeducation			ICBT - control	0
			-problem solving				
	Discussion forum, 32	Measurement 4/99 (4%)	**IACT (8 wks)**	stress	PSS	IACT - control	– [d]
			-mindfulness & acceptance-based techniques			ICBT - IACT	0
			-behavioral therapy	**Disease-related physical**			
			-cognitive therapy				ICBT - control
			-psychoeducation	sleep quality	ISI	IACT - control	0
						ICBT - IACT	0
				Disease-related impact			
				–	–	–	–

Note. [a]DASS-A=Depression Anxiety Distress Scales - Anxiety; DASS-D=Depression Anxiety Distress Scales - Depression; DASS-S=Depression Anxiety Distress Scales - Stress; HADS-A=Hospital Anxiety and Depression Scale - Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; IACT=Internet-based acceptance and commitment therapy; ICBT = internet-based cognitive behavioral therapy; ICBT^{+} = ICBT with added hand massage; ISI=Insomnia Severity Index; ITT=intent-to-treat analysis; MADRS-S=Montgomery-Åsberg Depression Rating Scale self-rating; PSS=Perceived Stress Scale, [b]0 =no statistically significant effects, – =statistically significant effect indicating a reduction in the outcome, + =statistically significant effect showing an increase in the outcome, [c]$p < .05$, [d]$p \leq .01$.

CHAPTER 6

Tailored therapist-guided internet-based cognitive behavioral treatment for psoriasis: a randomized controlled trial

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ABSTRACT

Objective: Patients with somatic conditions, such as psoriasis, frequently suffer from high burden of their disease in daily life and might benefit from internet-based cognitive behavioral therapy (ICBT) tailored to their adjustment problems. The aim of this multicenter randomized controlled trial was to examine the effects of therapist-guided, individually tailored ICBT in a clinical sample of patients with psoriasis.

Methods: A total of 131 patients with psoriasis, who were screened for a psychological risk profile, were randomized to either care as usual (CAU, $n = 66$) or ICBT in addition to CAU ($n = 65$). Participants filled out standardized self-report questionnaires assessing physical and psychological functioning and impact on daily activities at baseline, post-treatment assessment, and 6-month follow-up.

Results: In covariate-controlled linear mixed-model analyses, significantly larger improvements in ICBT compared to CAU were found in the primary outcomes physical functioning ($p = .03$, $d = 0.36$) and impact on daily activities ($p = .04$, $d = 0.35$), but not in psychological functioning ($p = .32$), up to 6 months after treatment compared to baseline. In explorative analyses, the working alliance measured at the beginning of ICBT treatment predicted improved physical ($p = .02$) and psychological ($p < .001$) outcomes.

Conclusions: Results underline the promise of therapist-guided, individually tailored ICBT to improve physical functioning and reduce the impact of psoriasis on daily activities in patients with a psychological risk profile. Establishing a good therapeutic relationship early on may be an important factor that influences treatment outcomes in personalized ICBT interventions. Further research is needed to evaluate ICBT effectiveness in additional samples and to explore its underlying mechanisms.

INTRODUCTION

Psoriasis is one of the most common immune-related chronic dermatological conditions [1] and is known for its high disease burden in daily life [2]. Patients frequently experience problems with mood, distress, and social impairments in addition to the burden of physical symptoms [3–6]. These problems may also negatively impact upon skin status, disease course, adherence, and dermatological treatment success [7–11]. Patients with a psychological profile of elevated levels of distress (an estimated 30–40%) are known to be at risk for long-term adjustment problems [3, 12] and might benefit from cognitive behavioral therapy (CBT), as it has shown to improve physical and psychological functioning in patients with chronic somatic conditions [13–16], including dermatological conditions [17–20]. Over the last decade, CBT has increasingly been offered online, which may facilitate intervention reach, increase cost-effectiveness and time-efficiency, and reduce possible barriers to following a psychological intervention [21, 22].

While systematic reviews show favorable effects of internet-based CBT (ICBT) for chronic somatic conditions [23–25], research in dermatological conditions is scarce. One randomized controlled trial (RCT) showed positive effects of unguided ICBT on anxiety and quality of life in patients with psoriasis but was limited by high dropout rates [26]. Therapist guidance may improve adherence [27, 28] and treatment effects [29–31], and patients tend to prefer guidance in ICBT [22, 32]. Furthermore, ICBT is usually based on standardized protocols [33], whereas recent findings underline the promise of less studied individually tailored interventions [34–36].

Despite the promising effects of therapist-guided, individually tailored ICBT in other conditions, its effects have not been examined in dermatological conditions. Possible predictors and correlates of treatment outcomes, including the therapeutic relationship [37, 38] and adherence [39], also remain unexplored in this group. Therefore, this study examined the effectiveness of therapist-guided, individually tailored ICBT for patients with psoriasis, expecting greater improvements in physical and psychological functioning and reduced impact on daily activities in ICBT compared to care as usual (CAU). In addition, sociodemographic, disease-related, and treatment-related predictors and correlates of treatment effects were explored.

METHODS

Participants and procedure

Study participants were recruited through outpatient dermatology departments of one academic and three non-academic hospitals and through the Dutch Psoriasis Association (Figure 1). Inclusion criteria were a diagnosis of psoriasis, age ≥ 18 years,

and a positive psychological risk profile (i.e. Impact of chronic Skin Disease on Daily Life (ISDL) score of ≥ 5 for anxiety and/or ≥ 21 for negative mood [40, 41]). Exclusion criteria were psychological (i.e. diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) [42]) and/or physical comorbidity interfering with the study protocol, current psychological treatment, current photo(chemo)therapy, pregnancy, lack of access to a computer and/or internet, and illiteracy.

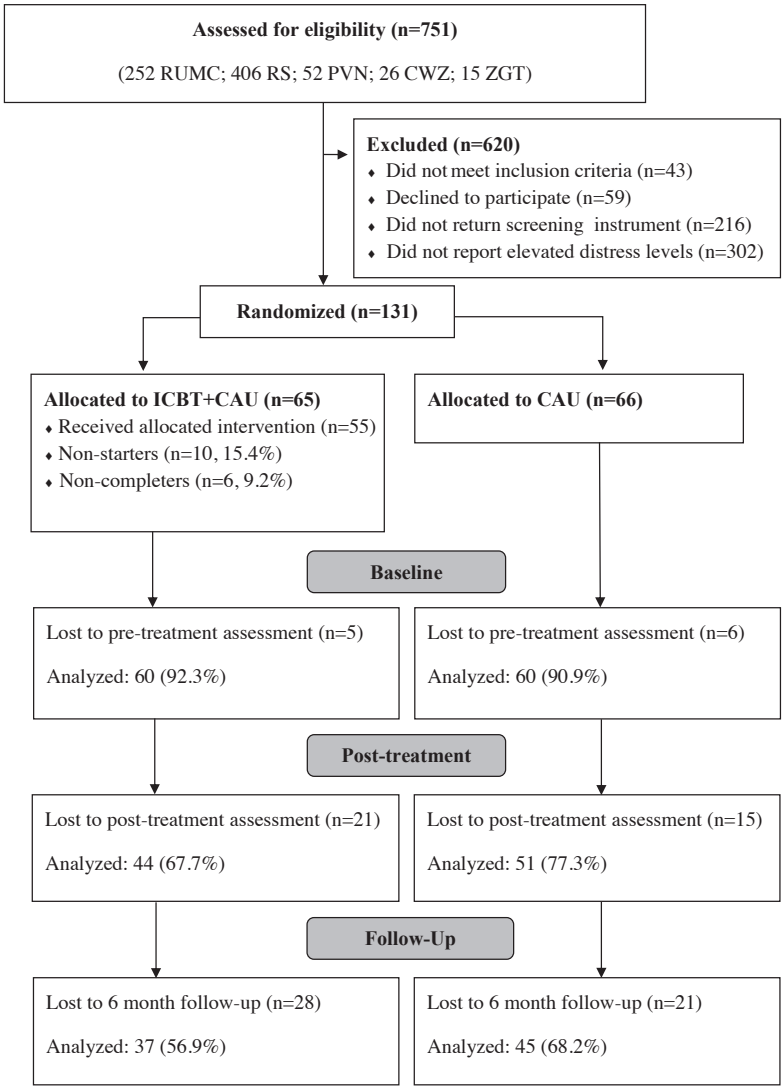

Figure 1. Consort flow diagram of participants. CAU, Care as usual; CWZ, Canisius-Wilhelmina Hospital, Nijmegen; ICBT, internet-based cognitive behavioral treatment; PVN, Dutch Psoriasis Association; RS, Rijnstate Hospital, Velp; RUMC, Radboud university medical center, Nijmegen; ZGT, Ziekenhuis Groep Twente, Almelo.

This study had an open-label parallel-group RCT design. An independent person randomized the participants (allocation ratio: 1:1) using a computerized program that minimized on age, gender, educational level, recruitment site, self-assessed disease severity, and medication use. The patients were randomized to either CAU (regular dermatological care) or ICBT in addition to CAU. A member of the research team informed the participants by phone and letter about treatment assignment. ICBT interventions took place between July 2010 and October 2014. Measurements were collected between June 2010 and April 2015. Study assessments were conducted at baseline, post-treatment assessment (CAU: 6 months after baseline), and 6-month follow-up (CAU: 12 months after baseline). The study was approved by the regional medical ethics committee, registered in the Dutch Trial Registry (NTR2436), and conducted in accordance with the Declaration of Helsinki [43]. All participants provided written informed consent.

ICBT intervention

Patients randomized to the ICBT condition received an internet-based, therapist-guided CBT intervention aimed to reduce the impact of psoriasis on daily life, which was based on previous evidence- based face-to-face interventions [41, 44]. The intervention consisted of five flexible treatment modules containing a broad variety of cognitive and behavioral techniques focused on themes that patients often experience problems with: itch, pain, fatigue, negative mood, and social relationships. The participants started with two face-to-face intake sessions with their therapist (a psychologist), in which individual treatment goals were discussed. Next, patients received a telephone-based instruction of the intervention website by a researcher to ensure that they were capable of working with the program from home. The patients then started with the individually tailored ICBT intervention by logging on to the secure intervention website. Choice of treatment modules and individual assignments within these modules were determined based on individual patient goals, therapist's judgment, and screening procedures [see also 45]. The patients received personalized written feedback on their assignments from their therapist approximately once a week. Intervention duration and content varied between participants, depending on treatment goals, with a mean duration of 25 ± 12 weeks (range 1–57 weeks). For a more detailed description of ICBT modules, therapists, intervention use, and adherence, see supplementary methods and results.

Instruments

Primary and secondary outcomes

The primary outcome was the impact of psoriasis on daily life, measured on three domains, for which total scores were computed (composite scores: the overall average of normalized (z-)scores of the questionnaires included in each domain): (1) psychological

functioning, consisting of negative mood (ISDL) [40], anxiety (ISDL) [40], and depressive symptoms (Beck Depression Inventory) [46, 47]; (2) physical functioning, consisting of itch (ISDL) [40] and fatigue (Checklist Individual Strength) [48]; and (3) impact on daily activities, consisting of role limitations due to physical health problems and role limitations due to emotional problems (RAND-36 Health Status Inventory) [49, 50]. Secondary outcomes consisted of clinician-rated (Psoriasis Area and Severity Index, PASI) [51] and self-reported disease severity (self-administered PASI) [52], and dermatological treatment compliance.

Predictors and correlates of treatment outcome

Sociodemographic (age, sex, educational level, and marital status), disease-related (disease severity and duration), and treatment-related variables (working alliance between patient and ICBT therapist: Working Alliance Inventory - Short Form [53–55], ICBT adherence, website logins) were examined as possible predictors and correlates of treatment outcomes. Further measurement details of all study variables can be found in the supplementary methods and results.

Data analysis

Baseline characteristics were compared with t-tests and χ^2 tests. Primary analyses were conducted using linear mixed-effects modeling, which has superior qualities with regard to missing values [56] and makes use of all available data, making this a full intention-to-treat analysis. Models were fitted with full information maximum-likelihood estimation. Between-group effects at post-treatment assessment and follow-up were analyzed with baseline scores of dependent variables as covariates. Time was operationalized as a continuous variable, and post-treatment assessment varied across participants as a result of different intervention lengths. Fixed linear effects of time and condition were included as well as random effects of intercept. Primary analyses were conducted including all variables included in the randomization (age, sex, educational level, recruitment site, systemic medication use, etanercept use, and disease severity) as covariates [57]. In secondary analyses, results were reported (1) without covariates (see Results) and (2) excluding ICBT dropouts/non-starters (see suppl. methods and results).

Between-group Cohen's *d* type of effect sizes were calculated, dividing the difference in the estimated marginal means of the primary analyses of the two groups by their pooled pre-treatment SD. Within-group Cohen's *d* effect sizes were calculated by dividing the difference in pre- and post-treatment assessment means by pre-assessment SDs. Effect sizes of 0.2, 0.5, and 0.8 were considered small, moderate, and large, respectively [58]. Unstandardized effect sizes were defined as raw mean differences between ICBT and CAU.

Pearson's correlation coefficients were calculated between change in primary outcomes (residual gain scores) and selected sociodemographic, disease-related, and treatment-related variables [60]. All analyses were conducted in IBM SPSS v21. A power analysis with 80% power indicated that a sample size of two groups of 65 patients was needed, assuming the effect size $d = 0.50$ ($\alpha = .05$), based on previous ICBT studies for physical and psychological conditions [61]. Statistical significance was accepted at $p < .05$. In explorative analyses examining correlates of treatment effects, tendencies towards significant effects ($p < 0.10$) were not reported for stringency reasons.

RESULTS

Between June 2010 and November 2013, 751 patients were screened, and 131 patients were randomized to either ICBT ($n = 65$) or CAU ($n = 66$). Means and SDs of selected sociodemographic and disease-related variables are presented in Table 1, and baseline values on primary outcomes and their subcomponents, as well as secondary outcomes, are presented in Tables 2 and 3. These values did not differ between groups ($p \geq .10$), with the exception of a tendency towards higher levels of fatigue ($p = .08$) and higher clinician-rated disease severity ($p = .03$) in ICBT compared to CAU. Disease severity was generally mild to moderate, with 7.6% of patients having severe psoriasis (PASI > 10) [62].

Table 1. Baseline socio-demographic and disease-related characteristics of internet-based cognitive behavioral treatment (ICBT) and care as usual (CAU) groups

Characteristic	ICBT+CAU (*n* = 65)	CAU (*n* = 66)
Gender (male)	33 (50.8)	34 (51.5)
Age (years)	52.69 ± 11.27 (24-73)	53.45 ± 13.81 (19-79)
Married/ living together	46 (70.8)	53 (80.3)
Educational level		
Primary	1 (1.5)	4 (6.1)
Secondary	44 (67.7)	43 (65.2)
Tertiary	20 (30.8)	19 (28.8)
Disease severity (PASI)[a]	5.99±5.61(1-31)[c]	4.20±2.87(0-13)[c]
Disease severity (SAPASI)[a]	5.27± 3.29 (1-19)[c]	4.48±2.41 (0-12)[c]
Disease duration (years)	18.03 ± 13.76 (0-59)[c]	15.16 ± 16.35 (0-65)[c]
Systemic treatment[b]	25 (44.6)[c]	17 (29.3)[c]

Note. Data are presented as mean ± SD (range) or n (%), as appropriate. Abbreviations: CAU, care as usual; ICBT, internet-based cognitive behavioral treatment; PASI, Psoriasis Area and Severity Index; SAPASI, Self-assessed PASI. [a]Due to unequal distribution of PASI and SAPASI scores, transformed variables were used in analyses (see Methods section). Untransformed scores are displayed in this table, [b]Number of patients reporting use of systemic treatment, [c]*n* = 2-12 missings.

Table 2. Means and SDs of each measurement point on primary outcome measures (i.e. total scores) and their subcomponents, including results of linear mixed models analyses and accompanying effect sizes

Measurement	ICBT			Care as usual			Standardized effect size	Unstandardized effect size (95% CI)	Linear mixed models	
	Mean	SD	*n*	Mean	SD	*n*			Effect	*p*-value
Psychological functioning										
Total score (composite)										
Pre	0.02	0.87	60	-0.01	0.85	59				
Post	-0.51	0.74	44	-0.29	0.92	49			Time	0.22
Follow-up	-0.49	0.90	37	-0.41	0.84	45	0.17	0.14 (-0.14 to 0.43)	Group	0.32
Negative mood (ISDL)[a]										
Pre	5.29	3.77	60	5.39	3.72	58				
Post	3.69	3.36	44	4.60	3.21	49			Time	0.35
Follow-up	3.86	3.65	37	4.11	3.53	45	0.06	0.06 (-0.28 to 0.40)	Group	0.74
Anxiety (ISDL)										
Pre	21.85	4.61	60	22.10	4.58	60				
Post	19.36	4.37	43	21.02	5.74	48			Time	0.28
Follow-up	19.45	5.38	37	20.27	5.03	45	0.24	1.09 (-0.57 to 2.74)	Group	0.20
Depressive symptoms (BDI)										
Pre	12.78	7.50	60	11.50	6.23	58				
Post	8.46	5.34	45	8.89	6.82	49			Time	0.24
Follow-up	8.53	6.72	37	8.69	6.36	45	0.15	1.01 (-1.28 to 3.30)	Group	0.38
Physical functioning										
Total score (composite)										
Pre	0.11	0.73	60	-0.12	0.79	58				
Post	-0.55	0.75	43	-0.36	0.73	48			Time	0.13
Follow-up	-0.48	0.77	37	-0.55	0.68	42	0.36	0.27 (0.02 to 0.52)	Group	0.03
Fatigue (CIS-f)										
Pre	37.70	10.68	60	34.31	10.30	59				
Post	30.77	12.46	44	33.58	9.19	49			Time	0.09
Follow-up	31.19	11.65	37	31.40	10.09	44	0.37	3.84 (0.09 to 7.59)	Group	0.04
Itch (ISDL)										
Pre	9.44	3.50	60	9.06	3.75	59				
Post	7.09	3.51	44	7.44	3.67	49			Time	0.44
Follow-up	7.44	3.32	37	6.88	2.97	43	0.17	0.61 (-0.56 to 1.77)	Group	0.30
Impact on daily activities										
Total score (composite)										
Pre	0.03	0.71	58	-0.04	0.89	57				
Post	0.38	0.55	43	0.25	0.88	46			Time	0.12
Follow-up	0.37	0.69	37	0.34	0.79	43	0.35	0.28 (0.01 to 0.55)	Group	0.04
Emotional role functioning (RAND-36)										
Pre	78.16	35.07	58	67.54	39.89	57				
Post	86.36	23.09	44	76.09	38.27	46			Time	0.05
Follow-up	87.39	26.47	37	85.61	32.47	44	0.33	12.12 (0.64 to 23.61)	Group	0.04
Physical role functioning (RAND-36)										

Table 2. Means and SDs of each measurement point on primary outcome measures (i.e. total scores) and their subcomponents, including results of linear mixed models analyses and accompanying effect sizes (continued)

Measurement	ICBT			Care as usual			Standardized effect size	Unstandardized effect size (95% CI)	Linear mixed models	
Pre	53.02	41.90	58	58.89	43.09	60				
Post	72.09	36.68	43	73.94	40.03	47			Time	1.00
Follow-up	70.95	41.04	37	70.45	40.08	44	0.32	13.34 (0.46 to 26.22)	Group	0.04

Note. All means and SDs are presented as uncorrected scores. Abbreviations: BDI, Beck Depression Inventory; CI, confidence interval; CIS-f, Checklist Individual Strength - fatigue; ICBT, internet-based cognitive behavioral treatment; ISDL, Impact of Skin Disease on Daily Life; RAND-36, RAND-36 Health Status Inventory. [a]Due to unequal distribution of IHDL negative mood, transformed variables were used in analyses (see Methods section). Untransformed scores are displayed in this table.

Table 3. Means and SDs of each measurement point on secondary outcome measures, including results of linear mixed models analyses and accompanying effect sizes

Measurement	ICBT			Care as usual			Standardized effect size	Unstandardized effect size (95% CI)	Linear mixed models	
	Mean	SD	n	Mean	SD	n			Effect	*p*-value
Clinician-assessed disease severity (PASI)[a]										
Pre	5.99	5.61	54	4.20	2.87	56				
Post	5.04	4.59	25	3.79	2.94	42			Time	.34
Follow-up	4.76	3.47	22	3.40	2.63	37	0.02	0.01 (-0.32 to 0.35)	Group	0.94
Self-assessed disease-severity (SAPASI)[a]										
Pre	5.27	3.29	59	4.48	2.41	54				
Post	4.61	5.39	44	3.95	2.26	43			Time	1.00
Follow-up	4.51	3.32	35	3.75	2.03	42	0.25	0.16 (-0.12 to 0.45)	Group	0.25
Dermatological treatment compliance										
Pre	3.96	1.11	59	4.09	1.03	58				
Post	4.02	1.21	41	4.02	0.98	44			Time	0.82
Follow-up	3.91	1.22	31	3.89	1.20	40	-0.11	-0.12 (-0.52 to 0.28)	Group	0.55

Note. All means and SDs are presented as uncorrected scores. Abbreviations: ICBT, internet-based cognitive behavioral treatment; PASI, Psoriasis Area and Severity Index; SAPASI, self-assessed PASI. [a]Due to unequal distribution of PASI and SAPASI scores, transformed variables were used in analyses (see Methods section). Untransformed scores are displayed in this table.

Attrition

A total of 73.3% of patients filled out post-treatment measurements, and 62.6% completed 6-month follow-up measurements (Figure 1). The ICBT intervention dropout rate was 26.2%: ten patients did not start treatment (nonstarters, 15.4%), six patients dropped out during treatment (non-completers, 9.2%), and one patient (1.5%) died during treatment as a result of comorbidity unrelated to the treatment. Reported reasons

for ICBT dropout and differences between completers and dropouts can be found in the supplementary methods and results.

ICBT treatment satisfaction

Patients in the ICBT group who filled out post-treatment evaluation questionnaires (n = 41) were satisfied with the ICBT intervention and gave the overall intervention a mean score of 7.64 ± 1.71 and user friendliness 7.72 ± 1.32 out of 10. A majority of 85.3% of patients would recommend the treatment to a friend or relative with a chronic somatic condition, and 87.7% of patients believed the treatment would have long-term positive effects (somewhat/probably/certainly); 60% of patients indicated a preference for internet-based treatment over other forms of treatment (phone-based: 5.0%, face to face: 27.5%) for future treatment, and an additional 7.5% gave internet-based treatment a shared first place with one or more other modalities.

Primary outcomes

Results on primary outcomes and their subcomponents, including effect sizes, are presented in Table 2 and Figure 2.

Psychological functioning

In linear mixed-model analyses controlling for previously specified covariates, no significant differences were found between ICBT and CAU regarding psychological functioning at post-treatment assessment and 6-month follow-up (p = .32) or on its subcomponents negative mood, anxiety, and depressive symptoms (all $p \geq .20$). The lack of significant main effects of time ($p \geq .22$) indicated that these outcomes were stable across post-treatment assessment and 6-month follow-up. Similar results were obtained in secondary analysis including no other covariates than baseline values of the dependent variable ($p \geq .19$).

Physical functioning

Significantly larger improvements in ICBT compared to CAU were found for physical functioning up to 6 months after treatment compared to baseline ($F(1,76.29) = 4.60$, $p = .03$, $d = 0.36$), with significant effects for fatigue ($F(1,74.53) = 4.16$, $p = .04$, $d = 0.37$) but not for itch ($p = .30$). These outcomes were stable across post-treatment assessment and 6-month follow-up, with the exception of fatigue, which tended to be lower at post-treatment assessment than at 6-month follow-up (p = .09). In secondary analysis including no other covariates than baseline values of the dependent variable, a tendency towards greater improvement in ICBT compared to CAU was found for fatigue (p = .08) and no significant between-group differences for itch or total physical functioning ($p \geq .16$).

Impact on daily activities

Significantly larger improvements in ICBT compared to CAU were found for impact on daily activities up to 6 months after treatment compared to baseline ($F(1,81.48) = 4.18$, $p = .04$, $d = 0.35$), with significant effects on both subcomponents: role limitations due to emotional problems ($F(1,132) = 4.36$, $p = .04$, $d = 0.33$) and role limitations due to physical health problems ($F(1,81.99) = 4.25$, $p = .04$, $d = 0.32$). The improvements in role limitations due to emotional problems at post-treatment assessment were further enlarged at follow-up ($p = .047$), while other outcomes remained stable. In secondary analysis including no other covariates than baseline values of the dependent variable, no between-group differences were found ($p \geq .17$).

Disease severity and compliance

Results on self-reported and clinician-assessed disease severity and dermatological treatment compliance, including effect sizes, are reported in Table 3. No between-group differences were found for any of these outcomes, with or without covariates (all *p*-values ≥ .25).

Within-group improvements

For primary outcome measures, ICBT within-group improvements were large for physical functioning ($d = 0.81$ - 0.90) and moderate for psychological functioning ($d = 0.59$ - 0.61) and impact on daily activities ($d = 0.48$ - 0.51). CAU within-group improvements were small to moderate for physical functioning ($d = 0.30$ - 0.56), psychological functioning ($d = 0.33$ - 0.47), and impact on daily activities ($d = 0.33$ - 0.43).

Predictors and correlates of treatment effects

To explore which patients benefitted most from treatment, treatment-related variables (working alliance with the therapist, treatment duration, and ICBT adherence including patient ratings, therapist ratings, and website logins) were correlated with change in primary outcomes. Results indicated that a better working alliance with the therapist at the beginning of treatment was associated with greater pre- to post-treatment assessment improvements in psychological ($r = –.66$, $p < .001$) and physical ($r = –.42$, $p = .02$) functioning but not with change in impact on daily activities ($r = .18$, $p = .34$). No significant associations of change in primary outcomes with treatment duration, ICBT adherence were found, nor with the sociodemographic and disease-related variables age, sex, educational level, disease duration, and disease severity (all *p*-values ≥ .17).

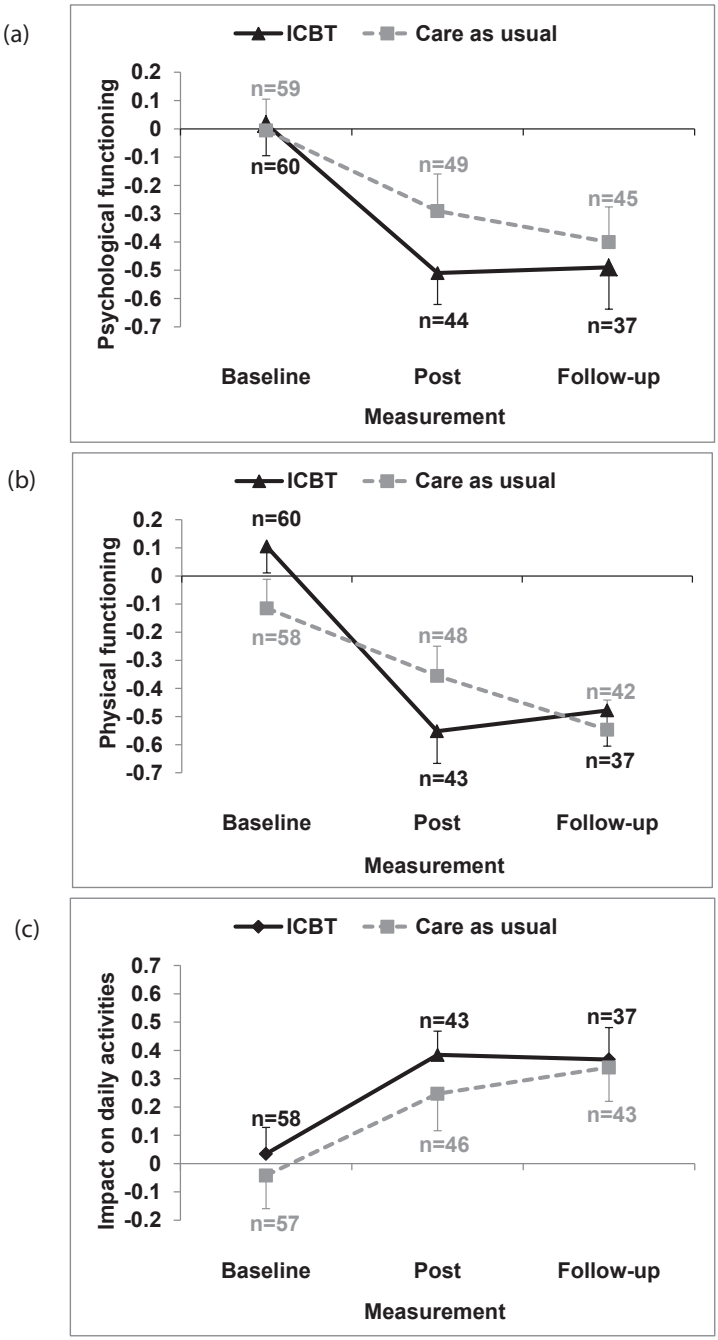

Figure 2. Baseline, post-assessment, and 6-month follow-up scores on primary outcome measures (i.e. total scores of psychological functioning (a), physical functioning (b), and impact on daily activities (c)) for internet-based cognitive behavioral therapy (ICBT) and care as usual (CAU) groups, presented as means ± SEM. Negative scores indicate improved psychological and psychological functioning in (a) and (b), and positive scores indicate reduced impact on daily activities in (c).

DISCUSSION

This first trial on the effectiveness of individually tailored, therapist-guided ICBT for patients with psoriasis who had a psychological risk profile indicated that ICBT as an adjunct to CAU had more beneficial effects on physical functioning and the impact of psoriasis on daily activities compared to CAU alone. When analyzing who benefits most from ICBT, the working alliance between patient and therapist measured at the beginning of treatment was related to improved physical and psychological outcomes, suggesting that the establishment of a good patient-therapist relationship early on is of considerable importance in guided ICBT.

Results on primary outcomes showed significantly larger improvements in ICBT compared to CAU on physical functioning and impact on daily activities. Effects on physical functioning were driven by improvements in fatigue, which is a frequent and disabling symptom in many chronic inflammatory conditions [63]. Patients often characterize fatigue as one of the most burdensome aspects of their condition [63], which was also reflected in the current trial; mean baseline scores were above the cut-off point for extreme fatigue [48], while means on other outcomes were comparable to norm groups of healthy individuals. In addition, the fatigue module was frequently chosen as the preferred treatment module in this trial. ICBT patients also improved more on impact on daily activities, indicating that patients who received ICBT felt significantly less limited by their physical health and emotional problems in performing their work or daily activities than patients who received CAU. In contrast, no significant between-group effects were observed for psychological functioning. This is surprising, considering that patients were screened for elevated levels of distress and that negative mood was a frequently applied treatment module. Despite screening, baseline psychological functioning scores were generally comparable to healthy populations, as many patients scored just above cut-off values, and 22% of the sample that scored above cut-off values at screening did not fulfil these criteria anymore at baseline. As meta-analyses suggest that patients with higher distress scores demonstrate larger CBT effects [64, 65], distress levels may have been too low for patients to benefit sufficiently from ICBT. Low baseline scores were also cited as a reason for the small effects found in a recent meta-analysis on (I)CBT for long-term conditions (i.e. effect sizes of 0.20 - 0.21 for anxiety and depression [66], comparable to an earlier meta-analysis [24]).

Moderate to large ICBT effects were found for primary outcomes and their subcomponents, which were comparable to similar tailored face-to-face CBT interventions [41, 67]. However, between-group effect sizes were small, which was explained by larger than expected CAU effects. This may also explain why significant effects for physical functioning were found for fatigue but not for itch: post-treatment ICBT effect sizes were similar for itch and fatigue, while CAU effects were moderate for itch and small to non-

existent for fatigue. As high standards of care are generally associated with greater CAU effects on physical and psychological outcomes [68], the fact that 42% of patients were recruited from a university medical center might have played a role in these findings. The timing of participant recruitment may have also contributed; patients were often recruited when starting dermatological treatment and many patients reported changes in systemic medication during the trial. In future research, differential screening procedures may decrease these confounding effects and possibly optimize treatment effects by screening patients who experience elevated distress levels despite being on a stable dermatological regimen, for example.

A better therapeutic relationship (working alliance) measured early in treatment showed moderate to large correlations with improvements in physical and psychological outcomes, supporting the relevance of the therapeutic relationship in ICBT. These findings are in line with evidence in face-to-face CBT [69–71] and expand upon scarce evidence from studies on internet-based interventions [38, 72–75]. Associations of early working alliance scores with treatment outcome were somewhat higher than those observed in previous studies, possibly because the therapeutic relationship is of greater importance in highly personalized interventions. Treatment outcomes were not associated with the number of logins or treatment length, partially corresponding with previous conflicting evidence [39, 76, 77]. While logins and treatment length have advantages in being objective measures, they may not adequately reflect interaction with treatment content and user experiences.

The characteristics of this study differed in some important ways from many previously conducted ICBT studies. ICBT was compared to CAU in a clinical sample, including a 6-month follow-up, while most ICBT studies have typically included community-based and self-referred samples, waiting-list comparisons, and post-treatment data only [for a summary, see 24]. While significant effects were found in this trial, the effects were typically small and were not all found in secondary analyses that did not include prespecified covariates. Consistent with our findings, recent meta-analytic evidence shows that the effects of ICBT are typically smaller in studies with a CAU than a waiting-list comparison and in clinical samples than in community-based samples, and the effects are often non-significant on the rare occasion that long-term follow-up results are meta-analyzed [78–80]. This underlines the need for further in-depth research regarding the influence of methodological, sample, and intervention characteristics on trial results.

Both the limitations and strengths of the present study have to be considered. Firstly, similar to previous studies [for a summary, see 24], a substantial proportion of patients did not complete ICBT and/or failed to return questionnaires. In line with previous evidence, attrition rates were higher in ICBT than in CAU [81]. While dropout rates were somewhat lower than in a study of non- tailored ICBT for psoriasis [26], the fact that they were generally comparable to previous studies does not support the often-cited

idea that tailored interventions are associated with lower dropout rates. However, the majority of dropouts were non-starters and therefore not exposed to treatment content. Furthermore, the relatively long ICBT duration, i.e. a mean duration of 25 weeks compared to 8 weeks in many other interventions [24], may have increased dropout rates, which often increase progressively with intervention duration [82]. Lower baseline disease severity was associated with higher ICBT dropout, possibly because these patients experienced a lower disease burden and were therefore less motivated to adhere to a program aimed to decrease the impact of psoriasis on daily life. The main strengths of the current study include the application of a unique individually tailored and therapist-guided intervention in a target population that is generally underserved when it comes to psychological support. Methodological strengths include the multicenter RCT design comparing ICBT to CAU in a clinical sample, including a 6-month follow-up.

To conclude, individually tailored, therapist-guided ICBT led to significantly greater improvements compared to CAU for physical functioning and impact on daily activities in a clinical sample of patients with a psychological risk profile. The therapeutic relationship showed moderate to large associations with better treatment effects, illustrating the importance of this relationship in guided ICBT. The results of this trial underline the promise of ICBT for dermatological conditions in a clinical setting, which is supported by previous studies in other conditions showing that ICBT interventions can be transferred to clinical practice with sustained effects and moderate to large effect sizes [83]. Future research should focus on the working mechanisms and provide further evidence on how well these interventions translate into clinical practice. Furthermore, future research in additional samples (e.g., higher levels of distress and disease severity) should extend these findings to be able to draw robust conclusions on the effectiveness of individually tailored, therapist-guided psychological interventions for dermatological conditions.

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SUPPLEMENTARY METHODS AND RESULTS

1. Outcome measures

Primary outcome measures

The primary outcome of this study was the impact of psoriasis on daily life, measured on three domains, for which total (composite) scores were computed by taking the overall average of standardized (z-)scores of the questionnaires included in each domain. All questionnaires were administered in paper-and-pencil format.

Psychological functioning

Psychological functioning was assessed with a total score of three previously validated measures: the Negative Mood (6 items, Cronbach's α = .88 in the current study) and Anxiety (ten items, α = .79) scales of the ISDL [40], and the total score of the revised version of the Beck Depression Inventory [BDI-II; 46, 47] (21 items; α = .85). Higher scores reflect greater levels of negative mood, anxiety, and depressive symptoms, respectively. Higher total scores reflect worse psychological functioning.

Physical functioning

Physical functioning was assessed with a total score of two frequently reported symptoms in psoriasis: fatigue and itch. Fatigue was assessed with the 8-item fatigue subscale of the Checklist Individual Strength [CIS; 48], with higher scores reflecting higher levels of fatigue (α = .92). Intensity and duration of itch was assessed with a 4-item subscale of the ISDL [40], with higher scores reflecting greater itch intensity and duration (α = .81). Higher total scores reflect lower physical functioning.

Impact on daily activities

Impact on daily activities was assessed with a total score of two subscales of the previously validated RAND-36 Health Status Inventory [49, 50], assessing the extent of role limitations due to physical health problems (four items, α = .88) and role limitations due to emotional problems (three items, α = .81), with higher scores reflecting fewer role limitations in each of the two domains. Higher total scores reflect lower impact on daily activities.

Secondary outcome measures: disease severity and compliance

Patient-rated disease severity was assessed with the widely used and validated Self-Administered Psoriasis Area and Severity Index (SAPASI; [52]), consisting of silhouettes of the front and back of a body on which patients can mark their affected body areas, as well as three visual analogue scales to assess the erythema, induration, and scaliness

of the average lesion. Scores on the SAPASI can range from 0 to 72, with higher scores indicating more severe psoriasis.

Clinician-rated disease severity was assessed with the Psoriasis Area and Severity Index (PASI), in which a clinician (i.e. a dermatology research nurse) assigned a numerical value of 0 to 6 to the area of involvement for four body regions, and rated erythema, desquamation, and induration of the plaques for each region on 5-point scale, with higher overall scores (range 0 - 72) signifying greater disease severity [51].

Dermatological treatment compliance was assessed with a 5-item questionnaire (α = .94), asking how often patients adhered to treatment prescriptions/recommendations regarding hormone ointments, other ointments, medications, other professional care, and other prescriptions/recommendations. Each question could be answered on a scale from 1 to 5, ranging from less than once a week to seven days a week, or could be answered as 'not applicable'. Total scores were constructed by calculating the mean of applicable items, with higher scores indicating greater compliance.

ICBT treatment satisfaction

Patients' satisfaction with the ICBT intervention, and their evaluation of its user-friendliness, was rated on a 10-point scale with higher scores reflecting higher satisfaction and greater user-friendliness. Patients were also asked to rate to which degree they though the intervention would have a sustained positive effect and whether they would recommend the intervention to a friend or family member with a chronic somatic condition, on a four-point scale ranging from 'no' to 'certainly'.

Sociodemographic and disease-related predictors of treatment outcome

Sociodemographic variables were assessed with a general checklist assessing patients' gender, age, educational level, and marital status. Disease severity was assessed with the SAPASI [52] and PASI [51] described above. Disease duration was assessed with an item asking how old the patient was when the psoriasis diagnosis was given, which was then subtracted from the age of the patient.

Treatment-related predictors and correlates of treatment outcome

The working alliance between patient and ICBT therapist (i.e. the mutual agreement on the goals and tasks of a therapeutic intervention, in the context of a positive affective bond [55]) was assessed at the beginning of treatment (after face-to-face intakes, but before starting the internet-based treatment) by the client version of the 12-item (short version) Working Alliance Inventory [WAI-S; 53, 54], using the overall alliance score. Treatment duration was defined as the number of weeks patients spent on ICBT treatment, excluding mutually agreed upon weeks of non-activity (e.g., vacation). Adherence to ICBT was assessed from three perspectives: 1) patient evaluation of their own

adherence, 2) therapist rating of patient's adherence, and 3) intervention website usage. Patient-rated adherence was assessed at post-treatment with the following four items: "During treatment, I have fully completed all assignments", "During treatment, I have worked intensively on my treatment goals", "During treatment, I have often practiced and applied what I have learned in daily life", and "During treatment, the internet-based treatment was a regular part of my daily life". Therapist-rated adherence was based on the same 4 items, in which the therapist rated the patient on these items. Both ratings were found to be reliable (patient rating: $\alpha = .67$; therapist rating: $\alpha = .94$). Intervention website usage was defined as the total number of website logins during treatment and average number of logins per week, assessed by monitoring https-server requests.

2. Data analysis: normal distribution

All continuous variables were checked for normality (skewness and kurtosis < 1.5) and adjusted if necessary and possible. A skewed distribution on the physical role limitations rank score was observed at baseline. As data transformations did not lead to significant improvements, unadjusted scores were used for analyses. SAPASI and PASI scores showed substantial skewness and kurtosis, which was corrected for by square root transformation and replacing two (PASI) or four (SAPASI) outlying cases with the next highest scores (skewness and kurtosis < 1.5 after transformation) [59].

3. ICBT intervention, dropout, and sensitivity analysis

ICBT modules

An overview of the frequency of the ICBT treatment modules that were applied is presented in Table S1. The modules negative mood (58%), itch (51%), and fatigue (45%) were applied most often, while the modules pain (11%) and social relationships (17%) were applied in a minority of cases. The majority of patients ($n = 30$; 55%) worked on two treatment modules during treatment, while 16 patients worked on one module (29%) and 8 patients (15%) worked on three modules.

Table S1. Internet-based cognitive behavioral treatment: overview of treatment modules, in patients who started treatment (n = 55)

	Treatment module				
	Negative mood	**Fatigue**	**Itch**	**Pain**	**Social relationships**
Primary module[a]	17 (31%)	14 (25%)	16 (29%)	4 (7%)	2 (4%)
Secondary module[b]	14 (25%)	11 (20%)	10 (18%)	1 (2%)	2 (4%)
Tertiary module[c]	1 (2%)	0 (0%)	2 (4%)	1 (2%)	5 (9%)
Not applied	23 (42%)	30 (55%)	27 (49%)	49 (89%)	46 (83%)

Note. n = 1 patient started ICBT but dropped out after the first few messages, prior to commencing any modules. [a] Module that patients have worked on for the longest time, compared to the other modules, [b] Module that patients have worked on for a shorter amount of time than the primary module, [c] Module that patients have worked on for a shorter amount of time than the secondary module.

ICBT therapists

Therapist guidance in ICBT was given by a total of six female therapists (mean age = 29.67 ± 8.76), all having at least a Master's degree in Clinical and/or Health Psychology, with previous therapist experience ranging from 0 to 7 years (mean = 2.17 ± 2.79). Three therapists had finished further postgraduate training as healthcare psychologists (i.e. 'GZ psychologists'). All therapists were supervised by a senior clinical psychologist with post-academic training in cognitive behavioral treatment.

ICBT duration

Mean intervention duration (excluding non-starters) was 25 weeks (± 12 weeks), ranging from 1-57 weeks. During the intervention, a period of ≥ 4 weeks of no contact with the therapist was observed in 20% of patients (n = 13) and ICBT treatment was temporarily put on hold due to personal circumstances in 34% of patients (n = 22). ICBT duration was calculated excluding the mutually agreed upon weeks of inactivity.

ICBT dropout

Overall intervention dropout was 26.2%, consisting of ten non-starters (15.4%) and seven dropouts (10.8%). The ten non-starters did not start treatment for various reasons: personal or familial circumstances (n = 3), lack of time (n = 2), physical comorbidity (n = 1), psychological comorbidity (n = 1), not wanting to come for intake sessions (n = 1), lack of computer skills (n = 1), or unknown reasons (n = 1). The 6 non-completers reported the following reasons: alleviated symptoms/complaints (n = 1), deteriorated symptoms (n = 1), personal or familial circumstances (n = 1), physical/psychological comorbidity (n = 1), lack of computer skills (n = 1) or unknown reasons (n = 1). Lastly, one of the dropouts was a patient who died during the treatment as a result of comorbidity unrelated to the treatment.

Differences between completers and dropouts

Intervention completers had higher baseline self-reported disease severity (p = .03) than non-starters/non-completers. Measurement completers were significantly older (p = .04) and showed a tendency towards a greater impact of psoriasis on daily activities (p = .09) than measurement dropouts.

ICBT completers: Sensitivity analysis

In sensitivity analyses excluding ICBT dropouts/non-starters (n = 16), tendencies towards larger effects in ICBT compared to CAU were found for the primary outcomes physical functioning (p = .051) and impact on daily activities (p = .097). In subcomponents of these primary outcomes, significant between-group effects were found for fatigue (p = .04) and trends on role limitations due to physical (p = .06) and emotional (p = .09) health problems.

CHAPTER 7

Economic evaluation of a tailored therapist-guided internet-based cognitive behavioral treatment (ICBT) for patients with psoriasis: a randomized controlled trial

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ABSTRACT

Objective: Internet-based cognitive behavioral treatment (ICBT) has shown to be (cost-) effective for patients with chronic somatic conditions. However, ICBT (cost-)effectiveness studies in psoriasis, a chronic inflammatory skin disease associated with impaired physical and psychological functioning, are lacking. In this study, the cost-effectiveness of individually-tailored therapist-guided ICBT was examined in patients with psoriasis.

Methods: An economic evaluation from a societal perspective was performed alongside a randomized controlled trial (Trial Registry Number NTR2436). Patients who were screened for a psychological risk profile were randomized to regular dermatological care (CAU; $n = 66$) or ICBT added to CAU ($n = 65$). Outcomes were assessed up to 6 months post-treatment and included patient utilities, healthcare costs, productivity losses, and incremental costs per quality-adjusted life year (QALY) gained. Cost-effectiveness was analyzed in bootstrapped samples using 1) incremental cost-effectiveness ratios (ICERs) and 2) incremental net monetary benefit (INMB) analyses correcting for baseline values and confounders.

Results: No significant between-group differences were found in QALYs and costs at post-treatment and 6-months follow-up in ICER and INMB analyses. However, in post-hoc subgroup analyses, ICBT was found to be cost-effective specifically for patients with: 1) higher self-assessed disease severity (60% of ICERs in dominant quadrant; 78% chance of being cost-effective at a willingness to pay [WTP] of €20,000), and 2) higher self-perceived impact of psoriasis on daily life (78% of ICERs in dominant quadrant; 95% chance of cost-effectiveness at WTP of €20,000).

Conclusion: Offering ICBT to psoriasis patients was only cost-effective for patients with relatively high self-assessed disease severity and patients who experience a relatively high self-perceived impact of psoriasis on daily life. These results suggest that it is clinically relevant to screen for these characteristics prior to ICBT, in order to offer cost-effective care.

INTRODUCTION

Psoriasis is a common immune-mediated chronic inflammatory condition in which patients experience scaly skin lesions that may itch or bleed [1]. The lifelong care associated with having psoriasis leads to substantial societal costs, including ongoing direct costs of medication and health care use, but also substantial indirect costs including productivity losses [e.g., 2-5]. Furthermore, impairments in health-related quality of life (HRQoL) in patients with psoriasis have been found to be comparable to other chronic diseases such as cardiovascular diseases, cancer, and diabetes [6]. The high prevalence (approximately 2-3% of the population) and the substantial physical, psychological, and economic burden of psoriasis emphasizes the need for (cost-)effective treatment options [7–9]. Growing evidence suggests that psychological interventions should be part of these treatment options and may decrease physical and psychological symptoms in chronic skin conditions [e.g., 10–12].

Scarce previous studies have shown that interventions based on cognitive behavioral therapy (CBT) can be effective in reducing physical and psychological symptoms in patients with chronic skin conditions [10–12]. The central idea behind CBT is that the way people make sense of the world affects their feelings and behavior. In this relatively short-term and goal-oriented treatment form, cognitive distortions and dysfunctional beliefs are challenged in order to improve psychological complaints [13]. In order to improve access to care and potentially enhance its cost-effectiveness, CBT interventions are increasingly being offered online: internet-based CBT (ICBT). Systematic reviews have demonstrated the effectiveness of ICBT in other patient samples [e.g., 14–16] and evidence on ICBT cost-effectiveness is accumulating [17–21], even though studies in patients with dermatological conditions are lacking. Thus far, only one study has examined the effectiveness of unguided ICBT in patients with psoriasis, and demonstrated that this intervention was able to improve anxiety and quality of life [22]. The effectiveness of therapist-guided ICBT for patients with psoriasis has thus far only been examined in our recent randomized controlled trial (RCT), which demonstrated significant improvements in physical functioning and decreased disease impact on daily activities, as compared to regular dermatological care [23].

Regarding cost-effectiveness, two studies have provided preliminary support for the idea that distance-delivered psychological interventions may decrease costs in patients with skin conditions: adding internet-based or phone-based self-management to regular dermatological care had similar effects and decreased societal costs compared to regular care alone in patients with psoriasis [24] and atopic dermatitis [25]. Therapist guidance may be an important factor influencing cost-effectiveness, as a recent systematic review showed that particularly guided internet-based interventions were more cost-effective than a variety of comparison conditions, including care as usual, face-to-face CBT, telephone counseling, and unguided ICBT [26]. However, no studies to date have examined the cost-effectiveness of guided ICBT in patients with psoriasis.

In the current study, the cost-effectiveness of an individually-tailored, therapist-guided ICBT intervention is examined. In a multicenter randomized controlled trial (RCT), this intervention has been shown to significantly improve physical functioning and decrease disease impact on daily activities as compared to regular dermatological care [23]. However, it remains unknown to what extent these clinical benefits outweigh the costs from a societal perspective. Therefore, an economic evaluation was performed alongside the RCT, with the hypothesis that ICBT in addition to regular dermatological care is cost-effective from a societal perspective.

MATERIALS AND METHODS

Design

This economic evaluation from a societal perspective was conducted alongside an open-label parallel-group randomized controlled trial (RCT; allocation ratio: 1:1) examining the effects of an Internet-based cognitive behavioral treatment offered in addition to care as usual (ICBT+CAU; intervention group) as compared to care as usual alone (CAU, consisting of regular dermatological care; control group). The methodological details of the study have been described elsewhere [23] and will be briefly summarized here. The study was approved by the regional medical ethics committee (i.e. Commissie Mensgebonden Onderzoek regio Arnhem – Nijmegen) and registered in the Dutch Trial Registry (NTR2436). The study was conducted in accordance with the Declaration of Helsinki [27] and all participants gave written informed consent before entering the study.

Participants

Study participants were patients with psoriasis recruited through four outpatient dermatology departments and through the Dutch Psoriasis Association. Inclusion criteria were a diagnosis of psoriasis, age ≥ 18 years, and a positive psychological risk profile (i.e. Impact of chronic Skin Disease on Daily Life (ISDL) score of ≥ 5 for anxiety and/or ≥ 21 for negative mood [23, 28]). Exclusion criteria were psychological and/or physical comorbidity interfering with the study protocol, current psychological treatment, current photo(chemo) therapy, pregnancy, lack of access to a computer and/or internet, and illiteracy.

ICBT intervention

Patients randomized to the intervention condition participated in individually-tailored, therapist-guided ICBT aimed at reducing the impact of psoriasis on daily life. The intervention consisted of five flexible treatment modules focused on the following themes: itch, pain, fatigue, negative mood, and social relationships. Participants started with two face-to-face intake sessions with a psychologist, in which individual treatment goals

were mutually determined. Choice of treatment modules and individual assignments within these modules were determined based on treatment goals, therapist judgment, and screening procedures. Patients received personalized written feedback on their assignments from their therapist, approximately once a week. Intervention duration and content varied between participants, depending on treatment goals, with a mean duration of 25 weeks (± 12 weeks, range = 1-57 weeks). For more details regarding intervention content, see our paper on the effectiveness of this intervention [23].

Outcomes

To assess cost-effectiveness from a societal perspective, the below mentioned measures of costs and effects were administered at baseline, post-treatment (ICBT: end of treatment, CAU: 6 months after baseline), and 6 months post-treatment (ICBT: 6 months after end of treatment, CAU: 12 months after baseline).

Utilities and quality-adjusted life years

Quality of life from a health perspective was measured by the EuroQol questionnaire [EQ-5D-3L; 29]. This generic self-report questionnaire consists of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents rate their state of health on each of these domains on one of three levels (no problems = 1; some problems = 2; extreme problems = 3). Based on this questionnaire, utility scores were calculated, using the Dutch tariff, as a preference-based measure of quality of life anchored at 0 (death) and 1 (perfect health) [30]. Quality-Adjusted Life Years (QALYs) area under the curve was calculated using the trapezium rule [31]. In order to examine the percentage of participants who reached a stable clinically significant improvement in health-related quality of life, the difference between pre-treatment scores and the mean of post-treatment and 6 months follow-up scores on the EQ-5D utility values were calculated. The cut-off score for minimal clinically important difference (MCID) was set at 0.05, based on a recent systematic review on use of quality of life instruments in RCTs of psoriasis [32].

Cost evaluation

Societal costs included in this study were 1) healthcare sector costs (i.e. self-reported healthcare and medication use), 2) patient travel costs for healthcare use, 3) costs associated with loss of productivity in paid self-reported labour (i.e. absenteeism and presenteeism), and 4) ICBT intervention costs.

Healthcare costs were calculated based on the Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness (TIC-P) [33] and included psoriasis-related healthcare use (i.e. care provided by dermatologists and dermatology nurses), care by the general practitioner and company doctor, psychological/psychosocial care (e.g.,

care provided by a psychologist, psychiatrist, or social worker), and care provided by alternative medicine practitioners. Healthcare use costs were calculated by multiplying the healthcare use with unit prices that were estimated based on the TIC-P [33] and the Dutch manual for cost analysis in healthcare [34].

Medication costs were calculated by multiplying the daily defined doses by the prices for medication retrieved from the Dutch national tariff list (www.medicijnkosten.nl). Taken into account were dermatological treatment-related systemic medication and medication prescribed for psychological conditions. Costs of topical treatments were excluded, as reliable information on topical treatment use could not be obtained based on the included self-report questionnaires. Furthermore, as these costs are much lower than other (systemic) medication costs, topical treatments were not the expected cost drivers in this study.

Patient travel costs for healthcare use were calculated by multiplying a price of €0,19 per kilometre with the average distance in kilometres from the patients' houses to the reported healthcare facilities used (i.e. hospitals, GPs, pharmacies), in accordance with general guidelines from the Dutch manual for cost analysis in healthcare [34].

Loss of productivity costs (i.e. absenteeism and presenteeism) were calculated using the friction cost method, and were based on modules of the PROductivity and Disease Questionnaire [PRODISQ; 35]. Productivity costs were calculated by multiplying the overall average costs of productivity loss per hour [i.e. €34.97; 34] by the amount of hours that patients were absent or experienced a suboptimal work performance because of their illness.

ICBT intervention costs were calculated based on 1) IT costs for intervention development, hosting, and technical support, 2) ICBT therapist salary costs, based on time spent on intake sessions and online/telephone guidance of participants, 3) patient travelling expenses for face-to-face intake sessions, and 4) salary costs of a research assistant for an instruction session of the intervention website by telephone. As having a computer with Internet access was part of the inclusion criteria, costs for computer and internet access were considered sunk costs and were, therefore, not included in the analysis.

In accordance with the Dutch manual for cost analysis in healthcare [34], the time that patients spent on this intervention was assumed to be adequately reflected in estimates of their QoL, and were therefore not monetarily rated, to prevent double counting. It was estimated that 30% of the population of psoriasis patients would be eligible for the ICBT treatment and 10% of these patients would be reached. Therefore, costs of ICBT use per patient were calculated by dividing the total intervention costs by the number of patients corresponding to this 10% that would be treated using the ICBT intervention. For intervention development costs, an amortization period of 5 years was assumed. All costs were updated to 2015 by applying Dutch price indices when needed. Missing data on costs and effects were imputed using the last-observation-carried-forward (LOCF) method to correct for possibly selective non-response.

Statistical analysis

Between-group differences in costs at baseline and follow-up were calculated using independent-samples t-tests based on bootstrapped samples (1000 replications), as a non-parametric way to incorporate uncertainty. Cost-effectiveness results were analyzed according to intention-to-treat principles and were also based on bootstrapped samples. Differences in costs and QALYs between ICBT and CAU were analyzed for the study period of 12 months. An incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in costs between ICBT and CAU by the difference in their effects (i.e. QALYs).

As correcting for confounders was not possible in the analysis based on ICERs the net monetary benefit (NMB) was used as a dependent variable in regression analyses. In these analyses we examined the influence of 1) potential differences in baseline costs and 2) potential confounders. Corresponding with the analytic strategy of the previous RCT, the baseline dependent variable and the confounders age, sex, educational level, work status, recruitment site, self-reported systemic antipsoriatic medication use, and self-assessed (Self-Administered Psoriasis Area and Severity Index [SAPASI; 36]) and clinician-assessed disease severity (Psoriasis Area and Severity Index [PASI; 37]) were included as covariates [23]. When needed, covariates were log-transformed and winsorized in order to reduce the influence of outliers and reach a normal distribution (i.e. for baseline costs and self-assessed and clinician-assessed disease severity). The confounder work status, operationalized as currently having a paid job (0 = no, 1 = yes), was added in this study due to its specific relevance for costs of productivity losses. NMB was calculated as follows: NBM = (WTP x Effects) – Costs, where WTP is short for willingness to pay (in Euros). Incremental NBM (INBM) can be defined as the difference between two NBMs and a positive INBM in this study can be interpreted as the added value in Euros of the ICBT intervention versus CAU. Results were based on a general linear model that was bootstrapped 1000 times.

In case no main cost-effectiveness would be shown, post-hoc secondary analyses would be conducted by conducting the ICER-based analyses described above separately for high and low-scorers on clinically relevant constructs, in order to examine whether the intervention was cost-effective specifically for clinically relevant subgroups. In our previous publication reporting the effectiveness of this intervention [23], patients in this sample were shown to have relatively low levels of disease severity and psychological distress. Resultantly, we hypothesized that results may be more pronounced when patients had experienced a greater disease burden, corresponding with the overall goal of the intervention to reduce the impact of psoriasis on daily life (e.g., greater disease severity, higher levels of distress, larger impact of the condition on daily life). Therefore, we explored this idea further in the current study in four post-hoc subgroup analyses. Subgroups were constructed by applying a median split on baseline values, resulting in a group of high-scorers versus low-scorers on the following constructs: 1) self-assessed

disease severity [SAPASI; 36]; 2) clinician-assessed disease severity [PASI; 37]; 3) psychological distress (Impact of chronic Skin disease on Daily Life [ISDL] composite z-score of anxiety and negative mood subscales [ISDL; 28]), in line with screening of the psychological risk profile in the RCT; and 4) self-perceived impact of psoriasis on daily life [ISDL; 28]. For measurement details, see [23, 38].

RESULTS

Sample characteristics

Baseline sociodemographic and disease-related characteristics of the study sample, consisting of 131 participants, can be found in Table 1, and a flow diagram of study participants is presented in Figure 1. Sociodemographic and disease-related characteristics did not significantly differ between the intervention and control group ($p \geq .10$), with the exception of a higher clinician-rated disease severity in the intervention group ($p = .03$) and a trend indicating that patients in the intervention group used systemic antipsoriatic medication more often ($p = .07$). A small number of patients reported a co-morbid psoriatic arthritis diagnosis (ICBT: $n = 11$; CAU: $n = 5$, $p = .12$); this number was too small to compare cost-effectiveness outcomes for patients with and without this diagnosis.

Table 1. Baseline characteristics of internet-based cognitive behavioral treatment plus care as usual (ICBT+CAU) and care as usual (CAU) groups

Characteristic	ICBT+CAU ($n = 65$)[a]	CAU ($n = 66$)[a]
Gender (male)	33 (50.8)	34 (51.5)
Age (years)	52.69 ± 11.27 (24-73)	53.45 ± 13.81 (19-79)
Married/ living together	46 (70.8)	53 (80.3)
Educational level		
Primary	1 (1.5)	4 (6.1)
Secondary	44 (67.7)	43 (65.2)
Tertiary	20 (30.8)	19 (28.8)
Work status		
Employed (paid job)	35 (53.8%)	26 (48.5%)
Unemployed	25 (38.5%)	32 (39.4%)
Missing	5 (7.7%)	8 (12.1%)
Disease duration (years)	18.03 ± 13.76 (0-59)[b]	15.16 ± 16.35 (0-65)[b]
Disease severity (PASI)	5.99 ± 5.61(1-31)[b]	4.20 ± 2.87(0-13)[b]
Disease severity (SAPASI)	5.27 ± 3.29 (1-19)[b]	4.48 ± 2.41 (0-12)[b]
Systemic treatment[c]	25 (44.6)[b]	17 (29.3)[b]
HRQoL utility (EQ-5D)	0.75 (0.21)[b]	0.76 (0.20)[b]

Note. CAU = care as usual; EQ-5D = European Quality of Life-5 Dimensions Questionnaire; HRQoL = health-related quality of life; ICBT = internet-based cognitive behavioral treatment; PASI = Psoriasis Area Severity Index; SAPASI = Self-assessed PASI. [a]mean ± SD (range) or *n* (%), [b]*n* = 2-12 missings, [c]number of patients reporting use of systemic antipsoriatic medication.

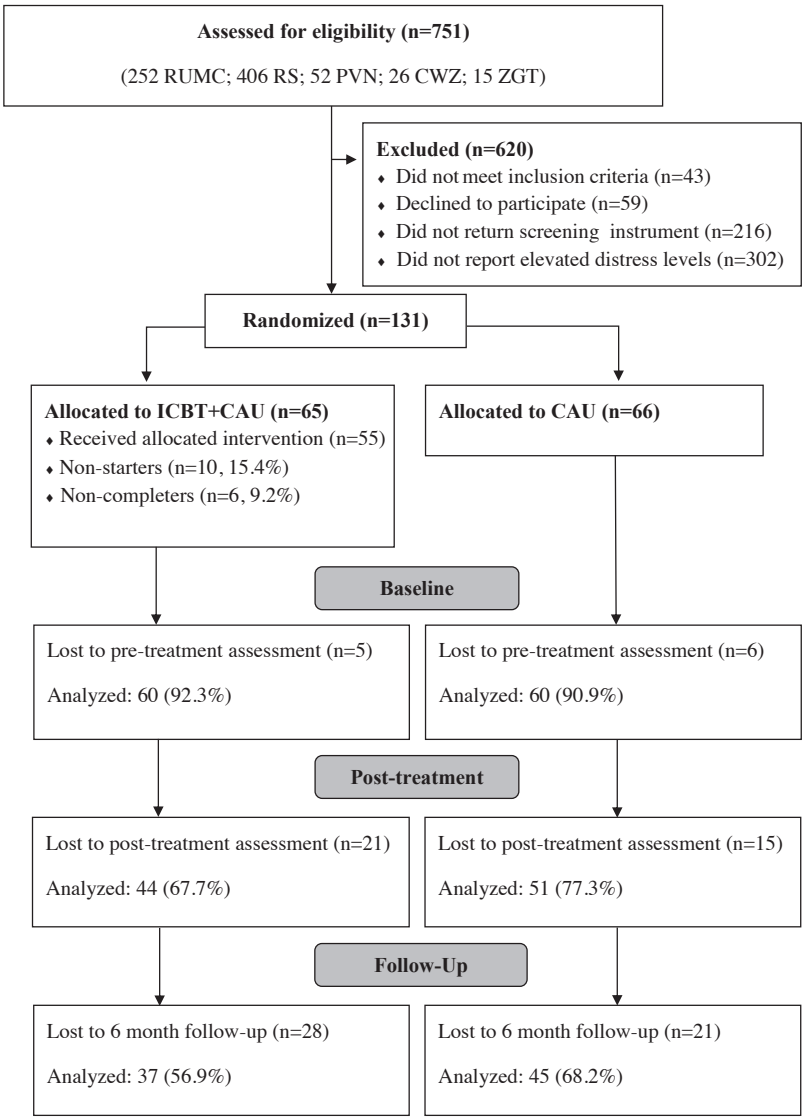

Figure. 1. CONSORT flow diagram of study participants. CWZ = Canisius-Wilhelmina Hospital, Nijmegen; PVN = Dutch Psoriasis Association; RS = Rijnstate Hospital, Velp; RUMC = Radboud university medical center, Nijmegen; ZGT = Ziekenhuis Groep Twente, Almelo.

Cost-effectiveness

At baseline, patients reported an average EQ-5D utility score of 0.75 (SD = 0.20); this value did not differ between groups (p = .58). A clinically significant improvement on the EQ-5D (i.e. MCID ≥ 0.05) was observed in 20 out of 59 intervention participants (33.9%)

and in 16 out of 60 control group participants (26.7%); this percentage did not differ between groups ($\chi^2(1) = 0.74$, $p = .39$). Baseline societal costs in the intervention group were €3,984 (SD = €5,824) compared to €2,843 (SD = €4,506) in the control group, which did not significantly differ between groups ($p = .22$). Mean costs in the intervention and control groups, based on the 6-months follow-up period (i.e. post-treatment and 6 month follow-up measurements), are presented in Table 2. None of these costs (i.e. for healthcare use, medication use, patient travel, absenteeism, presenteeism, and total costs) differed between the two groups ($p \geq .16$).

Table 2. Mean (±SD) costs in Euros for the internet-based cognitive behavioral treatment plus care as usual (ICBT+CAU) and care as usual (CAU) groups, based on the six months follow-up period, indexed to the year 2015

Cost category	ICBT+CAU	CAU
Health care use	€1,032 (1525)	€1,431 (2405)
Medication use	€1,409 (3958)	€1,109 (3917)
Patient travel costs	€237 (265)	€252 (382)
Absenteeism	€1,279 (3799)	€906 (2952)
Presenteeism	€2,251 (7225)	€1,731 (4748)
ICBT intervention	€497	*n.a.*

Note. CAU = care as usual; ICBT = internet-based cognitive behavioral treatment, *n.a.* = not applicable.

ICER analysis

Results from the 1000 bootstrapped replications of mean QALYs and total costs for the 12-month study period are presented in Table 3. In a base case analysis, no differences between groups were found on effectiveness (mean QALY difference = -0.014; 2.5 to 97.5 percentile = -0.062 to 0.038) or costs from a societal perspective (mean difference = €1,295; 2.5 to 97.5 percentile = -€1,502 to €4,176) at both post-treatment and 6 months follow-up ($p \geq .45$). Figure 2 presents the cost-effectiveness plane containing a scatterplot of the simulated ICERs. The majority of ICERs (58%) appear in the northwest quadrant, suggesting that ICBT+CAU was inferior to CAU alone (i.e. larger societal costs and smaller HRQoL gains in the intervention group). There was a 24% probability that the intervention resulted in greater HRQoL improvements, but at higher societal costs (northeast quadrant). Eleven percent of ICERs were located in the southwest quadrant, indicating reduced societal costs in ICBT+CAU compared to CAU alone, but also inferior gains in HRQoL. Lastly, 7% of the ICERs were located in the southeast quadrant, indicating that ICBT was associated with greater improvements in HRQoL and less societal costs, compared to CAU.

Table 3. Mean QALYs and costs for the internet-based cognitive behavioral treatment plus care as usual (ICBT+CAU) and care as usual (CAU) groups as a result of 1000 bootstrapped replications

	ICBT+CAU		Care As Usual		Δ QALY	Δ Costs
	QALY	costs	QALY	costs		
Average	0.78	€6,641	0.79	€5,346	-0.014	€1,295
2.5 percentile	0.75	€4,849	0.76	€3,604	-0.062	-€1,502
97.5 percentile	0.81	€8,789	0.83	€7,339	0.038	€4,176

Note. CAU = care as usual; ICBT = internet-based cognitive behavioural treatment; QALY = quality adjusted life years.

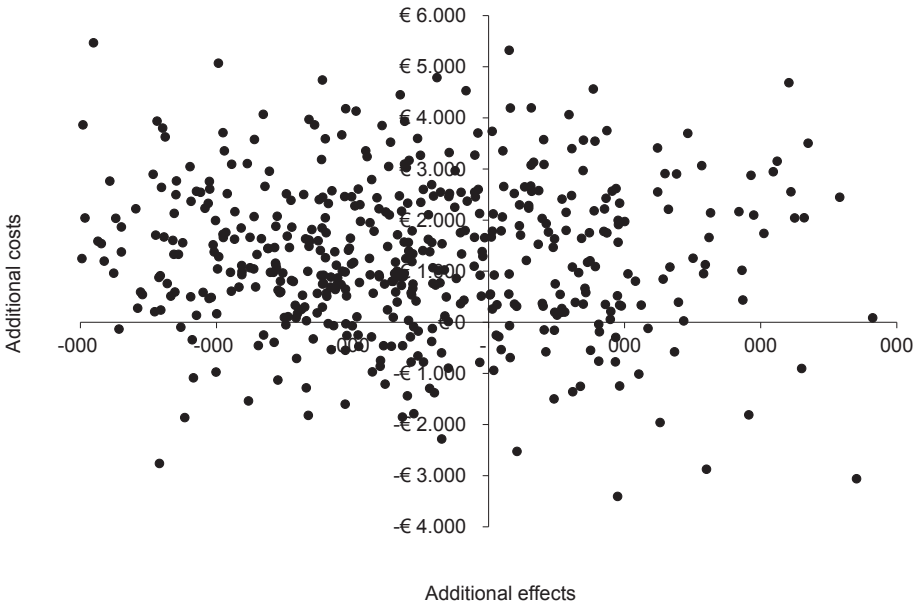

Figure 2. Cost-effectiveness plane: Base case analysis.

INMB analyses: correcting for relevant confounders

In *uncorrected* analyses, the incremental net monetary benefit (INMB) value at a WTP of 0 was -€1,305 (95% CI = -€4,573 to €1,985), indicating non-significantly larger societal costs in the intervention group than in the control group at post-treatment and 6 months follow-up (p = .46). Considering that a statistically non-significant lower improvement on the EQ-5D in the intervention group compared to the control group was found, a WTP acceptability curve would be irrelevant. Therefore, upcoming analyses focused on the INMB at a WTP of 0, thereby essentially analysing between-group differences in costs. When *correcting for baseline costs*, the INMB became positive (€268; 95% CI = -2686 - 3047), which increased when including previously specified confounders (€1,335; 95%

CI = - €2,261 - €4,660); however, group differences remained non-significant (p = .84 and .47, respectively).

Subgroup analyses

Because the intervention group did not show overall cost-effectiveness, subgroup analyses on clinically relevant subgroups were conducted. All subgroups were constructed using median split procedures. Main outcomes concerning costs and QALYs, as well as the percentage of ICERs in the dominant quadrant (i.e. ICBT is associated with lower costs and higher effects than CAU), are presented in Table 4.

Table 4. Results of the base case and subgroup analyses concerning costs and QALYs for the internet-based cognitive behavioral treatment plus care as usual (ICBT+CAU) and care as usual (CAU) groups, and the % of dominant ICERS based on 1000 simulations

		ICBT+CAU		Care as Usual		
Subgroups		Costs	QALY	Costs	QALY	% southeast (dominant)
Self-assessed disease severity (SAPASI)	high	€8,152	0.81	€8,746	0.76	60
	low	€5,181	0.74	€3,308	0.80	0
Clinician-assessed disease severity (PASI)	high	€8,902	0.79	€7,008	0.85	0
	low	€4,619	0.79	€4,515	0.79	28
Distress (ISDL)	high	€8,704	0.75	€3,850	0.76	0
	low	€4,535	0.81	€6,829	0.84	14
Impact of disease on daily life (ISDL)	high	€7,294	0.74	€9,856	0.71	78
	low	€4,935	0.80	€2,948	0.85	0

Note. CAU = care as usual; ICBT = internet-based cognitive behavioural treatment PASI = Psoriasis Area and Severity Index; QALY = quality adjusted life years; SAPASI = Self-Administered PASI.

1. Self-assessed disease severity

Figure 3 presents the cost-effectiveness plane for patients with a) high self-assessed disease severity (i.e. SAPASI ≥ 4.76, n = 56), and b) low self-assessed disease severity (i.e. SAPASI ≥ 4.76, n = 57). In patients with *high SAPASI scores*, the majority of ICERs (i.e. 60%) were located in the southeast (dominant) quadrant. A further 35% of ICERs were located in the northeast quadrant. In contrast, in patients with *low SAPASI scores*, nearly all ICERs (i.e. 98%) were located in the northwest (inferior) quadrant. Figure 4 shows the cost-effectiveness acceptability curve (CEAC) for patients with *high self-assessed disease severity*, which illustrates that, given a WTP of €20,000 per QALY gained, the probability that ICBT is cost-effective compared to CAU is 78%, rising to 92% given a WTP of €80,000.

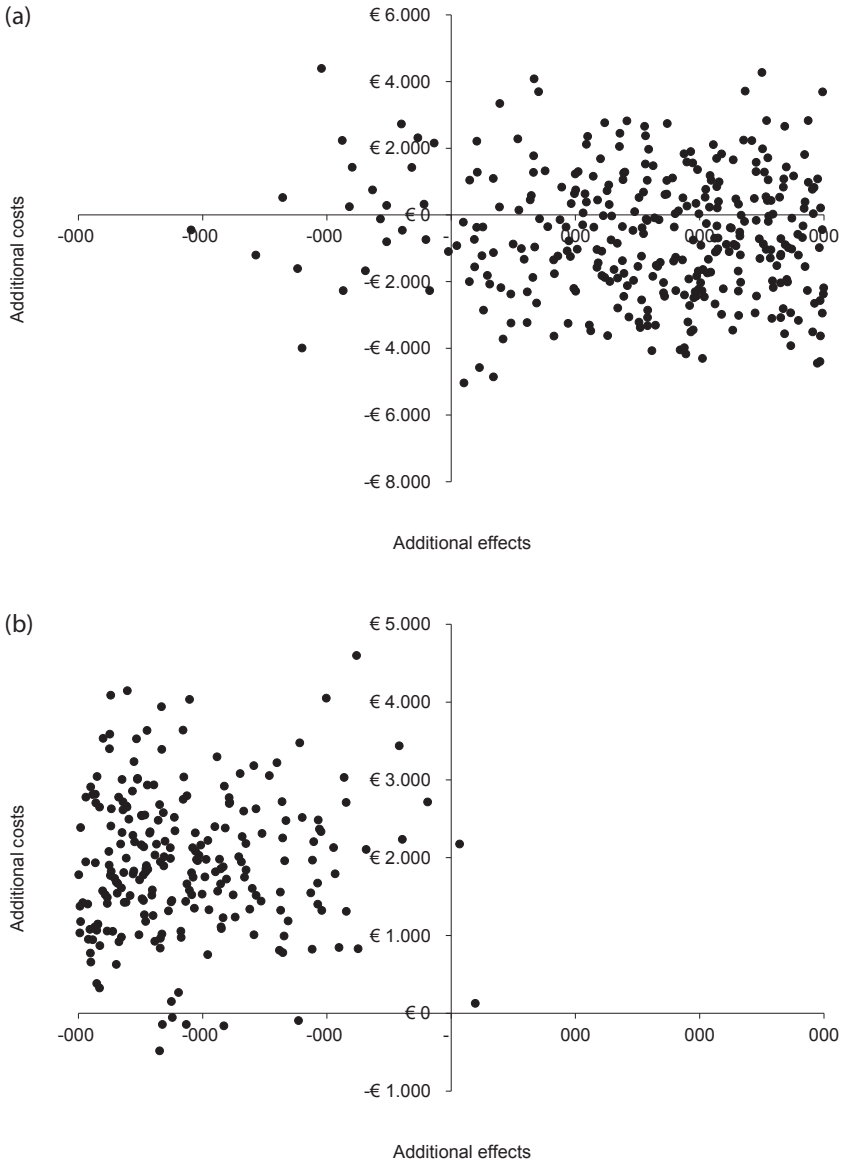

Figure 3. Cost-effectiveness plane subgroups: Self-assessed disease severity (Self-assessed Psoriasis Area and Severity Index). a = high self-assessed disease severity, b = low self-assessed disease severity.

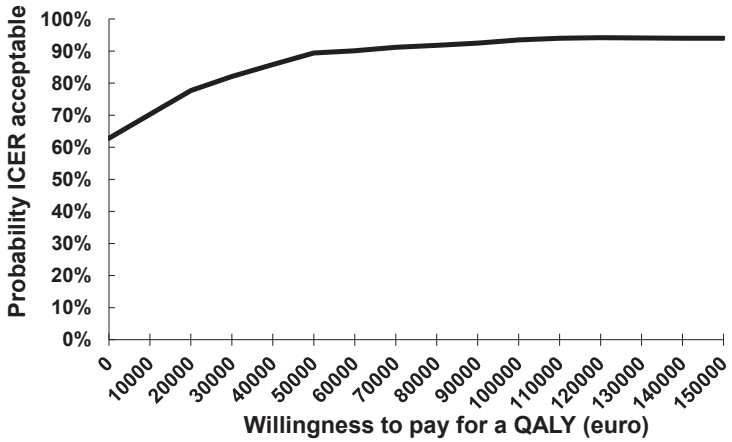

Figure 4. Cost-effectiveness acceptability curve comparing for the internet-based cognitive behavioural treatment in addition to CAU (ICBT+CAU) to care as usual alone (CAU), for patients with high self-assessed disease severity (Self-assessed Psoriasis Area and Severity Index).

2. Clinician-assessed disease severity

Figure S1 presents the cost-effectiveness plane for patients with 1) high clinician-assessed disease severity (i.e. PASI ≥ 3.9, *n* = 53), and 2) low clinician-assessed disease severity (i.e. PASI ≥ 3.9, *n* = 56). In patients with *high clinician-assessed disease severity* (i.e. PASI ≥ 3.9, *n* = 53), ICBT generally resulted in lower costs and lower effects compared to CAU (i.e. 86% of ICERs in northwest inferior quadrant). In patients with *low clinician-assessed disease severity* (i.e. PASI ≥ 3.9, *n* = 56), 31% of ICERs were in the northeast quadrant and 28% of ICERS were in the southeast quadrant. The mean bootstrapped ICER was €21,430 per QALY gained, and given a WTP of €20,000 per QALY gained, the probability that ICBT is cost-effective compared to CAU is 52%, rising to 57% at a WTP of €80,000.

3. Psychological distress

Figure S2 presents the cost-effectiveness plane for patients with a) high psychological distress (i.e. IHDL composite z-score ≥ -.10, *n* = 59, and b) low psychological distress (i.e. IHDL composite z-score ≥ -.10, *n* = 59). In patients with *high psychological distress*, 78% of ICERs were located in the northwest (inferior) quadrant. The remaining 22% of ICERs were located in the northeast quadrant. In patients with *low psychological distress*, most ICERs (i.e. 82%) were in the southwest quadrant. The mean bootstrapped ICER for low psychological distress was €91,278 per QALY gained.

4. Impact of psoriasis on daily life

Figure 5 presents the cost-effectiveness plane for patients with a) high self-perceived impact of psoriasis on daily life (i.e. IHDL impact ≥ 16, *n* = 56), and b) low self-perceived impact of psoriasis on daily life (i.e. IHDL impact ≥ 16, *n* = 59). In patients with *high*

self-perceived impact on daily life, 78% of ICERS were located in the southeast (dominant) quadrant. In patients with *low self-perceived impact on daily life,* 97% of ICERs were in the northwest (inferior) quadrant. Figure 6 shows the CEAC for patients with *high self-perceived impact on daily life*, which illustrates that, at a WTP of €20,000 per QALY gained, the probability that ICBT is cost-effective compared to CAU is 95%, rising to 96% at a WTP of €80,000.

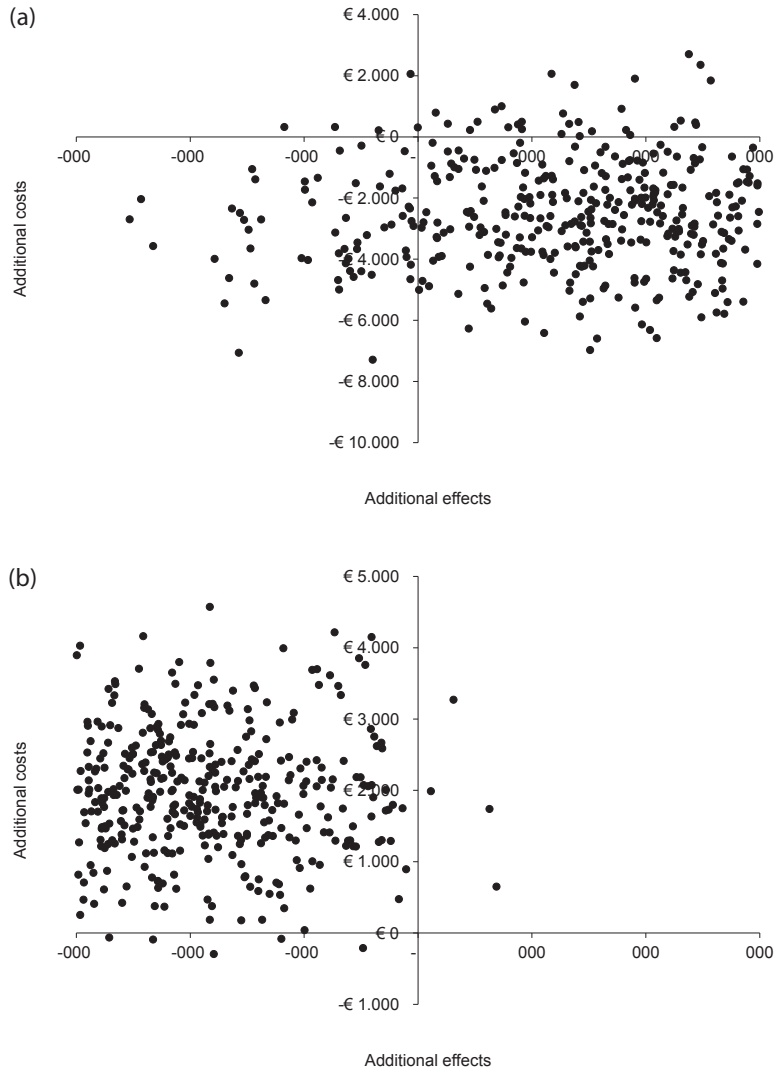

Figure 5. Cost-effectiveness plane subgroups: Impact of psoriasis on daily life (Impact of chronic Skin disease on Daily Life - disease-related impact subscale). a = high impact on daily life, b = low impact on daily life.

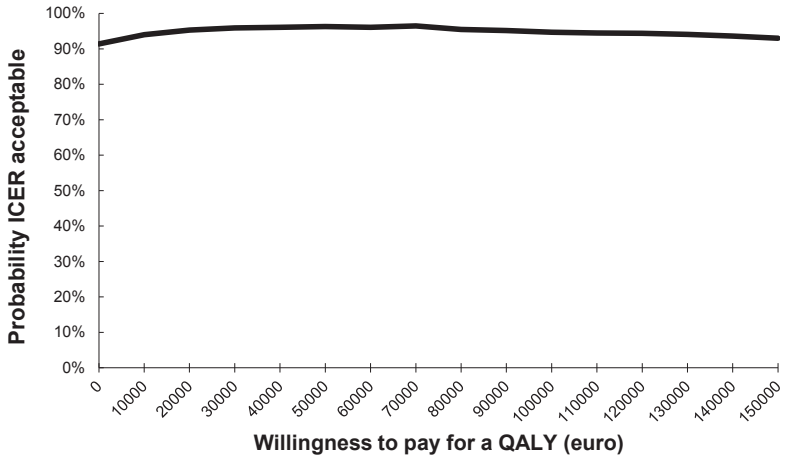

Figure 6. Cost-effectiveness acceptability curve comparing for the internet-based cognitive behavioural treatment in addition to CAU (ICBT+CAU) to care as usual alone (CAU), for patients with high self-perceived impact of the disease on daily life (Impact of chronic Skin disease on Daily Life - disease-related impact subscale).

DISCUSSION

In this study, the cost-effectiveness of individually-tailored therapist-guided ICBT for patients with psoriasis and a psychological risk profile was examined from a societal perspective. Previous RCT results showed that this intervention significantly decreased the impact of psoriasis on daily activities and improved physical functioning [23]. In the current cost-effectiveness analysis, ICBT in addition to CAU was found to have similar effects on HRQoL as CAU alone and led to similar costs to society during a follow-up period of 6 months. Post-hoc subgroup analyses demonstrated that the intervention was cost-effective specifically for patients with higher self-assessed disease severity and higher self-perceived impact of psoriasis on daily life, which suggests that targeting the intervention specifically at those groups may be a cost-effective approach.

The finding that ICBT could not be considered cost-effective in comparison to CAU in the overall sample is not in line with previous cost-effectiveness studies in various conditions [26], nor with preliminary evidence of reduced costs following distance-delivered psychological interventions in patients with chronic skin conditions [24, 25]. These findings may be partly explained by a baseline imbalance in costs and the generic measurement of HRQoL in a dermatological patient sample. First, costs in the ICBT group were already higher than in the CAU group at baseline, although the difference was not

statistically significant. This likely explains why costs at post-treatment and 6-months follow-up were also statistically non-significantly higher in the ICBT condition and suggests that this cost difference may not be attributable to the ICBT intervention. Instead, it may have been related to the fact that patients in the ICBT group had significantly higher disease severity, more often had a paid job (i.e. more possibilities of productivity losses), and were more often using systemic antipsoriatic medication (i.e. higher medical costs), although the last two differences were not statistically significant. In fact, the negative cost difference disappeared when baseline costs were controlled for in INMB analyses, illustrating the confounding effect of baseline costs. Moreover, the generic measure of HRQoL that was used to quantify effects (i.e. EQ-5D) may not have sufficiently captured intervention effects in patients with psoriasis, as it may not be specific enough to detect important aspects of HRQoL in dermatological samples [39, 40]. Furthermore, previous reviews demonstrated that the EQ-5D-3L showed limited responsiveness to change, especially for small to moderate changes in health status, as well as ceiling effects, across a range of conditions [41–44]. A ceiling effect was also observed in this study, with 22% of participants having the highest possible score at baseline, increasing to 28% at post-treatment and 6-month follow-up. Last, responsiveness in patients with psoriasis may be specifically impaired in the upper limits of the EQ-5D [45], which may have caused problems in the current trial in which EQ-5D utility values were on the high end of what is typically observed in psoriasis patients [46].

Subgroup analyses clearly showed that ICBT was cost-effective for two specific patient groups: those with higher self-assessed disease severity and those who experience a larger impact of psoriasis on daily life. ICBT was considered most cost-effective for patients who experienced a relatively high impact of psoriasis on daily life, corresponding with the overall therapeutic goal of the intervention: to reduce the burden of psoriasis in daily life. This may also be a reason why we did not find that ICBT was more cost-effective for patients with higher levels of psychological distress; perhaps its operationalization (i.e. elevated levels of anxiety and negative mood) was too generic to capture the specific impact of psoriasis in daily life. A possible explanation for the fact that we did not find ICBT to be cost-effective for patients with higher clinician-assessed disease severity may be that self-assessed disease severity reflects more subjective components of the disease experience, including not only objective disease severity, but also patient burden. This more subjective disease burden may be more relevant for psychological interventions than objective disease severity, which may explain their differential results. Alternatively, clinician-assessed disease severity may have been less reliable in the current study, as it was not always measured at the same time as other measures (i.e. questionnaires) that were filled out at home for logistic reasons.

The findings that ICBT was considered cost-effective for subgroups of patients with higher levels of self-assessed disease severity and a larger impact of psoriasis on daily

life are highly clinically relevant. They give a clear indication of who might benefit most from this intervention and suggest that offering ICBT specifically to these groups may be the most cost-effective approach. Furthermore, for both subgroups, societal costs in the ICBT+CAU group were actually lower than in the CAU group at post-treatment and 6-months follow-up. This indicates that intervention costs are offset by societal cost reductions, and suggests that even at a willingness to pay of 0, the intervention would most likely be cost-effective for these subgroups. This is a relevant consideration for implementation, as usually new health interventions are associated with increased costs compared with regular care.

To our knowledge, this is the first empirical study reporting on the cost-effectiveness of ICBT in patients with chronic skin conditions. Methodological strengths include the high internal validity by the RCT design, the use of validated outcome measures, and the 6-month follow-up allowing an evaluation of the longer-term cost-effectiveness from a societal perspective. Furthermore, the study was conducted as an open-label trial in outpatient departments of several academic and non-academic hospitals, and was thus a good reflection of daily clinical practice. This is important for the generalizability of cost-effectiveness results. The fact that we were able to show that ICBT was cost-effective for relevant subgroups of this relatively well-treated sample (i.e. low PASI scores) can be considered a strength of the intervention, which further underlines its clinical relevance. Lastly, this cost-effectiveness analysis was one of the few to date that took into account indirect costs (i.e. productivity losses), which increases the generalizability of results. A recent review of health economic analyses of psoriasis showed that only 9 of the 60 included articles took indirect costs into account [47], despite cost-of-illness studies that illustrate the large impact that psoriasis has on occupational disability [48–51].

This study had a number of possible limitations, which give rise to several suggestions for future research. First, costs and QALY estimates were based on a relatively short follow-up of 6 months. A longer duration with more measurements might have led to more accurate estimates and would have increased the ability to capture late effects. Second, despite screening for elevated levels of distress, mean distress and disease severity levels of the study sample were relatively low. This raises the question whether the intervention would have been more (cost-)effective in a different sample. Furthermore, it has important consequences for the interpretation of subgroup analyses, as the majority of patients in the subgroups had at most moderate disease severity and distress levels. Therefore, further studies should be conducted in samples with higher disease severity and distress, and they should also focus on samples screened for relatively high levels of perceived impact of the condition on daily life and self-assessed disease severity, as results of our study suggest that the intervention may be considered cost-effective in these groups. Third, the current study used a non-disease-specific measure (EQ-5D) to calculate QALYs for the cost-effectiveness analysis, which might have been

too generic to assess clinically relevant improvements in dermatology patients and may not adequately measure disease-specific aspects of HRQoL in patients with psoriasis [40]. Therefore, it is recommended that dermatology-specific measurements to reliably assess improvements brought about by psychological interventions are developed to aid future cost-effectiveness research in these groups. Fourth, like most internet-based interventions, the study suffered from a number of missing data, which were handled by applying the conservative LOCF method. Last, like most economic evaluations conducted alongside RCTs, the current study was powered to detect differences in primary outcomes and not differences in costs. Similarly, post-hoc subgroup analyses were based on small samples, and therefore results should be replicated in larger samples.

In conclusion, while the ICBT intervention was not considered cost-effective in comparison to regular dermatological care in the overall study sample, subgroup analyses suggested that it was cost-effective for two specific patient groups: those patients who experience high self-assessed disease severity and those who experience a high impact of the condition in daily life. Considering that these are typical target groups for whom psychological interventions are commonly indicated, screening for these characteristics prior to offering ICBT may be both cost-effective and clinically relevant.

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SUPPORTING INFORMATION

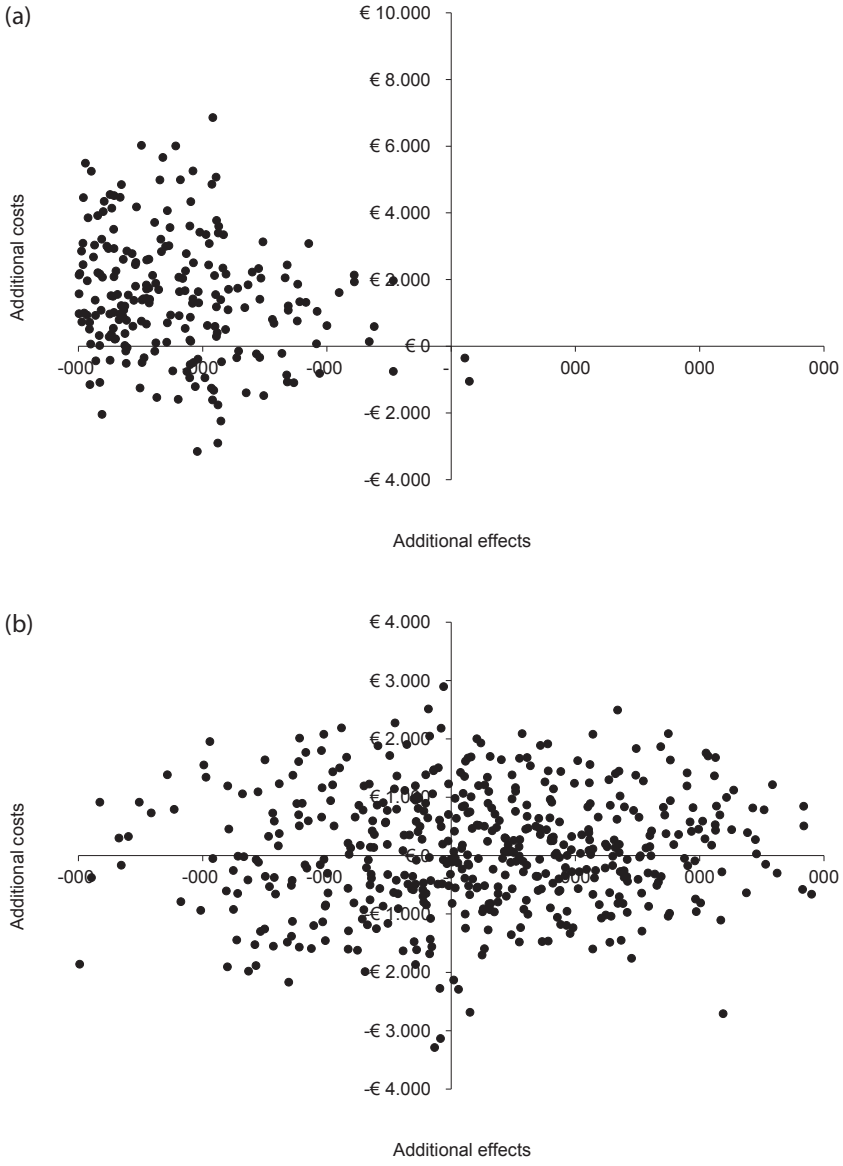

Figure S1. Cost-effectiveness planes subgroups: Clinician-assessed disease severity (Psoriasis Area and Severity Index). a = high clinician-assessed disease severity, b = low clinician-assessed disease severity.

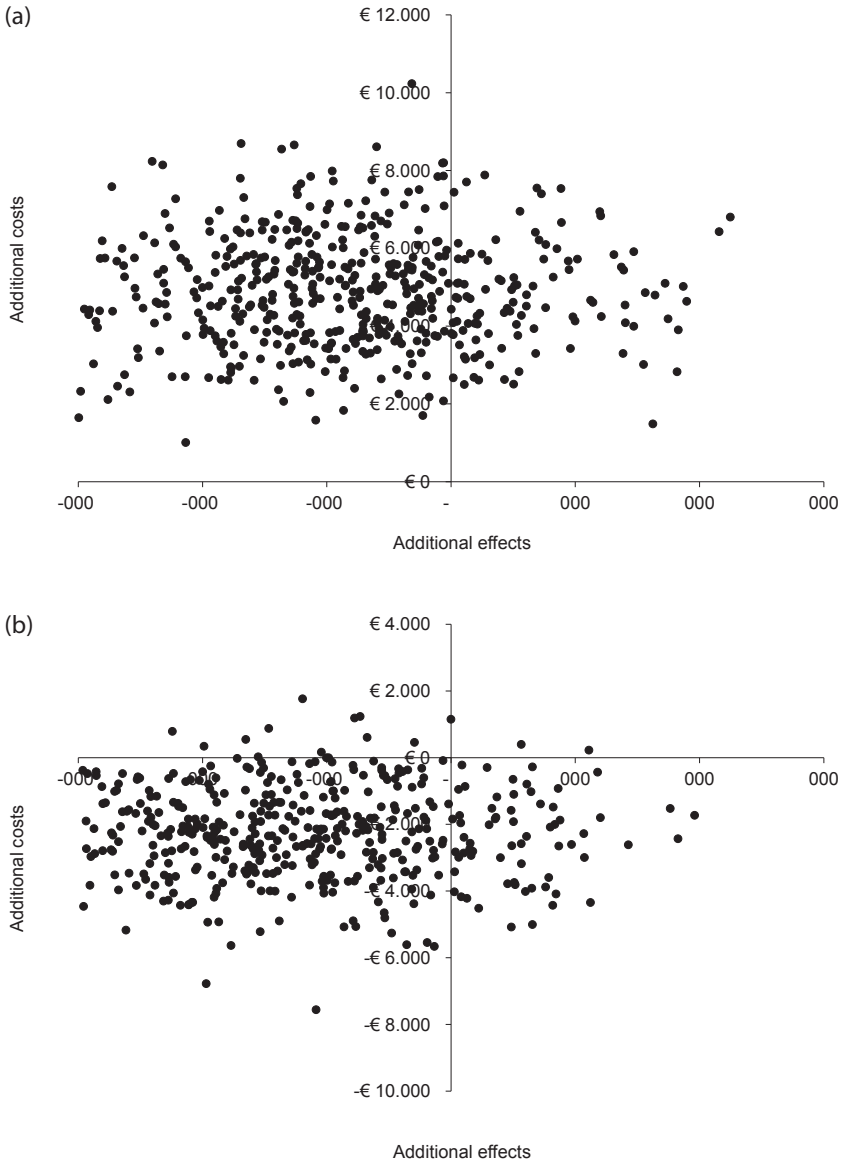

Figure S2. Cost-effectiveness planes subgroups: Psychological distress (Impact of chronic Skin disease on Daily Life - anxiety and negative mood subscales). a = high psychological distress, b = low psychological distress.

CHAPTER 8

Summary

Chronic skin conditions are common and associated with a significant psychosocial impact on daily life, including impairments in psychological and physical functioning. This impact is not only a consequence of living with a chronic skin condition; it can also play a significant role in disease exacerbation, as increased psychological distress can result in disease flares in inflammatory skin conditions. Although the psychosocial impact of chronic skin conditions is increasingly recognized, research on psychological factors influencing chronic skin conditions, and evidence-based psychological treatments for these groups, are relatively scarce. The field of research and medicine that involves this complex interaction between psychological factors and the skin is termed psychodermatology; a field that is considered upcoming. This thesis aimed to expand the current literature in psychodermatology by presenting the results of studies focused on 1) new concepts in psychodermatology, specifically aspects of body awareness; 2) new methods in psychodermatology to assess existing concepts of relevance, specifically both direct and indirect methods to assess predictors of perceived stigmatization and implicit stigmatization-related bias; and 3) new psychological treatment methods in psychodermatology, specifically the effectiveness and cost-effectiveness of individually-tailored therapist-guided internet-based cognitive behavioural treatment (ICBT). The majority of the studies presented in this thesis have been conducted in patients with psoriasis, as an illustrative example of a common chronic skin condition.

PART I. CONCEPTS 2.0: THE ROLE OF BODY AWARENESS IN CHRONIC SKIN CONDITIONS

In **Chapter 2**, we examined the potential role of body awareness in patients with psoriasis. Because the treatment of psoriasis often relies heavily on self-care, patients are typically required to play an active role in managing their skin condition. This suggests that body awareness may be particularly relevant in psoriasis; however this had not been researched before. We developed a new questionnaire to assess body awareness: the Body Attention, Ignorance and Awareness Scale (BAIAS). Results showed that this questionnaire reliably measures three aspects of body awareness: 1) being aware of and paying mindful attention to bodily signals (attention); 2) self-perceived importance of, and general attitude towards, body awareness (awareness); and 3) not recognizing and/or ignoring bodily signals (ignorance). When examining associations with physical and psychological functioning, especially the ignorance subscale was found to be related to reduced functioning. Given the association between body ignorance and worse psychological functioning, and the negative influence of impaired psychological functioning on treatment outcomes, it may be clinically important to screen for aspects of body awareness in patients with chronic skin conditions.

PART II. METHODS 2.0: EXPLICIT AND IMPLICIT MEASURES OF PERCEIVED STIGMATIZATION

In Chapters 3 and 4, the concept of stigmatization was examined using two different approaches: administering a validated self-report questionnaire to examine predictors of perceived stigmatization (Chapter 3), and using computerized reaction time tasks to examine implicit cognitive and behavioral biases to stigmatization-related stimuli (Chapter 4).

In **Chapter 3**, predictors of self-reported perceived stigmatization were examined in patients with psoriasis. In this cross-sectional study, patients filled out self-report questionnaires to assess perceived stigmatization, as well as potential sociodemographic, disease-related, personality, illness cognition, and social support predictor variables. We found that 73% of patients experienced stigmatization to some degree, and that perceived stigmatization correlated with all five categories of potential predictor variables. Perceived stigmatization was found to be particularly predicted by sociodemographic, disease-related, and personality variables in multiple regression models. These results may provide input for effective screening and intervention development, as they provide indications on which patients are especially vulnerable regarding perceived stigmatization.

In **Chapter 4**, we examined implicit cognitive and behavioral bias to disease-related and social threat-related stigmatization stimuli in patients with alopecia and psoriasis, as well as in their significant others. Indirect tasks were used to measure reaction times to stimuli related to skin conditions and social threat. We found that patients with alopecia were significantly slower than healthy controls to name the colors of disease-related words in a modified Stroop task. This attentional bias to disease-related stimuli was also found in their significant others. In patients with psoriasis and their significant others, no attentional bias was found on the Stroop task. Instead, a behavioral bias was found when they were asked to respond to pictures of disgusted faces in an approach-avoidance task. It was shown that patients with psoriasis showed increased behavioral avoidance of these faces compared with controls. This behavioral bias was also found in their significant others. These results suggest that implicit stigmatization-related processes may differ across skin conditions, with people with psoriasis being more affected by social reactions (i.e. disgusted faces) and people with alopecia by disease-related cues. Furthermore, the results suggest that these biases may extend to patients' significant others.

PART III. TREATMENT 2.0: INTERNET-BASED COGNITIVE BEHAVIORAL TREATMENT

In Chapters 5, 6, and 7 of this thesis, we focused on the effectiveness and cost-effectiveness of internet-based cognitive behavioral treatment (ICBT) to reduce the psychosocial impact of chronic somatic conditions (and particularly psoriasis) in daily life.

In **Chapter 5**, we examined the current state of the art of ICBT in adult patients with chronic somatic conditions. In a review and meta-analysis, we described and evaluated the effectiveness of guided ICBT. A total of 23 randomized controlled trials were included and standardized mean differences between the intervention and control conditions were calculated and pooled for three outcome categories: general psychological outcomes, disease-related physical outcomes, and outcomes related to the impact of the condition on daily life. Results showed that guided ICBT can be an effective treatment for general psychological outcomes (small effects), disease-related physical outcomes (small to large effects), and outcomes related to the impact of the condition on daily life (small to large effects). Furthermore, explorative analyses revealed that longer treatment duration was associated with larger effects on depressive symptoms. Future research in separate chronic somatic conditions is needed to corroborate these results, as analyses were based on a relatively small number of comparisons.

In **Chapter 6**, we described the results of a multicenter randomized controlled trial on the effectiveness of individually-tailored and therapist-guided ICBT in patients with psoriasis who were screened for a psychological risk profile of elevated levels of distress. Patients were randomized to either ICBT in addition to regular dermatological care or regular care alone. Controlling for relevant covariates, the ICBT group showed significantly greater improvements in physical functioning (consisting of itch and fatigue) and impact on daily activities (consisting of physical and emotional role functioning). No differences were observed in psychological functioning (consisting of depressive and anxious symptoms), nor in the secondary outcomes disease severity and dermatological treatment compliance. The relationship between therapist and patient measured at the beginning of treatment was found to be predictive of improvements in physical and psychological outcomes, underlining the importance of a good therapeutic relationship in personalized ICBT interventions.

Last, in **Chapter 7**, the cost-effectiveness of individually-tailored and therapist-guided ICBT for patients with psoriasis was examined, by conducting an economic evaluation alongside the randomized controlled trial. Outcomes were assessed up to 6 months post-treatment and included patient utilities, healthcare costs, productivity losses, and incremental costs per quality-adjusted life year gained. Cost-effectiveness was analyzed in bootstrapped samples using 1) incremental cost-effectiveness ratios and 2) incremental net monetary benefit analyses correcting for baseline values and confounders. Results demonstrated that offering ICBT to patients with psoriasis was not

considered cost-effective in the overall sample, but was cost-effective for two specific patient groups: patients with relatively high self-assessed disease severity and patients who experience a relatively high self-perceived impact of psoriasis on daily life. These results suggest that it may be clinically relevant to screen for these characteristics prior to ICBT, in order to offer cost-effective care.

The results of this thesis underline psychological aspects related to chronic skin conditions that have remained relatively unexplored to date, such as the relevance of body awareness and non-conscious processes associated with perceived stigmatization. Furthermore, this thesis showed for the first time that individually-tailored and therapist-guided ICBT can be effective in reducing the impact of chronic skin conditions in daily life, and cost-effective for subgroups of patients with relatively high self-assessed disease severity and a relatively large self-perceived impact of the condition on daily life. Future research may build upon the findings of this thesis to further enlarge our knowledge on explicit and implicit aspects of the psychosocial burden of chronic skin conditions, and how this burden may be decreased by optimizing psychodermatological interventions and implementing them in clinical practice.

CHAPTER 9

General Discussion

The substantial psychosocial impact of chronic skin conditions is increasingly recognized, with psychodermatological research to date focusing mainly on showing that patients with chronic skin conditions are at increased risk for psychological problems, including elevated levels of distress, anxiety and depressive symptoms [e.g., 1, 2]. Far less is known about potential risk and resilience factors for impaired physical and psychological functioning in this patient group. Furthermore, evidence-based psychological interventions to improve physical and psychological functioning are scarce. The studies in this thesis were designed to help fill these gaps in the current literature, by examining 1) new concepts in psychodermatology that are possible predictors of relevant disease outcomes (i.e. aspects of body awareness in Chapter 2), 2) new methods in psychodermatology to assess existing concepts of relevance (i.e. both direct and indirect methods to assess predictors of perceived stigmatization (Chapter 3) and implicit stigmatization-related bias (Chapter 4)), and 3) new psychological treatment methods in psychodermatology to reduce the impact of psoriasis in daily life (i.e. effectiveness and cost-effectiveness of individually-tailored therapist-guided internet-based cognitive behavioral treatment [ICBT] in Chapters 5, 6, and 7). The results of these studies are summarized in Chapter 8. In this final chapter, the findings of these studies will be discussed, including methodological considerations, recommendations for future research, implications for clinical practice, and an overall conclusion.

CONCEPTS 2.0: THE ROLE OF BODY AWARENESS IN CHRONIC SKIN CONDITIONS

Dermatological disease management, such as treatment adherence, has long been recognized as an important issue in the management of psoriasis, as the literature to date shows that adherence to topical and systemic treatment is generally poor [3–5]. Patients are required to take an active role in their own treatment regimen, as they need to take time to apply topical treatments on a regular basis. Therefore, body awareness in patients with skin conditions may be adaptive, as it leads to patients paying adequate attention to bodily symptoms such as dry skin and responding with appropriate self-care behavior. Consequently, a lack of body awareness may be a risk factor for adverse outcomes. However, body awareness had not been examined in patients with chronic skin conditions, nor had instruments been developed to assess specifically the aspect of not recognizing bodily signals and/or of ignoring them. In Chapter 2, we introduced the Body Attention, Awareness and Ignorance Scale (BAIAS) as a new measure to assess body awareness in people with a dermatological condition, and showed that it could reliably measure three aspects of body awareness: body ignorance, body attention, and general body awareness. Particularly the aspect of not recognizing bodily signals and/or ignoring them, as reflected in body ignorance, was found to be related to impairments

in physical and psychological functioning. This suggests that it may be relevant to assess body awareness in this patient group and to pay special attention in clinical practice to those patients who do not recognize or ignore bodily signals in clinical practice, as this may be an indicator for adverse outcomes.

As this was the first study to examine body awareness in patients with chronic skin conditions, many questions remain for future research. First, the properties of the concept of body awareness, and how each of its components relates to relevant outcomes and mechanisms, should be further examined. For example, a lack of body awareness may be related to a lack of emotional awareness as is seen in alexithymia, as physical and emotional sensations often co-occur; emotions are often associated with physical sensations and emotional awareness partly relies on the perception of internal bodily signals [6-8]. The difficulty in distinguishing feelings from bodily sensations is one of the characteristics of alexithymia [9], and a lack of body awareness as well as emotion awareness has been found in individuals suffering from pain disorders such as lower back pain [8]. Second, it may be relevant to examine indirect methods for assessing body awareness. It could be hypothesized that aspects of impaired body awareness may be captured by implicit measures, in light of the potential lack of awareness in afflicted individuals. Third, norm scores for the BAIAS should be established for patient and healthy samples, as it remains unknown how our sample compares to other groups and whether patients with psoriasis and healthy controls differ with regard to levels of body awareness. Fourth, the BAIAS should be compared with other measures of body awareness [e.g., 10] to further assess its psychometric properties, including its convergent validity. Fifth, prospective studies are needed to examine causal relationships between aspects of body awareness and physical and psychological functioning, to study whether body ignorance is indeed a risk factor for impaired functioning.

If prospective studies confirm that body ignorance is indeed a risk factor, interventions may be developed to target this factor in clinical practice. In order to increase body awareness in patients with skin conditions, a possible intervention component that might be further examined is mindfulness. In other populations, mindfulness interventions have been found to improve aspects of body awareness [e.g., 11, 12, 13]. Furthermore, increased body awareness is suggested to be one of the core working mechanisms of mindfulness interventions [14, 15], and several of the few studies available have already shown promising effects of mindfulness for chronic skin conditions [16-19]. In addition, an aspect of body awareness similar to our operationalization of body ignorance was recently found to mediate the effect of a mindfulness intervention in patients with chronic pain and co-morbid depression [14]. The meditation components of mindfulness interventions may help to improve body awareness, given that meditation procedures commonly emphasize body awareness by instructing individuals to notice subtle changes in the body. Future research should focus on working

mechanisms and explore the potential mediating role of aspects of body awareness in psychological interventions.

METHODS 2.0: EXPLICIT AND IMPLICIT MEASURES OF PERCEIVED STIGMATIZATION

Having a visible skin conditions such as psoriasis is often accompanied by an altered appearance. This can have substantial psychosocial consequences, as others may stare, make negative remarks or even avoid the individual afflicted with the condition. Perceived stigmatization is recognized as an important aspect of the psychosocial burden of psoriasis; it is associated with significant distress and has been found to be an important predictor of disability [e.g., 20, 21-23]. Its widespread impact was underlined in Chapter 3 of this thesis, which showed that the vast majority of patients with psoriasis (73%) had experienced stigmatization to some degree. Furthermore, it was found that perceived stigmatization could be predicted by sociodemographic, disease-related and personality variables. Although prospective studies are needed to disentangle cause and effect, the predictors found in this study increase our understanding of which patients may be especially vulnerable to stigmatization-related problems. This may aid further development of screening and intervention procedures.

In this study, in line with other studies, perceived stigmatization was assessed with a self-report questionnaire [24]. While self-report measures provide valuable information in reflecting patients' conscious experience as they perceive it in hindsight, they probably do not capture the rapid and reflexive responses associated with initial reactions. These have been theorized to be at least as important in influencing behavior, but have remained largely unexplored in previous research in psychodermatology [25]. Therefore, in Chapter 4, we examined these rapid and reflexive responses to stigmatization-related stimuli using computer-based reaction time tasks: Approach-Avoidance Tasks [26] and a modified version of the Emotional Stroop Task [27]. Stigmatization can be accompanied by reflexive disgust reactions of others, which can be considered a defensive response: disgust initiates avoidance in order to prevent potential contamination [28, 29]. As stigmatization is commonly experienced by patients with psoriasis, they may fear or actually be confronted with disgust reactions [30, 31]. Therefore, patients may process disgusted facial expressions differently than healthy controls, and we hypothesized that this would be reflected in implicit reflexive processes in the form of an avoidance bias. This was found in Chapter 4: in an Approach-Avoidance Task consisting of pictures of emotional facial expressions, both patients with psoriasis and their significant others showed greater behavioral avoidance of disgusted faces than controls. A similar bias was not observed in patients with alopecia (i.e. a dermatological condition characterized

by hair loss), who instead were characterized by an attentional bias to disease-related words.

The fact that biases were also observed in patients' significant others, is consistent with the idea of courtesy stigma, also known as stigma by association [32, 33]: this idea suggests that people associated with stigmatized individuals may be the targets of stigma as well, simply by being connected to a stigmatized person [34-36]. Furthermore, significant others may experience a substantial burden due to a patient's condition, and this burden may also be reflected in these biases [37]. The differences in response latencies of patients and their significant others versus controls are still open to various interpretations, as the tasks that were used to assess attentional and behavioral bias were specifically designed for this study and their psychometric properties need to be further examined. Furthermore, the results should be interpreted with caution, as they were based on a relatively small between-group effect and groups differed on various characteristics. However, the avoidance effect we found in psoriasis was specific for disgust and was not found for other negative and positive facial expressions included, and disgust is a prominent feature in stigmatization responses [e.g., 38]. Therefore, the tentative conclusion can be drawn that this effect may be attributed to an automatic stigmatization-related avoidance reaction, probably stemming from a coping reaction to perceived negative responses to the skin condition. Similarly, the fact that people with alopecia were significantly slower to name the color of the ink of hair-related words than the ink color of other word categories suggests that they might suffer from a disease-related attentional bias.

The task we used to assess behavioral avoidance consisted of a symbolic form of approach-avoidance behavior, operationalized as joystick movements towards or away from the screen. This approach may be viewed by some as too artificial to represent real-life behavior; however previous research has shown that important cognitive and affective components of approach-avoidance behavior can be captured in how people respond to stimuli in computer-based tasks. Furthermore, these tasks have the advantage of allowing more precise reaction time measurements of very fast processes that probably cannot be captured in real-world settings [39]. A research design incorporating virtual reality may be promising for future research, as it combines the ability to measure reactions precisely with an increased 'real world' experience [39].

The stigmatization-related biases found in patients with chronic skin conditions may have important clinical implications. Given that previous studies in other samples show that attention and avoidance biases may be successfully retrained [40-44], future research may examine paradigms in which patients with chronic skin conditions who experience high levels of perceived stigmatization and an avoidance bias towards disgusted faces are trained to redirect their attention towards neutral or positive stimuli. A similar approach may be used to retrain an attention bias to disease-related words,

for example by using attention bias modification paradigms [45]. Future research should explore whether retraining these attention and avoidance biases is feasible, and whether this would subsequently lead to a reduction in perceived stigmatization and fear of negative evaluation.

TREATMENT 2.0: INTERNET-BASED COGNITIVE BEHAVIORAL TREATMENT

In light of the substantial psychological and psychosocial impact of chronic skin conditions, psychological interventions that help patients with adjustment problems to cope with their condition and its consequences in daily life may be a valuable addition to regular dermatological care. However, research on psychological interventions for chronic skin conditions is scarce, and evidence-based interventions that have been implemented in clinical practice are largely unavailable. In order to help fill this gap in current literature, this thesis studied the potential of an innovative individually-tailored therapist-guided internet-based cognitive behavioral treatment (ICBT). A systematic evaluation of the overall effectiveness of previous studies on ICBT in patients with chronic somatic conditions is provided in Chapter 5, followed by an evaluation of the effectiveness (Chapter 6), and cost-effectiveness (Chapter 7) of an individually-tailored, therapist-guided ICBT intervention designed to reduce the impact of psoriasis in daily life.

Effectiveness of guided ICBT for chronic somatic conditions: a meta-analysis

In order to assess the overall effectiveness of ICBT for patients with chronic somatic conditions, a meta-analysis was conducted of previous studies of guided ICBT interventions. This was the first meta-analytic review providing a disease-transcending overview, examining overall effectiveness on broad domains of functioning of relevance to the majority of patients. The results showed that guided ICBT had overall small effects on generic psychological outcomes and small to large effects on disease-specific physical outcomes and outcomes relating to the impact of the condition on daily life. The generally low heterogeneity observed between studies for the outcomes included provided support for the validity of this overarching approach of examining broad domains of functioning in various patient populations. However, several limitations warrant discussion. For example, as only 23 studies could be included and not all studies used the same outcomes, the number of comparisons contained in each analysis was typically small. As the analyses compared effect sizes based on various outcome measures (e.g., standardized scores on various measures of depressive symptoms), and were based on different samples (e.g., various somatic conditions), we emphasize that these are broad estimates that should be further consolidated in future research.

Individually-tailored and guided ICBT for psoriasis: a randomized controlled trial

The overall beneficial effects of guided ICBT for patients with chronic somatic conditions suggest that this may also be a feasible approach for patients with chronic skin conditions. However, no studies have been conducted in this patient group. We therefore conducted a multicenter randomized controlled trial to examine the effectiveness (Chapter 6), and cost-effectiveness (Chapter 7) of ICBT in patients with psoriasis. An important strength of these studies was that they were largely conducted in a clinical setting. This has the benefit of allowing an evaluation of whether a treatment works in real-world settings in routine daily practice. Given that randomized controlled trials (RCTs) are generally considered as the 'gold standard' providing the highest level of evidence, this trial design significantly contributes towards the establishment of evidence-based interventions in patients with psoriasis, especially in light of the paucity of previous trials. Furthermore, the primary analyses included both post-treatment and 6-months follow-up measurements, allowing a longer term evaluation of intervention effects. Lastly, as the effectiveness and cost-effectiveness of guided ICBT for patients with chronic skin conditions to date has not been examined, the economic evaluation had considerable added value. In the sections below, the effectiveness and cost-effectiveness of the intervention will be discussed, as well as several aspects of the intervention.

Effectiveness of tailored and guided ICBT for patients with psoriasis

Results of the RCT showed that individually-tailored therapist-guided ICBT was effective in improving physical functioning and reducing the impact of psoriasis on activities in daily life, but not in improving psychological functioning, in patients with psoriasis screened for elevated levels of distress. Moderate to large within-group improvements were found on primary outcomes in the ICBT condition. However, the magnitude of between-group effects of ICBT compared to regular dermatological care was small. This was in line with our previous meta-analysis on effects of guided ICBT for chronic somatic conditions (Chapter 5), but contrasted with our expectation that tailored treatment might increase effect sizes. Several factors may have contributed to these findings. First and foremost, the fact that patients' distress levels were relatively low, which is more elaborately discussed below, may have meant that there was limited room for improvement. Second, patients in the care as usual (CAU) condition improved more than was expected, possibly due to regression to the mean and/or to the effects of dermatological treatment. Alternatively, the fact that patients received extra appointments for study assessments conducted by care professionals may have also played a role in terms of an attention effect that may explain improvements in the control group. Third, methodological characteristics such as the clinical setting, the care as usual comparison condition, and the statistical analysis that included both post-treatment and 6 months

follow-up measurement in the same analysis have been associated with smaller effect sizes in previous literature [e.g., 46]. However, these study characteristics improve ecological validity by representing longer-term effects in a real-world setting with a relevant comparison condition; therefore we consider these to be strengths of our study. Given these results, we conclude that ICBT may be beneficial for patients with psoriasis in terms of improving physical functioning and reducing the impact of the condition on daily activities.

Screening for elevated levels of distress

In order to select the target group for individually-tailored and therapist-guided ICBT, prior to trial inclusion patients were screened for heightened levels of distress [47-53]. As elevated baseline distress levels were shown to be associated with better psychological treatment outcomes in other studies [54, 55], this group may benefit most from ICBT. Screening for distress in clinical practice and offering a tailored intervention to patients with elevated distress levels has the potential benefit of enhancing the timely identification of both patients at risk and those with existing psychological problems. However, several aspects of the screening procedures applied warrant some more discussion.

First, although cut-off scores for elevated distress levels were based on previous research [50-52], there remains a risk that patients who score close to the cut-off scores may be classified incorrectly. This risk may have increased due to the fact that patients with a psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV-TR; 56], and patients in current psychological treatment (i.e. patients generally characterized by high distress levels), were excluded prior to filling out screening questionnaires. Consequently, the majority of patients scored just above the cut-off boundaries and the selected target group for ICBT was relatively narrow and arguably limited in its generalizability. Second, in line with previous literature [57, 58], a subgroup of patients who screened positive at screening no longer fulfilled these criteria at baseline. Third, despite their elevated levels of distress, the patients included had not sought prior psychological treatment. This subgroup of patients not previously identified except through current screening may be less adherent to treatment [58]. In a recent study, one third of patients with skin cancer were identified as in need of psychological care, but only 11.5% requested such support [47]; this illustrates that the need for support and desire for support do not necessarily correspond. It is likely that this, together with the relatively low levels of distress, dampened intervention effects, which were generally small in the current trial. It is therefore recommended that the results from this study be further substantiated in future research on the effects of tailored and guided ICBT in patients screened for higher levels of distress, taking into account patient needs and motivation. Conducting semi-structured interviews prior to study inclusion might help to ensure that ICBT is the best treatment choice for participants [59].

Tailoring and therapist guidance in ICBT

Two important characteristics of our ICBT intervention were individual tailoring and therapist-guidance. Based on previous research, it was expected that adherence rates and effectiveness would benefit from both of these characteristics. In systematic reviews comparing guided and unguided ICBT interventions, both between and within studies, guided interventions typically show greater treatment effects [60-62] and greater adherence rates [61]. In our trial, in the evaluation questionnaires filled out by ICBT participants, personal contact with the therapist was consistently rated as one of the most positive elements of the intervention. Furthermore, the importance of therapist guidance was reflected in the association between the patient-therapist relationship and treatment results: a better working alliance at the beginning of treatment showed moderate associations with greater effects of treatment on physical and psychological functioning. Given that previous literature generally shows that working alliance ratings are very similar for online and face-to-face treatments [63, 64], the concern often raised by therapists that a therapeutic alliance may not develop well in online interventions seems unfounded. However, taking into account the mixed results of previous research regarding the predictive value of the working alliance for therapeutic outcomes [63, 64], it may be important for future research to identify moderators of alliance-outcome associations and further explore the specific aspects of the patient-therapist relationship that facilitate positive outcomes. The fact that the intervention was individually tailored sets it apart from most other, typically standardized, ICBT interventions.

The therapist in consultation with the patient chose one or more of five possible treatment modules, based on the mutually determined treatment goals, and each module could be further tailored as the therapist selected those assignments most suitable for the individual patient. This offers important advantages, as it acknowledges and meets patient preferences, and treatment can be adapted according to each patient's characteristics [59]. An individually-tailored therapist-guided intervention may fit well into a stepped care model of ICBT, starting with unguided ICBT for patients with mild adjustment problems, standardized guided ICBT for patients with moderate problems, and individually-tailored guided ICBT for patients with moderate, more complex, problems [59, 65], in which patients experience multiple problems in daily life and/or comorbidity [66]. A tailored approach, including the ability to work on multiple individually-determined treatment goals, may be specifically relevant for patients with chronic somatic conditions, since these conditions typically affect multiple aspects of patients' lives, including both physical and psychological functioning.

A recent review found moderate to large effects for tailored ICBT for anxiety and depression [67], underlining the potential effectiveness of this approach. Our trial showed beneficial effects of individually-tailored ICBT compared to care as usual in patients with psoriasis, and a similar trial from our research group also showed beneficial effects

compared to care as usual in patients with rheumatoid arthritis [68]. These findings demonstrate the feasibility and potential effectiveness of this approach for patients with chronic somatic conditions. Future studies may focus on expanding the evidence base for individually-tailored treatments in these groups, for example by directly comparing the effectiveness of individually-tailored versus standardized treatments in order to show the added value of tailored treatments. Furthermore, the role of patient and therapist preferences regarding the order of modules/assignments may be further explored, as well as the effects of different orders and combinations of modules in individually-tailored ICBT in general, in order to optimize treatment procedures [69].

Dropout in ICBT

Despite individual tailoring and therapist-guidance, ICBT adherence rates were not higher than what has been on average found in previous trials. A total of 26.2% of patients dropped out of the ICBT condition, compared to a median of 29% in our previous meta-analysis of ICBT for chronic somatic conditions (Chapter 5). This may be related to the relatively long intervention duration (i.e. an average of 25 weeks, compared to 6 weeks in many other interventions [70]): longer interventions are typically associated with higher dropout rates [71]. Furthermore, the fact that participant recruitment was based on screening in regular dermatological care as compared to recruitment based on advertising in the community in many other studies may have led to a less intrinsically motivated sample. The majority of dropouts (i.e. 15.4% of patients) were non-starters. These patients dropped out before having seen the intervention; therefore, their decision to drop out could not have been related to intervention content. Reported reasons for dropout were largely unrelated to the intervention, such as occurrence of comorbidity. Future research should aim to find strategies to further reduce dropout rates in internet-based interventions, which show somewhat higher dropout rates than face-to-face interventions [72]. Therefore, it remains important to further investigate factors that are associated with adherence and outcomes. Results of our randomized controlled trial (Chapter 6) suggest that the degree to which patient and therapist agree on the tasks and goals of the treatment, as well as the affective bond between patient and therapist, are predictors of treatment outcomes in ICBT. Recent research further suggests that treatment credibility and intrinsic motivation are important factors in increasing adherence [73]. In line with what is seen in studies of placebo effects, patients' belief in the effectiveness of the treatment may have a strong effect on outcomes [74, 75], and therefore it may be relevant to enhance treatment credibility and strengthen expectancy effects. Furthermore, we recommend focusing on what makes patients engage in an ICBT intervention and which features best suit patient needs and preferences.

Timing of ICBT

Recruitment strategies for the RCT in most centers entailed patients who attended the outpatient dermatology department being invited to participate. Consequently, patients were often selected when a dermatological treatment regimen was either started or adapted. Furthermore, as the typical duration of our study was one year, changes in medication use (e.g., switching from topical to systemic or biological medication) occurred frequently. New biological treatments, for example, can greatly reduce the severity of the condition and offer benefits beyond the skin, in terms of a reduction in psychological morbidity [76]. While the fact that average disease severity remained stable over the course of post-treatment and follow-up suggests that intervention effects were not related to decreases in disease severity, it may be recommended for future research and clinical practice to employ a strategy in which an ICBT intervention is offered to patients who consistently display elevated levels of distress over time despite multiple visits to a dermatologist.

Cost-effectiveness of ICBT for patients with psoriasis

An economic evaluation from a societal perspective was conducted alongside the RCT. Results showed that the ICBT and CAU groups had similar costs and effects at post-treatment and 6 month follow-up. Thus, in the overall study sample, in contrast to previous reviews showing that ICBT is cost-effective in a range of conditions [77-79], the ICBT intervention could not be considered cost-effective in comparison to regular dermatological care. Previously mentioned factors such as low baseline levels of distress and disease severity, intervention timing, care as usual comparison, and recruitment procedures, may have played a role in these findings. Another potential explanation may lie in the fact that the effects were assessed with the EQ-5D-3L. This generic questionnaire is the most frequently used measure in cost-effectiveness analysis, and its advantages include the calculation of quality-adjusted life years (QALYs) that can be compared across trials and patient populations. However, this generic measure consists of broad dimensions, and with three answer categories per question, leaves limited room for nuance. Previous reviews suggest that it may not adequately measure disease-specific aspects of quality of life in patients with psoriasis [80] and that it shows limited responsiveness to change and ceiling effects across a range of conditions [81]. Considering that a ceiling effect was also observed in our study, and EQ-5D scores were already relatively high at baseline, there may have been limited room for improvement.

Subgroup analyses showed that ICBT may be cost-effective for two specific patient groups: those who experience relatively high self-assessed disease severity, and those who experience a relatively high burden of psoriasis in daily life. This gives a clear indication of patients for whom ICBT would be a cost-effective treatment strategy, suggesting that it may be clinically relevant to screen for higher levels of self-reported disease sever-

ity and impact of psoriasis on daily life prior to ICBT, in order to offer cost-effective care. Both can be measured with brief self-report questionnaires [24, 82], which increases the feasibility of screening for these characteristics in clinical practice.

Clinical implications and implementation of ICBT

The positive results of the multicenter randomized controlled trial suggest that it may be beneficial to implement ICBT in clinical practice. The conditions for effective implementation of ICBT in the Netherlands are favorable: the Dutch government actively stimulates the implementation of internet-based interventions [83], and 94% of the Dutch adult population in general, and 82% of Dutch chronically ill individuals, report using the Internet [84]. The feasibility of offering ICBT to patients with chronic somatic conditions is supported by the results of one of our previous studies, which showed that patients with psoriasis and rheumatoid arthritis perceived more benefits than disadvantages of ICBT [85]. The relatively small number of non-completers (excluding non-starters) and overall positive intervention evaluations from ICBT participants in our RCT further illustrates that the intervention is feasible from the patient perspective. Furthermore, use of internet-based interventions in primary care facilities is relatively high in the Netherlands: a recent study showed that online psychological self-management interventions are currently used by 49% of the mental health counselors in general practice [86].

Although future research should further evaluate the cost-effectiveness of ICBT in different samples, the current intervention was shown to be relatively inexpensive, and offering ICBT as an addition to regular care did not lead to significantly higher costs from a societal perspective. Future research may examine the effectiveness of this ICBT intervention in patients with a co-morbid mood disorder, representing a substantial proportion of the patient population, who were excluded from the current trial [e.g., 1, 2, 87]. Various trials have shown that ICBT can be effective for patients with various DSM diagnoses [excluding severe cases; 59]. As tailored interventions may be especially suited for patients with more severe complaints [65], it seems feasible to develop an alternative screening procedure in which patients with co-morbid mood or anxiety disorders can participate. Furthermore, based on the findings of our cost-effectiveness study, focusing the ICBT intervention on a target population of patients who experience a relatively large burden of the skin condition on daily life, and/or who have a relatively high self-assessed disease severity may be both clinically relevant and cost-effective.

FUTURE DIRECTIONS IN PSYCHODERMATOLOGY

The aim of the studies presented in this thesis was to advance current knowledge on the assessment and treatment of the psychosocial impact of chronic skin conditions. Several remaining gaps in the literature that may be addressed in future research are highlighted in this section.

First, there is a relative lack of literature on potential risk and resilience factors for impaired physical and psychological functioning in patients with chronic skin conditions. Previous psychodermatological studies have mainly focused on examining the level of impaired psychological functioning in patients with chronic skin conditions [e.g., 1, 2, 87-91]. However, it remains unclear which characteristics are associated with greater risk for impaired psychological and physical functioning in this patient group. In this thesis, aspects of body awareness and stigmatization were found to be related to impairments in physical and psychological functioning; this suggests that the presence of these aspects (e.g., not recognizing bodily signals and/or ignoring them, or high levels of perceived stigmatization) may be a risk factor for impaired functioning in patients with psoriasis. These and other possible risk factors, such as dysfunctional coping strategies, maladaptive illness cognitions, and disease-related implicit biases, should be explored further in longitudinal studies in diverse chronic skin conditions, in order to shed more light on potential risk groups and develop evidence-based tailored interventions that take these characteristics into account.

Second, future research could further explore the assessment and clinical relevance of implicit biases in chronic skin conditions. In our study on implicit stigmatization-related biases in chronic skin conditions, we focused on two types of cognitive biases: attention and approach-avoidance biases. However, cognitive bias can also occur for memory and interpretation, and it may be hypothesized that stigmatized groups such as patients with chronic skin conditions show memory and interpretation biases for socially threatening stimuli. For example, stigmatized patients may recall stimuli related to social threat more easily than other stimuli, and may interpret ambiguous stimuli as socially threatening. These and other potential biases in patients with chronic skin conditions could be further explored. Furthermore, possibilities for clinical applications to target these cognitive biases should be examined. Potentially, ICBT interventions may be augmented with online cognitive bias modification modules [CBM; 92, 93] to target the implicit biases in patients with chronic skin conditions that were observed in Chapter 4. Promising effects of CBM programs on reducing implicit bias and improving physical and psychological wellbeing have already been observed in other populations, including individuals suffering from pain and social anxiety [40-44]. However, remaining questions about the methodological quality of some of the earlier studies on cognitive

bias modification [94, 95] highlight the need to examine how these interventions may be optimized and for whom and under which circumstances they may be effective.

Third, the overall effectiveness of psychodermatological treatments should be further examined. Although the first studies to examine the effects of psychological interventions in chronic skin conditions date from over three decades ago [for an overview see: 96], current evidence of the effects of such interventions is still thin due to the very small number of studies [e.g., 97]. Our RCT advances knowledge in this field by, for the first time, examining the effectiveness of individually-tailored and therapist-guided ICBT in patients with psoriasis, and showing that it can be effective in improving physical functioning and reducing the impact of psoriasis on daily activities. Given that the intervention was found to be cost-effective specifically in patients who experience a larger impact of the condition on daily life and those with higher self-reported disease severity, the results may be further substantiated by trials that examine the effects for these subgroups in particular. Furthermore, future research may examine the effects of individually-tailored guided ICBT in patients with more elevated levels of distress, since distress levels were relatively low in our sample. Last, it may be interesting to directly compare the effects for patients with a recent compared to a long-standing diagnosis, as well as for individually-tailored versus standardized treatments.

A potential way to augment (I)CBT interventions is to combine them with elements of serious gaming. In light of previous research indicating the potential and effectiveness of serious games to promote health and showing that interest and enjoyment are important factors in increasing use of online interventions [e.g., 98, 99-101], the addition of serious gaming elements may promote both the adherence to and the effectiveness of internet-based interventions. Furthermore, based on research on dual-process models [102], there may be much to gain by combining interventions directed at changing cognitions and behavior on an explicit level (e.g., CBT-based interventions) with serious gaming intervention elements designed to influence implicit processes by incorporating principles of attention bias modification and approach-avoidance training. Future research could examine whether these innovative multimodal intervention combinations may result in synergistic treatment effects.

Furthermore, effectiveness of current psychodermatological interventions may be further enhanced by exploring new fields of application. While current interventions typically aim to improve physical and psychological outcomes, the potential of psychodermatological interventions to improve pharmacological outcomes remains relatively unexplored. A considerable number of patients with psoriasis are on systemic treatments, which can be highly expensive (e.g., biological treatments) and can cause significant side effects [103]. Psychodermatological (internet-based) interventions may be developed that incorporate pharmacological conditioning combined with expectancy training with the aim of enhancing pharmacological effects. Previous research in

relation to other conditions has suggested that a combination of automatic (e.g., conditioning) and conscious (e.g., verbal or written suggestions) expectancy training may be able to decrease pharmacological doses while maintaining treatment effects [e.g., 104-107]. These applications remain relatively unexplored in patients with dermatological conditions and may hold considerable promise for reducing medication costs and improving patient wellbeing.

Last, several focus points for research on ICBT in general can be identified. While the efficacy and effectiveness of ICBT has been shown across a range of mental and physical health conditions [e.g., 59], the evidence for cost-effectiveness of ICBT is much more scarce [77-79] and needs to be further established. Furthermore, relatively little is known about predictors, moderators, and mediators of treatment outcomes. In the current study, the therapeutic alliance at the beginning of treatment was associated with change in two out of the three primary outcomes, suggesting that this alliance may be a predictor of treatment success in tailored and guided ICBT. The specific cognitive behavioral mechanisms causing therapeutic changes in health outcomes need to be further explored. Most ICBT interventions consist of a broad range of intervention elements, which complicates the study of working mechanisms and effective intervention ingredients. Dismantling studies may shed more light on specific mechanisms of change, for example by comparing the effects of interventions with and without selected key characteristics. Once more has been learned about the mechanisms of change and moderating factors, it will become possible to better predict treatment success and provide a clear answer to the question of which clients are most suitable for internet-based treatment and what works for whom. A final focus point for research could be to conduct studies on the effects of integrating ICBT into routine care, given that there is substantial and accumulating evidence for its effects in various physical and mental health populations [e.g., 70, 108, 109-112].

CONCLUSIONS

The overall results of this thesis highlight aspects of the psychosocial burden of chronic skin conditions such as psoriasis that have remained relatively unexplored to date. Furthermore, they demonstrate that guided ICBT can be effective in reducing this burden as well as cost-effective for specific patient groups. Future studies may build upon these findings to further enlarge our understanding of implicit and explicit processes related to the psychosocial burden of dermatological conditions, and of how this burden may be decreased by optimizing current psychodermatological interventions and implementing them in clinical practice. Three main conclusions can be drawn from this thesis:

1. New concepts in psychodermatology, in particular aspects of body awareness, are of relevance for physical and psychological functioning in patients with chronic skin conditions. Specifically the aspect of not recognizing or ignoring bodily signals is related to impaired physical and psychological functioning in patients with psoriasis.
2. A large proportion of patients with psoriasis feels stigmatized, the extent of which can be predicted by sociodemographic, disease-related, and personality characteristics. New assessment methods in psychodermatology demonstrated that the experience of stigmatization may also affect patients with chronic skin conditions (and their significant others) on an automatic, non-conscious level, as demonstrated by the specific implicit attentional and behavioral stigmatization-related biases found in these groups.
3. New psychological treatments, specifically therapist-guided ICBT, were found to be effective for patients with chronic somatic conditions. Individually-tailored therapist-guided ICBT was shown to be effective in improving the physical functioning and reducing the impact of psoriasis on the daily activities of patients with the condition. Despite a general lack of cost-effectiveness of this intervention, it was found to be cost-effective for clinically relevant subgroups of patients with higher self-reported disease severity and a greater experienced impact of the skin condition on daily life.

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Samenvatting

List of Publications

PhD Portfolio

Dankwoord

Curriculum Vitae

Chronische huidaandoeningen komen veel voor en gaan regelmatig gepaard met een grote invloed op het dagelijks leven van patiënten, zoals beperkingen in het psychologisch en lichamelijk functioneren. Deze gevolgen van een chronische huidaandoening kunnen ook een belangrijke rol spelen in de verergering van de huidaandoening. Hoewel de rol van psychologische factoren bij chronische huidaandoeningen steeds meer erkend wordt, is er tot nu toe nog maar relatief weinig onderzoek verricht naar psychologische factoren die van invloed zijn op chronische huidaandoeningen. Ook zijn er nog maar weinig psychologische behandelingen voor deze patiëntgroepen onderzocht. Het vakgebied binnen het wetenschappelijk onderzoek en de klinische praktijk dat zich bezighoudt met het complexe samenspel van psychologische factoren en de huid wordt psychodermatologie genoemd. Dit proefschrift heeft als doel om een bijdrage te leveren aan het vakgebied van de psychodermatologie, door wetenschappelijk onderzoek gericht op 1) nieuwe concepten binnen de psychodermatologie, zoals lichaamsbewustzijn; 2) nieuwe methoden binnen de psychodermatologie, zoals het gebruik van zowel directe en indirecte methoden bij het meten van stigmatisatie en 3) nieuwe psychologische behandelmethoden binnen de psychodermatologie, zoals de (kosten)effectiviteit van een door een coach begeleide online cognitief gedragstherapeutische behandeling. Het overgrote deel van de studies in dit proefschrift is uitgevoerd bij patiënten met psoriasis, als illustratief voorbeeld van een veelvoorkomende chronische inflammatoire huidaandoening.

DEEL I. CONCEPTEN 2.0: DE ROL VAN LICHAAMSBEWUSTZIJN BIJ CHRONISCHE HUIDAANDOENINGEN

In **Hoofdstuk 2** onderzochten we de potentiële rol van lichaamsbewustzijn bij patiënten met psoriasis. Omdat zelfzorg van groot belang is bij de behandeling van veel huidaandoeningen, zoals psoriasis, wordt over het algemeen van patiënten verwacht dat zij een actieve rol spelen bij de behandeling van hun aandoening. Dit zou erop kunnen duiden dat lichaamsbewustzijn met name van belang kan zijn bij psoriasis, wat nog niet was onderzocht. We ontwikkelden een nieuwe vragenlijst om lichaamsbewustzijn te meten: de Body Attention, Ignorance and Awareness Scale (BAIAS). De resultaten lieten zien dat deze vragenlijst op een betrouwbare wijze drie aspecten van lichaamsbewustzijn kan meten: 1) het zich bewust zijn van lichamelijke signalen en hier aandacht aan schenken (*Aandacht*); 2) het door de persoon ervaren belang en attitude ten aanzien van lichaamsbewustzijn (*Bewustzijn*); 3) het niet herkennen en/of negeren van lichamelijke signalen (*Ignoreren*). Het onderzoek naar verbanden van lichaamsbewustzijn met lichamelijk en psychologisch functioneren liet zien dat met name de subschaal *Ignoreren* samenhing met verminderd functioneren. Omdat verminderd psychologisch functioneren

een negatieve invloed kan hebben op behandeluitkomsten, kan het daarom klinisch relevant zijn om lichaamsbewustzijn in kaart te brengen bij patiënten met chronische huidaandoeningen.

DEEL II. METHODEN 2.0: EXPLICIETE EN IMPLICIETE METHODEN OM ERVAREN STIGMATISATIE TE METEN

In **Hoofdstuk 3 en 4** werd stigmatisatie onderzocht door verschillende expliciete en impliciete methoden via vragenlijsten (hoofdstuk 3) en computertaken (hoofdstuk 4).

In **Hoofdstuk 3** werden voorspellers van ervaren stigmatisatie onderzocht via zelfrapportagevragenlijsten bij patiënten met psoriasis. In dit onderzoek vulden patiënten vragenlijsten in waarmee ervaren stigmatisatie gemeten werd, naast vragenlijsten over 5 soorten mogelijke voorspellers van ervaren stigmatisatie: sociaal-demografische variabelen (bijv. leeftijd en geslacht), ziekte-gerelateerde variabelen (bijv. ziekte-ernst en ziekteduur), persoonlijkheidsvariabelen (bijv. een hogere score op aspecten van de type D persoonlijkheid, waarbij mensen de neiging hebben om negatieve emoties te ervaren en emoties niet gemakkelijk kunnen uiten in hun sociale omgeving), ziektecognities (bijv. acceptatie van de aandoening en hulpeloosheid ten opzichte van de aandoening) en sociale steun variabelen (bijv. het aantal goede vrienden dat iemand aangeeft te hebben en de mate waarin iemand sociale steun ervaart). De resultaten lieten zien dat 73% van de patiënten zich in meer of mindere mate gestigmatiseerd voelde. Ervaren stigmatisatie werd met name voorspeld door sociaal-demografische, ziekte-gerelateerde en persoonlijkheidsvariabelen. Deze resultaten kunnen mogelijk gebruikt worden voor de ontwikkeling van screeningsinstrumenten en effectieve interventies, aangezien hiermee aanwijzingen kunnen worden verkregen over welke patiënten kwetsbaar zijn voor ervaren stigmatisatie.

In **Hoofdstuk 4** werd onderzocht in hoeverre patiënten met huidaandoeningen, en hun naasten, vertekeningen laten zien in hoe ze reageren op stimuli die met ervaren stigmatisatie te maken hebben. We maakten gebruik van computertaken om reactietijden te meten terwijl patiënten met alopecia en psoriasis reageerden op stimuli die te maken hadden met huidaandoeningen en sociale dreiging. In een aangepaste Stroop taak werden deelnemers onder andere ziekte-gerelateerde woorden (bijv. schilfers of haaruitval) en neutrale woorden (bijv. deurknop of fluitketel) aangeboden, waarbij de woorden in verschillende kleuren werden weergegeven. Uit de resultaten bleek dat patiënten met alopecia langzamer reageerden dan mensen zonder huidaandoeningen in het benoemen van de kleuren van ziekte-gerelateerde woorden dan in het benoemen van de kleuren van neutrale woorden. Deze vertekening in de aandacht voor ziekte-gerelateerde stimuli werd ook gevonden bij hun naasten. Bij patiënten met psoriasis en

hun naasten werd dit niet gevonden. Bij deze groepen werd echter wel een vertekening in hun reacties gevonden met behulp van een computertaak waarbij zij werden gevraagd om met een joystick foto's van gezichten met verschillende gezichtsuitdrukkingen te benaderen of te vermijden. De resultaten lieten zien dat patiënten met psoriasis vooral de foto's van gezichten met een walgende gezichtsuitdrukking sneller vermeden, vergeleken met mensen zonder huidaandoening. Deze vertekening werd ook gevonden in hun naasten. De resultaten duiden erop dat impliciete ervaringen van stigmatisatie mogelijk verschillen tussen huidaandoeningen, waarbij mensen met psoriasis meer beïnvloed worden door sociale reacties (met name walgende gezichtsuitdrukkingen) en mensen met alopecia door ziekte-gerelateerde signalen. Daarnaast suggereerden de resultaten dat deze vertekeningen ook van toepassing zijn op de naasten van deze patiënten.

DEEL III. BEHANDELING 2.0: COGNITIEVE GEDRAGSTHERAPIE AANGEBODEN VIA INTERNET

In Hoofdstuk 5, 6 en 7 van dit proefschrift werd de effectiviteit en kosteneffectiviteit van cognitieve gedragstherapie aangeboden via het internet (eCGT) onderzocht met betrekking tot het verminderen van de invloed van chronische lichamelijke aandoeningen (in het bijzonder psoriasis) op het dagelijks leven.

In **Hoofdstuk 5** werd een overzicht gegeven van de huidige stand van zaken in het onderzoek naar de effectiviteit van begeleide eCGT behandelingen bij volwassen patiënten met een chronische lichamelijke aandoening. In totaal werden er 23 gerandomiseerde gecontroleerde studies opgenomen in deze review en meta-analyse. Op basis van de samengevoegde resultaten van deze individuele studies werd de overkoepelende effectiviteit berekend voor drie soorten uitkomstmaten: algemene psychologische uitkomstmaten (bijv. angstklachten en depressieve klachten), lichamelijke uitkomstmaten (bijv. pijn en vermoeidheid) en uitkomstmaten ten aanzien van de invloed van de aandoening op het dagelijks leven (bijv. ziekte-gerelateerde kwaliteit van leven). De resultaten lieten zien dat begeleide eCGT kleine effecten had op de algemene psychologische uitkomstmaten en kleine tot grote effecten had op lichamelijke uitkostmaten en de invloed van de aandoening op het dagelijks leven. Daarnaast lieten de resultaten zien dat een langere eCGT behandelduur samenhing met grotere effecten op depressieve klachten. Toekomstig onderzoek in afzonderlijke chronische lichamelijke aandoeningen is nodig om deze resultaten verder te ondersteunen, gezien dit overzichtsartikel gebaseerd was op een relatief klein aantal studies.

In **Hoofdstuk 6** werden de resultaten beschreven van een studie waarin de effectiviteit van een begeleide eCGT behandeling op maat werd onderzocht bij patiënten met

psoriasis. Bij deze patiënten was met behulp van vragenlijsten vastgesteld dat zij een psychologisch risicoprofiel hadden, bestaand uit een verhoogd distress niveau. De deelnemende patiënten werden op basis van kans toegewezen aan ofwel de groep die eGCT ontving als aanvulling op de normale dermatologische zorg, ofwel aan de groep die alleen de normale dermatologische zorg ontving. Nadat er gecontroleerd werd voor relevante variabelen (bijv. ziekte-ernst en medicatiegebruik) liet de eCGT groep een grotere verbetering zien in het lichamelijke functioneren (jeuk en vermoeidheid) en de invloed van de aandoening op het dagelijks leven (rolbeperkingen ten gevolge van emotionele en lichamelijke problemen). Er werden geen verschillen tussen de twee groepen gevonden op het gebied van psychologisch functioneren (angstklachten en depressieve klachten), noch in de secundaire uitkomstmaten ziekte-ernst en therapietrouw bij de dermatologische behandeling. De relatie tussen therapeut en patiënt, gemeten aan het begin van de eCGT behandeling, bleek voorspellend te zijn voor verbeteringen in het lichamelijk en psychologisch functioneren. Dit onderstreept het belang van een goede therapeutische relatie in gepersonaliseerde eCGT behandelingen.

Als laatste werd in **Hoofdstuk 7** de kosteneffectiviteit van begeleide eCGT behandeling op maat onderzocht bij patiënten met psoriasis, door middel van een economische evaluatie die gelijktijdig werd uitgevoerd met de effectstudie. In deze economische evaluatie werden de maatschappelijke kosten van de twee onderzoeksgroepen (begeleide eCGT behandeling op maat versus alleen de normale dermatologische zorg) afgezet tegen de verkregen verbetering in ziekte-gerelateerde kwaliteit van leven in beide groepen gemeten tot 6 maanden na de eCGT behandeling. De kosten die in dit onderzoek in kaart werden gebracht waren bijvoorbeeld de kosten voor de ontwikkeling en het onderhoud van de eCGT behandeling, de kosten voor zorgverbruik van de deelnemers en de kosten door ziekteverzuim. De resultaten lieten zien dat begeleide eCGT op maat voor patiënten met psoriasis niet kosteneffectief bleek te zijn in de gehele steekproef, maar wel kosteneffectief was voor twee specifieke patiëntgroepen: patiënten met relatief hoge zelf-gerapporteerde ziekte-ernst en patiënten die een relatief hoge invloed van de aandoening op het dagelijks leven ervaren. Deze resultaten geven aan dat het mogelijk klinisch relevant kan zijn om deze kenmerken bij patiënten in kaart te brengen voorafgaand aan de eCGT behandeling, om kosteneffectieve zorg aan te kunnen bieden aan deze groepen.

De studies uit dit proefschrift onderstrepen het belang van nog niet eerder onderzochte psychologische concepten bij chronische huidaandoeningen, zoals de relevantie van lichaamsbewustzijn en van impliciete processen gerelateerd aan stigmatisatie. Bovendien liet dit proefschrift voor het eerst zien dat begeleide eCGT op maat effectief kan zijn in het verminderen van de invloed van chronische huidaandoeningen op het dagelijks leven, en kosteneffectief kan zijn voor subgroepen van patiënten met een relatief hoge zelf gerapporteerde ziekte-ernst en hoge ervaren invloed van de aandoening

op het dagelijks leven. Toekomstig onderzoek kan voortbouwen op de resultaten uit dit proefschrift om de psychodermatologische kennis te vergroten en hieraan gerelateerde interventies te optimaliseren voor implementatie in de klinische praktijk.

INTERNATIONAL PUBLICATIONS

van Beugen S, van Middendorp H, Ferwerda M, Smit JV, Zeeuwen-Franssen MEJ, Kroft EBM, de Jong EMGJ, Donders ART, van de Kerkhof PCM, Evers AWM. Predictors of perceived stigmatization in patients with psoriasis. Br J Dermatol. Advance online publication. doi: 10.1111/bjd.14875.

Ferwerda M, **van Beugen S,** van Middendorp H, Spillekom-van Koulil S, Donders ART, Visser H, van Riel PCLM., Evers AWM. A tailored guided internet-based cognitive-behavioral intervention for patients with rheumatoid arthritis as an adjunct to standard rheumatological care: results of a randomized controlled trial. Pain. Advance online publication. doi: 10.1097/j.pain.0000000000000845.

van Beugen S, Ferwerda M, Spillekom-van Koulil S, Smit JV, Zeeuwen-Franssen MEJ, Kroft EBM, de Jong EMGJ, Otero ME, Donders ART, van de Kerkhof PCM, van Middendorp H, Evers AWM. Tailored therapist-guided internet-based cognitive behavioral treatment for psoriasis: a randomized controlled trial. Psychother Psychosom. 2016;85: 297-307.

van Beugen S, Maas J, van Laarhoven AIM, Galesloot TE, Rinck M, Becker ES, van de Kerkhof PCM, van Middendorp H, Evers AWM. Implicit stigmatization-related biases in individuals with skin conditions and their significant others. Health Psychol. 2016;35: 861-65.

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van Middendorp H, Kool MB, **van Beugen S**, Denollet J, Lumley MA, Geenen R. Prevalence and relevance of Type D personality in fibromyalgia. Gen Hosp Psychiatry. 2016;39: 66-72.

van Beugen S, Ograczyk A, Ferwerda M, Smit JV, Zeeuwen-Franssen MEJ, Kroft EBM., de Jong EMGJ, Zalweska-Janowska A, Donders ART, van de Kerkhof PCM, van Middendorp H, Evers AWM. Body attention, ignorance and awareness scale: assessing relevant concepts for physical and psychological functioning in psoriasis. Acta Derm Venereol. 2015;95: 444-50.

van Beugen S, Ferwerda M, Hoeve D, Rovers MM, Spillekom-van Koulil, S, van Middendorp H, Evers AWM. Internet-based cognitive behavioral therapy for patients with chronic somatic conditions: a meta-analytic review. J Med Internet Res. 2014; e88.

Ferwerda M., **van Beugen S**, van Burik A, van Middendorp H, de Jong EMGJ, van de Kerkhof PCM, van Riel PLCM, Evers AWM. What patients think about E-Health; Patients' perspective on internet-based cognitive behavioral treatment for patients with rheumatoid arthritis and psoriasis. Clin Rheumatol. 2013;32: 869-73.

Nyklíček I, Mommersteeg PMC, **van Beugen S**, Ramakers C, van Boxtel GJ. Mindfulness-based stress reduction and physiological activity during acute stress: a randomized controlled trial. Health Psychol. 2013;32: 1110-13.

Nyklíček I, **van Beugen S**, Denollet J. Effects of mindfulness-based stress reduction on distressed (Type D) personality traits: a randomized controlled trial. J Behav Med. 2012;36: 361-70.

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Van Beugen S. Het belang van lichaamsbewustzijn bij patiënten met huidaandoeningen. Nederlands Tijdschrift voor Dermatologie en Venereologie. 2016;26: 477-8.

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SUBMITTED ARTICLES

van Beugen S, Ferwerda M, van Middendorp H, Smit JV, Zeeuwen-Franssen MEJ, Kroft EBM, de Jong EMGJ, van de Kerkhof PCM, Kievit W, Evers AWM. Economic evaluation of a tailored therapist-guided internet-based cognitive behavioral treatment for psoriasis. Submitted for publication.

Institute for Health Sciences
Radboudumc

PhD PORTFOLIO

Name PhD student: S. van Beugen	**PhD period:**	***15-03-2010 – 15-12-2016***
Department: Medical Psychology	***Promotor(s):***	***Prof. dr. A.W.M. Evers,***
Graduate School: Radboud Institute for Health Sciences		***Prof. dr. P.C.M. van de Kerkhof***
	Co-promotor(s):	***Dr. H. van Middendorp***

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- RIHS workshop: evalueren van complexe interventies	2010	0.1
- RIHS Workshop: Curing the TMI syndrome	2010	0.1
- RIHS introduction course	2010	1.75
- Reference manager workshop Radboudumc	2010	0.1
- Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2010, 2014	1.95
- RIHS workshop: How to convince the editor	2010	0.1
- Research School Experimental Psychopathology (EPP): Basic statistical course: practical data analysis	2010	1.0
- EPP: Riding the third wave of CBT	2011	1.0
- EPP: Advanced Statistical course: multilevel analysis	2011	1.0
- EPP: Test construction	2012	1.0
- EPP: Advanced Statistical course: mediation analysis	2012	1.0
- EPP: Mind-Body	2012	1.0
- Maastricht University: cost-effectiveness course	2013	1.75
- EPP: Towards DSM-5 and beyond	2013	1.0
b) Seminars & lectures		
- IFPA conference, Stockholm, Sweden (invited speaker)	2012	1.5
- IFPA conference, Stockholm, Sweden (2x invited speaker)	2015	1.5
- LUMI psychodermatology seminar, Tallinn, Estonia	2016	0.2
c) Symposia & congresses		
- Psychology & Health conference, Lunteren (visitor)	2010	1.0
- Medicine 2.0 conference, Maastricht (visitor)	2010	1.0
- EPP day, Utrecht (visitor)	2010	0.5
- EPP day, Utrecht (visitor)	2011	0.5
- ARPH conference, Lunteren (2x oral)	2011	1.0
- VGCT conference, Veldhoven (oral)	2011	0.5
- Health Valley conference, Nijmegen (oral)	2012	0.5
- EPP day, Utrecht (visitor)	2012	0.5
- NCBEP (RIHS): annual science day (visitor)	2012	0.2
- Netherlands Society for Research on Internet Interventions (NSRII) symposium, Amsterdam (oral)	2012	0.2
- NVPD psychodermatology symposium, Amsterdam (visitor)	2012	0.2
- ARPH conference, Enschede (oral)	2013	1.0
- ESDaP conference, Denmark (oral)	2013	1.0

- NCEBP (RIHS) symposium: Working together on personalized healthcare, Nijmegen (laptop demonstration)	2013	0.2
- Medicine 2.0, Londen, United Kingdom (oral)	2013	1.0
- Epp day, Utrecht (visitor)	2013	0.5
- NSRII symposium, Maastricht (visitor)	2013	0.3
- ISRII conference, Valencia, Spain (oral)	2014	1.0
- ARPH conference, Groningen (oral)	2014	1.0
- ARPH conference, Gent, Belgium (poster and oral)	2015	1.0
- EPP PhD day, Utrecht (oral)	2015	0.5
- ESDaP conference, St. Petersburg, Russia (oral)	2015	1.0
- NSRII symposium, Leiden (oral)	2015	0.2
- Psoriasis Vereniging Nederland symposium – World psoriasis day. Lunteren (oral)	2016	0.5
- European Association for Behavioural and Cognitive Therapies (EABCT) congress, Stockholm, Sweden (oral)	2016	1.0
d) Other		
- eHBM executive committee member	2010-2012	1.0
- NSRII executive committee member	2012-present	1.0
- NVPD financial audit committee member	2013-present	0.2
- Junior Researchers Seminar 'ehealth Support Committee (ESC)', member	2010-2012	1.0
- Junior Researchers Seminar Medical Psychology	2011-2012	1.0
- Journal reviewer for 'Health Psychology'	2016	0.1
- Journal reviewer for 'Acta Dermato Venereologica'	2016	0.1
TEACHING ACTIVITIES		
e) Lecturing		
- Leiden University: Bachelor course 'Perspective on Career Planning (POCP) – seminar teacher	2015-2017	15.0
- Master course 'Innovations in eHealth care' – Lecture on eHealth in cognitive rehabilitation	2015-2017	1.0
f) Supervision of internships / other		
- Thesis supervisor Master Health Psychology, Radboud University. Thesis: The role of Type D personality in patients with psoriasis	2011	1.0
- Thesis supervisor Master Health Psychology, Radboud University. Thesis: De rol van automatische processen bij patiënten met psoriasis: een exploratief onderzoek.	2012	1.0
- Minor research Project supervisor Research Master Behavioral Science, Radboud University (3 students). Topic: implicit processes in patients with chronic skin conditions.	2012	1.5
- Thesis supervisor Master Clinical Neuropsychology (CNP), Leiden University. Thesis: Source monitoring and hallucinations in Parkinson's disease	2015	1.0
- Thesis supervisor Master Clinical Neuropsychology (CNP), Leiden University (5 students). Thesis: The effect of watching masticatory videos on masticatory function, quality of life and cognitive ability of elderly people with dementia	2015-2016	5.0
- Thesis supervisor Master Clinical Neuropsychology (CNP), Leiden University. Thesis: Exploring associations between attention bias and interpretation bias with anxiety in clinically anxious youth	2016	1.0
- Thesis supervisor Master Clinical Neuropsychology (CNP), Leiden University. Thesis: Will cerebellar transcranial direct current stimulation improve cognitive function?	2016	1.0
TOTAL		**64.25**

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Sylvia

CURRICULUM VITAE

Sylvia van Beugen werd op 11 maart 1984 geboren te 's-Hertogenbosch. Zij groeide op in Hedel, een dorp nabij 's-Hertogenbosch. Na het behalen van haar VWO diploma aan het ds. Pierson college in 's-Hertogenbosch, begon zij aan de studie psychologie aan de Universiteit van Tilburg. Ze koos voor de richting Psychologie en Gezondheid en behaalde in 2006 haar Bachelordiploma. Vervolgens rondde zij in 2009 twee Masteropleidingen aan de Universiteit van Tilburg af: de Master Psychologie en Geestelijke Gezondheid en de Research Master in de Medische Psychologie. Na voltooiing van haar opleiding werd zij in 2010 als junior onderzoeker aangesteld op de afdeling Medische Psychologie van het Radboudumc. Daar verzamelde zij de data die ten grondslag lagen aan de hoofdstukken in dit proefschrift. In 2013 volgde zij haar promotor Professor Andrea Evers naar de Universiteit Leiden, alwaar zij als onderzoeker en docent werd aangesteld bij de sectie Gezondheids-, Medische en Neuropsychologie. Aan de Universiteit Leiden rondde zij haar proefschrift af en gaf zij onderwijs in de Bachelor- en Masteropleiding Psychologie. Gedurende haar promotieonderzoek maakte zij deel uit van het dagelijks bestuur van de Netherlands Society for Research on Internet Interventions (NSRII) en de Werkgroep eHealth in Behavioral Medicine (eHBM). Zij heeft tijdens haar promotieonderzoek verschillende presentaties (o.a. op uitnodiging) verzorgd op nationale en internationale congressen. In 2013 ontving zij tijdens het congres van de European Society for Dermatology and Psychiatry de Essay Prize voor haar onderzoek over impliciete stigmatisatie-gerelateerde processen bij patiënten met huidaandoeningen (Hoofdstuk 4 van dit proefschrift) en in 2016 ontving zij de Herman Musaph Stichting Literatuurprijs voor haar publicatie over lichaamsbewustzijn bij patiënten met psoriasis (Hoofdstuk 2 van dit proefschrift). Haar promotieonderzoek maakte deel uit van de Nederlands-Vlaamse onderzoeksschool Experimentele Psychopathologie (EPP) en van de onderzoeksschool Radboud Institute for Health Sciences (RIHS). Momenteel werkt Sylvia van Beugen als onderzoeker bij de sectie Gezondheids-, Medische en Neuropsychologie van de Universiteit Leiden aan een onderzoeksproject gericht op de doorontwikkeling van een serious gaming en eHealth interventie voor zowel gezonde als chronisch zieke populaties (ERC Proof of Concept Grant). Ook is zij docent in de Bachelor- en Masteropleiding Psychologie bij de sectie Gezondheids-, Medische en Neuropsychologie aan de Universiteit Leiden.