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SEVERE HEALTH ANXIETY

NOVEL APPROACHES TO DIAGNOSIS AND PSYCHOLOGICAL TREATMENT

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Severe health anxiety: Novel approaches to diagnosis and psychological treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background: It has long been known that severe health anxiety is a common psychiatric condition associated with significant distress, functional impairment, and societal costs. Nevertheless, challenges remain with regard to the diagnosis and treatment of this disorder. As to diagnostic assessment, a recent shift in diagnostic taxonomy for individuals with severe health anxiety has led to a need for reliable instruments to aid clinicians and researchers in assessing the new diagnoses somatic symptom disorder (SSD) and illness anxiety disorder (IAD). As to treatment, individual face-to-face cognitive behaviour therapy (FTF-CBT) is the most researched and widely recommended treatment for severe health anxiety, but the availability of FTF-CBT is poor. Therapist-guided internet cognitive behaviour therapy (G-ICBT) may improve the scalability of evidence-based treatment, but it is unclear if this treatment could be efficacious and cost-effective also if delivered without a therapist or as book-form bibliotherapy. It is also unclear if the effect of G-ICBT is non-inferior to that of FTF-CBT.

Aims: To develop, and evaluate the inter-rater reliability of, a structured diagnostic interview for the assessment of SSD and IAD (Study I). Also, to evaluate the efficacy of three forms of minimal-contact cognitive behaviour therapy for severe health anxiety (Study II) and to investigate their long-term efficacy and cost-effectiveness (Study III). Last, to determine if G-ICBT is non-inferior to FTF-CBT in the treatment of severe health anxiety (Study IV).

Methods: The inter-rater reliability of a new structured diagnostic interview for SSD and IAD was estimated based on concordance between the ratings of an interviewer and an independent clinician who listened to recorded interviews (Study I). The effects of different forms of minimal-contact cognitive behaviour therapy for severe health anxiety were also studied in two randomised controlled trials (RCTs). The first RCT (N=132) compared G-ICBT, unguided internet cognitive behaviour therapy (U-ICBT), and cognitive behavioural bibliotherapy (BIB-CBT) to a waiting-list control (WLC) condition. Primary outcome was short-term change in health anxiety, as measured with the 64-item Health Anxiety Inventory (Study II). Among the secondary outcomes of this trial were long-term symptom levels up to 1 year after treatment, and cost-effectiveness as based on the incremental cost-effectiveness ratio (ICER) vs. the WLC (Study III). The second RCT (N=204) compared G-ICBT to FTF-CBT based on a non-inferiority criterion of 2.25 points on the 18-item Short Health Anxiety Inventory (d=0.3), as assessed over the 12-week treatment period (Study IV).

Results: The inter-rater reliability of diagnostic decisions regarding SSD and IAD based on the new structured instrument – the Health Preoccupation Diagnostic Interview (HPDI) – was moderate (κ=.59) for clinical trial applicants, perfect (κ not applicable) for healthy controls, and almost perfect (κ=.85) for the pooled sample (Study I). G-ICBT, U-ICBT, and BIB-CBT all produced large waiting-list controlled reductions (d=0.80–1.27) in health anxiety (Study II). These effects were then sustained one year after treatment, and cost-effectiveness was high (waiting-list controlled ICERs=£ -134–416) for all three treatment formats (Study III).

In the comparison of G-ICBT to FTF-CBT, the upper limit of the one-sided 95% confidence interval for the difference in change over the 12-week treatment period was 1.98 based on intention-to-treat data, and 2.17 based on per-protocol data. Both estimates were below the non-inferiority margin of 2.25 points, indicating that G-ICBT is not inferior to FTF-CBT in the treatment of severe health anxiety (Study IV).

Conclusions: As hypothesised, the inter-rater reliability of SSD and IAD can be satisfactory if diagnoses are based on the HPDI, though the psychometric properties of this instrument need be studied further (Study I). G-ICBT, U-ICBT, and BIB-CBT are efficacious and cost-effective treatments for severe health anxiety, with the potential to greatly increase treatment availability, not least in the primary and medical care context (Studies II and III). Because G-ICBT is not inferior to FTF-CBT (Study IV), G-ICBT may be regarded as a first-line treatment for severe health anxiety, which calls for further implementation of this treatment format in routine care.

LIST OF PUBLICATIONS

I. **Axelsson E**, Andersson E, Ljótsson B, Wallhed Finn D, Hedman E. The Health Preoccupation Diagnostic Interview: inter-rater reliability of a structured interview for diagnostic assessment of DSM-5 somatic symptom disorder and illness anxiety disorder. *Cogn Behav Ther* 2016; **45**: 259-69.

II. Hedman E, **Axelsson E**, Andersson E, Lekander M, Ljótsson B. Exposure-based cognitive-behavioural therapy via the internet and as bibliotherapy for somatic symptom disorder and illness anxiety disorder: randomised controlled trial. *Br J Psychiatry* 2016; **209**: 407-13.

III. **Axelsson E**, Andersson E, Ljótsson B, Hedman-Lagerlöf E. Cost-effectiveness and long-term follow-up of three forms of minimal-contact cognitive behaviour therapy for severe health anxiety: results from a randomised controlled trial. *Behav Res Ther* 2018; **107:** 95-105.

IV. **Axelsson E**, Ljótsson B, Andersson E, Björkander D, Hedman-Lagerlöf M, Hedman-Lagerlöf E. Cognitive behaviour therapy for health anxiety via the internet vs. face-to-face treatment: a randomised controlled non-inferiority trial. *Manuscript.*

CONTENTS

LIST OF ABBREVIATIONS

BIB-CBT	cognitive behavioural bibliotherapy
CBT	cognitive behaviour therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
ERP	exposure and response prevention
FTF-CBT	individual face-to-face cognitive behaviour therapy
G-ICBT	therapist-guided internet cognitive behaviour therapy
HAI	Health Anxiety Inventory, 64-item version
HPDI	Health Preoccupation Diagnostic Interview
IAD	illness anxiety disorder
IAS	Illness Attitude Scales
ICD-11	International Statistical Classification of Diseases and Related Health Problems 11
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
NNT	number needed to treat
PP	per-protocol
QALYs	quality-adjusted life years
RCT	randomised controlled trial
SHAI	Short Health Anxiety Inventory, 14- or 18-item version
SMD	standardised mean difference
SSD	somatic symptom disorder
U-ICBT	unguided internet cognitive behaviour therapy
WI	Whiteley Index
WLC	waiting-list control

1 INTRODUCTION

B. *Death series*

1) Being at a burial.
2) Being at a house mourning.
3) The word *death*.

[…]

C. *Illness series*

1) Hearing that an aquiantance has cancer.
2) The word *cancer*.

[…]

From: Wolpe J. The systematic desensitization treatment of neuroses. J Nerv Ment Dis 1961; 132: 189-203. Reproduced with permission.

Around 1960, Joseph Wolpe (1915–1997) laid out the basics of a therapeutic practice which would eventually evolve into exposure-based therapies as we know them today [1, 2]. First in a case series, Mrs. A was described as suffering from a phobia "concerning illness and death" which "had its origin during childhood". After approximately twelve sessions per hierarchy ("death" and "illness", see above), Mrs. A was reported to have overcome this fear altogether.

At the time, severe health anxiety was regarded to "respond rather badly" to psychotherapy [3], and a widespread idea was that a pathological fear of severe disease is always secondary to another psychiatric condition [4]. In contrast, in the opinion of Wolpe, there was no doubt that the excessive fear described by Mrs. A was a problem in its own right, and that it was to be approached in more or less the same way as other syndromes that we now refer to as anxiety- or obsessive-compulsive spectrum disorders.

Today, we know that severe health anxiety is a common problem with negative consequences for both the individual and society at large. A large number of clinical trials have also corroborated that cognitive behaviour therapy, which typically has much in common with the practices of Wolpe, is a highly efficacious treatment for severe health anxiety [5, 6]. However, the availability of this type of treatment is still poor, and a major challenge of evidence-based mental health is to develop new strategies to reach and help as many patients as possible [7].

The present thesis describes the development of new and efficacious methods of delivering exposure-based cognitive behaviour therapy for severe health anxiety. My hope is that the work here presented will contribute to reduced suffering and increased quality of life for the many suffering from this understudied condition.

Stockholm, September 2018

1.1 SEVERE HEALTH ANXIETY

1.1.1 A tentative definition

Severe health anxiety, approximately the same thing as hypochondriasis [a], is a psychiatric condition characterised by a persistent and excessive fear of, or preoccupation with, having or acquiring a serious health condition, such as terminal cancer or a progressive neurological disorder. This fear or preoccupation leads to clinically significant distress or functional impairment [8], and is typically accompanied by a preoccupation with bodily symptoms [9] and a strong fear of death [10]. The conviction of being ill can be strong, but not delusional. A brief clinical vignette is presented below:

Ever since the death of her mother, Judy has gradually become more aware of her body and day-to-day physical sensations. Almost every time she experiences aches and pains, a slight nausea, fatigue, or muscle twitching, Judy worries about having cancer, a serious motor neuron disease, or an undiscovered heart defect. In an attempt to cope with the risk of being ill, Judy spends most nights researching medical information, explanations for her symptoms, and shopping for dietary supplements on the internet. In order to rule out the possibility of having a severe disease, Judy thoroughly examines her body for lumps, dots, and rashes at least two times a day, and also visits her general practitioner several times per month. So far, Judy has always been reassured by her doctor that her symptoms are not a sign of serious disease. This usually gives Judy a strong sense of relief, but it is typically not long before she is struck by the thought that something might have been missed. At the very least, she begins to worry about some other disease within the next few days. The persistency of Judy's health anxiety has not only caused her sleep problems, but also taken a toll on her social and family life. Judy regularly discusses the seriousness of her symptoms with her partner, who has become gradually more frustrated with the situation, especially as Judy has become more preoccupied also with the health of her children. The thought of being seriously ill – perhaps even dying – has made Judy lose interest in many everyday activities, and she rarely gets in touch with her friends. On several occasions, Judy has also found the thought of having cancer so unbearable that she called in sick from work. Judy feels as though her body has become her worst enemy, and that she is always prepared for the worst. She would do anything to be certain, once and for all, that her symptoms are not worth worrying about.

a. The terms are often (but not always) used interchangeably, and their exact meanings vary over contexts. Whereas "hypochondriasis" is the traditional term, "health anxiety" and "severe health anxiety" are newer terms preferred by many researchers and clinicians to (1) reduce stigma [11], (2) emphasize similarities with other psychiatric conditions such as social anxiety disorder and general anxiety disorder [12 13], and (3) signal that worry about health is a dimensional phenomenon (i.e., it varies by degree) [14, 15]. "Hypochondriasis" can refer either to a specific psychiatric diagnosis such as the hypochondriasis diagnosis of the DSM-IV, ICD-10, or ICD-11 (which all differ in terms of diagnostic criteria), or (more loosely) to a clinically significant form of worry about health, as sketched here (1.1.1). See also: 1.1.2–1.1.5.

1.1.2 Categorical versus dimensional perspectives

Severe health anxiety has a broad set of cognitive, behavioural, and emotional characteristics. For example, individuals with this condition are prone to react to disease-related stimuli [16], and are more likely than others to interpret bodily symptoms as indicative of disease [17]. On average, individuals with severe health anxiety also utilise more health care than others [18].

In the general population such characteristics are highly correlated, and it is thus possible to regard health anxiety as a continuous psychological trait, i.e., a relatively stable pattern of cognition and behaviour which ranges on a continuum [19]. In the present thesis, I henceforth use "health anxiety" to refer to this continuous trait, and "severe health anxiety" to denote the psychiatric condition in which the level of health anxiety has reached clinical significance. Notably, however, there appears to exist no non-arbitrary threshold to separate severe health anxiety from milder, presumably benign, forms of health anxiety [20-22].

Historically, the categorical view of severe health anxiety as distinct from milder forms of health worries has nonetheless been more common than the dimensional view, and there may be advantages of both perspectives. For example, whereas the dimensional perspective facilitates the measurement of change, the categorical perspective could be argued to facilitate health care decisions, and constitute the foundation of evidence-based medicine [23].

1.1.3 Diagnosis: the categorical perspective

There is no expert consensus on the appropriate diagnostic criteria for severe health anxiety. Numerous taxonomies have been proposed; both historically [24-32] and in recent years [33-39]. The precise boundaries between severe health anxiety and many other conditions such as functional somatic syndromes and obsessive-compulsive disorders are also disputed [40-42]. This complicates comparison between studies, as well as research in the field in general.

1.1.3.1 Somatic symptom disorder and illness anxiety disorder

The most well-known, researched, and widely cited taxonomy for psychiatric syndromes is the Diagnostic and Statistical Manual of Mental Disorders (DSM), which is published by the American Psychiatric Association. The DSM is periodically revised as based on consensus (expert committees), and now exists in its fifth edition (DSM-5). According the DSM-5, most individuals with severe health anxiety meet criteria for somatic symptom disorder (SSD) or illness anxiety disorder (IAD) [38]. An overview of key diagnostic criteria for SSD, IAD, and other common diagnoses in severe health anxiety is presented in Table 1. Two noteworthy differences between SSD and IAD are the presence of clear somatic symptoms in SSD but not IAD, and the much broader psychological core criterion in SSD as compared with IAD.

There are three diagnostic specifiers for SSD. First, SSD can be classified as mild, moderate, or severe, as based on the presence of somatic symptoms and also the presence of excessive thoughts, anxiety, and/or behaviours. Second, there is a pain specifier, which denotes if pain is the primary somatic symptom or not. Third, there is a persistency specifier, which denotes whether the patient suffers from severe symptoms, marked impairment, and if the duration is

more than six months. There are two IAD specifiers. Patients may be classified as displaying excessive health-care seeking (i.e., care-seeking type) or avoidance of health care (i.e., care-avoidant type).

Table 1. Four psychiatric diagnoses to consider in severe health anxiety.

Taxonomy	DSM-IV	ICD-11	DSM-5	
Diagnosis	Hypochondriasis	Hypochondriasis	SSD	IAD
Psychological core criterion	A preoccupation with the fear or idea of having a serious disease	A persistent preoccupation with or fear about having a serious disease	Either (1) disproportionate and persistent thoughts about the seriousness of-, (2) a persistently high level of anxiety about-, or (3) excessive time and energy devoted to somatic symptoms or health	A preoccupation with having or acquiring a severe illness, a high level of anxiety about health, and the individual is easily alarmed about his or her health status
Somatic symptoms	Yes, the fear or idea is based on the misinterpretation of bodily symptoms	Yes, the fear or idea is associated with the misinterpretation of bodily symptoms	Yes, but not mild somatic symptoms	No or only mild somatic symptoms
Somatic symptoms may be explained by a severe disease	No, the preoccupation persists despite medical reassurance	No, the preoccupation persists despite medical reassurance	Yes, but the psychological reaction has to be excessive	Yes, but the psychological reaction has to be excessive
Excessive illness behaviour	Common but not required [1]	Yes	Common but not required	Yes
Minimum duration	Six months	No	Typically six months	Six months

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5; IAD, illness anxiety disorder; ICD-11, International Statistical Classification of Diseases and Related Health Problems 11; SSD, somatic symptom disorder.
[1] The individual has consulted health care, but not necessarily to an excessive extent.

1.1.3.2 On the abandonment of DSM-IV hypochondriasis

As illustrated in Table 1, the prototypical diagnosis for severe health anxiety in the DSM-IV was hypochondriasis. The DSM-5 work group that oversaw removal of the hypochondriasis

diagnosis also revised the "somatoform disorders" chapter of the DSM-IV as a whole. Most of these diagnoses (i.e., including pain disorder, somatisation disorder, and undifferentiated somatoform disorder) were criticised for having overlapping and seemingly arbitrary criteria. They were also criticised for being difficult to use in clinical practice [43], one reason being the difficulty in declaring somatic symptoms "medically unexplained", and another reason being that "hypochondriasis" had become a pejorative term.

The solution was to merge most of the somatoform disorders into one, namely the SSD diagnosis. Instead of requiring the patient's somatic symptoms to be medically unexplained, the idea was to base a diagnosis on the presence of an excessive psychological reaction to the present health state (i.e., disproportionate thoughts, emotions, and/or behaviours). The IAD diagnosis was then added for those with severe health anxiety who do not experience distinct somatic symptoms. The assumption of the American Psychiatric Association was that of those who met criteria for DSM-IV hypochondriasis, approximately 75% would meet criteria for SSD, and approximately 25% would instead meet criteria for IAD [38].

1.1.3.3 Reception and empirical status of SSD and IAD

The transition from DSM-IV hypochondriasis to DSM-5 SSD and IAD has resulted in both optimism [44, 45] and controversy [39, 41]. On the one hand, the introduction of SSD resonated with previous suggestions to combine different somatoform or functional somatic disorders [46-49], and with observed overlaps in key clinical characteristics [50, 51]. On the other hand, a common view among researchers has also been that it is not clear that it is meaningful to separate individuals with severe health anxiety based on the presence (or non-presence) of somatic symptoms [39, 52, 53]. When I initiated my PhD project in 2013, little empirical work had been done to explore this and other aspects of these new disorders. Over and above the DSM-5 field trials [54], all studies of SSD and IAD had been based on post hoc research criteria [53, 55-57], and there existed no structured interview to aid clinicians and researchers in assessing these diagnoses to study them further.

1.1.4 Symptom scales: the dimensional perspective

Dimensional assessment of health anxiety is typically, though not always [58-60], based on self-rated questionnaires [61-70] or continuous visual analogue scales [71, 72]. One of the first scales to gain recognition as a valid measure of health anxiety was the Whiteley Index (WI). The WI was developed in the 1960s and based on clinicians' definitions of "hypochondriasis" [73], and is still used as a symptom measure and outcome in clinical research [74-77].

In the early to mid-1980s came the Illness Attitude Scales (IAS) which instead was based on statements made by patients who displayed abnormal illness behaviour [78] or thought that they had an undiagnosed disease [79]. As in the case of the WI, the IAS has been referred to as the "gold standard for dimensional evaluation of hypochondriacal symptoms" [80] and used as outcome in several clinical trials [81-83].

Two decades later, the Health Anxiety Inventory was developed in an attempt to capture the cognitive, emotional, and behavioural characteristics of DSM-IV hypochondriasis [14]. In the development of this scale, particular attention was also devoted to differentiating between individuals with high levels of health anxiety and those with actual somatic disease but not severe health anxiety. The Health Anxiety Inventory exists in one original 64-item version (HAI), and two shortened 18-item and 14-item versions (SHAI) [84]. The HAI and SHAI have both gained recognition as psychometrically sound [14, 84, 85], and like the WI and IAS, the HAI and SHAI have also been used as primary outcome in clinical trials [86-88].

1.1.4.1 Facets of the health anxiety construct

A research topic that has received much attention is the dimensionality of health anxiety, i.e., whether there exist meaningful and relatively distinct components into which the health anxiety construct can be segmented. A commonly cited early principal component analysis indicated that the WI can be divided into (I) bodily preoccupation, (II) disease phobia, and (III) disease conviction [73]. A commonly cited finding is that the IAS can be regarded as measuring (I) the cognitive and emotional characteristics of health anxiety and (II) illness behaviour [80]. It is also common to refer to the IAS subscales introduced by the original author, which are: (I) worry about illness, (II) concerns about pain, (III) health habits, (IV) hypochondriacal beliefs, (V) fear of death, (VI) disease phobia, (VII) bodily preoccupation, (VIII) treatment experience, and (IX) the effects of symptoms [79]. As to the HAI and SHAI, factor analyses are indicative of two or three factors. These have typically been interpreted as (I) illness likelihood (i.e., the fear of, and conviction of having, a serious illness), (II) negative consequences (i.e., catastrophic beliefs about having a serious illness), and in the case of three factors: (III) body vigilance [14, 84]. On the whole, facets of health anxiety have varied much between different scales and populations [80, 85, 89]. This being said, my impression is that (a) the fear or conviction of being ill and (b) bodily preoccupation or vigilance both appear to have explained a significant amount of variance, and emerged as distinct though correlated factors, in many studies.

1.1.5 Prevalence, demographics, and natural course

Severe health anxiety is highly prevalent, though it is difficult to say precisely how prevalent. Typically, severe health anxiety has not been included in large-scale epidemiological surveys [90], and estimates are difficult to contextualise due to differences in operationalisation and methodology [91]. Factors likely to influence estimates include, but are not limited to:

- Classification being based on either a self-rated questionnaire or clinical assessment
- The precise choice of questionnaire, cut-off score, and/or diagnosis (see 1.1.3, 1.1.4)
- The extent to which differential diagnoses are surveyed
- If differential diagnoses are surveyed, the precise interpretation of the relationship between severe health anxiety and common differential diagnoses
- Whether medical reassurance from a qualified health care professional is seen as a prerequisite for severe health anxiety, whether a medical examination is routinely conducted within the study itself, and if so the extent of this examination

General population prevalence figures based on questionnaire cut-offs have been presented in the range of 6.4 to 8.3% [92-94]. With the added requirement that the fear has lasted for at least six months despite medical reassurance, the prevalence sinks to around 3.4% [8]. If differential diagnoses are also ruled out, and there is a requirement of clinically significant distress or functional impairment, most prevalence figures are closer to 0.1–0.6% [95, 96]. This most restrictive operationalisation corresponds to the hypochondriasis diagnosis of the third and fourth versions of the DSM, on which most research on severe health anxiety has been based. Prevalence figures are notably higher among patients in medical care, where British estimates based on questionnaire cut-offs are in the range of 17.5–24.7% [97].

It is commonly speculated that the prevalence of severe health anxiety is on the increase due to the emergence of the internet as a source of health-related information [98]. Although this has face validity insofar as health-related information seeking has been shown to increase health anxiety [99], and online searches are no exception [100], there is no reliable way to determine if the prevalence of severe health anxiety is higher today than it was twenty or fifty years or ago. It may also be noted that there is a history of similar speculations regarding the impact of societal changes on health anxiety. In the 1960s, a presumed increase in the prevalence of severe health anxiety was attributed to “a spreading perversion of individualism” [101], in the 1940s an increase was attributed to “the press and other agencies” [102], and in the 1930s: ”a decay of belief in a Divine providence” [103].

Severe health anxiety is probably evenly distributed over genders and ages, and can debut at any age [8, 91, 104]. For example, based on data from a recent clinical trial, I found that patients reported experiencing their first episode of severe health anxiety between 5 and 67 years of age, and that their present episode had lasted for 0.5 to 49 years. The finding that high levels of health anxiety can be seen also in children and adolescents has been replicated in several samples [61, 105-108].

As to natural course, the longest longitudinal study of severe health anxiety that I am aware of was 4–5 years, after which (54/85) 64% of medical outpatients diagnosed with DSM-III-R hypochondriasis still met criteria for this diagnosis. Studies by other research groups have been based on follow-up periods around 1 year, and presented figures of 16%, 48%, and 49% [109]. It is thus probably the case that approximately half of cases diagnosed with severe health anxiety are to be regarded as "chronic", in the sense that spontaneous remissions is not to be expected within the next few years.

1.1.6 Comorbidity, quality of life, and functional impairment

On average, individuals with severe health anxiety report lowered quality of life [93, 110], and psychiatric comorbidity rates are high. For example, one study based on sampling from the general population of Australia compared individuals with severe health anxiety to those without severe health anxiety and found an odds ratio of 8.2 (95% CI, 4.2–16.0) for major depressive disorder, 10.6 (95% CI, 5.3–21.5) for panic disorder, and 9.3 (95% CI, 4.5–19.2) for generalised anxiety disorder [8]; similar to the comorbidity of other anxiety disorders [111].

Severe health anxiety is associated with functional impairment, not least in terms of cognitive and social capacities, as well as reduced capacity for emotion regulation [8, 18, 110, 112, 113]. A high level of health anxiety is associated with low self-rated health [114], which in turn is a strong predictor of mortality even if health state and impairment is controlled for [115]. A higher level of health anxiety is also predictive of a higher probability of ischaemic heart disease, regardless of whether common cardiovascular risk factors such as heritability and lifestyle factors are taken into account [116].

1.1.7 Socioeconomic implications

As a consequence of functional impairment, heightened health care utilisation [94, 95, 117, 118], and sick leave [8, 112], severe health anxiety is associated with considerable societal costs. This has been seen also in the Scandinavian context, where a Norwegian study has indicated that severe health anxiety is a strong predictor (crude OR=5.34 [95% CI, 3.69–7.75]) of disability pension award during 1–7 years of follow-up, and that the predictive power of health anxiety remains after adjustment for variables such as gender, income, general anxiety, and somatic conditions [119]. There are also tentative results from Denmark indicative of an increase in sickness-related benefits [120] and health care costs [18] in individuals with severe health anxiety. The effects of such costs are underscored by the high prevalence of severe health anxiety in early years, in combination with the high probability of a chronic course (see 1.1.5).

1.1.8 Neurobiology

Although the specific neurobiology of health anxiety has rarely been studied, it is reasonable to assume that functional and structural neurobiological correlates of severe health anxiety largely coincide with those of fear learning and anxiety disorders [121-123], as well as correlates of functional somatic conditions and interoceptive awareness [124, 125]. In other words, it is

reasonable to expect heightened health anxiety to be associated with deviations in activity of areas such as the amygdala, hippocampus, insula, anterior cingulate-, and prefrontal cortex.

However, results have not been fully in line with this hypothesis. A recent study indicated that in response to health-related threat, high health anxiety was not associated with increased activation of the amygdala or anterior cingulate cortex [126]. More in line with expectations, an earlier study showed that when exposed to words shown to elicit arousal in panic disorder (e.g., "heart attack"), individuals with panic disorder and individuals with severe health anxiety showed equally slowed reaction times and also similar deviations in brain activity (e.g., increased activation of prefrontal areas, thalamus, and the middle temporal cortex) as compared to healthy controls [127].

As to structural correlates, one research group has presented preliminary evidence that health anxiety is associated with small left and right orbitofrontal cortex, large left but not right thalamus, small pituitary gland, but no deviations in caudate nucleus or anterior cingulate cortex volumes [128, 129]. Studies cited under this segment have however been small, none of the findings have been replicated, and it is also unclear in which way functional and structural brain correlates are causally related to the aetiology or development of severe health anxiety.

1.1.9 Aetiology and maintenance

Health anxiety is modestly heritable with additive genetic factors explaining 10–37%, and non-shared environmental factors accounting for up to 63–90%, of the variance in facets of the construct [130]. In contrast, the contribution of shared environmental factors appears to be approximately zero. This is comparable to the core symptoms of other anxiety disorders such as panic disorder and generalised anxiety disorder [131].

Anecdotal evidence is sometimes cited to support the idea of a link between health anxiety and specific traumatic experiences, but most studies of specific environmental causes of severe health anxiety suffer from substantial methodological shortcomings [132-134]. In most cases, designs have been cross-sectional and based on retrospective reporting vulnerable to reporting bias. Studies have generally not taken genetic variation into account, and risk factors have also not been shown to be specific for severe health anxiety (as opposed to other anxiety disorders). Given these many shortcomings, it is only natural that findings with regard to specific environmental risk factors for the development of severe health anxiety have typically not withstood replication [135, 136].

This being said, authors of a recent systematic review of childhood and family factors in the development of severe health anxiety argued for a possible association with experiences of illness during childhood, including the experience of illness or death of a parent [137]. For example, a recent study revealed that young adults (18–25 years old) with ill parents reported a higher mean level of health anxiety than young adults whose parents were not ill (d=0.21) [138]. There is a need for further research into such putative environmental risk factors for severe health anxiety.

1.1.9.1 A cognitive-behavioural model

In the cognitive-behavioural field, the norm is to conceptualise severe health anxiety as an anxiety disorder, comparable to conditions such as panic disorder and generalised anxiety disorder [12]. As in the case of all anxiety disorders, more is known about what maintains the condition than about what it is that causes it. Though it is common to refer to "*the* cognitive-behavioural model" of severe health anxiety [139, 140], there have been several attempts at understanding health anxiety based on cognitive- or learning theory [13, 141-147], and also several influential models of similar constructs [148, 149]. While most models of health anxiety and similar phenomena show considerable overlap, they also have their particularities, and some [150] have little in common with the current mainstream view of severe health anxiety.

A long-standing learning theory view of severe health anxiety is based on a two-factor model which incorporates respondent and operant learning [151]. This model stipulates that a neutral stimulus (e.g., talk of cancer) is coupled with an unconditioned stimulus (e.g., the death of a loved one), which produces an unwanted emotional response (e.g., fear, anxiety) that is conditioned on the neutral (now conditioned) stimulus (factor 1). Negatively reinforced behaviours then become contingent on the conditioned stimulus, and maintain the conditioned response over time (factor 2). That is, in the example given, avoidance of talk of cancer may be reinforced by the short-term reduction in fear and anxiety. Avoidance of health-related stimuli (negatively reinforced in the short term or not [152]) maintains the fear over time, by preventing new learning to change how the individual reacts to similar stimuli in the future. More could be said with regard to the controversy over the role of language and previous experience in relation to learning [153], the fact that the two-factor model leaves no apparent room for biology to explain why certain fears develop more easily than others [154], and why particular individuals appear to be more prone to fear learning than others. However, an exhaustive discussion of such matters lies beyond the scope of this thesis.

Since the 1980s, it has become common to analyse health anxiety based on cognitive theory, which emphasises the role of information processing and beliefs in relation to perception and emotion [155]. More specifically, cognitive theorists have commonly argued that the activation of dysfunctional assumptions such as "my body is weak and susceptible to illness" is likely to result in an increased focus on bodily processes and a bias toward the interpretation of bodily symptoms as indicative of disease [147]. There has been speculation that in many cases, dysfunctional assumptions may result from early life experiences, such as being frequently encouraged to seek health care [147]. Though health anxiety has been demonstrated to correlate with this type of dysfunctional assumptions [156, 157], no longitudinal study has, to my knowledge, shown that these typically precede other dimensions of severe health anxiety.

Figure 1 illustrates a typical cognitive-behavioural model of how severe health anxiety is maintained over time. The model stipulates that an episode of health anxiety is initiated by one or several stimuli (A); either internal (e.g., headache) or external (e.g., a health-related text). This trigger is perceived in such a way that it gives rise to anxiety or fear about health (B); an emotional response that involves physiological changes such as increased heart-rate

and increased muscle tonus. Attention is increasingly devoted to health-related threats, such as those present in the own body (C). This leads to more stimuli (e.g., physical sensations) being viewed as threats, and threats being experienced as more intense (D). This, in turn, gives rise to behavioural responses (E), which persist because they reduce anxiety and/or fear in the short term, but also contribute to maintaining high levels of health anxiety over time.

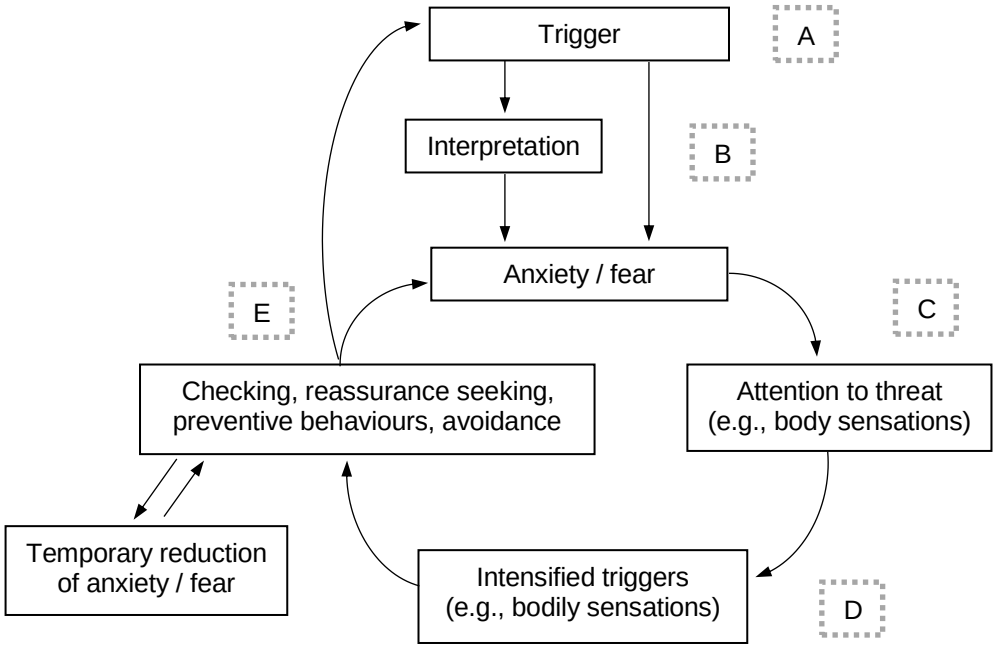

Fig. 1. Cognitive-behavioural model of severe health anxiety. Based loosely on the model of Hedman, Linde, Leiler, Andersson, Axelsson, and Ljótsson [158], in turn based on the work of Furer, Walker, and Stein [144].

In accordance with the model (Figure 1), there is experimental evidence to support the claim that individuals with high levels of health anxiety are more prone than others to view health- and illness-related stimuli as threats to their own personal health [17, 159] (A–B), and to direct their attention to such stimuli [16, 160-162] (C). Individuals with high levels of health anxiety also tend to have a biased perception of health-related cues, such as their own heart rhythm [163, 164]; a finding which ties in with a large empirical literature on the influence of expectancy over perception [165, 166], including interoceptive awareness [167]. A simple verbal instruction to attend to one's body is enough to induce a significant increase in the number of somatic sensations experienced, and such effects are most pronounced in individuals with high levels of health anxiety [168] (D). Studies support the view that health anxiety behaviours can lead to short-term reductions in health anxiety [169, 170], and also that, over slightly longer time periods, an increase in health anxiety behaviours can lead to an increase in health anxiety [99], and that a reduction in health anxiety behaviours leads to a gradual decrease in health anxiety [72, 81, 170]. (E). In conclusion, there is firm evidence that cognitive and attentional distortions are implied in severe health anxiety, and that health anxiety behaviours maintain the condition over time.

However, why health anxiety behaviours have these effects is not entirely clear. From the standpoint of learning theory, negatively reinforced illness behaviours (e.g. frequent symptom checks) are thought to maintain severe health anxiety because they prevent habituation to aversive stimuli (e.g. unattended and unfamiliar physical sensations). Alternatively, illness behaviours may primarily serve to prevent new learning of other, more adaptive, responses to the same stimuli [171]. Warwick [13] was early to propose three cognitively-oriented hypotheses regarding the mechanisms behind the detrimental effect of excessive illness behaviours in severe health anxiety. First, many illness behaviours (e.g. regular pulse checks) may prevent individuals with severe health anxiety from learning that their feared outcomes (e.g. to suffer a heart attack) would not come true even if they acted differently (e.g. stopped monitoring their pulse). Second, some illness behaviours paradoxically bring about new triggers for health anxiety. For example, repeated pinching and scratching aimed at examining rashes might irritate the skin, and monotonous movements aimed at assessing hand mobility and strength may induce fatigue and numbness. Third, illness behaviours may continuously serve to remind individuals with severe health anxiety of the very fear that they are trying to escape. For example, an individual that routinely examines his or her stool for blood indicative of colorectal cancer may be primed to think of this disease when confronted with ambiguous stimuli, and may also be more likely than others to notice minimal anomalies.

1.1.10 Summary and current directions

Severe health anxiety is characterised by a persistent and excessive fear of, or preoccupation with, having or acquiring a serious health condition, and may be regarded as an extreme form of health anxiety; a multifaceted psychological trait which incorporates cognitive, emotional, and behavioural dimensions. According to the DSM-5, most individuals with severe health anxiety meet criteria for somatic symptom disorder (SSD) or illness anxiety disorder (IAD). Prior to the present project, little research had been devoted to SSD and IAD, and there was a need for a structured diagnostic instrument to aid clinicians and researchers studying these disorders further.

The prevalence of severe health anxiety in the general population is approximately 0.5–5%, but much higher in the primary care and medical clinic context. The disorder not only leads to significant suffering, impairment, and lowered quality of life for the individual, but is also responsible for sizable societal costs. Although little is known about the aetiology of severe health anxiety, there is strong evidence that the disorder is at least to some degree maintained through negatively reinforced illness behaviours.

1.2 COGNITIVE BEHAVIOUR THERAPY (CBT) FOR SEVERE HEALTH ANXIETY

1.2.1 A typical protocol

The treatment that enjoys the largest evidence base in the treatment of severe health anxiety is cognitive behaviour therapy (CBT); an umbrella term to denote a heterogeneous family of psychological treatments primarily based on cognitive and/or learning theory [5, 13, 172, 173]. CBT for severe health anxiety is typically based on the type of model presented under 1.1.9.1, and typically involves the following components:

- Self-monitoring
- Psychoeducation
- Exposure and response prevention and/or cognitive restructuring techniques

Self-monitoring is a practice where the patient is instructed to register, or keep some sort of journal, of the situations believed relevant for the problem at hand. This is usually intended both to increase the patient's understanding for his or her own difficulties, and as a means to collect information necessary for working with exposure and/or cognitive techniques (below).

Psychoeducation is the provision of information about psychological processes believed to be of relevance for the patient, such as how learning-, attentional-, and physiological processes contribute to the emergence and maintenance of health anxiety. This too can be seen either as an intervention in its own right, or as a prerequisite for working with other interventions.

In exposure and response prevention (ERP), patients systematically approach aversive stimuli (i.e., exposure) while refraining from attempts at short-term anxiety reduction (i.e., response prevention) [174]. An example would be reading feared texts about a particular disease and thereby inducing health anxiety, without taking steps to reduce this emotional response, e.g., by discussing symptoms with others or visiting a health-care professional. Exposure exercises may be either interoceptive, in vivo, or imaginal [172]. Interoceptive exposure is exposure to physical sensations, typically produced through standardised exercises. Patients may for example be encouraged to hyperventilate so as to induce acute respiratory alkalosis and symptoms such as nausea and palpitations. In vivo exposure is exposure to "real life" outer stimuli such as a hospital or a newspaper article. Finally, imaginal exposure is exposure to anxiety-inducing thoughts and mental images, such as those of how it would be to develop motor neurone disease.

Cognitive restructuring techniques have as their common aim to change characteristics of the patient's cognition, and specifically those aspects believed to maintain severe health anxiety. In practice, what is referred to is usually interventions based on a particular strain of theory about cognition, and in particular abnormal cognition in psychopathology [147, 155] (see also 1.1.9.1). One common way of accomplishing cognitive restructuring is through so called behavioural experiments [175], where exposure to triggers for health anxiety is used as a means of subjecting the patient's health-related assumptions and predictions about the world to

empirical investigation. In concrete terms, a patient who avoids heavy training due to a fear of myocardial infarction may for example be asked to engage in training as a behavioural experiment, with the aim of testing the hypothesis that this will lead to a heart attack.

There is a discussion among researchers and clinicians about the relationship between behavioural experiments and ERP [175-177]. The terms are reflective of theoretical emphasis; the former having grown out of cognitive-, and the latter of behaviour therapy [175, 178]. The aim of ERP has traditionally been seen as achieving extinction (unlearning) of responses to triggers for anxiety, and most treatments incorporating ERP have instructed patients to complete a large number of exposure exercises with the aim of achieving habituation; a reduction of the emotional response, thought to be indicative of new learning [171, 179, 180]. In contrast, treatments based on behavioural experiments have traditionally emphasised the importance of changing dysfunctional thoughts and assumptions through the process of collaborative empiricism [181], i.e., that the patient and therapist engage in a joint investigation into the empirical status of the patients' thoughts and beliefs, and that behavioural experiments are designed so that they target specific thoughts intended for evaluation [175].

Contrary to long-held dogma, there is preliminary evidence that habituation (at least the degree to which habituation is achieved within each exposure session) is not predictive of outcome in exposure therapy [171], and that rather than being a corrective process by which a fear memory is gradually diminished or replaced, exposure works by producing non-fear associations which coexist and "compete" with the fear memory [182]. There are experimental studies which suggest that the efficacy of exposure therapy may be determined by other factors than habituation, including the variability of exposure, the degree to which the outcome of an exposure session is unexpected, and the degree to which a broadening of the patient's behaviour repertoire is achieved [171, 183]. This theoretical framework may be relevant for both exposure and behavioural experiments, and has further blurred the line between the two, which are also likely to be approximately equally efficacious in the treatment of severe health anxiety [184].

1.2.1.1 The protocol here investigated

In the clinical trials detailed in this thesis (see 3.2–3.5), CBT for severe health anxiety was based on a mainstream CBT model of severe health anxiety (see 1.1.7.1). The initial phase of treatment focused on self-monitoring and psychoeducation, and subsequent work focused on ERP. The rationale for ERP focused primarily on the importance of habituation, and was thus a relatively traditional exposure-based CBT with little reference to cognitive theory. Brief mindfulness exercises were also introduced as a method of inducing and enhancing exposure, e.g., by reducing covert (i.e., unobservable) negatively reinforced illness behaviours, such as symptom-checking and worrying about heath. For an overview of the treatment, see Table 2.

Table 2. Schematic overview of the treatment protocol investigated in this thesis.

Module/ Session	Main theme	Main homework exercise
1	Introduction to health anxiety and CBT	Behaviour diary, mindfulness exercise
2	A model of severe health anxiety	Idiosyncratic model, mindfulness exercise
3	Interoceptive exposure	Interoceptive exposure, mindfulness exercise
4	Response prevention	Response prevention, mindfulness exercise
5	Exposure in vivo	Exposure and response prevention
6	Imaginal exposure	Exposure and response prevention
7	Imaginal exposure, thoughts about death	Exposure and response prevention
8	Common obstacles to exposure	Exposure and response prevention
9–10	Exposure continued	Exposure and response prevention
11	Summary of the treatment, relapse prevention	Exposure and response prevention, summary
12	Focus on the future	Exposure and response prevention, relapse prevention, how to deal with health care

Abbreviations: CBT, cognitive behaviour therapy.

1.2.2 Less common protocols

There exists a number of therapies which could be said to be based on cognitive- or learning theory, but which employ a combination of treatment components that is unconventional and relatively experimental in the treatment of severe health anxiety. Some of these less common protocols have nevertheless been included in influential reviews of CBT for severe health anxiety [185, 186], where, unfortunately, no distinction was made in relation to the most common type of protocol that is the main focus of this thesis (1.2.1). For sake of clarity, here follows a description of less common protocols that have been tried for severe health anxiety, and an attempt at briefly highlighting why these differ from the conventional form of CBT for severe health anxiety.

Acceptance and commitment therapy is a treatment which does not employ ERP or cognitive strategies in the conventional sense. Unlike traditional CBT, the treatment is explicitly built around increasing psychological flexibility, which is the ability to "[get in contact with] the present moment fully as a conscious human being, and based on what the situation affords, [change] or [persist] in behaviour in the service of chosen values" [187]. Acceptance and commitment therapy has been demonstrated to be efficacious for severe health anxiety in one pilot study and one RCT with a large waiting-list controlled effect [188, 189]. A pilot study has also indicated that it is feasible to deliver acceptance and commitment therapy for severe health anxiety via the internet [190].

Attention training therapy is concerned with the reduction of self-focused attention believed to elicit and exacerbate health anxiety [191]. There is a connection to cognitive theory in that lowered attention to physical sensations is believed to lead to more accurate beliefs about symptoms [192], but attention training therapy does not involve any other varieties of cognitive restructuring or exposure. Attention training therapy has been demonstrated to be efficacious for severe health anxiety in one small case series study [192]. A small RCT (N=36) also found no significant difference in the effect on health anxiety in comparing three weeks of attention training therapy to three weeks of response prevention (d=0.11) [72].

Behavioural stress management is based on the assumption that some react to stress with severe health anxiety, and the intervention aims to reduce this reactivity by relaxation training, problem solving, and health-promoting behaviours such as physical training and a dietary changes. Unlike conventional CBT for severe health anxiety, behavioural stress management does not involve ERP or cognitive restructuring. Behavioural stress management for severe health anxiety has been evaluated in two RCTs. Both RCTs were indicative of large within-group effects, and one trial reported a large waiting-list controlled effect on health anxiety [71, 193]. When compared to conventional CBT, behavioural stress management has been shown to be inferior, but the difference has been small to moderate in size [71, 193], with no difference at long-term follow up [71]. In one of the RCTs, behavioural stress management was delivered via the internet, which shows that this is a viable format [193].

Explanatory therapy is a straightforward educational program which emphasises the role of perception and emotions in relationship to somatic symptoms. As in conventional CBT, a key aim is to make the patient aware of how selective attention to bodily processes is likely to increase health anxiety over time, and the provision of information is also intended to lead to extinction of "the emotional component" of severe health anxiety [194]. However, unlike in the case of conventional CBT, explanatory therapy does not involve orthodox exposure or cognitive techniques. Instead, distraction from aversive stimuli is encouraged, and medical reassurance is seen as a component of the intervention [194]. Explanatory therapy has been efficacious in one RCT with a large waiting-list controlled effect on health anxiety [195].

Metacognitive therapy does not aim to challenge dysfunctional assumptions about health in the same way as conventional CBT. Instead, the treatment focuses on reducing worry and maladaptive coping by changing negative metacognitive beliefs (e.g., "It is impossible for me to stop worrying about my health if there is no medical explanation for my symptoms"), and by incorporating attention training techniques in the treatment. Metacognitive therapy has showed promise in a single case design study of four patients, which demonstrated large reductions in health anxiety that were sustained at six months follow-up [196].

Mindfulness-based cognitive therapy combines some of the educational aspects of conventional CBT with a strong emphasis on mindfulness meditation. The treatment aims to develop a more accepting and less reactive stance towards thoughts and emotions, and also to prevent future relapse [146]. There is also an emphasis on approaching aversive thoughts with curiosity and feelings of compassion [197], and to engage with the present moment in a way thought to be incompatible with anxiety [146]. However, the treatment does not involve conventional ERP or cognitive techniques. Mindfulness-based cognitive therapy has been shown to produce a reduction in health anxiety in one small pilot study [198], and was superior to a treatment-as-usual condition in one RCT [199].

Problem-solving therapy is, like conventional CBT, a practical and highly structured treatment, but the focus of the treatment is on acquiring problem solving as a coping skill, rather than working with exposure or cognitively-oriented strategies. A controlled trial (N=48) where the treatment allocation was a function of admission date did not show any

noteworthy difference in effect between six weeks of problem-solving therapy and six weeks of education in accordance with a conventional CBT model. There was a moderate to large reduction of health anxiety in both groups, and this was sustained up to six months after treatment [200].

1.2.3 Treatment delivery formats

There are many ways to deliver CBT. In the present thesis, *minimal-contact CBT* denotes those delivery formats which involve little or no contact with a therapist. Regardless of delivery format, CBT for severe health anxiety rests on the same theoretical foundation and behavioural strategies (see 1.1.9.1 and 1.2.1).

1.2.3.1 Individual face-to-face CBT (FTF-CBT)

Individual face-to-face CBT (FTF-CBT) is the most researched and widely recommended form of CBT for severe health anxiety, and anxiety disorders in general [201]. In FTF-CBT, the patient has regular meetings with a therapist, and most of the communication is done face-to-face. The treatment is approximately 5–15 weeks long, with weekly 30–60-minute sessions [5]. Between these sessions, the patient engages in homework exercises and applies the treatment principles in everyday life. This work is typically guided by the use of worksheets, which are completed in pencil and paper format, and continuously reviewed at each treatment session.

1.2.3.2 Minimal-contact CBT (G-ICBT, U-ICBT, and BIB-CBT)

In conventional therapist-guided internet CBT (G-ICBT), the treatment content is conveyed in text form, via a secure online treatment platform where the patient is assigned a personal account (Figure 2). The text is usually approximately 100–150 A4 pages long, and segmented into 5–15 chapters, commonly referred to as *modules*, which include educational material and instructions for behaviour change.

Throughout the treatment, the patient communicates with a therapist through asynchronous, email-like, text messages via the treatment platform. The therapist is the same over the entire treatment period, but the role of the therapist is somewhat different to that in FTF-CBT. In G-ICBT, the focus is more on emotional and technical support, and less on psychoeducation [202]. This is because the treatment content is highly structured, and most information necessary to induce behaviour change is already provided in the modules [203, 204].

It is typically the case that the patient is expected to complete approximately one module per week, which is to say that the patient is expected to read the material, work with the intended homework exercises, and answer a series of written questions intended to stimulate reflection and feedback to the therapist. In other words, like FTF-CBT, G-ICBT is a practical treatment where the patient is expected to complete the equivalent tasks and behaviour changes, and the typical length of G-ICBT (ca 8–12 weeks) is also very similar to that of FTF-CBT.

Access to new treatment modules is typically given sequentially by the therapist, at the pace at which modules are completed by the patient. As in FTF-CBT, several procedures of the

treatment are guided by the use of worksheets. These are presented on the treatment platform, completed and stored online, and can be accessed by both the patient and therapist (Figure 2).

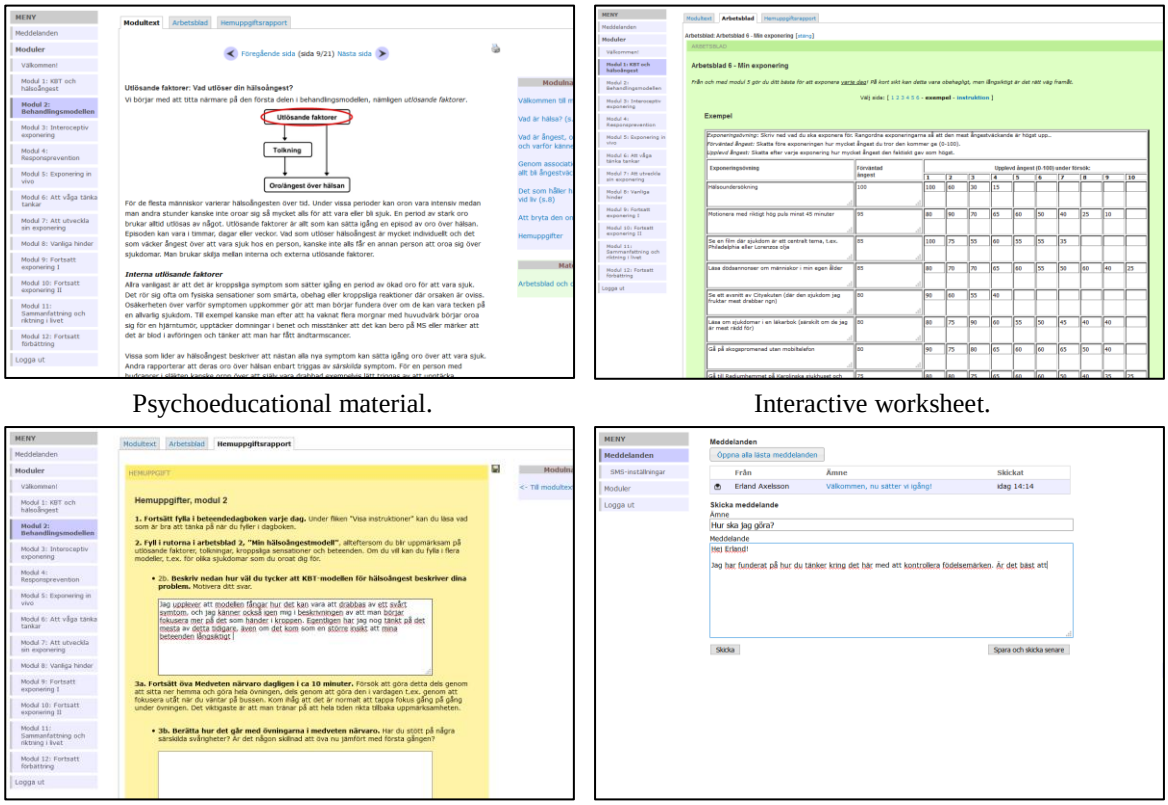

Fig. 2. Online treatment platform in therapist-guided internet cognitive behaviour therapy (G-ICBT).

A slightly different treatment format is unguided internet CBT (U-ICBT), which as the name suggests is the very same thing as G-ICBT but without a therapist. That is, as in the case of G-ICBT, the patient is expected to work with the treatment content which is presented in text form, divided into modules, on a web-based platform. As is the case with G-ICBT, the basic tenet of U-ICBT is also that the patient is to work with the very same types of exercises and behaviour changes as in FTF-CBT [205].

In cognitive-behavioural bibliotherapy (BIB-CBT), CBT is administered via a structured self-help text which is presented in book form rather than on an online platform [206, 207]. Thus, the modules of G-ICBT and U-ICBT take the form of book chapters, and the aim is to convey the information necessary for the patient to work with the same exercises and strategies thought to produce therapeutic effects in FTF-CBT. BIB-CBT can imply various degrees of therapist support; anywhere from no support at all, to several face-to-face sessions with a therapist [208].

1.2.4 Systematic review of RCTs of CBT for severe health anxiety

Techniques reminiscent of present-day CBT were used in the treatment of severe health anxiety at least as early as the 1960s [1]. Yet it is only since the mid-1990s that the effects of CBT on this condition have been evaluated in RCTs; often regarded as a gold standard design of clinical trials to inform evidence-based practice, due to the control over confounding variables [23, 209]. Here follows a systematic literature review of RCTs to compare CBT (see 1.2.1 for details) to at least one other condition in the treatment of severe health anxiety. I searched PubMed and PsycINFO last on June 7th, 2018, and assessed all references from previous reviews [5, 173, 185, 186].

Not counting the present project, the search identified 13 RCTs [71, 75-77, 81, 83, 86-88, 193, 210-212], which involved 20 comparisons of CBT and a control (total unique N=1491): 9 vs. a waiting-list, 4 vs. another psychological intervention, 2 vs. treatment-as-usual, 2 vs. an antidepressant, 2 vs. a pill placebo, and 1 vs. a psychological placebo. Meta-analyses are here based on random effects models fitted under restricted maximum likelihood, self-report symptom measures, and the Hedges' *g* effect size, for which it is common to interpret absolute values of 0.20 as small, 0.50 as moderate, and 0.80 as large [213]. Heterogeneity among studies is reported based on the Q- and I^2-statistics, where the latter denotes the percentage of the variance between studies attributable to true differences between studies rather than random (sampling) error. A common way to interpret I^2 is that 25%, 50%, and 75% stand for low, moderate, and high heterogeneity, respectively [214]. The aggregate overall controlled effect size of all comparisons (Figure 3) was large (g=0.86 [95% CI, 0.61–1.11]), and as expected given the great variety in control groups, heterogeneity was large (Q_{19}=83, P<.001; I^2=80%).

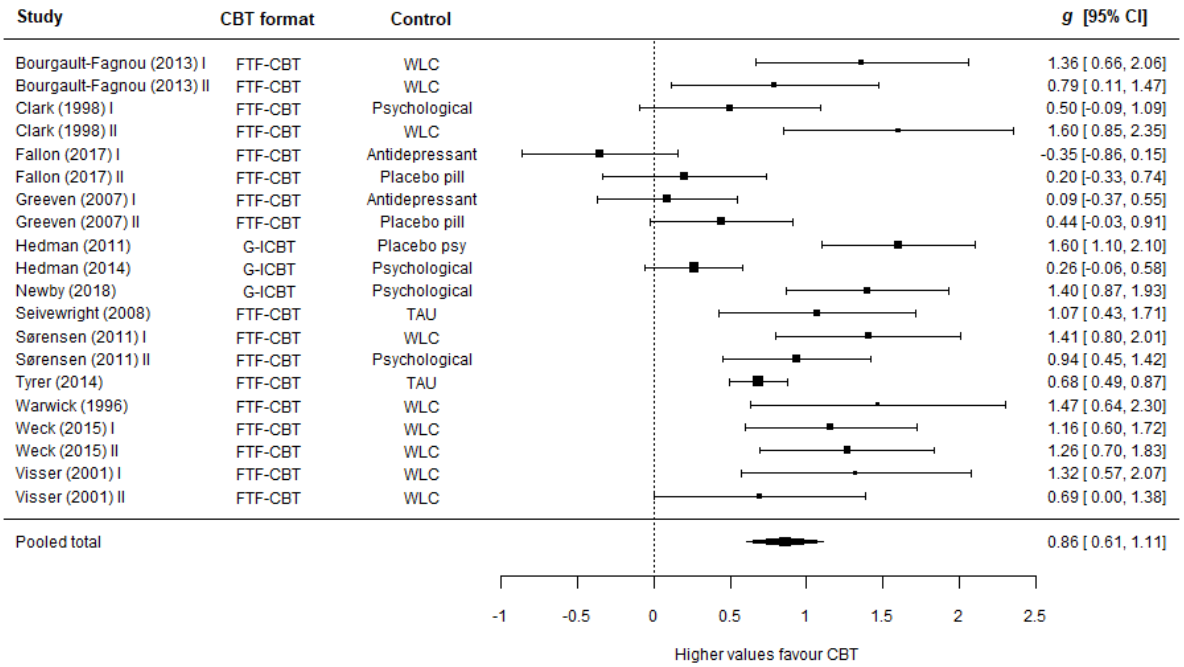

Fig. 3. Meta-analysis of self-rated health anxiety in randomised controlled trials of cognitive behaviour therapy versus another condition in the treatment of severe health anxiety. Random-effects model fitted under restricted maximum likelihood, and with effects expressed as Hedges' *g*. Abbreviations: CBT, cognitive behaviour therapy; FTF-CBT, individual face-to-face cognitive behaviour therapy; G-ICBT, therapist-guided internet cognitive behaviour therapy; Placebo psy, psychological placebo; TAU, treatment-as-usual; WLC, waiting-list.

1.2.4.1 Efficacy of individual face-to-face CBT (FTF-CBT)

Ten of the 13 RCTs concerned FTF-CBT, and the mean number of sessions in these trials was 11.1 (SD=4.2). Based on 13 unique FTF-CBT groups, the aggregate within-group effect on health anxiety was large (*g*=1.64 [95% CI, 1.38–1.90]), with moderate heterogeneity (Q_{12}=26, *P*<.011; I^2=59%). There was also a large pooled within-group effect on secondary symptoms of depression (*g*=0.91 [95% CI, 0.69–1.14]) and general anxiety (*g*=0.94 [95% CI, 0.50–1.38]).

Nine out of fifteen comparisons were against a waiting-list, and based on these the aggregate controlled effect of FTF-CBT was large (*g*=1.22 [95% CI, 0.99–1.44]). Heterogeneity was non-significant (Q_8=6, *P*<.672; I^2=0%), and there was no indication of publication bias. In the largest RCT of FTF-CBT for health anxiety, 445 patients with DSM-IV hypochondriasis in British medical clinics were randomised to five to ten sessions of FTF-CBT or to a treatment-as-usual condition. At the primary endpoint one year after inception there was a 2.98 point (95% CI, 1.09–4.23) advantage of FTF-CBT, equivalent to *g*=0.68, on the 14-item SHAI [86].

Responder rates in FTF-CBT, defined as the proportion of patients who saw their symptoms decrease by a clinically significant degree, were reported based on three of the RCTs [76, 77, 215]. The aggregate responder rate in FTF-CBT was 57% (95% CI, 44–70%), with one study reporting NNT=2.0 (95% CI, 1.5–3.1) versus a waiting-list over six weeks [76]. Remission rates for FTF-CBT, defined as the proportion of patients who scored below a cut-off for severe health anxiety, have only been reported in two RCTs [86, 215], with an aggregate remission rate of 38% (95% CI, 11–65%). Clinically significant improvement after FTF-CBT, defined as a reliable reduction in symptoms combined with a score below a cut-off for severe health anxiety [216], was estimated to be 54% (95% CI, 42–66%) based on two RCTs [75, 83].

As to controlled effects on secondary symptom domains, the aggregate waiting-list controlled effect on depression was moderate (*g*=0.61 [95% CI, 0.28–0.93]; 9 comparisons), and so was the effect on general anxiety (*g*=0.70 [95% CI, 0.41–0.99]; 7 comparisons). Based on the four RCTs which explored the long-term effects of FTF-CBT on health anxiety around 5–6 months after treatment [71, 210, 211, 217], the within-group change in the FTF-CBT-group from post-treatment was approximately zero (*g*=0.01; [95% CI, -0.27–0.29]), and there was a small advantage over treatment-as-usual [86, 210], but no significant controlled effect against behavioural stress management [71] or pharmacotherapy [217]. Three RCTs presented data from a 12-month follow-up [71, 86, 211], and the aggregate within-group change from post-treatment was larger, in the direction of an increase in symptoms, but still not significant (*g*=0.24 [95% CI, -0.01–0.49]).

1.2.4.2 Efficacy of therapist-guided internet CBT (G-ICBT)

Three out of the 20 comparisons concerned G-ICBT. Because these three RCTs had different control groups, their outcomes are here described separately. First, one RCT (N=81) compared 12 weeks of exposure-based G-ICBT (1.2.1.1) to an attention control condition where patients took part in an online forum. There were large controlled reductions in health

anxiety as measured with the HAI (g=1.60), and also in secondary symptoms of depression (g=1.19) and general anxiety (g=1.04) [88]. The improvement of the G-ICBT group was sustained up to one year after treatment [218].

A second RCT (N=158) compared the same exposure-based G-ICBT protocol to internet behavioural stress management, and found a small controlled effect of G-ICBT on health anxiety (g=0.26), but no difference in terms of secondary symptoms of depression (g=0.05), general anxiety (g=0.09), or functional impairment (g=0.00). The within-group effect of G-ICBT was large, and the improvement of the G-ICBT group was sustained at follow-up, six months after treatment [193].

A third RCT (N=102) by another research group was published in parallel with the present project, and compared 12 weeks of G-ICBT to a condition where patients were provided with fortnightly online educational content pertaining to anxiety, and offered contact with a clinician via e-mail or phone. At post-treatment, there was a large controlled effect of G-ICBT on health anxiety (g=1.40), and moderate controlled effects on depression (g=0.44), general anxiety (g=0.78), and functional impairment (g=0.53). The proportion of missing data in this trial was relatively high, with (37/51) 73% in G-ICBT vs. (32/51) 63% in the control condition completing the post-treatment assessment, and (31/51) 61% of the G-ICBT group completing the three-month follow-up. Although this means that the effect sizes are likely to be distorted, the controlled effect on health anxiety was so large that the main conclusion that G-ICBT was more efficacious than the control group is likely to be valid [87].

1.2.4.3 Risk of bias

Based on the criteria of the Cochrane collaboration [219], the risk of bias pertaining to the health anxiety outcomes aggregated in this systematic review was relatively low (Figure 4). The largest threat in this respect was incomplete outcome data, and the employment of inadequate imputation techniques. I did not rate the criterion "blinding of outcome assessment" because all outcomes used for the systematic review were self-rated, and it is debatable if this should generate a rating of "high" or "low" risk of bias.

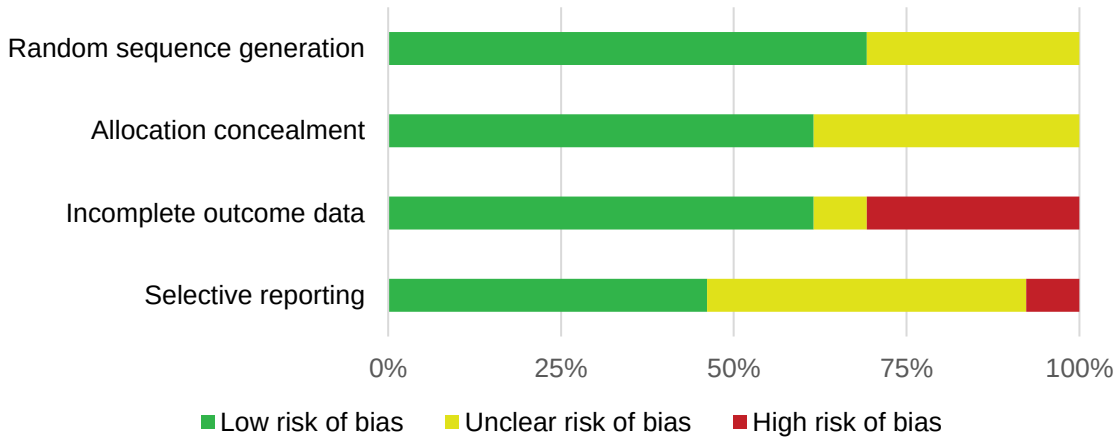

Fig. 4. Ratings based on the Cochrane collaboration's tool for assessing the risk of bias.

1.2.5 Predictors of treatment effect

A handful of studies have investigated predictors of treatment effect in CBT (in any format) for severe health anxiety [220-224]. It should however be noted that very different sets of putative predictors have been investigated in different studies, that studies have been based on very different types of statistical models (and promising models have never been validated in new samples), that there have been clear limitations with regard to statistical power and restriction of range, and that studies have been based on stepwise regression procedures known to produce biased parameter estimates and be susceptible to multiple comparison, ordering, and overfitting effects [225, 226]. The most stable finding has been that higher baseline health anxiety [220, 222-224, 227] is predictive of larger treatment effect, perhaps reflective of regression towards the mean. Larger effects may also possibly be predicted by lower baseline depression [173, 224], stronger therapeutic alliance [220, 228], and higher treatment adherence [220, 224], but probably does not depend (at least to a noteworthy degree) on demographic characteristics such as gender, age, or socioeconomic status [220-224, 227, 228].

1.2.6 Evidence for delivery formats

1.2.6.1 Efficacy of individual face-to-face CBT (FTF-CBT)

Based on the systematic review presented above, FTF-CBT for severe health anxiety has a large effect on health anxiety, large effects on secondary symptoms of depression and general anxiety, and improvements are maintained at least up to six months after treatment. This has been corroborated by non-controlled trials [6], including well-reported single-case designs [169], as well as at least one cluster-randomised trial [74]. FTF-CBT has been shown to work in clinical practice [86], and it is efficacious also based on outcomes assessed by clinicians [81, 212].

The waiting-list controlled effect of FTF-CBT on health anxiety is comparable to the effect on core symptoms of other anxiety disorders such as panic disorder, social anxiety disorder, and generalised anxiety disorder [229]. In terms of response, remission, and clinically significant improvement, the effects of FTF-CBT are also similar to those seen in other anxiety disorders, where the typical finding is that approximately half of the sample meet such criteria at post-treatment [230]. It is debatable if FTF-CBT for severe health anxiety meets the American Psychological Association criteria for an “empirically supported treatment” [231] (i.e., the highest level of evidence), which requires superiority over a placebo or another active treatment in at least two independent trials by independent research groups. This is because one out of two RCTs where FTF-CBT has been demonstrated to be more efficacious than an active control was a cooperative project involving two research groups [71, 211]. My conclusion is nevertheless that the evidence base for FTF-CBT in the treatment of severe health anxiety is strong.

1.2.6.2 Efficacy of minimal-contact CBT (G-ICBT, U-ICBT, and BIB-CBT)

Prior to the present project, no direct comparisons of FTF-CBT, G-ICBT, U-ICBT, or BIB-CBT had been done in the treatment of severe health anxiety. Speculation into the relative

efficacy of these delivery formats therefore had to be based either on indirect comparison of effects in different studies, or on direct comparison of effects on other psychiatric conditions.

The three RCTs surveyed under 1.2.4.2 suggest that the effects of G-ICBT on severe health anxiety can be similar to those of FTF-CBT. This is in line with the more than 100 RCTs of G-ICBT in the treatment of psychiatric and somatic conditions [232], where at least 38 RCTs have focused on the treatment of anxiety disorders [233]. A recent meta-analysis based on direct comparisons of G-ICBT and FTF-CBT for psychiatric and somatic conditions demonstrated an aggregated controlled effect size that was close to zero (g=0.05 [95% CI, -0.09–0.20]) [234]. In other words, it is probably the case that for most patients and most conditions, G-ICBT is as efficacious as FTF-CBT. It could however be that the difference in effect depends on the condition to be treated. Prior to this project, a direct comparison between G-ICBT and FTF-CBT in the treatment of severe health anxiety had never been conducted.

As to minimal-contact CBT without a therapist, two published clinical trials of BIB-CBT could be of interest, but could not be included in the systematic review (1.2.4). First, a small RCT (N=40) saw promising waiting-list controlled effects of four weeks of BIB-CBT, but was based on an unconventional operationalisation of severe health anxiety, and large group differences in symptom levels at baseline [235]. Second, another waiting-list controlled trial (N=40) focused on patients who met criteria for DSM-IV hypochondriasis. This trial also showed promising results, but did not employ randomisation and also suffered from a high level of attrition [236]. These methodological limitations make it difficult to draw conclusions about the efficacy of BIB-CBT for severe health anxiety.

For most conditions, a typical finding has been that therapist-guided CBT (e.g., G-ICBT) is more efficacious than unguided CBT (e.g., U-ICBT and BIB-CBT). A meta-analysis of 2014 identified eight direct comparisons of G-ICBT and U-ICBT for any psychiatric disorder [237], and found that G-ICBT (i.e., therapist support) was associated with a slightly larger effect on primary symptom measures (SMD=-0.27 [95% CI, -0.45–-0.10]), and also better odds for treatment completion (OR=2.76 [95% CI, 1.68–4.53]). Similarly, a review of internet CBT published in 2007 [205] showed a strong positive correlation (ρ=0.75; P<0.01) between the time that therapists spent per patient and effect on the primary outcome. It is however difficult to interpret the latter finding because likely confounders such as treatment length and means of recruitment were not taken into consideration. It should also be noted that recent direct comparisons of G-ICBT and BIB-CBT [238-240] have shown surprisingly similar results of these treatment formats.

1.2.7 Mediators of change

Given that CBT has now been demonstrated to be efficacious for severe health anxiety, the focus of research has increasingly turned not only to the challenge of dissemination but also attempts at further increasing treatment efficacy and understanding mechanisms of change. One way of approaching these issues is through the study of mediators of treatment effect; i.e., variables which change subsequent to an intervention and prior to change in an outcome

[241]. There is preliminary evidence that the effect of G-ICBT on core features of health anxiety (disease conviction and fear and worry about illness) is mediated by lowered perceived risk of disease, less attention devoted to symptoms, and reduced intolerance of uncertainty, but not perceived awfulness of disease [242]. Based on a more loose conceptualisation of mediation as purely an interaction of growth curves, the waiting-list controlled effect of FTF-CBT on health anxiety also appears to be mediated by a reduction in dysfunctional attributions of bodily symptoms [184], and the effect G-ICBT over and above behavioural stress management on health anxiety appears to be mediated by an increase in non-reactivity to inner experiences [243]; the ability to experience emotions, thoughts, and physical sensations without reacting on them [244].

1.2.8 Cost-effectiveness and cost-utility

Cost-effectiveness refers to the study of effects in relation to costs, in the comparison of possible courses of action [245]. Most cost-effectiveness analyses are based on the incremental cost-effectiveness ratio (ICER), defined as the difference in condition effects divided by the difference in condition costs [245]. Effects can be measured in various ways, either with highly disease-specific measures or through the use of health measures intended to be meaningful regardless of the condition under study (i.e., *cost-utility* analysis) [246]. Quality-adjusted life years (QALYs), calculated as mean quality of life multiplied by years, is the most widely used measure of this sort [247]. Costs can be calculated from the perspective of a wide variety of stakeholders, such as from a societal-, health care-, or clinic's perspective. Given that ICER point estimates can be difficult to interpret [248], it is also commonplace to report sensitivity analyses based in Monte Carlo simulation or bootstrapping [245].

The cost-effectiveness of FTF-CBT for severe heath anxiety has, to my knowledge, been studied based on data from two RCTs. First, a pilot study of FTF-CBT in a genitourinary medicine clinic reported an ICER of £ 33 per point reduction on the HAI up to the one-year follow-up, as based on a health care perspective and compared to treatment as usual [210]. Second, a large multicentre trial (N=445) investigated the cost-effectiveness of FTF-CBT delivered by non-expert clinicians, compared to treatment as usual, for patients in medical clinics. The results were suggestive of cost-effectiveness in terms of effect on health anxiety (ICER: £ 56 per point reduction on the HAI up to the two-year follow-up) and also suggestive of cost-utility as based on the commonly cited guideline of £ 20 000 per QALY [249] put forth by the British National institute for health and care excellence (societal perspective ICER: £ 14 169 per QALY, up to the two-year follow-up) [86].

The cost-effectiveness of G-ICBT has also been studied in two clinical trials. First, one study found that G-ICBT was more cost-effective than an attention control condition (ICER: £ -1 244 per additional case in remission up to the post-treatment assessment), and also found evidence of cost-utility (ICER: £ -6 533 per QALY up to the post-treatment assessment), as based on a societal perspective [218]. A second study compared G-ICBT to internet-based behavioural stress management, and presented a cost-effectiveness ICER of $ 2214 per additional case of clinically significant improvement up to the post-treatment assessment, and

a cost-utility ICER of $ 10 000 per QALY up to the post-treatment assessment, as based on a societal perspective [250]. Available studies thus suggest that CBT, especially in the minimal-contact format, has the potential to be a cost-effective treatment for severe health anxiety.

1.2.9 Availability of CBT

Most patients with severe health anxiety prefer psychological treatment over medications [251], but there is a shortage of qualified therapists [252], the availability of CBT is poor [7], and treatment for severe health anxiety is seldom offered [253]. The availability of CBT is also unevenly distributed between geographical regions, as illustrated by both a recent British study [254] and figures from the Swedish National board of health and welfare [252]. Because minimal-contact treatments have the potential to facilitate treatment dissemination and dramatically improve the availability of psychological treatment for common psychiatric conditions, further development of such treatment formats has been identified by experts as an important research topic in clinical psychology [7].

1.2.10 Advantages of minimal-contact treatment formats

An important advantage of minimal-contact CBT (e.g., G-ICBT, U-ICBT, and BIB-CBT) compared with conventional FTF-CBT is that less (or no) therapist time is needed. For example, a typical finding is that G-ICBT requires approximately 10 minutes of therapist time per patient and week [88]. This not only has the potential to reduce treatment costs, but also makes it possible to treat more patients; especially in health care sectors where there is a shortage of clinicians with adequate training in CBT. The highly structured text-based format also reduces the risk that therapists deviate from the intended treatment ("therapist drift" [255]).

Minimal-contact CBT may potentially have a democratising effect on mental health care. Without the need for face-to-face meetings, social stigma is less likely to interfere with health care seeking. Because the patient is not required to travel to a clinician, individuals living in rural areas, those living far from clinics, and those who are not fluent in the majority language may still be offered treatment. Because communication with a therapist is either non-existent or typically done though an email-like system, there is also usually no need to work with the treatment during any particular time of the day, meaning that the treatment is easier to access for patients with irregular schedules.

Last but not least, there may be benefits for the therapist, who is free to communicate with the patient at any time, without the need to schedule appointments. If the treatment is delivered online, there is also the advantage that self-rated questionnaires for symptom measurement can be seamlessly integrated with the treatment platform. Because the therapist is able to treat significantly more patients, and geographical distances are no barrier to treatment, G-ICBT may offer an efficient way of achieving certain types of clinical expertise, perhaps especially with regard to rare conditions. This, in turn, may have beneficial effects also for the patient.

1.2.11 Summary and current directions

Cognitive behaviour therapy (CBT) is the gold standard psychological treatment for severe health anxiety, and usually includes components of self-monitoring, psychoeducation, and exposure or cognitive restructuring techniques. Traditionally CBT has taken the form of FTF-CBT, but the availability of this type of treatment is poor. Recent years has seen increased interest in minimal-contact treatment formats such as therapist-guided internet CBT (G-ICBT), unguided internet CBT (U-ICBT), and cognitive behavioural bibliotherapy (BIB-CBT). Compared with FTF-CBT, minimal-contact CBT has several advantages, including that much less therapist time is needed per treatment. Prior to the present project, it was however unclear if unguided minimal-contact CBT such as U-ICBT and BIB-CBT can be efficacious for severe health anxiety. As to G-ICBT, this format had been found to produce large effects on health anxiety, but had never been directly compared to FTF-CBT in an RCT.

2 AIM OF THE THESIS

The general aim of this thesis was to develop and evaluate new technologies to facilitate the assessment of common diagnoses, and increase the availability of efficacious treatments, for severe health anxiety. Specific aims were:

I. To develop, and evaluate the inter-rater reliability of, a structured clinical interview for diagnostic assessment of DSM-5 SSD and IAD. We hypothesised that the inter-rater reliability of the interview would be adequate.

II. To investigate the short-term efficacy of G-ICBT, U-ICBT, and BIB-CBT for severe health anxiety. We hypothesised that all three treatments would be more efficacious than a waiting-list control condition. A secondary aim was to conduct a tentative comparison of the three treatments.

III. To investigate the long-term efficacy, cost-effectiveness, and cost-utility of G-ICBT, U-ICBT, and BIB-CBT for severe health anxiety. We hypothesised that the symptom levels of all three treatments groups would remain stable up to the one-year follow-up, and that all three treatments would be more cost-effective than a waiting-list condition, as assessed over the main phase of the trial. A secondary aim was to compare the treatments in terms of efficacy and cost-effectiveness.

IV. To investigate if G-ICBT is non-inferior to FTF-CBT for severe health anxiety. We hypothesised that G-ICBT would not be inferior to FTF-CBT, and that the symptom levels of both treatment groups would remain stable up to six months after treatment.

3 STUDIES

3.1 STUDY I: THE HEALTH PREOCCUPATION DIAGNOSTIC INTERVIEW: INTER-RATER RELIABILITY OF A STRUCTURED INTERVIEW FOR DIAGNOSTIC ASSESSMENT OF DSM-5 SOMATIC SYMPTOM DISORDER AND ILLNESS ANXIETY DISORDER

3.1.1 Background and aims

With the DSM-5, two new diagnoses, SSD and IAD, were introduced for sufferers of severe health anxiety. The aim of Study I was to develop a structured diagnostic interview for the assessment of DSM-5 SSD and IAD, and to evaluate its inter-rater reliability. The primary hypothesis was that the inter-rater reliability in discriminating between SSD, IAD and non-diagnostic cases would be adequate.

3.1.2 Methods

Initial development of the Health Preoccupation Diagnostic Interview (HPDI) was based on expert consensus and pilot testing in patients at the mental health division of a primary care clinic. Diagnostic interviews based on the HPDI were then conducted with applicants for a clinical trial of severe health anxiety (n=52), and with matched healthy controls (n=52) before, based on the recorded interviews, separate diagnostic assessments were done by another, blinded, clinician. Cohen's κ was the primary measure of inter-rater agreement.

3.1.3 Results

The inter-rater reliability of the HPDI in the assessment of SSD and IAD was moderate to almost perfect (κ=.85 for the pooled sample). As for the diagnostic specifiers, the reliability of the SSD severity and persistency specifiers were estimated to be slight to fair (κ=.08–.30), the reliability of the SSD pain specifier was moderate (κ=.45), and there was perfect agreement on the IAD care-seeking specifier (κ=1). Disagreement on diagnosis was primarily related to the severity of somatic symptoms, and the differential diagnosis of panic disorder.

3.1.4 Personal reflection

Study I gave me insights into both psychometric methods and the day-to-day practice and pitfalls of clinical research. This study also gave me practical experience of the importance of open and frequent, scheduled and non-scheduled, communication between those involved in the same research project.

3.2 STUDY II: EXPOSURE-BASED COGNITIVE-BEHAVIOURAL THERAPY VIA THE INTERNET AND AS BIBLIOTHERAPY FOR SOMATIC SYMPTOM DISORDER AND ILLNESS ANXIETY DISORDER: RANDOMISED CONTROLLED TRIAL

3.2.1 Background and aims

Prior to Study II, G-ICBT had been found to be efficacious with specific effects on severe health anxiety [88, 193], but CBT without a therapist had only been studied in pilot trials with significant limitations [235, 236]. The primary aim of Study II was to evaluate if minimal-contact CBT for severe health anxiety is efficacious not only in the form of G-ICBT, but also if delivered without therapist support or as book-form bibliotherapy. This was also the first clinical trial of CBT for severe health anxiety to recruit participants based on DSM-5 SSD and IAD. We hypothesised that G-ICBT, U-ICBT and BIB-CBT would be more efficacious than a waiting-list control (WLC). Secondary aims were to investigate if symptom levels were sustained six months after treatment, and to conduct a preliminary comparison of the effects of G-ICBT, U-ICBT, and BIB-CBT.

3.2.2 Methods

We recruited 132 participants with severe health anxiety operationalised as SSD or IAD, who were randomised in a 1:1:1:1 ratio to 12 weeks of G-ICBT, U-ICBT, BIB-CBT, or WLC. All treatments were primarily based on ERP, and were identical except for the administration format. Primary outcome was the time*group interactions indicative of waiting-list controlled change on the HAI in mixed linear models, from pre- to post-treatment. Remission rates were estimated based on clinically significant improvement [216].

3.2.3 Results

G-ICBT, U-ICBT, and BIB-CBT were more efficacious than the WLC, and improvements in the treatment groups were maintained up to six months after treatment. The waiting-list controlled effects were large and similar (d=0.80–1.27), and there was no significant difference in symptom course between the three active treatments (Ps=.432–.715). Approximately 47–53% of patients in CBT were in remission at the 6-months follow-up.

3.2.4 Personal reflection

The greatest challenge of Study II has been the communication of results and assessment of clinical implications. This trial was a hybrid between a feasibility and dismantling trial. While the primary aim was to assess if CBT without a therapist (i.e., U-ICBT and BIB-CBT) is an efficacious and feasible treatment alternative for severe health anxiety, the trial also allowed for comparison against the G-ICBT condition which only differed from the U-ICBT in terms of therapist involvement. It is important to recognise that the trial was powered to allow for comparisons against the WLC, but that it was underpowered to study small to medium sized effects between the treatments based on null-hypothesis testing.

3.3 STUDY III: COST-EFFECTIVENESS AND LONG-TERM FOLLOW-UP OF THREE FORMS OF MINIMAL-CONTACT COGNITIVE BEHAVIOUR THERAPY FOR SEVERE HEALTH ANXIETY: RESULTS FROM A RANDOMISED CONTROLLED TRIAL

3.3.1 Background and aims

Prior to Study III, the long-term efficacy and cost-effectiveness of G-ICBT for severe health anxiety had been demonstrated [218], but little was known about unguided CBT. The primary aim of Study III was to investigate the cost-effectiveness and long-term effects of three forms of minimal-contact CBT on severe health anxiety. We hypothesised that G-ICBT, U-ICBT, and BIB-CBT would all be more cost-effective than the WLC, and that improvements would be maintained up to the one-year follow-up. A secondary aim was to conduct a tentative comparison of the cost-effectiveness and long-term efficacy of the three active treatments.

3.3.2 Methods

Study III was based on the same RCT as Study II. The analysis of effects in relation to costs was based on the ICER (1.2.8), and separate analyses were done of remission rates (i.e., cost-effectiveness) and QALYs (i.e., cost-utility). Separate analyses were also done from the perspective of society, health care, and the clinic, respectively. QALYs were estimated based on the EuroQol-5D [256] with Swedish norms [257], and remission was estimated based on the reliable change index [216] and an established cut-off point for identifying clinical cases of severe health anxiety based on the HAI [258]. Costs were estimated based on the Trimbos and institute of medical technology assessment cost questionnaire for psychiatry [259]. Change in health anxiety over the follow-up period was modelled with linear mixed effects models.

3.3.3 Results

G-ICBT, U-ICBT, and BIB-CBT were more cost-effective than the WLC, given that society is willing to pay up to £ 416 per case of severe health anxiety in remission over the 12-week treatment period. Up to the one-year follow-up, health anxiety levels were maintained or further lowered, without significant differences between the treatments. If the willingness to pay for additional effects is very low or zero, BIB-CBT is probably more cost-effective than G-ICBT and U-ICBT as modelled from a societal perspective, up to one year after treatment.

3.3.4 Personal reflection

In working with Study III, it became increasingly clear to me that an obstacle in health economics is the scarcity of previous work on which to base value judgments with regard to cost-effectiveness, and especially under scenarios not based on QALYs. My strategy in addressing the challenge of missing data as well as the lack of common guidelines for the conduct of cost-effectiveness analyses was to present a series of analogous analyses, each based on different assumptions about the data, and perspectives on cost-effectiveness an cost-utility. My hope is that this will enable the reader to get a more nuanced and multifaceted understanding of the outcome of the trial.

3.4 A PRIMER ON NON-INFERIORITY TRIALS

Most clinical trials are so called *superiority* trials, designed to test the hypothesis that one condition (e.g., treatment) is more effective than another. In most cases, this is investigated based on null hypothesis significance testing, i.e., estimation of the probability of an observed outcome given that the null hypothesis is true. If, given that the null hypothesis is assumed to be true, the observed outcome is highly improbable ($P<.05$), this justifies rejection of the null hypothesis and the alternative hypothesis is corroborated.

Another scenario is when the hypothesis is that one condition is at least as effective as – i.e., non-inferior to – another. This type of hypothesis is common in cases where a new treatment is developed to address a problem for which there already exists another more established intervention. In a conventional superiority framework, null hypothesis significance testing does not allow for this type of hypothesis to be investigated because the absence of a true effect is per definition the null hypothesis, and cannot be proven. Regardless of sample size, a non-significant difference between two groups could just be due to insufficient power.

The idea behind a *non-inferiority* trial is that instead of proving the absence of a true effect, it is possible to demonstrate with sufficient certainty that there is no true between-group effect large enough to be of any practical interest. Therefore, prior to the analysis of non-inferiority, it is necessary to decide on the smallest true effect that would be of clinical interest. The value chosen for this so called *non-inferiority margin* (Δ) should be such that if the true effect is smaller than Δ, it is not clinically significant. This is usually understood to mean that no point on the confidence interval for the difference between conditions should be indicative of an effect equal to Δ or larger in favour of the more established treatment. In pharmaceutical research, a common recommendation is for Δ to be no larger than half of the placebo-controlled effect of the established treatment [260].

Most guidelines for non-inferiority trials recommend that the main analysis is repeated both from an intention-to-treat (ITT) perspective (i.e., with data from all participants of the trial), and a per-protocol (PP) perspective (i.e., with data from treatment completers only) [261]. This is because, in the non-inferiority framework, both perspectives have clear advantages and disadvantages. In the ITT analysis, because all participants are included in the analysis, both groups are representative of the original population from which they were randomly sampled, and there is control over confounders of the effect of treatment condition on the outcome. However, unlike in superiority trials, ITT analysis is not a conservative method because should adherence be poor, this could potentially lead to the fabrication of "non-inferiority" because the course of non-adherent participants is likely to be similar regardless of condition. The PP analysis is the mirror image to its ITT equivalent, and has the advantage that all participants in the analysis were exposed to the intended protocol, but the disadvantage that because non-adherent participants were excluded from analysis, there could be an issue of selection bias or confounding [260].

3.5 STUDY IV: COGNITIVE BEHAVIOUR THERAPY FOR HEALTH ANXIETY VIA THE INTERNET AND AS FACE-TO-FACE TREATMENT: A RANDOMISED CONTROLLED NON-INFERIORITY TRIAL

3.5.1 Background and aims

The most well-established psychological treatment for severe health anxiety is FTF-CBT, but access to FTF-CBT is poor. G-ICBT is a new treatment format which enables wider dissemination of evidence-based treatment. Less therapist time is needed per treatment, and the intervention is more flexible with regard to time and geographical obstacles. G-ICBT is the type of minimal-contact CBT that has been most convincingly found to be efficacious in the treatment of severe health anxiety, but it has never been compared directly to FTF-CBT. The aim of study IV was to investigate if G-ICBT is non-inferior to (i.e., at least as efficacious as) FTF-CBT in the treatment of severe health anxiety, and we hypothesised that G-ICBT would be non-inferior to FTF-CBT in the reduction of health anxiety. A secondary aim was to compare the effect of G-ICBT and FTF-CBT on secondary symptoms of general anxiety, depression, and functional impairment.

3.5.2 Methods

Study IV presents the main outcome of a randomised controlled non-inferiority trial based at a primary care clinic, where patients (N=204) were randomised to G-ICBT or FTF-CBT. Treatments were 12 weeks long and identical except for the administration format. Primary outcome was based on the one-sided confidence interval for the coefficient of the group*time interaction on the 18-item SHAI, which was measured with weekly intervals over the treatment period. A non-inferiority margin (Δ) of 0.3 d, equivalent to 2.25 points on the SHAI, was chosen based on (1) the controlled effect of FTF-CBT against waiting-list and treatment as usual conditions [173], (2) evidence pertaining to patients' beliefs about clinical significance [262], and (3) clinical judgment. Non-inferiority was assessed both from an ITT and PP perspective. Secondary outcomes were also based on self-rated questionnaires.

3.5.3 Results

The modelled difference in change between G-ICBT and FTF-CBT over the treatment period was -0.0003 points favouring G-ICBT (Figure 5), and the upper limit of the one-sided 95% confidence interval was 1.9774 in favour of CBT as based on intention-to-treat data, and 2.1717 in favour of CBT as based on per-protocol data. Both upper bounds for the confidence interval were thus lower than the non-inferiority margin (Δ) of 2.25, indicating that G-ICBT is non-inferior to FTF-CBT. The difference in effect on health anxiety was not moderated by treatment preference (P=.122), baseline health anxiety (P=.062), or the path of referral (i.e., routine care vs. not routine care; P=.357), and there were also no significant differences in effect on secondary symptoms.

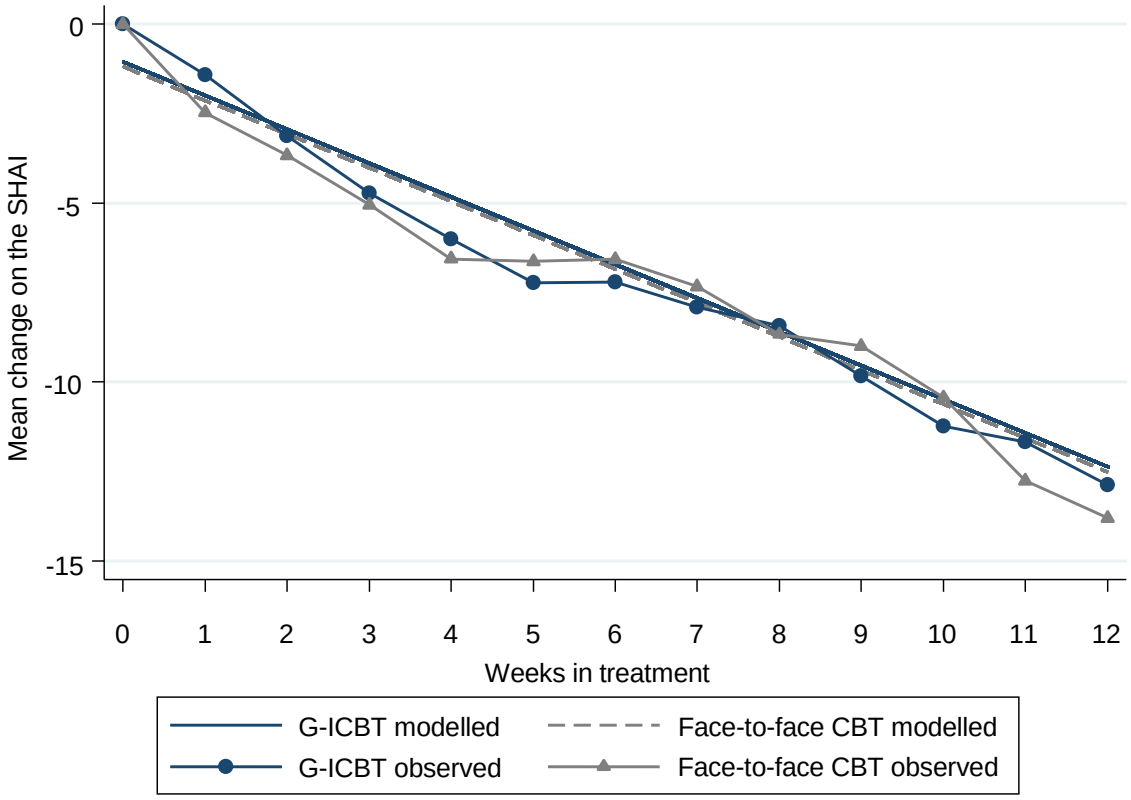

Fig. 5. Main outcome of Study IV. Observed and modelled change in health anxiety over 12 weeks in treatment, by treatment group. Estimates are based on the fixed portion of mixed effects models and intention-to-treat data (i.e., all patients in the study were included). Error bars are omitted for clarity of presentation. CBT=individual cognitive behaviour therapy. G-ICBT=therapist-guided internet cognitive behaviour therapy. SHAI=18-item Short Health Anxiety Inventory.

3.5.4 Personal reflection

Study IV is without doubt the part of this project which demanded the most amount of hard work, and also the trial in which I feel that I was able to work more or less as an independent researcher. For me, amongst the most rewarding aspects of this trial was to offer supervision of others involved in the project, and to ensure that high treatment fidelity was achieved.

Please note that, in an attempt to avoid jargon, the manuscript detailing the proceedings of Study IV refers to severe health anxiety (i.e., the clinically significant condition) as “health anxiety” which, in this thesis, is otherwise used to denote the dimensional trait. Note also that the same manuscript refers to the 18-item Short Health Anxiety Inventory (SHAI) simply as the “Health Anxiety Inventory” (“HAI”).

3.6 ETHICAL CONSIDERATIONS

All four studies here presented were approved by the regional ethics review board of Stockholm (2013/375-31/5, 2014/1530-31/2), proceeded in line with the declaration of Helsinki [263] and good clinical practice [264], and followed Swedish and European jurisdiction for the management of data and personal information. Four particularly important ethical concerns were: (1) the implementation of informed consent, (2) the risk of adverse outcomes, (3) the management and presentation of data, (4) and transparency of the research process.

In both trials here reported, informed consent was given via a minimalistic online form. Both the phrasing of the information given, and the method of administration, was described in the ethics application and submitted for review by the ethics review board. The text presented to the study applicants clearly stated that participants could withdraw their consent at any time.

In order to ensure the wellbeing of all participants, symptoms were continuously monitored through the course of both trials. In cases of severe deterioration or suicidality, participants were contacted and referred to routine health care services. The implementation of a waiting-list condition in Study II–III was seen as justified because so little was known about unguided treatments for severe health anxiety, and more information could potentially be used to help those in need. It was also ensured that participants were crossed over to an active treatment after the main phase of the trial (see 4.6.3).

All studies involved the management of sensitive information, and a number of precautions were therefore taken to safeguard the personal integrity of all participants. The web-based online treatment platform employed two-factor authentication, all data traffic was protected through the use of 128-bit encryption, and completed symptom questionnaires could only be accessed by researchers working with the trial. Data were stored on secure servers and in locked journal cabinets. Whenever results of the trial were communicated, these results were anonymised and analysed at group level.

One of several threats to the transparency of clinical research is publication bias, i.e., that the probability of publication is contingent on the outcome of the study. In an attempt to be as transparent as possible with the method and proceedings of the trials, both were preregistered at ClinicalTrials.gov (NCT01966705, NCT02314065), and all publications based on the trials included a reference to the corresponding online protocol.

4 GENERAL DISCUSSION

4.1 SUMMARY OF FINDINGS

This thesis presents new evidence pertaining to the assessment and treatment of severe health anxiety. A preliminary finding is that DSM-5 SSD and IAD can be reliably assessed based on a new structured diagnostic interview (i.e., the HPDI). In addition, two RCTs contributed to the development and dissemination of treatments for severe health anxiety. First, it was found that minimal-contact CBT – also without a therapist – can be an efficacious and cost-effective treatment for severe health anxiety. Second, therapist-guided internet CBT (G-ICBT) was found to be at least as efficacious as individual face-to-face CBT (FTF-CBT) for severe health anxiety. At follow-up, the effects of all treatments under investigation were also found to be sustained over time. I believe that the findings of Study II–IV have important clinical implications for the treatment and management of severe health anxiety, as detailed below.

4.2 ARE DIAGNOSES OF SSD AND IAD BASED ON THE HEALTH PREOCCUPATION DIAGNOSTIC INTERVIEW (HPDI) SUFFICIENTLY RELIABLE?

It appears to be possible to diagnose DSM-5 SSD and IAD based on the HPDI with adequate inter-rater reliability, though the assessment of the SSD persistency and severity specifiers are probably not sufficiently reliable (Study I). To my knowledge, there exists only one other published study of the inter-rater reliability of a diagnostic procedure for SSD and IAD. This study was based on the Anxiety and Related Disorders Interview Schedule for DSM-5, and the inter-rater reliability of SSD and IAD was largely on par with the results of Study I. Also as in Study I, the most common reason for non-concordance was disagreement over the severity of somatic symptoms [52]. In addition, one study has presented adequate inter-rater reliability figures for SSD [54], and another study has presented adequate inter-rater reliability of IAD [265], as based on procedures where the two disorders were not assessed in parallel.

A limitation of Study I was that only diagnoses from two clinicians could be compared, which means that the agreement over diagnoses was conflated with the agreement of two specific clinicians. Another limitation was that the number of patients with IAD was small (n=7). It is thus too early to say with certainty how reliable the HPDI would be in the hands of most clinicians, and there is a need for further studies with other clinicians and samples.

In clinical practice, the utility of SSD and IAD as diagnoses in severe health anxiety is not clear. My suspicion is that, in line with data published after initiation of the present project [52, 87], SSD is typically predictive of a slightly larger effect of CBT on health anxiety, but that this effect can be explained by slightly higher mean baseline health anxiety. In a pooled analysis based on data from all patients in CBT in Study II–IV (N=303), the effect of having IAD only bordered on being significant (P=.050), with a small and not clinically significant effect size. If baseline health anxiety was included as a predictor in the model, the effect of diagnosis was no longer near-significant (P=.231). Thus, if there is a true effect of diagnosis (SSD vs. IAD) as a moderator of the effect of CBT on health anxiety, it is probably not very

important, and when the level of health anxiety is known, SSD and IAD may not add much clinically useful information. Nevertheless, the HPDI allows for further exploration into this and other hypotheses pertaining to DSM-5 SSD and IAD.

4.3 IS UNGUIDED CBT EFFICACIOUS FOR SEVERE HEALTH ANXIETY?

As hypothesised, all three minimal-contact treatments (i.e., G-ICBT, U-ICBT, and BIB-CBT) had large waiting-list controlled effects on health anxiety, and also small to medium sized effects on secondary symptoms of general anxiety, depression, and functional impairment (Study II–III). This indicates that the involvement of a therapist is not necessary to achieve large effects in CBT for severe health anxiety, and that unguided CBT can have mean effects similar those of FTF-CBT (1.2.4.1). Strengths of Study II were the randomised controlled design, and the fact that all therapies were based on the same treatment content. The main finding that U-ICBT and BIB-CBT can be highly efficacious is in line with previous work demonstrating that unguided treatments can be efficacious for common psychiatric disorders [266], though the effect sizes of U-ICBT and BIB-CBT were slightly larger than anticipated.

As to long-term effects, improvements made in G-ICBT, U-ICBT and BIB-CBT were sustained over time. This is in line with a previous study of G-ICBT for severe health anxiety [218], and also studies of BIB-CBT for depression, obsessive-compulsive disorder, and social anxiety disorder [238-240]. The long-term course was also at least as promising as that seen in most follow-up studies of FTF-CBT for severe health anxiety (1.2.4.1).

The large effects of these unguided treatments ought to be generalised with caution, due to the highly structured treatment context. It was for example the case that participants knew that the trial had a specific end date, and all participants also received weekly SMS reminders to complete their online assessments, which most likely had a positive effect on treatment adherence. Although the prerequisites for the efficacy of pure self-help treatments need be studied further, Study II clearly shows that unguided minimal-contact CBT can be highly efficacious for severe health anxiety given the right circumstances.

4.4 IS UNGUIDED CBT COST-EFFECTIVE FOR SEVERE HEALTH ANXIETY?

As hypothesised, G-ICBT, U-ICBT, and BIB-CBT were more cost-effective than the WLC, as assessed over the 12-week treatment period (Study III). It was also found that BIB-CBT probably is the most cost-effective treatment format if the willingness to pay is low (i.e., if society is not willing to pay for additional beneficial effects). Important strengths of Study III were that several minimal-contact treatments could be compared, and that various scenarios were explored with regard to costs and assumptions about the data.

The main outcome was similar to that of an earlier study which found that G-ICBT was more cost-effective than an attention control condition [218]. Both in that study and Study III, cost-effectiveness versus the non-treatment control was more a question of a difference in effect, than a difference in costs. In both studies, the reduction in monthly costs was larger in CBT than in the no-treatment group, but in Study III the cost of G-ICBT and BIB-CBT outweighed

the advantage in gross total costs. It is not unlikely that, had the patients been followed over a longer time-frame, there had been a net cost advantage of all forms of CBT versus the WLC. Nevertheless, the net costs of all forms of minimal-contact CBT investigated were very small, and especially considering their apparent efficacy.

Under most scenarios, none of the treatments showed promise in terms of cost-utility, which is also in line with a previous study of FTF-CBT [267]. In Study III, the effects on QALYs were small, and it thus appears that the primary justification for implementation of the type of CBT here investigated should be its effect on health anxiety rather than effects on QALYs. One possible explanation for the small effect on QALYs is that the measure is heavily dependent on physical, as opposed to psychosocial, impairment, at least if based on the EuroQol-5D [256] on which one of five items concerns mobility (i.e., the ability to walk and move freely) and one concerns self-care (primarily the ability to take care of personal hygiene and get dressed), which are relatively unaffected domains of functioning in severe health anxiety [113].

Limitations of Study III were the relatively high proportion of missing data at the one-year follow-up, and that the WLC was crossed over to an active treatment. Whether or not the treatments were more cost-effective also depends on the willingness to pay, and there exists no recognised criterion for the cost-effectiveness of interventions for severe health anxiety. The choice of a criterion for cost-effectiveness is not solely determined by empirical data, but is also by ethical, ideological, and practical considerations.

4.5 IS G-CIBT NON-INFERIOR TO FTF-CBT FOR SEVERE HEALTH ANXIETY?

As hypothesised, G-ICBT is at least as efficacious as FTF-CBT in the treatment of severe health anxiety. That is, for the majority of patients with severe health anxiety, it is likely that if FTF-CBT works, G-ICBT works as well. This finding is in line with previous comparisons of G-ICBT and FTF-CBT for other psychiatric disorders [234], and underscores the potential of G-ICBT to increase the availability of CBT for severe health anxiety on a wider scale. To my knowledge, Study IV is yet the largest randomised controlled comparison of individual FTF-CBT to G-ICBT for any psychiatric or somatic condition [234].

The effects of G-ICBT on severe health anxiety have now been investigated in five RCTs, and if one is willing to consider the provision of fortnightly online educational content as a psychological treatment [87], it could be argued that the treatment format meets the American Psychological Association criteria for an empirically supported treatment (i.e., the highest level of evidence). Based on a meta-analytic approach, the pooled within-group effect of G-ICBT on health anxiety has been 1.74 *g* (Table 3), comparable to 1.64 of FTF-CBT (1.2.4.1).

Table 3. Within-group effects of therapist-guided internet cognitive behaviour therapy (G-ICBT) for severe health anxiety.

Study	n	Effect size (*g* [95% CI]) pre- to post-treatment			Effect size (*g* [95% CI]) pre-treatment to follow-up [a]		
		Health anxiety	Depression	Functional impairment	Health anxiety	Depression	Functional impairment
Hedman et al. (2011) [88]	40	1.93 (1.39, 2.46)	1.29 (0.80, 1.77)	No data	1.83 (1.50, 2.16)	0.97 (0.51, 1.44)	No data
Hedman et al. (2014) [193]	79	1.77 (1.40, 2.15)	0.77 (0.45, 1.10)	0.51 (0.19, 0.83)	1.93 (1.40, 2.46)	0.91 (0.57, 1.24)	0.55 (0.22, 0.88)
Study II	32	1.53 (0.97, 2.09)	0.50 (0.00, 1.00)	0.89 (0.38, 1.41)	1.90 (1.31, 2.49)	0.43 (-0.07, 0.92)	0.93 (0.41, 1.44)
Study IV	102	1.65 (1.33, 1.96)	0.83 (0.54, 1.11)	0.68 (0.40, 0.96)	1.87 (1.27, 2.47)	0.85 (0.57, 1.14)	0.68 (0.40, 0.96)
Newby et al. (2018) [87]	51	1.90 (1.40, 2.41)	1.01 (0.56, 1.46)	0.93 (0.48, 1.37)	1.88 (1.35, 2.41)	1.07 (0.59, 1.54)	0.73 (0.27, 1.19)
Total, pooled [b]	**304**	**1.74 (1.55, 1.93)**	**0.86 (0.69, 1.03)**	**0.69 (0.51, 0.87)**	**1.86 (1.66, 2.05)**	**0.86 (0.69, 1.03)**	**0.68 (0.50, 0.86)**

[a] The follow-up periods were the following: 12 months for Hedman et al. (2011), 6 months for Hedman et al. (2014), 12 months for Study II, 6 months for Study IV, and 3 months for Newby et al. 2018.

[b] Meta-analysis based on a random-effects model fitted under restricted maximum likelihood.

Non-inferiority was seen despite the fact that patients rated the strength of their relationship with their therapist slightly lower in G-ICBT than in FTF-CBT. In line with Study II–III, this is support for the idea of that there may be characteristics of G-ICBT, perhaps including the highly-structured treatment format, which compensate for a weaker therapeutic alliance.

Strengths of Study IV included the high treatment fidelity, that therapists were balanced over the two conditions, that the treatments were delivered in a routine care environment at a primary care clinic, that 13 measurement points and mixed models allowed for stable models of change with little room for prediction error [268], and that the main outcome was the same regardless of whether the analysis was based on an ITT or PP framework. Another finding which speaks for the internal validity of Study IV is that in both G-ICBT and FTF-CBT, there was a dose-response relationship between adherence (i.e., the number of modules or sessions completed) and effect on health anxiety.

A limitation of Study IV was that only approximately one third of the patients were recruited through routine care. Notably, however, the recruitment path did not appear to moderate the effect of CBT on health anxiety. For a detailed discussion of generalisability, see 4.6.1–4.6.2. There was also no diagnostic assessment at treatment termination, but this is seldom seen in trials treatment for severe health anxiety, see 4.6.4 [22].

4.6 GENERAL METHODOLOGICAL ISSUES AND POTENTIAL THREATS TO VALIDITY

4.6.1 On the operationalisation of severe health anxiety and generalisability to DSM-IV hypochondriasis

Unlike in previous trials by our research group where the inclusion of participants was based on a diagnosis of DSM-IV hypochondriasis [88, 193], inclusion in Study II–IV was based on DSM-5 SSD and IAD. This was because the DSM-5 is intended to replace the DSM-IV, the SSD and IAD diagnoses were intended for individuals with severe health anxiety, and the DSM is the most widely used taxonomy for research and work with psychiatric disorders.

Based on the comparison of diagnostic criteria (Table 1), it is evident that SSD and IAD do not correspond precisely to DSM-IV hypochondriasis. The SSD diagnosis is relatively broad, and it is possible to meet full criteria for SSD without meeting full criteria for DSM-IV hypochondriasis (1.1.3.2). This may be either (a) due to an excessive preoccupation with somatic symptoms without a fear of having or acquiring as severe illness, (b) due to a shorter duration (i.e., while DSM-IV hypochondriasis requires a duration of at least six months, the SSD criterion is more vague), or (c) because there has been no medical reassurance (e.g., due to phobic avoidance of medical evaluation). Moreover, it is also possible to meet full criteria for IAD without meeting full criteria for DSM-IV hypochondriasis, primarily because in IAD the fear of illness need not be based on the misinterpretation of physical symptoms.

Nevertheless, my impression is that the samples presented in this thesis were remarkably similar to the samples of the two previous trials of G-ICBT for severe health anxiety by our

research group, where inclusion was instead based on DSM-IV hypochondriasis (Table 4). This is probably because most other eligibility criteria were kept unchanged, and all trials employed more or less the same recruitment strategy. All four trials of G-ICBT were advertised to clinicians and the public under the heading "Do you worry a lot about your health?", a key item of the WI [73], which is widely acknowledged as a valid measure of health anxiety. All advertisements clearly stated that the trial was intended for individuals with "a persistent fear of being ill or acquiring a disease". It was also explained to all applicants that treatment would focus on a fear of having or acquiring a serious health condition, as opposed to, for example, chronic pain.

For sake of validation, in addition to the assessment of SSD and IAD, in the present project we also assessed DSM-IV hypochondriasis, and found it to be present in approximately 9 of 10 patients (Table 4). In Study IV, the most common reason for not meeting full criteria for hypochondriasis (n=13) was that the patient had not been given medical reassurance (n=7), followed by too short duration (n=5), and that the fear was not based on the misinterpretation of bodily symptoms (n=1). Thus, the reason that the participants did not meet full criteria for DSM-IV hypochondriasis was not that they did not fear having or acquiring a severe illness. Rather, the type of patient that was recruited for the present project, but not the two previous trials of G-ICBT by our research group, was either characterised by the avoidance of health care, or a slightly shorter duration of severe health anxiety. This was confirmed during the latter half of Study IV, when the last 48 patients diagnosed with SSD were asked about their primary catastrophic belief (i.e., what they feared most) with regard to their symptoms. All these patients worried most either about disease and/or death, and not some other outcome.

In a pooled analysis of all patients in CBT in Study II–IV (N=303), whether the patients met full criteria for DSM-IV hypochondriasis was not a predictor of the main outcome (P=.982). In summary, though results may not generalise to other forms of SSD where there is no fear of having or acquiring a severe health condition, it appears sensible to regard all patients from the present project and the two previous trials by the research group as having been sampled from the same population; one of individuals with severe health anxiety.

Table 4. Comparison of severe health anxiety samples in clinical trials of minimal-contact cognitive behaviour therapy. Frequency or Mean (SD), range.

	Previous RCTs by the research group		RCTs presented here		Healthy controls [c] (N=91)
	Hedman et al. (2011) [88]	Hedman et al. (2014) [193]	Study II–III	Study IV	
Sociodemographics					
Age	39, 25–69	42 (13), 21–75	38 (13), 20–72	39 (12), 18–78	48 (18), 18–99
Female	74%	79%	74%	70%	68%
Education > USS	72%	78%	80%	75%	89%
Married or de facto	86%	84%	87%	82%	75%
Employed and working	78%	69%	70%	67%	63%
Severe health anxiety					
Hypochondriasis	100% [a]	100% [a]	89%	94%	0%
Age of onset	21	26 (11), 5–65	26 (13), 5–67	27 (13), 3–75	Not applicable
HAI	107	104 (20), 49–151	109 (23), 50–171	107 (21), 51–164	30 (12), 9–62
At least 67 points? [258]	No data	96%	94%	97%	0%
IAS	69	68 (12), 38–107	69 (14), 31–96	68 (11), 37–92	21 (8), 4–44
Bodily preoccupation [269]	No data	No data	9 (2), 5-12	9 (2), 4–12	2 (2), 0–6
WI	11	11 (2), 4–14	11 (2), 6–14	11 (2), 4–14	1 (1), 0–4
Item 4: "Do you worry a lot about your health?" [b]	No data	No data	99%	100%	0%
Other clinical variables					
Depression (MADRS-S)	13	12 (7), 0–32	13 (7), 1–31	14 (7), 0–36	3 (3), 0–19
General anxiety (BAI)	21	18 (9), 0–41	20 (11), 1–47	20 (10), 0–53	No data
Anxiety sensitivity (ASI)	26	23 (11), 3–52	26 (12), 1–57	25 (11), 0–54	No data
Disability (SDS)	No data	9 (7), 0–25	11 (7), 0–27	11 (7), 0–27	No data
Antidepressant medication	32%	16%	22%	19%	0%

Abbreviations: ASI, Anxiety Sensitivity Index (0–64); BAI, Beck Anxiety Inventory (0–63); HAI, 64-item Health Anxiety Inventory (0–192); IAS, Illness Attitude Scales (0–108); MADRS-S, Montgomery-Åsberg Depression Rating Scale (0–54); SDS, Sheehan Disability Scale (0–30). USS=upper secondary school (Swedish gymnasium), equivalent to International standard classification of education (ISCED) level 3. WI, 14-item Whiteley Index with dichotomous response options (0–14).

[a] Eligibility criterion

[b] This was also the heading of the advertisements for the clinical trials.

[c] Controls were recruited via newspaper ads [85].

4.6.2 On the generalisability to routine care

Another important question is that of generalisability to routine care, which is likely to vary much depending on the specific type of routine care. Patients with severe health anxiety are found throughout the health care system; in both primary care, specialised medical care, and psychiatric clinics, and it is thus conceivable to offer minimal-contact CBT for severe health anxiety in a large number of contexts. There are patient groups, such as very old patients, patients with substantial medical comorbidities, and patients with chronic pain, who were not well represented in the present project, and for whom it would not be sensible to generalise too broadly. However, even though 41–57% of applicants for Study II–IV were excluded from participation, many of the eligibility criteria, such as the requirement that patients meet criteria for a principal diagnosis indicative of severe health anxiety (responsible for 35% of exclusions), are also implemented in routine care, albeit in a more informal manner. Under many routine care scenarios, there is reason to suspect that patients and conditions have much in common with those in our studies (see Table 5).

In order to evaluate the generalisability of Study II–IV, it is probably most informative to consider specific examples. One example of high relevance is the Internet psychiatry unit at Karolinska university hospital in Stockholm, which is a recognised provider of G-ICBT in routine care. The treatment format at this clinic is similar to that of Study IV, namely with referral from routine care or self-referral via the internet, face-to-face assessment, and approximately 10–12 weeks of treatment. The online treatment platform is also very similar to those used for the present project, and G-ICBT protocols for other anxiety disorders have made a successful transition from efficacy studies to routine care [270, 271]. Even though patients at the Internet psychiatry unit are likely to have a lower average level of education than the patients of Study II–IV, most variables indicate that the effects of G-ICBT seen in the present project are likely to generalise to routine care at this clinic.

Another possibility is to implement minimal-contact CBT for severe health anxiety in primary care. Based on comparison with two Scandinavian primary care samples (Table 5), the age and gender distribution as well as the comorbidity rates are likely to be similar in clinical practice, but as in the case of the Internet psychiatry unit, the proportion of patients with a high level of education is likely to be lower than in the trials presented here.

Sociodemographic data has typically not been predictive of therapeutic outcome in RCTs of G-ICBT for severe health anxiety [220, 224]. Likewise, a pooled analysis of all patients in CBT in Study II–IV (N=303) did not show any moderating effect of the level of education (P=.606). However, being married or having a partner was associated with a smaller treatment effect (3.0p on the 18-item SHAI over 12 weeks; P=.034), and so was being employed (2.3p on the 18-item SHAI; P=.035). These effects are clinically significant (>2.25p) but small, and none remained statistically significant when (a) both predictors were included in the same model or (b) baseline health anxiety was included. Both effects were in a direction which suggests that the treatment effect might be larger (not smaller) in many routine care samples. There is thus reason to be optimistic about the generalisability of effects to many routine care contexts.

Table 5. Comparison between the samples here presented and Scandinavian routine care and general population samples. Frequency or Mean (SD).

	Study II–IV	Routine care G-ICBT PD sample	Primary care FTF-CBT mixed disorder sample	Primary care SHA sample	Liaison psychiatry FTF-CBT SHA sample	General population SHA sample *	Swedish adults
Sociodemographics							
Age	38 (12)	37 (11)	37 (11)	38 (11)	37 (11)	42 (14)	41
Female	72%	61%	72%	80%	63%	50%	50%
Education > USS	77%	47%	61%	No data	No data	No data [d]	42%
Married or de facto	84%	57%	73%	No data	63%	29%	62–65%
Employed and working	68%	56%	No data	No data	No data [b]	No data	58%
Clinical variables							
Principal disorder	SHA	PD	CMD	SHA	SHA	No data	N/A
Health anxiety (HAI)	108 (22)	No data	No data	No data	106 [c]	No data	No data
Depression (MADRS-S)	14 (7)	14 (8)	17 (8)	No data	No data	No data	No data
Comorbid anxiety disorder or OCD	62%	20%	No data [a]	42%	No data	No data	No data
Major depressive disorder	19%	14%	No data [a]	15%	28%	No data	5%
On antidepressant	20%	32%	13%	No data	21%	No data	12%
Reference		271	275	18	211	95	272-274

Abbreviations: CMD, common mental disorders (mixed); HAI, 64-item Health anxiety inventory (0–192); MADRS-S, Montgomery-Åsberg depression rating scale (0–54); N/A, not applicable; OCD, obsessive-compulsive disorder; PD, panic disorder; USS=upper secondary school (Swedish gymnasium), equivalent to International standard classification of education (ISCED) level 3.

[a] 52% had at least one comorbid psychiatric disorder of any kind.

[b] 74% including students. The corresponding figure in Study II–IV was 80%.

[c] HAI score estimated based on the 14-item Short Health Anxiety Inventory (SHAI).

[d] 40% had not completed Canadian high school.

* Please note that contrary to all other samples here cited, this was not a Scandinavian sample. The study was based in Montreal, Canada.

4.6.3 On the choice of a waiting-list control

There is evidence to suggest that waiting-list conditions in the context of RCTs typically do not provide valid estimates of natural course [276]. In other words, waiting-list controlled effects should typically not be interpreted as "change over and above that without treatment". The implementation of a waiting-list control could also be ethically problematic, considering that approximately 17% of patients with common psychiatric disorders have been estimated to deteriorate if on a waiting-list [277].

What, then, was the point of implementing a waiting-list condition in Study II–III? First, prior to the present project, no RCT had convincingly investigated the effects of U-ICBT or BIB-CBT for severe health anxiety, and little was known about the effects of these interventions. The inclusion of a waiting-list was therefore an attempt to control for rudimentary processes such as regression towards the mean, without the risk of prematurely disregarding U-ICBT and BIB-CBT as viable treatment options should the treatments be inferior to another active treatment [278]. Second, most previous RCTs of CBT for severe health anxiety have made comparisons against a waiting-list condition, and comparisons between the present studies and previous are thus facilitated. Third, there was the issue of convenience and cost. It was much easier and less demanding to implement a waiting-list condition than another active condition, attention control condition, or psychological placebo. A drawback of attention control and psychological placebo controls is also that these tend to differ much between trials, and that comparisons against such comparators may be at least as difficult to interpret.

4.6.4 On the choice of outcomes

A common critique of self-rated outcome measures is that it is unclear to which extent they correspond to more objective measures such as observer data, register data, biomarkers, and everyday functioning. While I agree that it had been informative to look at other measures as well, it is important to keep in mind that – in terms of the primary outcome of Study II and IV – self-rated questionnaires are the closest to a "gold standard" measure of health anxiety as one would come. This is the type of measure that has been used by most other clinical trials in the field [5], and it is also commonly used in epidemiological research on health anxiety [92, 93].

An alternative to self-rated questionnaires had been to focus on continuous measures rated by a clinician. The general pattern in research on psychiatric disorders is however that self-rated and independently-rated outcomes tend to be highly correlated, the only clear difference being that independently-assessed measures typically show less variance [279], which makes standardised effect sizes larger, and gives slightly higher power to detect true differences in for example anxiety. However, the difference in precision is not large, and advantages of the self-report format include the ease of administration and the fact that comparisons against other clinical trials of CBT for severe health anxiety (1.2.4) are more straightforward. The repeated measurement which formed the basis for the precise statistical analysis of Study IV had been remarkably difficult and time-consuming if based on measures rated by a clinician.

A third possibility had been to use a psychiatric diagnosis as a criterion of remission and primary outcome of Study II and IV. Though this is the preferred approach in most of medical research, none of the two trials here presented incorporated diagnoses as outcome. While this is a limitation, I do not believe it to be as significant as it had been in the case of many other conditions. This is partly because, as explained in the introduction (1.1.3), there is no strong consensus on diagnostic criteria to capture severe health anxiety, and also because the division between pathological and non-pathological health anxiety is likely to be arbitrary [22]. The strong emphasis on continuous outcomes in the field of health anxiety is illustrated by the fact that out of the 13 RCTs surveyed under 1.2.4, only one [88] involved diagnostic assessment at post-treatment. The use of a dichotomous outcome had also severely impeded the statistical power of both trials, to the extent that it had not been possible for our research group to recruit the sample size needed for a non-inferiority trial of G-ICBT and FTF-CBT.

4.7 WHAT DO THE NUMBERS MEAN?

The results of the present project are almost universally presented in terms of numbers. For example, Study IV revealed that, based on the 18-item SHAI, the mean within-group change in G-ICBT from baseline to the post-treatment assessment was 1.65 *d*. But, from the patient's perspective, what does such a number really mean?

Before treatment, the average patient in Study II–IV suffered from a high level of health anxiety, typical of most clinical trials in the field. Most patients reported that they spent much time worrying about health, that they were "often afraid [of having] a serious illness", and often worried about dying. Most indicated that they were "constantly aware of bodily sensations or changes", and that they always worried about sensations or bodily changes without a clear cause. A clear majority of patients reported that they thought there was something wrong with their body, and that they found it difficult to believe their doctor when told that they had nothing to worry about. Most believed that their friends and family would characterise them as "a hypochondriac".

Before treatment, most patients stated that they were impaired in their daily work or studies, though typically not to a large degree and most were working full time. The effect of health anxiety was strong on emotional and social capabilities. (The typical patient reported being severely emotionally affected.) Most saw themselves as somewhat impaired in their capacity to engage in social activities, and moderately impaired with regard to their capacity to engage in family life and home activities. The typical patient had some, though not severe, difficulty sleeping, and scored above the cut-off for mild depression. Most reported planning their days, and abstaining from activities, in order to reduce or manage their physical symptoms.

After treatment, the health anxiety level of the average patient was much reduced, though still around the clinical cut-off for severe health anxiety. Most reported that they still occasionally worried about their health, having a serious illness, and dying. They were also still sometimes aware of their bodily sensations or changes. The fear was however not as constant, and not as intense, as before treatment. Most responses changed from "often" to "sometimes", "strong"

to “mild” and so on. This was also the case in terms of impairment and secondary difficulties. The average patient still reported being emotionally affected to a small degree, though most did not think that their health anxiety still interfered with their work or social life. The mean depression score was below the cut-off for mild depression, and after treatment, most patients no longer reported planning their days to reduce or manage their symptoms. This being said, the treatment response was very different from patient to patient. Whereas approximately every other patient in CBT was both reliably improved and scored below the cut-off for severe health anxiety at the post-treatment assessment, approximately one fourth was reliably improved but did not score below the cut-off, and one fourth was not reliably improved.

4.8 CLINICAL IMPLICATIONS

The work here presented has important clinical implications. First, the promising effects of CBT without therapist support (Studies II–III) indicate that this is likely to be an ideal treatment format for medical clinics that need offer treatment for severe health anxiety, but do not have the resources to conduct conventional FTF-CBT or G-ICBT. Both U-ICBT and BIB-CBT are experimental treatments for severe health anxiety, and effects need be replicated. The prospect of delivering efficacious psychological treatment for a psychiatric condition not too long ago considered difficult to treat even with conventional face-to-face therapies – and doing so entirely without the involvement of a therapist – is worthy of notice.

G-ICBT appears to be non-inferior to FTF-CBT and should thus be regarded as a first-line treatment for severe health anxiety (Study IV). Considering the advantages of this treatment format, e.g., in terms of therapist time needed per treatment, and flexibility with regard to schedule and geography, further implementation and evaluation of G-ICBT in routine heath care is likely to be highly cost-effective, and has the potential to substantially increase the availability of CBT for those suffering from severe health anxiety.

There is, however, still room for FTF-CBT. For some patients, G-ICBT may not be a feasible or practical intervention; an example being those with severe difficulties reading and writing. On the other hand, there are also patients likely to benefit more from G-ICBT than FTF-CBT; an example being those living far from health care clinics. Because the relative strengths and limitations of G-ICBT and FTF-CBT are likely to vary over settings, the most efficient way of delivering CBT (e.g., as G-ICBT, FTF-CBT, stepped care, or some sort of hybrid format) for severe health anxiety is likely to differ over sectors of the health care system. A reason to offer both treatment formats is also that it is yet unknown if non-responders in one type of treatment (e.g., G-ICBT) are likely to gain from a change of treatment format (e.g., from G-ICBT to FTF-CBT) in the event of a second treatment attempt.

As noted above, the availability of efficacious treatments for severe health anxiety is poor, and the reality for most patients with severe health anxiety is not that they are offered best-practice FTF-CBT, or even psychological treatment of any kind. A broader implementation of G-ICBT is thus typically not a question of abandoning another best-practice treatment, but rather a transition to an efficacious treatment from no treatment at all.

4.9 SUGGESTIONS FOR FUTURE RESEARCH

There are numerous viable areas of future research into the classification and treatment of severe health anxiety. One important line of research concerns the implementation and evaluation of G-ICBT and other forms of minimal-contact CBT for severe health anxiety in routine care. Another particularly important line of research concerns the large proportion of non-responders in all forms of CBT for severe health anxiety. Here follows a list of viable questions for future investigation:

- Do the new DSM-5 diagnoses for severe health anxiety predict the effect of CBT or provide information about psychological processes that could be targeted in CBT?
- What are the effects of G-ICBT, U-ICBT, and BIB-CBT for severe health anxiety in (particular sectors of) routine care?
- What are the most cost-effective ways of implementing G-ICBT and FTF-CBT for severe health anxiety in (particular sectors of) rotuine care?
- What are the relative effects of G-ICBT and FTF-CBT for severe health anxiety in the very long term?
- Does the use of automated weekly reminders significantly increase the effect of U-ICBT and BIB-CBT for severe health anxiety, and if so how is this effect optimised?
- Would it be possible to predict the main outcome of CBT for health anxiety based on more sophisticated statistical models?
- What is the ideal length of CBT for severe health anxiety?
- What is the necessary training for a therapist in G-ICBT for severe health anxiety?
- What can be done for partial responders and non-responders after CBT?
- What is predictive of adverse events in CBT for severe health anxiety, and how can these events be avoided or minimised?
- To what extent do the effects of minimal-contact CBT, and CBT for severe health anxiety in general, generalise to other cultural contexts and health care systems?

4.10 CONCLUDING REMARKS

Based on this thesis, there now exists a promising structured interview specifically designed for the assessment of DSM-5 SSD and IAD. U-ICBT and BIB-CBT demand little health care resources but nevertheless appear to be efficacious treatments for severe health anxiety, and thus deserve further use and evaluation. Importantly, it has also been shown that G-ICBT is at least as efficacious as FTF-CBT in the treatment of severe health anxiety. The availability of CBT for this patient group can thus be markedly improved through wider implementation of G-ICBT in routine care.

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