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ASPECTS OF COMMON MENTAL DISORDERS IN PRIMARY CARE

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Aspects of Common Mental Disorders in Primary Care
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With love to my husband Henrik and my children Elsa, Alma, and Albert.

Popular science summary of the thesis

Common mental disorders are an important and growing problem in society. Conditions such as depression, anxiety, and stress-related disorders cause suffering, reduced function, and sick leave. Most people seek help for these problems in primary care. Several factors can make it challenging for general practitioners (GPs) to find the correct diagnosis and treatment. Patients may have symptoms that could be caused by more than one common mental disorder or by physical, social, and economic difficulties. Finding the correct treatment (for example, antidepressants, psychotherapy, or sick leave) can also be complicated by a lack of knowledge about which treatments are feasible and effective for primary care patients with specific disorders.

Study I examined people on sick leave for mental disorders and compared the diagnosis on the sick leave certificate with the diagnoses found during a structured psychiatric interview. It also investigated how these diagnoses and the person's self-rated symptom severity correlated with sick leave length.

Primary care research in other countries has shown better care coordination helps many patients with common mental disorders. Those studies found that structured care plans, enhanced teamwork, and special care coordinators (care managers) produced better results than usual care for patients with depression in both the short and long term. The first large Swedish intervention study on care managers for patients with depression also found good short-term effects. This study tested care managers for patients with depression at 23 primary care centers in Västra Götaland and Dalarna. However, long-term follow-up of the patients was needed (Study II), as was a better understanding of GPs' experiences of working with care managers for patients with depression (Study III).

Guidelines for treating depression and anxiety recommend cognitive behavioral therapy (CBT) and antidepressants. However, it is still not clear how effective CBT is for one of the most common anxiety disorders, generalized anxiety disorder. The symptoms of this disorder, which include but are not limited to constant, uncontrollable worry, often lead to chronic pain, dizziness, irritability, sleep problems, and depression. There are CBT methods for treating generalized anxiety disorder, such as intolerance-of-uncertainty therapy and metacognitive therapy, but no previous studies on how these therapies can be used in primary care or the effects they have in primary care patients. As many patients with generalized anxiety disorder seek primary care mainly for physical symptoms, their willingness to receive psychological treatment has also been unclear. Study IV was a pilot trial that investigated the feasibility of a larger study comparing intolerance-of-uncertainty therapy and metacognitive therapy for generalized anxiety disorder in primary care.

The results of Study I showed that in the structured interview, many patients on sick leave for depression, anxiety disorder, and stress-induced exhaustion disorder met criteria for diagnoses other than the one on their sick leave certificate. For example, 76% of patients on sick leave for stress-induced exhaustion disorder met the criteria for ongoing depression. Only 65% of those on sick leave for depression met the depression criteria. Sick leave length did not differ by sick leave certificate diagnosis. Instead, people who reported the most severe symptoms had the longest sick leave (65 days for those with the least severe symptoms, 235 days for those with the most severe symptoms). Those who met the Swedish criteria for stress-induced exhaustion disorder were on sick leave significantly longer (on average 144 days) than those who did not (84 days).

Study II showed that after 12 months, patients with mild to moderate depression who were assigned a care manager had significantly less severe depressive symptoms and significantly higher quality of life than those who received usual care. By 24 months, the usual care group had improved to the level of the care manager group, while the care manager group maintained their improvements. Patients assigned a care manager reported significantly higher confidence that they would receive professional support and information from the primary care center.

GPs who worked with care managers had mixed experiences (Study III). Some described great relief that someone else could support the patients and felt confident that the care manager followed the patient's progress and reported back to them as needed. They thought the support of care managers might be all that some patients needed and could help prevent medicalization of life-related problems. Other GPs were more concerned that the care manager's role was unclear and overlapped with the roles of psychotherapists or GPs. GPs could express concern that rather than providing support, the extra care manager contacts might burden depressed patients. Several of the GPs also felt that patients with more severe symptoms and recurring and more complex problems needed care managers more than the patients with mild to moderate depression. The study made it clear that introducing care managers requires training in the care team and a shared and clear understanding of everyone's roles.

Study IV showed that it is feasible to conduct a study in primary care that compares intolerance-of-uncertainty therapy and metacognitive therapy for patients with generalized anxiety disorder. The pilot study at Liljeholmen Primary Health Care Center recruited 64 patients who met the diagnostic criteria for generalized anxiety disorder as a primary diagnosis. They were randomly assigned to either intolerance-of-uncertainty therapy or metacognitive therapy and were treated by the primary care center's regular psychosocial team. The sessions were recorded, and outside experts reviewed selected recordings to check how well the therapists delivered the treatment and how well they followed the treatment protocol. It was relatively easy to recruit patients. Dropout from

the metacognitive therapy group was higher than from the intolerance-of-uncertainty therapy group but lower than in similar studies conducted in psychiatric outpatient care. In the follow-up survey, the patients reported that they were satisfied with the treatment they received and with being included in the study, which suggests that it is feasible to provide psychological treatment for generalized anxiety disorder in primary care.

Both treatments significantly reduced worry and depressive symptoms, but metacognitive therapy was more effective. Quality of life and functional capacity only improved after metacognitive therapy. In both therapy groups, improvements were stable at the 6-month follow-up.

In summary, people on sick leave for common mental disorders seem to fulfill criteria for several psychiatric diagnoses. The question is whether this represents comorbidity or perhaps overlap in diagnostic criteria for common mental disorders. More severe symptoms result in longer sick leave, as does fulfilling the diagnostic criteria for stress-induced exhaustion disorder (Study I).

Care managers (as a supplement to usual care) have a better effect on depressive symptoms and quality of life than usual care, even after a year. Two years later, patients who had a care manager still have more confidence that they will receive professional support and information from their primary care center than patients who received usual care, but no other differences in symptoms or quality of life were seen after that length of time (Study II). GPs had mixed experiences of working with care managers for patients with depression. The findings suggest that care managers can strengthen and improve care but that the care manager's role in the care team must be clear (Study III).

Study IV showed that it is feasible to conduct a randomized controlled trial in primary care comparing two CBT methods for patients with generalized anxiety disorder. Both intolerance-of-uncertainty therapy and metacognitive therapy had large effects, reducing worry significantly, but metacognitive therapy had a significantly greater effect. Study IV shows promising results that can be investigated in a larger study.

Populärvetenskaplig sammanfattning

Psykisk ohälsa är ett stort och växande problem i samhället och tillstånd som depression, ångestsjukdomar och stressrelaterade besvär orsakar stort lidande, nedsatt funktionsförmåga och sjukskrivning för många människor. De flesta söker hjälp i primärvården och tidigare forskning visar att det många gånger förekommer samsjuklighet både med psykiska och kroppsliga besvär, samt att socioekonomiska faktorer inverkar, vilket sammantaget kan göra det komplicerat att hitta rätt diagnos och behandling. Det finns även risk för medikalisering av vanliga reaktioner på svårigheter i livet. Det behövs mer kunskap om behandling av stress-relaterade tillstånd såsom utmattningssyndrom samt om vilka insatser som är mest effektiva för patienter med depression och generaliserat ångestsyndrom inom primärvården. Studie I undersöker individer sjukskrivna för psykisk ohälsa och jämför diagnos från sjukintyget med vilka diagnoser som hittas vid en strukturerad psykiatrisk intervju. Studie I undersöker också hur dessa diagnoser och personernas självskattade symtombörda korrelerar med sjukskrivningslängd.

Forskning från primärvård i andra länder har visat att många patienter med psykisk ohälsa blir hjälpta av bättre samordning av vården. Strukturerade vårdplaner, förstärkt teamarbete och särskilda vårdsamordnare (oftast sjuksköterskor) har visats ge bättre resultat än vanlig vård på både kort och lång sikt för patienter med depression. En stor studie med 23 deltagande vårdcentraler i Västra Götaland och Dalarna har visat goda effekter på kort sikt för patienter med mild till måttlig depression. Det saknas dock långtidsuppföljning av patienterna (Studie II) och det saknas kunskap om hur distriktsläkarna upplever att arbeta med vårdsamordnare för patienter med depression (Studie III).

I riktlinjer för depression och ångestsjukdomar rekommenderas behandling med kognitiv beteendeterapi (KBT) och antidepressiva läkemedel. Stödet för KBT är dock inte lika starkt för generaliserat ångestsyndrom som för andra ångestsyndrom. Generaliserat ångestsyndrom karakteriseras av ständig, okontrollerbar oro, muskelspänning och andra besvär som ofta leder till kronisk värk, yrsel, irritabilitet, sömnproblem och depression. Dessa patienter söker ofta vård i primärvården. Det finns KBT-metoder för behandling av generaliserat ångestsyndrom, t ex intolerans-för-osäkerhets terapi och metakognitiv terapi, men det saknas studier på hur de kan tillämpas eller vilka effekter de har för patienter i primärvård. I och med att många patienter söker huvudsakligen för kroppsliga symtom finns också en osäkerhet om de är villiga att få psykologisk behandling för sina besvär. I Studie IV studeras genomförbarhet i ett pilotprojekt som jämför de två KBT-behandlingarna för patienter med generaliserat ångestsyndrom i primärvård.

Resultaten från studie I visade att många patienter sjukskrivna för depression, ångestsyndrom och utmattningssyndrom uppfyllde kriterier för andra diagnoser än det

de var sjukskrivna för enligt den strukturerade intervjun. Till exempel så uppfyllde 76 % av patienterna sjukskrivna för utmattningssyndrom kriterierna för pågående depression, medan en mindre andel, 65 % av dem sjukskrivna för depression uppfyllde depressionskriterierna. Ingen skillnad avseende sjukskrivningslängd kunde ses för de olika sjukskrivningsdiagnoserna, vilket delvis motsäger resultat från tidigare epidemiologiska studier. Däremot så var de som uppfyllde de svenska kriterierna för utmattningssyndrom i bedömningen sjukskrivna mycket längre (i medel 144 dagar) än de som inte gjorde det (84 dagar). De med svårare symtom, oavsett om det var depressions- eller utmattningssymtom hade längst sjukskrivning. Det kunde skilja mellan 65 dagar för dem med lägst symtombörda till 235 dagar för dem med högst.

Studie II visade att patienter som tilldelats en vårdsamordnare under de tre första månaderna av sin depression även vid 12 månader hade mindre depressiva symtom och högre livskvalitet än de som fick vanlig vård. Vid 24 månader hade dessa skillnader försvunnit och kontrollgruppen utan vårdsamordnare hade nått samma nivåer som gruppen med vårdsamordnare hade bibehållit. Två år efteråt svarade patienter som tilldelats en vårdsamordnare att de hade högre förtroende för att få professionellt stöd och information från vårdcentralen än de andra patienterna.

Distriktsläkare som arbetat med vårdsamordnare för patienter med depression hade blandade erfarenheter, vilket kom fram i fokusgruppsdiskussionerna. En del beskrev lättnad av att någon annan kunde stötta patienterna, de kände sig trygga med att vårdsamordnaren följde upp förloppet och rapporterade tillbaka till dem. De lyfte också att vårdsamordnarens stödjande kontakt kanske var det enda som behövdes för vissa patienter, och att det kunde bidra till minskad onödig medikalisering. Andra distriktsläkare var bekymrade över att vårdsamordnarens roll var otydlig och överlappande, dels gentemot psykoterapeuter och dels gentemot sin egen roll. Många upplevde att de själva var vårdsamordnare och att det snarare blev sämre om patienterna skulle ha många olika kontaktytor, särskilt när det gällde sköra patienter med depression. Flera av läkarna upplevde också att det var andra patienter än de med mild till måttlig depression som hade störst behov av vårdsamordnare, såsom patienter med svårare symtom, återkommande och mer komplexa problem. Läkarna upplevde att vårdsamordnarna påverkade deras eget arbete och en slutsats av Studie III var att förändringsarbete och införande av en ny funktion kräver gemensam förståelse och träning i teamet för att förtydliga allas roller.

Studie IV visade att det var möjligt att göra en studie som jämför två olika KBT-behandlingar för patienter med generaliserat ångestsyndrom i primärvård. Pilotstudien från Liljeholmens Vårdcentral rekryterade 64 patienter som uppfyllde diagnoskriterier för generaliserat ångestsyndrom som primär diagnos. De lottades till antingen intolerans-för-osäkerhets terapi eller metakognitiv terapi och fick behandling av vårdcentralens ordinarie psykosociala team. Sessionerna spelades in och granskades för

kompetens och följsamhet av externa experter på respektive metod. Det gick förhållandevis lätt att rekrytera patienter, bortfallet var något högre från metakognitiv terapi men lågt i jämförelse med andra liknande studier från psykiatrisk öppenvård. I uppföljningsenkät rapporterade patienterna att de var nöjda med behandlingen de fått och med att ingå i studien, vilket tolkas som att det går att ge psykologisk behandling mot generaliserat ångestsyndrom i primärvård.

Båda behandlingarna minskade oro och depressiva symtom, men metakognitiv terapi visade större effekt. Livskvalitet och funktionsförmåga förbättrades bara av metakognitiv terapi. Förbättringen var stabil i båda grupper efter 6 månader.

Slutsatserna kan sammanfattas med att personer sjukskrivna för psykisk ohälsa verkar uppfylla kriterier för flera psykiatriska diagnoser, frågan är om det står för samsjuklighet eller kanske för att de diagnostiska kriterierna för psykiatriska tillstånd överlappar. Hög symtombörda och uppfyllande av de svenska utmattningssyndromkriterierna ger längre sjukskrivning (Studie I).

Vårdsamordnare för patienter med depression har bättre effekt på depressionssymtom och livskvalitet även ett år efter interventionen. Två år efter har patienter som haft vårdsamordnare fortfarande högre förtroende för att kunna få professionellt stöd och information av vårdcentralen jämfört med dem som fått vanlig vård, men i övrigt sågs inga skillnader på symtom eller livskvalitet längre (Studie II). Läkarna hade blandade erfarenheter av arbetet med vårdsamordnare för patienter med depression, slutsatsen blev att vårdsamordnare kunde stärka och förbättra vården men att vårdsamordnarrollen i teamet måste vara tydlig för att det ska fungera (Studie III).

Studie IV visar att det är möjligt att göra en studie som jämför två KBT-metoder för patienter med generaliserat ångestsyndrom i primärvård. Båda metoder minskade oro, men metakognitiv terapi hade större effekt på oro, nedstämdhet, livskvalitet och funktionsförmåga. Studie IV visar lovande resultat som kan ligga till grund för en större studie.

Abstract

Depression and anxiety disorders are common in the general population. Primary care is the first line of care for people with common mental disorders. This doctoral project investigated aspects of common mental disorders, including diagnostic procedures and interventions in primary care.

Study I was an observational study of 480 people in the regions of Stockholm and Västra Götaland on sick leave for common mental disorders. It used structured psychiatric interviews (M.I.N.I.) and symptom severity scales (MADRS-S, KEDS) to investigate the relationship between sick leave certificate diagnoses for common mental disorders and diagnoses made in the psychiatric interviews. It also examined length of sick leave by diagnoses on certificates, interview diagnoses, and symptom severity. Many participants fulfilled the criteria for mental disorders other than the sick leave certificate diagnosis. For example, 76% on sick leave for stress-induced exhaustion disorder (SED) and 67% on sick leave for anxiety disorder fulfilled the criteria for depression (p=0.041). Diagnoses on certificates were not associated with sick leave length. Fulfilling SED criteria was associated with longer sick leave (144 vs. 84 days, p<0.001), as were more severe symptoms. Thus, sick leave certificate diagnoses do not reflect the diagnoses obtained in structured psychiatric interviews. This could mirror the changing and overlapping nature of the symptoms of common mental disorders and suggests that findings based on sick leave certificate diagnoses should be interpreted with caution. The association between longer sick leave and more severe symptoms or fulfilling SED criteria is clinically relevant and worth further study.

Study II used data from the PRIM-CARE cluster randomized controlled trial (RCT) at 23 primary care centers (11 intervention, 12 control) in Västra Götaland and Dalarna to compare the 12- and 24-month effectiveness of care managers to usual care for primary care patients with depression (n=376: 192 intervention, 184 control). Patients with care managers had less severe symptoms (MADRS-S, p=0.02) and higher quality of life (EQ-5D, p=0.01) at 12 months. Improvements in patients without care managers meant that this was no longer the case at 24 months (MADRS-S, p=0.83, EQ-5D, p=0.88). Responses to a study-specific postal questionnaire at 24 months showed that patients with care managers were more confident that they could get information (53% vs 38%; p=0.02) and professional emotional support (51% vs 40%; p=0.05). Care managers for primary care patients with depression therefore seem superior to usual care in the long term, as it took up to 24 months for patients without care managers to achieve the same improvements as patients with care managers achieved in 6 months and maintained long-term. Moreover, patients with care managers had more confidence in future care.

Study III explored the views and experiences of general practitioners (GPs) who worked with the care managers in the PRIM-CARE study to better understand the GPs' perspectives on this organizational change. Transcripts from five focus-group discussions with GPs were analyzed with qualitative content analysis. GPs thought care managers could ensure care quality while freeing GPs from case management. They could also feel concern about role overlap, think that care managers should be assigned to patients who need them the most, and express the belief that transition to a chronic care model required change. In summary, GPs could see benefits to assigning care managers to patients with depression. However, they expressed concern about role overlap and emphasized the need to clarify care managers' role in the care team.

Study IV was an RCT pilot trial that investigated the feasibility and effectiveness of two cognitive behavioral therapy (CBT) protocols for generalized anxiety disorder (GAD) in primary care, intolerance-of-uncertainty therapy (IUT) and meta-cognitive therapy (MCT). Feasibility measures included recruitment, drop-out, patients' perceptions of participation and treatment, and therapists' competence in and adherence to protocol. Effectiveness measures, assessed at pre-treatment, post-treatment, and 6 months, included worry, depressive symptoms, functional impairment, and quality of life. The recruitment process was smooth, dropout was low, and patients were satisfied with treatment (scale 0–6, median 5.17, SD 1.09). Therapists' competence and adherence to protocol were rated weak to mediocre. Both therapies effectively reduced worry with large effect sizes (Cohen's d IUT = –2.69, 95% confidence interval [–3.63, –1.76] and Cohen's d MCT = –3.78 [–4.68, –2.90]). MCT resulted in statistically superior improvements (d = –2.03 [–3.31, –0.75]). Results were maintained at 6 months. It is thus feasible to conduct an RCT comparing IUT and MCT in primary care patients with GAD. Both treatments effectively reduce worry, but MCT seems superior. A full-scale RCT is required to confirm these findings.

List of scientific papers

I.   Af Winklerfelt Hammarberg, S., Westman, J., Hange, D., Finnes, A., Björkelund, C., Hällgren, J., Skoglund, I., Nager, A. (2022). Outcomes of psychiatric interviews and self-rated symptom scales in people on sick leave for common mental disorders: an observational study. BMJ Open, 12(6), e057745. doi:10.1136/bmjopen-2021-057745

II.   Af Winklerfelt Hammarberg, S., Björkelund, C., Nejati, S., Magnil, M., Hange, D., Svenningsson, I., Petersson, E., André, M., Udo, C., Ariai, N., Wallin, L., Wikberg, C., Westman, J. (2022). Clinical effectiveness of care managers in collaborative primary health care for patients with depression: 12- and 24-month follow-up of a pragmatic cluster randomized controlled trial. BMC Prim Care, 23(1), 198. doi:10.1186/s12875-022-01803-x

III.   Af Winklerfelt Hammarberg, S., Hange, D., André, M., Udo, C., Svenningsson, I., Björkelund, C., Petersson, E., Westman, J. (2019). Care managers can be useful for patients with depression but their role must be clear: a qualitative study of GPs' experiences. Scandinavian Journal of Primary Health Care, 37(3), 273-282. doi:10.1080/02813432.2019.1639897

IV.   af Winklerfelt Hammarberg, S., Toth-Pal, E., Jansson-Fröjmark, M., Lundgren, T., Westman, J., Bohman, B. (Submitted Manuscript.) Intolerance-of-uncertainty therapy versus metacognitive therapy for generalized anxiety disorder in primary health care: a randomized controlled pilot trial

CONTENTS

List of abbreviations

CBT	Cognitive behavioral therapy
CTS-R	Cognitive Therapy Scale-Revised
DSM	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D	EuroQol five Dimension Scale
GAD	Generalized Anxiety Disorder
GP	General practitioner
ICD	International Statistical Classification of Diseases and Related Health Problems
IUT	Intolerance-of-uncertainty therapy
KEDS	Karolinska Exhaustion Disorder Scale
M.I.N.I.	Mini International Neuropsychiatric Interview
MADRS-S	Montgomery-Asberg Depression Rating Scale - Self-assessment
MCT	Metacognitive therapy
MCT-CS	Metacognitive Therapy Competency Scale
PHQ-9	Patient Health Questionnaire 9
PSWQ	Penn State Worry Questionnaire
RCI	Reliable Change Index
RCT	Randomized controlled trial
SED	Stress-induced exhaustion disorder
SWLS	Satisfaction With Life Scale
WHODAS	World Health Organization Disability Assessment Schedule

1 Introduction

The World Health Organization has estimated that 29% of people will experience a common mental disorder during their lifetime (1). People often seek primary care for symptoms that may arise because of a common mental disorder (e.g., depression or anxiety), a somatic disorder (e.g., hypothyroidism), or in reaction to a stressful life event (e.g., bereavement) (2). Primary care is tasked with distinguishing the causes of these symptoms so that each patient can receive the treatment and support most likely to help them recover. For most people with common mental disorders, primary care has become the main source of treatment and support (2).

Around the world, efforts have been made to address the need for improved care for people with common mental disorders (3, 4). Studies have investigated the prevalence and outcomes of sick leave in people with such disorders (5, 6). Structured psychiatric interviews have been developed and implemented in psychiatric care (7, 8) but are rarely used in primary care (9, 10). Collaborative care models, which often include care managers, have been tested and implemented in primary care (11). Cognitive behavioral therapy (CBT) has been found effective for different common mental disorders in multiple settings around the world (12–14), and efforts are underway to test various CBT protocols and increase access to CBT in primary care (12, 15, 16).

This thesis addresses several challenges to providing primary care for patients with common mental disorders by investigating diagnoses of common mental disorders in primary care and interventions for patients with these disorders.

2 Literature review

2.1 Common mental disorders in primary care

Common mental disorders include depression, anxiety disorders, adjustment disorders, and other reactions to stress or stressful life events. Common mental disorders are prevalent. According to the World Health Organization, approximately 17% of the population fulfils the diagnostic criteria for at least one such disorder (1), and the majority seek care in primary health care (1, 2, 17). Studies show that conditions tend to overlap over time and are often comorbid with somatic symptoms and diagnoses (18–21). Common mental disorders lead to suffering and impairment for patients and high costs for society (1).

In the past twenty years, research on common mental disorders has led to improved evidence-based treatment and care for people with these disorders (22–24). Revised clinical treatment guidelines, including for primary care, have been implemented in many countries (1). The recommended first line of treatment for mild to moderate depression and anxiety disorders is cognitive behavioral therapy (CBT) and/or antidepressant treatment. Many countries, including Sweden, have made efforts to increase the availability of such recommended treatment to primary care patients (1, 2). Moreover, revised guidelines have led to the introduction of collaborative care models, including care managers, for primary care patients with common mental disorders (11, 25).

2.1.1 Depression

Worldwide, more than 300 million people have depression, an estimated 4.4% of the population, which makes this mood disorder the world's most common mental disorder (1). Depression is characterized by sadness and loss of interest in most things for at least two weeks. Symptoms can be mild to severe and include fatigue (mental and physical), restlessness, anxiety, difficulty sleeping, difficulty concentrating and taking initiatives/making decisions, feelings of worthlessness and guilt, and changes in appetite and weight. Severe depression can also lead to suicidal ideation and suicide attempts. To meet the diagnostic criteria for depression (26, 27), the person's symptoms must affect their level of functioning.

Diagnosing depression can be challenging. For instance, depressive episodes can be difficult to separate from severe grief or adjustment disorders (28), as these disorders may occur on their own, may trigger a depressive episode, or may be intensified by the presence of depression. Moreover, a patient who presents with depression may have another mood disorder, such as bipolar disorder or recurrent/persisting depression (27).

Guidelines recommend assessment of symptom severity and suicide risk, treatment with CBT or interpersonal therapy and/or antidepressant medication, and thorough follow-up (23, 24).

2.1.2 Anxiety disorders and related disorders

Anxiety disorders and phobias have a one-year prevalence of 7.3% and a lifetime prevalence of 20% to 30% (1, 29). They are characterized by excessive fear and worry that differs from the nervousness or anxiousness that most people experience in response to stress or threatening situations (27). Anxiety disorders are classified by the core fear, for example, fear and avoidance of social situations in social phobia, and fear and avoidance of the physical symptoms of panic attacks in panic disorder (27). To diagnose an anxiety disorder, symptoms must affect the person's functioning (27).

Obsessive-compulsive disorder and post-traumatic stress disorder were historically classified as anxiety disorders (27). Like anxiety disorders, they are characterized by excessive anxiety and reactions to fear. In obsessive-compulsive disorder, fear and avoidance behaviors are directed toward unpleasant and disturbing thoughts and repeated protective actions, while in post-traumatic stress disorder, the reactions are related to involuntarily reliving the trauma.

Guidelines recommend CBT as the first-hand treatment for anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder, and antidepressant medication as the second-hand choice (23, 24). Differential diagnosis is crucial, as CBT protocols are specific to each disorder (30). For instance, CBT includes exposure to the specific fears and situations related to the disorder.

2.1.3 Generalized anxiety disorder

Generalized anxiety disorder (GAD) is one of the most common anxiety disorders (31, 32). Approximately 5% of the population of European and North American countries meet the criteria for GAD at some point during their lives (31, 33, 34). GAD is characterized by persistent and excessive worry about things that can go wrong in everyday life, such as responsibilities at work or at home and health (27). The persistent worry leads to muscle tension and is often accompanied by physical symptoms (e.g., restlessness, fatigue, difficulty concentrating, dizziness, problems sleeping) (27) and secondary somatic consequences (e.g., chronic pain, irritable bowel syndrome, medically unexplained symptoms) (35-38). Moreover, people with GAD have an increased risk for other mental disorders, such as depression and adjustment disorders (35, 36). These somatic and psychiatric health problems often motivate people with GAD to frequently attend primary care (36, 39, 40), which in turn may lead to extensive physical examinations and investigations (37, 40). Previous research shows that GAD often goes undetected and thus untreated in primary care patients (33, 35-37, 41).

Accordingly, the disorder leads to disability and suffering, as well as high costs for society (1, 35, 42).

For a diagnosis of GAD, ongoing worry must have been present for at least six months and affect functioning (27). In contrast to the guidelines for other anxiety disorders, for GAD, guidelines recommend antidepressant medication as the first-hand treatment and CBT as the secondary choice (23, 24). In primary care, treatment for GAD thus consists mainly of antidepressant medication, and primary care patients with GAD have limited access to CBT (33, 37).

2.1.4 Stress-related disorders, including adjustment disorder and stress-induced exhaustion disorder

In contrast to normal reactions to life events and stress, which include stress reactions such as depressive symptoms and anxiety, some people get more persistent and severe reactions that can be classified as adjustment disorders (27, 43). The symptoms of adjustment disorders are similar to those of GAD and depression. They include increased worry, sadness, irritability, sleep difficulties, and problems concentrating but are clearly related to an identifiable stressor or life event within the past three months (27). The symptoms must affect functioning, and the negative impact on daily activities must be disproportionate to the event (27). Cultural, personal, and socioeconomic factors may influence reactions to life events and stress (43). It can therefore be difficult to diagnose adjustment disorders and to measure their prevalence (43). Brief supporting interventions are recommended rather than antidepressants, sick leave, or psychotherapy (43).

Stress-induced exhaustion disorder (SED) is a related but more severe reaction to prolonged stress (44). In 2005, the National Board of Health and Welfare developed Swedish ICD-10 criteria for this condition and assigned it the diagnostic code F43.8. Neither the criteria nor the diagnosis is found in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (26) or the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (27). SED is characterized by physical and mental symptoms of exhaustion that have persisted for at least two weeks and developed in response to one or more identifiable stressors present for at least six months. The criteria include cognitive difficulties such as reduced initiative, impaired memory, emotional instability, sleep difficulties, and physical symptoms such as pain, dizziness, palpitations, and increased sensitivity to sound (44, 46). To fulfill the diagnostic criteria, the symptoms must have led to reduced function and work ability. From 2005 to 2018, SED was used as a secondary diagnosis if the patient also met the criteria for depression or GAD. Since 2018, SED can be used as a primary diagnosis even if the patient meets the criteria for depression or GAD.

Because the diagnostic criteria for SED have not been validated in international research, it is challenging to ascertain its prevalence outside Sweden. In Region Stockholm, the combined prevalence of adjustment disorder and SED increased from 1.0% to 2.7% between 2007 and 2017 (17). In Sweden, approximately 30% of sick leave longer than two years is caused by SED (45). Several studies have sought to clarify the etiology of the condition and to identify effective treatments (46, 47). However, a recent scoping review of 89 studies concluded that it is currently not possible to determine the etiology of SED, the best treatment, or the diagnostic validity of the construct (48). This is because all the studies have been performed in the Nordic countries, mainly Sweden, with small samples and few or no objective or replicable measures (48). Research to date suggests that workplace interventions have the best effect on recovery and return to work for people with SED (47).

2.2 Sick leave for common mental disorders – what do we know?

Common mental disorders are the major cause of sick leave in many countries (6, 49–52). Sick leave can be necessary for people with severe symptoms of common mental disorders such as depression (53, 54). However, sick leave can also be a risk factor for worsened symptoms and additional problems (5, 50, 55, 56). For instance, long-term sick leave is associated with increased severity of phobic symptoms (56) and comorbidity (50), raised risk of financial stress (54), social isolation (52), and high costs for societies and social welfare systems (1, 45).

Swedish national guidelines recommend no or short sick leave for anxiety disorders and short or part-time sick leave for depression but state that longer sick leave may be necessary for SED or recurrent depression (57). Sick leave certificates, which can include up to three diagnoses, are required to include free-text information about the symptoms and objective findings that cause the patient's loss of function (52) and inability to work (57).

Previous epidemiological research on sick leave certificate diagnoses from European countries (58-60) and a systematic review of observational studies (5) have concluded that diagnoses of stress reactions, depression (59), and depression combined with anxiety are common causes of long-term and repeated sick leave (58). More severe mental symptoms (5, 60) and comorbid and recurrent diagnoses (5, 61) are associated with both short- and long-term sick leave (5). Regardless of diagnosis, anxiety symptoms, specifically anxiety and phobic reactions related to work, seem to be correlated with long-term (>12 weeks) sick leave (55, 56), and a Swedish study showed that primary care patients with high scores on multiple mental symptom severity scales had lower perceived ability to work (62).

The process of sick leave certification is especially challenging if diagnosis must be based on subjective health complaints rather than objective findings, as is the case with

most common mental disorders (63-67). Several studies have investigated GPs' experiences of sick leave certification for patients with subjective health complaints (64, 66, 68-70). These studies illuminate several challenges and dilemmas that GPs face in the sick leave certification process, as well as different and often individual coping strategies (65, 69). Few if any previous studies have addressed the processes that GPs use to diagnose mental disorders and symptom severity in sick leave certification.

2.3 Diagnosis of common mental disorders in primary care

People with mental disorders can seek primary care for a wide variety of symptoms, which makes the process of psychiatric diagnosis challenging for GPs (9, 71). Under- or misdiagnosis, even of more severe disorders, can occur when patients emphasize somatic symptoms or stressful life situations during consultations (71, 72). However, the reverse is also true. Normal reactions to stress or life events (e.g., bereavement), such as symptoms of anxiety, weariness, and depression, can be medicalized, leading to the overdiagnosis of mental disorders (9, 73).

The procedures for diagnosing mental disorders in primary care are not as clearly described in guidelines as the procedures for diagnosing somatic disorders. Whereas most somatic disorders can be diagnosed with objective findings (e.g., from blood tests), the diagnosis of mental disorders is based mainly on the patient's descriptions of symptoms and how well the symptoms fit criteria in diagnostic manuals (27, 74) that have not been developed specifically for use in primary care (75).

Accurate diagnoses are crucial to providing appropriate treatment, and Swedish national guidelines recommend adding a structured interview to the clinical procedure for diagnosing mental disorders (23). The Mini International Neuropsychiatric Interview (M.I.N.I.) (8) is a structured psychiatric interview based on the DSM (27) that detects at least some mental disorders with fair to good sensitivity and specificity (9) and is feasible to use in primary care (9, 76). However, not all diagnoses (e.g., adjustment disorders and SED) are represented in M.I.N.I. The extra step that M.I.N.I. adds to the consultation is a further obstacle to its use, and GPs can also think that instruments like M.I.N.I. conflict with open consultation methods (10). Thus, in primary care, mental disorders are often diagnosed based on clinical presentation, sometimes complemented with the results of brief screening instruments or self-rated symptom severity scales for mental disorders (77).

2.3.1 Measures of symptom severity, daily function, and quality of life

There are several symptom severity scales for common mental disorders, such as the Montgomery-Asberg Depression Rating Scale (MADRS) (78, 79) and the Generalized Anxiety Disorder 7-item scale (GAD-7) (80). Such instruments were developed to follow the severity of symptoms over time after a diagnosis has been made in a structured

interview (24). In clinical practice, symptom severity scales are sometimes useful in diagnostic assessment (9, 81, 82). For instance, the nine-item Patient Health Questionnaire (PHQ-9) (83) uses DSM criteria and is a rapid way to identify depressive symptoms (84). However, symptom severity scales should not be used as main diagnostic instruments. Symptom severity scales are also used in clinical effectiveness and treatment studies, as the main outcome of such studies is often reduced symptom severity.

Daily function is another important clinical outcome in patients with common mental disorders, as reduced function is a criterion for diagnosing all such disorders (26, 27). Scales have therefore been developed to measure function. Examples include but are not limited to the World Health Organization Disability Assessment Schedule (WHODAS) (85) and the EuroQol five Dimension Scale (EQ-5D) (86). Quality of life is an additional important clinical outcome that can be measured with a variety of instruments, such as the EQ-5D (86) and the Satisfaction with Life Scale (SWLS) (87).

2.4 Improving care for patients with common mental disorders via collaborative care

Much effort has been invested in improving treatment and follow-up of common mental disorders in primary care (22, 88). For instance, studies have investigated the effectiveness of collaborative care models (11, 25), which typically include care managers who coordinate patient care (11, 25). Care managers are often specially educated nurses, and their tasks include enhanced patient support and follow-up, as well as regular contact with and feedback to GPs and other relevant professionals (11, 25). In addition to care managers, collaborative care can also include simplified guidelines and development of structured care plans with enhanced and structured patient follow-up, use of decision support systems, and efforts to improve collaboration and teamwork (11, 25).

Collaborative care models have been successfully implemented to improve care coordination for patients with chronic somatic diseases (89-91) and common mental disorders (11, 91, 92). According to two meta-analyses of randomized controlled trials conducted outside Sweden, collaborative care for depression and anxiety improves patients' symptoms, mental quality of life, and care satisfaction more than usual care in both the short and long term (11, 93). Studies have also shown that for people with comorbid somatic conditions and depression, collaborative care results in better physical health outcomes than usual care (91, 92). A meta-analysis that examined RCTs from several countries concluded that collaborative care might be cost effective, but that cost-effectiveness might differ by health system (94).

Primary care is organized differently in different countries, and prior to 2015, care managers had not been tested for patients with depression in Swedish primary care.

Thus, a research group based at the University of Gothenburg designed a pragmatic cluster randomized controlled trial, PRIM-CARE, to investigate the short- and long-term clinical effectiveness and the cost-effectiveness of care managers for primary care patients with depression in the regions of Västra Götaland and Dalarna.

The post-intervention and 6-month follow-ups showed that patients assigned a care manager had better guideline-concordant antidepressant use and less severe depressive symptoms than patients who received usual care (95). More patients with care managers achieved remission and returned to work (95). The intervention was also cost-effective (96). However, it is important to evaluate organizational changes over long periods of time, to test whether they are effective in the long term before implementing them more broadly (97). The evaluation of the long-term effectiveness of care managers for primary care patients with depression was the aim of Study II.

PRIM-CARE also aimed to explore health care professionals' experiences of collaborative care and the introduction of care managers for primary care patients with depression. The care managers in the PRIM-CARE study described their role as working together in teams at the center to provide patients with additional support and follow-up. They thought they constituted a safety net for the patients (98). The care managers perceived themselves as person-centered and as increasing the continuity and accessibility of primary care for these patients (98).

To achieve a fuller picture of people's experiences of organizational change, it is important to explore the perspectives of all the groups affected by the change (99). In the PRIM-CARE study, health center managers and GPs were also affected by the change. An exploration of participating health care center managers' experiences found that most were positive to introducing care managers and considered it a high priority (100). They identified support from colleagues and directors and team members' cooperative skills and positive attitudes as factors that facilitated the introduction of care managers for patients with depression. Barriers to their introduction included high staff workload, shortage of staff, and extensive requirements and demands from regional healthcare management (100).

Previous qualitative studies of GPs' experiences of care managers found that GPs could appreciate care managers for providing relief from heavy workloads (101-103), and that GPs appreciated the regular and structured follow-up provided by care managers, including the results of symptom severity scales (101, 103). The studies also showed that GPs found it preferable to work at the same location as the care manager and to have face-to-face discussions about patients' treatment and care (101, 102). On the other hand, previous qualitative studies also found that GPs could lack understanding of the collaborative care model for patients with depression, especially the role of the care manager in the team (101, 102). Furthermore, GPs could question the cost-effectiveness

of collaborative care. For example, they were concerned that by adding extra personnel to the team, collaborative care would increase expenses at the primary care center (101, 103). Moreover, they could find that care managers' demands for frequent meetings and quick responses about patients added to their already full schedules. GPs could therefore prefer that care managers contact them informally and only if patients' symptoms worsened (104). The experiences and views of GPs in the Swedish PRIM-CARE study are explored in Study III of this thesis.

2.5 Cognitive behavioral therapy in primary care

Since its introduction in the 1980s, cognitive behavioral therapy (CBT) has proven to be an effective treatment for common mental disorders (12-14). Thus, it is recommended as a first-line treatment in guidelines and national recommendations for depression and anxiety disorders (23, 24).

Patients who seek primary care often have multiple simultaneous health problems and overlapping conditions. Treatment options for these conditions can be limited, and some are of questionable effectiveness or carry a risk of harm. Examples include sick leave for anxiety (50, 56, 105), narcotic analgesics for chronic pain (106), and benzodiazepines for anxiety or insomnia (107). CBT, on the other hand, has few side effects (108), and can be effective in reducing symptoms and/or increasing function not only in people with common mental disorders but also in people with certain somatic symptoms or conditions such as tinnitus (109), irritable bowel syndrome (110), and chronic pain (13, 111). The success of CBT has led to actions to increase the availability of CBT in primary care in many countries (15, 16, 112). Moreover, during recent years CBT has developed into several different protocols for different disorders (13). Each protocol addresses the construct(s) identified as the key component(s) of the treated disorder (113) while retaining the main theoretical framework and methods of CBT. Some CBT protocols are supported by more evidence than others (113). Even for well-supported protocols, most evidence comes from settings outside primary care, and the majority of protocols remain untested in primary care.

Currently, guidelines recommend CBT as the first-line treatment for all anxiety disorders except for GAD (23, 24). Guidelines for GAD recommend antidepressant medication as the first treatment choice and CBT as a secondary choice (23, 24). Thus, primary care patients with GAD mainly receive antidepressants and sometimes sick leave (33, 35). They have limited access to CBT (33, 35, 36) even though meta-analyses suggest that several CBT protocols for GAD are effective (114, 115). However, it remains unclear which CBT protocol for GAD is the most effective and which is the most suitable for use in primary care settings (36, 115-117). This is because there are few studies per protocol, many studies have had small sample sizes and used waitlist controls, and few have been carried out in primary care settings (12, 114, 115).

It is important to investigate which CBT protocol is the most feasible and effective in primary care and whether existing protocols, developed in specialized care, should be modified to better meet the needs and circumstances of primary care. For instance, would it be possible to deliver treatment in fewer sessions while maintaining effectiveness? This would be desirable in primary care, as it would make CBT for GAD accessible to more patients. Additionally, several aspects of the feasibility of delivering CBT for GAD in primary care were unclear. One question was whether therapists working in primary care could provide treatment comparable to that provided in specialized psychiatric care. Another was whether primary care patients with GAD, who typically seek primary care for somatic complaints, would be open to psychological treatment. Hence, Study IV tested the feasibility of an RCT comparing two CBT protocols for GAD in primary care.

2.5.1 Intolerance-of-uncertainty therapy

Intolerance-of-uncertainty therapy (IUT) is one of the most-used CBT protocols for GAD in Sweden (118, 119). IUT is based on the theory that people with GAD have trouble tolerating uncertainty about future situations and turn to worry in the belief that worrying will give them more control and help them cope with the situations (118, 119). The protocol contains self-monitoring to increase awareness of these beliefs and behaviors, as well as education about tolerating uncertainty and evaluating worry-related beliefs (119). Patients learn to discriminate between problematic situations and the emotional response to such situations and to separate worry about two categories of uncertain situations. The first kind of uncertain situation is an actual problem in everyday life, such as failing to meet a deadline. The second is a hypothetical situation, such as the possibility of accident, illness, or loss (119). Patients learn to manage the actual situations with problem-solving techniques. To increase their tolerance for uncertainty, they receive mental exposure training about the hypothetical situations and the core fears that make these situations so frightening (119). Research has shown that IUT reduces GAD symptoms significantly more than waitlisting or applied relaxation (113, 120).

2.5.2 Metacognitive therapy

Another CBT protocol for treating GAD is metacognitive therapy (MCT) (121). Instead of being based on the idea that GAD originates from worry about two categories of uncertain situations, MCT is based on the theory that GAD arises from and is maintained by two types of worry (122). The first, type 1 worry, is characterized by the perception that worry is positive and will help the person cope with threatening situations (121, 122). The second, "type 2 worry," also called metacognition or meta-worry, is the worry that worry itself is negative, specifically that it is dangerous, uncontrollable, and harmful (121). By challenging cognitions about both types of worry, MCT aims to help patients develop

alternative coping strategies and behaviors (122). This is accomplished by asking probing questions; identifying relevant situations, reactions, and beliefs; and carrying out worry modulation experiments (121, 123, 124). Two studies have shown that MCT is more effective than other CBT protocols at reducing worry in patients with GAD (125, 126).

IUT and MCT were chosen for the feasibility RCT in Study IV because research in psychiatric outpatient care shows that both protocols effectively reduce the symptoms of GAD (126). Moreover, IUT and MCT protocols and teachers were available to the research group.

3 Research aims

General aim

The aim of this doctoral project was to investigate aspects of common mental disorders, including diagnostic procedures and interventions in primary care.

Specific aims

Study I: The main aim was to investigate the correspondence between diagnoses on sick leave certificates and diagnoses made in structured psychiatric interviews. Secondary aims were to investigate length of sick leave by diagnoses on sick leave certificates, diagnoses made in structured interviews and symptom severity.

Study II: This study aimed to compare the long-term effectiveness of care management and usual care for primary care patients with depression on depressive symptoms, remission, quality of life, self-efficacy, confidence in care, and quality of care 12 and 24 months after the start of the intervention.

Study III: The aim was to explore general practitioners' (GPs') views on and experiences of working with care managers for patients treated for depression in primary care.

Study IV: The primary aim was to investigate the feasibility of a full-scale RCT to compare the effects of IUT and MCT in primary health care patients with GAD. A secondary aim was to explore the preliminary effectiveness of the two treatments on measures of worry, depression, functional impairment, and quality of life.

4 Materials and methods

This thesis includes four studies (Table 1). Study I used data from an RCT in Region Stockholm and an observational study in Region Västra Götaland. Studies II and III were part of PRIM-CARE, a cluster randomized controlled trial in primary care in the regions of Västra Götaland and Dalarna. PRIM-CARE evaluated care managers for patients with depression. Study II was the long-term follow-up of patients in the PRIM-CARE study. Study III applied qualitative content analysis to focus group interview transcripts to explore GPs' experiences of working with care managers in the PRIM-CARE study. Study IV was a pilot RCT that evaluated the feasibility and the preliminary effectiveness of two CBT-based psychotherapies, IUT and MCT, for primary care patients with GAD.

Study	Aim	Design	Participants	Data	Analysis
	Table 1. Studies in the thesis				
I	Investigate the correspondence between diagnoses on sick leave certificates and diagnoses made in structured psychiatric interviews.	Observational	480 patients on sick leave for common mental disorders	Sick leave certificates from patient records/social insurance register, diagnoses from structured psychiatric interviews, patient-reported symptom severity	Descriptive and analytic statistics
II	Compare the long-term effectiveness of care management and usual care for primary care patients with depression 12 and 24 months after the start of the intervention.	Cluster randomized controlled trial	376 primary care patients with mild to moderate depression (192 intervention; 184 control)	Patient-reported outcomes gathered via postal questionnaires	Descriptive and analytic statistics
III	Explore GPs' views on and experiences of working with care managers for patients treated for depression in primary care.	Focus-group study	29 GPs	Focus group discussions	Qualitative content analysis
IV	Investigate the feasibility of a full-scale RCT to compare the effects of IUT and MCT in primary health care patients with GAD. Secondarily, to explore the preliminary effects of the two treatments.	Randomized controlled pilot trial	64 patients with GAD at Liljeholmen Primary Health Care Center	Feasibility: Patient flow, therapist factors from recorded sessions, patient questionnaire Effectiveness: Patient-reported symptom severity	Descriptive and analytic statistics

GAD, generalized anxiety disorder; GP, general practitioner; IUT, intolerance of uncertainty therapy; MCT, metacognitive therapy

4.1 Design, participants, and setting

Study I

This observational study used data from two studies of people on sick leave for common mental disorders, an RCT from Region Stockholm (127) and an observational study from Region Västra Götaland (128). In Region Stockholm, participants on sick leave for common mental disorders were invited by letter from the Swedish Social Insurance Agency and by advertisements in the press. In Region Västra Götaland, patients on sick leave for mental disorders were invited by rehabilitation coordinators at 28 primary care centers. Both studies included people who had been on sick leave for a common mental disorder for between two weeks and 12 months, were between 18 and 64 years, and were employed at least 20 hours per week. Exclusion criteria were currently being on sick leave for longer than 12 months, severe mental disorders, post-traumatic stress disorder, substance use disorder, and inability to understand Swedish.

Studies II and III

Studies II and III were part of the PRIM-CARE cluster randomized controlled trial in the regions of Västra Götaland and Dalarna, which started in 2014 and ended in 2018 (95). Primary care centers in the two regions were invited to participate. Each primary care center was considered a cluster, and each cluster was allocated to the care manager intervention or care as usual. Patients at the primary care centers aged 18 to 64 years with newly diagnosed (<1 month) mild to moderate depression (ICD F32, F33, MADRS-S scores <35) were invited to participate. Study II was the long-term (12- and 24-month follow-up) of patients in PRIM-CARE. Exclusion criteria included inability to speak Swedish and current diagnosis of cognitive impairment, bipolar disorder, psychosis, or substance use disorder.

Study III was a qualitative study that explored GPs' views and experiences of working with care managers for patients with depression. GPs at primary care centers in the intervention group were invited to participate in focus group discussions at their workplace. Five focus groups with a total of 29 participating GPs were held in the two regions. The interviews took place at urban and rural centers in areas of varying socioeconomic status.

Study IV

Study IV was a pilot RCT investigating the feasibility of a full-scale RCT in regular primary care to evaluate the effectiveness of two CBT protocols for GAD: IUT and MCT. It also evaluated the preliminary effectiveness of the protocols. Participants were patients at Liljeholmen Primary Care Center in Stockholm who had a primary diagnosis of GAD. Patients were excluded from the study if they were younger than 18 years, unable to

speak Swedish, or had a severe psychiatric disorder, cognitive impairment, substance use disorder, or other ongoing psychological treatment.

4.2 Procedure, variables, and instruments

Study I

People on sick leave for common mental disorders who responded to the invitation, met the study criteria, and provided written informed consent were assessed at inclusion. Self-reported symptom severity and background characteristics were gathered, and structured psychiatric interviews were performed by trained nurses and psychologists. Recruitment of participants and data collection are described in more detail in the two previous studies that provided the data for Study I (127, 128).

Background characteristics (age, sex, marital status, educational level, and employment status) were self-reported. Antidepressant use and psychological treatment were self-reported and monitored in medical records. Sick leave certificate data, such as the main sick-leave certificate diagnosis, the degree (percentage of full-time) of sick leave, and the length of sick leave were gathered from the Social Insurance Agency register in Region Stockholm and from medical records in Region Västra Götaland. The main sick leave diagnosis was obtained from the most recent sick-leave certificate available at inclusion. Data on the length and degree of sick leave were gathered 12 months after inclusion.

Psychiatric diagnoses were made with the Mini International Neuropsychiatric Interview (M.I.N.I.) (8) version 6.0, which is based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (27). As M.I.N.I. does not include criteria for stress-induced exhaustion disorder (SED; Swedish ICD code F43.8), the Self-rated SED instrument (s-ED) was used to assess whether a patient met the diagnostic criteria for SED (44).

Depressive symptoms were measured with the Montgomery-Asberg Depression Rating Scale – Self-rating version (MADRS-S) (78, 79). The scale has nine items and asks the respondent to rate their depressive symptoms over the past three days on a 0 to 6 Likert scale. Total scores range from 0 to 54. A score of 0 through 12 is interpreted as no or mild depressive symptoms, 13 through 19 as mild symptoms, 20 through 34 as moderate symptoms, and 35 through 54 as severe symptoms (78, 79).

The severity of SED symptoms was measured with the Karolinska Exhaustion Disorder Scale (KEDS) (129). KEDS has nine items. Respondents use a 0 through 6 Likert scale to rate symptoms of mental and physical exhaustion over the past two weeks. Total scores range from 0 to 54 and scores >19 indicate SED (129).

Studies II and III

Study II

A total of 23 primary care centers accepted the invitation to participate in PRIM–CARE and were included in the study (95). The primary care centers were randomized to the intervention (n=11) or the control (n=12) condition. Patients with newly diagnosed mild to moderate depression were invited to participate. After providing written informed consent, patients at intervention centers received an appointment with a care manager and patients at control centers received an appointment with a study nurse. The care manager or study nurse used the depression module of PRIME–MD (130) to confirm the diagnosis of depression and MADRS–S to assess depression severity (78). Baseline data on self–reported depressive symptoms and other outcomes were gathered at inclusion. Follow–up data were gathered via postal questionnaires at 6, 12, and 24 months.

At intervention primary care centers, a nurse received five days of training in delivering the intervention as a care manager (95). The nurse worked 20% to 25% of full time as care manager and attended monthly support meetings held by study personnel. GPs and primary care center managers received two days of training. A research assistant visited the intervention centers weekly to provide support and monitor adherence to the study protocol.

The intervention was 12 weeks long. It started with a one–hour meeting between the care manager and patient to co–develop a care plan. The care manager followed up the plan by telephoning the patient every other week to monitor depressive symptoms (MADRS–S), encourage behavioral activation, and support adherence to medication and recovery. At the end of the intervention, the care manager co–developed an individual relapse prevention plan with the patient. Care managers also maintained regular contact with the patient's GP, therapist, and other caregivers to inform them of changes such as worsening symptoms or side effects of medication. Patients at the intervention centers could also call the care manager as needed.

At control primary care centers, participating patients were assessed by the study nurse and then received usual care. According to national guidelines, usual care consists of treatment with antidepressants and/or psychotherapy and rapid follow up with the GP. A study nurse visited the control centers regularly to monitor adherence to protocol and to gather data on routine care from patients' medical records.

The primary outcome was severity of depressive symptoms as measured with MADRS–S (78). In addition, 50% reduction in MADRS–S scores and remission was analyzed. Remission was operationalized as MADRS–S scores <12.

Health-related quality of life was measured with the EuroQuol-five dimension-3L scale, English tariff (EQ-5D) (86, 131). This scale measures three levels of health-related quality of life (no problems, some problems, and extreme problems) in five areas, including mobility, self-care, everyday activities, pain/discomfort, and anxiety/depression.

Self-efficacy, confidence in care, and quality of care from a patient perspective were also investigated at the 24-month follow-up. A 20-item study-specific questionnaire inspired by similar questionnaires in previous studies was used. Responses to the items about self-efficacy and confidence in care were provided on a 5-level Likert scale that ranged from not at all confident to completely confident. Responses were dichotomized prior to analysis (not at all confident to moderately confident versus very confident to completely confident). Responses to the statements about quality of care from a patient perspective were similarly provided on a 5-level Likert scale that ranged from not at all true to completely true. These responses were also dichotomized prior to analysis.

Background characteristics were gathered at baseline and included age, sex, working, marital status, whether the patient was born in or outside a Nordic country, educational level, leisure-time physical activity, smoking and alcohol habits, sick leave in the last year, and whether the patient was on sick leave at baseline.

Antidepressant medication and psychotherapy were monitored through self-report at each follow-up.

Study III

Study III was a qualitative study that explored GPs' views on and experiences of working with care managers during the PRIM-CARE study. GPs at intervention centers were invited to participate in a focus group discussion that took place at the center where they worked. GPs at five primary care centers took part in the focus group interviews. Participants were given oral and written information and provided written informed consent prior to the focus group. Two researchers were present at each focus group interview. A researcher with prior experience of conducting focus group interviews moderated the discussion. The moderator used a topic guide with open-ended questions that was developed for the study. The other researcher acted as an observer. Each focus-group discussion took about 60 minutes, was audio recorded, and was transcribed verbatim prior to analysis.

Study IV

Before the start of this feasibility study, psychotherapists participated in a one-day workshop on the protocol that they would use. Workshops consisted of lectures and

exercises and were conducted by two clinical psychologists with extensive experience of the relevant protocol.

Patients who visited their GP at Liljeholmen Primary Care Center for mental health problems and/or medically unexplained symptoms were referred to the psychotherapist team for diagnostic assessment with M.I.N.I. version 7.0 (8). Those who met the criteria for GAD as a primary diagnosis were invited to participate. After the patient provided written informed consent, a study nurse gathered information on baseline characteristics and symptom severity. An administrator (blinded) used a web-based service to perform the randomization. Randomization was conducted with a 1:1 ratio, and the randomization list was created in blocks of four or six using a random order of block size.

The two treatments, IUT (119) and MCT (121) were protocol-based. Both treatments were provided individually for up to 12 sessions. The psychotherapists were given the flexibility of delivering the therapy in fewer sessions if their clinical judgment indicated that it was appropriate for the individual patient. Providing psychotherapists with this flexibility is consistent with the instructions in the original manuals (119, 121).

Psychotherapists' competence in the treatment that they provided and their adherence to the treatment protocol was assessed by reviewing recordings of the same session for three randomly selected patients from each psychotherapist. All treatment sessions were audio recorded so the psychotherapists would not know which session the researchers would select to assess competence and adherence. Session five was chosen to ensure that a treatment and not a session including assessment was reviewed.

Feasibility measures

Feasibility was assessed as flow of recruitment, retention, participants' willingness to receive psychological treatment, and psychotherapists' competence in and adherence to the treatment protocols.

Participants completed a questionnaire post-treatment about perceptions of participating in the study and of the treatment. Questions covered experiences of the assessments, procedures, and treatments. Assessment of psychotherapists' competence in and adherence to the protocol was conducted by four clinical psychologists and/or psychotherapists. One assessed competence in IUT; another, competence in MCT; a third, adherence to IUT; and a fourth, adherence to MCT. The assessors were trained in assessing competence and experienced in providing the treatment that they assessed. Competence in IUT was assessed with the Cognitive Therapy Scale-Revised (CTS-R) (132), and competence in MCT was assessed with the Metacognitive Therapy Competency Scale (MCT-CS) (133). Adherence to the treatment

protocols was assessed with two measures that were developed for the present study, one for IUT and one for MCT. These measures were designed to cover the treatment content in sessions four to seven.

Effectiveness measures

Severity of worry was measured with the Penn State Worry Questionnaire (PSWQ) (134). Severity of depressive symptoms was assessed with the Patient Health Questionnaire (PHQ-9) (83). Functional impairment was assessed with the WHO Disability Assessment Schedule (WHODAS) 2.0 (85). Quality of life was assessed with the Satisfaction with Life Scale (SWLS) (87).

4.3   Analysis

4.3.1 Statistical analysis – Studies I, II, and IV

Continuous variables were described with means, medians, and standard deviations (SDs) and categorical variables with numbers and percentages. Comparisons between groups were performed with t tests for continuous variables and chi-square tests for categorical variables in Studies I and II. Statistical tests were two-tailed, and p-values <0.05 were considered statistically significant.

Study I

Statistical analyses of baseline characteristics were conducted prior to combining the data from the RCT in Region Stockholm and the observational study in Region Västra Götaland. The variable "net sick leave days" was analyzed as a count outcome. Regression analysis was used to determine factors associated with the number of net sick leave days while controlling for associations that could affect the results. To account for model overdispersion, negative binomial regression models (135) were used to estimate sick leave rate ratios with 95% confidence intervals. All models were adjusted for age, sex, education, and treatment. Analyses were carried out with SAS 9.4 (SAS Institute, Inc., Cary, NC).

Study II

Mean intra-individual change in depressive symptoms and quality of life in the intervention group and control group were compared with mixed model analysis with repeated measures, adjusted for the type of primary care center (sparse versus medium to high patient inclusion rate) and the patient's age, sex, educational level, use of antidepressant medication, and variable-related scores at baseline (136). Because of sparse data from some of the primary care centers, it was not possible to adjust for the cluster randomization. Analyses were carried out with SPSS (IBM Corp. 2017.Version 25.0. Armonk, NY), and SAS (SAS Institute Inc. 2013. Version 9.4 Cary, NC).

Study IV

For feasibility measures, proportions, means, and SDs were calculated. Differences in dropout between groups were investigated with Fisher's exact test, and differences in session attendance were investigated with an independent t test. To evaluate treatment effects, multilevel modeling was used to estimate the effects of time and of time by group on continuous outcome measures from pre-treatment to post-treatment and from post-treatment to follow-up. A first-order autoregressive structure with homogenous variances provided the best fit and was thus used as the covariance structure. Models were built in a stepwise fashion, starting with a basic model with a fixed intercept, then adding random parameters (intercept and slope), and finally adding a time by group interaction term to the model.

Cohen's d was used to calculate standardized effect sizes for between-group effects at each assessment (137) using the SD for the pooled sample at pre-treatment (138) and the pooled sample SD at post-treatment (for post-treatment to follow-up). For model based d, 95% CIs were calculated (137). Missing data were estimated using maximum likelihood estimation, data from all participants were used according to the principle of intention-to-treat.

Treatment response was assessed with the reliable change index (139), and the reliable change was defined as a change of 7 points or more on the PSWQ. Combining this reliable change with two different cut-offs of 53 or 47 points on the PSWQ as used in previous studies (125, 126) were applied as defining recovery. Differences in reliable change and recovery rates between groups were investigated with Fisher's exact tests. Analyses were performed with SPSS (IBM Corp. 2020. Version 27.0. Armonk, NY).

4.3.2 Qualitative analysis – Study III

The transcribed focus-group discussions were analyzed with qualitative content analysis as described by Graneheim and Lundman (140, 141), with an inductive approach (141, 142). To start the process, the researchers read the text several times to get a sense of the whole and then discussed their first impressions. Using a spreadsheet, they then divided the text into meaning units. The meaning units relevant to the aim were shortened into condensed meaning units, which remained close to the text in meaning. The condensed meaning units were labeled with codes that expressed their content. Similarities and differences were used to sort the codes into subcategories and categories. To help ensure trustworthiness, all researchers reflected on and discussed the emerging categories and their potential meaning until they reached consensus.

4.4 Ethical considerations

The four studies included in the thesis have ethical approval.

Study I: Regional Ethical Review Board in Stockholm (Dnr: 2012/2109–31, 2013/1870–32), and the Regional Ethical Review Board in Gothenburg (Dnr: 577–13).

Study II and III: Regional Ethical Review Board in Gothenburg, Sweden (Dnr: 903–13, Dalarna: T975–14, long term: T963–15, T598–18, focus group: T403–15). Registered at ClinicalTrials.gov: NCT02378272.

Study IV: Regional Ethical Review Board in Stockholm (Dnr: 2018/505–31). Registered at ClincalTrials.gov: NCT03621371

The four studies were conducted in accordance with the World Medical Association Declaration of Helsinki (143). Participation in the studies was voluntary. Before they provided written informed consent, participants received oral and written information about the study, including information about how data would be handled and reported and the confidentiality and anonymization of information.

Consideration of ethics is necessary in research, and risks to patients must be weighed against potential benefits (144). Equator guidelines and checklists were used as tools to check for and prevent bias. The STROBE checklist for observational studies (145) was used in Study I, the CONSORT checklist for RCTs (146) was used in Study II and Study IV, and the COREQ checklist for qualitative research (147) was used for Study III. The trial protocols were registered in Clinical Trials.gov.

5 Results

Study I

A total of 480 participants, 300 from Region Stockholm and 180 from Region Västra Götaland, were included in the study (Table 2).

Table 2. Baseline characteristics of the population in Study I	
	n=480
Age – Mean (SD)	44.9 (9.3)
Female gender, n (%)	374 (78)
Education, n (%)	
University	259 (54)
High school/Upper secondary school	116 (24)
Elementary school	17 (4)
Vocational training	88 (18)
Diagnosis on sick leave certificate, n (%)	
Depression	157 (33)
Anxiety disorder	54 (11)
Stress–induced exhaustion disorder	269 (56)
MADRS–S mean (SD)	20.9 (7.9)
KEDS mean (SD)	28.3 (8.2)

MADRS-S, Montgomery-Asberg Depression Rating Scale – self-rating version; KEDS, Karolinska Exhaustion Disorder Scale. Adapted from "Outcomes of psychiatric interviews and self-rated symptom scales in people on sick leave for common mental disorders: an observational study," by Af Winklerfelt Hammarberg, S et al. (2022). BMJ open, 12(6), e057745 (DOI: 10.1136/bmjopen-2021-057745). CC BY-NC.

In the study, many patients fulfilled the criteria for diagnoses other than the one that was listed on their sick leave certificate. More participants on sick leave for SED (76%) and on sick leave for anxiety disorders (67%) than on sick leave for depression (65%) met the M.I.N.I. diagnostic criteria for ongoing depression (p=0.041). Over half the participants on sick leave for depression met the criteria for SED (63%) and almost half met the criteria for anxiety disorders (42%). The sick leave certificate diagnoses of anxiety generally corresponded to those made with M.I.N.I. (p<0.001).

There was no significant difference in the length of sick leave (mean net sick leave days) by diagnosis listed on the sick leave certificates. However, sick leave length did differ by diagnosis made in the structured psychiatric interviews (s–ED and M.I.N.I.). Participants who met the Swedish SED criteria were on sick leave significantly longer than participants who did not meet these criteria (144 vs. 84 days; p<0.001). This result was sustained even when participants diagnosed with depression and/or GAD were excluded from the analysis (169 vs. 115 days; p=0.035). Sick leave length did not differ significantly between participants who did and did not have an anxiety disorder. However, those with ongoing depression had significantly shorter sick leave than those who did not have ongoing depression (112 vs. 156 days; p=0.023). These results persisted after adjustment for potential confounders, including age, sex, education, and treatment.

Symptom severity was positively associated with length of sick leave. The correlation was linear, and the pattern was similar for symptoms of depression measured with MADRS–S and symptoms of SED measured with KEDS. Participants with mild depressive or SED symptoms were on sick leave for approximately 65 days (RR: 0.64; 95% CI: 0.46–0.89; p=0.007), whereas participants with the most severe symptoms were on sick leave for 236 days (RR: 2.20; 95% CI: 1.48–3.27; p<0.001).

Study II

There was no significant difference in loss to follow-up in the intervention and control groups at either the 12- or the 24-months follow-up. A total of 75% of patients responded at 12 months and 66% at 24 months. The background characteristics of the intervention and control groups did not differ significantly at baseline or either follow-up.

Twelve months after baseline, the patients who were assigned a care manager had less severe depressive symptoms than the patients who had usual care (95% CI: –3.50 to –0.26; p=0.02). At 24 months, the patients with care managers had maintained their symptom improvement, and the symptoms of the patients with usual care had improved to the same level as in the intervention group (95% CI: –1.53 to 1.90; p=0.83) (Figure 1).

Figure 1. Depressive symptoms[1] from baseline to 24 months in the intervention group and control group
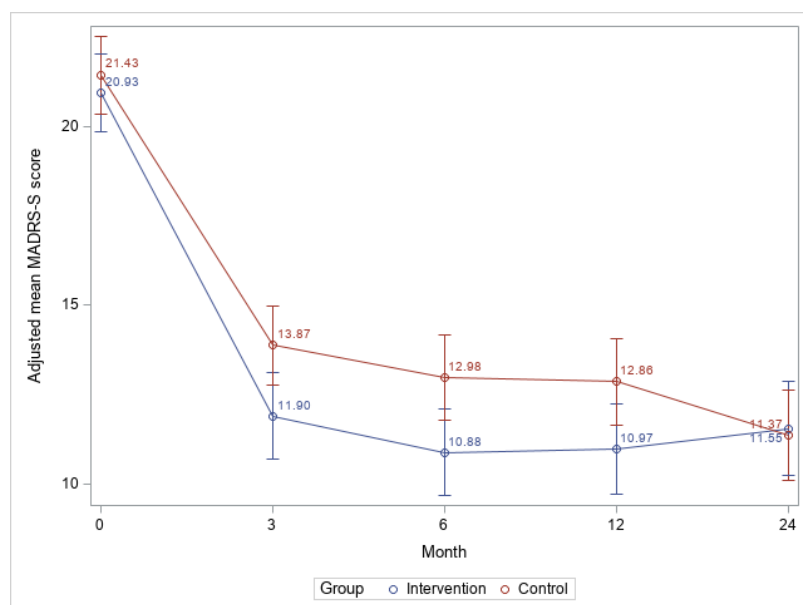
MADRS-S: Montgomery-Asberg Depression Rating Scale – Self rating version.
[1]Measured with MADRS-S. P12 months=0.02; P24 months=0.83. From "Clinical effectiveness of care managers in collaborative primary health care for patients with depression: 12- and 24-month follow-up of a pragmatic cluster randomized controlled trial," by Af Winklerfelt Hammarberg, S. et al. (2022). BMC primary care, 23(1), 198 (https://doi.org/10.1186/s12875-022-01803-x). CC BY 4.0 (http:// creativecommons.org/licenses/by/4. 0/).

A similar pattern was observed in self-reported quality of life, which at 12 months was significantly higher in the patients assigned a care manager than in those with usual care (95% CI: 0.01 to 0.11; p=0.01). As with depressive symptoms, at 24 months, the patients with care managers had maintained their quality of life, and the quality of life of the patients with usual care had improved to the same level (95% CI: -0.05 to 0.05; p=0.88).

There were no significant differences between the intervention group and control group in the two proxies of clinically meaningful change used in the study on either follow-up occasion. These included a 50% reduction in depressive symptoms and remission, which was operationalized as a MADRS-S score <12.

Responses to the study-specific questionnaire, which was sent at the 24-month follow-up, indicated that there were differences in patients' confidence in care. Significantly more patients who received the intervention than who received usual care had confidence that they would get professional emotional support (p=0.05) and information about their illness/symptoms (p=0.02) from their primary care center. However, self-efficacy did not differ between the two groups.

Study III

A total of 29 GPs participated in the five focus group discussions. Their ages ranged from 28 to 66 years, 16 were men, and 13 were women. Participants' working experience ranged from a few years as medical residents to over 20 years as GPs.

GPs had diverse experiences of working with care managers for patients with depression. The qualitative content analysis showed that their experiences could be separated into four main categories: *Care managers ensure care quality while freeing GPs from case management, Concern about role overlap, Care managers should be assigned to patients who need them the most*, and *Transition to a chronic care model requires change*. Each of the four main categories had subcategories that can be illustrated with quotes from the focus group discussions (Table 3).

Table 3. Categories, subcategories and examples of quotes in Study III		
Category	Subcategory	Examples of quotes
Care managers ensure care quality while freeing GPs from case management	Providing support for patients Providing security and relief for GPs Ensuring coordinated care for patients	*"So it feels like a big relief that you can hand over to her, just those . . . it's important for patients that someone just gets in touch."* *"I would see it as a coordinator, another voice that . . . takes care of the patient, that sees to it that the depression doesn't escalate, that a situation that demands radically different treatment doesn't develop, threat of suicide or something else like that."*
Concern about role overlap	GPs are already care managers Too many caregivers disrupt patient contact The roles of care managers and psychotherapists seem to compete	*"Then it's like I probably know the patient best so I'm actually the care manager, anyway I think, me as the doctor."* *"They drop out because they experience too many people around them, and maybe they've told us something hard and don't want to tell a lot of people about it."* *"In the best of all possible worlds it would in fact be good to have a therapist here."*
Care managers should be assigned to patients who need them the most	Patients with life difficulties need care managers Patients with severe mental health problems have a greater need for care managers	*"Good if you impartially ask yourself the question 'Does the patient really need to see a doctor?' when the patient contacts primary health care. Problems can be medicalized unnecessarily."* *"Yes, but I believe that the one who had a high MADRS–S score [severe depression] . . . clinically that it was the right level [to be assigned a care manager]."*
Transition to a chronic care model requires change	Care managers change the way GPs work Depression treatment becomes more like other chronic disease treatment	*"Above all, you have to get used to using them. You're used to one way of working that's the norm, then that you do it in this [other] way."* *"This is a huge group of patients because psychiatry in primary health care [is] enormous and growing, and those patients should also be cared for. We have specialized personnel for high blood pressure, for diabetes, for COPD at the health care center. It's clear we should have that for this, too, as it's become a big part of our mission."*

Study IV

Recruitment to this pilot randomized controlled study went smoothly. A total of 64 patients diagnosed with GAD participated (Table 4).

Table 4. Baseline characteristics of participants in Study IV

	IUT (n=33)	MCT (n=31)
Age, M (SD)]	37.1 (11.6)	35.7 (10.8)
Sex (female)	81.8%	80.6%
Civil status		
Married or cohabiting	54.5%	80.6%
Living alone	45.5%	19.4%
Completed educational level		
High school or lower	63.6%	67.7%
College or higher	36.4%	32.3%
Occupational status		
Employed or student	90.9%	90.3%
Unemployed, on sick leave, or retired	9.1%	9.7%
Country of birth (Sweden)	93.3%	80.6%
Duration of GAD, years M (SD)	14.8 (12.0)	14.1 (13.2)
Previous CBT	50.0%	51.7%

IUT, intolerance-of-uncertainty therapy; MCT, metacognitive therapy; GAD, generalized anxiety disorder; CBT, cognitive behavioral therapy.

There were significant differences in the average number of MCT and IUT sessions attended. Participants in MCT took part in fewer sessions (mean 8.5) than participants in IUT (mean 10.5) (p=0.03). Dropout was significantly higher from the MCT than the IUT group (6 vs. 1, (p=0.037). Dropout from MCT occurred at different stages of therapy and for varied reasons. The patient who dropped out of IUT did so after the first session in connection with a marked increase in symptoms that required another kind of treatment.

The analyses of responses to the study-specific questionnaire showed that overall, participants were satisfied with the treatment they received and with participating in the study (M=5.17, SD=1.09 on the Likert scale from 0 to 6). Most also agreed to some extent with the statement that their symptoms had psychological causes (M=4.69, SD=1.22). They found the number of measures and the pace of treatment just right ("lagom" in Swedish) (M=3.25, SD=0.88).

There were no significant differences in the competence of therapists by therapy. However, mean adherence to protocol, as measured by raters who used a study-specific instrument, differed significantly between the two therapies. The IUT therapists had significantly higher mean adherence than the MCT therapists (p=0.05).

The secondary aim of investigating preliminary effectiveness showed that both therapies significantly reduced worry from pre-treatment to post-treatment (Table 5), and effect sizes were large (IUT: $F_{(58.82)}=32.54$, $p<.001$; MCT: $F_{(66.84)}=71.85$, $p<.001$). However, MCT was significantly more effective than IUT in reducing worry ($F_{(128.92)}=9.88$, $p=.002$). The improvements remained stable in both therapy groups between post-treatment and the 6-month follow-up (IUT: p=0.980; MCT: p=0.283).

Table 5. Estimated marginal means and standard deviations for the PSWQ, PHQ-9, WHODAS, and the SWLS from pretreatment to 6-month follow-up

	Group	Pre-treatment M (SD)	Mid-treatment (Session 5) M (SD)	Post-treatment M (SD)	Follow-up M (SD)
PSWQ	IUT	67.9 (3.6)	62.8 (5.3)	55.8 (7.5)	56.3 (10.3)
	MCT	64.9 (4.8)	55.4 (5.8)	42.1 (7.5)	46.3 (8.3)
PHQ-9	IUT	9.5 (4.0)	8.2 (3.6)	6.4 (3.3)	5.7 (3.2)
	MCT	10.3 (3.2)	7.4 (2.8)	3.3 (2.4)	5.5 (2.7)
WHODAS	IUT	23.2 (4.4)	Not assessed	20.6 (3.4)	18.9 (5.5)
	MCT	24.4 (4.2)	Not assessed	14.9 (2.4)	17.0 (3.9)
SWLS	IUT	20.5 (3.7)	Not assessed	22.1 (3.0)	23.8 (3.7)
	MCT	19.2 (3.4)	Not assessed	24.2 (2.5)	25.2 (4.2)

PSWQ, Penn State Worry Questionnaire; PHQ-9, Patient Health Questionnaire 9; WHODAS, World Health Organization Disability Assessment Schedule 2.0; SWLS, Satisfaction with Life Scale; IUT, intolerance-of-uncertainty therapy; MCT, metacognitive therapy.

The investigation of reliable change showed that 96.3% of the participants who took part in MCT and 71.9% who took part in IUT experienced a reliable improvement in worry (defined as a decrease of ≥7 points in PSWQ scores). The improvement in the MCT group was statistically significantly greater than in the IUT group (p=0.031), and one participant in the IUT group experienced a reliable deterioration (defined as an increase of ≥7 points in PSWQ scores) (139). The analysis of recovery, which applied two different PSWQ thresholds from previous studies, showed that regardless of threshold, significantly more participants in the MCT group than in the IUT group reached and remained recovery at the 6-month follow-up (47-point cut-off (125): MCT 60.9% vs. IUT 21.4%, χ^2=10.28, p=0.001; 53-point cut-off (126): MCT 73.9% vs. IUT 39.3%, χ^2=11.60, p=0.001).

The analyses of depressive symptoms showed that both therapies significantly reduced such symptoms (PHQ-9) from pre-treatment to post-treatment (Table 5) (IUT: p=0.023; MCT: p<0.001) and that these improvements were maintained at the 6-month follow-up (IUT: p=0.38; MCT: p=0.113). MCT reduced depressive symptoms significantly more than IUT (F(158.16)=4.73, p=.031).

Additional analyses showed that MCT but not IUT improved quality of life (SWLS) between pre- and post-treatment (Table 5) (MCT: p=0.001; IUT: p=0.213). A similar pattern was observed for functional impairment (WHODAS), only MCT resulted in improved scores (MCT: p<0.001; IUT: p=0.058).

6 Discussion

6.1 Summary of main findings

Study I, which investigated the relationship between sick leave certificate diagnoses, diagnoses from structured psychiatric interviews, symptom severity, and sick leave length, found low correspondence between participants' sick leave certificate diagnosis and the diagnoses found in structured psychiatric interviews. Many participants fulfilled diagnostic criteria for mental disorders other than the sick leave certificate diagnosis. Sick leave was longer for participants who fulfilled the Swedish criteria for SED and had more severe symptoms.

In the long-term follow-up of the effectiveness of care managers for patients with depression, Study II, patients with depression who had care managers maintained their previous improvements in depressive symptoms and quality of life 12 and 24 months after the care manager intervention. Patients with usual care, on the other hand, required 24 months to reach the same level of improvement. There were no significant differences between groups in 50% symptom reduction or recovery at 12 or 24 months, but patients who had care managers seemed to have higher confidence in future support and information from the primary care center than patients with usual care.

Study III, which explored GPs' experiences of working with care managers for patients with depression, found that experiences varied. On the one hand, GPs could express that working with a care manager gave them a feeling of security and relief. On the other, GPs were concerned about potential role overlap and had to adjust to working with a new care model. They also identified patient groups that they believed were in more need of a care manager than patients with mild to moderate depression.

In Study IV, the pilot RCT that compared the feasibility and preliminary effectiveness of IUT and MCT for primary care patients with GAD, patients with GAD were willing to participate in the study and were satisfied with the treatment they received. Dropout was low and therapists showed some competence. Together, these findings suggest that it is feasible to perform a full-scale RCT comparing IUT and MCT in primary care. The preliminary evaluation of the effects of the therapies showed that both significantly reduced worry and depressive symptoms from pre-treatment to post-treatment. Effect sizes were large. From post-treatment to the 6-month follow-up, effects on outcome measures were maintained. MCT was the superior treatment for all outcomes from pre-treatment to post-treatment. More MCT than IUT participants experienced a reliable reduction in worry and had recovered from GAD. Moreover, on average, MCT was two sessions shorter than IUT.

6.2 Contextualization of research results

Study I

Two main results of Study I provide information relevant to interpreting the findings of previous reports and studies based on sick leave certificate diagnoses. The first of these findings is that sick leave certificate diagnoses did not capture the full picture of patients' common mental disorders, such as their main and comorbid diagnoses or symptom severity. The literature search for this thesis identified no previous studies comparing sick leave certificate diagnoses with diagnoses from structured psychiatric interviews. This is therefore a novel finding, which makes it difficult to contextualize. For example, it is unclear whether the finding is generalizable to beyond the study population. However, the result suggests that the validity of conclusions based on sick leave certificate diagnoses should be interpreted with caution, at least in the Swedish context (e.g., conclusions about the prevalence and severity of disorders in people on sick leave for common mental disorders).

The second result with implications for interpreting research based on sick leave certificate diagnoses is that these diagnoses were not associated with sick leave length in the Study I population. The result suggests that caution is called for in interpreting the results of studies on sick leave length for common mental disorders if diagnoses in those studies are based solely on sick leave certificate data. However, this finding may not be generalizable outside Sweden, as it contrasts with the results of a meta-analysis of studies from across the world (5) and later studies from several countries (58, 59). Those studies found that sick leave certificate diagnoses of depression, recurring mental health problems and depression combined with anxiety were associated with long-term sick leave (5, 58–60) whereas stress-related mental disorders were associated with short-term sick leave (58, 59).

Unlike the sick leave certificate diagnoses, the diagnoses from the structured psychiatric interviews in Study I were associated with length of sick leave. For instance, people who fulfilled the criteria for SED had significantly longer sick leave than those who did not fulfill SED criteria. The finding persisted even after excluding people who fulfilled the criteria for ongoing depression and/or GAD, which overlapped with SED criteria when the study was performed. It is challenging to interpret this finding in the context of studies from other countries, as the diagnosis of SED is exclusive to Sweden, and we do not know what diagnosis patients who fulfilled the SED criteria would have received elsewhere. However, if SED would have been diagnosed as severe depression or GAD in other health care contexts, the Study I finding could be in line with the international findings of longer sick leave for patients with depression and/or anxiety (5, 58, 59). Supporting this interpretation is the Study I finding that more severe symptoms were associated with longer sick leave, regardless of whether they were measured with

KEDS (SED severity scale) or MADRS-S (depression severity scale). The correspondence between more severe symptoms and longer sick leave is also consistent with the results of previous research (5, 55, 60).

Study II

Although previous studies from outside Sweden had evaluated the long-term effects of collaborative care for primary care patients with depression, PRIM-CARE was the first large trial to evaluate care managers for patients with depression in Swedish primary care. Earlier PRIM-CARE analyses found that patients assigned a care manager recovered significantly faster than patients with usual care (95). Study II found the improvements in depressive symptoms in patients assigned a care manager were maintained at 12 and 24 months and that it took up to 24 months for patients who received usual care to experience the same improvements. These findings are similar to those of earlier meta-analyses of studies from outside Sweden that showed that collaborative care improved depression outcomes more than usual care for up to two years (11, 93). Study II thus confirms that care managers are also effective in the long term in Swedish primary care.

In Study II, quality of life was significantly higher at 12 but not 24 months in patients assigned a care manager. Similarly, one of the previous systematic reviews found that collaborative care can lead to better quality of life than usual care also in the long term (11). Moreover, in keeping with other studies (11), patients with care managers in Study II had significantly more confidence that they would be able to get professional emotional support and adequate information from the primary care center. This suggests that they might be more satisfied with care, an idea consistent with the results of previous systematic reviews that found evidence that care managers result in greater patient satisfaction than usual care (11).

Study III

There are several previous qualitative studies and systematic reviews of GPs' and other health professionals' experiences of collaborative care for patients with depression in primary care (101, 103). As structure and other aspects of primary health care differ between countries, GPs' experiences of care managers could also differ in important ways. Study III seems to have been the first to explore GPs' experiences of care managers for patients with depression in Sweden.

The GPs in Study III felt that the care managers ensured care quality while freeing GPs from case management. This is in keeping with the results of other qualitative studies, which have found that GPs view care managers as providing them with relief from heavy workloads (101, 103). The GPs in Study III expressed feelings of security and relief that someone else was also following up the patients, including with symptom severity

scales, and providing regular feedback to the GPs. That finding is congruent with the findings of previous studies, in which GPs described that regular feedback was an important positive aspect of working with care managers (101). An additional similarity in findings was the importance of shared patient records and face-to-face communication at a shared workplace (101).

In Study III, the GPs were concerned about potential role overlap. GPs could see themselves as care managers, which meant that they questioned the need for this new role in the care team. Similarly, a German study found that GPs were worried that care managers could disrupt GP–patient relationships (103). Like the GPs in Study III, GPs in the German study were concerned that having a care manager could burden vulnerable patients by requiring them to communicate with too many care contacts. Another similarity between the findings of Study III and of previous studies (101, 103) was GPs' concern about cost-effectiveness. GPs could feel that the cost of care managers would compete with other funding priorities, such as more time for patient visits with GPs or enhanced access to psychotherapists.

GPs expressed the idea that care managers should be assigned to patients who needed them the most. In part, this finding could be an artifact of the study design, which limited care managers to patients with mild to moderate depression for the duration of the study. On the other hand, it is a finding in common with previous studies, in which GPs expressed a wish for more autonomy in assigning care managers to patients (101). The Study III GPs could feel that some patients just needed someone to talk to, and a care manager could be an ideal person to fill this role. Assigning care managers to these patients could reduce the risk of medicalizing non-medical problems or situations. The GPs in Study III also wanted the freedom to assign care managers to patients with more severe symptoms and chronic and complex mental health problems.

The GPs in Study III expressed the idea that transition to a chronic care model requires change. They had to get used to the new way of working, and it was not always easy. Previous studies have shown that health care professionals transitioning to collaborative care models can require interprofessional team training rather than uniprofessional training (101, 148), which is what the Study III GPs received. Perhaps the Study III GPs would have found the transition easier if they had been offered team training together with the new care managers and other professionals on the care team. It is also possible that at least some of the GPs found the transition challenging because they experienced feelings of loss (the feeling that care managers were taking over part of their role as GPs). Loss aversion could help explain why the care managers were generally more positive about their new role than were the GPs (149): a perceived loss is more impactful than a perceived gain of similar magnitude (149).

Study IV

There are two previous studies comparing MCT to other CBT protocols in the treatment of GAD. Both were conducted in psychiatric outpatient care and neither aimed to test feasibility (125, 126). Study IV succeeded in recruiting approximately the same number of patients with GAD (n=64) as the two previous studies in outpatient care: n=121 (126) and n=60 (125). Moreover, dropout was low compared to the previous studies (125, 126) and to a meta-analysis of drop-out rate in psychological studies (150). Thus, it is feasible to recruit primary care patients to a future RCT comparing the IUT and MCT protocols and to retain them in the study.

To assess the feasibility of carrying out IUT and MCT in primary care, it was particularly important to assess therapists' competence in and adherence to protocol following brief training in the therapies. This is because future transferability of any positive RCT results depends on whether regular therapists in primary care can competently provide therapy in line with the protocols after relatively brief training. Only one of the two previous studies assessed adherence (126), but the assessment was carried out differently than in Study IV, so it is difficult to compare the ratings. Neither of the previous studies assessed therapist competence.

As in the two previous studies (125, 126), the CBT protocols reduced worry significantly. MCT was superior to other CBT protocols, including IUT, in the two previous studies (125, 126), as in Study IV. The findings of Study IV about depressive symptoms and recovery were also consistent with those of the two earlier studies (125, 126). Specifically, both IUT and MCT reduced depressive symptoms and promoted recovery, but MCT resulted in significantly greater improvements. Participants' improvements were maintained at the six-month follow-up in Study IV, as in the previous two studies (125, 126). In Study IV, MCT also outperformed IUT in improving quality of life and reducing functional impairment. Neither of the two previous studies investigated these outcomes (125, 126)

Like Study IV, one previous study compared IUT and MCT delivered in a flexible number of sessions (up to 12 in Study IV and up to 14 in the previous study) (126). Study IV found that participants in the MCT group reached their improvements in statistically significantly fewer sessions than participants in the IUT group, but this was not the case in the previous study (126). In that study, there was no difference in the number of sessions that study completers attended in the IUT and MCT groups.

6.3 Methodological considerations

The four studies were conducted in regular primary care, which increases the generalizability of the results to regular primary care in Sweden. Studies I, II, and III recruited participants from two regions in Sweden and participating primary care centers came from urban and rural areas of varying socioeconomic status. Exclusion

criteria were kept to a minimum, which also strengthens the generalizability of the results. Generalizability was reduced, however, by the exclusion of people who did not understand Swedish and those with substance use disorders, two important groups of primary care patients. An additional strength of Studies I, II, and IV was the use of validated instruments, although several instruments in the studies were not validated (the follow-up questionnaires in Study II and Study IV and the adherence assessment scales in Study IV). In Studies II and IV, randomization was carried out by an independent administrator blinded to the identity of the primary care centers (Study II) and patients and therapists (Study IV). Dropout was monitored and analyzed. Moreover, in Studies I, II, and IV, data were gathered by independent study personnel, which reduced the risk of assessment bias.

Study I

The large number of participants examined with structured interviews (n=480) was a strength of Study I. However, the delay between sick leave certification and the structured interviews was a limitation because some participants may have developed a different disorder or experienced recovery during the time between sick leave certification and the interview. Furthermore, the lack of international validation of the diagnostic criteria and instruments for SED could help explain the overlapping diagnoses found in the interviews. This limitation underscores the need for more research to assess whether SED is a separate mental disorder or represents symptoms of depression and anxiety in the context of long-term stress.

Study I analyzed data gathered in two previous studies that differed from each other in design and had primary aims other than the aims of Study I. The study also had a risk of selection bias due to the recruitment procedures in the two studies. Participants who chose to respond to the study invitation in both regions and thus may have differed from other people on sick leave for common mental disorders in Sweden. This self-selection could also help explain the high proportion of participants who had a university education. Social insurance reports from Sweden (45) and previous studies from several countries show that a low level of education is a risk factor for long-term sick leave, including for common mental disorders (5, 45, 51, 52, 151). Thus, the educational level of the study population was not representative of the educational level of the general population of people on sick leave for these disorders. Moreover, in at least one other study, severity of anxiety symptoms was the most important predictor of sick leave length (55). It was thus a limitation that Study I did not assess anxiety symptoms.

Study II

Long term follow-up is important for evaluating organizational changes, such as the care manager intervention (97). The long-term follow-up in Study II was thus a strength of the PRIM-CARE study. A further strength was cluster randomization at the primary care

center level, which reduced the risk of contamination bias (152, 153). However, cluster randomization also resulted in limitations, such as inability to blind patients or staff to intervention status. Sparse data from some primary care centers also meant that it was not possible to adjust for cluster effects.

Another limitation of Study II was loss to follow-up, especially at 24 months. The number of patients lost to follow-up was similar in the intervention group and control group, but there could have been important differences between those who did or did not respond to the postal questionnaires in either or both groups. Furthermore, the questionnaire on self-efficacy and patients' confidence in care was unvalidated. Thus, caution is needed in interpreting findings based on that questionnaire.

Study III

The inductive approach to the content analysis and the use of focus-group discussions to gather data were appropriate methods for exploring GPs' experiences (142, 154, 155). Focus-group discussions were guided by two open questions rather than a fixed interview guide, which enriched the discussions and facilitated the inductive approach. The presence of an observer at the focus-group discussions in addition to the moderator was a further strength of the study.

Further strengths were the participation of both publicly and privately run primary care centers in two regions of Sweden, which increased variation and strengthened the potential transferability of the results. Additionally, the participation of male and female GPs with varying lengths of work experience helped enrich discussions and further increase the variety of experiences represented in the data. One potential limitation was that the manager of the primary care center was present at two focus-group discussions, which could have influenced the conversation.

Another factor that could affect the interpretation of data gathered in Study III was researchers' prior understanding based on their previous experiences and views. Researchers' varied backgrounds, along with reflection and discussion among the researchers during analysis helped reduce moderate the influence of such individual experiences and views on the interpretation.

Study IV

An RCT is the optimal design for clinical treatment trials. When the feasibility of a full-scale trial is uncertain, feasibility testing can help determine whether and how an RCT can be undertaken (156). A strength of the pilot trial in Study IV was the number of patient-related outcomes. In addition to the severity of symptoms of worry and depression, outcomes included functional impairment, quality of life, medication use, sick leave, and participants' perceptions of the treatments and of study participation.

However, all effectiveness outcomes were patient-reported, and the results could have been strengthened by an objective assessment or interview post-treatment or at follow-up.

Several psychotherapists provided treatment to the patients in the study, and these therapists received regular supervision, which was another strength of the study. Furthermore, all sessions were audio-recorded, the therapists were blinded to which session would be assessed, and the therapists' competence in and adherence to protocol were evaluated by independent assessors.

The results of Study IV, particularly the preliminary results on treatment effectiveness, should be interpreted with caution, as the study had limitations. Because the primary aim was to test feasibility, sample size was not estimated. The generalizability of the findings was reduced because only one large primary care center in an urban area participated. Moreover, the patient questionnaire at post-treatment and the treatment adherence scales were not validated, the assessors had no training in using these scales, and only a small portion of the recorded sessions were assessed for competence and adherence. Another limitation was that therapists were not randomized to one of the two intervention protocols but could choose which protocol they would deliver. Thus, their interest and competence in the treatment they provided may have biased the results.

6 Conclusions

Sick leave certificate diagnoses do not reflect the diagnoses obtained in structured psychiatric interviews. This could mirror the changing and overlapping nature of the symptoms of common mental disorders and suggests that findings based on sick leave certificate diagnoses should be interpreted with caution. The association between longer sick leave and more severe symptoms or fulfilling SED criteria is clinically relevant and worth further study. (Study I)

Care managers for primary care patients with depression seem superior to usual care in the long term, as it took up to 24 months for patients without care managers to achieve the same improvements as patients with care managers achieved in 6 months and maintained long-term. Moreover, patients with care managers had more confidence in future care. (Study II)

GPs could see benefits to assigning care managers to patients with depression. However, they expressed concern about role overlap and emphasized the need to clarify care managers' role in the care team. (Study III)

It is feasible to conduct an RCT that compares IUT and MCT in primary care patients with GAD. Both treatments effectively reduce worry, and effects were maintained at a six-month follow-up. MCT resulted in larger improvements in all outcomes. A full-scale RCT is required to confirm these findings. (Study IV)

7 Points of perspective

The four studies in this thesis add knowledge about different aspects of common mental disorders in primary care patients. They also shed light on the complexity of common mental disorders in primary care and raise questions in need of further clinical research.

Study I showed that SED symptoms overlapped with the symptoms and diagnosis of depression. This raises the question of whether SED and depression should be separate diagnoses or whether SED might be depression that occurs in the context of stress. This has important clinical implications for treatment and sick leave, and additional research is warranted to help clarify this issue. The finding that patients with more severe symptoms had longer sick leave suggest a need for targeted interventions to support the recovery of these patients and their return to work. The results of Study I also raise the question of why the diagnosis on sick leave certificates did not correspond to the diagnosis made in structured psychiatric interviews. This question could be investigated in future qualitative studies to illuminate diagnostic process for common mental disorders in primary care.

Study II showed that care managers speed recovery from mild and moderate depression and that this recovery is maintained long term. The findings also tentatively suggest that increased self-efficacy may not underlie these findings, but that patients' increased confidence in future care might have contributed the speed and maintenance of recovery. Future studies have the potential to clarify which components of collaborative care interventions are most effective to improve recovery, as well as the mechanisms behind these improvements.

The reasons behind GPs' varying experiences of working with care managers for patients with depression (Study III) remain unclear. Such information is relevant to understanding which contexts could benefit the most from care managers. For instance, it is possible that care managers are most useful in contexts where access to and continuity of care from GPs and/or psychotherapists is insufficient. Moreover, Study III also illuminated GPs' concern that patients with the most severe and complex problems would benefit the most from a care manager.

Study IV found that it would be feasible to carry out an RCT of two CBT protocols for GAD in regular primary care. Moreover, both protocols were effective, and MCT was the most effective. If the findings are repeated in larger studies with longer follow-ups, it should be possible to introduce more primary care patients to an effective treatment for GAD. Care-seeking patterns in primary care patients with GAD, sick leave for somatic and mental symptoms in these patients, and cost-effectiveness are other important outcomes worthy of investigation in a full-scale RCT.

Studies like the four in this thesis performed in regular clinical practice are crucial for the development of primary care. Because, if they include a truly representative patient population, and if well-designed, such studies can provide clinically meaningful and applicable knowledge and an accurate basis for decision-making in primary care.

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