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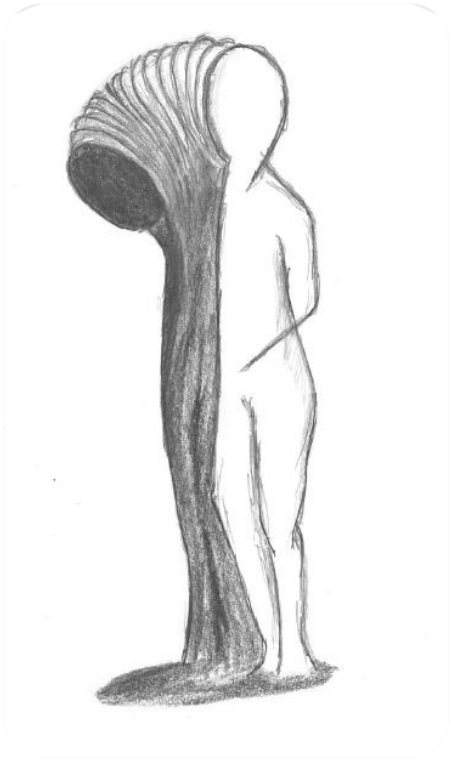

PhD Thesis

Rasmus Moeskjær Schwarz

Improving functioning in patients with affective disorders

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Name of department: The Early Multimodular Prevention and Intervention Research Institution (EMPIRI), Mental Health Centre, Northern Zealand, Copenhagen University Hospital – Mental Health Services CPH, Copenhagen, Denmark
Department of Clinical Medicine, University of Copenhagen, Denmark

Author: Rasmus Moeskjær Schwarz, MD

Title: Improving functioning in patients with affective disorders

Supervisors: Maj Vinberg, Professor, MD, PhD, DMSc
Lars Vedel Kessing, Professor, MD, DMSc

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Assessment committee: Professor Julie Midtgaard, MSc, PhD (Chairperson)
- University of Copenhagen, Denmark
Associate Professor Ole Köhler-Forsberg, MD, PhD
- Aarhus University, Denmark
Professor Katherine Burdick, MA, PhD
- Harvard University, United States

Frontpage: "*The hidden side",* drawing by Einar Schwarz (with permission)

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Preface

During my time working in child and adolescent psychiatry, my interest in the functioning of patients started to grow. As psychopathology is often less pronounced and developed in younger patients, the diagnostic process relies heavily on the presence and severity of functional impairment. Making the transition to adult psychiatry, it quickly became evident not only how pronounced the psychopathology could become but also how severely impaired patients' functioning in everyday life could be. And in particular, how functional impairment often persists in patients, long after the “acute” episode or phase has passed. While working as a PhD student, I have had the privilege of interviewing numerous patients about their ability to handle everyday life, and gained extensive knowledge about functioning, both from a professional/clinical and patient point of view. Often, functional impairment is more severe than has been previously realised. Many patients have told similar stories, of how we, as clinicians, have told them that the treatment is working and depression and mania “scores” are almost normal, but how the patients themselves are not feeling that life is back to normal. How they still can’t read a book, handle work, or even go grocery shopping, or how they have lost their social life and never participate in any leisure activities anymore. What are we, as clinicians and as a healthcare system, missing in our treatment programs? Many patients benefit greatly from psychiatric treatments, but other patients to a lesser extent. Functional outcomes might have the potential to drive a more patient-oriented approach. Further, there might be inherent limitations in a “one size fits all” approach to treatment. There is a call for developing more personalised treatments across all areas of medicine and healthcare.

The current thesis is a body of work seeking to further explore functioning and functional impairment in patients with affective disorders and investigating the possible beneficial effects of a personalised treatment approach targeting multiple areas related to patient functioning.

Acknowledgements

The work presented in this thesis results from the combined efforts and work of many people (too numerous to mention). Research is built on team efforts, and only through collaboration, can new discoveries be made.

First and foremost, I would like to thank all patients who participated, providing us with insight and data through extensive assessments, interviews, and questionnaires. A thanks to Mental Health Centre Northern Zealand and Psychiatric Centre Copenhagen and the trusty clinicians, who referred patients.

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To my fellow PhD student Jon, thank you for sharing an office, engaging in enlightening academic discussions on psychiatry (and less academic but nonetheless illuminating discussions on music and pop culture), and becoming a dear friend.

I thank my family, particularly my father, Einar, for drawing the incredible artwork on the front page of the thesis and my late grandfather, Vagn, for being my continuous academic inspiration.

Lastly, my deepest and most heartfelt gratitude to my beautiful, loving wife, Randi, for supporting me and allowing me to pursue my aspirations, and to my wonderful children, Liv and Gry, you are the true pride and joy of my life.

Rasmus Moeskjær Schwarz, Hillerød, April 2024

Papers included in the thesis

The thesis is based on the following four papers and complies with the University of Copenhagen Graduate School of Medical Sciences guidelines:

Paper I: Rasmus Schwarz, Lone Decker, Ida Seeberg, Kamilla Woznica Miskowiak, Lars Vedel Kessing, Maj Vinberg. "Affective disorders: eliminate WArning signs and REstore functioning—AWARE—a randomised controlled multimodule intervention study, presentation of design and intervention." BMJ Open, online 2022 May 26. Doi: 10.1136/bmjopen-2021-058839.

Paper II: Rasmus Schwarz, Kamilla Woznica Miskowiak, Mie Skovmand Christensen, Lars Vedel Kessing, Maj Vinberg. "Affective disorders: eliminate WArning signs And REstore functioning: AWARE. Results from a randomised controlled multimodular intervention study targeting functioning in patients with affective disorders." [Under review, Psychological Medicine].

Paper III: Rasmus Schwarz, Klaus Munkholm, Mie Skovmand Christensen, Lars Vedel Kessing, Maj Vinberg. "Functioning in patients with major depressive disorder in remission: a systematic review and meta-analysis." [Submitted March 2024, Journal of Affective Disorders].

Paper IV: Rasmus Schwarz, Kamilla Woznica Miskowiak, Lars Vedel Kessing, Maj Vinberg. "Clinical and personal predictors of functioning in affective disorders: exploratory results from baseline and 6-month follow-up of a randomised controlled trial." [Submitted March 2024, Journal of Psychiatric Research].

English Summary

Affective disorders, bipolar disorder (BD) and unipolar depressive disorder (UD), are among the leading causes of disability globally. Functioning is an essential and meaningful outcome in affective disorders. It is well established in BD that functioning in a large group of patients is impaired even after remission of affective episodes. New treatment options and strategies are hence needed, with improvement of functioning as the main outcome. Further, comprehensive knowledge of predictors of functional impairment in patients with affective disorders is warranted. Surprisingly, long-term functioning during remission has not been investigated systematically in patients with UD.

The thesis is based on three studies: a randomised controlled trial (Study 1, Paper I and Paper II), a systematic review and meta-analysis (Study 2, Paper III), and an exploratory study based on data from Study 1 (Study 3, Paper IV).

Study 1 is a randomised controlled trial investigating the effect of a six-month multimodal personalised intervention targeting functioning (AWARE) compared with treatment as usual (TAU) in patients with BD and UD. The study included 103 patients with BD or UD in partial or full remission who were randomised in a 1:1 ratio to AWARE or TAU. Compared with TAU, the AWARE intervention was not superior at improving performance-based functioning (primary outcome, measured by Assessment of Motor and Process Skills (AMPS)). Post-hoc subgroup analyses showed that AWARE was superior to TAU in improving AMPS scores in patients with cognitive impairment. AWARE was significantly superior to TAU on secondary outcomes of functioning and patient-reported stress and cognition. In conclusion, despite the lack of a statistically significant effect on the primary outcome using performance-based measurement of functioning, the AWARE study indicates beneficial effects of a multimodal personalised treatment approach targeting functioning in patients with affective disorders.

Study 2 is a systematic review and meta-analysis investigating global functioning in patients with major depressive disorder (MDD) in full and partial remission compared with healthy control individuals (HC) and potentially moderating effects of sociodemographic and clinical factors. Forty-two studies were included, comprising a total of 17999 patients with MDD and 35550 HC. The results showed that, compared with HC, patients with MDD in partial or full remission had markedly lower levels of functioning despite not being in a current episode of major depression. Male sex was associated with more impaired functioning. As reporting of

further sociodemographic and clinical factors was limited among the included studies, further robust analyses regarding the potentially moderating effect of other factors were not possible. The various scales used in the included studies highlight the need for consensus on a golden standard for measuring functioning.

Study 3 is an exploratory study based on pooled data of the participants from both allocation groups included in Study 1 (103 patients with BD or UD), investigating the effects of clinical and personal factors (personality traits, coping styles and childhood trauma) on functioning. Among the clinical factors, depression severity was associated with functioning. Further, the results show that personal factors such as maladaptive coping styles and childhood trauma might be associated with functional impairment, and childhood trauma even seems to have a negative impact on improvement in functioning over time.

The thesis emphasises the need for effective interventions targeting functioning in patients with affective disorders, even in patients with low levels of mood symptoms. A strong understanding of factors causing and contributing to impaired functioning is needed to develop future effective interventions. Despite increasing research, further studies are required, particularly in patients with UD. In essence, functioning should be considered as a main outcome in patients with affective disorders.

Dansk Resumé (Danish Summary)

Affektive lidelser, bipolar lidelse (BD) og unipolar depressive lidelse (UD), er blandt de førende årsager til nedsat funktionsevne globalt. Funktionsevne er et essentielt og meningsfyldt effektmål ved affektive lidelser. Det er veletableret ved BD, at funktionsevnen hos en stor gruppe patienter er svækket selv efter remission af affektive episoder. Derfor er der brug for nye behandlingsmuligheder og strategier, med forbedring af funktion som primært mål. Yderligere er der behov for en større viden om prædiktorer for funktionsevne nedsættelse hos patienter med affektive lidelser. Overraskende, er langtids-funktionsevnen hos patienter med UD i remission ikke tidligere blevet undersøgt systematisk

Afhandlingen er baseret på tre studier: et randomiseret kontrolleret forsøg (Studie 1, Artikel I og II), et systematisk review og meta-analyse (Studie 2, Artikel III) og et eksplorativt studie baseret på data fra Studie 1 (Studie 3, Artikel IV).

Studie 1 er et randomiseret kontrolleret forsøg, der undersøgte effekten af en seks måneder lang multimodal individualiseret intervention målrettet funktion (AWARE) sammenlignet med vanlig behandling (TAU), hos patienter med BD og UD. Studiet inkluderede 103 patienter med BD eller UD i delvis eller fuld remission, som blev randomiseret i forholdet 1:1 til AWARE eller TAU. Sammenlignet med TAU var AWARE-interventionen ikke bedre til at forbedre præstationsbaseret funktion (primært effektmål, målt ved Assessment of Motor and Process Skills (AMPS)). Post-hoc undergruppeanalyser viste, at AWARE var TAU overlegen med hensyn til at forbedre AMPS-score hos patienter med objektivt målt kognitiv svækkelse. Med hensyn til sekundære resultater af funktion samt patientrapporteret stress og kognition var AWARE signifikant bedre end TAU. Det kan konkluderes, at på trods af manglen på en statistisk signifikant effekt på det primære effektmål ved brug af præstationsbaseret måling af funktion, indikerer AWARE-studiet gavnlige effekter af en multimodal individualiseret behandlingstilgang rettet mod funktion hos patienter med affektive lidelser.

Studie 2 er en systematisk gennemgang og metaanalyse, der undersøgte global funktion hos patienter med moderat til svær depression (MDD) i fuld og delvis remission sammenlignet med raske kontrolpersoner (HC), samt potentielt modererende virkninger af sociodemografiske og kliniske faktorer. Toogfyrre studier blev inkluderet, omfattende i alt 17999 patienter med MDD og 35550 HC. Resultaterne viste at patienter med MDD i delvis eller fuld remission har markant lavere funktionsevne end HC, på trods af ikke at være i en aktuel episode af moderat til svær

depression. Mandligt køn var forbundet med mere nedsat funktionsevne. Grundet begrænset rapportering af yderligere sociodemografiske og kliniske faktorer blandt de inkluderede studier, var yderligere robuste analyser vedrørende den potentielt modererende effekt af andre faktorer ikke mulige. De forskellige skalaer, anvendt i de inkluderede undersøgelser, understreger behovet for konsensus om en gylden standard for måling af funktionsevne.

Studie 3 er et eksplorativt studie, baseret på samlede data fra deltagerne fra begge allokeringsgrupper inkluderet i Studie 1 (103 patienter med BD eller UD), der undersøgte virkningerne af kliniske og personlige faktorer (personlighedstræk, copingstrategier og barndomstraumer) på funktionsevnen. Blandt de kliniske faktorer var sværhedsgraden af depression forbundet med funktion. Resultaterne viste også at personlige faktorer, såsom uhensigtsmæssige copingstrategier og barndomstraumer, kan være forbundet med funktionsevne nedsættelse, og at barndomstraumer kan have negativ indvirkning på bedring af funktionevnen over tid.

Afhandlingen understreger behovet for effektive interventioner målrettet funktionevnen hos patienter med affektive lidelser, selv hos patienter med mindre grad af affektive symptomer. En bedre forståelse af faktorer, der forårsager og bidrager til nedsat funktionsevne, er nødvendig for at udvikle fremtidige effektive interventioner. På trods af øget forskningsaktivitet er der behov for flere studier, især hos patienter med UD. I bund og grund bør funktionevne anskues som et centralt effektmål hos patienter med affektive lidelser.

Abbreviations

ADL:	Activities of Daily Living
AMPS:	Assessment of Motor and Process Skills
AWARE:	Affective disorders: eliminate WArning signs And Restore functioning
BD:	Bipolar Disorder
CTQ:	Childhood Trauma Questionnaire
CISS:	Coping Inventory for Stressful Situations
COBRA:	Cognitive Complaints in Bipolar Disorder Rating Assessment
DSM:	Diagnostic and Statistical Manual of Mental Disorders
FAST:	Functional Assessment Short Test
GAF:	Global Assessment of Functioning
HDRS-17:	Hamilton Depression Rating Scale (17-item version)
HC:	Healthy Control Individuals
ICD:	International Classification of Disease
ICF:	The International Classification of Functioning, Disability and Health
MCID:	Minimal clinically important differences
MDD:	Major Depressive Disorder
PSS:	Perceived Stress Scale
RCT:	Randomised Controlled Trial
SCIP:	Screen for Cognitive Impairment in Psychiatry
SDS:	Sheehan Disability Scale
SOFAS:	Social and Occupational Functioning Assessment Scale
TAU:	Treatment as usual
TMT:	Trail Making Test
UD:	Unipolar Depressive Disorder
WHO:	World Health Organization
WHODAS 2.0:	World Health Organization Disability Assessment Schedule 2.0
WHOQOL:	World Health Organization Quality of Life
YMRS:	Young Mania Rating Scale

Terminology

Major depressive disorder and unipolar depressive disorder: In Study 1 and Study 3, including a mixed sample of patients with unipolar depressive disorder (UD) and bipolar disorder (BD), the term UD is used to distinguish the two disorders clearly. Study 2 only included data from patients with UD, and in the original paper, the term major depressive disorder (MDD) is used. To create coherency with the papers, the term UD is generally used throughout the thesis when referring to Study 1 and Study 3, and MDD is used when referring to Study 2. However, as only patients with major depression (not minor depression) were included in Study 1 and Study 3, the two terms UD and MDD can be used interchangeably throughout the thesis. In the thesis, UD and MDD thereby include the ICD-10 diagnoses of single depressive episode F32.1-F32.3 and of recurrent depressive episodes F33.1-F33.4, and the DSM-5 diagnosis of Major Depressive Disorder.

Global functioning, overall functioning and functioning: The terms are interchangeable and refer to how well a patient is functioning across multiple domains or areas of functioning. The terms global and overall functioning are generally used in contexts where it is emphasised that the referral is not limited to one or a few domains but encompasses patient functioning as a whole.

"360-degree" intervention: Refers to the fact that the intervention includes a broad range of treatment modules targeting the patient and outcome from "all" angles.

Outline of the thesis

The thesis is based on four papers divided into three studies:

- Study 1 is a randomised controlled trial investigating the effects of the AWARE intervention presented in Paper I and Paper II. Paper I is the published trial protocol, and Paper II presents results on the primary and secondary outcomes of the trial.
- Study 2 is a systematic review and meta-analysis presented in Paper III. Study 3 is an exploratory study, presented in Paper IV.
- Study 3 is based on pooled data from the intervention and control group participants in Study 1.

The thesis begins with an Introduction, presenting the background of the thesis, and the aims and hypothesis for each of the three studies. In the methodology and results sections, each of the three studies is presented separately. The discussion section begins with separate discussions on each of the three studies, followed by a discussion on the strengths and limitations, and implications of the thesis (combining all three studies). Functioning as an outcome in clinical research and the measurement thereof is discussed in the section “Reflections on functioning”. The discussion section ends with a discussion on future research, and finally, the thesis ends with a conclusion.
The Appendix contains the four original papers and the declarations of co-authorships.

Introduction

Background

Functioning in patients with affective disorders

Affective disorder, bipolar disorder (BD) and unipolar depressive disorder (UD), are among the leading causes of disability and burden of disease globally[1]. The lifetime prevalence of BD is 1-2%[2]. Estimates of the lifetime prevalence of UD vary widely and should be interpreted with caution. The lifetime prevalence averages 11% across countries[3], with the highest rates of 21% found in some European countries[4]. The onset of affective disorders is typically in youth or early adulthood, and the disorders are characterised by affective episodes of depression and, in addition, hypomania and/or mania in BD[3,5]. During affective episodes, functional impairment is present and is part of the diagnostic criteria[6,7]. During periods of remission with little or no affective symptoms, functional impairment may, however, persist, and functioning is often continuously impaired in patients[8,9]. Impairment can affect global functioning or specific domains such as occupational functioning, social functioning, or self-care[10]. Residual depressive symptoms are one of the major predictors of functional impairment. However, the causes are multifactorial, and many other factors can cause or contribute to impairment[11]. Functioning is an essential and meaningful outcome in affective disorders, both from an individual, clinical and societal perspective[12].

In patients with BD, there is cumulative evidence of functional impairment during remission and identification of main factors contributing to and predicting functional outcomes. A meta-analysis from 2020 found a high prevalence of impairment of global functioning of 58.6% in patients with BD when assessed during remission. The domain with the highest impairment prevalence was occupational functioning (65.6%)[8]. Residual depressive symptoms and cognitive impairment are some of the strongest predictors of functional impairment[13]. However, many other clinical and sociodemographic factors, educational level, number of affective episodes, comorbid disorders (psychiatric and somatic), and substance abuse, are associated with functional impairment[11,13,14].

In patients with depression, long-term functioning during remission has not been investigated systematically. Some studies have reported rates of functional impairment in patients with UD like that seen in patients with BD[15,16]. Functioning is increasingly recognised as a valuable

outcome in UD and included in clinical studies[9]. Long-term follow-up studies find debilitating effects of UD with continuous poor functioning even after 25 years[17,18]. In Denmark, impairment of long-term occupational functioning is supported by data on high rates of disability pensions among patients with UD, with a national report by the Danish Health Authorities showing that depression accounts for 35% of disability pensions[19]. This finding highlights the importance of functional outcomes from a clinical perspective and their economic and societal impact. In the US alone, the financial burden of adults with UD has increased to more than 320 billion, with workplace costs as the largest and fastest-growing component of the cost[20]. Like in BD, residual depressive symptoms and cognitive impairment are associated with functional impairment[21-23]. Further, unrecognised bipolar disorder might also be related to functional impairment in UD[24]. Predictors of functional impairment are, however, not as well studied in UD as in BD. Personal factors such as the personality trait neuroticism[25], maladaptive coping styles[26], and the experiences of childhood trauma[27] are predictors of worse outcomes in UD and BD. Still, the impact of these factors on measures of functioning is less elucidated[28].

Assessment of functioning

Dorland's illustrated medical dictionary defines global functioning as an "*evaluation of a patient's functional level, including ability to perform activities of daily living, done to prescribe or evaluate rehabilitation measures*"[29]. The WHO's International Classification of Functioning, Disability and Health (ICF)[30] has been the international standard and framework to describe and measure functioning in patients with physical and/or psychiatric illness since 2001. Functioning in the ICF is defined as "*all body functions, activities and participation*", while "*impairments, activity limitations and participation restrictions*" is defined broadly as "disability"[30]. Environmental factors, personal factors, and health conditions are categorised and recognised in ICF in terms of their effects on functioning and disability. WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)[31] is recommended in The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[6] as the preferred scale for measuring functioning in patients across all psychiatric diagnoses as the domains are based upon the conceptual framework of ICF. There are various ways of assessing functioning. Overall, functioning measures can be divided into three categories[32]: 1) subjective (self-reported/patient-reported outcome) with self-administered questionnaires such as WHODAS 2.0 Questionnaire and Sheehan Disability Scale (SDS)[33] 2) semi-objective (clinician-rated) interview based such as Functional Assessment Short Test (FAST)[34], Global Assessment of Functioning (GAF)[35] and Social and Occupational Functioning Assessment Scale (SOFAS)[36] 3) objective (performance based) measures such as

Assessment of Motor and Process Skills (AMPS)[37] and University of California, San Diego Performance-Based Skills Assessment (UPSA)[38] (sometimes labelled "functional capacity"). Subjective and semi-objective measures have mainly been utilised in studies of patients with affective disorders[9,10,39].

Interventions aimed at improving functioning

The high prevalence of functional impairment in patients with affective disorders highlights the potential limited effect of presently available treatment options. This warrants the development of new treatments and strategies for improving functional impairment. A systematic review investigating the effects of antidepressants on functioning in patients with UD concluded that while antidepressive medications improve functioning, there is often a lack of synchronicity between the improvement of affective symptoms and functional impairment, and many patients continue to experience functional impairment even after treatment with antidepressants[9]. Applying the general and broadly accepted treatment approach mainly aimed at improving affective symptoms and episodes might result in failure to detect continuous functional impairment in a proportion of the patients. Although functioning is acknowledged as a central and meaningful outcome in affective disorders[10,12], few studies have tested interventions aimed at improving functioning as the primary outcome[40,41]. Functioning is often only included as a secondary or tertiary outcome. Further, most research in this area has mainly focused on cognition, while trials of interventions for improving functioning are limited. Although cognitive remediation trials show promising effects on cognitive functions, cognitive gains often fail to improve patients' global functioning due to limited transfer to real-world functioning[42]. The limited effects might also be due to the inherent limitations of only utilising one treatment modality. It has therefore recommended to investigate the effects of multimodal interventions to address this issue[42,43]. Trials investigating the effectiveness of multimodal interventions in affective disorders are lacking. However, a recent review and meta-analysis concluded that there is evidence of the effect of multimodal interventions and that interventions with more modalities included were more effective[44]. As in all fields of medicine, there is a call for a more personalised approach to treatments tailored towards the characteristics of each patient. With the heterogeneous nature of affective disorders (regarding phenomenology, illness trajectory, and response to treatment) combined with the multidimensional nature of functional outcomes (with several domains and predictors of outcome), a personalised treatment approach might be particularly beneficial[45].

In conclusion, functional impairment is prevalent in patients with affective disorders during phases of remission, and new treatment options and strategies are needed, with improvement of functioning as the main outcome. Intervention trials investigating the effects of multimodal interventions with a personalised approach have been called for. Further, a better understanding of predictors of functional impairment might aid in developing effective interventions.

Aims

In Study 1, we aimed to test the effect of a personalised 360-degree multimodal intervention targeting functioning (AWARE) compared with treatment as usual in patients with BD or UD, in a randomised controlled trial.

In Study 2, we aimed to investigate global functioning in patients with major depressive disorder (MDD) in remission compared with healthy control individuals in a systematic review and meta-analysis. Further, we aimed to investigate the effect on global functioning of prespecified potential moderating sociodemographic and clinical factors.

In Study 3, we aimed to identify clinical and personal factors associated with functional impairment at baseline and explore whether these factors predict improvement in performance-based functioning measured at six months follow-up. Study 3 was an exploratory study based on data from Study 1.

Hypotheses

In Study 1, we hypothesised that the AWARE intervention would be superior in improving functioning (performance-based) compared with TAU. Further, we hypothesised that AWARE would be superior in improving secondary outcomes of functioning, cognition, stress, and quality of life.

In Study 2, we hypothesised that patients with MDD in remission would have lower global functioning compared with healthy control individuals. Further, we hypothesised that the effect would be moderated by one or more of the prespecified sociodemographic and clinical factors.

In Study 3, we hypothesised that clinical factors (early age of onset, more affective episodes, and higher affective symptom scores) and personal factors (higher neuroticism scores, maladaptive coping styles, and more childhood trauma) are associated with more functional impairment at baseline and less functional improvement after six months.

Methodology

Methods Paper I and II - Study 1

Study Design and Participants

Study 1 is an open-label, outcome assessor-blinded, parallel-arm, randomised controlled trial investigating the effects of a 6-month individualised/personalised 360-degree multimodal intervention (AWARE) compared with treatment as usual (TAU) in patients with BD and UD. The trial was conducted at two Mental Health Centres in the Capital Region of Denmark. Participants were randomly assigned in a 1:1 ratio to either AWARE or TAU. The algorithm used was block randomisation with randomly varied block sizes, stratified on sex, age group (18–34 years and 35–65 years), and diagnosis (BD and UD). Assessments were done at baseline (before randomisation) and endpoint/follow-up (6 months). Due to the nature of the intervention, the study was conducted with an open-label design, but assessors were blinded to treatment allocation. The trial was registered at ClinicalTrials.gov (NCT04701827) prior to inclusion of the first participant. Ethical approval was obtained from The Regional Ethics Committee in the Capital Region of Denmark (protocol number H-20029748) following the ethical aspects as declared in the Helsinki-Declaration-2, and all procedures involving patients complied with these ethical standards. Data permission was obtained from the Danish Data Protection Agency (j.nr. P-2020-1216).

The trial was conducted at the Mental Health Centre Northern Zealand and Psychiatric Centre Copenhagen. Patients potentially eligible for inclusion were referred to the trial by their therapists. Patients meeting the following inclusion/exclusion criteria listed were eligible for inclusion: ”*Men or women, age 18–65 years with a diagnosis of BD or unipolar major depressive disorder by WHO International Classification of Disease 10th edition (ICD-10) diagnostic criteria; current state of remission or partial remission (defined as Hamilton Depression Rating Scale, 17-items (HDRS-17) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) scores of ≤14); impaired functioning defined as a score ≥11 according to the Functional Assessment Short Test (FAST) (Rosa et al., 2007); and ability to participate in two-thirds of the planned intervention visits. Exclusion criteria were: Severe physical disorder interfering with daily living; ongoing alcohol or substance abuse; electroconvulsive therapy treatment within the last 3 months before inclusion; dementia or*

inability to cooperate with the study, including inability to speak and read Danish" (Paper I and Paper II)[46,47]. All participants gave written informed consent before inclusion.

The Intervention

The manualised AWARE (Affective disorders: eliminate WArning signs And Restore functioning) intervention is a comprehensive multimodule individualised intervention, targeting mediators/enhancers of functioning in patients with affective disorders based on the International Classification of Functioning, Disability and Health (ICF) Brief Core Set for UD[48] and BD[49]. The intervention comprises five modules targeting: "*1. ADL (Activities of Daily Living) ability as a part of carrying out daily routines; 2. Mood symptoms, medication and side effects; 3. Social, relatives and network; 4. Physical health, including Body Mass Index (BMI), biomarkers and exercise; 5. Cognition, circadian rhythm measured as sleep quality, and coping (stress reduction)*" (Paper I)[47]. These modules were chosen as they target potentially modifiable predictors of functioning in patients.

Based on the baseline assessments, a targeted individual intervention profile for each patient was mapped out at a transdisciplinary meeting, headed by a psychiatrist, consisting of a medical doctor, an occupational therapist, and a nurse. At the meeting, a medical doctor (RS) presented the clinical history of the patient, and clinical data from the baseline assessment. Further, the same medical doctor presented the results of the diagnostic interview, clinical assessment scales, and questionnaires from the baseline assessment. Results of the AMPS assessment conducted in the patient's home were presented by an occupational therapist. For each patient, the relevant intervention modules were chosen based on the areas of most impairment/worst scores from the baseline assessments. Based on the intervention modules utilised in each individual patient, one primary therapist from the transdisciplinary group was chosen.

The AWARE intervention included 6–14 planned visits/sessions (based on individual needs, up to 18 sessions were allowed).
In the first session, the patient was orally (and in written format, if requested by the patient) presented with a comprehensive overview of the results of the baseline assessments by a medical doctor and the primary therapist. The patient was then asked about desired areas of improvement and treatment goals. The primary therapist and patient then together settled on which intervention modules the treatment program would be composed of (a minimum of one module

and a maximum of three modules in any combination) based on the recommendations made by the transdisciplinary group and the patient's wishes.

The following two to 13 intervention sessions addressed the prioritised treatment goals following the intervention manual that describes each module in detail. At each intervention visit, either a medical professional or an occupational therapist was present. The intervention sessions were planned flexibly, and the intervention sessions were held both in the hospital clinic and in the patient's home environment. Relatives were involved in one or more intervention sessions, if relevant. Midway through the intervention period (at three months), a medical doctor (RS) held an evaluation meeting with the patient, including assessment of functioning (FAST) and mood symptoms (HDRS-17 and YMRS).

Before the last session of the intervention, a transdisciplinary meeting was held to perform a status and a treatment plan involving the relevant actors in the further treatment, such as, psychiatrists, psychologists, the general practitioner, social workers or relatives. At the last session (session 14), the patient was presented with an evaluation of the intervention and the plan/recommendations for future actions and treatment as recommended by the transdisciplinary group. Further, the patient was asked to evaluate the intervention and the extent to which the goals were achieved. During the intervention period, the patients were required to participate in two-thirds of the planned sessions to complete the intervention. The AWARE intervention was given as a potential “add-on” treatment, as there were no restrictions regarding which other outpatient treatments the patients were allowed to receive during the trial.

Outcomes

The prespecified primary, secondary, and tertiary outcomes were published in the protocol (Paper I)[47]. The primary outcome was performance-based assessment of functioning at 6-month follow-up measured by the Assessment of Motor and Process Skills (AMPS)[37].

AMPS is a standardised observation-based assessment of two activities of daily living (ADL) tasks. The two tasks are individually selected for each patient based on a short interview and must be well-known, meaningful and challenging for the patient. The AMPS manual holds 125 standardised tasks. The evaluation of the quality of the performance comprises scores for ADL Process skills (level of timeliness and organisation skills) and ADL Motor skills (level of physical effort/clumsiness), with both scores also reflecting the safety and independence of the performance. The performance of the patient is scored for 26 items/skills on a four-point scale,

and scores are imputed into the AMPS software, where the final AMPS Motor and Process scores are generated after adjustment for the difficulty of the chosen performed tasks[50].
The AMPS measures are found to be valid and reliable across diagnostic groups, including mental disorders[51]. AMPS has high interrater reliability, and is sensitive to changes over time, with a minimal clinically meaningful difference (MCID) defined as ≥0.3[51,52]. AMPS assessment can only be performed by occupational therapists who are licensed, calibrated AMPS raters.

The secondary and tertiary outcomes were:

- Functional outcomes: interview-based (FAST and Activities of Daily Living Interview (ADL-I)[53]), and patient-reported/questionnaires (WHODAS)
- Cognitive outcomes: objective/performance-based (Screen for Cognitive Impairment in Psychiatry (SCIP)[54], Trail Making Test A and B (TMT)[55]) and patient-reported/questionnaires (Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)[34])
- Patient-reported stress (Perceived Stress Scale (PSS)[56])
- Patient-reported quality of life (World Health Organization Quality of Life (WHOQoL)[57])

Assessments and Procedures

The baseline assessment was carried out over two days before randomisation. The assessment consisted of both observational/performance-based measures, interviews, questionnaires, physical examination, and blood samples. The full assessment battery is presented in Paper I[47].
The diagnoses were made according to ICD-10 with The Mini International Neuropsychiatric Interview (MINI)[58] by a trained medical doctor (RS) in consultancy with a psychiatrist (MV) when needed. Randomisation was done successively in the week following the baseline assessment. Participants were informed about their allocation the following day. The participants in the TAU arm were not provided any information regarding the results of the baseline assessments during the study period. Still, they were offered an overview of the results of the baseline- and endpoint assessments after the endpoint assessment was completed.
Assessors blinded to treatment allocation performed assessments at endpoint six months after the date of randomisation. Before the endpoint assessment, patients were instructed not to disclose information about allocation during the endpoint assessment. Unfortunately, one outcome

measure (FAST) could not be performed unblinded due to logistical reasons despite being planned as an assessor-blinded outcome. Blinding was preserved on all remaining outcomes. All AMPS assessments and ADL-I interviews at baseline and endpoint were performed in the patient's home environment, while the remaining assessments were performed at the hospital clinic.

Statistical Analyses

Differences between allocation groups (AWARE and TAU) on the primary and secondary outcomes were analysed using an Analysis of Covariance (ANCOVA) model, as defined a priory in the protocol, and conducted using an intention-to-treat (ITT) approach. The findings were presented in two models, unadjusted (model 1) and adjusted for age, sex, diagnosis and number of affective episodes (model 2). The results are presented as mean differences, 95% CIs, and p values, with effect sizes calculated as partial eta-squared (η2p). The significance level was set at $p < 0.05$. The statistical analyses performed are described in detail in Paper 2. The following notes can be added:

1. The protocol (Paper I)[47] states that the outcomes will be analysed using "repeated measures" ANCOVA. As each outcome was measured only two times (baseline and endpoint) and two allocation groups are present (AWARE and TAU), it is not necessary to use a repeated measures model and a "standard" ANCOVA (with baseline value of the outcome as a covariate) is sufficient and more appropriate compared with a repeated measure model. This model was therefore chosen for the analyses in consultancy with two statisticians at The University of Copenhagen.
2. The protocol states (Paper I)[47] that missing values of the outcome measures will be implemented with the last observation carried forward. This plan was thought to be the three-month assessment. However, we were not able to conduct a full three-month blinded assessment of all participants due to a lack of workforce. In the final analyses, no values were implemented for missing values. Still, a dropout analysis was conducted to compare baseline characteristics (and available data collected at endpoint) between participating and non-participating patients in the assessment of the primary outcome at the endpoint. Comparisons were made using independent samples t-tests, Pearson chi-square, and Fisher`s Exact Test.

Exploratory analysis made on primary outcome (AMPS) were: 1) the change from baseline to endpoint (delta) was analysed between groups (paired t-test) 2) the number of responders (improvement in AMPS score of ≥0.3 from baseline to endpoint) in each group was compared (Pearson chi-square). Further, subgroup analyses were made stratifying on cognitive impairment at baseline (SCIP total score <70 vs ≥70)), age group (18-35 vs 36-65), disability pension status (yes vs no) and baseline HDRS-17 score (full remission vs partial remission). The analyses were performed in IBM SPSS statistics.

Power Calculation

At study inception, prior to inclusion, a power calculation was made based on an MCID on the AMPS score of 0.3, and an AMPS score SD of 0.3 in this population[59]. It was estimated that data from 104 patients would be needed to reject the null hypothesis with a power of 95% and a significance level of 0.05 (risk of Type 1 error). Accounting for dropout, the goal for inclusion was set at 120 participants.

Methods Paper III - Study 2

Search Strategy and Selection Criteria

Study 2 is a systematic review and meta-analysis of global functioning in patients with MDD in remission or partial remission. The protocol was pre-registered in the PROSPERO database (CRD42023386730). A systematic search was performed using PubMed, EMBASE, and PsycINFO databases. Title/abstract screening, full-text screening, data extraction, and bias assessment were performed by two independent investigators (differences were resolved by a third senior investigator). Studies were included if they met the following inclusion/exclusion criteria "*(1) Adult patient samples (age≥18); (2) Diagnosis/former diagnosis of MDD per International Classification of Disease (ICD)[60] or DSM[6]; (3) Remission (including full remission defined as a score on The 17-item Hamilton Depression Rating Scale (HDRS-17)[61] ≤7, or Montgomery-Asberg Depression Rating Scale (MADRAS)[62] ≤8, or partial remission defined as HDRS-17 ≤14, or MADRS ≤20) when functional assessment was performed (or by other validated systematic evaluation including cut off on The Beck Depression Inventory (BDI)[63], The HDRS-6[64], Remission from Depression Questionnaire (RDQ)[65] or Quick Inventory of Depressive Symptomatology (QIDS-SR)[66], or according to The Mini-International Neuropsychiatric Interview (MINI)[58] or by counting DSM or ICD criteria for MDD); (4) Data on global functioning compared with HC or assessed with a validated scale; (5) Studies including a sample of N>10 individuals remitted from MDD. Exclusion criteria: (1) Studies on mixed populations (e.g., including participants with bipolar disorder or schizophrenia) not reporting data for the participants with MDD separately; (2) Studies not published in English, French or German*" (Paper III)[67]. No restrictions regarding study design were applied. The risk of bias in included trials was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists.

Data Analysis

The primary outcome was global functioning in patients with MDD in full or partial remission compared with healthy control individuals (or global functioning assessed on a validated scale, without comparison with HC). The secondary outcome was the potential moderating effect of prespecified sociodemographic and clinical factors. The data on the primary comparison (MDD vs HC) was meta-analysed as standardised mean differences (SMD). The mean raw score for patients with MDD was calculated for each global functioning scale used in the studies. The statistical analyses were conducted using random-effects models. Subgroup and meta-regression analyses assessed the association between the prespecified sociodemographic and clinical variables with the effect size. A detailed description of the data analysis is presented in Paper III.

Methods Paper IV - Study 3

Study Design and Participants

Study 3 is an exploratory study on predictors of functioning and functional improvement over time, including patients with BD or UD enrolled in Study 1. For this study, we combined the data from patients in the intervention and control groups in Study 1. The data on functioning used in Study 3 were functional impairment at baseline measured with FAST. Further, to assess functional improvement/development over a 6-month period, data on performance-based functioning measured at baseline and at the 6-month follow-up using AMPS was used. The difference between AMPS score at baseline and follow-up (Delta) was used to measure functional improvement. Data on clinical factors were collected at the baseline interview. Age of onset and number of affective episodes were estimated based on the diagnostic interview (MINI), and depressive and manic symptoms were assessed with HDRS-17 and YMRS, respectively. Data on personal variables were obtained through questionnaires at baseline. Personality traits were assessed with the Eysenck Personality Inventory (EPQ)[68]. The EPQ is made of 100 items. Scores are calculated for the personality traits neuroticism and extroversion, with higher scores indicating higher levels of a trait. Coping strategies were assessed with the Coping Inventory for Stressful Situations (CISS)[69]. The CISS is made of 48 items. Scores are calculated for task, emotional, avoidance, distraction and social, with higher scores indicating a more prominent use of a coping style. Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ)[70]. The CTQ is made of 28 items. Scores can be calculated for dimensions of emotional-, physical- and sexual abuse, and emotional-, and physical neglect. Further, a combined total score can be calculated, with higher scores indicating the experience of more overall childhood trauma. For the present study, only the total score on CTQ was used.

Statistical analyses

Pearson correlations were performed for each of the clinical and personal variables and functioning (Spearman correlations for non-normally distributed variables). The clinical and personal variables with statistically significant correlations were imputed into multiple linear regression models with functioning as the dependent variable. Hierarchical multiple regression analysis was performed in models/blocks. Model 1 was a force-entered block with control variables (age, sex and diagnosis (BD vs UD). Consecutive models with blocks of clinical variables and personal variables (in that order) were entered, but only variables with statistical significance in correlation analyses were entered. Correlations and multiple regressions were performed for baseline FAST and AMPS Process Delta, separately. AMPS Process Delta was

the measure used for functional improvement. It was calculated as the difference between AMPS Process score at baseline and follow-up for each patient (AMPS Process endpoint – AMPS Process Baseline = AMPS Process Delta). The analyses were performed in IBM SPSS statistics.

Results

Results Paper I and II - Study 1

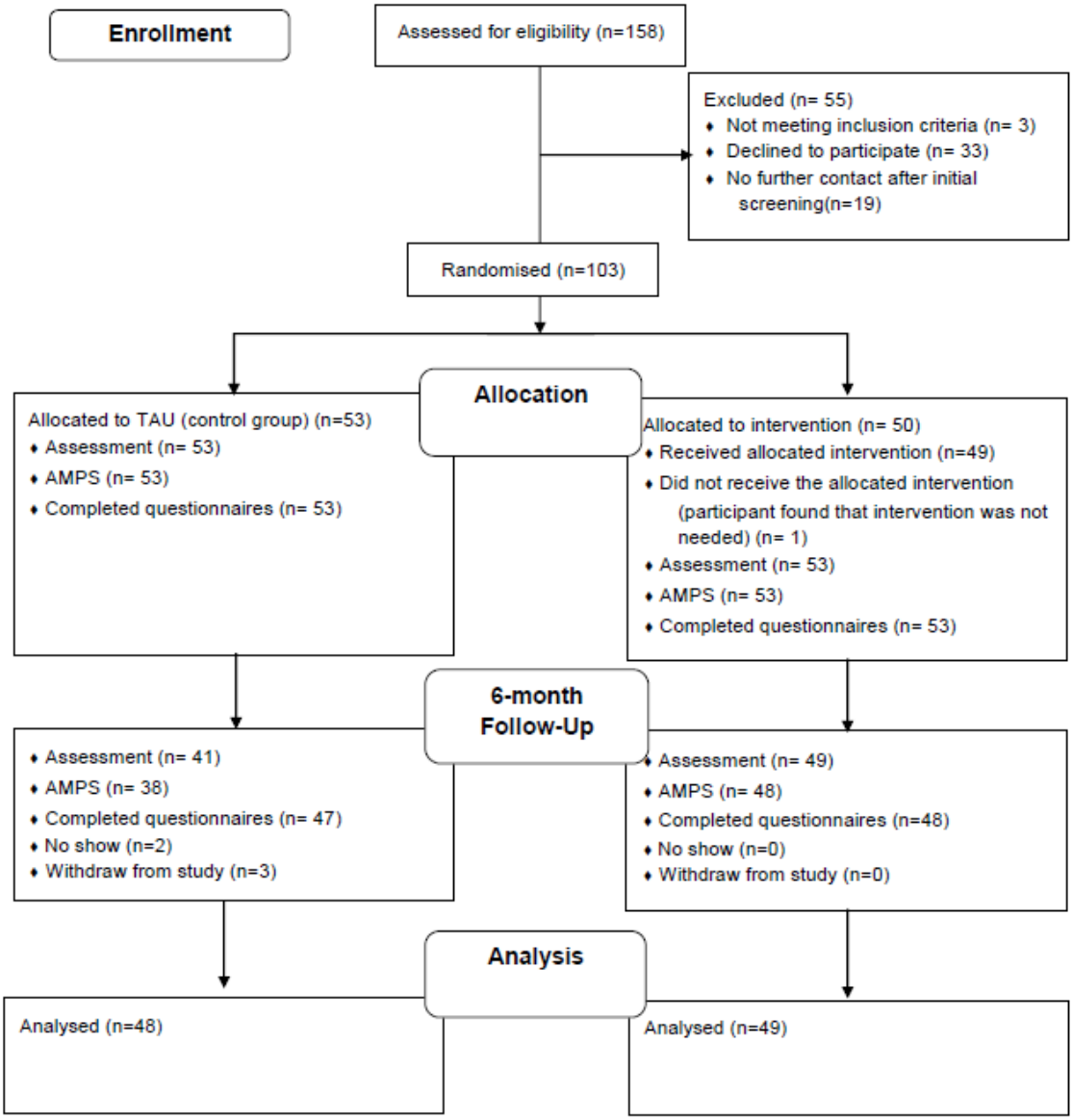
Participants and results of the primary outcome

A total of 103 patients were included in the study recruited between February 1, 2021, and January 31, 2023. Fifty were allocated to AWARE treatments and 53 to TAU. **Figure 1** displays participant flow. Baseline characteristics of the included patients by treatment group are presented in **Table 1**. Baseline characteristics were well-matched between the two groups. Dropout rates were low in both allocation groups (AWARE 2.0% (1/50) and TAU 9.4% (5/53)). However, regarding the primary outcome (AMPS) fewer patients participated in this assessment at the endpoint, and the number of patients completing the AMPS assessment at the endpoint was significantly higher in the AWARE group compared with TAU (AWARE 96.0% (48/50), TAU 71.7% (38/53) (Fishers Exact Test, P=0.001)).

Patients in the intervention group received and completed 12 (median, IQR 4) AWARE sessions each during the trial. During the trial, there was no difference in the other psychiatric treatments that the intervention and control groups received.

(Corresponding to Figure 1 in Paper II)[46]

Figure 1. Study 1 flow-diagram



(Corresponding to Table 1 on Paper II)[46]

Table 1. Sociodemographic and clinical characteristics of the included patients with bipolar or unipolar disorders according to treatment group

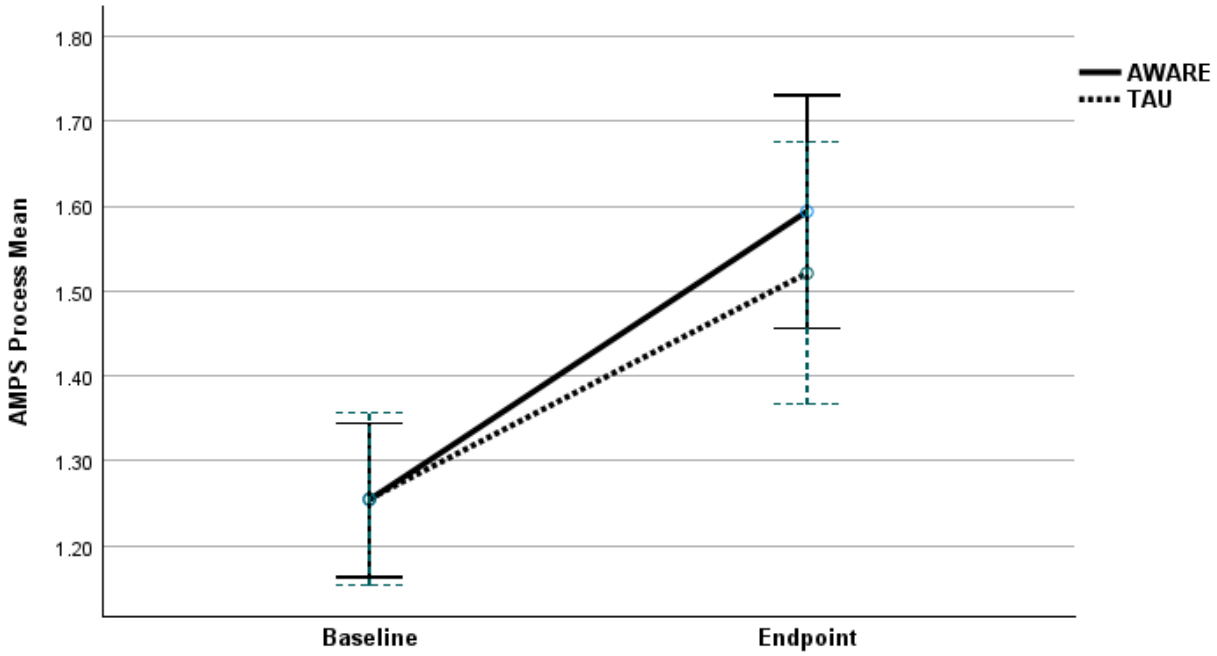
Randomisation group	AWARE (n=50)	TAU (n=53)
Sociodemographic:		
Age, mean (s.d.)	41.64 (12.75)	39.92 (12.29)
Sex, female, n (%)	33 (66.00)	34 (64.15)
Education years, mean (s.d.)	13.61 (2.40)	13.83 (2.75)
Marital status yes, n (%)	15 (30.00)	14 (26.42)
Employment status "employed", n (%)	11 (22.00)	15 (28.30)
Disability Pension, n (%)	10 (20.00)	3 (5.66)
Student, n (%)	4 (8.00)	9 (16.98)
Diagnosis:		
Unipolar, n (%)	15 (30.00)	17 (32.08)
Bipolar, n (%)	35 (70.00)	36 (67.92)
Age at illness onset, mean (s.d.)	20.38 (8.30)	20.34 (8.57)
Number of episodes:		
Depressive, median [IQR]	10 [13]	9 [11]
Manic (only for Bipolar 1), median [IQR]	2 [4]	1 [4]
Hypomanic (only for Bipolar 1 and 2), median [IQR]	10 [21]	10 [10]
Clinical:		
Time in remission/partial remission months, mean (s.d.)	6.48 (9.64)	5.96 (8.06)
HDRS-17 total score, mean (s.d.)	9.48(3.41)	9.75 (2.85)
YMRS total score, mean (s.d.)	2.40 (2.29)	2.98 (2.51)
Psychiatric comorbidity, n (%)	10 (20.00)	13 (24.53)
Previous suicide attempts, n (%)	8 (16.00)	16 (30.19)
Previeous received ECT, n (%)	7 (14.00)	3 (5.66)
Previeous hospitalisation, n (%)	31 (62.00)	24 (45.28)
Number of hospitalisations, median [IQR]	1 [3]	0 [2]
FAST total, mean (s.d.)	37.76 (10.06)	35.53(10.22)
SCIP total, mean (s.d.)	69.56 (15.18)	67.83 (12.35)
Body mass index, mean (s.d.)	29.09 (6.84)	29.01 (6.89)
Medical comorbidity (yes), n (%)	28 (56.00)	22 (41.51)
Current medication:		
Lithium, n (%)	19 (38.00)	21 (39.62)
Antipsychotics, n (%)	26 (52.00)	22 (41.51)
Antidepressants, n (%)	21 (42.00)	22 (41.51)
Anticonvulsics, n (%)	27 (54.00)	26 (49.06)
Benzodiazepines, n (%)	16 (32.00)	11 (20.75)
Others, n (%)	34 (68.00)	34 (64.15)

AWARE, Affective disorders: eliminate WArning signs And REstore functioning; TAU, Treatment As Usual; IQR, Interquartile Range; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; ECT, Electroconvulsive Therapy; FAST, Functioning Assessment Short Test; SCIP, Screen for Cognitive Impairment in Psychiatry.

Results on the primary outcome (AMPS) showed no effect of AWARE over TAU on the AMPS Process or Motor scores at endpoint, neither in unadjusted nor adjusted analyses. In the unadjusted analyses (only baseline AMPS scores as a covariate) the mean difference between groups on AMPS process was 0.07 (CI 95 -0.11-0.26, p=0.434) and the mean difference on AMPS motor was 0.06 (CI 95 -0.17-0.291, p= 0.590). In the adjusted analysis (age, sex, diagnosis, number of affective episodes and baseline AMPS scores as a covariates) the mean difference on AMPS process was 0.10 (CI 95 -0.10-0.29, p=0.319) and the mean difference on AMPS motor was 0.11 (CI 95 -0.11-0.33, p= 0.3). The changes in AMPS Process scores from baseline to endpoint in the AWARE and TAU groups are presented graphicly in **Figure 2**.

(Corresponding to Figure 2 in Paper II)[46]

Figure 2. Changes in mean AMPS (Assessment of Motor and Process Skills) Process scores (with 95% confidence intervals) from baseline to endpoint according to treatment group (the active Affective disorders: eliminate WArning signs And REstore functioning (AWARE) and the Treatment As Usual (TAU) Group



Secondary Outcomes

There was no effect of AWARE over TAU on self-reported functioning (WHODAS and ADL-I), quality of life (WHOQOL), or cognition measured by SCIP and TMT B. However, there was an improvement in other secondary outcomes of stress, cognition, and functioning. AWARE improved stress (measured by PSS) compared with TAU in unadjusted (B=-2.86, CI 95 -5.54; -0.19, p= 0.036) and adjusted analyses (B=-2.89, CI 95 -5.58; -0.207, p= 0.04). The effect sizes were small ($\eta 2p$ =0.047 and $\eta 2p$ =0.049, respectively). AWARE was superior to TAU in improving subjective cognitive functioning, with a strong trend in the unadjusted analysis (B=-2.55, CI 95 -5.10; 0.00, p= 0.05) and statistically significant in the adjusted analysis (B=-2.8, CI 95 -5.37; -0.23, p= 0.033). The effect size was small ($\eta 2p$ =0.051). Finally, there was a statistically significant effect of AWARE compared with TAU on functioning measured by FAST and the effect sizes were large in both unadjusted and adjusted analyses (effect size Model 1; $\eta 2p$ =0.149, Model 2; $\eta 2p$ =0.0158). For a full overview of the secondary and tertiary outcomes results, please see Paper II (Table 2)[46].

Exploratory Analyses

Exploratory analysis of the change in AMPS Process scores from baseline to endpoint in each allocation group individually (paired t-test) showed that both groups had statistically significant and clinically relevant improvement during the trial. The mean difference from baseline to endpoint in the AWARE group was 0.34 (CI 95 0.46- 0.21, p <0.001) and 0.34 (CI 95 0.51-0.18, p <0.001) in the TAU group. The number of responders in each group with a clinically relevant improvement of ≥0.3 logit from baseline to endpoint on AMPS was 26 (54.2 %) in the AWARE group and 18 (47.4 %) in the TAU group (no statistically significant difference between groups (Pearson chi-square p= 0.531)).

Exploratory subgroup analyses showed statistically significant and clinically relevant effects on AMPS Process scores of AWARE over TAU in patients with cognitive impairment at baseline (defined as a SCIP total score below 70, AWARE n=21, TAU n=17) in unadjusted (B=0.33, CI 95 0.02; 0.64 p=0.038) and adjusted models (B=0.42, CI 95 0.10; 0.74 p=0.013). The effect sizes were medium to large ($\eta 2p$ =0.12 and $\eta 2p$ =0.18 respectively). Results of additional subgroup analyses stratifying on age group, disability pension status and baseline HDRS score (partial vs full remission) were not statistically significant.

Participants reported no adverse events associated with the intervention. The completion rate of the AWARE treatment group was high at 98.0% (49/50), and the number of patients hospitalised during the trial period did not differ significantly between the AWARE and TAU groups.

As there was a higher dropout rate in the TAU group regarding the primary outcome (AMPS), analyses were made comparing other available data measures at endpoint between participants in the TAU group who participated in AMPS assessment vs participants who did not. Depression scores (HDRS-17) measured at endpoint were significantly higher in the dropouts (14.80 SD 5.76) vs completers (9.19 SD 5.57) ($p=0.042$). Differences in baseline characteristics between the patients participating in the assessment of AMPS at endpoint vs patients who did not were also analysed. Lower SCIP scores at baseline were found in the non-completers (61.40 SD 11.70) compared with the completers (70.37 SD 11.80). However, the number of patients who had a previous history of psychiatric hospitalisation was significantly lower in the group of patients who did not participate in the assessment of AMPS at the endpoint (10 patients (66.6%) vs 14 (36.8 %), Pearson chi-square $p= 0.049$). No other significant differences were found in the remaining analyses of baseline characteristics.

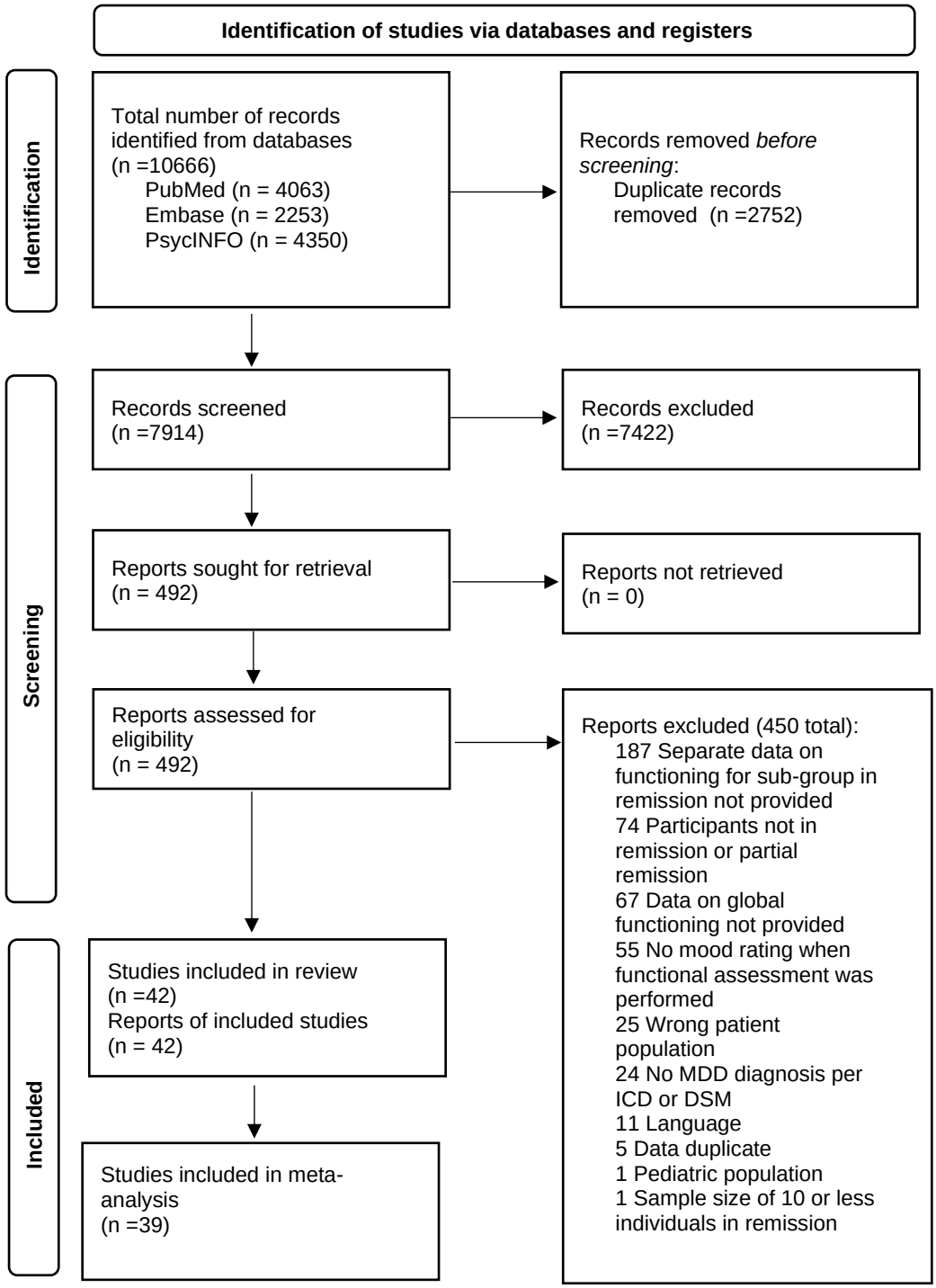
Results Paper III - Study 2

Included Studies

The study selection process is summarised in **Figure 3**. Overall, forty-two studies published between 2001 and 2023 were included in the review, including a total of 17999 patients with MDD in full or partial remission and 35550 HC. The characteristics of the included studies are summarised in Table 1 in Paper III. The mean age of patients with MDD in full or partial remission ranged from 23 years to 70 years (22 years to 69 years in HC). GAF was the functioning scale most frequently used in the included studies (14 studies). Out of the 42 included studies, 15 studies had both patients with MDD and HC, while 27 studies had only patients with MDD. Meta-analyses were performed on 39 studies that included data on 17462 patients with MDD and 35520 HC, as three studies did not provide the necessary data for meta-analysis.

(Corresponding with Figure 1 in Paper III)[67]

Figure 3. Overview of the study selection process.

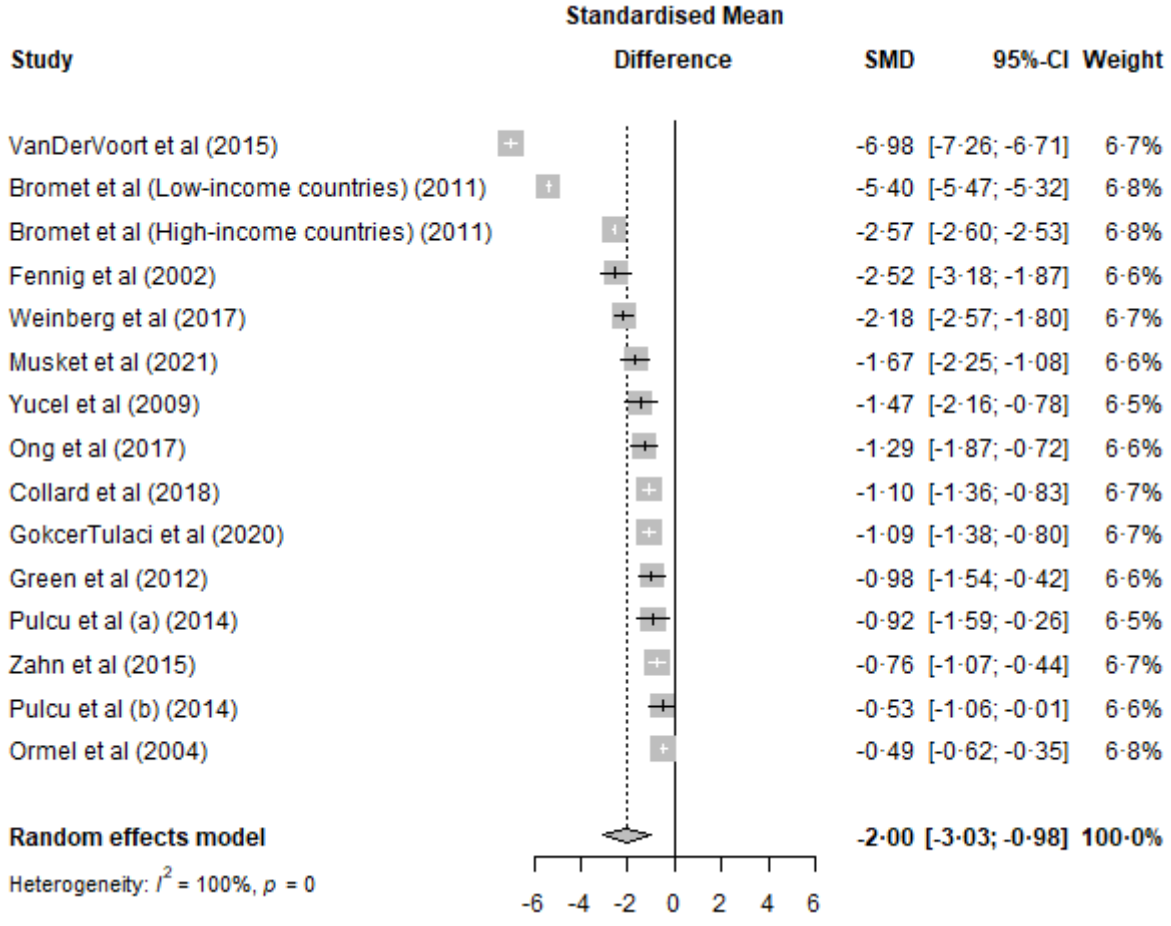


Results of the meta-analysis

Fourteen studies were used for the meta-analysis comparing global functioning of patients with MDD and HC. Patients with MDD in full or partial remission had lower levels of/more impaired global functioning compared to HC (SMD -2.00, 95% CI: -0.9 to -3.03, 15 comparisons, I2: 99.8%). The forest plot is presented in **Figure 4**. A sensitivity analysis was also performed by removing the two studies with the largest effect sizes and the results still showed that patients with MDD had impaired global functioning compared with HC (SMD -1.35, 95% CI: -0.92 to -1.78, 13 comparisons, I2: 99.0%).

(Corresponding with Figure 2 in Paper III)[67]

Figure 4. Forest plot of comparison of global functioning of patients with major depressive disorder in full or partial remission with healthy control individuals.



There was a large body of missing data in the analyses of the potentially moderating effect of the prespecified sociodemographic and clinical factors, as the reporting of these was lacking in the included studies. The only items reported in ten or more of the included studies were the mean age of patients with MDD and the sex distribution. The meta-regression analyses found a negative association between a higher proportion of males among patients with MDD and global functioning compared with HC (b = 0.05, 95% CI: -0.02 to -0.09, 11 comparisons). However, the mean age of patients with MDD did not significantly affect the difference in functioning between patients and HC (b = 0·003, 95% CI: -0·02 to 0·03, 11 comparisons). In subgroup analyses, the difference in functioning between patients with MDD and HC did not differ between studies conducted in a non-clinical, clinical, or mixed population (p = 0.53).
Separate meta-analyses were conducted for mean scores in patients with MDD of the nine different scales used to assess global functioning in the included studies. The most frequently used scale was GAF. The result of the meta-analysis on the GAF scale was a mean score of 79.16 (95% CI: 75.14 to 83.19, I2: 97.0%). Forest plots and results for each scale, including GAF, are presented in the Appendix of Paper III.
The funnel plot did not indicate publication bias (Appendix of Paper III).
Assessing the methodological quality and reporting of the included studies it was found that important information regarding the study participants' demographics and the setting (location and time) of the studies was not reported or needed to be clarified in most studies involving HC. Similarly, in most studies involving only patients with MDD, the reporting could have been more transparent with respect to inclusion criteria and demographic information on participants. However, in other domains, most studies meet the JBI appraisal criteria.

Results Paper IV - Study 3

Results

A total of 103 patients with BD or UD in partial or full remission were included in the study. Functional impairment measured at baseline was moderate to severe (FAST, mean 36.61, SD 10.15). The baseline characteristics of included patients are presented in **Table 2**. A total of 86 patients participated in the 6-month follow-up assessment of performance-based functioning (AMPS). Thus, analyses regarding baseline FAST are based on all 103 participants, whereas the analyses of improvement in functioning (AMPS Process Delta) are based on the 86 participants who completed the 6-month follow-up assessment.

(Modified/shortened version of Table 1 in Paper IV)[71]

Table 2. Baseline characteristics of patients with bipolar disorder and unipolar disorder (n=103)

Sociodemographic:	
Age, mean (SD)	40.75 (12.48)
Sex, female, n (%)	67 (65.0)
Years of education, mean (SD)	13.72 (2.67)
Diagnosis:	
Unipolar, n (%)	32 (31.1)
Bipolar, n (%)	71 (68.9)
Age at illness onset, median [IQR]	18 [9]
Number of episodes:	
Depressive, median [IQR]	10 [15]
Manic (Bipolar 1), median [IQR]	2 [4]
Hypomanic (Bipolar 1 and 2), median [IQR]	10 [15]
Clinical:	
Time in remission/partial remission months, mean (SD)	6.21 (8.82)
HDRS-17 total score, mean (SD)	9.62 (3.12)
YMRS total score, mean (SD)	2.69 (2.41)
Personal factors	
EPQ:	
Neuroticism, mean (SD)	14.44 (5.21)
Extroversion, mean (SD)	11.04 (5.20)
CISS:	
Task, mean (SD)	44.97 (10.69)
Emotional, mean (SD)	45.53 (10.12)
Avoidance, mean (SD)	38.50 (8.69)
Distraction, mean (SD)	18.48 (5.27)
Social, mean (SD)	13.13 (4.42)
CTQ, mean (SD)	54.74 (14.58)

SD, Standard Deviation, IQR, Interquartile Range; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; Eysenck Personality Questionnaire; CISS, Coping Inventory for Stressful Situations; CTQ, Childhood Trauma Questionnaire.

The relationship between clinical and personal variables and 1) baseline functioning (FAST) and 2) functional improvement (AMPS Process Delta) was explored. The results of the correlation analyses are presented in detail in Table 2 in Paper IV[71]. In summary, baseline FAST score significantly correlated with depressive symptoms (HDRS-17), neuroticism (EPQ), emotional coping (CISS) and childhood trauma (CTQ). They were all positive correlations. Functional improvement (AMPS Process Delta) significantly correlated with childhood trauma (CTQ) as the only baseline clinical or personal variable (a negative correlation). There were no statistically significant results on remaining clinical and personal variables.

The results of the hierarchical multiple linear regression model analysing the effect of the clinical and personal predictor variables on baseline FAST scores (adjusted for age, sex and diagnosis) are presented in **Table 3**. In Model 1 (explaining 14.1 % of the variance in FAST scores) age was a significant predictor ($\beta = 0.351$, $p < 0.001$), with higher age being associated with higher FAST scores (more functional impairment). HDRS-17, added in Model 2, was a statistically significant predictor of FAST ($\beta = 0.541$, $p < 0.001$), with higher HDRS-17 scores being associated with higher FAST scores. Model 2 explained an additional 24.8 % of the variance in FAST compared with Model 1 ($p < 0.001$).
Model 3, adding the personal factors neuroticism (EPQ), emotional coping (CISS) and childhood trauma (CTQ), explained an additional 5.2 % of the variance in FAST ($p < 0.05$). Among the personal factors, emotional coping ($\beta = 0.184$, $p < 0.05$) and childhood trauma ($\beta = 0.166$, $p < 0.05$) were statistically significantly associated with FAST scores, as higher scores on both scales (more emotional coping and more childhood trauma) were associated with higher FAST scores. Neuroticism (EPQ) was not statistically significantly associated with FAST scores.
Model 3, combining the variables age, sex, diagnosis, HDRS-17, neuroticism, emotional coping and childhood trauma, explained 42.7 % of the variance in FAST scores.

(Corresponding with Table 3 in Paper IV)[71]

Table 3. Hierarchical multiple linear regression models of clinical and personal variables and baseline FAST score in patients with bipolar disorder and unipolar disorder (n=103)

	Model 1 β	Model 2 β	Model 3 β
Variables			
Age	0.351***	0.212*	0.224**
Sex	-0.172	-0.043	0.002
Diagnosis	-0.005	0.035	0.031
HDRS-17		0.541***	0.486***
EPQ Neuroticism			-0.050
CISS Emotional			0.184*
CTQ			0.166*
Model			
R^2	0.166	0.414	0.467
Adjusted R^2	0.141	0.39	0.427
R^2 Change	0.166	0.248	0.052
F	6.586***	17.337***	11.88***
F Change	6.586***	41.506***	3.111*

*p < 0.05 ** p < 0.01 *** p < 0.001

B, regression coefficient; β, standardised regression coefficient; HDRS-17, The 17-item Hamilton Depression Rating Scale; EPQ, Eysenck Personality Questionnaire; CISS, Coping Inventory for Stressful Situations; CTQ, Childhood Trauma Questionnaire.

The results of the hierarchical multiple linear regression model analysing the effect of the personal predictor variables CTQ on functional improvement measured as AMPS Process Delta (adjusted for age, sex and diagnosis) are presented in Table 4 in Paper IV[71]. In summary, none of the control variables in Model 1 (age, sex and diagnosis) were predictors of AMPS Process Delta (improvement in functioning). As there were no significant results in correlation analyses for clinical variables, no model containing clinical variables was added. Childhood trauma (EPQ) added in Model 2, was a statistically significant predictor of AMPS Process Delta ($p < 0.05$), as more childhood trauma was associated with less improvement in functioning.

Discussion

Discussion Paper I and II - Study 1

Main findings

In Study 1, 103 patients were included, with 50 patients allocated to the intervention (AWARE) and 53 to the control group (TAU). Compared with TAU, the AWARE intervention was not superior in improving performance-based functioning as measured by AMPS (primary outcome) at 6 months follow-up, with no difference between the two groups. Therefore, the negative results of the primary outcome did not confirm our hypothesis. Compared with TAU, the AWARE group significantly improved on several secondary and tertiary outcomes of self-reported cognitive impairment (COBRA) and perceived stress (PSS) (still, the effect sizes were small), and clinician-rated functioning (FAST) with a large effect. There was no difference between the AWARE and TAU groups on secondary outcomes of functioning as measured by the WHODAS 2.0 questionnaire, QoL as measured by the WHOQoL questionnaire, cognitive impairment measured by SCIP and TMT-B, or ADL ability assessed with ADL-I. Post-hoc subgroup analyses on the primary outcome, AMPS, showed that patients with cognitive impairment at baseline in the AWARE group improved significantly in performance-based functioning compared with TAU.

Comparison to other studies

Few prior studies have aimed to improve functioning in patients with affective disorders in remission. The most extensive study comparable to the present study was an RCT conducted in Spain in 2013, investigating the effects of a 21-week functional remediation program (21 sessions) compared with psychoeducation and treatment as usual in 239 patients with BD[40]. Functioning was the primary outcome, measured by FAST. Functional remediation was superior when compared with treatment as usual, but not compared with psychoeducation. Besides only including patients with BD, the restrictive inclusion criteria were the main difference compared with the AWARE study (Study 1). Three months of remission was required prior to inclusion, and the remission criteria were an HDRS-17 score of ≤8. Further, included patients were excluded/discontinued during the study if they had an onset of an affective episode or were hospitalised[40]. Compared with Study 1, the included patients were less severely ill, and the natural course of patients relapsing into affective episodes (resulting in increased functional impairment) is not accounted for in the Spanish trial. Therefore, the results of the Spanish trial are based on a more selected patient population, causing limited generalisability of the results

compared with Study 1. It should also be noted that, compared with psychoeducation, functional remediation was not superior. In Denmark, a psychoeducational program is part of the standard treatment. In Study 1, the control group (TAU) might, therefore, have benefited from the additional effect of psychoeducation, which might be a contributing factor to the lack of effect on the primary outcome (AMPS) compared with TAU in Study 1. In Study 1, there was a positive effect on functioning as measured by FAST, similar to the Spanish trial. However, FAST was assessed unblinded in our study (further discussion on this issue in the "Strengths and limitations"-section).

The Spanish research group, has recently conducted another study testing a multimodal approach similar to the AWARE intervention, integrating cognitive and functional enhancement, healthy lifestyle, psychoeducation, and mindfulness[41]. The inclusion criteria in that study were expanded, with remission defined as HDRS-17 score of ≤14, similar to the criteria applied in Study 1. Results showed a significant effect on FAST in the intervention group compared with treatment as usual. However, only preliminary results were published as the trial was stopped prematurely in 2020 due to the COVID-19 crisis[41]. The Spanish research group has recently published a study protocol for a RCT, investigating the effect of functional remediation on functional impairment and neurocognitive dysfunctions[72].

A recent review and meta-analyses investigated the effect of multimodal interventions on different outcomes in patients with BD[44] and found a significant impact on functioning. However, the results were based on only two smaller studies (<25 participants in each allocation group), and functioning was a secondary outcome in the included studies[44].

Functioning has been included as a secondary outcome in trials of cognitive remediation programs, showing mixed results in both BD and MDD[73,74]. Based on a review of the effects of cognitive remediation in patients with affective disorders, the International Society for Bipolar Disorder (ISBD) Targeting Cognition task force made clear recommendations for future studies investigating the effect of multimodal interventions and including outcomes of "real-world functioning"[42] in line with the design of Study 1.

Perhaps the most prominent difference between previous studies and Study 1 is the use of a performance-based measure of functioning (AMPS) as the primary outcome in our study (further discussion on this issue in the "Strengths and limitations"-section).

Strengths and limitations

Study 1 had several limitations. First, the main limitation was the duration of the intervention. Six months may not provide sufficient time to improve overall functioning by implementing treatment strategies across different areas of functioning. In particular, the intervention duration might have been too short, given the severity of the patients' overall illness. The patients who participated in the study had significant functional and cognitive impairment at inclusion, according to their baseline FAST and SCIP scores (please see **Table 1**). As a result, they required extensive intervention in various areas of functioning. Additionally, the patients had a history of multiple affective episodes, which is known to be associated with a poor response to interventions[75]. In addition to a high number of recurrent episodes, many patients had a history of previous hospitalisations, and were mostly unmarried, and unemployed, which are known predictors of non-response to treatment [76].

Second, the higher number of patients on disability pension in the AWARE (20%) vs TAU (6%) group, might have limited the potential for considerable improvement in the AWARE group compared with TAU. It could also be speculated that these patients might be less motivated for improvement (however, no statistically significant results were found in analyses stratifying on disability pension status). It might be considered a limitation that no measurements of motivation for change were administered in the study. Studies aiming to improve functional outcomes might benefit from including measures of motivation at baseline, such as the University of Rhode Island Change Assessment Scale (URICA)[77], since the implementation of interventional strategies in everyday life, to some extent, depends on the patient's motivation. Higher motivation measured at baseline can be a significant predictor of adherence and positive treatment outcomes in clinical trials[78].

The third limitation was the sample size. The target sample size, as determined by the pre-study power calculation (n=120), was not obtained. Nonetheless, 103 patients were included, which was close to the target sample size, and just one patient short of the 104 patients required to complete the study to obtain a power of 95%, as calculated in the pre-study power calculation. The study was carried out during the COVID-19 crisis and recruitment was done during lockdown periods. This affected inclusion flow, and despite intense recruitment efforts and an extension of the inclusion period of one month, the final sample obtained was 103. However, inspection of the 95% confidence intervals of the mean difference between groups on the primary outcome (the estimate for AMPS process in the unadjusted analysis was 0.07 (CI 95 -

0.11-0.26, p=0.434) and in the adjusted analysis 0.10 (CI 95 -0.10-0.29, p=0.319)) reveals that the interval does not overlap with MCID of 0.3, thereby making it very unlikely that an increase in the sample size, would have rendered clinically relevant results. The study, however, could have been better powered regarding some of the secondary outcomes of patient-reported functioning (WHODAS 2.0) and quality of life (WHOQOL), as can be seen from the broad confidence intervals on the estimated mean difference between AWARE and TAU on these outcomes, which spans across values of clinically relevant effects and no effect. Regarding the post-hoc subgroup analyses, which revealed beneficial effects of the AWARE intervention compared with TAU on the primary outcome, the limited sample size limits the robustness of this find, as the number of patients included in this analysis is even smaller. In general, sub-group analyses should be interpreted with caution[79].

The choice of having a performance-based measure of functioning as the primary outcome resulted in several limitations. First, a direct comparison with other studies is limited, as previous studies have used interview-based functioning measures. Second, the performance-based assessment in patients' homes caused dropout on this primary outcome and resulted in missing data as some participants refused to participate in the assessment at follow-up. It was also a challenge during the recruiting phase, as unwillingness to participate in AMPS assessment was the primary reason patients declined to participate. Third, it is possible that using a performance-based measure of functioning as the primary outcome in our study could limit the potential for significant improvement compared to using patient-reported measures as patients in remission have been found to be more severely functionally impaired on performance-based measures[59] and performance-based functioning might be more stable over time compared with other measures of functioning[80]. Thus, shorter-duration studies might mainly be prone to show effects on patient-reported and interview-based functioning outcomes and limited effects on performance-based functional outcomes. Nevertheless, performance-based outcomes also provide some strengths in eliminating the risk of reporting bias. As patients in the present study and comparable studies are not blinded to treatment allocation, reporting bias may be present, with patients who received the intervention tending to report outcomes more optimistically at follow-up[81]. The present study might not “benefit” from this effect as the primary functional outcome is performance-based. The effect reported in studies using patients-reported and interview-based functional outcomes might overestimate the positive effects in the intervention group due to reporting bias (even clinician-rated scales, such as FAST, rely to a large extent on what is reported by the patient).

The study had an overall low dropout rate in both allocation groups. However, there was a higher dropout/missing data on the primary outcome (AMPS) in the TAU group, as some patients were unwilling to participate in this assessment at the endpoint. The dropout analysis revealed that patients who did not participate in AMPS at follow-up had more cognitive impairment at baseline (lower SCIP scores) and more severe depressive symptoms at the time of follow-up (higher HDRS scores). As expected, the analyses show that the patients who dropped out of the TAU group had a higher disease burden during the study period. The missing data on the most severely ill patients in the control group, might have affected the results in favour of the control group. Another main limitation was the follow-up assessment of FAST, which was performed unblinded to treatment allocation, due to logistic reasons. The positive results on FAST, therefore have a high risk of bias. This is unfortunate, as FAST is the functional assessment scale used in comparable studies, but as the assessment of this outcome was done unblinded in the present study, the results are less comparable.

Including several treatment modalities in the AWARE intervention program is a considerable strength of the study and intervention, as multimodal interventions have been suggested as a possible beneficial approach to effectively improve multicausal outcomes such as functioning (as previously described). However, there are inherent limitations when studying the effects of multicomponent intervention programs. It is difficult to deduce which components of the treatment program are effective, and responsible for any beneficial effects found. Subgroup analyses on patients receiving different elements could be performed; however, in the present study, integrating five treatment modules used in various combinations, a much larger sample size would be required to have sufficient power in such analyses. Further, the core idea of the AWARE intervention program is to “personalise” the content of the intervention by choosing a combination of treatment modules based on the profile of the patient. Hence, group-level analyses on the effectiveness of the different modules become less relevant.

The pragmatic approach applied in the study, which involved broad inclusion criteria and a flexible intervention program, allows for high generalisability regarding real-world clinical patient populations with affective disorders and functional impairment. However, the inclusion of severely functionally impaired participants with both psychiatric and medical comorbidities may limit the potential for significant improvement in functional outcomes.

The main strengths of the study are: a) the comprehensive baseline assessment and intervention targeting the most well-known predictors of functional impairment in patients with affective disorders, b) the use of a multidisciplinary team in the planning and intervention phases, c) the blinded outcome assessment, and d) the AMPS assessment performed in patients home surroundings. Despite the disadvantages in recruitment and dropout caused by the home assessment, performing the assessment in the home environment provided a more extensive view and knowledge of the patient's functioning and everyday life.

Discussion Paper III - Study 2

Main findings

Study 2 is a systematic review and meta-analysis of global functioning in patients with MDD in partial or full remission including 42 studies, showing that patients with MDD have lower global functioning compared with HC. This supported our hypothesis. Considerable heterogeneity was present among the included studies, and the estimated mean difference between the two groups has high statistical uncertainty, as can be seen from the broad confidence intervals. However, even the most conservative/lowest end of the confidence interval represents a large effect size. Further, in the sensitivity analyses, the estimated difference still represented a large effect size after removing the two studies with the largest effect sizes, thereby supporting the robustness of the findings. Not all studies included in the meta-analysis provided data on HC. Therefore, the raw scores of each of the functioning scales used to assess global functioning in the included studies were meta-analyses separately for each scale. It is not possible to compare these results directly with HC, and most scales, unfortunately, do not have cut-off scores clearly defining functional impairment. The results do, however, provide some support for our main finding of functional impairment in patients with MDD. The summary results for the GAF scale, which was the most utilised scale in the included studies, showed global functioning in the range of "*slight impairment in social, occupational or school functioning*"[35]. Similarly, the summary results for the FAST scale were in the range of functional impairment as defined by the scale[82].

Comparison to other studies

The results cannot be compared directly with other reviews, as this, to our knowledge, is the first systematic review and meta-analysis published on functioning in patients with MDD in remission. A review looking at functional outcomes after treatment of depression in the acute phase of MDD, concluded that isolated monitoring of depressive symptoms without assessment of functioning is not sufficient, as many patients still have functional impairment post treatment[9]. Our results align with these findings and provide further evidence of the continuous prevalence of functional impairment in partial and full remission phases.

There is evidence of sex differences in the prevalence[83] and symptomatology[84] of MDD. However, evidence regarding sex differences in functioning and the severity of functional impairment is lacking. Based on the results of the present review, functional impairment is more severe in males during phases of remission compared with females. The reasons behind this might be multicausal. Men may be less likely to seek professional treatment in the earlier stages of illness and might less frequently be diagnosed with MDD, causing increasing severity and

progression of symptoms before receiving the diagnosis. The overall result might be a higher illness load in males with depression and less desirable functional outcomes long-term during remission.

The cognitive impairment associated with increasing number of affective episodes found in MDD[85] might be suspected to have resulted in higher age being a predictor of functional impairment in the present review. However, no association between higher age and difference in functioning was found between patients with MDD and HC.

The analyses of the effects of other potential moderators of functioning were negative, showing no effect. However, these results should be interpreted with caution, and are not compared with results from other studies, as the analyses for each were based on very limited data present in less than ten of the included studies.

Strengths and limitations

One of the main limitations in the evidence base in the present review is the lack of clear consensus on a golden standard for measuring functioning in patients with MDD. It was specified in the inclusion criteria that only studies measuring global functioning were eligible for inclusion, eliminating substantial variation that would arise from including studies measuring sub-domains of functioning such as social or occupational functioning. Differences were, however, present among the scales used for assessing global functioning in the included studies regarding the number of sub-domains measured as part of global functioning, time frame, and assessment method (both self-reported and clinician-assessed scales were used). Despite the recommendations in the DSM-5 identifying WHODAS 2.0 as the preferred scale for assessment of functioning, the scales most frequently utilised in the included studies were GAF, SOFAS, and SDS.

Another prominent limitation in the evidence base in the present review was the limited data on clinical and demographical variables (besides sex and age) provided in the included studies, as was also reflected by the risk of bias assessment. This is particularly problematic in the context of the high heterogeneity among the studies analysed, as this heterogeneity remains largely unexplained in the analyses. Sex was identified as a moderating factor of functioning, explaining some heterogeneity. The various different functioning scales used are likely the reason behind a portion of the heterogeneity. Age and clinical setting were not prominent factors causing heterogeneity bases on the analysis. However, missing data caused the possible moderating

effects of factors, such as the number of previous depressive episodes and hospitalisations, age at onset, and time in remission to be left unexplored.
Finally, a limitation in the evidence base was the lack of HC in most included studies, thereby limiting the number of studies being analysed for the primary outcome comparing MDD with HC to 14.

Besides limitations of the evidence base, a number of study-level limitations are present.
First, all analyses are based on study-level data, not individual patient data. As the analyses are based on aggregate data from each included study, it is not possible to directly deduce associations on the individual level in each study. Incorrect assumptions based on group-level data are known as "ecological fallacy"[86]. For example, the results showing more severe functional impairment in males need to be further investigated in studies with individual patient data to verify the association on that level.
Second, the risk of confounding cannot be ruled out. The risk of bias assessment showed that confounding factors were generally well accounted for in the included studies with HC (Paper III appendix)[67]. However, there is still a risk of unmeasured confounding and residual confounding in the included studies. The possible risk of confounding from sociodemographic factors was generally low in the included studies, as HC were matched on age, sex and socioeconomic status. However, regarding a history of substance abuse (which is known to be associated with impaired functioning[11]), most studies did not provide detailed information on how this was assessed, and residual confounding cannot be ruled out.
Third, it is possible that not all eligible studies were identified and included in the study. Functioning is often not a primary or main outcome in studies, but rather a secondary outcome and functioning results might not be clearly stated in the abstracts and are often only briefly mentioned in the articles. Further, many different terms may be applied, such as "psychosocial functioning", "disability", or "impairment". However, we applied a very broad search strategy and included many articles for full-text review (and assessed the references of the included articles systematically), thereby substantially limiting the risk of overlooking eligible studies.

Discussion Paper IV - Study 3

Main findings

Study 3 is an explorative study of the 103 patients with BD and UD in full or partial remission included in Study 1, investigating the associations between clinical and personal factors, and baseline functioning, and improvement in functioning measured at 6-month follow-up.
As hypothesised, depression severity was associated with more functional impairment at baseline, also after adjusting for age, sex and diagnosis in the regression analysis. Further, as hypothesised, the use of emotional coping strategies and more childhood trauma was associated with more functional impairment at baseline, also after adjusting for age, sex, diagnosis and depressive symptom severity in the regression analysis. The personality trait neuroticism was associated with baseline functioning in correlation analyses, however, not after adjusting for age, sex, diagnosis and depressive symptom severity in the regression analysis. This is likely caused by depression symptom severity being a confounding variable in the association between neuroticism and functioning. The most prominent finding in the study is the results on childhood trauma, with more childhood trauma not only being associated with functional impairment at baseline, but further shown to be a predictor of less functional improvement measured at 6-month follow-up, in line with our hypothesis. However, contrary to our hypotheses, the clinical factors of age of illness onset and number of affective episodes were not associated with functioning in any analyses, nor were coping strategies/styles of task, avoidance, distraction and socially oriented coping. Other than childhood trauma, no clinical or personal variables were found to be associated with functional improvement. No associations were found between manic symptoms and functioning, however, as can be seen from the low YMRS scores in **Table 2** (mean 2.69, SD 2.41), the included patients had almost no manic symptoms. Among the controlling factors used in the regression analyses, only age was associated with functioning, as higher age was associated with more functional impairment at baseline.

Comparison to other studies

The impact of personal factors such as the personality trait neuroticism, coping styles, and childhood trauma is less well-studied in the context of functioning in patients with affective disorders, but they are known to predict poorer outcomes[28,87].
Experiences of childhood trauma were shown to have a negative impact on functioning and functional improvement over time in the present study. Childhood trauma has been well-established as a predictor of poor treatment response in patients with affective disorders[88].

Associations between childhood trauma, social functioning and cognitive impairment have been found in recent systematic reviews[27,28]. The negative effects of childhood trauma on functioning might be multicausal and complex. Childhood trauma is associated with a less-favourable profile on multiple clinical and social variables throughout patients' lives, such as illness course[89,90], presence of comorbidities[91], maladaptive behavior[92], affective instability[93] and poor social skills[94]. Therefore, the functional impairment caused by childhood trauma might be particularly challenging and treatment-resistant due to its complex nature. In the present study, a more prominent use of emotional coping was found to be associated with functional impairment. It is likely that patients relying mostly on emotional coping, may be less prone to directly confronting and handling challenges associated with daily living, thereby leading to impaired functioning. In patients with affective disorders, emotional coping has been linked to worse outcomes and increased risk of relapse of depressive episodes[26,95]. In line with previous studies, depression severity was associated with functional impairment at baseline in the present study[96]. Contrary to our hypothesis, however, baseline depression severity and the remaining clinical variables did not predict functional improvement measured at follow-up. The findings on depressive symptoms are in line with what is concluded in a systematic review, stating that, in most studies, the baseline severity of depressive symptoms is not a predictor of functional improvement at follow-up (however, this review was based on studies on patients in a depressive episode at baseline)[9].

Strengths and limitations

The study had several limitations. It was exploratory, and no adjustments for multiple testing were made, which increases the risk of incidental significant findings (Type 1 error). The sample size was limited to 103 patients. Due to the limited sample size, only a limited number of variables could be analysed in the multiple regression models. Variables other than clinical and personal variables, such as cognitive variables, were not included in the analyses, which are known to play a key role in functioning[13]. The included patients were a mixed sample of patients with BD (68.9%) and UD (31.1%). The effects of predictor variables on functioning may differ between the two diagnoses. However, the overlap is significant (for further discussion on using a mixed population of BD and UD patients, please see "General strengths and limitations of the thesis").

The patients included in the present study were a pooled sample of patients allocated to the intervention and control groups in Study 1. As baseline data on clinical and personal variables and functioning measured with FAST at baseline were collected before randomisation/allocation,

those data are not influenced by the different treatments patients received during the trial. As presented in the results section of Study 1, there was no difference in the primary outcome (AMPS) at follow-up between the intervention and control group (and the assessment was done blinded to allocation groups), thereby justifying the pooling of data on AMPS from patients in the intervention and control group in the present study. It is a limitation that the different treatments patients received prior to and during the trial are not accounted for in the analyses in the present study. Different medical treatments might be associated with differences in functional outcomes in patients with affective disorders, which is not accounted for in the present study[11].

In the multiple linear regression models, it was possible to control for the possible confounding variables of age, sex and diagnosis. However, other possible confounding variables of the included clinical and personal factors and functioning were not accounted for in the analyses. Socioeconomic status might act as a confounder[97]. Data on the socioeconomic status of the included patients was obtained but not used in the analyses. Included patients were not allowed to have ongoing substance abuse during the trial or in the three months leading up to the trial. However, a history of previous substance abuse before this time period, might also act as a confounder.

General strengths and limitations of the thesis

In the following section, the general limitations and strengths of the thesis are presented and discussed. The main limitation is the lack of clear consensus on a golden standard for measuring functioning in patients with affective disorders. As described in the introduction section, ICF is the standard for describing and measuring function across all diagnoses and illnesses, as provided by the WHO. However, ICF is not a measure of overall functioning but a tool for assessing and describing functioning and disability within selected areas. Thereby, ICF is essentially a language and framework on which functioning assessment tools can be based. As illustrated by the findings in Study 2 and in a recent review of functional outcome assessment in BD[10], there is a great variety of scales used in the literature for assessing functioning in patients with affective disorders. It should be noted that the findings show that WHODAS 2.0 (based on ICF and recommended by the DSM-5) is not currently widely used. Two main issues can be identified regarding WHODAS 2.0. First, as with many of the available functioning scales, there is no clear consensus on an MCID measured by WHODAS 2.0. Second, as was illustrated by the results in Study 1, the confidence intervals are very broad when measured in this population, and

a large population is therefore needed to detect significant differences between groups. These qualities might make the scale a less favourable choice in clinical trials.

Another limitation is the mixed sample used in Study 1 and Study 3, combining patients with BD and UD. Ideally, trials could be conducted on each patient group separately. However, as only patients with major depressive disorder (not minor depression) were included from the secondary hospital sector, the high illness load of the UD patients included made them more comparable to patients with BD. In Study 1, primary and secondary outcomes analyses were adjusted for diagnoses (BD vs UD) to account for possible differences between the two patient groups. Further, in study 3 diagnosis was not associated with functional outcomes in any analyses, supporting the decision to combine the patients in the trial. However, as the overall sample size is limited, and the proportion of patients with UD was smaller (31.1%), there is a risk of not detecting a difference that might actually be present due to limited power (Type 2 error). Pooling of patients with affective disorders is not uncommon in studies. Besides similarities in the symptomatology of BD and UD, there is an underlying genetic overlap between the two diagnoses[98,99]. Further, 10-15 % of patients with a diagnosis of UD will later convert to a diagnosis of BD[100]. It is reasonable to include patients with BD and UD in the same sample due to significant overlap in symptoms and prognosis, although there may be differences in how the predictors influence overall functioning.

Finally, the thesis revolves around the functioning of patients in remission. However, "remission" is not clearly defined in BD and UD. Cut-off scores on commonly used depression scales such as HDRS-17 and MADRS are generally well-established, but criteria on the timeframe/duration of the remission period are not captured by these scales. Partial remission is even less well-defined but is prevalent longitudinally in many patients[101]. Although residual depressive symptoms are more prevalent in partial remission compared with remission, partial remission is still characterised by the absence of a current major depressive episode[102]. The inclusion of patients with partial remission in trials of remitted patients has been encouraged to improve generalisability[42]. Including patients with full and partial remission increases the generalisable of the results of the thesis to a broader population of patients with affective disorders.

It is a considerable strength of the thesis that we performed a clinical trial with functioning as the primary outcome, thereby providing insights for a solution to the issue of functional impairment in patients with affective disorders in remission. Further, it is a strength that the thesis

(hopefully) is a step toward intensifying the focus on functioning in patients with MDD, as Study 2 provides extensive insight into the available data in the literature.

Reflections on Functioning

Functioning is an important and meaningful outcome for patients with affective disorders. It is a patient-centered outcome with advantages over measures such as quality of life as functioning can be more "objectively" measured and compared among patients. Functioning has advantages over other outcome measures, such as cognitive outcomes, as results are more generalisable to real-world functioning and seek to directly address the issues of daily life the patient is experiencing. As underlined by the high prevalence of functional impairment in patients in remission, functional outcomes can provide valuable information on the success (or lack thereof) of long-term treatment response, which standard depression or mania scales might overlook. The various ways of assessing functioning each have inherent advantages and disadvantages. Questionnaires can be easily applied, but reporting relies strictly upon the insight and credibility of the patient. Clinician-rated measures based on interviews are more "objective" but require time and training of clinicians, and the impact of the quality of reporting by the patient cannot be denied. Performance-based measures eliminate reporting bias and can be applied in a highly standardised manner. However, this assessment is more time-consuming, more logistically challenging, and requires even greater training of assessors.

Applying some measure of functioning could be considered relevant in almost all research involving patients with affective disorders and in daily clinical routines.

Implications and Future Research

Overall, the findings show that functional impairment is prevalent in patients with affective disorders during phases of remission from acute affective episodes. These results are in line with the growing body of evidence supporting the prevalence and severity of functional impairment in patients with BD and UD. The findings have direct clinical implications regarding standard clinical practice for monitoring patients with affective disorders. Patients are primarily monitored with assessments of depressive and manic symptoms across all illness phases. Functioning might be monitored to some extent, but often limited to certain sub-domains such as occupational functioning, and rarely are regular assessments with validated functioning scales applied as a part of standard care. Routine assessments of functioning could be applied regularly

(every 6 or 12 months and following phases of acute affective episodes) using FAST as this is a validated scale, easy to apply, relatively short and therefore not overly time-consuming in a tight clinical setting. Standardised use of FAST, with the registration of scores in patient's journals, would also allow for valuable longitudinal data on functioning to be extracted and analysed in aid of gaining a deeper understanding of the development of functional impairment in patients, identifying positive and negative predictors of functioning, and developing effective treatment strategies. The findings in the present thesis also warrant an increased clinical awareness of certain factors, such as male sex, a history of childhood trauma, and subclinical depressive symptoms that might be associated with worse functional outcomes in patients with affective disorders. The call for increased focus on functional outcomes may be even more necessary in patients with UD, as continuous functional impairment in these patients may be further under-recognised than in those with BD.

Effective interventions targeting functioning are needed in patients with affective disorders. Future studies investigating the effects of longer-term (both in terms of duration of the intervention and post-intervention follow-up assessments) personalised interventions are warranted. Positive and negative predictors of functioning should be studied longitudinally in larger cohorts in both BD and UD. Personal factors such as childhood trauma and coping strategies should be considered as additional predictors of functioning.
Future studies are encouraged to apply different measures of functioning, across the three assessment modalities (self-reported, clinician-rated, and performance-based), however, being aware of the benefits and limitations of each assessment method. Future studies should extend the investigation of functioning to populations of patients with UD and BD, as evidence on prevalence, predictors, and effective interventions in patients with UD is lacking. Exploratory analyses of Study 1 and Study 3 showed that patients with cognitive impairment as the primary cause of functional impairment might be more responsive to treatment. In contrast, functional impairment caused by more complex mechanisms, such as inherent behavioural patterns and a history of childhood trauma, might be more difficult to treat. Although these results should be interpreted with caution, a more prominent focus on the history of childhood trauma in future studies is suggested.

Conclusion

The thesis emphasises the need for effective interventions targeting functioning in patients with affective disorders, even in patients with low levels of mood symptoms. Regardless of the limitations of Study 1, the negative results of the primary functional outcome, despite patients receiving a comprehensive intervention program, highlight the extent and severity of functional impairment in this patient population. The thesis shows that functional impairment in patients with UD in remission has not been given the same research attention as for patients with BD. Still, functional impairment is prevalent in patients with UD as well. A strong understanding of factors causing and contributing to impaired functioning is needed to develop future effective interventions in patients with affective disorders. Despite increasing research future studies are required, particularly in patients with UD. In essence, functioning should be considered a main outcome in patients with affective disorders in both clinical and research settings.

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Appendix (Papers)

Paper I

Rasmus Schwarz, Lone Decker, Ida Seeberg, Kamilla Woznica Miskowiak, Lars Vedel Kessing, Maj Vinberg. “Affective disorders: eliminate WArning signs and REstore functioning—AWARE—a randomised controlled multimodule intervention study, presentation of design and intervention.” BMJ Open, online 2022 May 26. Doi: 10.1136/bmjopen-2021-058839.

BMJ Open

Affective disorders: eliminate WArning signs and REstore functioning—AWARE—a randomised controlled multimodule intervention study, presentation of design and intervention

Rasmus Schwarz ,[1,2] Lone Decker,[3] Ida Seeberg,[4] Kamilla Woznica Miskowiak,[5,6] Lars Vedel Kessing ,[2,7] Maj Vinberg[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Rasmus Schwarz; rasmus.einar.vagn.schwarz@regionh.dk

ABSTRACT

Introduction Affective disorders are associated with impaired overall functioning and quality of life (QoL). Despite different medical and psychological treatment options, the prognosis remains largely unchanged. Consequently, the field needs new intervention strategies especially targeting patient groups with impaired functioning. This study aims to improve functioning and QoL in patients with affective disorders using a comprehensive 360° intervention.

Methods and analysis Affective disorders: eliminate WArning signs And REstore (AWARE) functioning is a randomised, controlled, parallel-group design study. Participants will be 120 outpatients, men or women, aged 18–65 years, with a diagnosis of bipolar disorder or major depressive disorder. Inclusion requires an objectively rated impaired functioning defined as a score ≥11 according to the Functioning Assessment Short Test. Participants will be randomised to 6-month AWARE intervention or treatment as usual (TAU). The AWARE intervention is a 360° multimodal intervention based on the International Classification of Functioning Brief Core Set for bipolar and unipolar disorder targeting functioning.

The primary outcome is improvement of observation-based activities of daily living (ADL) ability using Assessment of Motor and Process Skills. Secondary outcomes are changes from baseline to endpoint in functioning, QoL, stress, cognition and physical health. Our hypothesis is that the AWARE treatment in comparison with TAU will improve observed ability to perform ADL, patients self-perceived level of functioning and QoL.

Status: currently recruiting patients.

Ethics and dissemination Ethical approval has been obtained from The Regional Ethics Committee in the Capital Region of Denmark. All patients will be provided oral and written information about the trial before informed consent is obtained. The study results will be disseminated by peer-review publications. If the present AWARE intervention shows beneficial effects, the goal is to use it as a template for future interventions addressing disability in patients with affective disorders as well as for patients within other diagnostic categories.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial is an open label randomised multimodule intervention study with blinded outcome assessment, which is designed to evaluate the effect of a 360° multimodal intervention on functioning and quality of life in patients with bipolar and unipolar disorder.
⇒ A considerable strength of the study is the comprehensive assessment and intervention, targeting most well-known factors contributing to impaired functioning.
⇒ Observer-based measures of activities of daily living ability as part of functioning conducted in the patients' homes and thereby everyday life.
⇒ A limitation is that some patients might be unwilling to participate due to assessment/observations in patients' home surroundings at baseline and endpoint.
⇒ Another limitation is the duration of the intervention, which is limited to 6 months.

Trial registration number NCT04701827; Clinicaltrials.gov.

INTRODUCTION

Unipolar disorder (UD) and bipolar disorder (BD) have a major impact on patients' functioning and quality of life (QoL) and are among the leading course of lost years of work.[1] Measured by disability-adjusted life year, these affective disorders are among the 10 leading causes of disability globally.[2] The total costs of BD in the USA in 2015 were estimated to be more than US$202.1 billion,[3] and it is estimated that one-third of the expenses for sickness leave in the European Union is due to severe mental illness with affective disorders accounting for the largest proportion of this cost.[4] Affective disorders are also associated with major somatic

disorders[5] mainly cardiovascular disorders,[6] obesity[7] and non-insulin-dependent diabetes.[8] Putative reasons for these conditions and the increased mortality observed in patients with affective disorders[9] include a more sedentary lifestyle[10] as well as abnormal sleep patterns,[11 12] leading to disturbed diurnal rhythm that also impact daily functioning.[13]

Despite different medical and psychological treatment options, the prognosis for affective disorder remains largely unchanged for many patients.[14] Consequently, the field needs new intervention strategies especially targeting the patient groups having impaired functioning. Therefore, our group conducted a pilot study using a performance-based assessment tool, including patients with BD in remission assessed in their home surroundings. These patients (mean age 35 years) had an observed ability to perform activities of daily living (ADL) below the mean of healthy persons at the same age,[15] and their ADL ability was equivalent to healthy persons between 60 and 85 years. Thus, having an ADL ability as being 30 years older, they exhibited increased physical effort, clumsiness or fatigue and/or efficiency, leading to concern for safe task performance.[15] Furthermore, concerning cognition, impaired processing speed was significant associated with more difficulties in performing ADL.[16] Finally, a similar pattern has been observed among patients with UD.[17–19]

The International Classification of Functioning, Disability and Health (ICF)[20 21] is recommended as a conceptual model to describe functioning and disability within mental health in general.[22–24] Most research on functioning and disability has focused on the component *body functions and body structures,* that is, cognition. Fewer studies have addressed the component *activities and participation,*[22] including self-care and domestic life, also termed ADL, including tasks such as personal hygiene, eating, reading and more complex home maintenance tasks for example, cleaning, cooking and shopping.[20 25] Studies assessing ADL ability show that patients with affective disorders have limited ability to perform ADL tasks.[26–28] This ability is required for independent living and represents the basis for other activities, including work and leisure. Accordingly, interventions targeting functioning should address many aspects of disability: activity limitations and participation restrictions, physical activity and metabolic abnormalities, disturbed circadian rhythm, cognitive impairment and finally daily perceived stress.

The main focus of Affective disorders: eliminate WArning signs And REstore functioning (AWARE) is to improve functioning and QoL in patients with affective disorders in everyday life using a comprehensive multimodal 360° intervention. The AWARE intervention represents an integrated treatment avenue to improve functioning in patients with affective disorders.[29] Including the experiences from our previous randomised studies[30 31] and the described pilot study,[16] we have established a manual used for the present intervention (*Decker L, Schwarz R, Vinberg M, AWARE, Intervention manual, Unpublished*). Currently, other multimodal studies, including patients in the more *impaired stages of the disorders* are scarce.

METHODS AND ANALYSIS

Aim

This pragmatically randomised controlled trial aims to investigate the effect of a 360° multimodal intervention based on the ICF Brief Core Set for BD[32] and UD[33] targeting functioning in the AWARE arm in comparison with treatment as usual (TAU). See online supplemental figure 1 for a flow diagram of the trial.

Main hypothesis

It is hypothesised that the AWARE arm in comparison with TAU will: (1) improve observed ADL ability assessed with the Assessment of Motor and Process Skills (AMPS)[25] (primary outcome), (2) improve functioning assessed with Functioning Assessment Short Test (FAST)[34] and WHO Disability Assessment Schedule V.2.0 (WHODAS)[35] and QoL measured with WHO Quality of life questionnaire (WHOQoL)[36] (secondary outcomes). In addition, exploratory analyses will involve investigation of the effects of AWARE on cognition and physical health (tertiary outcomes).

Participants

Study participants will be 120 outpatients. Inclusion criteria are

- men or women, age 18–65 years with a diagnosis of BD or major depressive disorder by WHO International Classification of Disease 10th edition (ICD-10) diagnostic criteria.
- Current state of remission or partial remission (defined as Hamilton Depression Rating Scale, 17-items (HDRS-17)[37] and Young Mania Rating Scale (YMRS)[38] scores of ≤14).
- Impaired functioning defined as a score ≥11 according to the FAST.[34]
- Participants must be able to participate in two-thirds of the planned visits.

During the intervention, ongoing psychotherapy and outpatient medical treatments are all allowed.

Due to the pragmatic clinical design chosen to obtain high generalisability of results from the trial, bearing in mind the potential of translating the present results into everyday clinical settings, only a few exclusion criteria are applied. Exclusion criteria are;

- Severe somatic disorder interfering with daily living.
- Ongoing alcohol or substance abuse.
- Electroconvulsive therapy treatment within last 3 month before inclusion.
- Dementia or inability to cooperate with the study, including inability to speak and read Danish.

Patients will be invited to participate in the study following referral from the Psychiatric Centers in the Capital Region of Denmark, private practitioners and advertising through patients' advocacy.

Screening

The trial staff will establish the first contact via the patients' therapists. The patients will be given a booklet and the therapist refers to the project and the project manager. A researcher contacts interested patients and they will have a brief screening by telephone, in which basic study inclusion and exclusion criteria are reviewed. Eligible patient will be invited to an in-person conversation about the study, where participant information will be elaborated and where they can ask questions. The reflection time between the oral/written information and the later signature on the consent form will be estimated to a few days, but as noted in the participant information, according to the individual's needs.

Patient and public involvement

No patient involved.

Experimental design

The participants will be on inclusion, be randomised to participate in either 6 months of AWARE treatment or TAU. The control group will receive TAU consisting of the standard out patient mental health service routines in The Capital Region of Denmark, that is, treatment at their general practitioner, private psychiatrists or psychologists or the local community mental health Centre.

Randomisation and blinding

A total of 120 patients (completers 104, see 'Power calculation' section) will be randomised, and stratification is done for age (18–34 years vs 35–65 years), sex and diagnosis (BD vs UD) using Research Electronic Data Capture (REDCap).[39] The method used for randomisation is block randomisation to ensure a balance in sample size across groups. Block sizes are randomly varied intermittently between sizes of 2, 4 and 6, with randomly varying order of treatment allocation within blocks, to ensure the sequence from becoming predictable and avoiding possible selection bias.

The study is outcome-assessor-blind, and the allocation will under no circumstances be revealed to the outcome assessors. Allocation is done by the therapist, who will perform the randomisation in REDCap following each eligibility assessment. The allocation coding file in REDCap is accessible to neither the therapist performing the randomisation, the outcome assessors or anyone involved in the project, as user rights to access the coding file in REDCap are not granted. Participants will be instructed not to disclose any information concerning their treatment allocation during endpoint assessments.

Diagnostic interview and ratings

Participants will be rated in a face-to-face interview using semistructured interviews: to verify the psychiatric diagnosis, the participants will undergo a diagnostic interview using The Mini International Neuropsychiatric Interview.[40] The FAST is an interviewer–administered interview covering six areas of functioning: autonomy, occupational functioning, cognition, financial issues, interpersonal relationships and leisure time.[34] A FAST total score above 11 indicates functional impairment, with the thresholds of severity being: no impairment in functioning (scores between 0 and 11), mild impairment (scores between 12 and 20), moderate impairment (scores between 20 and 40) and severe impairment (scores between 40 and 72).[41] The FAST interview is used as initial screening regarding the functioning of participant candidates and is also administered at baseline and endpoint. A neuropsychological battery previous used by our group will be conducted at baseline and endpoint,[16] using Screen for Cognitive Impairment in Psychiatry—Danish version (SCIP-D),[42 43] Danish Adult Reading Test[44] and Trail Making Test A, Trail Making Test B.[45]

AMPS is a standardised observation-based assessment providing measures of the quality of ADL task performance.[25] The AMPS ADL ability measures are found valid and reliable across diagnostic groups, including mental disorders, and has high interrater reliability and are found to be sensitive over time to changes in ADL ability.[46 47] The procedure of administrating the AMPS is: during an interview, the patient selects two ADL tasks to perform. The tasks must be well known, meaningful and challenging for the patient to perform. In the manual, there are currently 125 standardised tasks calibrated in terms of the severity of the task. The ADL motor ability measure indicates how much effort or clumsiness the patient demonstrates, and the ADL process ability skills measure how timely and well organised the patient was during the observation. Both scales also reflect safety (risk of personal injury or environmental damage) and independence (need for physical or verbal assistance).

Participants' ADL task performance is assessed with AMPS at baseline and endpoint. In addition, participants perceived quality of ADL task performance is assessed at baseline and endpoint using the activities of daily living interview.[48] Affective symptoms are assessed using HDRS-17 and YMRS at baseline and after the intervention. Participants in the intervention group are further assessed after 3 months of the intervention using FAST, HDRS-17 and YMRS. Participants will undergo Standardised Assessment of Personality-Abbreviated Scale[49] at baseline. For further overview of the timing of the assessments, interviews and questionnaires, please see table 1.

Physical assessment

Physical assessment includes height and weight, waist circumference, blood pressure, pulse, assessment for medical side effects using a validated scale[50] and blood sampling biomarkers related to glucose and fat metabolism and inflammation. The latter includes plasma/serum concentrations of triglyceride, heamoglobin A1c and high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, lipid fraction and C reactive protein, and also including routine blood samples; haemoglobin, leucocytes, thrombocytes, sodium, potassium, creatinine, blood calcium,

Table 1 Schedule of enrolment and assessment

Timepoint	Preintervention	Baseline (preallocation) day 0	Midway 3 months	Endpoint 6 months	Follow-up 24 month
Enrolment:					
Project information; written and oral	X				
Written informed consent	X				
Eligibility assessment	X				
Assesments:					
Mood ratings	X	X	X	X	X
Primary outcome					
AMPS		X		X	
Secondary outcome					
FAST	X	X	X	X	X
PSS		X		X	X
WHODAS		X		X	X
WHOQoL		X		X	X
Tertiary outcome					
SCIP-D		X		X	X
TMT-A		X		X	X
TMT-B		X		X	X
Physical health		X		X	X
Other measures					
ADL-I		X			
CISS		X		X	X
COBRA		X		X	X
CTQ		X			
DART		X			
EPQ		X			
IPAQ		X		X	X
Life event questionnaire		X		X	X
OASIS		X		X	X
PSQI		X		X	X
SAPAS		X			
VSSS-54				X	

ADL-I, Activities of Daily Living Interview; AMPS, Assessment of Motor and Process Skills; CISS, Coping Inventory for Stressful Situations; COBRA, Cognitive Complaints in Bipolar Disorder Rating Assessment; CTQ, Childhood Trauma Questionnaire; DART, Danish Adult Reading Test; EPQ, Eysenck Personality Questionnaire Inventory; FAST, Functional Assessment Short Test; IPAQ, International Physical Activity Questionnaire; OASIS, Overall Anxiety Severity and Impairment Scale; PSQI, The Pittsburgh Sleep Quality Index; PSS, Cohen's Perceived Stress Scale; SAPAS, Standardised Assessment of Personality—Abbreviated Scale; SCIP-D, Screen for Cognitive Impairment in Psychiatry—Danish version; TMT-A, Trail Making Test A; TMT-B, Trail making Test B; VSSS-54, Verona Satisfaction Scale-Affective Disorder; WHODAS, WHO Disability Assessment Schedule 2.0; WHOQoL, WHO Quality of Life.

aspartate aminotransferase, bilirubin, alkaline phosphatase and thyroid-stimulating hormone (TSH).

Questionnaires

For an overview of the used questionnaires and timing, please see table 1. Patients reported outcome measures obtained via surveys at baseline and after 6-month intervention (or TAU) are: general health (a modified version of the Danish National Health Profile survey,[51] QoL (WHO Quality of life (WHOQoL),[36] disability (WHODAS),[35] stress (Cohen's Perceived Stress Scale (PSS),[52] anxiety (Overall Anxiety Severity and Impairment Scale),[53] cognitive impairment (Cognitive complaints in bipolar disorder rating assessment),[54] sleep (Pittsburgh Sleep Quality Index),[55] physical activity and exercise (International Physical Activity Questionnaire),[56] coping strategies (Coping Inventory for Stressful Situations),[57] recent and former severe life events (Life event questionnaire used by Kendler and colleagues (Danish version)),[58] depressive symptoms (Major Depression Inventory),[59] manic symptoms (Altman Self-Rating Mania Scale)[60] and, at follow-up, the Verona Satisfaction Scale-Affective Disorder[61] measuring level of satisfaction with resent psychiatric treatment. At baseline, only personality dimensions will be assessed using the Eysenck Personality Inventory[62] and childhood traumas using the Childhood Trauma Questionnaire.[63] These questionnaires will help

us to cover the 360° assessment and to evaluate the intervention. The questionnaires are used in clinical settings, translated into validated Danish versions and used in previous studies from our group.[16 64]

The intervention

The present intervention targets multiple aspects of the described enhancers of functioning based on the ICF Brief Core Set: (1) ADL ability as a part of carrying out daily routines, (2) mood symptoms, medication and side effects, (3) social, relatives and network, (4) physical health, including body mass index (BMI), biomarkers and exercise, (5) cognition, circadian rhythm measured as sleep quality and coping (stress reduction). Based on the assessments, a transdisciplinary group of clinical experts (medical professionals, nurses, social workers and occupational therapists) within the field of affective disorders will conduct a targeted individual intervention profile based on the five described pillars of ICF. The group is headed by MV (psychiatrist). The goals for the intervention are based on the areas where the patients have the lowest scores (most severe impairment). An intervention manual is developed and targets the described enhancers of functioning based on the comprehensive assessment procedure (see the Introduction section).

The AWARE intervention will include 6–14 visits. Visits 1–2: feedback on the 360° baseline assessments, including the results of all the questionnaires, the ADL observation and the physical and cognitive evaluation. Based on these goals, the individualised AWARE intervention will be set. Participants at first visit are the patient, a medical professional, an occupational therapist and other transdisciplinary professionals. This transdisciplinary group will conduct a targeted individual intervention profile, which will be discussed and shaped with the patients aiming to select one to three main goals (eg, problems with performing daily routines and mood symptoms). Visits 3–13: intervention sessions; the intervention will address the prioritised treatment goals following the intervention manual that describes each area in detail, and at each intervention visit, either a medical professional or an occupational therapist will be present. If relevant, relatives are involved in one or more intervention visits. A midway evaluation meeting with the patient will be held after 3 months of intervention, with an assessment of functioning (FAST) and mood symptoms (HDRS-17 and YMRS). There will be a transdisciplinary session after visit 13 aiming to perform a status and a treatment plan involving the relevant actors in the further treatment, for example, relatives, social workers, the general practitioner or psychiatrist. Visit 14. The last visit; the patient's evaluation of the intervention and the achieved goals. The patient is required to participate in two-thirds of the planned visits during the intervention period to complete the intervention. The intervention will be optimised following the template for intervention description and replication checklist and guide.[65]

Outcomes

The primary outcome is changes in ADL motor and process ability measures from baseline to endpoint according to scores on the AMPS. Patients will be observed and rated at baseline and after 6 months endpoint by blinded personnel trained in AMPS assessment.

Secondary outcomes are changes from baseline to endpoint in functioning using FAST and WHODAS V.2.0. and in QoL and stress using WHOQoL and PSS. Tertiary outcomes are cognition using a composite score assessed at baseline and after endpoint by blinded raters, and physical health change in observed side effects, BMI and biomarkers related to glucose and fat metabolism and inflammation.

Power calculation

Power calculation is based on changes in ADL ability on AMPS during the 6 months of study period. A clinically relevant difference between the two groups in change is defined as ≥0.3 logits with a mean SD of 0.3 logits. The statistic power to detect a clinically relevant improvement of ≥0.3 logits in the treatment group is 95% with alpha=0.05 for two-sample comparison of means including 104 patients. https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx. Assuming a 10%–15% dropout rate from baseline to treatment completion, we will recruit 120 participants to achieve a full 6-month completion and data set for 104 patients. The current dropout rate at endpoint (6 months) is 9% based on the first 11 patients.

Statistical analyses

Data from the randomised patients will be collected until dropout or the end of the study period. Differences from baseline (T_0) to after six months intervention (T_6) will be analysed, first unadjusted and then adjusted for age, sex, diagnosis, previously number of affective episodes and significant differences in current medication if these variables present with a $p \leq 0.1$ in univariate analyses (independent t tests). All comparative analyses between the treatment groups will be intention-to-treat using the last observation carried forward for missing values. Data will be analysed using repeated measures analyses of covariance with treatment group (AWARE vs TAU) as the between-group factor, time (baseline to 6 months) as the within-subject factor and adjustment for stratification variables (age, gender and diagnosis) to minimise effects of any baseline imbalances. The statistical threshold for significance is $p \leq 0.05$ (two tailed).

Data management

Personal information is obtained during the assessment of the participants, and data from patient records can be obtained as well if needed. Signed consent forms are uploaded to REDCap and kept in paper form in a locked filing cabinet. Data from neuropsychological test, questionnaires, demographics and interviews are entered into the REDCap database. The database REDCap meets the Good Clinical Practice requirements for data management and

storing. On exclusion or withdrawal from the study, the reason will be recorded. The Danish Data Protection Agency can conduct inspections to ensure that data management is handled in agreement with the legislation. The Danish Data Protection Agency operates independently of the study.

DISCUSSION

The present study investigates the effect of multimodal 360° intervention on ADL, functioning and QoL of BD and UD patients in remission or partial remission. Functioning is increasingly recognised as a central outcome in these patient groups and might even be considered more important than the syndromal outcome.

A recent review article suggests functional outcomes as a primary outcome in future studies of BD and finds a current lag of intervention studies specifically targeting functioning.[66] To the best of our knowledge, previous available intervention studies have primarily focused on cognitive aspects of functioning.[67 68] Several psychosocial interventions in adjunct to psychopharmacology have shown effectiveness in the treatment of BD, but none specifically targeting functioning as a primary outcome in patients in a remitted state.[69]

Strengths

A considerable strength of the AWARE study is the comprehensive 360° assessment, including the most known factors contributing to impaired functioning in BD and UD.[66] Therefore, we can base the individualised intervention on understanding the specific factors associated with, and causing, the impaired functioning of each patient. Considering the shortcomings of current available treatments and the scarcity of multimodal intervention studies as previously mentioned, we consider the AWARE intervention of great relevance in affective disorders.

To assess the participants' ability to perform ADL, we have explicitly chosen a performance-based assessment (AMPS) conducted in the patient's home surroundings. These observations are likely a better proxy to understand the daily hassles patients encounter than assessments conducted in clinical settings, and they might contribute to a greater focus on improving functioning.[70] In addition to AMPS and FAST, patients self-perceived level of functioning and ADL ability is assessed using WHODAS and ADL-I. Few previous studies include more than one measure of functioning, with some using observer-based measures and others using self-reported measures.[66] When assessing impairment in patients with BD, correlation between patients' subjective experience and objective measures is not present in all cases. This discrepancy might result from patients' own experience of impairment being influenced by subclinical depressive symptoms.[16]

The study has few exclusion criteria, making the study representative of, and applicable to, 'real-life' patient populations.

The randomised, controlled design of the study with blinded outcome assessment is an advantage as it reduces experimental bias.

LIMITATIONS

The timeframe of the AWARE intervention in the present study is 6 months. Some of the included patients might have years or even decades with significant functional impairment. Nevertheless, 6 months is a limited span of the treatment, and more time might be necessary to gain noteworthy improvements in functioning. Even if the intervention group shows significant improvement in functioning and QoL after 6 months, the improvement might not be sustained. To address the long-term effects, a 24-month follow-up is planned.

Current, ongoing substance abuse is one of the few exclusion criteria. Previous studies have found substance abuse to be one of the factors associated with functional impairment.[71] However, this is not addressed in the AWARE treatment programme, due to presumed problems with compliance and completion accompanying the substance abuse.

A crucial challenge for recruitment in this study is that some patients might be unwilling to participate due to the AMPS observation performed in the patients' home, which some may find 'intrusive'. So far, one of the 32 patients who has been screened for the trial has declined participation for this reason. Only two other patients have declined participation (one due to anxiety symptoms and the other because of lack of energy). In general, we expect patients to be positive towards participation, as the intervention targets vital areas of functioning persisting despite the patients' previous treatment/ treatments. The current participation rate is 91%.

ETHICS AND DISSEMINATION

The Regional Ethics Committee in the Capital Region of Denmark (protocol number H-20029748) approves the AWARE trial and the Danish Data protection agency (j. nr. P-2020–1216), and the trial was registered at Clinicaltrials.gov on 8 January 2021. The project is following the ethical aspects as declared in the Helsinki-Declaration 2. Important changes in the protocol will be reported to the Ethics Committee in the Capital Region of Denmark and the Danish Data Protection Agency. All potential participants will have written and oral information about the trial before informed consent is obtained. Participants are informed that they can withdraw from the trial at any time without this having any effect on their course of treatment thereafter. The Danish Data Protection Agency is at any given time entitled to audit trial conduct.

The study results will be disseminated by peer-review publications

If the present intervention shows a beneficial outcome for the AWARE arm, it can be used as a template for future treatment, addressing disability with a transdiagnostic approach (affective disorders, anxiety disorders and psychotic

disorders). This would support the use of specialised cross-disciplinary teams capable of bridging the different sectors to create a tailored individualised and cooperative intervention focusing on improving daily functioning.

There are no known or expected direct risks associated with participation in the study. Participants will be asked about adverse events at midway evaluation, endpoint interview, and in case of drop-out from the study. Data will be collected I REDCap.

Trial status

Enrollment of patients began on 1 February 2021. As of 1 October 2021, 32 patients were screened, and 29 patients included in the AWARE study. Recruitment completion is planned for 31 December 2022.

Author affiliations
[1]Research Unit, North Zealand Psychiatric Center, Hillerod, Copenhagen, Denmark
[2]Department of Clinical Medicine, University of Copenhagen Faculty of Health and Medical Sciences, Copenhagen, Denmark
[3]Department of Physiotherapy and Occupational Therapy, Metropolitan University College, Copenhagen, Denmark
[4]Department of Dialectical Behavior Therapy, North Zealand Psychiatric Center, Hillerod, Denmark
[5]Neurocognition and Emotion in Affective Disorder (NEAD) Group, Copenhagen Affective Disorder Research Centre (CADIC), Psychiatric Centre Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark
[6]Department of Psychology, University of Copenhagen, Copenhagen, Denmark
[7]Copenhagen Affective Disorder Research Centre (CADIC), Psychiatric Centre Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark

Contributors All authors meet the four criteria for authorship, as stated be ICMJE. The primary areas of contribution from each of the authors are listed below. MV conceived the study together with LD. MV, LD and RS wrote the study protocol. MV obtained the required funding for the study along with LD. MV and LD developed the intervention program and LD, RS and MV wrote the intervention manual. KWM and LVK contributed to revising the study protocol. IS and RS set up the study, assessments and questionnaires in the REDCap program. RS is responsible for carrying out the treatment with assistance from occupational therapists and nurses at Psychiatric Centre North Zealand, and under supervision of MV. RS has the primary responsibility for recruitment, enrolment, data collection, data analysis and interpretation of the data under supervision of MV. All authors have read and approved the present manuscript.

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Competing interests KWM has received consultancy fees from Lundbeck and Janssen-Cilag in the past 3 years. LVK has within the last 3 years been a consultant for Lundbeck and Teva. MV discloses within the last three years consultancy fees from Lundbeck, Sunovion and Janssen-Cilag. RS has received consultancy fees from Lundbeck and in the past 3 years.

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ORCID iDs
Rasmus Schwarz http://orcid.org/0000-0002-8808-1866
Lars Vedel Kessing http://orcid.org/0000-0001-9377-9436

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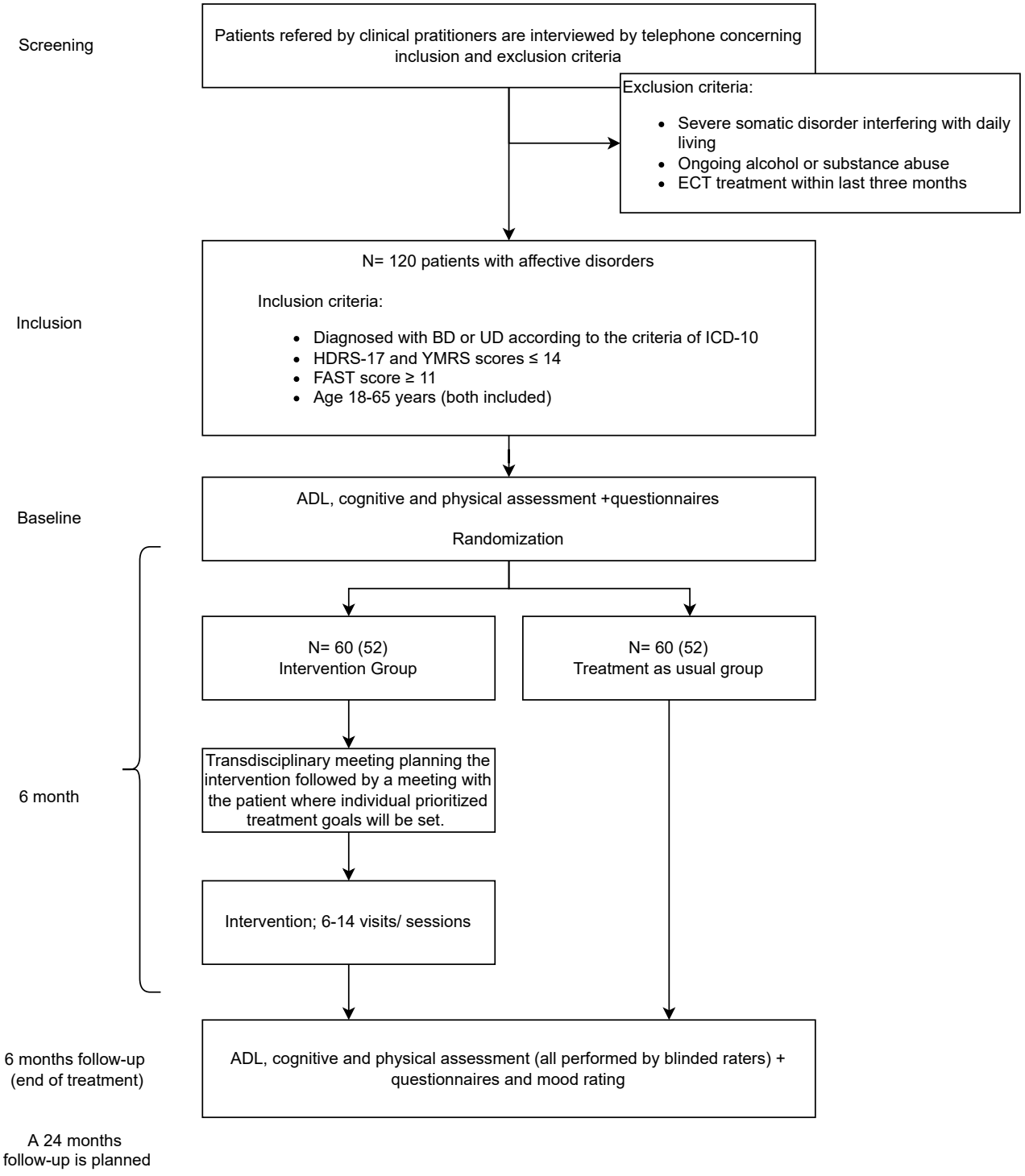
Screening
Patients refered by clinical pratitioners are interviewed by telephone concerning inclusion and exclusion criteria
Exclusion criteria:
Severe somatic disorder interfering with daily living
Ongoing alcohol or substance abuse
ECT treatment within last three months
Inclusion
N= 120 patients with affective disorders
Inclusion criteria:
Diagnosed with BD or UD according to the criteria of ICD-10
HDRS-17 and YMRS scores ≤ 14
FAST score ≥ 11
Age 18-65 years (both included)
Baseline
ADL, cognitive and physical assessment +questionnaires
Randomization
N= 60 (52)
Intervention Group
N= 60 (52)
Treatment as usual group
6 month
Transdisciplinary meeting planning the intervention followed by a meeting with the patient where individual prioritized treatment goals will be set.
Intervention; 6-14 visits/ sessions
6 months follow-up
(end of treatment)
ADL, cognitive and physical assessment (all performed by blinded raters) + questionnaires and mood rating
A 24 months
follow-up is planned

Paper II

Rasmus Schwarz, Kamilla Woznica Miskowiak, Mie Skovmand Christensen, Lars Vedel Kessing, Maj Vinberg. “Affective disorders: eliminate WArning signs And REstore functioning: AWARE. Results from a randomised controlled multimodular intervention study targeting functioning in patients with affective disorders.” [Under review, Psychological Medicine].

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Affective disorders: eliminate WArning signs And REstore functioning: AWARE. Results from a randomised controlled multimodular intervention study targeting functioning in patients with affective disorders

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Corresponding Author:	Rasmus Schwarz, M.D. Mental Health Centre, Northern Zealand, Copenhagen University Hospital Hillerød, DENMARK
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Mental Health Centre, Northern Zealand, Copenhagen University Hospital
Corresponding Author's Secondary Institution:	
First Author:	Rasmus Schwarz, M.D.
First Author Secondary Information:	
Order of Authors:	Rasmus Schwarz, M.D.
	Kamilla Woznica Miskowiak
	Mie Skovmand Christensen
	Lars Vedel Kessing, M.D., D.M.Sc.
	Maj Vinberg, M.D., D.M.Sc.
Order of Authors Secondary Information:	
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Affective disorders: eliminate WArning signs And REstore functioning: AWARE. Results from a randomised controlled multimodular intervention study targeting functioning in patients with affective disorders

Rasmus Schwarz[1,2], Kamilla Woznica Miskowiak[3,4], Mie Skovmand Christensen[1], Lars Vedel Kessing[2,3], Maj Vinberg[1,2]

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Corresponding author: Rasmus Schwarz, rasmus.moeskjaer.schwarz@regionh.dk
Dyrehavevej 48, 3400 Hillerød, Denmark
Orchid ID: 0000-0002-8808-1866

[1] The Early Multimodular Prevention and Intervention Research Institution (EMPIRI), Mental Health Centre, Northern Zealand, Copenhagen University Hospital – Mental Health Services CPH, Copenhagen, Denmark
[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen
[3]Copenhagen Affective Disorder Research Centre (CADIC), Psychiatric Centre Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark
[4]Department of Psychology, University of Copenhagen, Copenhagen, Denmark

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Abstract

Background: There is a compelling need for innovative intervention strategies for patients with affective disorders, given their increasing global prevalence and significant associated disability and impaired functioning. This study aimed to investigate whether a comprehensive multimodule individualised intervention (AWARE), targeting known mediators of functioning, improves functioning in affective disorders.

Methods: AWARE was a randomised, controlled, rater-blind clinical trial conducted at two centres in the Capital Region of Denmark. Participants were adults with bipolar disorder or major depressive disorder and impaired functioning. Participants were randomised to the six-month AWARE intervention or treatment as usual (TAU). The AWARE intervention is based on the International Classification of Functioning, Disability and Health (ICF) Brief Core Set for Bipolar and Unipolar Disorder.

The primary outcome was observation-based functioning using the Assessment of Motor and Process Skills (AMPS). Secondary outcomes were functioning, QoL, stress and cognition.

Results: Between February 2021 and January 2023, 103 patients were enrolled; 50 allocated to AWARE treatment and 53 to TAU (96 included in the full analysis set). There was no statistically significant differential change over time between groups in the primary outcome (AMPS), however, both groups showed a statistically significant improvement at endpoint. The AWARE intervention had a statistically significant effect compared with TAU on secondary outcomes of patient-reported stress and cognition, and functioning.

Conclusion: Compared with TAU, The AWARE intervention was ineffective at improving overall functioning on the primary outcome, presumably due to the short duration of the intervention. Further development of effective treatments targeting functioning is needed.

Trial Registration: Clinicaltrials.gov, NCT04701827

Introduction

The World Health Organization (WHO) ranks unipolar major depressive disorder (UD) and bipolar disorder (BD) among the leading causes of disability globally, with predictions of a further growing burden of these disorders (World Health Organization, 2017). The 1-year prevalence of UD is approximately 3-6 %, and around 1 % for BD (Kessing, 2020). The impact of affective disorders is considerable both from an individual and societal viewpoint, affecting many aspects of life and associated with both low quality of life, medical conditions, and a decreased lifespan of 8-12 years (Kessing, Ziersen, Andersen, & Vinberg, 2021). The impact on functional impairment is well established, not only during acute mood episodes and syndromic states but also during remission (Léda-Rêgo, Bezerra-Filho, & Miranda-Scippa, 2020). On the other hand, the effect of medical treatments on improving and restoring function is not as prominent as the effect on depressive symptoms (Kessing, Hansen, & Andersen, 2004; Sheehan, Nakagome, Asami, Pappadopulos, & Boucher, 2017). It is critical for patients to obtain and consistently retain normal functioning during remission. Despite the general recognition of functioning as a central and meaningful outcome in affective disorders (Chen, Fitzgerald, Madera, & Tohen, 2019; McKnight & Kashdan, 2009), few studies have tested interventions for improving functioning as the primary outcome (Torrent et al., 2013), with most research mainly addressing cognition (Miskowiak et al., 2022). Although cognitive remediation trials show promising effects on cognitive functions, cognitive gains often fail to improve patients' real-live functioning due to limited transfer to real-world functioning, and investigation of the effects of multimodal interventions is recommended (Miskowiak et al., 2022; Samamé, Durante, Cattaneo, Aprahamian, & Strejilevich, 2023).

The primary aim of the present randomised controlled trial (RCT) study was therefore to investigate whether a multimodal comprehensive 360-degree intervention named Affective disorders: eliminate WArning signs And REstore functioning (AWARE) improve global functioning in patients with affective disorders. The hypothesis was that patients receiving the AWARE intervention would achieve greater improvement in functioning compared with patients receiving treatment as usual (TAU).

Methods

Study design

The study was a randomised open-label clinical trial, with two treatment arms and blinded outcome assessment (rater-blind). The study was conducted at two centres in the Capital Region of Denmark (Psychiatric Centre Copenhagen and Psychiatric Centre Northern Zealand). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by The Regional Ethics Committee in the Capital Region of Denmark (protocol number H-20029748). All patients were provided oral and written information about the trial before written informed consent was obtained. Data permission was obtained from the Danish Data Protection Agency (j.nr. P-2020-1216). The study was registered at Clinicaltrials.gov. (NCT04701827) before inclusion started (registered on 8 January 2021) and a detailed study protocol has been published (Schwarz et al., 2022). A minor update in the trial registry was sent to Clinicaltrials.gov on 23 February 2022, regarding inclusion criteria age range (corrected from age 18-60 to 18-65) and target sample size (corrected from 140 to 120), as the original numbers were taken from an early protocol draft and did not reflect the final study design (as published in the final study protocol). The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) Statement (Moher et al., 2010). Patients were first recruited for the study on February 1, 2021.

Participants

The patients were assessed and diagnosed by specialists in psychiatry according to the ICD-10 (World Health Organization, 2005) and were asked to participate if the clinicians found that their overall functioning was impaired.

Inclusion criteria were: Men or women, age 18–65 years with a diagnosis of BD or unipolar major depressive disorder by WHO International Classification of Disease 10th edition (ICD-10) diagnostic criteria; current state of remission or partial remission (defined as Hamilton Depression Rating Scale, 17-items (HDRS-17) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) scores of ≤14); impaired functioning defined as a score ≥11 according to the

Functional Assessment Short Test (FAST) (Rosa et al., 2007); and ability to participate in two-thirds of the planned intervention visits. Exclusion criteria were: Severe physical disorder interfering with daily living; ongoing alcohol or substance abuse; electroconvulsive therapy treatment within the last 3 months before inclusion; dementia or inability to cooperate with the study, including inability to speak and read Danish. If patients did not fulfill the criteria for current state of remission or partial remission at initial screening, the patient was allowed further screenings during the inclusion period and was included if remission or partial remission was reached.
Sex/gender was collected as binary data (male and female). All participants gave written informed consent before participating in the study.

Randomisation and masking

The included patients were randomised with a 1:1 ratio to either 1) The intervention group with AWARE treatment + standard treatment/treatment as usual or 2) the control group with standard treatment/treatment as usual alone (TAU). Stratification was done for age (18–34 years vs 35–65 years), sex and diagnosis (BD vs UD). Block randomisation was used to ensure a balance in sample size across groups with randomly varied block sizes (2-6), and randomly varying order of treatment allocation within blocks. The random sequence was generated by an external clinical assistant, who did not participate in any other part of the study, and who was not involved in conducting the study. All participants were enrolled by the primary investigator (RS) and allocation was done in REDCap using the encoded random sequence (Harris et al., 2009). Due to the nature of the intervention the trial was an open-label design with no masking of allocation for the participants or the clinicians giving the intervention. The study was outcome assessor-blinded, and all outcome assessors were external assessors masked for allocation who did not participate in the treatment of participants or conducting the trial. Patients were carefully instructed not to disclose any information concerning their treatment allocation during endpoint assessments. FAST was the only outcome measure assessed unblinded (blinding of FAST was initially planned but due to practical reasons not possible).

Procedures

Upon referral to the study, patients' diagnosis was confirmed with The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and participants were assessed for eligibility according to the inclusion/exclusion criteria. Upon inclusion, the primary therapist (RS) implemented randomisation in a consecutive manner, with participants being informed about their allocation. Baseline assessments were conducted in the week preceding the randomisation. Blinded assessors carried out evaluations at endpoint (6 months after the randomisation date). These assessments comprised an assessment of functioning, mood ratings, cognitive testing, and questionnaires addressing quality of life, subjective cognitive complaints, and functioning. A detailed description was published in the study protocol (Schwarz et al., 2022).

The intervention

The manualised intervention has been described in detail elsewhere (Schwarz et al., 2022). In summary the AWARE intervention is a comprehensive multimodule individualised intervention, specifically targeting known mediators of functioning in these patients. The intervention is based on the International Classification of Functioning, Disability and Health (ICF) Brief Core Set for UD and BD (Ayuso-Mateos, Avila, Anaya, Cieza, & Vieta, 2013; Cieza et al., 2004). The five modules of the intervention targeted: "*1. ADL (Activities of Daily Living) ability as a part of carrying out daily routines; 2. Mood symptoms, medication and side effects; 3. Social, relatives and network; 4. Physical health, including Body Mass Index (BMI), biomarkers and exercise; 5. Cognition, circadian rhythm measured as sleep quality, and coping (stress reduction)"* (Schwarz et al., 2022).

Patients in the control group received TAU consisting of standard treatment in Denmark. Primary care outpatient treatment consists of treatments given by family doctors or private psychiatrists. Secondary care outpatient treatment can consist of treatment given by psychiatrist, psychologists, nurses, and social workers, as both group and individualised therapy and hospitalisation. Treatments are public and free of charge.

Outcomes

Primary outcome was change in Activities of Daily Living (ADL) motor and process ability from baseline to endpoint according to scores on the Assessment of Motor and Process Skills (AMPS)

(Fisher & Jones, 2012). The AMPS is sensitive over time to changes in ADL ability and has a high inter-rater reliability, and a clinically relevant change in AMPS score is considered as 0.3 logic (Fisher & Jones, 2012). AMPS is a standardised observation-based assessment of two individually selected well known, meaningful and challenging ADL Tasks. The evaluation comprises scores for ADL Process skills (level of timeliness and organization skills) and ADL Motor skills (level of physical effort/clumsiness), with both scores also reflecting the safety and independence of the performance. A detailed description of the AMPS instrument is found in the study protocol (Schwarz et al., 2022). All AMPS assessments were conducted in the patient's homes.

Secondary outcomes were changes from baseline to endpoint in self-reported functioning using WHO Disability Assessment Schedule (WHODAS 2.0.) (Organization., 2010) and FAST (Rosa et al., 2007), in quality of life and stress using WHO Quality of Life (WHOQOL) (Group, 1998) and Cohens Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983), and cognition objectively measured with SCIP (Screen for Cognitive Impairment in Psychiatry) (Purdon, 2005) and Trail Making A and B (Reitan, 1992). Tertiary/other prespecified outcomes were patient reported cognition using Cognitive complaints in bipolar disorder rating assessment (COBRA) (Rosa et al., 2013) and functioning measured with the ADL-Interview (ADL-I) (Wæhrens, Kottorp, & Nielsen, 2021). An overview and description of assessment scales and instruments can be found in Table 3 in the Supplementary Materials.

Outcome assessments were done at six months by calibrated AMPS raters (primary outcome) and research-trained, non-specialist, medical doctors. Assessment of all outcomes and completion of participant self-reported questionnaires were made at baseline and endpoint (six months post-randomisation).

Safety Assessment

Assessment of safety and adverse events was done systematically at months three and six of the intervention (mid-way and endpoint respectively) by query and registration of psychiatric hospitalisations.

Statistical analysis

The statistical analyses were defined á priori and conducted using an intention-to-treat (ITT) approach (Schwarz et al., 2022). Differences in the primary and secondary endpoints were analysed between the intervention and control group using an Analysis of Covariance (ANCOVA) model both unadjusted using only the baseline value of the endpoint as a covariate, and adjusted with sex, age, diagnosis and number of affective episodes as covariates. Outcome mean differences, 95% CIs, and p values are provided. Effect sizes were calculated as partial eta-squared (η^2_p). In addition, for the primary outcome, the change from baseline to endpoint (delta) was analysed between groups, and the number of responders in each group was compared. Significance levels were set at p values of below 0.05. Statistical analysis was performed in IBM SPSS Statistics.

Results

Between February 1, 2021, and January 31, 2023, 103 patients were enrolled and randomised. For full overview of screening, inclusion, and completion see Figure 1. Sociodemographic and clinical characteristics are presented in Table 1. There were no statistically significant differences in baseline characteristics between the two groups.

The overall dropout rate of both treatment arms was low, with no statistically significant difference between the two groups (Fishers Exact Test, P= 0.206); AWARE 2.0% (1/50) and TAU 9.4% (5/53), however, the number of patients assessed for the primary outcome (AMPS) at endpoint in the AWARE arm was significantly higher; 96.0% (48/50), compared with the TAU arm; 71.7% (38/53) (Fishers Exact Test, P=0.001).

Table 4, supplementary materials, shows the number of AWARE intervention sessions given to the intervention group, as well as the content of other psychiatric treatments the patients in the intervention and control group received during the trial. There was no difference in the content of other psychiatric treatments received by the intervention and control groups during the trial.

Primary outcome

The ANCOVA analysis addressing the treatment effect of the AWARE intervention compared with TAU on the primary outcome showed no statistically significant differential change over time

between the two groups. The unadjusted model including only baseline AMPS scores as a covariate, to account for the difference in treatment effect from baseline to endpoint, showed no significant mean difference between groups on AMPS process of 0.07 (CI 95 -0.11 -0.26, p=0.434) and no significant mean difference on AMPS motor of 0.06 (CI 95 -0.17 -0.291, p= 0.590). Adjusting for age, sex, diagnosis and number of affective episodes still revealed no statistically significant differences, with an adjusted mean difference on AMPS process of 0.10 (CI 95 -0.10 -0.29, p=0.319) and an adjusted mean difference on AMPS motor of 0.11 (CI 95 -0.11 -0.33, p= 0.3).

Exploratory analysis on the primary outcome

The number of responders in each group (defined as a clinically relevant improvement of ≥0.3 logit from baseline to endpoint on AMPS) was 26 (54.2 %) in the AWARE group and 18 (47.4 %) in the TAU group, with no statistically significant difference between groups (Pearson chi-square p= 0.531). When analysing the change in AMPS score from baseline to endpoint individually in each group using a paired t-test, both groups showed a statistically significant and clinically relevant improvement (AWARE: Mean difference 0.34 CI 95 0.46- 0.21, p <0.001 and TAU: Mean difference 0.34 CI 95 0.51- 0.18, p <0.001). The change in unadjusted AMPS Process scores from baseline to endpoint is graphicly presented in Figure 2. We conducted four exploratory sub-analyses in relation to the primary outcome, stratifying on age group, disability pension status, cognitive impairment, and baseline HDRS score.

Subgroup analyses stratifying on cognitive impairment at baseline (SCIP total score below 70, AWARE n=21, TAU n=17) showed a significant and clinically relevant effect of the AWARE intervention vs TAU on AMPS Process in both unadjusted (B=0.33, CI 95 0.02; 0.64 p=0.038) and adjusted models (B=0.42, CI 95 0.10; 0.74 p=0.013) in the cognitively impaired group. The effect sizes were η^2_p =0.12 (medium effect size >0.06) and η^2_p =0.18 (large effect size >0.14) respectively. There were no significant results on any of the models stratifying on age group, disability pension status and baseline HDRS score (results not presented in detail).

Secondary outcomes

The secondary outcome analyses between the AWARE and TAU group are presented in Table 3. There was a statistically significant difference on the perceived stress scale (PSS) -2.86 (CI 95 -5.54;

-0.19, p= 0.036) between the two groups in the model adjusting for baseline value, and still present in the model also adjusting for age, sex, diagnosis, and number of depressive episodes; -2.89 (CI 95 -5.58; -0.207, p= 0.04). The effect size was η^2_p =0.047 and η^2_p =0.049, respectively (small effect sizes <0.06). Further, there was a statistically significant differential difference in processing speed (measured by Trail Making A) of -7.24 (CI 95 -13.72; -0.77, p= 0.029) between the two groups in the model adjusting for age, sex, diagnosis and number of depressive episodes (small to medium effect size, η^2_p =0.06). Finally, there was a statistically significant differential change in functioning measured by FAST (see, Table 2) with a large effect size (effect size Model 1; η^2_p =0.149, Model 2; η^2_p =0.0158). There were no statistically significant differential changes between groups on remaining secondary outcomes, neither on sub-domains of WHODAS and SCIP (results not presented in detail).

Tertiary outcomes

Other prespecified outcome measures were ADL-I (no significant difference between groups) and COBRA (significant difference in adjusted model; p=0.033, with a small effect size; η^2_p =0.051). Unadjusted means for sociodemographics, clinical status and outcome measures at follow-up/endpoint are presented in Table 6 in Supplementary Materials.

Adverse events/safety

Spontaneously reported adverse events were recorded at a visit midway through the treatment program (3 months) and at endpoint. No participants reported adverse events associated with the treatment, and the AWARE treatment group had a high completion of 98.0 % (49/50), which further indicates treatment safety. The AWARE and TAU groups did not differ in the number of patients hospitalised during the intervention period (AWARE; 4/49 (8.2 %), TAU 4/42 (9.6 %), Pearson chi-square p= 0.819).

Drop out analysis

The trial had an overall low dropout rate, however fewer patients in the control group participated in the assessment of the primary outcome at endpoint. A dropout analysis comparing baseline characteristics of the patients participating in the assessment of the primary outcome at endpoint

vs patients who did not was made for the control group. The results are presented in Table 5 in the Supplementary Materials. The number of patients with a history of previous psychiatric hospitalisation was significantly lower in the patients not participating in the assessment of AMPS at endpoint (10 patients (66.6%) vs 14 (36.8 %), Pearson chi-square p= 0.049). The non-completers had a lower SCIP score at baseline (61.40 SD 11.70) compared with the completers (70.37 SD 11.80). All remaining differences in baseline characteristics did not reveal statistically significance. The dropouts were also compared on selected endpoint outcomes/measures, however data on all these outcomes was not available for all 15 participants. The scores on HDRS were significantly higher in the dropouts (14.80 SD 5.76) vs completers (9.19 SD 5.57) (p=0.042). There was no statistically significant difference on remaining endpoints. As data on AMPS at endpoint only was missing for two patients (4.0 %) in the intervention group, a statistical comparison of these two participants was not carried out.

Post hoc statistical power analysis

The trial included 103 patients, which was less than the calculated sample size of 120 patients in the protocol (Schwarz et al., 2022). Despite intense recruiting efforts (the study was conducted during three lock downs due to COIVD 19) and an extension of the recruitment period, the desired sample size was not achieved. However, post hoc statistical power analysis confirmed sufficient power to detect the minimum clinically important difference in the primary outcome (0.3 logit on AMPS). The power was >80% to detect a significant group difference ($p<0.05$).

Discussion

This randomised open label outcome assessor blinded clinical trial study investigated the effects of a multimodule individualised six months intervention on functioning in 103 patients with unipolar depressive disorder and bipolar disorder in full or partial remission at baseline, with impaired functioning. Patients were randomised to either the AWARE intervention or TAU. Compared with TAU, we did not confirm the hypothesised effects on our primary outcome measure, AMPS, in improving daily functioning in the intervention group. Both the intervention group and TAU group did, however, improve significantly in observer-based functioning (AMPS score) from baseline to endpoint. Patients in the active group showed a significant improvement in the non-blinded

secondary outcome measure of self-reported functioning (FAST score) relative to TAU, which was of a large effect size. They also reported a significant reduction in perceived stress and improved self-reported cognitive functions compared with TAU with small effect sizes. Finally, patients in the active group showed improvement in an objective measure of attention (TMT-A). The intervention did not affect quality of life or improved the overall cognitive scores (SCIP).

Notably, post hoc subgroup analysis revealed a statistically and clinically significant effect of the AWARE intervention in the patients with cognitive impairment (measured on SCIP) at baseline. Strategy-based cognitive remediation was a central part of the intervention program, and it is plausible that patients with cognitive impairment would benefit from the intervention.

Comparison with findings from other studies

The largest study with functioning as the primary outcome (conducted in Spain) found an effect of a two-year functional remediation program compared with treatment as usual in patients with BD (primary outcome FAST) (Torrent et al., 2013). This study mainly differed from our present trial by having a less severely ill population due to rigorous inclusion criteria (clinical remission for three months before entering the trial and HDRS-17 score of ≤8). It is worth noting that the trial compared functional remediation with both TAU and psychoeducation, with the effect of functional remediation not being superior to psychoeducation. As a psychoeducational program is a central part of the standard treatment given in Denmark, the control group (TAU) in our trial may have benefitted from this, contributing to the presents study lack of effect on the primary outcome AMPS. The effect on FAST found in the Spanish study (Torrent et al., 2013), was however replicated in the present study. Another study testing a more integrative approach similar to the AWARE intervention was performed in 2020, but the trial was stopped prematurely due to the SARS-CoV-2 crisis(Valls et al., 2021). Future studies replicating the effect of functional remediation are currently planned (Accardo et al., 2023; Zyto, Jabben, Schulte, Regeer, & Kupka, 2016).Trials of cognitive remediation programs have shown varying degrees of effectiveness on functional outcomes (Gomes et al., 2019; Vicent-Gil et al., 2022). The studies reporting positive effects on functional outcomes have used interview-based or patient-reported measures of functioning (Torrent et al., 2013; Valls et al., 2021; Vicent-Gil et al., 2022). These instruments rely to a large degree on information reported or relayed by the patient, which could raise a question about the

accuracy of the individual, both regarding insight and mood symptoms (Sheehan et al., 2017). Using an observer based measure of functioning as the primary outcome in our study, might limit the potential for significant improvement compared with patient reported measures, as patients have been found to be more severely functionally impaired on observer based measures (Decker L, 2017).

Strengths and limitations

The study has several limitations: 1) The limited duration of the intervention, with six months as possibly too short a span to implement treatment strategies on different areas of functioning and improve overall functioning 2) The participants had severe functional and cognitive impairment at baseline, as seen from FAST and SCIP baseline scores, thus requiring extensive intervention regarding many areas of functioning. Furthermore, the severity and length of the disorders are considerable, including participants with many previous mood episodes (ref. Table 1), which is associated with poor response to interventions (Scott et al., 2006) 3) The pragmatic nature of the study yields high generalisability regarding patients with affective disorders and functional impairment, however the broad inclusion of severely functional impaired participants with both psychiatric and medical comorbidities, may limit the potential for considerable improvement in the patients. The higher number of patients on disability pension in the AWARE group (20.00% vs 5.66% in TAU), may also have limited the potential for improvement among these patients, as their motivation might be lower. Regarding the primary outcome, we do not think this as a false negative finding caused by low power (type II error), as the obtained sample size was larger than needed based on post hoc power calculations. Power calculations were however not based on secondary outcomes. The blinded outcome assessment is a prominent strength, as it reduces bias. The lack of blinding in the assessment of FAST somehow limits a more directs comparison between our study and previous trials on this measurement (Léda-Rêgo et al., 2020; Torrent et al., 2013), as unblinded assessment is associated with a high risk of potential bias.

A considerable strength of the study is the comprehensive assessment and intervention, targeting the most well-known factors contributing to impaired functioning. Furthermore, functioning was assessed as both observer/performance-based measures of ADL ability (AMPS) as part of

functioning conducted in the patients' homes and thereby everyday life as well as patient-reported (WHODAS) and clinician-rated/interview based (ADL-I and FAST). Most studies only measure functioning with one of these modalities, which might limit the validity of the results, as each modality has its weaknesses and negative attributes (Sheehan et al., 2017). However, the use of AMPS assessment/observations in patients' home surroundings at baseline and endpoint was the primary cause of why referred patients declined to participate in the trial. Measuring functioning with AMPS also caused dropout/missing data on this outcome, as several participants who took part in the endpoint assessment were unwilling to complete the AMPS observation at the endpoint. The patients who did not participate in AMPS at the endpoint had lower SCIP scores at baseline and higher HDRS scores at the endpoint, pointing to these patients having a higher disease burden at the time of the study.

Implications

Despite the negative result of the primary outcome, the trial has implications regarding future research. First and foremost, the study highlights an unmet need for effective interventions targeting functioning in patients with affective disorders, even in patients with low levels of mood symptoms (defined as full or partial remission on HDRS-17). Only a few previous RCT intervention studies have used functioning as the primary outcome (Torrent et al., 2013; Valls et al., 2021). The multimodule individualised AWARE intervention was not superior to TAU on improving observer-based functioning. Nevertheless, patient-reported measures showed positive effects, indicating that participants found the intervention relevant and helpful.

Further, the subgroup analysis showed an effect of the AWARE intervention compared with TAU in patients with cognitive impairment at baseline, supporting a recent meta-analysis calling for multimodal interventions aiding transfer to real-world functioning in patients with objective cognitive performance deficits (Miskowiak et al., 2022). Functioning is an essential and relevant outcome in patients with affective disorder, and further development of effective treatments and treatment strategies explicitly targeting functioning are needed. The present trial finds possible beneficial effects of a multimodal approach in patients with functional impairment coinciding with

cognitive impairment. Based on the current finding, future trials/interventions targeting functioning should have a duration of more than six months.

Author contributions

MV conceived and designed study. MV and RS wrote the study protocol. MV obtained the required funding for the study along with RS. MV applied for the Data and the Ethical permissions. MV developed the intervention program and RS, MSC and MV wrote the intervention manual. KWM and LVK contributed to revising the study protocol. RS was responsible for setting up the study, assessments, and questionnaires in the REDCap program. RS was responsible for carrying out the treatment with assistance from occupational therapists and nurses at Psychiatric Centre North Zealand, and under supervision of MV. RS had the primary responsibility for recruitment, enrolment, data collection, data analysis, and interpretation of the data under supervision of MV. RS and MV wrote the manuscript drafts and revised the following version. All authors contributed to the writing of the manuscript, reviewed the results and approved the final version of the manuscript

Conflicts of interest

RS has within the last three years been a speaker/consultant for Lundbeck.
KWM has received honoraria from Lundbeck, Janssen-Cilag, Gideon Richter and Angelini in the past three years.
MSC has nothing to declare.
LVK has within the last three years been a consultant for Lundbeck and Teva.
MV has within the last three years been a speaker/consultant for Lundbeck and JanssenCilag.

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Transparency Declaration

The lead author (RS) affirms that the manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been registered and explained.

Data Availability

The data and analytic code supporting the findings of this study are available from the corresponding author (RS) upon reasonable request.

Tables and Figures in main text:

Table 1:

Table 1 Sociodemographic and clinical characteristics of the included patients with bipolar or unipolar disorders according to treatment group		
Randomisation group	AWARE (n=50)	TAU (n=53)
Sociodemographic:		
Age, mean (s.d.)	41.64 (12.75)	39.92 (12.29)
Sex, female, n (%)	33 (66.00)	34 (64.15)
Education years, mean (s.d.)	13.61 (2.40)	13.83 (2.75)
Marital status yes, n (%)	15 (30.00)	14 (26.42)
Employment status "employed", n (%)	11 (22.00)	15 (28.30)
Disability Pension, n (%)	10 (20.00)	3 (5.66)
Student, n (%)	4 (8.00)	9 (16.98)
Diagnosis:		
Unipolar, n (%)	15 (30.00)	17 (32.08)
Bipolar, n (%)	35 (70.00)	36 (67.92)
Age at illness onset, mean (s.d.)	20.38 (8.30)	20.34 (8.57)
Number of episodes:		
Depressive, median [IQR]	10 [13]	9 [11]
Manic (only for Bipolar 1), median [IQR]	2 [4]	1 [4]
Hypomanic (only for Bipolar 1 and 2), median [IQR]	10 [21]	10 [10]
Clinical:		
Time in remission/partial remission months, mean (s.d.)	6.48 (9.64)	5.96 (8.06)
HDRS-17 total score, mean (s.d.)	9.48(3.41)	9.75 (2.85)
YMRS total score, mean (s.d.)	2.40 (2.29)	2.98 (2.51)
Psychiatric comorbidity, n (%)	10 (20.00)	13 (24.53)
Previous suicide attempts, n (%)	8 (16.00)	16 (30.19)
Previeous received ECT, n (%)	7 (14.00)	3 (5.66)
Previeous hospitalisation, n (%)	31 (62.00)	24 (45.28)
Number of hospitalisations, median [IQR]	1 [3]	0 [2]
FAST total, mean (s.d.)	37.76 (10.06)	35.53(10.22)
SCIP total, mean (s.d.)	69.56 (15.18)	67.83 (12.35)
Body mass index, mean (s.d.)	29.09 (6.84)	29.01 (6.89)
Medical comorbidity (yes), n (%)	28 (56.00)	22 (41.51)
Current medication:		
Lithium, n (%)	19 (38.00)	21 (39.62)
Antipsychotics, n (%)	26 (52.00)	22 (41.51)
Antidepressants, n (%)	21 (42.00)	22 (41.51)
Anticonvulsics, n (%)	27 (54.00)	26 (49.06)
Benzodiazepines, n (%)	16 (32.00)	11 (20.75)
Others, n (%)	34 (68.00)	34 (64.15)

AWARE, Affective disorders: eliminate WArning signs And REstore functioning; TAU, Treatment As Usual; IQR, Interquartile Range; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; ECT, Electroconvulsive Therapy; FAST, Functioning Assessment Short Test; SCIP, Screen for Cognitive Impairment in Psychiatry.

Table 2:

Table 2 Results of the secondary and tertiary outcome measures at 6-months follow-up (endpoint) in patients with bipolar or unipolar disorders according to treatment group

	Model 1[a]			Model 2[b]		
Secondary outcome	Difference between AWARE and TAU	95 % CI	p	Difference between AWARE and TAU	95 % CI	p
WHODAS	-3.36	-8.75; 2.03	0.219	-3.96	-9.19; 1.27	0.136
WHOQoL Physical[c]	1.56	-4.36; 7.47	0.603	1.93	-3.90; 7.76	0.512
WHOQoL Psych[c]	0.41	-5.95; 6.76	0.899	1.07	-5.24; 7.38	0.736
WHOQoL Social[c]	1.27	-5.24; 7.79	0.699	1.49	-5.07; 8.04	0.653
WHOQoL Environment[c]	1.86	-3.12; 6.83	0.46	2.32	-2.68; 7.32	0.359
PSS	-2.86	-5.54; -0.17	0.036	-2.89	-5.58; -0.21	0.035
FAST[d]	-7.13	-10.76; -3.49	0.001	-7.27	-10.94; -3.61	0.001
SCIP	0.45	-2.93; 3.82	0.794	0.87	-2.50; 4.24	0.609
Trail Making A	-6.27	-12.79; 0.26	0.06	-7.24	-13.72; -0.77	0.029
Trail Making B	10.35	-3.67; 24.36	0.146	8.5	-5.77; 22.77	0.239
Tertiary outcome						
ADLI[c]	0.08	-0.36; 0.51	0.727	0.17	-0.27; 0.62	0.445
COBRA	-2.55	-5.10; 0.00	0.05	-2.8	-5.37; -0.23	0.033

AWARE, Affective disorders: eliminate WArning signs And REstore functioning; TAU, Treatment As Usual; WHODAS, World Health Organization Disability Assessment Schedule 2.0; WHOQoL, World Health Organization Quality of Life; PSS, Cohen's Perceived Stress Scale; Functional Assessment Short Test (FAST); SCIP, Screen for Cognitive Impairment in Psychiatry; ADLI, Activities Of Daily Living Interview; COBRA, Cognitive complaints in bipolar disorder rating assessment.

a. Model 1: Analysis of Covariance, unadjusted (only adjusted for baseline value)

b. Model 2: Analysis of Covariance, adjusted for age, sex, diagnosis and number of affective episodes (and adjusted for baseline value)

c. Indicates that a large score is favorable to the patient

d. Unblinded outcome assessment

Fig 1:

AWARE Trial CONSORT diagram

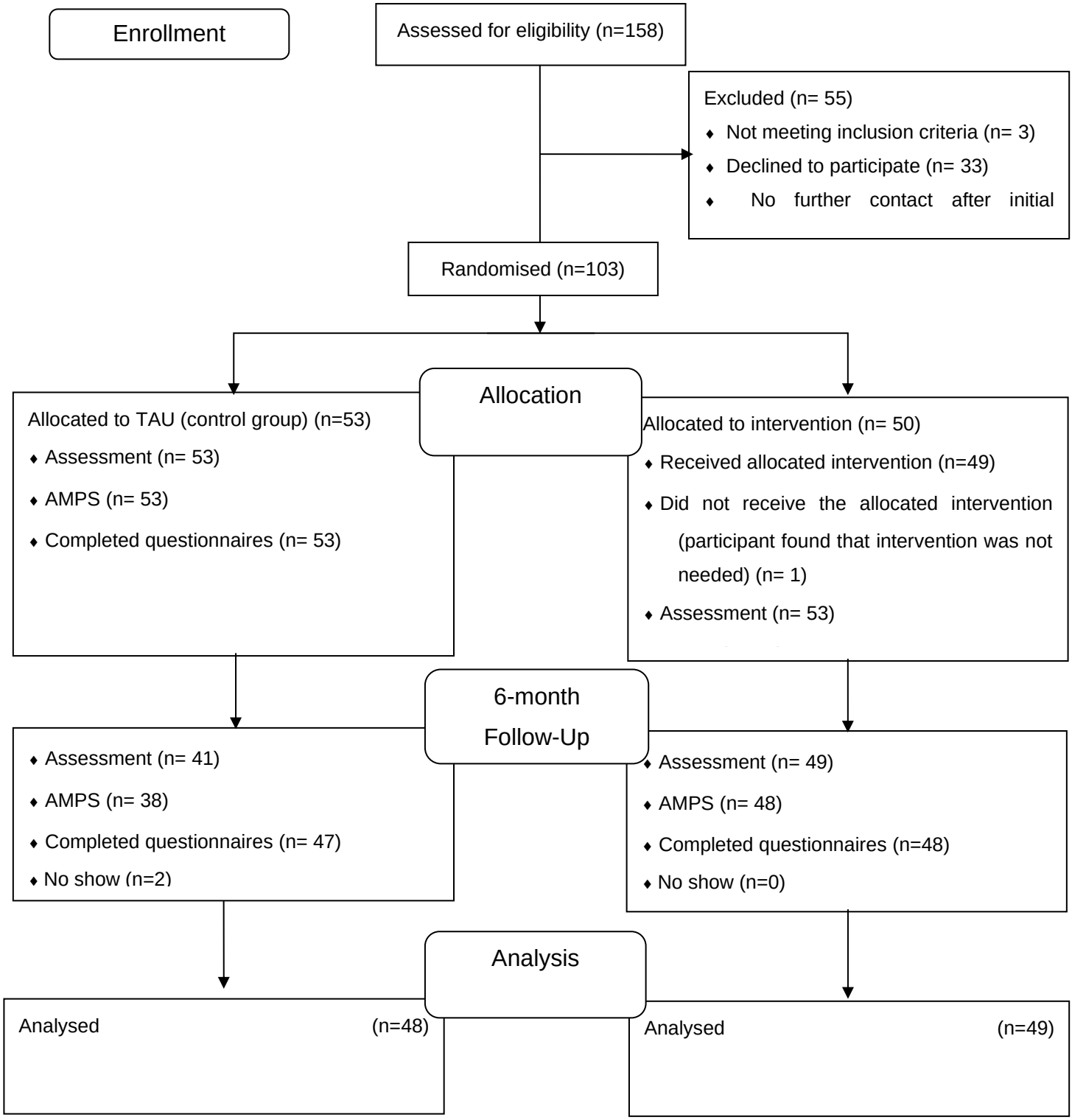
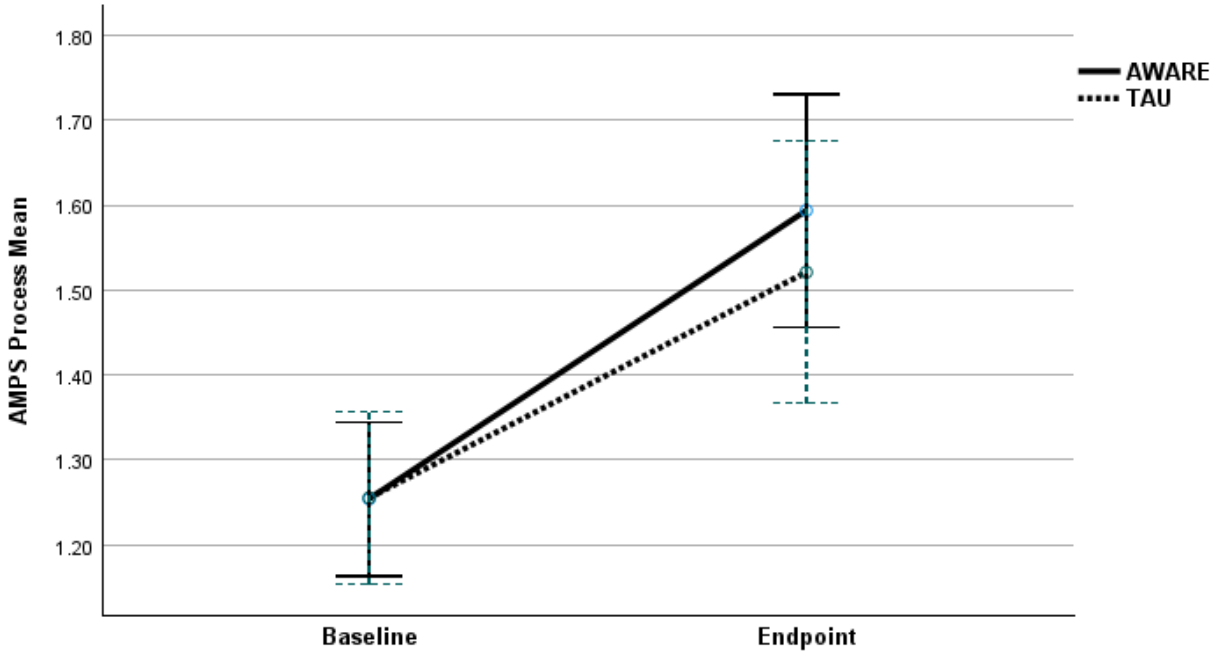


Fig. 2:

Changes in mean AMPS (Assessment of Motor and Process Skills) process scores (with 95% confidence intervals) from baseline to endpoint according to treatment group (the active Affective disorders: eliminate WArning signs And REstore functioning (AWARE) and the Treatment As Usual (TAU) Group



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Supplementary Materials

Table of Contents

Table 3 Overview of variables and measurements

Variables	Measurements	Assessment method	Total score range and interpretation
Activities of daily living (observer/performance-based functioning)	AMPS (Process)	Observation-based (performance based)	(-4)-3 Higher scores = better functioning
	AMPS (Motor)	Observation-based (performance based)	(-3)-4 Higher scores = better functioning
Patient-reported functioning	WHODAS	Questionnaire	0-100 Higher scores = worse functioning
Clinician rated/interview based functioning	FAST	Interview	0-72 Higher scores = better functioning
	ADL-I	Interview	(-5.84)-6.41 Higher scores = better functioning
Patient reported stress	PSS	Questionnaire	0-40 Higher scores = more stress
Quality of life	WHOQOL	Questionnaire	0-100[a] Higher scores = better quality of life
Cognitive performance	SCIP	Performance based	0-∞[b] Higher scores = better cognitive performance
	Trail Making Test A and B	Performance based	0[c]-600 Higher scores = better cognitive performance
Patient-reported cognition	COBRA	Questionnaire	0-48 Higher scores = more cognitive impairment
Depressive symptoms severity	HDRS-17	Interview	0-52 Higher scores = more symptoms
Manic symptoms severity	YMRS	Interview	0-60 Higher scores = more symptoms

AMPS, Assessment of Motor and Process Skills; WHODAS, World Health Organization Disability Assessment Schedule 2.0; FAST, Functional Assessment Short Test; ADLI, Activities Of Daily Living Interview; PSS, Cohen's Perceived Stress Scale; WHOQoL, World Health Organization Quality of Life; SCIP, Screen for Cognitive Impairment in Psychiatry; COBRA, Cognitive complaints in bipolar disorder rating assessment; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

a. Score is calculated for each of the four domains, with no total score combining the domains

b. No theoretical upper range

c. Theoretical lower range

Table 4 Content of treatment during the intervention period for completers of the study in the AWARE and TAU group

	AWARE (n=49)	TAU (n=46)	p= (two-sided)
AWARE sessions completed, median [IQR] (Range)	12 [4] (6-18)	-	
Patients treated in psychiatric secondary care setting, n (%)	40 (81.63)	35 (76.09)	0.508
Number of secondary care visits/sessions, median [IQR] (Range)	6 [10] (0-24)	10 [12] (0-31)	0.477
Number of secondary care phone consultations, median [IQR] (Range)	1 [2] (0-15)	1 [2] (0-12)	0.846
Patients treated in psychiatric primary care setting, n (%)	6 (12.24)	7 (15.22)	0.674
Patients not treated in psychiatric primary or secondary care settings, n (%)	2 (4.08)	0	0.166

AWARE, Affective disorders: eliminate WArning signs And REstore functioning; TAU, Treatment As Usual; IQR, Interquartile Range

Table 5 Comparison of baseline sociodemographic and clinical variables between patients in TAU with and without study dropout on primary endpoint (AMPS)			
	Dropuot n=15	Completion n=38	p= (Two-sided)
Age, mean (s.d.)	42.20 (14.05)	39.03 (11.61)	0.201[a]
Sex, female, n (%)	8 (53.33)	26 (68.42)	0.302[b]
Education years, mean (s.d.)	13.20 (2.66)	14.08 (2.77)	0.298[a]
Marital status yes, n (%)	3 (20,00)	11 (28.95)	0.732[c]
Employment status "employed", n (%)	4 (26.67)	11 (28.95)	0.868[c]
Diagnosis:			
Unipolar, n (%)	5 (33.33)	12 (31.58)	0.902[b]
Bipolar, n (%)	10 (66.67)	26 (68.42)	0.902[b]
Age at illness onset, mean (s.d.)	19.47 (9.60)	20.68 (8.24)	0.646[a]
Number of episodes:			
Depressive, median [IQR]	9 [14]	9 [11]	0.931[a]
Manic (only for Bipolar 1), median [IQR]	2 [4]	1 [8]	0.567[a]
Hypomanic (only for Bipolar 1 and 2), median [IQR]	10 [14]	10 [10]	0.767[a]
Clinical:			
Time in remission/partial remission months, mean (s.d.)	4.80 (5.20)	6.42 (8.96)	0.515[a]
HDRS-17 total score, mean (s.d.)	10.00 (2.83)	9.66 (2.90)	0.698[a]
YMRS total score, mean (s.d.)	2.87 (2.45)	3.03 (2.56)	0.837[a]
Psychiatric comorbidity, n (%)	3 (20.00)	10 (26.32)	0.736[c]
Previous suicide attempts, n (%)	5 (33.33)	11 (28.95)	0.754[b]
Previeous received ECT, n (%)	1 (6.67)	2 (5.26)	0.842[c]
Previeous hospitalisation, n (%)	10 (66.67)	14 (36.84)	0.049[b]
Number of hospitalisations, median [IQR]	1 [3]	0 [1]	0.097[a]
FAST total, mean (s.d.)	38.07 (9.33)	34.52 (10.50)	0.260[a]
SCIP total, mean (s.d.)	61.40 (11.70)	70.37 (11.80)	0.016[a]
Body mass index, mean (s.d.)	29.38 (5.19)	28.87 (7.52)	0.811[a]
Medical comorbidity (yes), n (%)	7 (46.67)	24 (63.16)	0.272[b]
WHODAS, mean (s.d.)	37.55 (17.56)	40.22 (15.74)	0.592[a]
PSS, mean (s.d.)	21.53 (4.61)	20.87 (6.40)	0.716[a]
Current medication:			
Lithium, n (%)	6 (40.00)	14 (36.84)	0.831[b]
Antipsychotics, n (%)	6 (40.00)	16 (42.10)	0.889[b]
Antidepressants, n (%)	6 (40.00)	16 (42.10)	0.889[b]
Anticonvulsics, n (%)	7 (46.67)	19 (50.00)	0.827[b]
Benzodiazepines, n (%)	1 (6.67)	10 (26.32)	0.149[c]
Others, n (%)			

AMPS baseline			
Process, mean (s.d.)	1.24 (0.34)	1.26 (0.27)	0.862[a]
Motor, mean (s.d.)	2.17 (0.32)	2.09 (0.33)	0.441[a]
Endpoint			
FAST total, mean (s.d.)[d]	45.40 (8.73)[e]	34.75 (14.02)[f]	0.108[a]
HDRS-17 total score, mean (s.d.)[d]	14.80 (5.76)[e]	9.19 (5.57)[f]	0.042[a]
WHODAS, mean (s.d.)[d]	37.92 (17.92)[g]	34.70 (16.35)[h]	0.590[a]
PSS, mean (s.d.)[d]	21.70 (6.80)[g]	20.11 (6.90)[h]	0.519[a]

TAU, Treatment As Usual; IQR, Interquartile Range; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; ECT, Electroconvulsive Therapy; FAST, Functioning Assessment Short Test; SCIP, Screen for Cognitive Impairment in Psychiatry; WHODAS, World Health Organization Disability Assessment Schedule 2.0; PSS, Cohen's Perceived Stress Scale; AMPS, Assessment of Motor and Process Skills.

a. independent samples t-test

b. Pearson chi-square

c. Fishers Exact Test

d. score at endpoint

e. based on n=5

f. based on n=36

g. based on n=10

h. based on n=37

Table 6 Data on sociodemographics, clinical status and outcome measures at follow-up/endpoint		
	AWARE n=49	TAU n=47
Sociodemographic:		
Employment status "employed", n (%)	12 (24.49)	10 (24.39)[a]
Number of episodes:		
Depressive, median [IQR]	11 [13]	11 [13][b]
Manic (only for Bipolar 1), median [IQR]	2 [4][c]	1 [5][d]
Hypomanic (only for Bipolar 1 and 2), median [IQR]	13 [20][e]	10 [11][f]
Clinical:		
Time in remission/partial remission months, mean (s.d.)	6.44 (7.25)	5.83 (6.44)[b]
HDRS-17 total score, mean (s.d.)	9.55 (6.43)	9.88 (5.82)[a]
YMRS total score, mean (s.d.)	2.02 (2.45)	2.15 (2.99)[a]
Previeous hospitalisation, n (%)	30 (61.22)	18 (42.86)[b]
Number of hospitalisations, median [IQR]	1 [3]	0 [2][b]
FAST total, mean (s.d.)	31.04 (12.97)	36.05 (13.86)[a]
SCIP total, mean (s.d.)	71.11 (15.57)[g]	68.97 (14.65)[h]
Body mass index, mean (s.d.)	28.73 (7.12)[i]	28.90 (6.86)[j]
Current medication:		
Lithium, n (%)	17 (34.69)	18 (39.13)[k]
Antipsychotics, n (%)	24 (48.98)	15 (32.61)[k]
Antidepressants, n (%)	21 (42.86)	18 (39.13)[k]
Anticonvulsics, n (%)	28 (57.14)	17 (36.96)[k]
Benzodiazepines, n (%)	15 (30.61)	10 (21.74)[k]
Others, n (%)	33 (67.35)	28 (60.87)[k]
Outcomes		
AMPS Process, mean (s.d.)	1.59 (0.46)[i]	1.52 (0.49)[h]
AMPS Motor, mean (s.d.)	2.32 (0.61)[i]	2.33 (0.49)[h]
WHODAS, mean (s.d.)	36.22 (19.92)[i]	35.39 (16.55)
WHOQoL Physical, mean (s.d.)	57.22 (19.03)[i]	59.35 (16.31)
WHOQoL Psych, mean (s.d.)	43.23 (21.64)[i]	43.88 (17.29)
WHOQoL Social, mean (s.d.)	53.30 (22.00)[i]	49.29 (22.44)
WHOQoL Environment, mean (s.d.)	67.06 (18.45)[i]	64.23 (16.14)
PSS, mean (s.d.)	19.13 (8.27)[i]	20.45 (6.84)
ADLI, mean (s.d.)	2.68 (1.05)[i]	2.70 (1.21)[h]
Trail Making A, mean (s.d.)	36.00 (26.83)[g]	37.66 (19.91)[h]
Trail Making B, mean (s.d.)	95.11 (82.15)[g]	84.57 (38.81)[h]

AWARE, Affective disorders: eliminate WArning signs And REstore functioning; TAU, Treatment As Usual; IQR, Interquartile Range; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; FAST, Functioning Assessment Short Test; SCIP, Screen for Cognitive Impairment in Psychiatry; AMPS, Assessment of Motor and Process Skills; WHODAS, World Health Organization Disability

Assessment Schedule 2.0; WHOQoL, World Health Organization Quality of Life; PSS, Cohen's Perceived Stress Scale; ADLI, Activities Of Daily Living Interview.

a. based on n=41
b. based on n=42
c. based on n=10
d. based on n=9
e. based on n=34
f. based on n=30
g. based on n=47
h. based on n=38
i. based on n=48
j. based on n=39
k. based on n=46

Paper III

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Corresponding Author:	Rasmus Schwarz, MD Mental Health Centre Northern Zealand Hillerød, DENMARK
First Author:	Rasmus Schwarz, MD
Order of Authors:	Rasmus Schwarz, MD
	Klaus Munkholm
	Mie Skovmand Christensen
	Lars Vedel Kessing
	Maj Vinberg

Functioning in patients with major depressive disorder in remission: a systematic review and meta-analysis

Rasmus Schwarz[1,2], Klaus Munkholm[3,4], Mie S Christensen[1], Lars V Kessing[2,3,4], Maj Vinberg[1,2,3]

Affiliations:

[1]Mental Health Centre Northern Zealand, The Early Multimodular Prevention and Intervention Research Institution (EMPIRI) - Mental Health Services CPH, Copenhagen, Denmark.

[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[3]Copenhagen Affective Disorder Research Centre (CADIC), Psychiatric Centre Copenhagen, Frederiksberg, Denmark

[4]Mental Health Centre Copenhagen, Copenhagen University Hospital - Mental Health Services CPH, Copenhagen, Denmark.

Corresponding author: Rasmus Schwarz, rasmus.moeskjaer.schwarz@regionh.dk

Dyrehavevej 48, 3400 Hillerød, Denmark

Orchid ID: 0000-0002-8808-1866

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Abstract:

Background: Major depressive disorder (MDD) is one of the leading causes of burden of disease globally. We aimed to investigate whether global functioning is impaired in patients with MDD in full or partial remission compared to healthy control individuals (HC).

Methods: We conducted a systematic review and meta-analysis according to the PRISMA guideline. We searched the databases PubMed, EMBASE and PsycINFO from January 1st 1980 to February 1st 2023. We included studies of adults with a diagnosis/former diagnosis of MDD with assessment of global functioning performed during a state of full or partial remission. The methodological quality was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist. Standardised mean differences (SMD) using random-effects models were calculated as the summary measure. We further performed meta-analyses of the mean raw score in patients with MDD for individual functioning scales.

Results: Forty-two studies, comprising 17999 patients with MDD and 35550 HC, were included, 14 of which included both patients with MDD in full or partial remission and HC. Global functioning was lower in patients with MDD in full or partial remission compared with HC (SMD -2.00, 95% CI: -0.9 to -3.03, 15 comparisons, I^2: 99.8%).

Limitations: Important information about the study participants and setting was not reported for most studies, or the reporting was unclear.

Conclusion: Patients with MDD have lower levels of functioning compared with HC also when in full or partial remission. Assessment of functioning should be an essential component of managing patients with MDD, also during remission.

Keywords: Major Depressive Disorder; Functioning; Remission

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Registration

Prospero registration reference number: CRD42023386730

Introduction

Major depressive disorder (MDD) is ranked among the three highest causes of burden of disease globally by the World Health Organization (WHO), and is predicted to become the leading cause of years lost to disability globally by the year 2030 (World Health Organization, 2008). Functioning is increasingly recognised as a main outcome of interest in MDD. The effects of antidepressant treatment on functioning in MDD are smaller than the effect on depressive symptoms, and functional deficits often persist even after remission from depressive symptoms has been achieved (D. V. Sheehan et al., 2017; Trivedi et al., 2009).

Global functioning is defined as an "*evaluation of a patient's functional level, including ability to perform activities of daily living, done to prescribe or evaluate rehabilitation measures*" (Dorland, 2011). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) recommends the WHO Disability Assessment Schedule (WHODAS 2.0) as the preferred scale for measuring functioning in patients across all psychiatric diagnoses as the domains are based upon the conceptual framework of WHO's International Classification of Functioning, Disability and Health (ICF) (American Psychiatric Association, 2013; World Health Organization, 2001, 2010). However, various scales are commonly used, such as the Global Assessment of Functioning (GAF) and the Sheehan Disability Scale (SDS) (American Psychiatric Association, 1994; David V Sheehan, 1986; D. V. Sheehan et al., 2017).

Despite the general clinical consensus that functional impairment is present and of significant importance in patients with MDD in remission, no systematic review has synthesised the evidence in the area. With the growing burden of MDD globally a comprehensive systematic review is highly warranted and relevant from a patient-, clinical-, and societal perspective. To fill this gap, we performed a systematic review with meta-analysis of functioning in patients with MDD in remission. The aims were to 1) investigate whether global functioning is impaired during the fully or partially remitted state in patients with MDD compared to healthy control individuals (HC) 2) explore the potential moderating effect of sociodemographic and clinical factors on functional impairment.

Methods

This systematic review with meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Page et al., 2021). The review protocol was pre-registered in the PROSPERO database (reference number CRD42023386730).

Selection criteria and search strategy

Studies were selected for review and data extraction, if they met the following inclusion/exclusion criteria: (1) Adult patient samples (age≥18); (2) Diagnosis/former diagnosis of MDD per International Classification of Disease (ICD) (World Health Organization, 2018) or DSM (American Psychiatric Association, 2013); (3) Remission (including full remission defined as a score on The 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1960) ≤7, or Montgomery-Asberg Depression Rating Scale (MADRAS) (Montgomery & Asberg, 1979) ≤8, or partial remission defined as HDRS-17 ≤14, or MADRS ≤20) when functional assessment was performed (or by other validated systematic evaluation including cut off on The Beck Depression Inventory (BDI) (Beck et al., 1961), The HDRS-6 (O'Sullivan et al., 1997), Remission from Depression Questionnaire (RDQ) (Zimmerman et al., 2013) or Quick Inventory of Depressive Symptomatology (QIDS-SR) (Rush et al., 2003), or according to The Mini-International Neuropsychiatric Interview (MINI) (D. V. Sheehan et al., 1998) or by counting DSM or ICD criteria for MDD); (4) Data on global functioning compared with HC or assessed with a validated scale; (5) Studies including a sample of N>10 individuals remitted from MDD. Exclusion criteria: (1) Studies on mixed populations (e.g., including participants with bipolar disorder or schizophrenia) not reporting data for the participants with MDD separately; (2) Studies not published in English, French or German. Studies including treated and/or untreated people with MDD were included. Inclusion was not restricted by the type of study/study design, but conference abstracts and unpublished articles were not included. Our primary outcome was global functioning measured on a validated scale. Studies providing data on work/occupational status alone, quality of life, or only a selected functional domain such as social functioning or cognition were not included.

Relevant studies were identified by systematic search in the PubMed, EMBASE and PsycINFO databases. The search strategy was developed in conjunction with previous extensive reviews on

functioning in bipolar disorder and used a range of terms to capture all potentially eligible results relating to global functioning (Léda-Rêgo et al., 2020). Search strategy is provided in the appendix (p 2). The search was limited to original papers published between January 1st 1980 and February 1st 2023, and studies in humans. Furthermore, to identify additional relevant studies, the reference lists of all included studies were screened for eligible reports by two independent review authors (MSC and RS). Additionally, we hand-searched the reference-lists of all included articles for potentially eligible articles.

Papers identified by searching the individual databases merged into one single database using the web-based collaboration software platform COVIDENCE, from which duplicates were removed (Covidence). Studies with overlapping samples were excluded; and the paper most compatible with our criteria was included. Data were obtained on a summary estimate level and individual patient-level data were not considered.

Two review authors (MSC and RS) independently screened all titles/abstracts and full-text versions of all relevant studies for eligibility. Decisions were based on consensus, or if necessary, by discussion with third senior review author (MV). The screening of titles/abstracts was done prioritizing sensitivity to allow for the inclusion of any potentially relevant study for further evaluation.

Data analysis

The data from the included studies were extracted by two review authors (MSC and RS) independently using an electronic data extraction form developed for this review (available upon request). The extracted data included author name, the study's year of publication and country, study design, setting, sample size, age, sex, the criteria for the definition of the remission/partial remission state, depression severity score, diagnostic instrument, exclusion criteria, and the prespecified possible moderators of functioning; number of previous depressive episodes, time since last depressive episode, age at onset, illness duration, number of hospital admissions, treatment with psychotropic medication, treatment with electroconvulsive therapy, co-morbid psychiatric or medical illness, substance dependence, personality disorder, psychosocial stress and neurocognition. Mean and standard deviation for global functioning outcomes and the global

functioning scale used in each study were extracted. One longitudinal study reported patients global functioning in remission at several time points, so the first timepoint was chosen (Kennedy et al., 2019). One study reported global functioning on more than one scale, and here the clinician rated scale was chosen before the self-rated scale (Nierenberg et al., 2019). In the case of reports of pooled studies, we sought data from the original studies; however, as data from the individual studies were not available in two instances, we extracted data from the pooled study report (Romera et al., 2014; D. V. Sheehan et al., 2011).

Two review authors (MSC and RS) independently assessed the methodological quality and the reporting of the included studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies and Case Series (Joanna Briggs Institute; Joanna Briggs Institute) Discrepancies were resolved by consensus with senior review authors (MV and KM).

We calculated standardised mean differences (SMD) as the summary measure, allowing for pooling of effect sizes across different functioning scales. We used the bias corrected Hedges' g (*g*), which provides a conservative estimate of the SMD where studies with small sample sizes are included in the analysis (Grissom & Kim, 2005). All analyses were performed as random-effects models, as variation in the true effect sized between studies was expected. The between-study heterogeneity was estimated using the Sidink-Jonkman estimator, and we applied the Hartung-Knapp adjustment.

Where studies reported the outcome of interest for separate groups that fulfilled our inclusion criteria, e.g., for participants in full and partial remission, respectively, we combined the groups (Julian PT Higgins et al., 2019). One study reported the standard deviation of the outcome to be zero, so we added 10*-10 to that value to include the results in the meta-analysis. For two of the scales used in the included studies, GAF and the Social and Occupational Functioning Assessment Scale (SOFAS), a higher score signifies better functioning, whereas, for the other scales, a higher score signifies lower functioning (American Psychiatric Association, 1994; Goldman et al., 1992). When calculating SMD, the value of the extracted scores on the GAF and the SOFAS was multiplied by -1, for all the studies to have the same direction of effect.

Sensitivity analysis was conducted to test the robustness of findings, by estimating the impact of extreme results on meta-analysis results. Subgroup and meta-regression analyses assessed the

association between multiple clinical and demographical variables with the effect size. To minimise the risk of spurious findings, subgroup and meta-regression analyses were only conducted provided the number of comparisons was approximately ten or more. The variables considered were pre-specified a priori (presented in the "data extraction" section"). The proportion of between-study variance explained by subgroup membership or moderator variables was calculated as R^2 and the difference between subgroup effect sizes was estimated by the *Q*-statistic. Meta-regression analysis was performed using a Z-distribution random effects Method of Moments model (Borenstein et al., 2009). Because of low study numbers, these were performed as separate univariate analyses. The meta-regression analyses were considered exploratory and correction for multiple testing was not done.

Heterogeneity between studies was investigated by the Q-statistic and the impact of heterogeneity on meta-analysis estimates was assessed by the I^2 statistic (Borenstein et al., 2009; J. P. Higgins et al., 2003). Publication bias was assessed using the Egger's test provided there were ten or more comparisons, and by inspection of funnel plots (Egger et al., 1997). Additionally, we calculated the mean raw score for patients with MDD in remission for each of the scales used in the individual studies separately.

All analyses were performed using R (R Core Team) and the meta package (Balduzzi et al., 2019).

Where data or information were not reported in the retrieved reports the corresponding authors were contacted in a standardised manner. Of the 15 authors we contacted, four replied, but the requested data were provided in only one case.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The searches identified 7914 studies after removing duplicates, and after screening of titles/abstracts, 492 full-text articles and reports were retrieved (see Figure 1). Forty-two studies,

comprising 17999 patients with MDD and 35550 HC, were included in the review (study characteristics are summarised in Table 1). Fifteen studies included both patients with MDD in remission or partial remission and HC, whereas 27 studies included patients with MDD in full or partial remission only. A total of 39 studies, including 17462 patients with MDD and 35520 HC, were included in the meta-analysis (Bromet et al., 2011; Cohen et al., 2013; Collard et al., 2018; Daniel et al., 2013; Ermis et al., 2021; Fennig et al., 2002; Furukawa et al., 2001; Gokcer Tulaci & Ekinci, 2020; Green et al., 2012; E. Harada et al., 2017; Kennedy et al., 2019; Kocsis et al., 2002; M et al., 2022; Musket et al., 2021; Nierenberg et al., 2019; Oakes et al., 2015; Ong et al., 2017; Ormel et al., 2004; Pérez et al., 2021; Erdem Pulcu et al., 2014; E. Pulcu et al., 2014; Riihimäki et al., 2015; Romera et al., 2010; Romera et al., 2014; Rothschild et al., 2014; Rytsala et al., 2006; Schennach et al., 2019; Shin et al., 2021; Tharoor et al., 2008; Van Der Voort et al., 2015; Vicent-Gil et al., 2022; Viinamaki et al., 2008; Weinberg & Shankman, 2017; Xiao et al., 2018; Yamada et al., 2015; Yang et al., 2020; Yucel et al., 2009; Zahn et al., 2015; Zhu et al., 2023). The main reason for exclusion of full-text articles was studies not providing separate data on functioning for the sub-group of patients with MDD in remission (list of all articles excluded at full-text screening with reason in appendix p 4). Fourteen studies were included in the meta-analysis of global functioning comparing patients with MDD and HC, with four studies (Collard et al., 2018; Fennig et al., 2002; Gokcer Tulaci & Ekinci, 2020; Yucel et al., 2009) conducted in a clinical setting, seven (Bromet et al., 2011; Green et al., 2012; Musket et al., 2021; Ormel et al., 2004; Erdem Pulcu et al., 2014; E. Pulcu et al., 2014; Zahn et al., 2015) in a non-clinical setting, and three (Ong et al., 2017; Van Der Voort et al., 2015; Weinberg & Shankman, 2017) in a mixed setting (participants recruited from both a clinical and non-clinical population). Information on mean age or sex distribution was not available for 18 and 14 studies, respectively. The mean age of patients with MDD in full or partial remission ranged from 23 years to 70 years, whereas the proportion of males in the studies ranged from 19% to 55%. Global functioning was measured by GAF in 14 studies (Daniel et al., 2013; Ermis et al., 2021; Fennig et al., 2002; Furukawa et al., 2001; Green et al., 2012; K. Harada et al., 2018; Musket et al., 2021; Ong et al., 2017; Erdem Pulcu et al., 2014; E. Pulcu et al., 2014; Schennach et al., 2019; Weinberg & Shankman, 2017; Yucel et al., 2009; Zahn et al., 2015), SDS (David V Sheehan, 1986) in eight (Kennedy et al., 2019; Oakes et al., 2015; Romera et al., 2014; Rothschild et al., 2014; D. V. Sheehan et al., 2011; Shin et al., 2021; Xiao et al., 2018; Zhu et al., 2023), SOFAS in seven (E. Harada et al.,

2017; Pérez et al., 2021; Riihimäki et al., 2015; Romera et al., 2010; Rytsala et al., 2006; Viinamaki et al., 2008; Yamada et al., 2015), WHODAS 2.0 in four (Bromet et al., 2011; Collard et al., 2018; Gokcer Tulaci & Ekinci, 2020; Van Der Voort et al., 2015), Functional Assessment Short Test (FAST) (Rosa et al., 2007) in three (M et al., 2022; Nierenberg et al., 2019; Vicent-Gil et al., 2022), Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002) in two (Cohen et al., 2013; Yang et al., 2020), Groningen Social Disability Schedule (GSDS) (Wiersma et al., 1988) in one (Ormel et al., 2004), Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987) in one (Kocsis et al., 2002), a modified, 12-item version of the WHODAS 2.0 scale in one (Sjonnesen et al., 2016), and a modified version of the WHODAS 2.0 with a range of the global score from 0 to 5 in one (Tharoor et al., 2008). For an overview of the global functioning scales used in the included studies and their interpretation see appendix (p 32).

As seen in Figure 2, functioning was lower in patients with MDD in full or partial remission compared with HC (SMD -2.00, 95% CI: -0.9 to -3.03, 15 comparisons, I^2: 99.8%). In a sensitivity analysis removing the two studies with the markedly largest effect sizes (Bromet et al., 2011; Van Der Voort et al., 2015), functioning remained lower in patients with MDD compared with HC (SMD -1.35, 95% CI: -0.92 to -1.78, 13 comparisons, I^2: 99.0%) (forest plot, appendix p 33).

Among the predefined potential moderators of the difference in global functioning between patients with MDD and HC, only the sex distribution and mean age of patients with MDD were reported in ten or more studies (meta-regression analyses in appendix p 34). There was a negative association between a higher proportion of males among patients with MDD and functioning compared with HC (b = 0.05, 95% CI: -0.02 to -0.09, 11 comparisons). There was no effect of the mean age of patients with MDD in the included studies on the difference in functioning between patients and HC (b = 0.003, 95% CI: -0.02 to 0.03, 11 comparisons). Subgroup analysis showed that the difference in functioning between patients with MDD and HC did not differ between studies conducted in a clinical population, a non-clinical population or a mixed population (random effects model, p = 0.53) (appendix p 35).

We performed meta-analyses of the mean raw score in patients with MDD for each scale used to assess functioning in the included studies (results for each scale in appendix p 36-38). For the most frequently used scale (GAF) the mean score was 79.16 (95% CI: 75.14 to 83.19).

Inspection of the funnel plot did not indicate publication bias (appendix p 39). The Egger test was not statistically significant (p = 0.64).

Details and an overview of the assessment of the methodological quality and reporting of the included studies are provided in the appendix (p 40-41). For most studies involving HC important information about the study participants and setting (demographics, location, and period) were not reported, or unclear (appendix p 41). For most studies involving only patients with MDD, the reporting could have been more transparent regarding aspects of inclusion and demographical information on participants (appendix p 40). In other domains most studies were considered to fulfill JBI appraisal criteria.

Three studies including patients with MDD in full remission were not included in the meta-analysis. Mean functioning was provided without SD in a pooled study (521 patients, mean SDS score = 7.1) (D. V. Sheehan et al., 2011). Data on functioning was provided as median and interquartile range in the second study (16 patients, 37.5% males, GAF median 89.5 (IQR 81.3-90) and 30 HC, 36.7% males, GAF median 90 (IQR 90-95)) (K. Harada et al., 2018). Number of participants was not provided in the third study (WHODAS 2.0 mean 14.4 (95% CI, 14.2 to 14.7)) (Sjonnesen et al., 2016). Mean age was not provided in any of the three studies.

Discussion

This first systematic review with meta-analysis of functioning in patients with MDD in full or partial remission incorporates data from 42 studies, comprising 17999 patients with MDD and 35550 HC. In concordance with general consensus, we found that patients with MDD in full or partial remission had lower global functioning in comparison with HC. The findings seem robust, as they are still statistically significant after removing studies with the largest effect sizes. However, there was considerable heterogeneity among the included studies. Factors such as sex distribution, clinical setting and the different functioning scales used, could be contributing factors of heterogeneity, but identification of potential factors was limited by the variables reported in the studies. The estimated effect size of the difference in global functioning in patients with MDD and HC was large, and despite the broad confidence interval caused be heterogeneity among the studies, even the lower part of the confidence interval (most conservative estimate) included large effect. The results

of the analysis of the mean raw score of each global functioning scale used in the study, while they cannot be directly compared with HC, support our main finding of impaired functioning in patients with MDD. Thus, the summary results for the most utilised scale in the studies (GAF) were in the range defined as "slight impairment in social, occupational, or school functioning" (71-80) (American Psychiatric Association, 1994), and on the FAST the mean score was well above the cut-off for normal functioning (higher score equals more impairment). Three studies could not be included in the meta-analysis, but it is unlikely that the data from these studies would have changed our results and conclusions.

The results align with previous studies, showing that monitoring of depressive symptoms alone in patients with MDD is not sufficient, as functional impairment can continue into syndromic remission states (D. V. Sheehan et al., 2017). The analysis of potential moderators of functioning showed a negative association between a higher proportion of males among patients with MDD and lower functioning in patients with MDD compared with HC. Although based on study-level characteristics, the finding may suggest that males in remission from MDD have lower functioning than females. It is well-established that MDD is more prevalent in women than men (Mikkelsen et al., 2022). Men might be less likely to consult medical professionals early in the illness course than women. Further, men might be less likely to receive a diagnosis of MDD. Hence, only more severe cases are diagnosed. Therefore, men with MDD might have higher severity of symptoms and lower functioning than women during depressive episodes, resulting in poorer functional outcomes carried over to remitted states. Sex differences of functioning in MDD remain largely understudied (Scott & Collings, 2010). Still significant sex differences in the symptomatology of MDD are well known (e.g., appetite and sleep disturbances are more frequent in women) (Cavanagh et al., 2017; Mikkelsen et al., 2022). One may suspect that the cognitive decline and medical comorbidities associated with higher age might result in lower levels of functioning. However, this assumption is not supported by the present study, where the mean age was not associated with a difference in functioning between patients and HC. None of the remaining predefined potential moderators were associated with effect size, but results should be interpreted cautiously (data for each present in less than ten studies). The setting for recruitment in the studies (clinical or non-clinical) did not moderate functioning, but this analysis was also likely limited by few studies within each setting.

Limitations

A primary limitation in the evidence base is the lack of consensus on a golden standard for measuring functioning, resulting in several different scales used in the included studies. We partially accounted for this by limiting the inclusion criteria to studies assessing global functioning, thereby avoiding the substantial variation caused by also including scales measuring only selected functional domains. However, even among the included global functioning scales, there is variation regarding assessment method (self-reported and clinician assessed), time frame, and the number of sub-domains considered part of global functioning. GAF, SOFAS, and SDS were most frequently used as assessment tools in the included studies, despite WHODAS 2.0 being the recommended scale by DSM-5 (American Psychiatric Association, 2013).

Identifying all relevant studies providing data on functioning was challenging, as functioning is often reported as a secondary or tertiary outcome, and the indexing in reference databases may not include functioning for these articles. Therefore, we applied an inclusive search strategy. We further screened the reference lists of all included reports, which did not result in the identification of further relevant studies, thereby strengthening our assumption that most (if not all) relevant published studies are included.

The 42 included studies provided surprisingly limited data on clinical and demographical variables (other than age and sex) with possible moderating effects on functioning. We were therefore unable to perform a comprehensive analysis of heterogeneity among the studies and so substantial unexplained heterogeneity remains. Most included studies did not include HC, thus our analysis comparing MDD patients with HC was limited to 14 studies. Considering the status of MDD as one of the leading causes of burden of disease globally the relatively few studies comparing MDD with HC is surprising. Finally, "remission" in MDD is not clearly defined, although cut off scores on main depression scales such as HDRS17 and MADRS are defined and widely accepted. We defined broad inclusion criteria, allowing for inclusion of as many relevant studies as possible, and further including studies with participants in partial remission as absence of current MDD also defines this state (Gülpen et al., 2023). Our findings are thus generalisable to the broader population of patients with MDD in remission. Data on the duration of remission (time since last depressive episode) was lacking in the studies. It is a strength that our results did not indicate publication bias. As

functioning is often considered a secondary outcome in studies, the risk of publication bias is likely low.

Our results support that functioning should be a primary outcome of interest in MDD and that symptomatic remission does not necessarily result in a normalisation of functional level. The results are based on mean values and do not offer insight into the proportion of patients in remission with functional impairment. Additional research is needed to determine these figures and the mediators of global functioning to be targeted by treatment.

Conclusion

In line with the general clinical consensus, however, now, for the first time supported by data synthesised in a systematic review and meta-analysis, patients with MDD in full or partial remission have lower global functioning compared with HC. Male sex seems to be a risk factor for lower functioning in patients with MDD, whereas age was not found to be a mediator of functioning levels. Functional assessments are recommended as an essential component of care, also during full or partial remission. Further research regarding factors associated with functioning status in patients with MDD in remission is warranted, as a clear understanding of these mediating factors is a central step towards developing new effective treatment strategies for improving functioning in patients with MDD.

Registration and protocol

The review protocol was pre-registered in the PROSPERO database (reference number CRD42023386730). Three minor amendments were added and registered in PROSPERO after the initial registration: 1) It was stated that only studies with a sample size of more than 10 individuals would be included 2) It was stated that in addition to studies assessing remission state with MADRS or HAMD17, studies assessing remission using other validated systematic evaluations of remission also would be eligible for inclusion 3) Are more detailed description of strategy for data synthesis and subgroup analysis in the planned meta-analysis was added.

Author Statement

RS: funding acquisition, conceptualisation, methodology, formal analysis, investigation, visualisation, writing of the original manuscript draft, and reviewing and editing the manuscript.

KM: methodology, formal analysis, data curation, visualisation, writing of the original manuscript draft, supervision, and reviewing and editing the manuscript.

MSC: investigation, reviewing and editing the manuscript.

LVK: conceptualisation, supervision, and reviewing and editing the manuscript.

MV: funding acquisition, conceptualisation, methodology, supervision, writing of the original manuscript draft, and reviewing and editing the manuscript.

Declaration of interest statement

RS has within the last three years been a speaker/consultant for Lundbeck.

KM declares no conflicts of interest.

MSC declares no conflicts of interest.

LVK has within the last three years been a consultant for Lundbeck and Teva.

MV has within the last three years been a speaker/consultant for Lundbeck and JanssenCilag.

Data sharing

Study data used in meta-analysis and analytical code are available from the corresponding author (RS) upon reasonable request. Data on global functioning extracted from the included studies are provided in the appendix (p 42).

Acknowledgements

We would like to thank authors of the included studies, in particular the authors who responded to requests for more information.

Table and figures:

Table 1. Characteristics of included studies.

	Origin	Study design	Sample	n	Age mean (SD)	Male (%)	Global functioning scale	MDD diagnostic criteria	Remission: Full	Remission: Partial	Setting
Bromet et al (2011)	Cross-continental (High-income countries)	Cross-sectional	MDD-IR	1,942	NA	NA	WHODAS 2.0	DSM-IV (CIDI)	No current DSM-IV MDE (CIDI)		NC
			MDD-IR	4,903	NA	NA					
			HC	20,096	NA	NA					
	Cross-continental (Low-income countries)		MDD-IR	1,073	NA	NA					NC
			MDD-IR	1,670	NA	NA					
			HC	10,608	NA	NA					
Cohen et al (2013)	North America	RCT	MDD-IR	821	42.3 (12.9)	38.8	WSAS	DSM-IV TR	QUIDS-SR≤5		PC, SC
Collard et al (2018)	Europe	Cohort	MDD-IR	147	70.4 (7.1)	34.8	WHODAS 2.0	DSM-IV (CIDI)	Absence of DSM-IV (CIDI) depression diagnosis		PS, SC
			HC	111	69.3 (6.7)	37.9					
Daniel et al (2013)	Europe	Cross-sectional	MDD-IR	25	50.60 (8.28)	36.0	GAF	DSM-IV TR	HDRS-17 ≤7		SC

Ermis et al (2021)	Europe	Case series	MDD-IR	16	41.4 (9.3)	43.75	GAF	DSM-VI	MADRS<10		SC
Fennig et al (2002)	Asia	Case-control	MDD-PR	30	49.77 (13.74)	50.0	GAF	DSM-VI		HDRS-17<12	SC
			HC	36	30.61 (9.78)	50.0					
Furukawa et al (2001)	Asia	Case series	MDD-IR	53	NA	NA	GAF	DSM-VI	HDRS-17 ≤7		PC, SC
GokcerTulaci et al (2020)	Europe	Case-control	MDD-IR	80	63.5 (3.9)	42.5	WHODAS 2.0	DSM-VI	HDRS-17 ≤7		SC
			MDD-PR	80	64.8 (4.72)	25.0				HDRS-17 8-18	
			HC	80	64.7 (3.82)	45.0					
Green et al (2012)	Europe	Case-control	MDD-IR	27	25.6 (7.5)	18.5	GAF	DSM-IV TR	MADRS≤10		NC
			HC	28	22.7 (3.5)	25.0					
Harada et al (2017)	Asia	Case-series	MDD-IR	158	47.7 (14.9)	49.4	SOFAS	DSM-IV TR	HAMD-17 ≤7		SC
			MDD-PR	165	44.8 (14.7)	46.7				HDRS-17 8-18	
Harada et al (2018)	Asia	Cohort	MDD-IR	16	NA	37.5	GAF				SC
			HC	30		36.7					
Kennedy et al (2019)	North America	RCT	MDD-IR	55	NA	NA	SDS	MINI	MADRS≤10		PC, SC
Kocsis et al (2002)	North America	RCT	MDD-PR (Sertraline Hydrochloride treatment)	77	40.8 (9.0)	37.7	LIFE	DSM-III-R		HDRS-17 ≤15	SC
			MDD-PR (Placebo)	84	42.4 (9.7)	31.0					

Musket et al (2021)	North America	Case-control	MDD-IR	32	31.23 (11.38)	35.50	GAF	DSM-VI (SCID-IV)	IDS-C ≤11	NC
			HC	30	31.93 (9.36)	36.70				
Nierenberg et al (2019)	Europe	RCT	MDD-PR (SSRI treatment)	49	47.9 (11.5)	30.6	FAST	DSM-IV TR		SC
			MDD-PR (SSRI + vortioxetine treatment)	52	45.9 (12.7)	21.2				
			MDD-PR (Vortioxetine treatment)	50	50.6 (10.0)	32.0				
Oakes et al (2015)	Cross-continental	RCT	MDD-IR (SSRI + edivoxetine treatment)	294	47.5 (11.9)	24.1	SDS	DSM-IV TR (MINI)	MADRS≤10	NA
			MDD-IR (SSRI + placebo)	292	46.9 (12.3)	22.6				
Ong et al (2017)	North America	Case-control	MDD-IR	30	27.9 (6.4)	27.0	GAF	DSM-VI (SCID-IV)	IDS-C ≤11 and no current MDD acording to SCID-IV	NC, PC, SC
			HC	27	28.4 (6.5)	37.0				
Ormel et al (2004)	Europe	Case-series	MDD-IR	216	NA	NA	GSDS	DSM-III-R (CIDI)	Absence of DSM-III-R (CIDI) MDE	NC
			HC	3,736	NA	NA				

Pérez et al (2021)	Europe	Cross-sectional	MDD-PR	583	49.7 (12.9)	29.0	SOFAS			Partial remission defined by DSM-IV criteria with a HDRS-6≥3	PC
Pulcu et al (a) (2014)	Europe	Case-control	MDD-IR	21	25.7 (7.8)	19.05	GAF	DSM-IV TR (SCID-1)	MADRS<10		NC
			HC	18	22.8 (3.0)	16.67					
Pulcu et al (b) (2014)	Europe	Case-control	MDD-IR	29	38.34 (5.9)	20.69	GAF	DSM-IV TR	No current MDD according to DSM-IV and not taking psychotropic medication		NC
			HC	29	38.0 (6.6)	34.48					
Riihimäki et al (2015)	Europe	Case-series	MDD-IR	51	52.0 (13.6)	19.61	SOFAS	DSM-IV (SCID-1)	No "current state of depression" defined by DSM-IV criteria (SCID-1)		PC
			MDD-PR	36	46.1 (13.8)	22.22				DSM-IV	

Romera et al (2010)	Europe	Case-series	MDD-IR	146	50.3 (15.0)	22.6	SOFAS	DSM-IV	HDRS-17 ≤7 and not meeting DSM-IV criteria for MDD		SC
			MDD-PR	146	50.7 (14.1)	22.6				HDRS-17 8-15 and not meeting DSM-IV criteria for MDD	
Romera et al (2014)	Europe	Pooled analysis of two RCT studies	MDD-IR	436	NA	29.6	SDS	DSM-IV	HDRS-17 ≤7		NA
Rothschild et al (2014)	Cross-continental	RCT	MDD-PR	483	NA	24.22	SDS	DSM-IV		MADRS≤15	NA
Rytsala et al (2006)	Europe	Case-series	MDD-IR	116	NA	NA	SOFAS	DSM-IV	No DSM-IV MDE criteria symptoms		SC
Schennach et al (2019)	Europe	Case-series	MDD-IR	301	45.7 (11.78)	32.0	GAF		HDRS-17 ≤7		SC
Sheehan et al (2011)	Cross-continental	Pooled analysis of three RCT studies	MDD-IR	521	NA	NA	SDS	DSM-IV (MINI)	HDRS-17 ≤7		NA
Shin et al (2021)	Asia	Case-series	MDD-PR (Patients in remission at 8 week follow-up)	62	51.19 (16.75)	29.03	SDS			HDRS-17 8-15	SC

			MDD-PR (Patients not in remission at 8 week follow-up)	72	51.47 (15.55)	34.72					
Sjonnesen et al (2016)	North America	Cross-sectional (epidemiologic study)	MDD-IR	NA	NA	NA	WHODAS 2.0 (12-item version)	DSM-IV MDE (CIDI)	No past month MDE on CIDI		NC
Tharoor et al (2008)	Asia	Cross-sectional	MDD-IR (subjects without chronic comorbid medical illness)	20	38.50 (5.53)	45.0	WHODAS 2.0 (modified version)	ICD-10	ICD-10 DCR criteria for recurrent depressive disorder in remission		SC
			MDD-IR (subjects with chronic comorbid medical illness)	20	41.0 (4.21)	55.0					
VanDerVoort et al (2015)	Europe	Case-control	MDD-IR (patients with history of single-episode MDD)	421	NA	NA	WHODAS 2.0	DSM-IV-TR (CIDI)			NC, PC, SC
			MDD-IR (patients with history of recurrent MDD)	542	NA	NA					
			HC	530	NA	NA					
Vincent-Gil et al (2022)	Europe	RCT	MDD-PR (INCREM treatment)	9	50.56 (6.88)	11.1	FAST	DSM-V		HDRS-17 <14	SC
			MDD-PR (Psychoeducation treatment)	9	51.22 (6.63)	55.6					

			MDD-PR (TAU)	8	53.75 (5.83)	12.5					
Vincent-Gil et al (2022)	Europe	Cross-sectional	MDD-IR	28	51.04 (11.49)	46.0	FAST	DSM-IV TR	HDRS-17 ≤7		SC
			MDD-PR	120	52.18 (9.41)	31.7				HDRS-17 8-18	
Viinamaki et al (2008)	Europe	Case-series	MDD-IR	52	NA	NA	SOFAS	DSM-III-R (SCID)	BDI ≤8		NA
			MDD-PR	22	NA	NA				BDI 9-14	
Weinberg et al (2017)	North America	Case-control	MDD-IR (history of non-melancholic depression)	56	23.05 (3.26)	30.4	GAF	DSM-IV (SCID)	No current DSM-IV criteria for MDD		NC, PC
			MDD-IR (history of melancholic depression)	29	23.34 (3.34)	42.3					
			HC	81	21.78 (2.85)	39.5					
Xiao et al (2018)	Asia	Cross-sectional	MDD-IR	770	44.4 (14.0)	37.7	SDS	ICD-10	QUIDS-SR≤5		SC
Yamada et al (2015)	Asia	Case-series	MDD-IR (Patients with theory of mind deficit)	42	46.38 (10.09)	54.76	SOFAS	DSM-IV	HDRS-17 ≤7		SC
			MDD-IR (Patients with no theory of mind deficit)	58	46.19 (9.24)	55.17					
Yang et al (2020)	Asia	Case-series	MDD-IR	60	46.5 (12.1)	35.0	WSAS	DSM-IV	HDRS-17 ≤7		SC
Yucel et al (2009)	North America	Case-control	MDD-IR	13	35.9 (13.9)	30.8	GAF	DSM-IV	HDRS-17 <7		SC
			HC	40	37.2 (10.1)	37.5					

Zahn et al (2015)	Europe	Case-control	MDD-IR	101	33.3 (12.2)	25.7	GAF	DSM-IV	MADRS≤10	NC
			HC	70	30.0 (12.4)	34.3				
Zhu et al (2023)	Asia	Case-series	MDD-IR	179	47.3 (13.8)	30.7	SDS	ICD-10	QUIDS-SR≤5	SC

MDD-IR= Major Depressive Disorder in remission. MDD-PR= Major Depressive Disorder in partial remission. HC= healthy control individuals. NC= non-clinical setting. PC= primary care setting. SC= secondary care setting. MDE=Major Depressive Episode. RCT= randomised controlled trial. CIDI=Composite International Diagnostic Interview. MINI= The Mini-International Neuropsychiatric Interview. QUIDS-SR=Quick Inventory of Depressive Symptomatology Self Report. HDRS=Hamilton Depression Rating Scale. MADRS=Montgomery–Åsberg Depression Rating Scale. IDS-C=The Inventory of Depressive Symptomatology, Clinician Rating. BDI=Beck Depression Inventory. WHODAS=World Health Organization Disability Assessment Schedule. WSAS=Work And Social Functioning. FAST= Functional Assessment Short Test. GAF= Global Assessment of Functioning. SOFAS= Social and Occupational Functioning Assessment Scale. SDS= Sheehan Disability Scale. GSDS= Groningen Social Disability Schedule. LIFE= Longitudinal Interval Follow-up Evaluation. NA=not available.

Figure 1. Overview of study selection process.

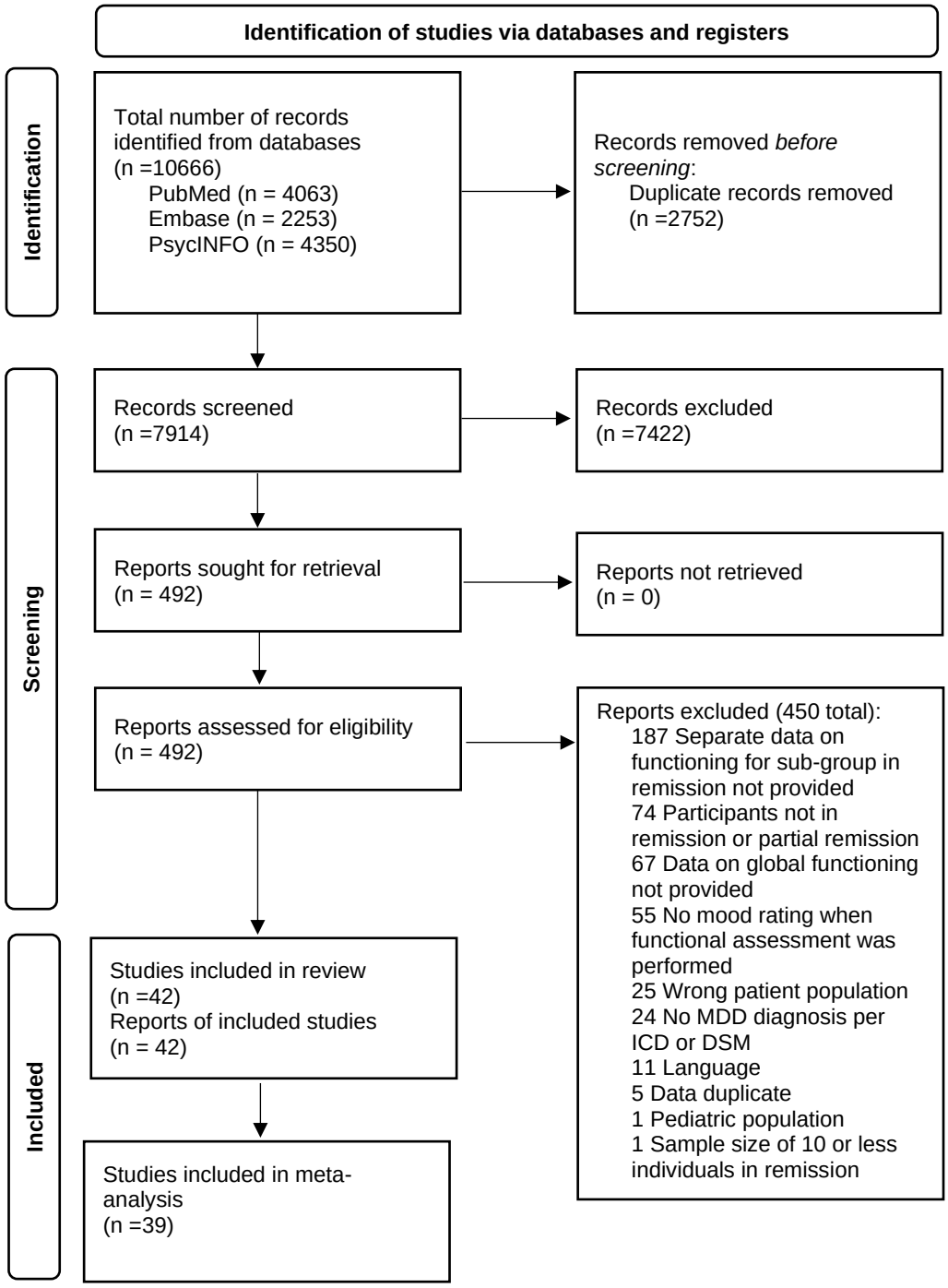
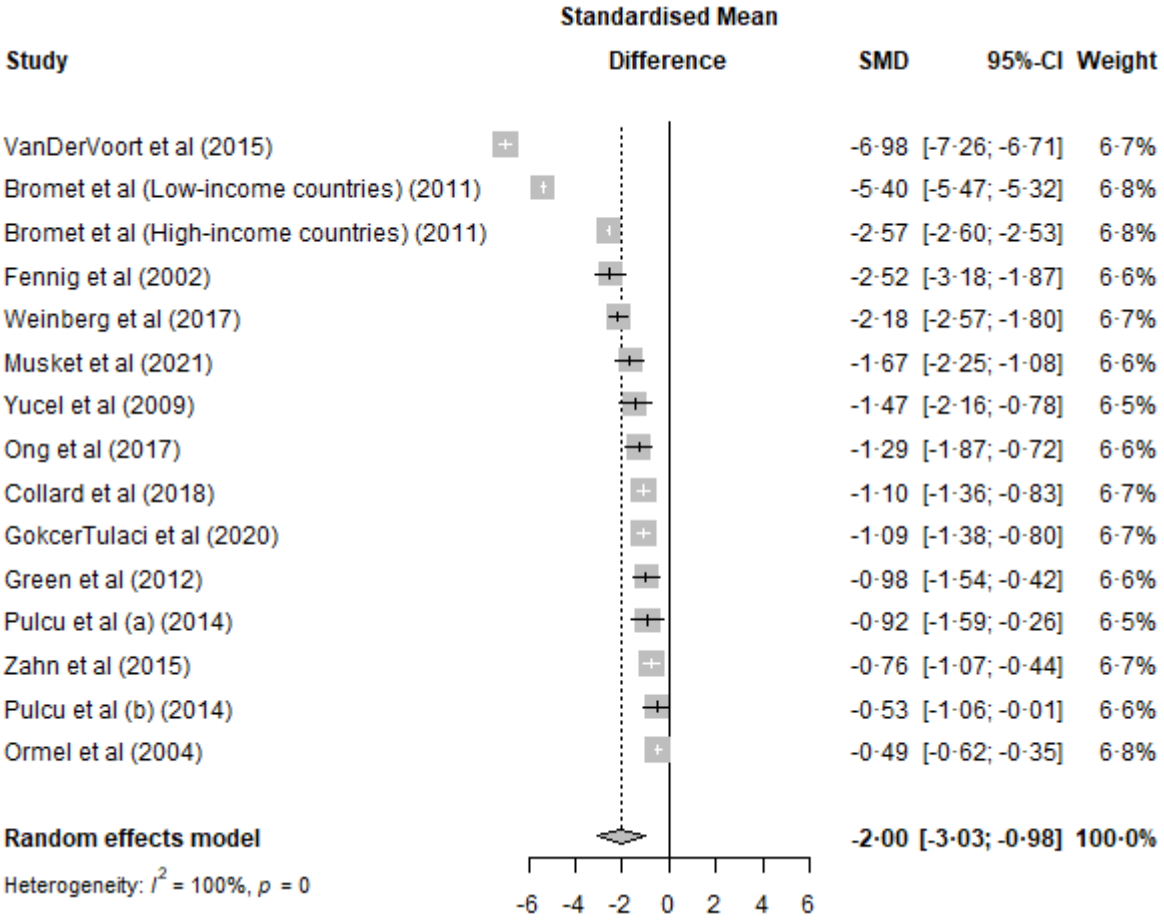


Figure 2. Forest plot of comparison of global functioning of patients with major depressive disorder in full or partial remission with healthy control individuals.



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Appendix/Supplementary Materials

Table of Contents

A: Search Strategy

Search strategy was performed in PubMed, EMBASE and PsycINFO using the following set of search terms using Medical Subject Headings (MeSH) when available; Construct A: major depressive disorder. Construct B: “functional assessment” OR “global functioning” OR "functional recovery OR "functional outcomes OR "functional disability OR "psychosocial functioning” OR "functional impairment” OR "Social and Occupational Functioning Assessment Scale" OR "SOFAS" OR "SDS OR "Sheehan disability scale" OR "University of California San Diego Performance-based Skills Assessment" OR "UPSA" OR "Assessment of Motor and Process Skills” OR "AMPS" OR "WHO Disability Assessment Schedule" OR "WHODAS" OR "Global assessment of functioning" OR "GAF" OR "Personal Social Performance" OR "Work and Social Adjustment Scale"[All Fields] OR "WSAS" OR "Functioning assessment short test” OR "international classification of functioning, disability and health".

Full search string as applied in PubMed:

(("Functional assessment"[All Fields] OR "global functioning"[All Fields] OR "functional recovery"[All Fields] OR "functional outcomes"[All Fields] OR "functional outcome"[All Fields] OR "functional disability"[All Fields] OR "psychosocial functioning"[All Fields] OR "functional impairment"[All Fields]) OR ("Social and Occupational Functioning Assessment Scale"[All Fields] OR "SOFAS"[All Fields] OR ("same day surg"[Journal] OR "sds"[All Fields]) OR (("sheehan"[All Fields] OR "sheehan s"[All Fields]) AND ("disabilities"[All Fields] OR "disability"[All Fields] OR "disabled persons"[MeSH Terms] OR ("disabled"[All Fields] AND "persons"[All Fields]) OR "disabled persons"[All Fields] OR "disabled"[All Fields] OR "disablement"[All Fields] OR "disablements"[All Fields] OR "disabling"[All Fields] OR "disablity"[All Fields]) AND ("scale s"[All Fields] OR "scaled"[All Fields] OR "scaling"[All Fields] OR "scalings"[All Fields] OR "weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "scale"[All Fields] OR "scales"[All Fields])) OR (("universiti"[All Fields] OR "universities"[MeSH Terms] OR "universities"[All Fields] OR "University"[All Fields] OR "university s"[All Fields]) AND ("California"[MeSH Terms] OR "California"[All Fields] OR "california s"[All Fields] OR "californias"[All Fields]) AND ("perform"[All Fields] OR "performable"[All Fields] OR "performance"[All Fields] OR "performance s"[All Fields] OR "performances"[All Fields] OR "performative"[All Fields] OR "performatively"[All Fields] OR "performatives"[All Fields] OR "performativities"[All Fields] OR "performativity"[All Fields] OR "performed"[All Fields] OR "performer"[All Fields] OR "performer s"[All Fields] OR "performers"[All Fields] OR "performing"[All Fields] OR "performs"[All Fields]) AND ("skill"[All Fields] OR "skilled"[All Fields] OR

"skillful"[All Fields] OR "skillfulness"[All Fields] OR "Skills"[All Fields]) AND ("assess"[All Fields] OR "assessed"[All Fields] OR "assessement"[All Fields] OR "assesses"[All Fields] OR "assessing"[All Fields] OR "Assessment"[All Fields] OR "assessment s"[All Fields] OR "assessments"[All Fields])) OR ("University"[Title] AND "California"[Title] AND "San"[Title] AND "Diego"[Title] AND "Performance-based"[Title] AND "Skills"[Title] AND "Assessment"[Title]) OR "upsa"[All Fields] OR "Assessment of Motor and Process Skills"[All Fields] OR "AMPS"[All Fields] OR ("WHO Disability Assessment Schedule"[All Fields] OR "whodas"[All Fields]) OR "global assessment of functioning"[All Fields] OR "GAF"[All Fields] OR "Work and Social Adjustment Scale"[All Fields] OR "WSAS"[All Fields] OR "functioning assessment short test"[All Fields] OR "international classification of functioning, disability and health"[MeSH Terms])) AND ("depressive disorder, major"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields] AND "major"[All Fields]) OR "major depressive disorder"[All Fields] OR ("major"[All Fields] AND "depressive"[All Fields] AND "disorder"[All Fields]) OR "major depressive disorder"[All Fields] OR "depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR ("major"[All Fields] AND "depressive"[All Fields] AND "disorder"[All Fields]))

B: Studies Excluded At Full-text Screening with Reason for exclusion

Full-text review exclusion criteria:

A: Separate data on functioning for sub-group in remission not provided

B: Participants not in remission or partial remission

C: Data on global functioning not provided

D: No mood rating when functional assessment was performed

E: Wrong patient population

F: No MDD diagnosis per ICD or DSM

G: Language

H: Data duplicate

I: Pediatric population

J: Sample size of 10 or less individuals in remission

ARTICLE	REASON FOR EXCLUSION
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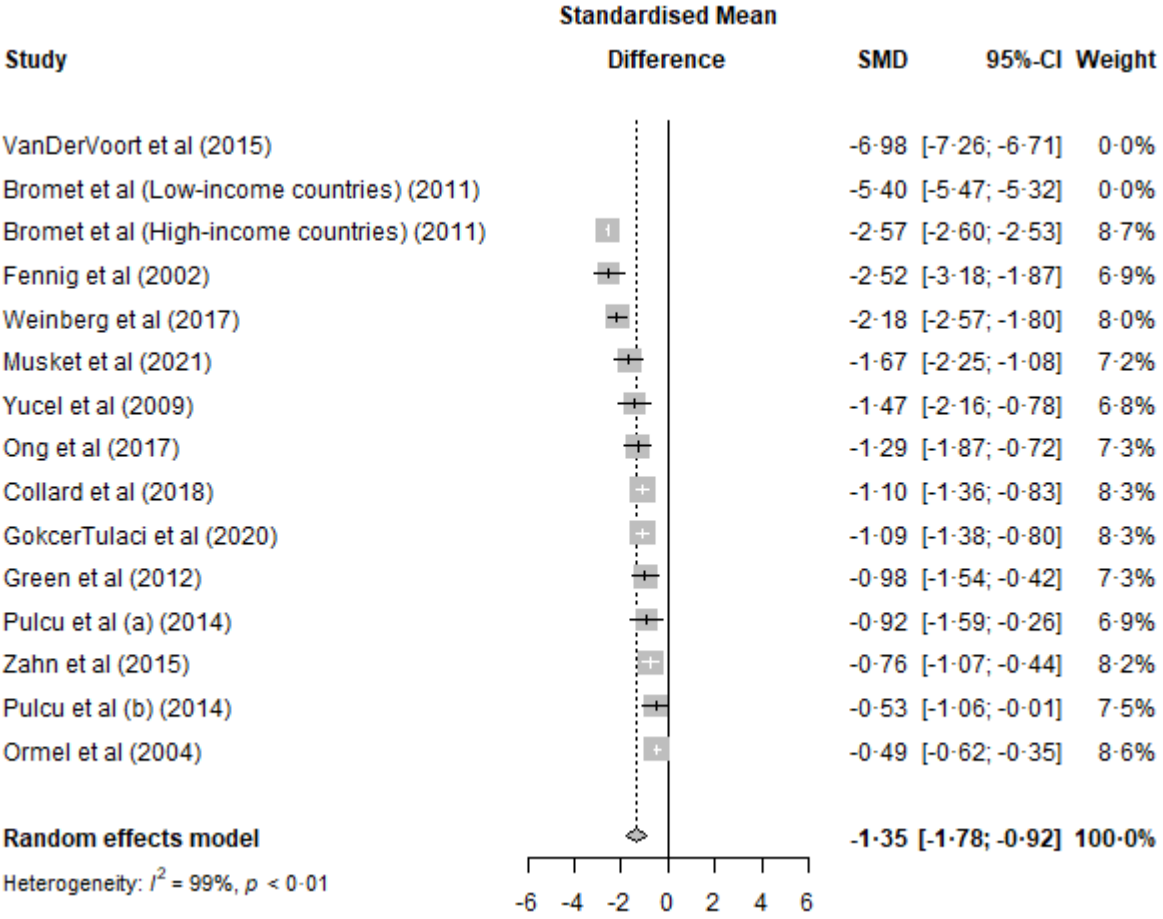
C: Table overview functioning scales

Table Overview of global functioning scales used in the included studies		
Measurements	Assessment method	Total score range and interpretation
WHODAS 2.0	Questionnaire	0-100 Higher scores = worse functioning
WHODAS 12-item version	Questionnaire	12-60 Higher scores = worse functioning
WHODAS 2.0 modified	Interview	0-5 Higher scores = worse functioning
FAST	Interview	0-72 Higher scores = worse functioning
GAF	Interview	0-100 Higher scores = better functioning
SOFAS	Interview	0-100 Higher scores = better functioning
SDS	Questionnaire	0-30 Higher scores = worse functioning
GSDS	Interview	0-23 Higher scores = worse functioning
LIFE	Interview	0-5 Higher scores = worse functioning
WHODAS, World Health Organization Disability Assessment Schedule; FAST, Functional Assessment Short Test; GAF, Global Assessment of Functioning; SOFAS, Social and Occupational Functioning Assessment Scale; SDS, Sheehan Disability Scale; GSDS, Groningen Social Disability Schedule; LIFE, Longitudinal Interval Follow-up Evaluation		

D: Forest plot studies with the largest effect size excluded



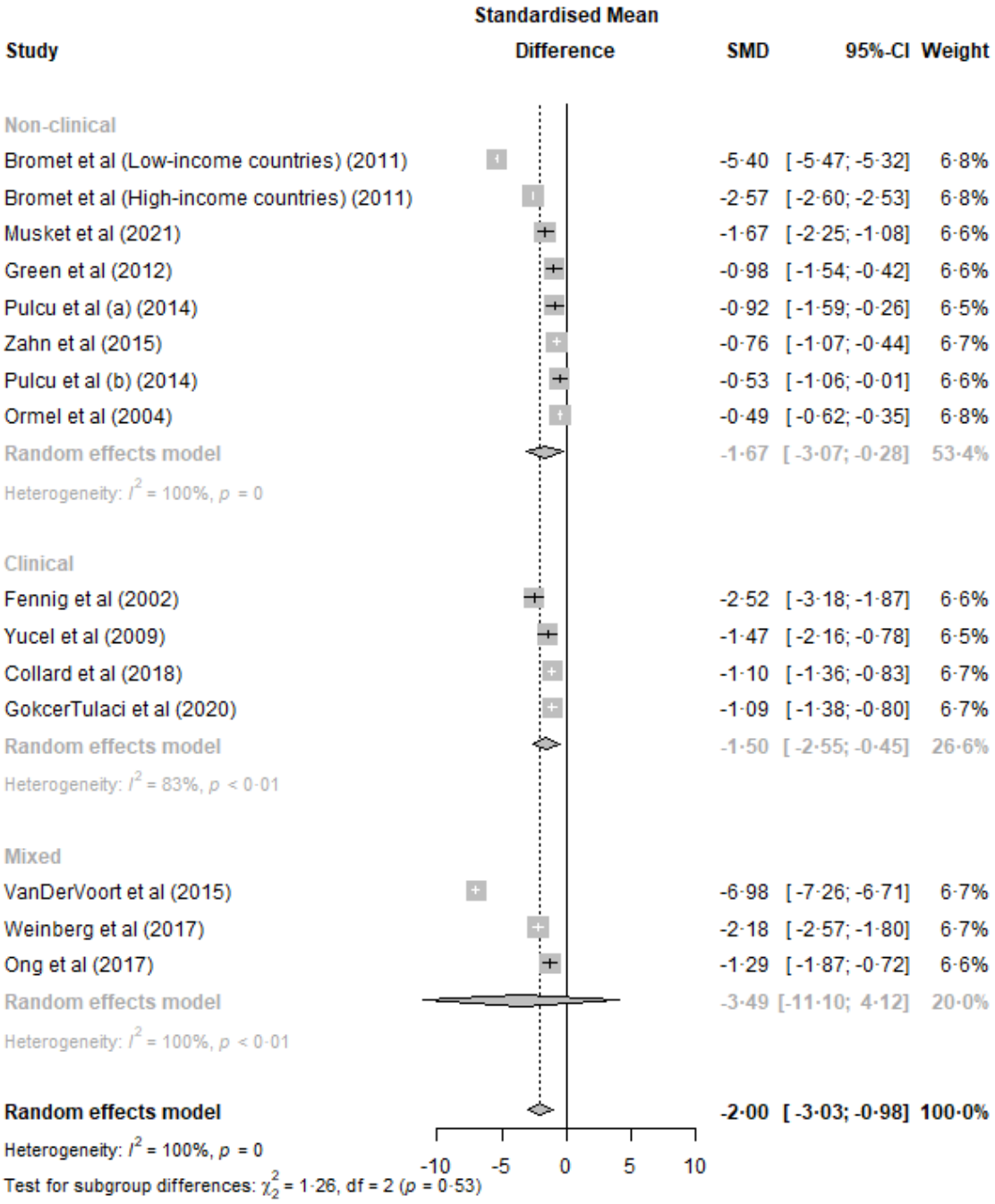
E: Meta-regression

Table Metaregression of the association between study demographical and clinical variables and effect size of functioning in patients with major depressive disorder compared with healthy control individuals.

	estimate	CI 95	N	p.value
Sex (% male)	-0.05	-0.09-(-0.02)	11	0.004
Mean age of patients with unipolar depression	0.002	-0.02-0.03	11	0.84
Mean MADRS score	0.16	-0.15-0.46	3	0.099
Mean age at onset	0.02	-0.02-0.06	5	0.249
Comorbid psychiatric disorder (%)	-0.01	-0.03-0.01	5	0.344
Mean HDRS17 score	-0.152	-2.19-1.89	3	0.520
Mean number of previous depressive episodes	0.010	-0.12-0.14	6	0.832
Mean time since last depressive episode (months)	-0.012	-0.67-0.64	1	0.840
Education duration of patients with unipolar depression (years)	0.48	-0.26-1.21	9	0.169
Time since last depressive episode (months)	-0.01	-0.67-0.64	3	0.840

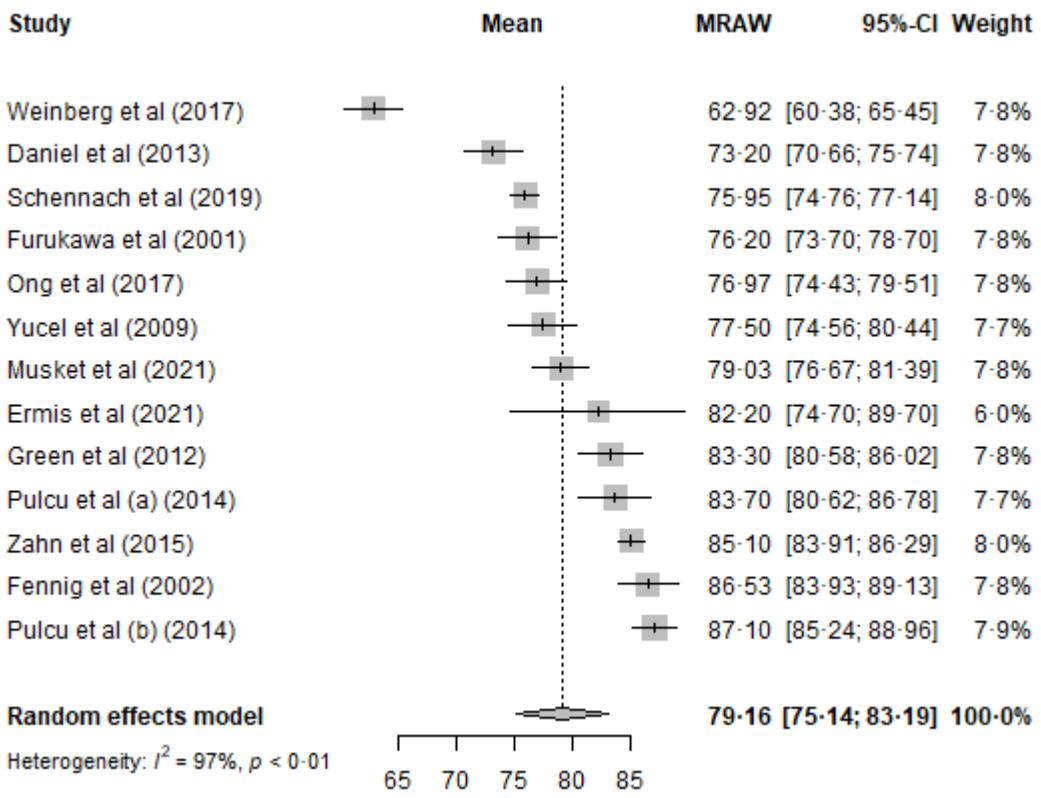
Data shown for all variables where data were available for 3 or more studies. MADRS: Montgomery-Asberg Depression Rating Scale; HDRS17: Hamilton Depression Rating Scale, 17 items.

F: Forest plot subgroups

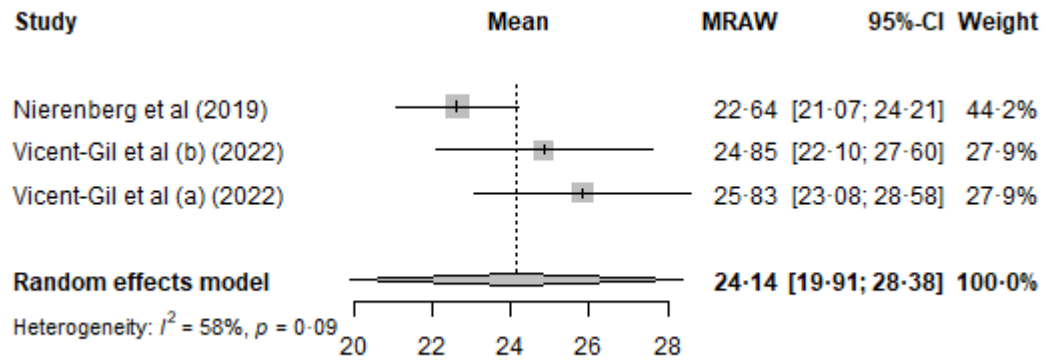


G: Forest plots for each functioning scale

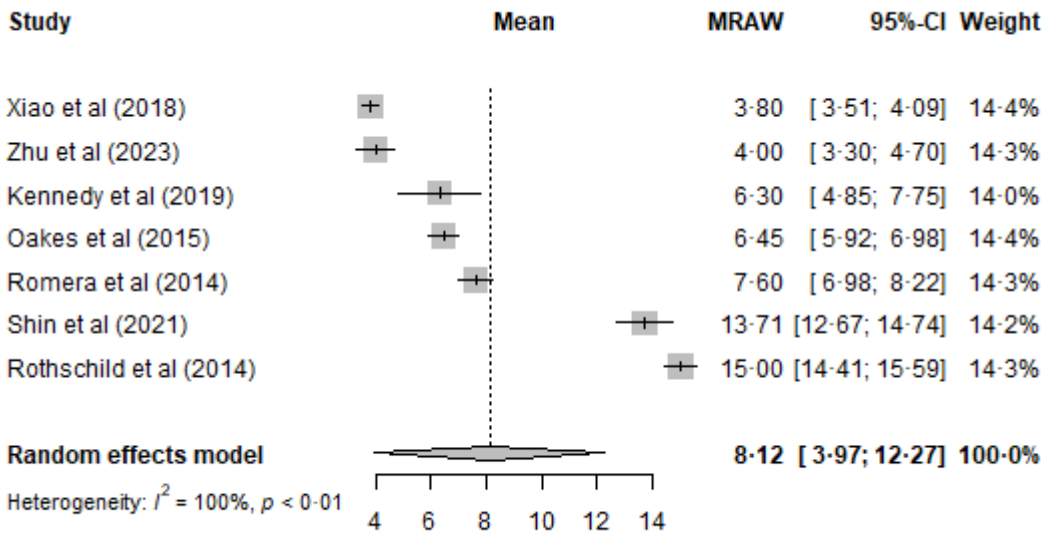
GAF:



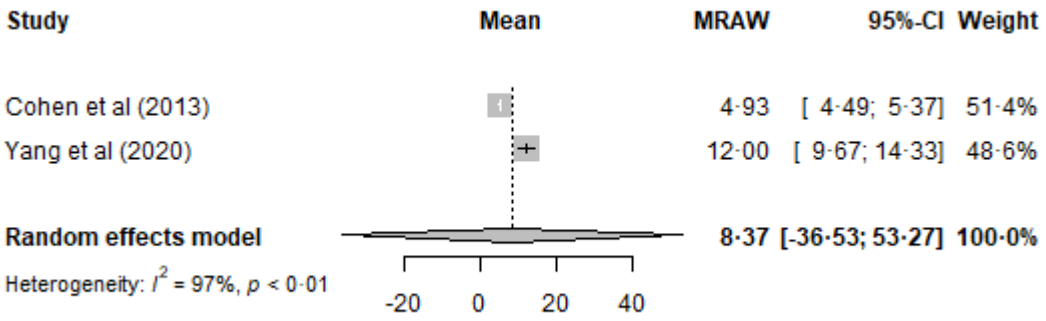
FAST:



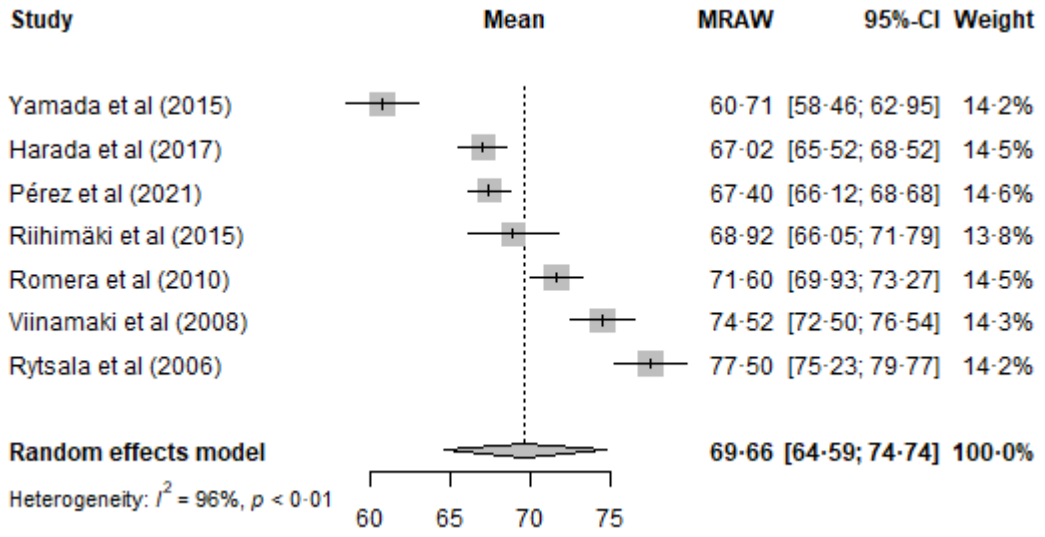
SDS:


Study
Mean
MRAW
95%-CI
Weight
Xiao et al (2018) 3·80 [3·51; 4·09] 14·4%
Zhu et al (2023) 4·00 [3·30; 4·70] 14·3%
Kennedy et al (2019) 6·30 [4·85; 7·75] 14·0%
Oakes et al (2015) 6·45 [5·92; 6·98] 14·4%
Romera et al (2014) 7·60 [6·98; 8·22] 14·3%
Shin et al (2021) 13·71 [12·67; 14·74] 14·2%
Rothschild et al (2014) 15·00 [14·41; 15·59] 14·3%
Random effects model 8·12 [3·97; 12·27] 100·0%
Heterogeneity: I^2 = 100%, p < 0·01
4
6
8
10
12
14

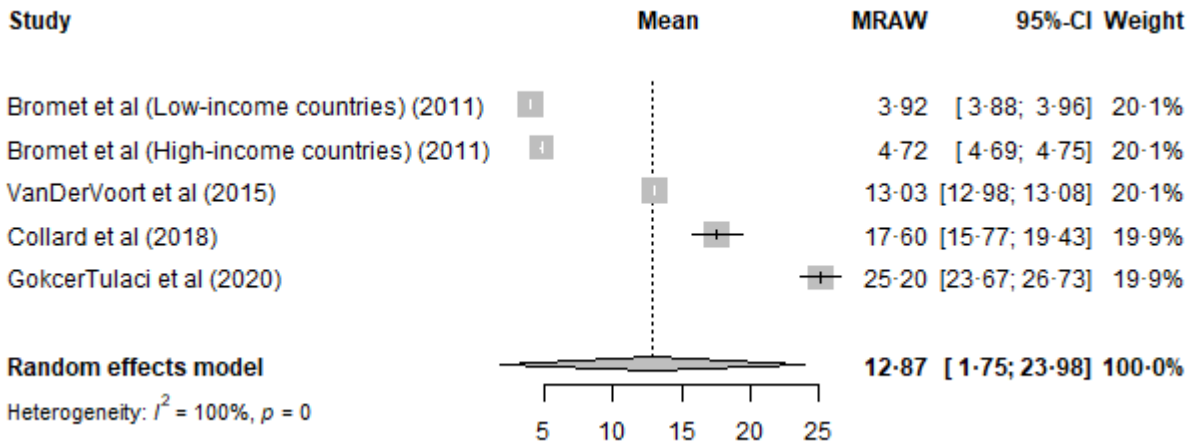
WSAS:


Study
Mean
MRAW
95%-CI
Weight
Cohen et al (2013) 4·93 [4·49; 5·37] 51·4%
Yang et al (2020) 12·00 [9·67; 14·33] 48·6%
Random effects model 8·37 [-36·53; 53·27] 100·0%
Heterogeneity: I^2 = 97%, p < 0·01
-20
0
20
40

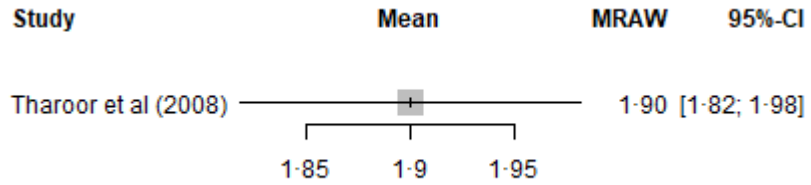
SOFAS:


Study
Mean
MRAW
95%-CI
Weight
Yamada et al (2015) 60·71 [58·46; 62·95] 14·2%
Harada et al (2017) 67·02 [65·52; 68·52] 14·5%
Pérez et al (2021) 67·40 [66·12; 68·68] 14·6%
Riihimäki et al (2015) 68·92 [66·05; 71·79] 13·8%
Romera et al (2010) 71·60 [69·93; 73·27] 14·5%
Viinamaki et al (2008) 74·52 [72·50; 76·54] 14·3%
Rytsala et al (2006) 77·50 [75·23; 79·77] 14·2%
Random effects model 69·66 [64·59; 74·74] 100·0%
Heterogeneity: I^2 = 96%, p < 0·01
60
65
70
75

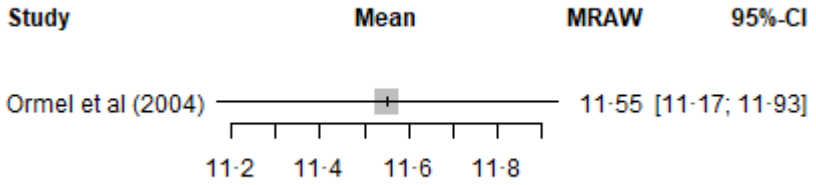
WHODAS 2.0:



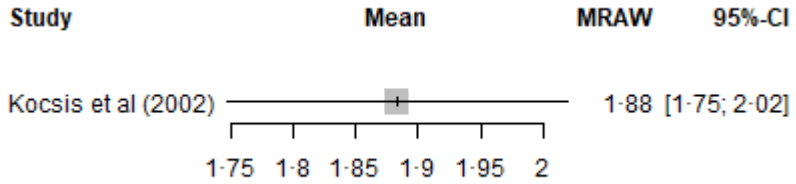
WHODAS 2.0 (modified, range 0-5):



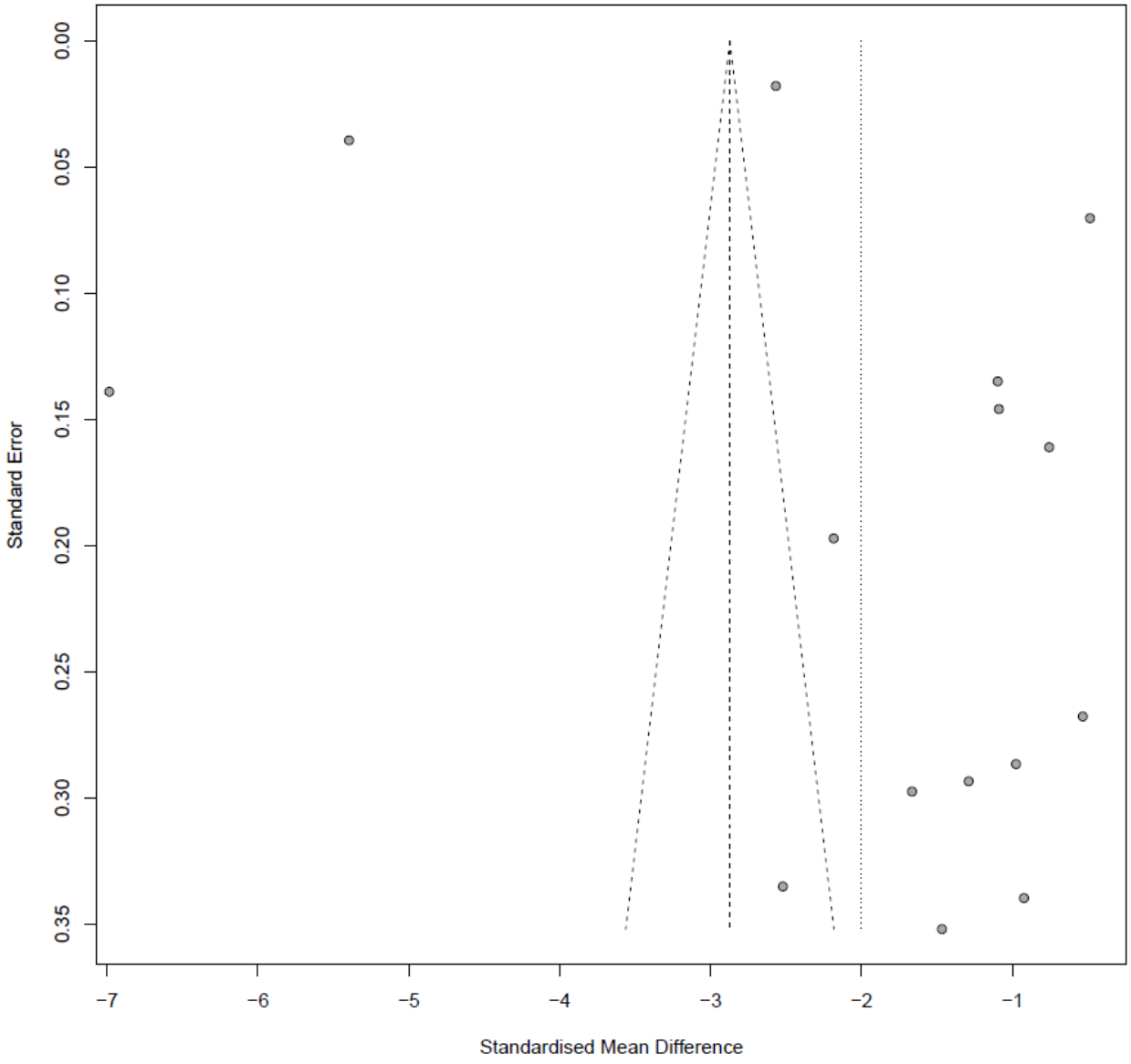
GSDS:



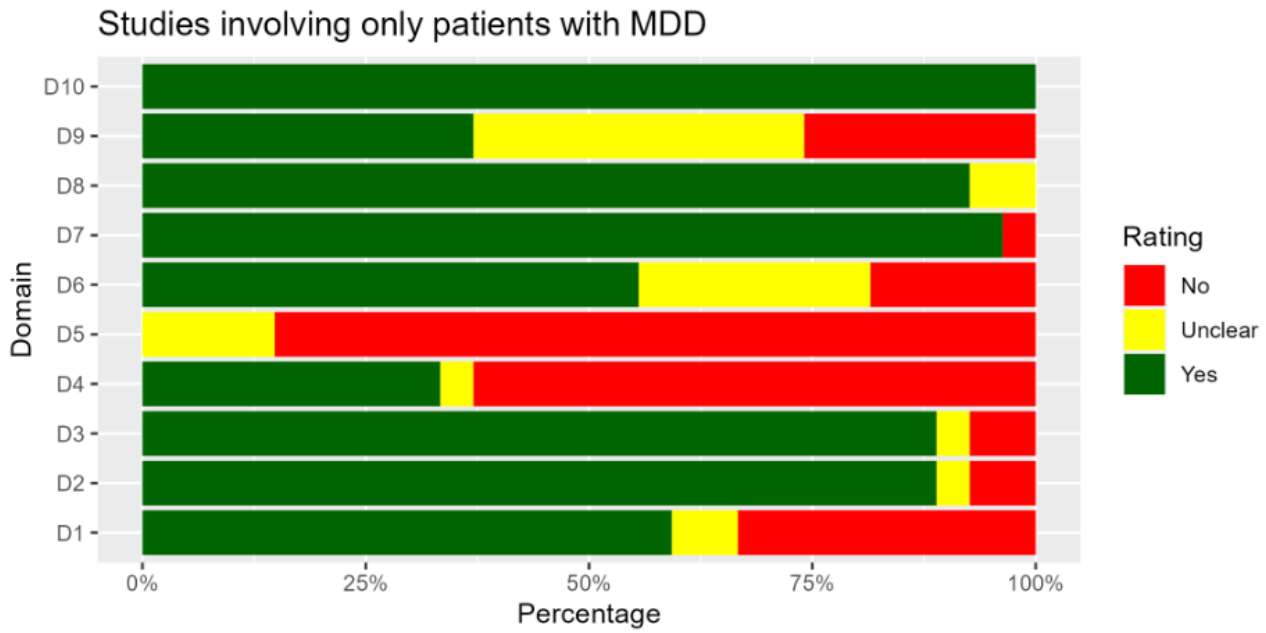
LIFE:



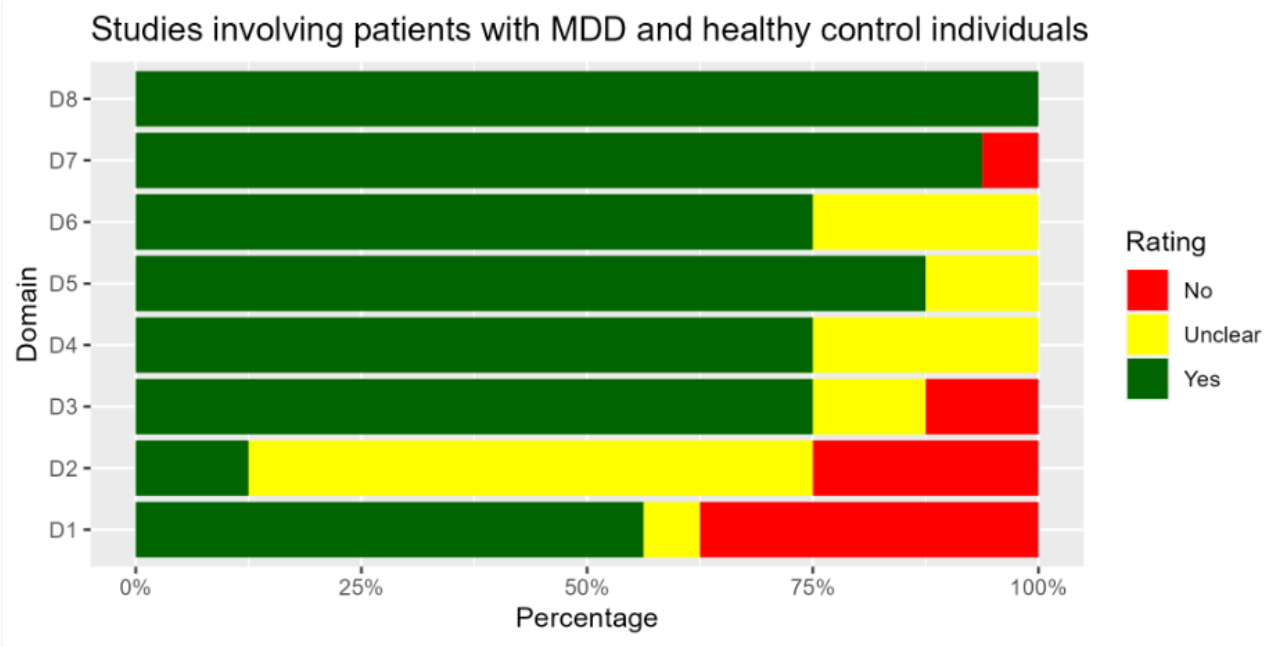
H: Funnel Plot



I: Scoring for risk of bias for each study



D1	Were there clear criteria for inclusion in the case series?
D2	Was the condition measured in a standard, reliable way for all participants included in the case series?
D3	Were valid methods used for identification of the condition for all participants included in the case series?
D4	Did the case series have consecutive inclusion of participants?
D5	Did the case series have complete inclusion of participants?
D6	Was there clear reporting of the demographics of the participants in the study?
D7	Was there clear reporting of clinical information of the participants?
D8	Were the outcomes or follow up results of cases clearly reported?
D9	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
D10	Was statistical analysis appropriate?



D1. Were the criteria for inclusion in the sample clearly defined?

D2. Were the study subjects and the setting described in detail?

D3. Was the exposure measured in a valid and reliable way?

D4. Were objective, standard criteria used for measurement of the condition?

D5. Were confounding factors identified?

D6. Were strategies to deal with confounding factors stated?

D7. Were the outcomes measured in a valid and reliable way?

D8. Was appropriate statistical analysis used?

Table extracted global functioning scores from individual studies

	Sample	n	Age mean (SD)	Male (%)	Global functioning scale	Extracted global functioning score mean (SD)
Bromet et al (2011)[35]	MDD-IR	1,942	NA	NA	WHODAS 2.0	6.8 (0.3)
	MDD-IR	4,903	NA	NA		3.9 (0.1)
	HC	20,096	NA	NA		3.0 (0.1)
	MDD-IR	1,073	NA	NA		5.2 (0.3)
	MDD-IR	1,670	NA	NA		3.1 (0.2)
	HC	10,608	NA	NA		1.3 (0.1)
Cohen et al (2013)[36]	MDD-IR	821	42.3 (12.9)	38.8	WSAS	4.93 (6.42)
Collard et al (2018)[37]	MDD-IR	147	70.4 (7.1)	34.8	WHODAS 2.0	17.6 (11.3)
	HC	111	69.3 (6.7)	37.9		6.9 (7.1)
Daniel et al (2013)[38]	MDD-IR	25	50.60 (8.28)	36.0	GAF	73.20 (6.49)
Ermis et al (2021)[39]	MDD-IR	16	41.4 (9.3)	43.75	GAF	82.2 (15.3)
Fennig et al (2002)[40]	MDD-PR	30	49.77 (13.74)	50.0	GAF	86.53 (7.26)
	HC	36	30.61 (9.78)	50.0		99.0 (0.00)
Furukawa et al (2001)[41]	MDD-IR	53	NA	NA	GAF	76.2 (9.29)
GokcerTulaci et al (2020)[42]	MDD-IR	80	63.5 (3.9)	42.5	WHODAS 2.0	16.6 (5.39)
	MDD-PR	80	64.8 (4.72)	25.0		33.8 (4.13)
	HC	80	64.7 (3.82)	45.0		15.9 (4.7)
Green et al (2012)[43]	MDD-IR	27	25.6 (7.5)	18.5	GAF	83.3 (7.2)
	HC	28	22.7 (3.5)	25.0		89.3 (4.7)
Harada et al (2017)[44]	MDD-IR	158	47.7 (14.9)	49.4	SOFAS	75.5 (10.7
	MDD-PR	165	44.8 (14.7)	46.7		58.9 (11.3)
Harada et al (2018)[71]	MDD-IR	16	NA	37.5	GAF	NA
	HC	30	NA	36.7		NA
Kennedy et al (2019)[21]	MDD-IR	55	NA	NA	SDS	6.3 (5.5)
Kocsis et al (2002)[45]	MDD-PR (Sertraline	77	40.8 (9.0)	37.7	LIFE	1.82 (0.90)

	Hydrochloride treatment)					
	MDD-PR (Placebo)	84	42.4 (9.7)	31.0		1.94 (0.87)
Musket et al (2021)[47]	MDD-IR	32	31.23 (11.38)	35.50	GAF	79.03 (6.82)
	HC	30	31.93 (9.36)	36.70		88.03 (3.03)
Nierenberg et al (2019)[22]	MDD-PR (SSRI treatment)	49	47.9 (11.5)	30.6	FAST	24.3 (10.4)
	MDD-PR (SSRI + vortioxetine treatment)	52	45.9 (12.7)	21.2		21.3 (9.2)
	MDD-PR (Vortioxetine treatment)	50	50.6 (10.0)	32.0		22.4 (9.9)
Oakes et al (2015)[48]	MDD-IR (SSRI + edivoxetine treatment)	294	47.5 (11.9)	24.1	SDS	6.6 (6.7)
	MDD-IR (SSRI + placebo)	292	46.9 (12.3)	22.6		6.3 (6.3)
Ong et al (2017)[49]	MDD-IR	30	27.9 (6.4)	27.0	GAF	76.97 (7.11)
	HC	27	28.4 (6.5)	37.0		85.85 (6.41)
Ormel et al (2004)[50]	MDD-IR	216	NA	NA	GSDS	11.55 (2.88)
	HC	3,736	NA	NA		10.46 (2.20)
Pérez et al (2021)[51]	MDD-PR	583	49.7 (12.9)	29.0	SOFAS	67.4 (15.8)
Pulcu et al (a) (2014)[52]	MDD-IR	21	25.7 (7.8)	19.05	GAF	83.7 (7.2)
	HC	18	22.8 (3.0)	16.67		89.4 (4.3)
Pulcu et al (b) (2014)[53]	MDD-IR	29	38.34 (5.9)	20.69	GAF	87.1 (5.1)
	HC	29	38.0 (6.6)	34.48		90.0 (5.6)
Riihimäki et al (2015)[54]	MDD-IR	51	52.0 (13.6)	19.61	SOFAS	73.1 (13.3)
	MDD-PR	36	46.1 (13.8)	22.22		63.0 (12.0)
Romera et al (2010)[55]	MDD-IR	146	50.3 (15.0)	22.6	SOFAS	80.4 (10.5)
	MDD-PR	146	50.7 (14.1)	22.6		62.8 (12.6)
Romera et al (2014)[24]	MDD-IR	436	NA	29.6	SDS	7.6 (6.57)
Rothschild et al (2014)[56]	MDD-PR	483	NA	24.22	SDS	15.0 (6.58)
Rytsala et al (2006)[57]	MDD-IR	116	NA	NA	SOFAS	77.5 (12.5)
Schennach et al (2019)[58]	MDD-IR	301	45.7 (11.78)	32.0	GAF	75.95 (10.56)

Sheehan et al (2011)[23]	MDD-IR	521	NA	NA	SDS	7.1 (NA)
Shin et al (2021)[59]	MDD-PR (Patients in remission at 8 week follow-up)	62	51.19 (16.75)	29.03	SDS	13.75 (6.15)
	MDD-PR (Patients not in remission at 8 week follow-up)	72	51.47 (15.55)	34.72		13.67 (6.14)
Sjonnesen et al (2016)[76]	MDD-IR	NA	NA	NA	WHODAS 2.0 (12-item version)	14.4 (NA)
Tharoor et al (2008)[60]	MDD-IR (subjects without chronic comorbid medical illness)	20	38.50 (5.53)	45.0	WHODAS 2.0 (modified version)	1.9 (0.22)
	MDD-IR (subjects with chronic comorbid medical illness)	20	41.0 (4.21)	55.0		1.9 (0.31)
VanDerVoort et al (2015)[61]	MDD-IR (patients with history of single-episode MDD)	421	NA	NA	WHODAS 2.0	12.3 (0.5)
	MDD-IR (patients with history of recurrent MDD)	542	NA	NA		13.6 (0.5)
	HC	530	NA	NA		8.0 (0.5)
Vincent-Gil et al (2022)[62]	MDD-PR (INCREM treatment)	9	50.56 (6.88)	11.1	FAST	21.22 (4.12)
	MDD-PR (Psychoeducation treatment)	9	51.22 (6.63)	55.6		28.78 (8.84)
	MDD-PR (TAU)	8	53.75 (5.83)	12.5		24.5 (6.09)
Vincent-Gil et al (2022)[46]	MDD-IR	28	51.04 (11.49)	46.0	FAST	3.68 (3.86)
	MDD-PR	120	52.18 (9.41)	31.7		31.0 (14.66)
Viinamaki et al (2008)[63]	MDD-IR	52	NA	NA	SOFAS	77.7 (7.6)
	MDD-PR	22	NA	NA		67.0 (7.0)
Weinberg et al (2017)[64]	MDD-IR (history of non-melancholic depression)	56	23.05 (3.26)	30.4	GAF	64.39 (11.62)

	MDD-IR (history of melancholic depression)	29	23.34 (3.34)	42.3		60.07 (12.23)
	HC	81	21.78 (2.85)	39.5		85.19 (7.84)
Xiao et al (2018)[65]	MDD-IR	770	44.4 (14.0)	37.7	SDS	3.8 (4.1)
Yamada et al (2015)[66]	MDD-IR (Patients with theory of mind deficit)	42	46.38 (10.09)	54.76	SOFAS	59.31 (11.56)
	MDD-IR (Patients with no theory of mind deficit)	58	46.19 (9.24)	55.17		61.72 (11.38)
Yang et al (2020)[67]	MDD-IR	60	46.5 (12.1)	35.0	WSAS	12.0 (9.2)
Yucel et al (2009)[68]	MDD-IR	13	35.9 (13.9)	30.8	GAF	77.5 (5.4)
	HC	40	37.2 (10.1)	37.5		83.5 (3.5)
Zahn et al (2015)[69]	MDD-IR	101	33.3 (12.2)	25.7	GAF	85.1 (6.1)
	HC	70	30.0 (12.4)	34.3		88.9 (2.7)
Zhu et al (2023)[70]	MDD-IR	179	47.3 (13.8)	30.7	SDS	4.0 (4.8)

MDD-IR= Major Depressive Disorder in remission. MDD-PR= Major Depressive Disorder in partial remission. HC= healthy control individuals. WHODAS=World Health Organization Disability Assessment Schedule. WSAS=Work And Social Functioning. FAST= Functional Assessment Short Test. GAF= Global Assessment of Functioning. SOFAS= Social and Occupational Functioning Assessment Scale. SDS= Sheehan Disability Scale. GSDS= Groningen Social Disability Schedule. LIFE= Longitudinal Interval Follow-up Evaluation. NA=not available.

Paper IV

Rasmus Schwarz, Kamilla Woznica Miskowiak, Lars Vedel Kessing, Maj Vinberg. “Clinical and personal predictors of functioning in affective disorders: exploratory results from baseline and 6-month follow-up of a randomised controlled trial.” [Submitted March 2024, Journal of Psychiatric Research].

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Clinical and personal predictors of functioning in affective disorders: exploratory results from baseline and 6-month follow-up of a randomised controlled trial

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Corresponding Author:	Rasmus Schwarz, MD Mental Health Centre, Northern Zealand Hillerød, DENMARK
First Author:	Rasmus Schwarz, MD
Order of Authors:	Rasmus Schwarz, MD
	Kamilla Woznica Miskowiak, PhD
	Lars Vedel Kessing, MD, DMSC
	Maj Vinberg, MD, DMSc
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Clinical and personal predictors of functioning in affective disorders: exploratory results from baseline and 6-month follow-up of a randomised controlled trial

Rasmus Schwarz[1,2], Kamilla Woznica Miskowiak[3,4], Lars Vedel Kessing[2,3], Maj Vinberg[1,2]

1. The Early Multimodular Prevention and Intervention Research Institution (EMPIRI), Mental Health Centre, Northern Zealand, Copenhagen University Hospital – Mental Health Services CPH, Copenhagen, Denmark
2. Department of Clinical Medicine, University of Copenhagen, Copenhagen
3. Copenhagen Affective Disorder Research Centre (CADIC), Psychiatric Centre Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark
4. Department of Psychology, University of Copenhagen, Copenhagen, Denmark

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Tables: 4

Corresponding author: Rasmus Schwarz, rasmus.moeskjaer.schwarz@regionh.dk
Dyrehavevej 48, 3400 Hillerød, Denmark
Orchid ID: 0000-0002-8808-1866

Abstract

Comprehensive knowledge of factors causing and sustaining functional impairment in patients with affective disorders is warranted. The aim is to investigate associations between clinical factors (such as affective symptoms) and personal factors (such as personality traits, coping strategies, and childhood trauma experiences) on functioning and improvement of functioning in patients with affective disorders.

This exploratory study includes data from 103 patients with bipolar disorder and unipolar depressive disorder. Clinician-rated functioning was assessed at baseline using the Functioning Assessment Short Test (FAST), and performance-based functioning was assessed at baseline and 6-month follow-up using the Assessment of Motor and Process Skills (AMPS). Data on clinical and personal factors were collected at baseline. Personal factors were measured by the Eysenck Personality Inventory (EPQ), Coping Inventory for Stressful Situations (CISS) and Childhood Trauma Questionnaire (CTQ). Pearson correlations and multiple linear regression models were used to analyse the association of clinical and personal factors with baseline functioning (FAST) and to identify predictors of improvement in functioning (AMPS) from baseline to follow-up.

At baseline, greater depressive symptom severity, the personality trait neuroticism, emotional coping, and childhood trauma all correlated with poorer functioning (higher FAST scores). In multiple linear regression models, depression severity, emotional coping and childhood trauma were significant predictors of poorer functioning. More childhood trauma was a predictor of less functional improvement measured by AMPS at 6-month follow-up.

In conclusion, maladaptive coping styles and depressive symptoms contribute to functional impairment in patients with affective disorders, while childhood trauma has a negative impact on long-term functional outcomes.

Keywords: Affective disorders, Bipolar disorder, Unipolar depressive disorder, Functioning, Childhood trauma, Coping strategies

Introduction

Affective disorders (bipolar disorder (BD) and unipolar depressive disorder (UD)) are associated with functional impairment, not only during affective episodes but also during periods of remission (Léda-Rêgo et al. 2020; Sheehan et al. 2017). Impairment is often present in several areas of functioning such as occupational functioning and social functioning, as well as impairment in overall/global functioning (Léda-Rêgo et al. 2020; Chen et al. 2019). As described in The International Classification of Functioning, Disability and Health (ICF), functional impairment is multicausal, resulting from a complex interplay of different factors such as health conditions, environmental factors and personal factors (WHO 2001).

We currently lack a comprehensive understanding of key factors causing and sustaining functional impairment in patients with affective disorders. Several clinical factors are associated with functional impairment, such as affective symptoms, number of affective episodes, cognitive impairment, comorbid disorders, and substance abuse in BD (Burdick et al. 2022; Gitlin and Miklowitz 2017; Nabavi et al. 2015). Similar factors, including residual depressive symptoms, impact functioning and risk of relapse in patients with UD (Romera et al. 2013; Nierenberg et al. 2010; Sheehan et al. 2017). In the ICF personal factors defined as "*coping styles, past and current experience and overall behaviour pattern*" (WHO 2001) are identified as variables that affect functioning. The potential role of personal factors, such as personality traits, coping strategies and experiences of childhood trauma, is less elucidated in the context of functioning in patients with affective disorders. The prevalence of childhood trauma is higher in patients with affective disorders (Vibhakar et al. 2019; Dualibe and Osório 2017) compared with the general population (Gilbert et al. 2009). The negative impact of childhood trauma is well established (Barczyk et al. 2023; Bourassa et al. 2023; Wegman and Stetler 2009), and childhood trauma was linked to functional impairment in a recent review, although based on limited evidence (Fares-Otero et al. 2023). Personality traits are stable patterns of behavior, feelings and thoughts (Conley 1984), of which neuroticism is a well-established predictor of negative outcomes. Neuroticism is the predisposition to experience psychological stress and a tendency to experience negative affect with higher levels indicating a more emotionally unstable individual prone to mood changes (Eysenck Hanse 1975). Neuroticism and maladaptive coping strategies such as emotion-oriented and avoidance coping are associated with worse outcomes in patients with affective disorders (Christensen and Kessing 2005; Dodd et

al. 2019; Liao et al. 2019; O'Connor et al. 2023). Additional research is needed to clarify the role of personal factors in predicting functional outcomes and the role of potential risk factors contributing to the lack of functional improvement seen in a large group of patients with affective disorders.
We performed the study Affective disorders: eliminate WArning signs And REstore functioning (AWARE) (Schwarz et al. 2022), a randomised controlled trial with blinded outcome assessment, investigating the effects of a personalised multimodule intervention targeting functioning (called the AWARE intervention) compared with treatment as usual (TAU) in patients with affective disorders. In summary, the AWARE intervention was superior to treatment as usual in improving secondary outcomes of cognition and stress but not regarding the primary outcome of functioning. Factors such as cognition, physical health and activities of daily living (ADL) ability were specifically targeted by the intervention. Thus, the negative results on functioning in the AWARE trial led us to explore the effects of other factors, such as personal factors, on functional impairment.

In the present exploratory study, the aims were to 1) identify factors associated with functional impairment at baseline and 2) identify predictors of improvement in performance-based functioning measured at six months follow-up. We hypothesised that early age of onset, more affective episodes, and higher affective symptom scores are associated with more functional impairment at baseline and less functional improvement at six months). We further hypothesised that higher neuroticism scores, maladaptive coping styles, and more childhood trauma are associated with more functional impairment at baseline and with less functional improvement at six months.

Material and methods

Participants

Included patients were participants with BD or UD enrolled in the AWARE trial, which was a randomised controlled trial with two allocation groups (results are reported elsewhere, Schwarz et al submitted). Data from patients in the intervention and control group in the AWARE trial are pooled together in the present study. Patients were recruited between February 1, 2021 and January 31, 2023 from two psychiatric centres in the Capital Region of Denmark (Mental Health Centre Northern Zealand and Psychiatric Centre Copenhagen). All patients had functional

impairment at inclusion and were in a state of full or partial remission. The inclusion criteria were: "*Men or women, age 18–65 years with a diagnosis of BD or unipolar major depressive disorder by WHO International Classification of Disease 10th edition (ICD-10)(World Health 2005) diagnostic criteria; current state of remission or partial remission (defined as Hamilton Depression Rating Scale, 17-items (HDRS-17)(Hamilton 1960) and Young Mania Rating Scale (YMRS)(Young et al. 1978) scores of ≤14); impaired functioning defined as a score ≥11 according to the Functional Assessment Short Test (FAST)(Rosa et al. 2007); and ability to participate in two-thirds of the planned intervention visits. Exclusion criteria were: Severe physical disorder interfering with daily living; ongoing alcohol or substance abuse; electroconvulsive therapy treatment within the last three months before inclusion; dementia or inability to cooperate with the study, including inability to speak and read Danish*" (Schwarz et al. 2022).

Data collected at baseline was made prior to randomisation/allocation and therefore not influenced by interventions in the trial. As results on the primary outcome of performance-based functioning (Assessment of Motor and Process Skills (AMPS)(Fisher and Jones 2012)) were negative in the trial (no difference between patients allocated to AWARE intervention and the control group (TAU), data on improvement/change in performance-based functioning in the two groups are pooled together for this present study. The 6-month follow-up AMPS assessment was done by assessors blinded to treatment allocation in the trial.

Assessments

Diagnoses were made according to ICD-10 using The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998). Interview-based (clinician-rated) functioning was assessed at baseline using FAST. Performance-based functioning was assessed at baseline and the 6-month follow-up with AMPS. Sociodemographic and clinical data was collected at baseline, along with data from questionnaires. Questionnaires were Eysenck Personality Inventory (EPQ) (Eysenck Hanse 1975), Coping Inventory for Stressful Situations (CISS) (Endler and Parker 1999) and Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 2003).

Functional impairment at baseline was measured by FAST, and performance-based functioning was measured at baseline and at 6-month follow-up with AMPS to assess functional

improvement. The FAST scale is used to evaluate overall functioning and functioning in different areas of life over the past 15 days. It consists of 24 items that cover six subdomains, including autonomy, occupation, cognition, financial issues, interpersonal relationships, and leisure time. The total score ranges from 0 to 72, with higher scores indicating more severe impairment. Based on the total score, functioning can be categorised into four categories: no impairment (0-11), mild impairment (12-20), moderate impairment (21-40), and severe impairment (>40) (Bonnín et al. 2018). The FAST has been validated for use in patients with BD (Rosa et al. 2007) and UD (Prado et al. 2019).

The AMPS was used to assess performance-based functioning. The score is based on a standardised evaluation of the performance quality of two individually selected activities of daily living (ADL) tasks. A total score is given for Process skills and Motor skills. AMPS is validated in mental disorders (Pan and Fisher 1994). AMPS is sensitive to changes over time, interrater reliability is high, with a clinically meaningful difference defined as ≥0.3 (Pan and Fisher 1994; Oakley et al. 2002). Only licensed, calibrated occupational therapists can administer the AMPS assessment.

Ethics

The study was approved by The Regional Ethics Committee in the Capital Region of Denmark (protocol number H-20029748) and comply with the Helsinki Declaration of 1975, as revised in 2008. All patients were provided oral and written information about the trial before written informed consent was obtained. Data permission was obtained from the Danish Data Protection Agency (j.nr. P-2020-1216).

Statistical analyses

All variables were assessed for normality and outliers. Scatterplots were used to assess linearity of the associations between each variable and the independent variable. Pearson correlations were performed on continuous, normally distributed variables and functioning. Spearman correlations were performed for non-normally distributed variables. Variables that showed statistically significant correlations were used in multiple linear regression, controlling for age, sex, and diagnosis, with functioning as the dependent variable. Multiple regression was performed as a hierarchical multiple regression analysis in models/blocks, with age, sex, and diagnosis (BD vs UD)

as control variables in Model 1. Variables in Model 1 was force entered, but clinical and personal variables were entered in separate models respectively only if there was statistically significance in correlation analyses. Pearson correlations and multiple regressions were conducted for baseline FAST and Delta AMPS Process, separately. Functional improvement was calculated as the difference between baseline and 6 months follow-up AMPS score (AMPS Process Delta= AMPS Process follow-up score minus AMPS Process baseline score). The analyses were performed in IBM SPSS statistics (version 29).

The clinical variables analysed as possible predictors of functioning and improvement of functioning were age of onset, number of affective episodes, depressive symptoms (HDRS-17 scores), and manic symptoms (YMRS scores). The personal variables analysed as possible predictors of functioning and improvement of functioning were: The personality traits neuroticism and extroversion (EPQ), Coping styles (CISS), and Childhood trauma (CTQ).

Results

We included 103 patients with BD or UD in partial or full remission. Baseline characteristics are presented in Table 1. The mean age was 40.75 (SD 12.48), and the sample consisted of 65.0% females. Patients had moderate to severe functional impairment according to FAST (mean 36.61, SD 10.15). A total of 74.1% (SD 22.9) of healthy individuals of the same age would have higher performance-based functioning than the included patients, according to baseline AMPS Process scores (the estimate is generated by the AMPS software when scores are calculated). Of the 103 patients included, 86 patients participated in the assessment of performance-based functioning at 6 months follow-up. Thus, the analyses concerning baseline FAST are based on n=103, whereas the analyses of improvement in functioning (AMPS Process Delta) are based on n=86. Baseline characteristics of the 86 patients participating in the assessment at 6 months follow-up are presented in the Supplementary Materials.

Table 1 *Baseline characteristics of patients with bipolar and unipolar disorder (n=103)*

Correlations between clinical and personal variables and baseline functioning and functional improvement respectively, are presented in Table 2. Pearson's correlation coefficient revealed a

statistically significant positive correlation with baseline FAST scores and HDRS-17, neuroticism, emotional coping, and childhood trauma respectively. The correlation was in the strong end for HDRS-17 (r=0.61) and weak to moderate for neuroticism (r=0.29), emotional coping (r=0.32), and childhood trauma (r=0.28). Childhood trauma was the only baseline clinical or personal variable that significantly correlated with functional improvement (AMPS Process Delta). However, the correlation was weak (r=-0.23).

Table 2 *Pearson correlations between clinical and personal variables and baseline FAST score (n=103) and change from baseline to endpoint in AMPS Process score (AMPS Process Delta, n=86) in patients with bipolar disorder and unipolar disorder*

Multiple linear regression models were performed to analyse the effect of the predictor variables adjusted for age, sex, and diagnosis. The results of the multiple regression models including clinical and personal variables and baseline FAST score are presented in Table 3. Model 1 shows that age, sex, and diagnosis explain 14.1 % of the variance in FAST scores and that age was a significant predictor ($\beta = 0.351$, $p < 0.001$). Patients with higher age had higher FAST scores (more functional impairment). After adding HDRS-17 in Model 2, an additional 24.8 % of the variance in FAST was explained. This was a statistically significant improvement in explanatory power compared with Model 1 (F Change = 41.506, $p < 0.001$). A higher HDRS-17 score at baseline was associated with higher FAST scores. After adding neuroticism, emotional coping, and childhood trauma in Model 3, an additional 5.2 % of the variance in FAST was explained, which was a statistically significant improvement in explanatory power compared with Model 1 (F Change = 3.111, $p < 0.05$). Among the personal variables emotional coping ($\beta = 0.184$, $p < 0.05$) and childhood trauma ($\beta = 0.166$, $p < 0.05$) had the largest impact on FAST scores, with higher (more) emotional coping and more childhood trauma being associated with higher FAST scores. Overall, Model 3 including the variables age, sex, diagnosis, HDRS-17, neuroticism, emotional coping, and childhood trauma explained 42.7 % of the variance in FAST scores.

Table 3 *Hierarchical multiple linear regression models of clinical and personal variables and baseline FAST score in patients with bipolar disorder and unipolar disorder (n=103)*

Table 4 shows the results of the hierarchical multiple linear regression models including the personal factor CTQ and change from baseline to endpoint in AMPS Process score (Delta) as the dependent variable. Model 1 shows that age, sex, and diagnosis were not predictors of AMPS Process Delta (improvement in functioning), and the model was not statistically significant ($F= 0.073$, $p > 0.05$). No model of clinical variables was added, as there were no significant results in correlation analyses for any of the clinical variables. In Model 2 adding the personal variables for which correlation analyses had shown significant correlations (only childhood trauma), showed that childhood trauma was a statistically significant predictor of AMPS Process Delta ($\beta = -0.244$, $p < 0.05$), with more childhood trauma predicting less improvement in functioning. $p > 0.05$

Table 4 *Hierarchical multiple linear regression models of personal variables and change from baseline to endpoint in AMPS Process score (AMPS Process Delta) in patients with bipolar disorder and unipolar disorder (n=86)*

Discussion

This explorative study of 103 patients with BD and UD in full or partial remission with functional impairment investigated the association between clinical and personal factors on baseline functioning and on the improvement in functioning over at 6-month follow-up. Consistent with our hypothesis, higher depression symptom severity at baseline correlated with lower functioning, even after controlling for age, sex, and diagnosis. Additionally, emotional coping and childhood trauma were linked to baseline functioning, also after adjusting for age, sex, diagnosis, and depression severity score among the personal factors. As hypothesised, more childhood trauma was a predictor of less improvement in functioning at 6 months measured by AMPS Process. The personality trait neuroticism (but not extroversion) correlated with functioning at baseline; however, the association did not persist after adjusting for depression severity scores in the regression analysis. Furthermore, neuroticism did not emerge as a predictor of improvement at the 6-month mark.

In line with the consistent association between depression severity and functional impairment (Romera et al. 2013), we found that subsyndromal symptoms in our partially or fully remitted

patients (HDRS-17 scores of ≤14) were a significant predictor of impaired functioning. However, contrary to our hypothesis, baseline HDRS-17 scores and other clinical variables such as age of illness onset and number of affective episodes were not predictors of functional improvement at 6-month follow-up. These results are clinically encouraging and point out that even though the single patient's illness course is severe, other factors seem to interact with and predict a more favorable outcome. A systematic review of the effect of antidepressant treatment on functional outcomes in patients with UD did, however, also in line with our findings, conclude that improvement in functional impairment is not related to depression severity at baseline in most studies (Sheehan et al. 2017). While baseline manic symptoms were not associated with functioning, this may be explained by almost no manic symptoms in the included patients, as seen from the low YMRS scores (mean 2.69, SD 2.41).

The impact of the investigated personal factors; the personality trait neuroticism, coping styles and childhood trauma on functioning is less well-studied in affective disorders, although they are known predictors of poorer outcomes (O'Connor et al. 2023; Fares-Otero et al. 2023). Among coping styles, a higher degree of emotional coping, was associated with functional impairment in the present study. Emotional coping has been associated with an increased risk of relapse of depressive episodes and worse outcomes in affective disorders (Christensen and Kessing 2005; Dodd et al. 2019). Patients who rely on emotional coping strategies may struggle to confront obstacles directly in daily life, leading to poorer functioning. Childhood trauma was associated with functional impairment at baseline. It was further shown to be the only baseline variable significantly predicting improvement of functioning, as experiences of childhood trauma had a negative impact on functional improvement. The impact of childhood trauma on treatment response is well-studied in patients with affective disorders, continuously shown to be a predictor of poor treatment response (Bourassa et al. 2023). Recent reviews have found evidence of an association between childhood trauma and poorer cognitive functioning (Barczyk et al. 2023) and social functioning (Fares-Otero et al. 2023). Our results are in line with these findings, further supporting the significant impact of childhood trauma on overall functioning and as a predictor of functional outcomes. The considerable effects of childhood trauma on multiple clinical and social variables throughout a patient's lifespan (Grillault Laroche et al. 2022; Paterniti et al. 2017), comorbidities (Agnew-Blais and Danese 2016), affective instability (Marwaha et al. 2016), emotional blunting

(Christensen et al. 2022), social skills (Dunn et al. 2018) and general maladaptive behavior (Cicchetti and Doyle 2016), might result in functional impairment, from which the treatment can be highly challenging. The addition of a modifier indicating a history of childhood trauma to the diagnosis of BD and UD has recently been suggested due to the distinct unfavorable nature and course of illness associated with childhood trauma (Teicher et al. 2022).

Due to the exploratory nature of the study, results were not adjusted for multiple testing, which increases the risk of potential incidental findings. The results are based on a limited sample size of 103 participants, limiting the potential for including many variables in the analyses. Clinical factors, particularly depressive symptoms, are well-known factors associated with functional impairment. These were included, in part also due to the potential confounding effect on personal factors and functioning, and in linear regression models, it was therefore possible to control for this effect.

The sample consisted of patients with BD (68.9%) and UD (31.1%). There may be differences between the two diagnoses in how the predictors influence overall functioning. However, given the significant overlap in symptoms and prognosis of these two affective disorders, it is reasonable to include them in the same sample. Further, all patients were recruited from the secondary hospital sector. Therefore, the patients with UD had high illness burden and severity, making this group more comparable to BD patients. Measuring improvement in an outcome by calculating the difference between the baseline and endpoint score (delta) might be problematic if a ceiling effect is present, limiting the potential for improvement in the participants with high scores at baseline. However, in the present study only patients with functional impairment were included, and impairment was prominent as seen from baseline functioning scores. The participants were a pooled sample of all patients allocated to the intervention and control group in the AWARE trial. However, there was no difference between the intervention and control group in AMPS scores at follow-up in the AWARE trial (*SCHWARZ et al submitted but not yet published*), and patients in both allocation groups received Danish psychiatric standard care during the follow-up period. There is not accounted for the different medical treatments patients received prior to allocation and during the 6-month follow-up period in the analyses. This is a limitation, as the different medical treatments may also be associated with different functional outcomes (Burdick et al. 2022).

In conclusion, residual affective symptoms and maladaptive coping style seem to contribute to functional impairment in patients with affective disorders. At the same time, childhood trauma was a predictor of worse functional outcomes in the long term. The effects of childhood trauma on multiple clinical and social variables throughout a patient's lifespan might result in functional impairment, from which the treatment can be challenging. Future longitudinal studies are warranted with larger samples and extended follow-up periods, to determine the role of personal factors as predictors of functional outcomes. A broad and comprehensive understanding of predictors of functional outcomes in patients with affective disorders could guide the development of more personalised interventions targeting these predictors and improving functional outcomes.

Data statement

The data supporting the findings of this study are available from the corresponding author (RS) upon reasonable request.

Acknowledgements

We would like to thank all participants in the study, the Mental Health Centre, Northern Zealand, and Psychiatric Centre Copenhagen for supporting the trial's conduct, and the funders for supporting the study.

Tables:

Table 1 Baseline characteristics of patients with bipolar disorder and unipolar disorder (n=103)	
Sociodemographic:	
Age, mean (SD)	40.75 (12.48)
Sex, female, n (%)	67 (65.0)
Years of education, mean (SD)	13.72 (2.67)
Diagnosis:	
Unipolar, n (%)	32 (31.1)
Bipolar, n (%)	71 (68.9)
Age at illness onset, median [IQR]	18 [9]
Number of episodes:	
Depressive, median [IQR]	10 [15]
Manic (Bipolar 1), median [IQR]	2 [4]
Hypomanic (Bipolar 1 and 2), median [IQR]	10 [15]
Clinical:	
Time in remission/partial remission months, mean (SD)	6.21 (8.82)
HDRS-17 total score, mean (SD)	9.62 (3.12)
YMRS total score, mean (SD)	2.69 (2.41)
Number of hospitalisations, median [IQR]	1 [2]
Functioning	
FAST total, mean (SD)	36.61 (10.15)
AMPS Process baseline, mean (SD)	1.25 (0.32)
Personal factors	
EPQ:	
Neuroticism, mean (SD)	14.44 (5.21)
Extroversion, mean (SD)	11.04 (5.20)
CISS:	
Task, mean (SD)	44.97 (10.69)
Emotional, mean (SD)	45.53 (10.12)
Avoidance, mean (SD)	38.50 (8.69)
Distraction, mean (SD)	18.48 (5.27)
Social, mean (SD)	13.13 (4.42)
CTQ, mean (SD)	54.74 (14.58)
Current medication:	
Lithium, n (%)	40 (38.8)
Antipsychotics, n (%)	48 (46.6)
Antidepressants, n (%)	43 (41.8)
Anticonvulsics, n (%)	53 (51.5)
Benzodiazepines, n (%)	27 (26.2)
Others, n (%)	68 (66.2)

SD, Standard Deviation, IQR, Interquartile Range; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; FAST, Functioning Assessment Short Test; AMPS, Assessment of Motor and Process Skills; EPQ, Eysenck Personality Questionnaire; CISS, Coping Inventory for Stressful Situations; CTQ, Childhood Trauma Questionnaire.

Table 2 Pearson correlations between clinical and personal variables and baseline FAST score (n=103) and change from baseline to endpoint in AMPS Process score (AMPS Process Delta, n=86) in patients with bipolar disorder and unipolar disorder

	r (FAST)	p	r (AMPS Process Delta)	p
Clinical factors				
Age of onset*	0.048	0.629	0.119	0.273
Number of affective episodes*	0.121	0.222	-0.082	0.452
Depressive symptoms (HDRS-17)	0.61	<0.001	-0.078	0.476
Manic symptoms (YMRS)	0.143	0.149	0.058	0.593
Personal factors				
EPQ:				
Neuroticism	0.292	0.003	-0.159	0.143
Extroversion	-0.1	0.317	-0.122	0.261
CISS:				
Task	-0.099	0.321	0.113	0.301
Emotional	0.316	0.001	-0.066	0.544
Avoidance	-0.161	0.105	0.049	0.654
Distraction	-0.058	0.564	0.001	0.991
Social	-0.186	0.059	-0.002	0.988
CTQ	0.283	0.004	-0.228	0.035

*Spearman correlation

FAST, Functioning Assessment Short Test; AMPS, Assessment of Motor and Process Skills; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; EPQ, Eysenck Personality Questionnaire; CISS, Coping Inventory for Stressful Situations; CTQ, Childhood Trauma Questionnaire.

Table 3 Hierarchical multiple linear regression models of clinical and personal variables and baseline FAST score in patients with bipolar disorder and unipolar disorder (n=103)

	Model 1 B (β)	Model 2 B (β)	Model 3 B (β)
Variables			
Age	0.286 (0.351)***	0.172 (0.212)*	0.182 (0.224)**
Sex	-3.655 (-0.172)	-0.895 (-0.043)	0.050 (0.002)
Diagnosis	-0.110 (-0.005)	0.756 (0.035)	0.678 (0.031)
HDRS-17		1.760 (0.541)***	1.582 (0.486)***
EPQ Neuroticism			-0.098 (-0.050)
CISS Emotional			0.184 (0.184)*
CTQ			0.116 (0.166)*
Model			
R^2	0.166	0.414	0.467
Adjusted R^2	0.141	0.39	0.427
R^2 Change	0.166	0.248	0.052
F	6.586***	17.337***	11.88***
F Change	6.586***	41.506***	3.111*

*p < 0.05 ** p < 0.01 *** p < 0.001

B, regression coefficient; β, standardised regression coefficient; HDRS-17, The 17-item Hamilton Depression Rating Scale; EPQ, Eysenck Personality Questionnaire; CISS, Coping Inventory for Stressful Situations; CTQ, Childhood Trauma Questionnaire.

Table 4 Hierarchical multiple linear regression models of personal variables and change from baseline to endpoint in AMPS Process score (AMPS Process Delta) in patients with bipolar disorder and unipolar disorder (n=86)

	Model 1 B (β)	Model 2 B (β)
Variables		
Age	0.001 (0.020)	0.001 (0.026)
Sex	-0.043 (-0.046)	-0.081 (-0.087)
Diagnosis	0.017 (0.018)	0.003 (0.003)
CTQ		-0.008 (-0.244)*
Model		
R^2	0.003	0.060
Adjusted R^2	-0.034	0.014
R^2 Change	0.003	0.050
F	0.073	1.297
F Change	0.073	4.956*

*p < 0.05

B, regression coefficient; β, standardised regression coefficient; CTQ, Childhood Trauma Questionnaire.

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Supplementary Materials

Table of Contents

Table 5 Baseline characteristics of patients with bipolar and unipolar disorder assessed with AMPS at 6-month follow-up (n=86)	
Sociodemographic:	
Age, mean (SD)	40.49 (12.41)
Sex, female, n (%)	58 (67.4)
Years of education, mean (SD)	13.82 (2.59)
Diagnosis:	
Unipolar, n (%)	27 (31.4)
Bipolar, n (%)	59 (68.6)
Age at illness onset, median [IQR]	18 [9]
Number of episodes:	
Depressive, median [IQR]	10 [14]
Manic (Bipolar 1), median [IQR]	2 [4]
Hypomanic (Bipolar 1 and 2), median [IQR]	10 [15]
Clinical:	
Time in remission/partial remission months, mean (SD)	6.52 (9.39)
HDRS-17 total score, mean (SD)	9.63 (3.16)
YMRS total score, mean (SD)	2.71 (2.42)
Number of hospitalisations, median [IQR]	1 [2]
Functioning	
FAST total, mean (SD)	36.30 (10.40)
AMPS Process baseline, mean (SD)	1.25 (0.31)
Personal factors	
EPQ:	
Neuroticism, mean (SD)	14.21 (5.10)
Extroversion, mean (SD)	11.26 (5.20)
CISS:	
Task, mean (SD)	45.31 (10.10)
Emotional, mean (SD)	45.81 (9.95)
Avoidance, mean (SD)	38.86 (8.59)
Distraction, mean (SD)	18.78 (5.30)
Social, mean (SD)	13.27 (4.32)
CTQ, mean (SD)	54.21 (14.05)
Current medication:	
Lithium, n (%)	31 (36.05)
Antipsychotics, n (%)	40 (46.51)
Antidepressants, n (%)	35 (40.70)
Anticonvulsics, n (%)	46 (53.49)

Benzodiazepines, n (%)	26 (30.23)
Others, n (%)	55 (63.95)

SD, Standard Deviation, IQR, Interquartile Range; HDRS-17, The 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; FAST, Functioning Assessment Short Test; AMPS, Assessment of Motor and Process SkillsEPQ, Eysenck Personality Questionnaire; CISS, Coping Inventory for Stressful Situations; CTQ, Childhood Trauma Questionnaire.