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Improving Functioning in Individuals with Transdiagnostic Mild–Moderate Depressive Symptoms: Evidence from the IDEA Randomised Controlled Trial and Beyond

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Improving Functioning in Individuals with Transdiagnostic Mild-Moderate Depressive Symptoms: Evidence from the IDEA Randomised Controlled Trial and Beyond

by

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Abstract

English

Depressive symptoms, whether primary or secondary to other conditions, are prevalent and linked to disability, reduced quality of life, and high economic costs. Exercise shows promise as a therapeutic add-on strategy for those with mild to moderate symptoms, though adherence is often hindered by sedentary behaviours common in this population. This thesis examines exercise-based interventions for enhancing functioning in individuals with transdiagnostic depressive symptoms through three studies. Study 1 systematically reviewed 15 studies (N = 2,064) investigating the effects of exercise on functioning and quality of life. While exercise generally benefits functioning and mental health, the results varied across studies depending on type, intensity, duration, and methods. Study 2 conducted a cross-sectional analysis of baseline data from 121 participants in a randomised controlled trial, revealing that greater impairment in general functioning was consistently associated with lower physical performance. Age and body mass index influenced some of these associations. Study 3, the IDEA (Improving Depressive Symptoms through Personalised Exercise and Activation) trial, tested a 4-week personalised, exercise-based intervention that included psychological guidance against a control group receiving general exercise recommendations (N=121). The main outcome measure was general functioning, with secondary outcomes including functional status, depressive symptoms, and well-being, assessed at 4-, 12-, and 36-weeks post-randomisation. General functioning showed significant between-group differences at all follow-ups favouring the experimental group and within-group improvements in this group were observed with the most pronounced effects occurring from baseline to week 12. The intervention led to sustained reductions in depressive symptoms and improvements in mental health aspects of functioning, and appeared to enhance well-being. The CG showed minimal changes across outcomes. Findings support the potential of integrating exercise-based interventions as an adjunct to standard care for addressing functional impairment in individuals with depressive symptoms. This is an important yet sometimes underexplored part of treatment. Multiple indications suggest that the IDEA intervention was beneficial in this regard. Future research with larger sample sizes should validate these findings, optimise adherence, establish more conclusive evidence regarding the interaction effects, and evaluate scalability across diverse clinical and community settings.

Català

Els símptomes depressius, siguin primaris o secundaris a altres malalties, són prevalents i estan relacionats amb la discapacitat, la qualitat de vida reduïda i els alts costos econòmics. L'exercici físic és una estratègia terapèutica complementària prometedora per a les persones amb símptomes lleus o moderats, encara que l'adherència sovint es veu obstaculitzada per comportaments sedentaris comuns en aquesta població. Aquesta tesi examina les intervencions d'exercici per millorar el funcionament en persones amb símptomes depressius transdiagnòstics mitjançant tres estudis. L'estudi 1 va revisar sistemàticament 15 estudis (N =2064) que investigaven els efectes de l'exercici sobre el funcionament i la qualitat de vida. Es va trobar que l'exercici generalment beneficia el funcionament i la salut mental, malgrat que els resultats varien segons el tipus, la intensitat, la durada i els mètodes. L'estudi 2 va dur a terme una anàlisi transversal amb dades basals de 121 participants en un assaig controlat aleatoritzat, revelant que una major afectació en el funcionament general s'associava repetidament amb un rendiment físic més baix. L'edat i l'índex de massa corporal van influir en algunes d'aquestes associacions. L'estudi 3, l'assaig IDEA (acrònim en anglès, que es tradueix com a Millorant els Símptomes Depressius mitjançant Exercici i Activació Personalitzats), va avaluar una intervenció de 4 setmanes basada en exercici personalitzat amb orientació psicològica, en comparació amb un grup control que només va rebre recomanacions generals d'exercici (N = 121). La principal mesura d'eficàcia va ser el funcionament general, i els resultats secundaris eren l'estat funcional, els símptomes depressius i el benestar, avaluats a les 4-, 12-, i 36 setmanes després de l'aleatorització. Es van observar diferències significatives entre grups en el funcionament general, afavorint el grup experimental, així com millores dins d'aquest grup amb els efectes més pronunciats entre l'inici de l'estudi i la setmana 12. La participació en la intervenció va comportar reduccions dels símptomes depressius que es van mantenir amb el temps, algunes millores en els aspectes del funcionament relacionats amb la salut mental i hi ha indicadors de millores en el benestar. Els resultats donen suport al potencial que té la integració d'intervencions d'exercici com a complement del tractament habitual per abordar el deteriorament funcional en individus amb símptomes depressius. Aquesta és una part important del tractament que està, sovint, poc explorada. Hi ha diversos indicis de què la intervenció IDEA va ser beneficiosa en aquest sentit. Les investigacions futures amb mides de mostra més grans haurien de validar aquests resultats, optimitzar l'adherència, establir evidències més concloents sobre els efectes d'interacció i avaluar-ne l'aplicabilitat en diferents entorns clínics i comunitaris.

Castellano

Los síntomas depresivos, sean primarios o secundarios a otras enfermedades, son prevalentes y están relacionados con la discapacidad, la calidad de vida reducida y los altos costes económicos. El ejercicio físico es una estrategia terapéutica complementaria prometedora para las personas con síntomas leves o moderados, aunque la adherencia a menudo se ve obstaculizada por comportamientos sedentarios comunes en esta población. Esta tesis examina las intervenciones de ejercicio para mejorar el funcionamiento general en personas con síntomas depresivos transdiagnósticos a través de tres estudios. El estudio 1 revisó sistemáticamente 15 estudios (N =2064) investigando los efectos del ejercicio sobre el funcionamiento y la calidad de vida. Se encontró que el ejercicio generalmente beneficia el funcionamiento y la salud mental, a pesar de que los resultados varían según el tipo, la intensidad, la duración y los métodos. El estudio 2 llevó a cabo un análisis transversal con datos basales de 121 participantes en un ensayo controlado aleatorizado, y reveló que una mayor afectación en el funcionamiento general se asociaba repetidamente con un rendimiento físico más bajo. La edad y el índice de masa corporal influyeron en algunas de estas asociaciones. El Estudio 3, el ensayo IDEA (acrónimo en inglés, que se traduce como Mejorando los Síntomas Depresivos mediante Ejercicio y Activación Personalizados), evaluó una intervención personalizada de ejercicio de 4 semanas que incluía orientación psicológica, y la comparó con un grupo control que solo recibía recomendaciones generales de ejercicio (N = 121). La principal medida de eficacia fue el funcionamiento general, y los resultados secundarios fueron el estado funcional, los síntomas depresivos y el bienestar, evaluados a las 4-, 12-, y 36 semanas después de la aleatorización. Se observaron diferencias significativas entre grupos en el funcionamiento general, favoreciendo al grupo experimental, así como mejoras dentro del mismo con efectos más pronunciados entre el inicio del estudio y la semana 12. La participación en IDEA conllevó reducciones de los síntomas depresivos mantenidas con el tiempo, algunas mejoras en aspectos del funcionamiento relacionados con la salud mental y hay indicadores de mejoría del bienestar. Los resultados apoyan el potencial de integrar intervenciones de ejercicio complementarias al tratamiento habitual para abordar el deterioro funcional en individuos con síntomas depresivos. Esta es una parte importante del tratamiento y, a menudo, poco explorada. Hay indicios de que la intervención IDEA fue beneficiosa en este sentido. Las investigaciones futuras con tamaños muestrales más grandes deberían validar estos resultados, optimizar la adherencia, establecer evidencia más concluyente sobre los efectos de interacción y evaluar la aplicabilidad en diferentes entornos clínicos y comunitarios.

Lay summary

Depressive symptoms affect millions of people globally, often making everyday activities like work, social interactions, and maintaining well-being more challenging. Exercise is known to benefit mental health, but many people with depressive symptoms struggle to stay active due to common sedentary behaviours. This research explored whether exercise can help improve daily functioning in individuals with depressive symptoms, regardless of their specific diagnosis, through three studies. The first study reviewed 15 previous studies and found that exercise generally helps with daily functioning and mental health. However, the benefits varied depending on factors such as exercise type, intensity, duration, and study methods. The second study found that people with greater difficulties in their daily activities also tended to have poorer physical performance, highlighting a link between overall functioning and physical health. The third study, known as the IDEA trial, included 121 participants and tested a 4-week personalised exercise programme that included psychological support. It was compared to a control group that received general exercise recommendations. Both groups continued their usual treatments, such as medication or psychotherapy, and their progress was assessed to measure their ability to manage daily tasks, mental health, and well-being at 4, 12, and 36 weeks after randomisation. Our study found that people who took part in an exercise programme functioned better in their daily lives compared to those who did not. The biggest improvements happened in the first 12 weeks and lasted over time. Those in the exercise group had fewer symptoms of depression, better mental health, and an overall boost in well-being, while the other group had little change. These results suggest that exercise could be a helpful addition to regular treatment of depressive symptoms, especially for improving daily life, which is sometimes overlooked. More research is needed to confirm these findings, improve programme adherence, understand how different factors interact, and explore how this approach could be expanded to different clinical and community settings.

Preface

This dissertation has been developed within the framework of the Doctoral Programme in Psychiatry of the Autonomous University of Barcelona. The research included herein has been conducted within the Mental Health Research Group of the Neurosciences Programme at the Hospital del Mar Research Institute and at the Mental Health Institute – Hospital del Mar premises.

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The core of the thesis is the IDEA (Improving Depressive Symptoms Through Personalised Exercise and Activation) randomised controlled single-blind trial. Initially, we conducted a narrative review on the topic, design, and methodology of the proposed research to document and refine the subject, which subsequently evolved into a systematic review. Concurrently, we designed and registered the IDEA study and published its protocol. Several secondary or exploratory analyses are expected to emerge from this main study, one of which focused on associations between physical health and functioning parameters at baseline and is part of the present thesis. The central question addressed by the thesis is whether a brief, personalised exercise-based intervention can improve the functioning of individuals with transdiagnostic depressive symptoms. Therefore, this thesis comprises three original studies: a systematic review, a randomised controlled trial, and a cross-sectional analysis of the baseline trial data, with details outlined below. The study protocol (Appendix A) and the systematic review (Appendix B) have already been published. The manuscript presenting the trial main results is currently in preparation.

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List of Abbreviations

1MSTS	1-minute sit-to-stand test
6MWT	6-minute walking test
ACSM	American College of Sports Medicine
BD	Bipolar disorder
BDI	Beck's Depression Inventory
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	Cognitive behavioural therapy
CES-D	Centre for Epidemiologic Studies Depression Scale
CG	Control group
CGI-S	Clinical Global Impression Scale-Severity
COVID-19	Coronavirus disease
DALYs	Disability-adjusted life years
DQOL	Diabetes Quality of Life Measure
DSM	Diagnostic and Statistical Manual of Mental Disorders
EG	Experimental group
EPA	European Psychiatric Association
FAST	Functional Assessment Short Test
GDS	Geriatric Depression Scale
GP	General practitioner
HAM-D	Hamilton Depression Rating Scale
HCL-32	32-item Hypomania Symptom Checklist
HGST	Handgrip strength test
HPA	Hypothalamic-pituitary-adrenal
HPG	Hypothalamic-pituitary-gonadal
HPT	Hypothalamic-pituitary-thyroid
ICD	International Classification of Diseases
IDEA	Improving Depressive Symptoms Through Personalised Exercise and Activation
IDN	Identification number
IDS	Inventory of Depressive Symptomatology

ITT	Intention-to-treat
MADRS	Montgomery- Åsberg Depression Rating Scale
MBCT	Mindfulness-Based Cognitive Therapy
MCS	Mental Component Summary
MDD	Major depressive disorder
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
N/S	Not specified
PA	Physical activity
PCS	Physical Component Summary
PDD	Persistent depressive disorder
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QLDS	Quality of Life in Depression Scale
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RDoC	Research Domain Criteria
SF-36	36-item Short-Form Health Survey
SIMPAQ	Simple Physical Activity Questionnaire
SNRI	Serotonin-noradrenaline reuptake inhibitors
SNS	Spanish National Health System
SSRI	Selective serotonin reuptake inhibitor
TAU	Treatment as usual
TCA	Tricyclic antidepressants
VAT	Value Added Tax
WHO	World Health Organization
WHO 5 WBI	World Health Organization- Five Well-Being Index
WHOQOL-BREF	World Health Organization Quality of Life Brief Version

Chapter 1. Introduction

1.1 Transdiagnostic nature of depressive symptoms

1.1.1 Definition of depressive symptoms

Depressive symptoms are the specific emotional, behavioural, cognitive, and physical manifestations that characterise the experience of depression. These symptoms can vary in severity and duration, collectively contributing to the clinical picture of depression.

In medical and psychological contexts, the term 'depression' is used in different ways: as a symptom— an individual experience or manifestation; as a syndrome— a cluster of symptoms that occur together; and as a disorder— a clinically recognised condition with defined diagnostic criteria and a significant impact on daily life. These distinctions help describe various aspects of mental health conditions.

This broad spectrum of symptoms is primarily characterised by the absence of positive affect, such as a loss of interest and enjoyment in ordinary activities, along with persistent low mood, sadness, irritability, emptiness, fatigue, changes in sleep and appetite needs and patterns, difficulty concentrating, negative thoughts, social withdrawal, restlessness and physical complaints. In severe cases, depressive symptoms can lead to suicide (1). However, these symptoms vary widely among individuals. For example, there are differences in the presentation of depressive symptoms in women versus men. While core symptoms such as persistent low mood and anhedonia are common across genders, women more often experience internalising symptoms like guilt, worthlessness, anxiety, and somatic complaints. In contrast, men are more prone to display externalising symptoms such as irritability, anger, restlessness, obsessive thoughts and risky behaviours (e.g., substance use) (2–4).

Depression severity spans a spectrum, characterised by varying frequencies and intensities of symptoms, as well as their duration and impact on personal and social functioning. It ranges from less severe forms like subthreshold and mild depression to more severe types such as moderate and severe depression (5). Individuals may exhibit different presentations depending on where they fall on this spectrum. At the milder end, someone might experience emotional distress and minor difficulties in functioning, such as trouble concentrating at work, while still managing daily activities. Conversely, at the severe end, individuals may endure overwhelming sadness, extreme fatigue that impairs self-care, and in some cases, even psychotic symptoms

or catatonia. At the extreme end of depressive severity is melancholia, characterised by distinct features such as pronounced psychomotor disturbances (e.g., retardation), significant impairments in cognitive functioning, and marked physical symptoms like appetite or sleep disruptions (6). While difficulties in concentration, decision-making, and ruminative thinking can occur in many forms of depression, these symptoms are particularly severe and pervasive in melancholia, distinguishing it from less severe or atypical presentations.

1.1.2 Symptom-based approaches

Traditionally, therapeutic research and drug regulatory administrations have followed a categorical model. Consequently, treatment guidelines and algorithms have been defined based on diagnoses rather than symptoms, syndromes, or other phenomenological descriptions. The existing categorical nosotaxis in mental health, including the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Classification of Diseases* (ICD), is usually established by consensus, often disregarding pathogenesis, which remains unknown for many disorders. As a result, psychiatric nosotaxis frequently deviates from formal taxonomy, with its categories being artificial rather than natural. This may partly explain the large number of redundant categories, the overlap of symptoms and syndromes and the changing (usually growing) number of conditions across time consecutive editions of the two main classifications. It may also account for the artefactual comorbidity that is common in psychiatry.

In practice, mental health professionals frequently encounter the reality that individuals do not fit neatly into these diagnostic categories. The limitations of the categorical model become evident when therapeutic guidelines, grounded in these diagnoses, fall short of addressing the complexities of individual cases. This approach often fails to account for the prevalence of comorbidity, underscoring a significant drawback: the inability to deliver truly personalised medicine. Consequently, the rigid diagnostic framework may hinder effective treatment and self-management of mental health conditions, highlighting the need for more nuanced and individualised approaches.

Transdiagnostic symptom-based approaches study the underlying cognitive and behavioural processes and/or common maintaining mechanisms in different disorders and are often suggested as a solution to the limitations of disorder-specific treatments, providing more adaptable interventions. These transcend categorical models and seek integration with dimensions, which is the axis of the functional treatment approach. Furthermore,

transdiagnostic approaches synthesise the underlying theoretical constructs and view cognitive and behavioural processes as a base and/or common maintenance for mental disorders. For example, the National Institute of Mental Health (NIMH) has shifted its interest towards Research Domain Criteria RDoC), assuming that mental health comprehension should be led by biology and symptoms and acknowledging that dimensions can occur across disorders (7). This approach makes room for more flexibility regarding treatment options, as it does not target specific diagnoses and allows individual differences to be respected.

According to the ICD, depression is categorized by its impact on mental health and its associated comorbidities. The International Classification of Functioning, Disability and Health (ICF), established by the WHO, complements this by providing a comprehensive framework that considers the impact of health conditions on an individual's functioning across various domains, including body functions, activities and participation, and environmental factors (8). This dual approach underscores the multifaceted nature of depressive symptomatology, emphasizing its effect on daily activities and participation.

Moving beyond narrow categorical diagnostic models, adopting dimensional, multiproblem and flexible approaches focusing on symptoms and common mechanisms aligns with the demand for personalised medicine (9,10). Transdiagnostic approaches to widespread depressive symptoms facilitate tailored treatment choices, ensuring individual needs are met. Additionally, factors such as the differential response to therapy, the diversity of biological factors underlying symptoms, potential drug interactions, and environmental factors are considered, thus promoting personalised care (11).

The path to precision medicine in mental health is being built, and various transdiagnostic treatment programs for affective disorders have been developed such as the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders, the Transdiagnostic Behavioural Therapy and the Transdiagnostic Approach to CBT (12–14). The first randomised controlled studies with positive results of these interventions serve as foundational research supporting the use of these interventions in clinical practice.

A symptom-based, dimensional view of mental health disorders has the practical advantage of genuinely respecting individual differences. Without rigid nosotaxis, mental health professionals can enrich each patient's clinical case description and address their specific needs.

One-size-fits-all (often ‘science-free’) categorical descriptions too often lead to diagnostic-driven therapeutic recommendations (also ‘science-free’ but dramatically ‘blockbustering’) that may not meet patients’ needs or take their existing capabilities into account. In other words, diagnostic-driven treatment algorithms frequently become a Procrustean bed: no one ever fits the therapeutic recommendations, rendering them often ineffective.

On the other hand, the very nature of symptom-based approaches—by respecting individual differences—enhances personalised medicine. The symptom-based paradigm in mental health becomes, by definition, transdiagnostic, a concept that describes much of daily clinical practice. On top of it, transdiagnostic approaches help deal/avoiding stigma and enhance dimensional research methodologies prone to deliver richer and fine-tuned outcomes.

1.1.3 Key conditions presenting with depressive symptoms

Depressive symptoms can be present in various disorders, conditions, and illnesses. In some cases, they play a primary role, constituting a stable diagnostic category known as depressive or mood disorders. The DSM-5 (15) classifies depressive disorders into the following specific categories: major depressive disorder (MDD), persistent depressive disorder (PDD), also known as dysthymia, disruptive mood dysregulation disorder, bipolar disorder (BD) with the most recent episode depressive, cyclothymic disorder, other specified depressive disorder, and unspecified depressive disorder. Also, women experience specific forms of depressive disorders, including premenstrual dysphoric disorder, peripartum depression, and perimenopausal depression, which are associated with changes in ovarian hormones.

Other mental health conditions where depressive symptoms are present are various, and the following list is not exhaustive: adjustment disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, seasonal affective disorder, and bereavement-related depression. Additionally, depressive symptoms often occur as secondary complications in numerous psychiatric and physical health conditions (16). For example, they can arise as complications of severe mental disorders like schizophrenia (17) and may worsen outcomes in somatic conditions such as Parkinson's disease, and cancer (18–24).

When these symptoms arise alongside major conditions, their impact deepens, intensifying the severity and complicating management of coexisting diseases like heart disease, migraines, and

vision impairments impairments (25). Depressive symptoms are strongly linked to poor cardiovascular health in a bidirectional relationship (26), and are associated with increased risks of weight gain, chronic illness, and premature death (89–91). These co-ocurring conditions highlight the importance of addressing depressive symptoms comprehensively to improve overall health outcomes.

1.1.4 Relevance of depressive symptoms

Individuals with depressive symptoms, regardless of their diagnoses, experience significant impacts on their social and work functioning, physical health, and overall mortality. These symptoms also make it difficult to enjoy activities, maintain relationships, and manage responsibilities.

Functional impairment

Depressive symptoms greatly impair overall functioning and are associated with a high level of suffering for those who experience them. The functional impairment associated with depression matches or exceeds that of severe chronic medical conditions, including in individuals with subthreshold depression, even in the long term. Moreover, this pattern of impaired functioning remains consistent across various types of depression and care settings, including depressive symptoms not meeting criteria for a depressive disorder, indicating consistent outcomes of impaired functioning compared to those with chronic medical conditions (27). In fact, depression is the most common cause of temporary work disability lasting more than 15 days, with an average duration of 167.9 days annually (28). For example, individuals with PDD often experience significant job productivity loss and tend to have less stable work histories compared to controls (29). Similarly, people with BD spend an average of 47.3% of their time unwell long-term, whose symptomatic course is dominated by depressive symptoms and accounts for one-third of their lives (30,31). These impairments in occupational and social functioning are key areas of concern within the ICF framework (32), which highlights the importance of addressing these barriers to improve overall well-being and participation in societal roles.

MDD is one of the main causes of disability worldwide, contributing to reduced life expectancy and increased risk of suicide. Even mild symptoms can worsen the quality of life and are often associated with functional impairment, increased mortality figures and risk of worsening to a more severe presentation and, even, suicidal ideation and attempts (33–35,1).

There is also a substantial body of evidence suggesting a link between depression and poor physical function (36) as well as functional decline (37). As a result, health goals have shifted to increasing disability-free years of life rather than only increasing life expectancy, reflecting the ICF's emphasis on functional health. In this scenario, functioning serves as the most effective outcome measure. It offers a practical, real-world perspective that is meaningful for both clinicians and patients. Thus, it serves as a more valuable indicator for designing health policies compared to syndrome-based outcomes.

Prevalence

Depressive symptoms are highly prevalent in clinical practice outside mental health services, with substantial variability between studies, ranging from 17% to 53% across different clinical specialties (38). These symptoms are also common in primary care settings, a key entry point for addressing mental health, where subthreshold presentations affect approximately 16% of patients (39). Women are typically overrepresented in depressive samples; for instance, the 2020 European Health Survey in Spain found that chronic depression was twice as prevalent in women as in men (40). These figures may even be underestimates, as many cases remain undiagnosed (41,42).

Depressive symptoms frequently co-occur with both psychiatric and somatic conditions, significantly affecting clinical and functional outcomes. Only about one-tenth of patients with depressive disorders have no additional psychiatric or chronic physical conditions, underscoring the high prevalence of comorbidities (43). Anxiety is the most common psychiatric comorbidity, affecting 34.3% of cases (44). Depressive symptoms are also prevalent among individuals with chronic illnesses such as epilepsy, Parkinson's disease (where up to one-third of patients experience depressive symptoms), dementia, and cancer (45–48).

Burden

The mental disorders that lead in disability-adjusted life years (DALYs) (59) and contribute significantly to the global disease burden are often accompanied by depressive symptoms, including MDD affecting over 264 million people, as well as anxiety disorders, BD, schizophrenia and substance use disorders (49,50).

Beyond its impact on well-being and quality of life, depression is one of Europe's most economically burdensome brain conditions, surpassing costs associated with psychotic, abuse, and cognitive disorders (51,52). Globally, depression and anxiety account for over 12 billion lost workdays annually (53). In the European Union alone, income loss linked to lower employment rates among those with depressive symptoms is estimated at €176 billion annually (54). In Catalonia, where this research took place, annual depression costs reach €735.4 million, covering both direct and indirect expenses (55). Overall, the bulk of societal costs from depressive symptoms stems from indirect costs, emphasising the need to prioritise functional recovery alongside symptom relief in treatment (56).

Course and prognosis

The course and prognosis of depressive symptoms are complex, influenced by a multitude of factors including onset, relapse, recurrence, and recovery. Depression can start at any age but often peaks in late adolescence or young adulthood, especially in women, who experience higher rates into middle age (49,57). Symptoms typically emerge gradually over days or weeks.

The course of depressive symptoms varies: some individuals experience one episode and fully recover, but 40%-60% of those with an initial depressive episode may face another (58,59), especially if residual symptoms remain post-treatment (60). Chronic and recurrent symptoms are common; subthreshold symptoms increase relapse risk, while achieving full symptom remission helps delay recurrence. Within 10%-25% of individuals with subthreshold symptoms develop MDD (61). The longer symptoms persist, the lower the likelihood of recovery, with some individuals experiencing chronic symptoms for years (58,59).

Recovery involves both symptom relief (symptomatic recovery) and a return to previous functional levels (functional recovery), with the latter often taking longer (62). The recovery journey is often nonlinear, with fluctuating symptoms and a lower likelihood of full recovery if symptoms persist. Recovery rates vary based on factors like age, comorbidities, support, and treatment approaches, and many individuals continue to face functional limitations despite symptomatic relief (63,64). Symptomatic recovery can occur relatively quickly for some (65), and maintaining higher functional levels despite symptoms may indicate a quicker, more complete recovery. Although symptoms' intensity is important, an individual's ability to manage daily roles and responsibilities offers deeper insight into recovery potential, suggesting

that functioning reflects a broader resilience that is key to long-term recovery. Thus, early, individualised treatment is crucial for improving this outcome (66)

1.2 Assessment of depressive symptoms and associated factors

Assessment

Depressive symptoms are typically screened using standardised questionnaires and clinical interviews conducted by mental health professionals. Several psychometric tools have been developed and validated to evaluate their presence, quantify severity, and course, which can ultimately guide treatment recommendations. The choice of instrument may depend on the setting, patient characteristics, the level of detail required and the needs of the assessment. Table 1 details some of the most used instruments to assess depressive symptoms in clinical practice. Many of the instruments listed are derived from broader parent scales or include subscales to capture specific symptom domains of depression. For instance, the IDS (Inventory of Depressive Symptomatology) is the parent scale, with the IDS-C (Clinician-administered version) and IDS-SR (Self-report version) being derived from it, along with its shortened version, the QIDS (Quick Inventory of Depressive Symptomatology). These tools often include domains or subscales that assess distinct aspects of depression, such as cognitive, somatic, and emotional symptoms. The Hamilton Depression Rating Scale (HAM-D), for example, also features multiple subscales that evaluate different symptom domains.

Table 1 Instruments commonly used to assess depressive symptoms

Instrument	Format	Items	Time	Structure
MADRS	Clinician-administered	10	20-30’	Single scale
PHQ-9	Self-report*	9	≤ 10’	Single scale
HAM-D	Clinician-administered	17	15-20’	Multiple subscales
BDI-II	Self-report or clinician-administered	21	10’	Single scale
IDS	Self-report or clinician-administered	30	10-20’	Multiple subscales
CES-D	Self-report*	20	20’	Single scale
GDS	Self-report*	30	10-30’	Single scale

***Note**. MADRS = Montgomery- Åsberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; HAM-D Hamilton Depression Rating Scale; BDI = Beck Depression Inventory; IDS = Inventory of Depressive Symptomatology; CES-D = Centre for Epidemiologic Studies Depression Scale; GDS = Geriatric Depression Scale*

** Primarily designed for self-reporting but can be adapted for clinician administration when necessary*

***Note on Structure**: 'Structure' refers to whether the instrument provides a single overall score or multiple subscales assessing distinct symptom domains (e.g., cognitive, somatic, and affective symptoms). Instruments with a single scale generate one total score, while those with multiple subscales assess different aspects of depression separately.*

Associated factors of depressive symptoms

Depression is not tied to a single abnormality or altered physiological system. Instead, it is a heterogeneous range of mental health problems characterised by symptoms that can manifest in individuals with various neurobiological alterations. Its aetiology is complex, involving a multifaceted interplay of biological, psychological and environmental factors.

Biological vulnerability

Genetic theories suggest that genes significantly influence susceptibility to depression, with higher concordance in monozygotic than dizygotic twins and a two-fold increased risk for individuals with a family history (67–69). Endocrine theories highlight how hormonal and neuroendocrine dysregulation, such as hypothalamic-pituitary-adrenal (HPA) axis hyperactivity leading to elevated cortisol and abnormalities in the hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-gonadal (HPG) axes affecting thyroid and sex hormones, contributes to depression (70–72). Additionally, elevated neuroinflammatory markers, like TNF-α and cytokines, are linked to more severe symptoms by disrupting brain function (73,74). Oxidative stress, resulting from an imbalance in reactive oxygen species and antioxidants, contributes to neurodegeneration in the brain, intensifying depressive symptoms

(75). Finally, many studies associate impaired neurotrophic signaling, particularly low brain-derived neurotrophic factor (BDNF), with depressive symptoms, although findings show significant variability (76).

Psychological and environmental vulnerabilities

Individuals with high psychological vulnerability are more susceptible to depression, especially when exposed to stressors or negative life events. Traits like neuroticism, which intensifies negative emotions, and negative cognitive styles, which skew interpretations of life events, elevate depression risk (77,78). Ruminative thinking and perfectionism further worsen symptoms by amplifying self-critical thoughts and limiting effective coping (79–81).

The diathesis-stress model suggests that depression often emerges when a 'biologically' predisposed individual faces significant psychosocial stress (82,83). Environmental stressors, including episodic events (e.g., job loss, bereavement) and chronic stressors (e.g., interpersonal conflict, caregiving responsibilities, financial strain), contribute to risk (84,85). Early trauma also sensitizes individuals to stress through lasting changes in stress response systems, making them more prone to depression. Moreover, depression can itself increase the likelihood of future negative life events, creating a feedback loop (86,87).

Other contributing factors

There are additional influences that can exacerbate or trigger depressive symptoms but are not necessarily the primary causes. Groups facing severe health limitations or those living in densely populated areas show higher rates of depressive disorders (85,88). Other demographic and health-related risk factors include advanced age (especially for those over 75), chronic illnesses, extreme body mass index (BMI) values, smoking, a sedentary lifestyle, and low income or educational levels. The prevalence of depressive symptoms tends to decrease as these factors improve (89).

Social factors play a significant role in mental health as well. Evidence shows that social isolation and lack of meaningful relationships increase feelings of loneliness, which, in turn, contributes to depressive symptoms (90). Substance abuse also has a strong connection to depression in a bidirectional way: each can increase the onset and severity of the other. Chronic substance use, especially, affects the brain's structure and function, worsening depressive symptoms over time and impacting overall health (91).

Certain chronic medical conditions such as diabetes, cardiovascular disease, and cancer further increase the risk of depressive symptoms (92–94). This elevated risk is due both to the stress of managing these illnesses and to biological changes or treatments involved in their care. Furthermore, poor sleep quality has a significant negative impact on mood and can contribute to the development or worsening of depressive symptoms (95,96).

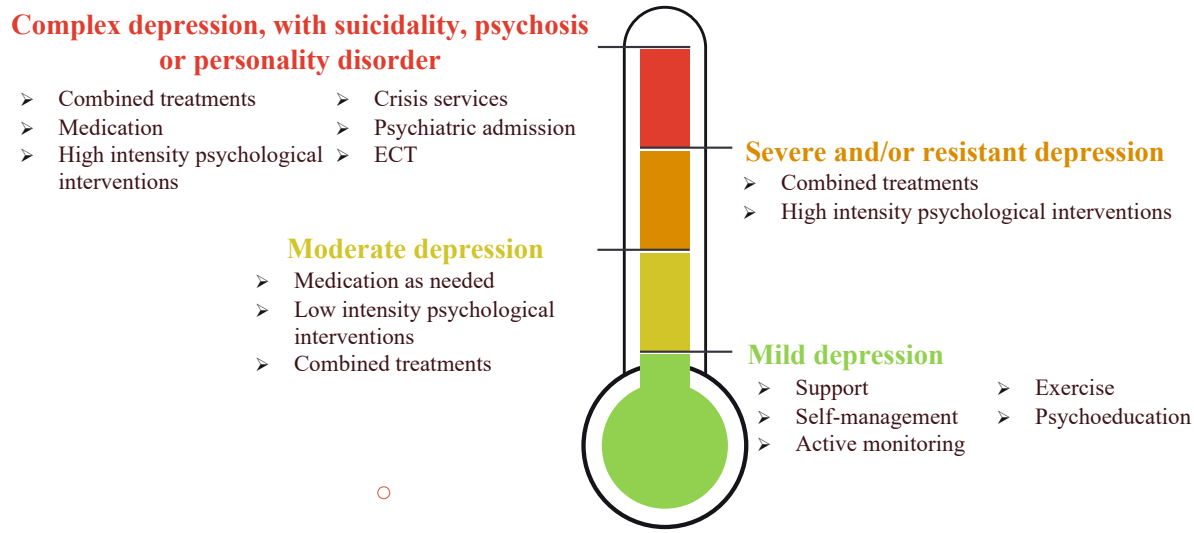
Environmental and socioeconomic factors add further complexity. Economic uncertainty, such as that caused by political upheaval, natural disasters, or financial crises, is associated with a higher prevalence of depression, especially among middle-aged and older individuals (97). Energy poverty, or lack of access to affordable energy, also has a notable negative impact on mental health, with those experiencing fuel poverty showing higher rates of depressive symptoms (98).

Climate and geographic influences affect susceptibility to depressive symptoms as well. For instance, exposure to air pollution has been linked to an increased risk of depressive episodes (99). Seasonal changes can influence circadian rhythms, which are closely tied to mood, and lower sunlight exposure has been correlated with higher levels of depression (100). Conversely, higher levels of solar radiation are linked to decreased psychological distress (101). Perceptions and awareness of climate change are consistently associated with depression and other adverse mental health effects (102). Some evidence even suggests that climate change could contribute to rising suicide rates in affected areas (103,104).

1.3 Treatment of depressive symptoms

Several factors must be considered in treatment choice, including severity, chronicity, comorbidity, suicide risk, psychosis, catatonic or melancholic features, functional status, prior treatment response and tolerability (105). Figure 1 provides an overview of the stepped care model in depression, a structured approach to treatment.

Figure 1 The stepped care model



Note. *Figure adapted from the National Institute for Health and Care Excellence (NICE) 2022. Retrieved from* https://www.nice.org.uk/guidance/ng222

1.3.1 Traditional treatments

1.3.1.1 Antidepressant medication

Pharmacotherapy is generally not recommended as a first-line treatment for subthreshold or mild to moderate depressive episodes, unless it aligns with the patient's preference. Antidepressants are generally introduced when depressive symptoms persist despite other interventions, or in cases where a patient has a history of severe unipolar depressive episodes. Selective serotonin reuptake inhibitors (SSRIs) are typically considered the first-line pharmacological option due to their favorable side effect profile and overall tolerability compared to tricyclic antidepressants (TCAs) (5,106,107). If SSRIs are ineffective, poorly tolerated, or contraindicated, serotonin-noradrenaline reuptake inhibitors (SNRIs), are often considered next (108). However, it is important to rule out a history of mania or hypomania before initiating treatment with antidepressants. This can be achieved by interviewing a relative or using validated tools such as the 32-item Hypomania Symptom Checklist (HCL-32) (109).

In Spain, the consumption of antidepressants has risen significantly, from 61 daily doses per 1,000 inhabitants in 2010 to over 98 doses in 2022 (110). Research supports that pharmacologic treatments can alleviate mild to moderate depressive symptoms, with ample evidence for sustained remission when antidepressants are continued. However, a large proportion of patients do not achieve remission with antidepressant monotherapy alone (111). Over half of

patients treated with first-line antidepressants do not achieve adequate response (defined as a ≥50% improvement in depression rating scale scores), with 50-66% failing to reach full remission (107,112), often necessitating additional treatment options, such as augmenting with other drugs alongside antidepressants. Nonetheless, antidepressants offer notable advantages: they are readily accessible, relatively affordable, and their effectiveness can typically be assessed within 2-4 weeks (113).

1.3.1.2 Psychological therapy

Psychological therapies are generally the first-line treatment for persistent subthreshold or mild to moderate depressive symptoms. In moderate to severe cases, they are often combined with antidepressants to improve outcomes. Several evidence-based psychotherapy approaches are effective in treating depressive symptoms, including cognitive-behavioral therapy (CBT), behavioural activation, interpersonal therapy, mindfulness-based cognitive therapy (MBCT), and problem-solving therapy.

CBT, the most extensively studied and widely recommended psychotherapy for depression (114,115), is a structured, time-limited approach that identifies and modifies negative thought patterns and behaviours to improve symptom management, making it a cornerstone of clinical guidelines (116) (5,116,117). Often integrated within CBT, behavioural activation also serves as an effective standalone treatment by encouraging engagement in enjoyable and meaningful activities, which helps counter the restrictive effects of depressive symptoms, thus enhancing mood and overall well-being (118). Another approach, MBCT, combines CBT with mindfulness practices from the Mindfulness-Based Stress Reduction programme (119). MBCT is particularly beneficial for reducing active symptoms and preventing relapse, especially in cases prone to recurrence (120–122). Meanwhile, interpersonal therapy and problem-solving therapy offer additional structured, skill-focused options. Interpersonal therapy enhances relationship dynamics and addresses conflicts, proving valuable when interpersonal issues are a core component of depression (123). Problem-solving therapy, on the other hand, builds practical skills to manage life stressors and and challenges, and has demonstrated efficacy across diverse populations (124,125), further enriching the therapeutic toolkit for depressive symptoms.

Beyond these established methods, other psychotherapies and integrative approaches are being tested, though results are inconclusive. Emerging modalities continue to expand treatment options, especially internet-based interventions. Online therapies, particularly CBT-based ones, have proven effective for mild to moderate depressive symptoms and show comparable effectiveness to in-person therapy when patients receive guidance or human interaction (126–131). Overall, evidence suggests that both first-line antidepressant and psychological monotherapies exhibit comparable effect sizes in treating depressive symptoms (132). However, a notable proportion of patients still do not achieve full response and remission, highlighting the ongoing need for advancements in treatment options (108,133). This growing body of evidence emphasizes the importance of providing diverse treatment formats, ensuring that psychological therapies are accessible and tailored to individual needs.

1.3.1.3 Treatment access and challenges

Since the last decade of the 20th century, advancements in pharmacological and psychological treatments for depression have introduced more options with improved tolerability and effectiveness, many of which have been extensively tested and recommended by professional guidelines. However, this progress has not led to a significant decrease in the global impact of the depression, largely because disparities in access to mental health services result in undertreatment being the norm rather than the exception for individuals with depressive symptoms (134). Effective treatments are essential, but their impact is severely limited when they reach only a small portion of those who need them. In low and middle-income countries the proportion of untreated depression ranges from 69.5% to 93.2% (41).

This issue is not confined to low-income countries like Burkina Faso, Congo, or Mali, where there are often fewer than one psychiatrist or psychologist per 100,000 people (135). Even in high-income countries like Spain (136), the availability of mental health professionals within the National Health System (SNS, from the Spanish acronym Sistema Nacional de Salud) falls short. There are fewer than six psychologists per 100,000 inhabitants (137) and the rate of psychiatrists is approximately 12.7 per 100,000 inhabitants (138), which is one of the lowest rates in Europe. As a result, there remains a considerable gap in access to mental health care in Spain.

Moreover, while antidepressant medication, psychotherapy, and their combination can be helpful, they do not work for everyone. Only a minority of patients with depressive symptoms achieve remission with first-line antidepressant monotherapy (112,139). This indicates that nearly half of the patients do not see significant symptom improvement after the first treatment. Furthermore, the response rate declines with each subsequent strategy, whether switching to or combining with a second medication. Other barriers that contribute to this treatment gap include structural barriers within healthcare systems, shortages in mental healthcare staff, and the stigma of mental illness, which often comes from misunderstanding or fear (140,141).

Given the widespread prevalence of depression, the critical need for timely and suitable treatments, and the barriers hindering access to psychotherapy, psychoeducation, and support interventions, the urgency for health systems to prioritise the exploration of alternative therapeutic strategies is undeniable. These strategies aim to effectively manage depressive symptoms and enhance patients' quality of life.

In this context, e-mental health —the delivery of mental health-related tools through the internet and related technologies (142)— emerged as a resource that could lighten the access gap at a lower cost (143). However, despite its promising effectiveness and the strong desire to proliferate e-mental health solutions, it has not yet led to a transformation in the delivery of mental health care (144). Users' adherence to e-health tools, a critical factor in managing depressive symptoms, has consistently been low, especially when these tools lack human guidance (145,146). This challenge highlights the importance of incorporating human contact into digital interventions. Indeed, online psychotherapy can be an efficacious treatment, but its effectiveness is contingent upon the presence of human contact, even if minimal (147). Unfortunately, this is a major barrier to scaling the low-cost treatments that e-health aims to offer in psychiatry.

Thus, there is an urgent need for further research to tailor interventions for individuals with depressive symptoms— unrestricted by diagnostic corsets— in a cost-effective and culturally acceptable manner. This is particularly crucial as health priorities have shifted towards increasing disability-free years of life rather than increasing life expectancy. To address this concern, multicomponent integrative strategies are gaining importance, particularly those focusing on lifestyle factors. This research field, known as lifestyle medicine, studies lifestyle

factors related to health and has begun to be considered a key approach for mental health concerns (148).

1.3.2 Depressive symptoms and exercise

1.3.2.1 Lifestyle medicine

There is broad and consistent evidence supporting the critical relationship between a healthy lifestyle and positive well-being, particularly in areas such as physical activity (PA), nutrition, sleep quality, and mindfulness (149). Recent treatment approaches emphasize integrating mental and physical healthcare to address complex health conditions, advocating for collaborative care models that coordinate both mental and physical health needs (150). Combined strategies that focus on lifestyle factors are gaining prominence in preventing and treating mental illness, particularly within the fields of lifestyle psychiatry (151) and lifestyle medicine (152). These approaches highlight the role of behavioural factors in mental health and their relationship with overall well-being (153–156).

PA has been well-established as a critical factor in both the prevention and management of non-communicable diseases, with vast evidence supporting its ability to improve mental health, quality of life, and overall well-being (157). PA is recognized as a key component of holistic recovery interventions for individuals with mental illness (158). Similarly, diet quality plays a significant role in mental health. A growing body of evidence links dietary patterns to depression, and obesity is consistently associated with poorer outcomes in depression, including lower treatment adherence and worse cognitive performance in both bipolar and unipolar disorders (159).

Various 'healthful diets' found across global regions and cultures, have been linked to reduced risks of depression. While many unsubstantiated 'magical diet cures' exist, serious observational studies suggest that diets rich in plant foods and lean proteins (especially fish), are protective against certain mental disorders. For example, dietary patterns like the Mediterranean Diet (160,161) or anti-inflammatory diets (162,163) are associated with better mental health outcomes. Conversely, Westernized diets, characterised by high intakes of saturated fats, refined carbohydrates, and processed foods, appear to have a detrimental effect (164,165). Modifying dietary habits can be an actual contributing factor in achieving better outcomes for depressive symptoms, including significant improvements in both depression and

anxiety (166). Thus, incorporating dietary interventions alongside standard treatments offers a promising complementary approach; however, further research is needed to refine it (167).

In addition to diet and PA, sleep is another critical modifiable lifestyle factor with significant implications for mental well-being. Sleep disturbances and poor sleep quality are not only symptoms of depression but can also serve as early warning signs for its onset. There is a strong bidirectional relationship between sleep and depression, where each can exacerbate the other (168). Interventions that promote sleep hygiene have proven effective in both preventing and alleviating depressive symptoms (169,170).

Given the clear links between lifestyle factors and mental health, lifestyle medicine programmes are increasingly seen as valuable tools in managing depressive symptoms. These programmes should be considered part of a comprehensive treatment plan tailored to individual characteristics and circumstances to maximize their effectiveness (171). The field of lifestyle medicine continues to grow, but further research is needed to better understand its efficacy and how it can be successfully implemented in public health settings. Co-creation processes that include all relevant stakeholders—with particular emphasis on contributions from individuals with lived experience—are widely recognised as one of the most effective approaches to designing impactful and sensible programmes.

1.3.2.2 Physical activity and depression

PA, typically defined as any movement requiring energy expenditure encompasses more than just exercise and includes activities like work-related tasks and household chores (172). The American College of Sports Medicine (ACSM) classifies different intensities of PA as light (1.1-2.9 METs), moderate (3.0-5.9 METs), and vigorous (≥6.0 METs), where METs are metabolic equivalents (173). Engaging in PA, even for a single session at moderate-to-vigorous intensity, can immediately enhance cognitive function (174), improve sleep (175), and positively affect mood, reducing stress levels in both clinical and non-clinical populations (176). In the long term, PA offers significant benefits to individuals with depression by enhancing physical health, improving cardiorespiratory capacity, and reducing the risk of metabolic disorders (177). PA also helps modulate the body's stress response and optimises its antioxidant capacity (178), which is relevant given the link between affective disorders and inflammation (179,180),

Research has demonstrated a strong association between low PA levels and a higher risk of developing mental disorders, such as depression and BD (181,182). Evidence suggests that PA is an effective preventive measure against depression, with a dose-response relationship offering long-term protective benefits (183). For example, PA during pregnancy reduces the risk of postpartum depression (184). Even PA levels below public health recommendations can significantly benefit mental health, with modest increases in activity leading to a notable reduction in depression risk (183). Engaging in half the recommended amount of PA lowers depression risk by 18%, meeting the recommendation reduces it by 25%, and doubling it reduces it by 28%, with sustained benefits over time (185).

In contrast, sedentary behaviour, defined as activities with low energy expenditure (≤1.5 METs), is associated with an increased risk of chronic mental and physical health issues, leading to higher morbidity and mortality rates (186,187). Interestingly, gender differences in PA are apparent, with women being less active than men in many countries (188).

Individuals with depression tend to be less physically active and more sedentary than those without the condition, often failing to meet public health PA recommendations (189). Such evidence reinforces the need to promote PA as a key strategy in mental health interventions, especially for individuals at risk or experiencing depressive symptoms.

1.3.2.3 Exercise as a treatment for depressive symptoms

A robust body of evidence supports exercise—a structured, planned, and repetitive subset of PA—as a powerful tool for improving overall well-being and alleviating mental disorders. Exercise has proven to have an anxiolytic effect, reduced depressive symptoms, and potentially decreased suicidal ideation (190,191). It is an evidence-based treatment for managing depressive symptoms, showing variable effect sizes across studies (192,193), with most rigorous studies reporting moderate effect sizes (194). When compared to non-active groups (e.g., waitlist, self-monitoring, placebo, health education), exercise results in a greater reduction in depressive symptoms (177,195).

Moreover, exercise has been suggested to be equally effective as antidepressant medications (e.g., SSRIs) and psychological therapy in reducing mild to moderate depressive symptoms in

adults, with some studies reporting similar effect sizes (196), and results are more modest when examining methodologically rigorous studies (adequate allocation concealment, intention-to-treat analysis, and blinded outcome assessment) (194). For individuals with severe depressive symptoms, exercise can serve as a beneficial adjunctive therapy to treatment as usual (TAU) (197). It also reduces depressive symptoms in individuals with chronic illnesses, indicating benefits for patients with comorbid non-psychiatric conditions (198,199). However, the long-term effectiveness of exercise in alleviating depressive symptoms remains underexplored, and more research is needed to draw firm conclusions about its lasting impact.

Key guidelines from organizations such as the European Psychiatric Association (EPA) (200), the Royal Australian and New Zealand College of Psychiatrists (RANZCP) (201), and the Canadian Network for Mood and Anxiety Treatments (CANMAT) (117) recommend exercise as a primary stand-alone treatment for mild to moderate depression and as an adjunctive therapy alongside other treatments for moderate to severe depression. Furthermore, exercise offers an outstanding opportunity to efficiently address the high incidence of cardio-metabolic health problems associated with depressive symptomatology, which contributes to the premature mortality gap between people with depression and the general population (202). At the biological level, moderate exercise is associated with positive effects on mood, potentially through mechanisms involving increased levels of neurotrophic factors such as BDNF (203). Additionally, exercise may influence neurotransmitter systems, cortisol and beta-endorphins levels, which contribute to its mood-enhancing effects. These biological interactions provide a basis for understanding how exercise can alleviate symptoms of affective disorders and reduce recurrence rates, ultimately supporting improvements in patients' quality of life (204).

Despite the benefits, access to exercise programmes varies widely between countries, regions, and healthcare systems, with Spain being an example where exercise is not yet a standard part of the primary care treatment framework and is largely absent from most mental health services and routine care.

1.3.2.4 Prescription of exercise

Currently, no specific type of exercise is universally favoured for improving depressive symptoms, as various modalities—including aerobic, resistance, and mind-body exercises like yoga—have demonstrated effectiveness (205,206). While exercise can reduce depressive

symptoms, regardless of the intensity of the exercise (207), increasing evidence suggests that vigorous-intensity activity may be more effective than light-intensity activity (177). However, the optimal dose-response regarding duration, frequency, volume, or intensity needed to activate the biological mechanisms for treating depressive symptoms remains uncertain, resulting in considerable variability in the intensity and structure of exercise programmes. Many studies fail to provide reproducible descriptions (189,190), but general prescriptions indicate that interventions should consist of cardiovascular and/or resistance exercises at moderate to vigorous intensity levels. Recommended frequency is at least 1 to 3 sessions per week, lasting 30 to 60 minutes per session, and programmes should span a minimum of 9 to 10 weeks, with settings tailored to personal preferences or group/outdoor environments.

Structured and time-limited exercise programmes are particularly effective for mild to moderate and subclinical depressive symptoms (5,117,201), with group regimes showing added benefits (208). These programmes promote not only physiological changes and improved sleep regulation but also enhance social interaction and support. Generally, exercise is a safe and well-tolerated treatment strategy with few adverse effects. However, it should be approached cautiously, tailored to individual limitations, needs, and capabilities, especially for individuals with acute physical health conditions affecting exercise capacity; consulting a physician for those with pre-existing health concerns is advisable. Table 2 compiles the exercise prescription recommendations from relevant guidelines and institutions that offer specific guidance for depression or depressive symptoms.

A critical factor for regular exercise adherence among individuals suffering from affective disorders is the guidance provided by qualified professionals (209). These professionals can customise prescriptions to fit individual fitness levels and specific needs, leading to better adherence and lower drop-out rates (210). However, the number of well-designed studies assessing the efficacy of prescribed and personalised exercise in routine clinical practice for depressive symptoms remains limited (211), reflecting insufficient mental health resources that employ exercise practitioners to develop personalised exercise plans. To understand the potential benefits of exercise in preventing and treating mental disorders, cross-collaboration between exercise science and mental health is essential (212), yet most physical medicine, exercise physiology, kinesiology, or rehabilitation programmes lack training on exercise-based treatments for depression.

Table 2 Recommendations for administering exercise to treat depression

Guidelines	Type	Intensity	Time	Frequency	Period	Setting
CANMAT (117)	Cardiovascular and/or resistance	Moderate-to-vigorous	≥ 30 min.	≥ 3 days/week	≥ 9 weeks	Personal preference
NICE (5)	Cardiovascular	Moderate	N/S*	≥ 1 day/week	10 weeks	Group and outdoors
RANZCP (201)	Cardiovascular and resistance	Vigorous	N/S	≥ 2-3 days/week	N/S	Personal preference
EPA (200)	Cardiovascular and/or cardiovascular and resistance	Moderate	45–60 min.	2-3 days/week	N/S	N/S

***Note**. CANMAT = Canadian Network for Mood and Anxiety Treatments; EPA = European Psychiatric Association; NICE = National Institute for Health and Care Excellence; N/S = Not specified; RANZCP = Royal Australian and New Zealand College of Psychiatrists*

**Previous NICE guidelines recommended a duration of 45-60 minutes, and many authors continue to assume that this recommendation remains valid.*

1.3.2.5 Barriers and facilitators

Depressive symptoms can hinder exercise participation, despite the well-documented benefits of exercise for individuals suffering from them. Symptoms such as fatigue, low motivation, insomnia, poor appetite and sadness often lead to a sedentary lifestyle, limit limiting one's ability to engage in exercise. This lack of PA may, in turn, contribute to the emergence of additional psychiatric symptoms, including self-defeating thoughts, unappropriated guilt, and regret, which further worsen both depression and anxiety (187).

Another barrier to exercise participation is the self-stigma associated with mental illness. This stigma reduces motivation and creates reluctance to engage in exercise programmes, particularly among individuals with psychiatric diagnoses. Physical health issues, such as obesity, chronic pain, and injuries, also present significant obstacles, exacerbating the difficulty of maintaining regular exercise routines (213).

The absence of adequate resources and professional support further limits exercise participation (214). Key challenges include a lack of dedicated funding for exercise programmes and the absence of specialised staff to coordinate these initiatives. Mental health professionals often lack the necessary knowledge and training to effectively integrate exercise into treatment plans. As a result, recommendations for PA are frequently vague or unsupported by sufficient

expertise, thus reducing the likelihood of their adoption as part of therapeutic interventions. Therefore, enhancing adherence and engagement to exercise and reducing barriers are challenges to overcome (209).

To overcome these barriers, several strategies must be implemented. Service providers should actively promote and tailor physical exercise programmes to meet each patient's specific needs. This requires proper training and the establishment of roles that support the integration of exercise into mental health care. Motivating patients to participate is also crucial, with exercise routines adapted to their individual health status and preferences. Patient-centred strategies, including customised exercise plans, should be developed to ensure that the PA is accessible and relevant to those in mental health services.

Although incorporating these strategies into routine mental health care is challenging, doing so is essential for effective intervention (213). Given the number of barriers faced by this highly sedentary population, targeted interventions are urgently needed to promote exercise participation and improve mental health outcomes.

Chapter 2. Aims and hypotheses

2.1 Primary aims

1. Synthesise the effect of exercise-based interventions on general functioning (e.g., daily activity limitations) and quality of life on individuals with transdiagnostic depressive symptoms (Study 1).
2. Characterise a population of adults presenting with transdiagnostic depressive symptoms at baseline in a sample drawn from a broader randomised controlled trial (Study 2).
3. Explore the relationship between physical performance and functional impairment in a population of adults presenting with transdiagnostic depressive symptoms. (Study 2)
4. Design an exercise-based group intervention for individuals with transdiagnostic depressive symptoms, based on personalised prescriptions and enhancement of motivation towards activity (Study 3).
5. Determine the differential effect of the above-mentioned intervention on functioning of patients with transdiagnostic depressive symptoms on top of usual care, by comparing an experimental group (Personalised group exercise-based intervention + fitness tracker) and a control group (general exercise recommendations + fitness tracker) (Study 3).

2.2 Secondary aims

1. Synthesise the impact of exercise-based interventions on clinical symptoms in adults with transdiagnostic depressive symptoms (Study 1).
2. Identify sociodemographic and health factors potentially influencing the association between general functional impairment and physical performance (Study 2).
3. Test the differential effect of the above-mentioned exercise-based intervention on well-being and depressive symptoms of this population, by comparing the study arms (Study 3).

2.3 Hypotheses

1. Individuals experiencing transdiagnostic depressive symptoms will demonstrate greater functional capabilities —understood as having fewer difficulties in participating in and maintaining daily or social activities— and an enhanced quality of life after participating in exercise-based treatments, as measured by validated questionnaires, compared to those receiving treatment as usual or other active interventions (Study 1).

2. Functional impairment, as measured by the Functioning Assessment Short Test (FAST) and 36-item Short-Form Health Survey (SF-36) summary scores, will be associated with worse physical health indicators, as measured by the 6-minute walking test (6MWT), handgrip strength test (HGST), and 1-minute sit-to-stand test (1MSTS), in a population with transdiagnostic depressive symptoms (Study 2).

3. Sociodemographic and health variables, including age, body mass index, tobacco use and menopause status, will influence the potential relationship between physical health parameters, measured by the 6MWT, HGST, and 1MSTS, and general functioning, as assessed by the FAST and SF-36 summary scores, in a population presenting with transdiagnostic depressive symptoms (Study 2).

4. Participation in IDEA (Improving Depressive symptoms through personalised Exercise and Activation), a brief group intervention promoting personalised exercise and activity in addition to usual care, will improve general functioning in participants with transdiagnostic depressive symptoms, as measured by the FAST, from baseline to weeks 4, 12 and 36, compared to those receiving general exercise recommendations and a fitness tracker (Control Group) (Study 3).

5. Participation in IDEA will improve perceived functional status in subjects presenting with transdiagnostic depressive symptoms, as measured by the SF-36, from baseline to weeks 4, 12 and 36, compared to Control Group (Study 3).

6. Participation in IDEA will improve depression severity in subjects presenting with transdiagnostic depressive symptoms, as measured by the PHQ-9, from baseline to weeks 4, 12 and 36, compared to Control Group (Study 3).

7. Participation in IDEA will improve well-being in individuals with transdiagnostic depressive symptoms, as measured by the WHO-5 Well-Being Index (WHO 5 WBI), from baseline to weeks 4, 12 and 36, compared to Control Group (Study 3).

Chapter 3. Methods

The present dissertation is the compendium of three studies with diverse methods and designs.

3.1 Study 1: Evaluating the effect of exercise-based interventions on functioning in people with transdiagnostic depressive symptoms: A systematic review of randomised controlled trials

Design and procedures

A systematic literature review was registered in PROSPERO (CRD42020186480) and conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (215).

Search strategy and study selection

A comprehensive search was conducted in PubMed, Scopus, and PsycInfo for records from database inception to April 2023, restricted to peer-reviewed journals and English, Spanish, Catalan, French, Italian, Portuguese, and German languages. The search strategy employed was (((depressive symptoms) OR (depression) OR (depressive disorders) OR (major depressive disorders)) AND ((exercise) OR (physical activity) OR (physical exercise)) AND (randomised controlled trial) AND ((therapy) OR (treatment))).

After the removal of duplicates, two authors (AG-E and NA-O) independently screened the titles and abstracts of all potentially eligible studies. Relevant full-text articles were retrieved for further review and examined by the two authors. Discrepancies were resolved by consensus with a third researcher (M.C.H). A fourth reviewer (F.C) was available for mediation throughout this process. Results were managed using Rayyan for systematic reviews (216) and the final list of included articles was imported into Mendeley Desktop reference management software (version 1.19.4, Elsevier).

Eligibility criteria

Studies were included if they: 1) were randomised controlled trials; 2) focused on exercise-based interventions (exercise constituted a core component of the therapeutic approach) ; 3) included a population of adults (aged ≥18 years) with depressive symptoms at study entry; 4) interventions included aerobic, anaerobic, or a combination of both activities in at least one study arm, 5) provided detailed information on exercise type, intensity, duration, and

frequency; 6) the comparators included TAU or any other active control group (CG); 7) provided quantitative data on psychosocial and occupational functioning, and/or quality of life and 8) used validated questionnaires to measure outcomes. Interventions where exercise was integrated into a broader therapeutic framework, such as programmes combining exercise with psychoeducation, cognitive-behavioural strategies, or other psychological interventions, were also included, provided the exercise component was a significant and structured element of the intervention. For instance, multi-component programmes were considered eligible if the exercise activities were clearly defined, systematically implemented, and could be quantitatively assessed as part of the study design.

Studies were excluded if they were observational, qualitative, quasi-experimental, or single-case. Additionally, pilot or preliminary results, unpublished articles, and trials focusing solely on pharmacological treatment were also excluded. Programmes where exercise was incidental or secondary to other therapeutic goals (e.g., solely psychoeducation, pharmacological therapy, or mindfulness activities) were excluded to ensure that the primary focus remained on exercise-based modalities.

Data extraction and data synthesis

Data from included studies were extracted into a pre-designed Excel form by two reviewers (A. G-E and N. A-O), including bibliographic information (e.g., authorship details and publication date), study characteristics (e.g., intervention type, setting, length, intensity, comparator arm) and sample characteristics (e.g., location, age, sex, depressive symptoms screening, assessment instruments), and summarised outcome data.

Data from included studies were synthesized narratively, following established guidance for narrative synthesis in systematic reviews. Studies were grouped by primary outcomes (general functioning, quality of life) and secondary outcomes (depressive symptoms). Data extraction and comparison involved extracting quantitative results, specifically p-values, to identify significant patterns. Additionally, qualitative observations, including descriptions of interventions and adherence rates, were noted to contextualize the findings. Identification of patterns and variability involved comparing the findings within and across groups to identify consistent trends, outliers, and sources of variability. Studies were examined for potential methodological differences, such as sample size, bias risk, or follow-up duration. Integration of evidence involved developing a narrative summary for each outcome, integrating evidence

across studies while acknowledging heterogeneity in methods and results. The extracted data were presented in summary tables.

Risk of bias

The risk of bias assessment was independently conducted by two authors (A. G-E and N. A-O), with discrepancies resolved by a third author (J. M-S). The Cochrane Collaboration's Risk of Bias Tool for randomised trials (217) and the RoB2 Excel tool were used to assess methodological quality. The effect of intervention assignment was evaluated as the 'intention-to-treat effect'. Bias was categorised as 'low' (−), 'high' (+), or 'unclear' (?) when details were insufficient, meaning that key methodological information—such as the randomisation process, blinding, or handling of missing data—was either missing or not described in enough detail to make a clear judgment.

3.2 Study 2: Association between physical health and functioning parameters in transdiagnostic depressive symptoms

Design and procedures

A cross-sectional analysis of baseline data from the IDEA RCT was conducted after study termination to characterise the associated factors of depressive symptoms. For full details on the depicted trial methodology see Study 3 and Appendix A.

Sample

The sample included 121 subjects, aged 18 to 65 years, presenting with mild to moderate depressive symptoms according to the Montgomery–Åsberg Depression Rating Scale (MADRS) (scores ranging from 16 to 34) irrespective of diagnostic entity. Additional inclusion criteria and recruitment details are provided in the Methods section of Study 3.

Variables

Functional status

Functional status is multifaceted and encompasses numerous domains.

- **General functioning**: measured by the FAST (218). It was initially developed for individuals with BD, and it is highly reliable, with a Cronbach's alpha of 0.909, strong test-retest reliability (intraclass correlation coefficients = 0.98), good concurrent validity ($r = -0.903$; $p < 0.001$), and sensitivity to variations in mental health status. It is a simple interviewer-administered instrument specifically designed for individuals with mental health disorders that comprises 24 items. It assesses impairment or disability in six main areas of functioning, namely: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Higher scores indicate greater functional difficulties. All items are rated on a 4-point scale: 0 = no difficulty, 1 = mild difficulty, 2 = moderate difficulty, and 3 = severe difficulty. The global score is obtained by summing up the scores of each item, with higher scores corresponding with worse functioning. The whole administration procedure often takes hardly six to eight minutes.

  Functional status: the SF-36 served as a complementary, broader measure of functional status (219,220). It is a 36-item, self-administered questionnaire used to

assess functioning and general health, demonstrating robust psychometric properties in terms of validity and reliability across diverse populations and settings globally. Cronbach's alpha coefficients typically exceed the recommended minimum of 0.7 for group comparisons in most subscales, particularly for Physical Functioning, Physical Role, and Emotional Role. Intraclass Correlation Coefficients range from 0.58 to 0.99. Construct validity is supported by lower scores in individuals with chronic illnesses or recent doctor consultations, along with age-related declines. SF-36 subscales correlate moderately to strongly (0.30-0.81) with clinical indicators like the General Health Questionnaire. In psychiatric populations, internal consistency is demonstrated with Cronbach's alpha values ranging from 0.60 to 0.92 (221). For the current study, only the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were used. The PCS reflects physical health, including physical functioning and pain, while the MCS assesses mental health, including emotional and social functioning. Scores range from 0 to 100, with higher values indicating better functioning.

Physical performance

The following physical performance measures were used as indicators or proxies of physical health and functional ability(222–224).

- **Functional Exercise Capacity**: assessed using the 6MWT (225) which evaluates the distance walked around a set circuit over 6 minutes as a submaximal test of aerobic capacity and endurance. The test score is determined by the distance covered by the subject in meters within the 6-minute duration. The 6MWT has demonstrated moderate to strong validity in depression, with correlations to cardiopulmonary exercise test-based maximal aerobic power ranging from r = 0.54 to 0.78 and intraclass correlation coefficients of ≥ 0.66 (226).
- **Functional lower extremity strength**: evaluated using the 1MSTS (227). The 1MSTS involves standing up from and sitting down on a chair as quickly as possible within one minute. The score is determined by counting the number of times the person completes the action. This test has shown high reliability in various contexts, with intraclass correlation coefficients ranging from 0.80 to 0.98 and coefficients of variation from 3.8% to 12.8%. It has also demonstrated validity, with significant correlations to the 6MWT and knee extension strength, ranging from 0.57 to 0.75 (228).

- **Isometric muscle strength of the hand and forearm muscles**: measured using the HGST (229) with a digital hand dynamometer (JAMAR®, Nottinghamshire, UK) (230). It is considered both reliable and valid for assessing muscle strength, with good ($r > 0.80$) test–retest reproducibility and excellent ($r = 0.98$) interrater reliability. Grip strength was measured three times per hand in the 2-handle position, with participants exerting maximum effort for approximately five seconds each time. The mean score from three attempts for each hand was recorded, and reported scores were based on the participants' dominant hand.

These measures were collected prior to any intervention to serve as baseline data for the cross-sectional analysis.

Covariates

We controlled for age, BMI, tobacco use, and menopause (for participants who were menopausal) in the partial correlation analyses, as these variables are known to influence both physical performance and general functioning. Age is a key determinant of physical performance, with natural declines in strength, endurance, and mobility, along with increased risks of chronic conditions significantly affecting outcomes. Similarly, BMI impacts physical health; higher BMI is linked to an increased risk of cardiovascular disease, diabetes, and musculoskeletal disorders, all of which can impair performance and contribute to functional decline. Tobacco use detrimentally affects health by reducing lung capacity, endurance, and cardiovascular fitness, interfering with both physical performance and general functioning. Controlling for tobacco use helps isolate the relationships being studied. Additionally, menopause is relevant to our predominantly female sample due to its association with physiological changes—such as hormonal fluctuations, loss of muscle mass, and decreased bone density—that can impact physical performance and functioning. By adjusting for these covariates, we aimed to reduce bias and ensure that the associations between general functioning and physical performance were not confounded by these factors.

Statistical analysis

All statistical analyses were processed using SPSS ver. 27 (IBM SPSS, Chicago, IL). To ensure comparability between the study groups, statistical tests were conducted on sociodemographic and clinical variables. Chi-square tests were used for categorical variables, while t-tests or Mann-Whitney U tests were used for continuous variables. Pearson correlation

coefficients were computed using the original IDEA RCT dataset to examine the relationships between physical performance indicators and general functioning measures at baseline. All necessary assumptions for using Pearson correlation were met, including the normal distribution of data and linearity of relationships, confirmed by scatterplots. To address potential confounding variables, partial correlations were calculated while controlling for sociodemographic and health-related variables, including age, BMI, tobacco use, and menopause. These covariates were handled in separate models rather than together to avoid issues related to multicollinearity, which could distort the relationships between the variables of interest. By adjusting for each covariate individually, we ensured that the influence of each factor on physical performance and general functioning was appropriately accounted for without introducing confounding effects. This approach is consistent with statistical best practices in cases where covariates may interact or overlap in their effects (e.g., age and menopause) and allowed for a clearer interpretation of the independent effects of the covariates. Significance level was set at $p < 0.05$.

3.3 Study 3: The IDEA trial: A single-blind randomised controlled study of a personalised exercise-based intervention for transdiagnostic depressive symptoms

Design and procedures

We conducted a 2-arm randomised single-blind controlled clinical trial named IDEA (Improving Depressive Symptoms through Exercise and Activation) to determine the efficacy of a personalised exercise-based intervention compared to TAU with a 36-week follow-up phase. Eligible participants were allocated to one of the following conditions: a) Experimental Group (EG): Personalised exercise group programme + fitness tracker + IDEApp or b) Control Group (CG): General exercise recommendations + fitness tracker + IDEApp. Random assignment to the control or active treatment condition was in a 0.95:1 ratio, slightly deviating from the planned 1:1 ratio. This minor imbalance, attributed to random variation, does not compromise the integrity or validity of our findings.

Before any study procedures began, participants were informed about the study characteristics. They were given a study information leaflet and a written informed consent form to sign. After signing the informed consent, an experienced psychologist assessed the participants. They confirmed or ruled out depressive symptomatology, administered the MADRS, and ensured that participants were eligible.

For further details on the depicted trial methodology see Appendix A. Prior to starting the trial, there were deviations from the original protocol due to unforeseen technical difficulties with IDEApp, an ad-hoc designed companion app. This app, which was designed to collect objective and self-reported data, as well as deliver motivational or awareness messages based on data from the fitness tracker, failed to function as intended. While the messaging system was not a critical component of the intervention, continuing with the initial design would have led to an invalid comparison between groups, as the intervention could not be delivered as originally envisioned. Therefore, it was essential to revise the study design to reflect the capabilities of the operational app.

To address these technical issues while maintaining the study's integrity, we opted to simplify the treatment arms. Originally, the study included three groups: two intervention groups (one with and one without motivational messaging) and a CG. With the motivational messaging

feature inoperable, the two intervention groups were consolidated into a single EG, which included the personalised exercise programme and the fitness tracker with IDEApp. This group was then compared against a CG, which received general exercise recommendations along with the fitness tracker and IDEApp. This adjustment ensured that the study remained feasible, allowing for a valid comparison between a clearly defined intervention and control condition, despite the absence of the app's messaging functionality.

Finally, the reduction in the number of treatment arms required a corresponding adjustment to the randomisation ratio. With only two groups remaining, the randomisation process was adapted to ensure the appropriate allocation of participants between the EG and CG. This modification was necessary to maintain the study's statistical power and ensure that the comparisons made between the groups could still yield meaningful and reliable results. The overall rationale for these deviations was to adapt to the technical limitations encountered and preserve the study's ability to address its primary research questions in a scientifically valid manner.

Ethics and Registration

The study received ethics approval from the Hospital del Mar Research Institute Drug Research Ethical Committee (Reference number: 2019/8816/I). The study protocol was registered on ClinicalTrials.gov (Identifier: NCT04857944) in April 2021.

Sample

We included 121 participants aged 18–65 years with mild to moderate depressive symptoms (MADRS score > 16 and < 34), who owned an Android-compatible smartphone, had basic skills using a smartphone, were fluent in Spanish, and could provide written informed consent to participate. Subjects were excluded if they had severe cognitive and/or physical impairment; cognitive deficits or developmental disorders; current psychotic, melancholic, or catatonic features; substance use disorders; modification of drug treatment (or its dose) in the last month; initiation of psychological treatment in the last month; initiation of biophysical treatment in the last month; BMI > 40; or physical disabilities.

Participants, regardless of group allocation, continued receiving their usual treatment (standard pharmacological and/or psychological treatment), prescribed and monitored by their treating

physician. All concomitant care and interventions were permitted if they had been implemented more than a month before study entry.

Recruitment took place from June 2021 to November 2023 at outpatient mental health centres, neurological and physical rehabilitation services, general practice services, and the post-COVID-19 (Coronavirus disease) unit affiliated with the Hospital del Mar Trust in Barcelona, Spain. Referrals to the study were made by psychiatrists, general practitioners, and clinical psychologists involved in the participants' treatment.

Study measures

Primary outcome measure

Given the great heterogeneity expected in the sample, the intervention was aimed at improving general functioning in the first place, understood as the difficulties experienced in participating and maintaining daily or social activities. Since the primary focus of the trial was to assess the efficacy of the IDEA intervention, the main outcome comparison was between the EG and the CG.

- **General functioning**: measured by the FAST, a simple interviewer-administered tool for individuals with mental health disorders. It includes 24 items assessing impairment in six functional areas. Higher scores indicate worse functioning. Further description, references, and psychometric information on this questionnaire are provided in the *Variables* section of Study 2 (Section 3.2).

Secondary outcome measures

- **Functional status**: the SF-36 served as a complementary, broader measure of functioning. It is a self-administered questionnaire assessing eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Scores for each domain are scaled from 0 to 100, with higher scores indicating better general health status and less disability. Further description, references, and psychometric information on this questionnaire are provided in the *Variables* section of Study 2 (Section 3.2).

- **Depressive symptoms**: measured by the PHQ-9 (231,232), which screens depressive symptoms and assesses their severity. It can also track changes experienced by patients over time. This self-administered and brief depression severity measure comprises 9

items with Likert-scale responses ranging from 0 to 3, referring to the past two weeks. Elevated scores suggest the presence of severe depression.

- **Well-being**: measured by the WHO 5 WBI (233,234). The WHO-5 WBI is a 5-item self-administered questionnaire used to assess current mental well-being. The rating scores range from 0 (at no time) to 5 (all the time), with total scores ranging from 0 to 100, where higher scores indicate better well-being.

We used validated Spanish versions for all questionnaires.

Assessment

Participants first underwent a clinical interview and baseline assessment, followed by an evaluation with a physiotherapist that played a crucial role in identifying their physical needs, capabilities, and limitations. This evaluation allowed for the creation of a personalised exercise prescription for those in the EG. It involved assessing any existing injuries or pathologies in specific areas of the body, such as the back, shoulders, arms, and legs, helping to pinpoint potential limitations and areas that required special attention. Additionally, the physiotherapist inquired about any pain or discomfort in different body parts, as well as any activities that participants may have had to stop due to pain or incapacity. These questions allowed the physiotherapist to tailor the intensity and types of exercises to each participant's condition. The evaluation also included exploring the participants' motivations by asking about activities they have enjoyed in the past, currently enjoy or wish to start, ensuring that the programme incorporated exercises they found engaging and motivating. By taking these factors into account, the physiotherapist created a personalised exercise prescription for each participant in the EG, ensuring it was both safe and motivating while addressing their individual needs and preferences. A detailed description of the exercise prescription is provided in the Interventions section.

After these assessments, study staff installed a custom app on all participants' smartphones and provided activity bands. In the first week after study entry, participants began using the devices and the IDEApp, which tracked their baseline PA and exercise throughout the trial. Following completion of the group sessions (after one month for the CG), all participants were monitored for eight months. Post-allocation assessments were conducted via telephone at 4 weeks (T1), while the 12-week (T2) and final 36-week (T3) assessments were conducted face-to-face,

mirroring the baseline assessment format. Figure 2 illustrates the key stages of the EG, and the time points and assessment tools are detailed in Table 3.

Figure 2 Timeline of the Experimental Group in the IDEA study

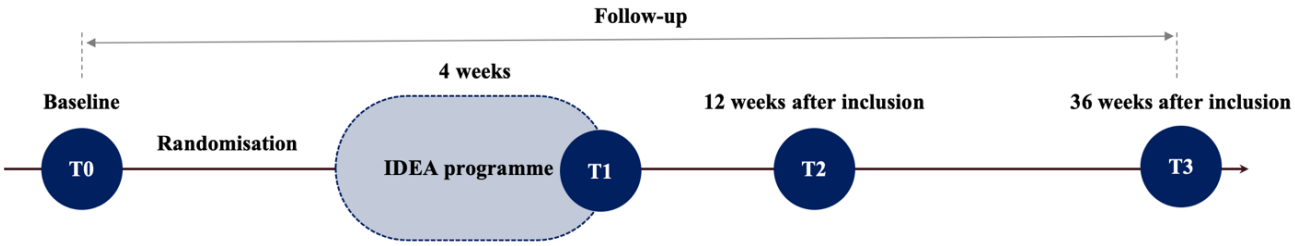


Table 3 Overview of IDEA trial assessment tools and time points, with measures analysed in this study indicated

	Enrolment	T0	4-Week group sessions	T1	T2	T3
Eligibility screen	✓					
Informed consent	✓					
Randomisation		✓				
Experimental Group			✓	✓	✓	✓
Control Group		✓		✓	✓	✓
Sociodemographic data*		✓				
Health habits and clinical data*		✓				
FAST*		✓		✓	✓	✓
SF-36*		✓		✓	✓	✓
WHO-5 WBI*		✓		✓	✓	✓
PHQ-9*		✓		✓	✓	✓
SIMPAQ		✓		✓	✓	✓
6MWT		✓			✓	✓
1MSTS		✓			✓	✓
HGST		✓			✓	✓
Activity monitoring		✓	✓	✓	✓	✓

***Note**. All listed instruments were administered to both the experimental group and the control group. FAST= Functional Assessment Short Test; SF-36 = 36-items Short-form Health Survey; WHO-5 WBI = World Health Organization Well-being Index; PHQ-9 = Patient Health Questionnaire; SIMPAQ = Simple Physical Activity Questionnaire; 1MSTS = 1-minute sit-to-stand test; HGST= handgrip strength test*

** Measures analysed in this study; other measures are part of the IDEA trial but are not included in the present analyses*

Interventions

The study involved specially designed materials, including group sessions and a mobile application.

Intervention design

1. Group sessions

   The primary aim of the intervention is to tailor exercise prescriptions and enhance motivation for PA by focusing on behavioural change and processes that encourage regular exercise and healthy habits. This was achieved through the IDEA programme, a brief group intervention developed by a collaborative team consisting of four psychologists, a psychiatrist a medical doctor specialising in Physical Medicine and Rehabilitation and a physiotherapist. Each member contributed insights from their field to ensure that the programme was both psychologically and physically appropriate. The co-creation process was conducted through a series of online meetings. In these sessions, the team discussed and integrated feedback from stakeholders (potential participants and healthcare providers), refining the programme's structure, content, and delivery methods to be both engaging and practical.

   After the initial design, we conducted a pilot study with four volunteers to test the feasibility of the IDEA programme. Participants provided detailed feedback on their experiences, which we used to identify areas for improvement and fine-tune the programme further. Adjustments were made to ensure the intervention was user-friendly and impactful, reflecting the participants' needs and preferences. By following this iterative and inclusive co-creation process, we were able to tailor the IDEA programme to the unique needs of our target population, ensuring that it was both evidence-based and user-centered.

   The programme consisted of six group sessions lasting 60 to 90 minutes each, accommodating four to six participants per session. Working in small groups facilitates faster integration and enables professionals to better identify participants' needs and while emphasizing the personal relevance of session content. These sessions occured once or twice a week over one month, held in a Physiotherapy room at Centre Fòrum–Hospital del Mar, which offers rehabilitation, sociosanitary, and mental health services. Group sessions

were led by a health psychologist (Psychology BSc, MSc) and a physiotherapist (Physiotherapy BSc, MSc) with accredited experience. Participants received materials, including a handout with individualised exercise prescriptions and a written summary of the content covered at the end of each session, as well as resistance bands for exercising. These bands allowed them to adjust the intensity and resistance levels of the exercises to suit their needs over time. An overview of the content covered in the six group sessions is provided in Table 4.

Table 4 Content overview of the IDEA group sessions

Week	Sessions and topics	Key points	Lead
1	1. Exercise and depressive symptoms	Programme introduction Explanation of session dynamics Depression and its relationship with exercise	MH and PM
2	2. Motivation towards exercise	Exploring and identifying participants' motivations	MH
	3. Introduction to exercise prescription	Introduction of the personalised exercise plan On-site practice	PM
3	4. Barriers to exercise	Exploring and identifying barriers to exercise	MH
	5. Review of the exercise prescription	Exercise practice Clarifying prescription doubts	PM
4	6. What now? Exercise maintenance	Exploring individual adherence strategies Programme review Addressing questions Providing feedback	MH and PM

***Note**. MH = Mental health team; PM = Physical medicine team*

2. Exercise prescription

The individualisation of the intervention revolves around tailoring the exercise prescription to each participant's specific needs and abilities. This process was designed to optimise the physical activity regimen based on the participant's level of sedentarism and physical capacity (more details to follow), which was assessed during the development of their personalised exercise plan.

Participants engaged in four types of exercises: stretching, aerobic, strength, and relaxation, with personalised prescriptions based on difficulty, intensity, and duration.

Three programmes were designed—gentle, moderate, and vigorous. Those with higher sedentary behaviour were assigned 45-minute sessions twice a week, while more active participants had 60-minute sessions three times a week. Participants had the option to choose the type of aerobic exercise they preferred based on factors like accessibility and familiarity. These could include walking, running, water aerobics biking or dancing. The intensity was determined based on their maximum age-related heart rate (220 minus age). Strength, stretching, and relaxation exercises were tailored from a range of options (see Appendix C, which contains a participant's handout with a moderate programme as an example) and were marked by the physiotherapist in the participants' handout. The participants' handout included: 1) Recommendations for performing physical activity, including photographs and descriptions of the recommended strength, stretching, and relaxation exercises, with images to facilitate understanding and proper execution; 2) Tables outlining the recommended programme, detailing the intensity, frequency, and duration for each exercise modality; and 3) A Borg Scale to guide participants on the target intensity level for their exercises.

Participants were guided on heart rate monitoring, aiming for 45-54% of maximum in low and moderate-intensity programmes and 70-89% in high-intensity. Participants with higher levels of sedentarism were prescribed lower intensity and shorter duration sessions, while those with lower levels of sedentarism had higher intensity and longer sessions. Group sessions included on-site practice of strength and stretching exercises, with participants receiving personalised brochures with instructions and photographs of their regimens. A guide was developed for professionals to facilitate the sessions. Table 5 provides further details regarding the structure of the exercise programmes.

Table 5 Structure of the IDEA exercise programme based on modality, intensity and duration

Programme	Modality	Frequency	Time	Sets x Reps	Rest	Intensity
Gentle Individuals with low physical activity levels	Stretching	2x/Week	10’			
	Aerobic	Daily	15’			Borg RPE scale 3-4 45-54% Max heart rate
	Resistance	2x/Week	10	1-2 sets x 10-12 reps	30”-60” based on personal recovery rate	Borg RPE scale 3-4 45-54% Max heart rate
	Relaxation	2x/Week	10’			
Moderate Moderately active individuals or with some level of physical activity	Stretching	3x/Week	10’			
	Aerobic	Daily	30’			Borg RPE scale 5-6 55%-69% maximum heart rate
	Resistance	3x/Week	15	2-3 sets x 10-15 reps	30”-60” based on personal recovery rate	Borg RPE scale 3-4 45-54% Max heart rate
	Relaxation	3x/Week	10’			
Vigorous Active individuals with higher fitness levels	Stretching	3x/Week	10’			
	Aerobic	Daily	30 – 40’			Borg RPE scale 7-8 70-89% Max heart rate
	Resistance	3x/Week	15	2-3 sets x 10-15 reps	30”-60” based on personal recovery rate	Borg RPE scale 3-4 45-54% Max heart rate
	Relaxation	3x/Week	10’			

Note. *RPE= Rating of perceived exertion*

3. App and fitness tracker

We, the same team that designed the group sessions, collaborated with computer engineers and two individuals with a lifetime history of depression to create a mobile application for tracking and storing participants' PA and sleep data. This app, IDEApp, not only measures changes in activity but also helps sustain motivation for exercise and maintain long-term benefits by syncing with a fitness tracker. IDEApp is a user-friendly tool that tracks both objective and self-reported data, with objective data including daily steps, aerobic exercise (minutes, distance, and heart rate), and sleep structure (duration, deep and light sleep). Participants self-report their exercise by selecting one of three options: relaxation, stretching, or strength and endurance.

To enhance accessibility, IDEApp offers language options in Spanish and Catalan and adjustable text sizes. Available on the Play Store, it is accessible only with a QR code provided by the project team. Figure 3 illustrates the app's functionality and layout.

Figure 3 Screenshots of IDEApp running

***Note**. A. Sign up screen allows access via QR code or user code, and language selection; B. Home screen allows to select the type of exercise performed: relaxation, stretching, or endurance and strength. C. Home screen with motivational notification based on user's daily activity and hours of sleep tracked by a smart band. English translation of the notification showed: 'You are doing great! Keep it up and you'll get out of the hole sooner than you think!'*

To ensure accurate monitoring and control, participants used the Xiaomi Smart Band 7, a wearable fitness tracker that provides real-time feedback on physical activity. While the device offers various functionalities, participants were specifically instructed on its use for tracking physical activity, heart rate, and sleep monitoring. Other features were available for personal use at their discretion. Both the app and the fitness tracker were used exclusively for data collection and documentation purposes, with neither having an interventional component.

Description of interventions

- EG: Participants followed a personalised exercise programme. After completing the baseline assessments, they received a smart band and had IDEApp installed on their mobile phones. They then attended the one-month IDEA group sessions. Following the short group-based intervention (from week 4 onward), participants were expected to continue their tailored exercise programme, which was adjusted in modality, intensity, and duration as recommended by the study physiotherapist. Participants were instructed to consistently use the smart band and IDEApp to monitor changes in activity and register the type of exercise when performed throughout the entire 8-month follow-up period, concluding at week 36. Participants did not receive continuous support to actively promote exercise retention. Instead, they relied on activity sheets that summarised the activities completed during the group sessions and their key takeaways, along with resistance bands, a personalised brochure featuring pictures and instructions for the recommended exercises to implement in their day-to-day activities during the follow-up phase.
- CG: Participants were given a brochure during the baseline assessment, which outlined the benefits of PA and offered general advice on exercising (see Appendix D). A member of the research team also installed IDEApp on their mobile phones, provided them with a smart band, and gave instructions on using both devices. Participants were expected to use the smart band and IDEApp continuously for the 8-month study duration.

A helpline was available to address any questions or issues related to the app and band use. Participants could withdraw from the study at any time, while investigators had the authority to remove participants for safety reasons or if they were unwilling or unable to

comply with study procedures (e.g., serious adverse events like hypomania or mixed features).

Allocation

During the baseline visit, participants were individually registered on the IDEApp web-based platform, which then randomly assigned them to one of the study arms while maintaining the following distribution:

- EG: Participants receiving the intervention, using the smart band and IDEApp (n =59 ,48.7%).
- CG: Participants receiving general exercise recommendations, using the smart band and IDEApp (n = 62,51.2%).

Participants were allocated to the condition furthest from the expected percentage of subjects assigned, ensuring an even distribution across groups at baseline, regardless of the number of participants.

Concealment mechanism

Allocation was concealed through the IDEApp web-based system and was accessible only upon request. To maintain allocation concealment, only one member of the research team responsible for evaluation could access the allocation placement. The allocation information indicated whether participants were assigned to the control or intervention condition. The purpose of knowing the allocation was to inform participants whether they needed to attend the IDEA group sessions.

Blinding

Due to the nature of the intervention, after participants were assigned to study conditions, they knew whether they had been placed in the EG or CG. As in most exercise trials, therapists knew if they were delivering the intervention. Independent raters were unaware of which group the patients had been allocated to. Other parties involved (i.e., clinicians, statisticians and principal investigators) remained blind to the randomisation procedure and group allocation.

Data collection management

Study data was collected, entered, and managed using REDCap electronic data capture tools hosted at the Hospital del Mar Research Institute, providing a secure and efficient method for robust data collection (235). Data was collected offline via the REDCap mobile app on an Android tablet and later synced to the REDCap server. Access to the data was controlled through a password system, with researcher activities governed by user-specific privileges. Original consent forms were securely stored numerically in locked cabinets, where they will be kept for five years after the study's completion, with strict restrictions on access to study files.

Confidentiality

To ensure participants' confidentiality during the study and the secure transmission of personal data, a security protocol was implemented in accordance with local Spanish laws. A 9-digit identification number (IDN) was generated for all participants throughout all study phases. The cross-reference of this IDN and patient identity was encrypted and stored in a database file on a computer. Participants were identified by their IDN and a random number assigned by the app, which served as their user code for accessing the app. Study participants authenticated themselves using a user or QR code when logging into the app. IDEApp did not collect personal information.

All data collected by the smart band and IDEApp were processed using technical and organisational security measures mandated by current legislation (Organic Law 3/2018, of 5th December, on Protection of Personal Data and guarantee of digital rights). The database was stored on a secure physical server at the Hospital del Mar Research Institute facilities, and the information was used solely for analyses related to the study objectives, remaining anonymous during and after the trial.

Sample size calculation

We calculated a sample size of 152, aiming for a power of 0.8 and an alpha level of 0.05. This calculation was based on clinical remission data, which we used as a proxy to infer functioning. To our knowledge, there is no established precedent for using functioning as the main outcome for physical exercise in depression, thus we estimated a Cohen’s d effect size of 0.5. This effect size was chosen to provide a reliable basis for calculations, considering the variability in clinical outcomes. Accounting for an expected drop-out rate of 20%, we planned for two groups of 76 subjects each.

Statistical analysis

All statistical analyses were conducted using SPSS ver. 27 (IBM SPSS, Chicago, IL). An initial descriptive analysis was performed to examine the distribution and identify missing values in the original dataset. Baseline participant sociodemographic, clinical and health characteristics were described by treatment arm. Further analyses followed an intention-to-treat (ITT) approach, including all participants based on their randomised allocation, regardless of the treatment received.

A series of mixed factorial ANOVAs were used to test the intervention's effectiveness across multiple outcomes, including FAST total and subdomain scores, SF-36 subscales and summary components, PHQ-9, and WHO-5 scores at all time points. This approach allowed us to analyse how outcome measures changed over time in both groups and assess main effects (group and time) as well as the interaction between them (group × time), meaning whether the change in measures over time differed between the groups. This method offers more statistical power and flexibility compared to simpler approaches, like regression or simple repeated measures, allowing for more precise detection of interactions and longitudinal effects. This maximizes the efficiency of the analysis and contributes to a better interpretation of longitudinal results.

Assumptions of normality were met due to the large sample size. Sphericity and homoscedasticity were checked, with Mauchly's test indicating violations of sphericity for some variables. Greenhouse-Geisser corrections for degrees of freedom were applied accordingly, and the Levene's test assessed homoscedasticity ($p \geq .05$). When variances were unequal, the Welch correction was applied.

Although not pre-specified, exploratory comparisons (simple effect analyses) were conducted to provide a more detailed understanding of the IDEA intervention's effectiveness. These analyses allowed for a more nuanced examination of within-group and between-group differences beyond the primary outcomes. Independent t-tests were used for between-group comparisons, while paired t-tests assessed within-group changes. To mitigate the risk of inflated Type I error due to multiple comparisons, Bonferroni correction was applied. While exploratory in nature, these analyses were deemed valuable in identifying patterns of change.

Missing data were handled using imputation methods—Last Observation Carried Forward (LOCF) when prior observations were available, and group-specific mean imputation when

not, generating a complete dataset and ensuring that group differences were preserved. The descriptive analysis was repeated on the imputed dataset to ensure consistency in the findings. Imputation was performed separately by subscales or items, depending on the structure of each assessment instrument, to maintain accuracy in calculating total scores.

Effect sizes were calculated using eta squared (η^2) to quantify the magnitude of observed differences, which measures the proportion of the total variance in the outcome variable that is attributable to the independent variable(s). According to Cohen's guidelines, η^2 values between .01 and .06 indicate small effects, .06 to .14 represent medium effects, and values above .14 suggest large effects.

Chapter 4. Results

4.1 Study 1: Evaluating the effect of exercise-based interventions on functioning in people with transdiagnostic depressive symptoms: A systematic review of randomised controlled trials

Reference: **García-Estela, A.**, Angarita-Osorio, N., Holzhausen, M.C., Mora-Salgueiro, J., Pérez, V., Duarte, E., Faulkner, G. & Colom, F., (2024). Evaluating the effect of exercise-based interventions on functioning in people with transdiagnostic depressive symptoms: A systematic review of randomised controlled trials. *Journal of Affective Disorders,* 351, 231-242. https://doi.org/10.1016/j.jad.2024.01.191

PMID: 38278328

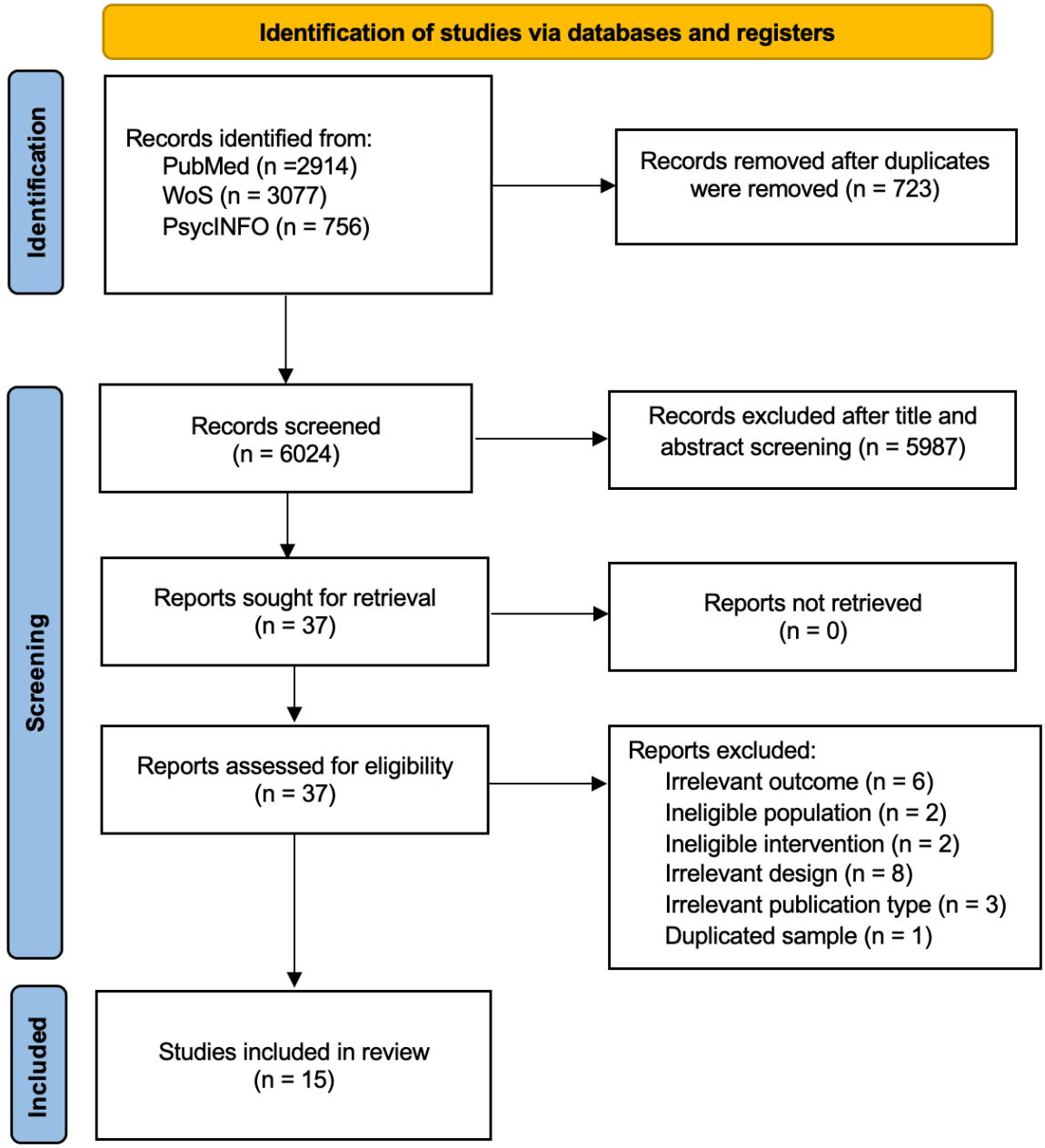
PROSPERO registration number: CRD42020137763

Descriptive results

Results of the search and included studies

Out of 6024 records initially identified, 37 full-text articles were screened after removing duplicates and conducting title and abstract screening. Of these, 22 articles were excluded for the following reasons: reporting irrelevant outcomes (n=6), not meeting eligibility criteria (n=4), irrelevant study type (n=8), irrelevant publication (n=3), and having a duplicated sample (n=1). Ultimately, 15 studies were included in this review. Figure 4 shows the flowchart of the selection process.

Figure 4 PRISMA flow diagram illustrating the identification, and selection process for the systematic review of studies



A total of 2064 participants were included in the studies, which were conducted in Australia (236), Brazil (237,238), Croatia (239), New Zealand (240), Portugal (241), Sweden (242,243), Taiwan (244), the United Kingdom (245,246), the USA (247–249) and Turkey (250).

Design

All studies had a randomised controlled trial design. Among them, 46.7% had two arms (249,240,245,241,246,238,250), 46.7% had three arms (248,236,242,244,239,237,243), and 6.7% had four arms (247). The intervention designs varied, with the most common being

exercise combined with TAU versus TAU alone (246,244,238,236,250). The choice of 'active' comparator interventions also varied, with CBT and health/disease education being the most frequently selected (249,244,239,237,243,247). See Table 6 for a summary of the intervention characteristics and comparator details of the included studies.

Participants

Seven studies included participants from non-clinical settings (236,238,242,244,247–249), seven from clinical settings (outpatients from mental health services, primary care, a diabetes clinic, and a rheumatology clinic) (240,245,241,246,239,237,243), and one study included participants from a mixed setting (volunteers from a nursing home) (250). All studies included participants with depressive symptoms, which were assessed using various instruments. The inclusion criteria varied across studies. For example, Klein et al. (1985) used RDoC and the Symptom Checklist-90-Revised for psychiatric outpatients. Callaghan et al. (2011) included participants receiving treatment for depression but did not employ symptom severity cut-points. Some studies relied on either DSM-IV, DSM-IV-TR, or ICD-10 for MDD criteria (241,242,246,247) or risk of depression (240). Other studies used instruments such as the BDI (249,250), the Geriatric Depression Scale (GDS) (236,244), the Patient Health Questionnaire (PHQ-9 and PHQ-2) (239,243), and the Hamilton Depression Rating Scale (HAM-D) (238), along with specific DSM-IV diagnostic criteria for MDD, minor depression, or dysthymia. Only one study did not employ screening measures for symptom severity or cut-off points (237). Participants' ages ranged from 30 (248) to 81 years (240), with a majority being female (70.25%). Table 7 provides an overview of the included study characteristics and findings of relevance.

Table 6 Summary of intervention characteristics and comparator details

Study	Intervention				
	Type	Setting and format	Length and frequency	Intensity	Comparator
Klein et al. (1984)	Aerobic	Home-based and individual	12 w, 2 times/w, 45' sessions	Tailored	1. Meditation 2. Interpersonal and cognitive therapy
Singh et al. (1997)	Strength	Onsite and group	10 w, 3 times/w, 50' sessions	Vigorous	Health education
Singh et al. (2005)	Strength + TAU	Onsite and group	8 w, 3 times/w, sessions of 65'sessions	Arm 1: Vigorous Arm 2: Light	TAU
Kerse et al. (2010)	Aerobic, balance and strength + TAU	Home-based and individual	24 w, 3 times/w, at least 30' sessions	Tailored	Social visits + TAU
Callaghan et al. (2011)	Aerobic + Psychosocial support + TAU	Onsite and group	4 w, 3 times/w	Tailored	Prescribed exercise + Psychosocial support + TAU
Mota-Pereira et al. (2011)	Aerobic + Usual pharmacotherapy + Accelerometer	Home-based and individual	12 w, 5 times/w, 30-45' sessions	Moderate	Usual pharmacotherapy + Accelerometer
Danielsson et al. (2014)	Aerobic + Usual pharmacotherapy	Onsite and mixed	10 w, 2 times/w, 50-60' sessions	Moderate/vigorous	1. Body awareness + Usual pharmacotherapy 2. Advice + Usual pharmacotherapy
Daley et al. (2015)	Aerobic + TAU	Home-based and individual	6 m, 3-5 times/w, final goal of 30' sessions	Moderate	TAU
Schuch et al. (2015)	Aerobic + TAU	Onsite and individual	2 w, 3 times/w	Tailored	TAU
Huang et al. (2015)	Aerobic and strength + TAU	Onsite and group	12 w, 3 times/w, 50' sessions	Moderate	1. CBT + TAU 2. TAU

Table 6 (continued) Summary of intervention characteristics and comparator details

Study	Intervention				
	Type	Setting and format	Length and frequency	Intensity	Comparator
Pibernik-Okanović et al. (2015)	Strength + flexibility	Onsite and group	6w, once/w, 90’ sessions	Light/medium	1.Psychoeducation+diabetes TAU 2. Diabetes education + TAU
Abrahão et al. (2016)	Arm 1: Aerobic + TAU Arm 2: Strength + TAU	Onsite and N/S	12 w, 3 times/w, 50’ sessions	Moderate/vigorous	Lupus education + TAU
Strid et al. (REGASSA study, 2015-2016) *	Aerobic, strength, or flexibility + Usual pharmacotherapy	Offsite and individual	12 w, 3h/w, 60’ sessions	Low, moderate, or high	1. Internet-based CBT + Usual pharmacotherapy 2. TAU
Lok et al. (2017)	Aerobic + TAU	Onsite and group	10 w, 4 times/w, 40’ sessions	N/S	TAU
de Groot et al. (2019)	Aerobic + Usual pharmacotherapy	Offsite and group	12 w, 6 monitored sessions, final goal of 150’ /w	Moderate	1. CBT + Usual pharmacotherapy 2. CBT + Exercise + Usual pharmacotherapy 3.Exercise 4. TAU

Note. 1RM = one-repetition maximum; CBT = Cognitive-behavioural therapy; HRR = heart rate reserve; N/S = Not specified; TAU =treatment as usual, W =week(s)

*We only considered Strid et al. as relevant for this SR. However, data on depressive symptoms was reported in Hallgren et al. (2015). We did not include the latter study to avoid data overlap from the same sample**.**

Table 7 Summary of study characteristics and key findings

Study	Sample				Screening	Functioning and/or Quality of life assessment	Findings of relevance
	N	Type	Mean age	% female			
Klein et al. (1984) USA	74	Community Volunteers	30.02	71.62	>60th percentile SCL-90-R + RDC	SF-36, SAS	Reduced social and leisure impairment with exercise ($p < .01$); overall social functioning improved only in meditation group.
Singh et al. (1997) USA	32	Community Volunteers	71.3	60.71	DSM-IV for MDD, minor depression, or dysthymia + BDI >12	SF-36	Significant improvements in SF-36 subdomains (Vitality, Bodily Pain, Role Emotional, Social Functioning) ($p <.05$).
Singh et al. (2005) Australia	60	Community Volunteers	69	55	DSM-IV for MDD, minor depression, or dysthymia + GDS >14	SF-36	Significant improvement across most SF-36 subdomains ($p <.0001$ to $p <.04$); high-intensity exercise superior in Vitality ($p = .048$).
Kerse et al. (2010) New Zealand	193	Primary care outpatients	81	59	DSM-IV or ICD-10 for MDD or risk + 3-question screen	SF-36	No significant differences were found between groups ($p = .06$). Both groups showed improvements in mental health ($p < .001$).
Callaghan et al. (2011) UK	38	Mental health outpatients	53.7	100	Monitoring/treatment for depression (no symptom severity)	SF-12, QLDS	No significant differences in functioning between groups ($p = .06$). QOL improved in the preferred intensity group ($p = .032$).
Mota-Pereira et al. (2011) Portugal	33	Mental health outpatients	47.52	57.57	DSM-IV for MDD (9-15 months)	GAF	Significant improvements in functioning at 8- and 12-week follow-ups compared to controls ($p = .006$).

Table 7 (continued) Summary of study characteristics and key findings

Study	Sample				Screening	Functioning and/or Quality of life assessment	Findings of relevance
	N	Type	Mean age	% female			
Danielsson et al. (2014) Sweden	62	Community Volunteers	45.4	77.4	DSM-IV for MDD (MINI)	GAF	No significant differences in functioning between groups ($p = .075$).
Daley et al. (2015) UK	94	Primary care outpatients	30.5	100	ICD-10 for MDD	SF-12, EQ-5D	No significant differences in SF-12 or EQ-5D scores at 6- and 12-month follow-ups ($p > .05$).
Schuch et al. (2015) Brazil	50	Hospital inpatients	40.3	74	DSM-IV for MDD (MINI) + HAM-D >25	WHOQOL-BREF	QOL domains improved post-intervention ($p < .05$)
Huang et al. (2015) Taiwan	57	Community Volunteers	76.53	52.6	GDS-15 $\geq$ 5	SF-36	SF-36 scores improved in the exercise group ($p < .001$)
Pibernik-Okanović et al. (2015) Croatia	209	Diabetes clinic outpatients	58.1	54	Subsyndromal depression (PHQ-2 + need for help)	SF-12	Significant improvement in MCS scores for both groups ($p < .001$); no changes in PCS ($p = .71$) and no group differences in any domains.
Abrahão et al. (2016) Brazil	63	Rheumatology clinic outpatients	42.9	96.8	No symptom severity assessment	SF-36	Improvements in multiple SF-36 subdomains (Vitality, Role Physical, Vitality, and Role Emotional) ($p < 0.05$) for the aerobic exercise group.
Strid et al. (REGASSA study, 2015-2016) Sweden	879	Primary care outpatients	43	73	PHQ-9 $\geq$10 + MINI interview	OQ-45	Exercise reduced functioning scores at 3 and 12 months ($p < .001$); effects comparable to iCBT with no differences between them.

Table 7 (continued) Summary of study characteristics and key findings

Study	Sample				Screening	Functioning and/or Quality of life assessment	Findings of relevance
	N	Type	Mean age	% female			
Lok et al. (2017) Turkey	80	Nursing home	Not reported	45	BDI score ≥ 10	SF-36	SF-36 scores improved in all subdomains ($p < .05$); no significant changes occurred in the CG after the intervention.
de Groot et al. (2019) USA	140	Community Volunteers	56	77	DSM-IV TR for MDD	SF-12, DQOL	SF-36 PCS improved in the CBT + exercise group ($p = .001$). MCS improved in all intervention groups (CBT: $p = .069$; CBT + Exercise: $p = .270$; Exercise: $p = .109$) but not in TAU. QOL improved significantly both in the CBT + Exercise ($p < .001$) and Exercise ($p = .001$) groups.

Note. *BDI = Beck Depression Inventory; DQOL = Diabetes Quality of Life; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition; DSM-IV TR = Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision; GAF = Global Assessment of Function; GDS = Geriatric Depression Scale; GDS-15 = 15-item Geriatric Depression Scale; EQ-5D = European Quality of Life 5 Dimensions; HAM-D = Hamilton Depression Scale; iCBT = Internet-based cognitive behaviour therapy; ICD-10 = International Classification of Diseases-10; MCS = Mental Component Score; MDD = Major depressive disorder; MINI = Mini-International Neuropsychiatric Interview; N/S = Not specified; OQ-45 = Outcome Questionnaire-45; PCS = Physical Component Score; PHQ-2 = Patient Health Questionnaire-2; PHQ-9 = Patient Health Questionnaire-9; QLDS = Quality of Life in Depression Scale; QOL; Quality of life; RDC = Research Diagnostic Criteria; SCL-90-R = Symptom Checklist-90-Revised; SF-36 = 36-Item Short Form Health Survey; SAS = Social Adjustment Self-Report Questionnaire; SF-12 = 12-Item Short Form Health Survey; WHOQOL-BREF = World Health Organization Quality of Life Brief Version*

Interventions

The interventions lasted for an average of 11.6 weeks, with 3 sessions per week, each lasting between 30-90 minutes. One trial did not mention duration and only indicated that assessments were conducted at discharge (238). Seven trials conducted group sessions (249,236,245,244,239,250,247), five conducted individual sessions (238,240,241,246,248), two studies used a combination of group and individual consultations (242,243), and one trial did not specify the format (237).

The most common type of exercise was aerobic, which was provided in ten trials (248,245,241,242,246,238,239,243,250,247). Two trials focused on strength exercises (236,249), while two others offered a combination of aerobic and strength exercise (240,244). In Abrahão et al. (2016), one group performed aerobic exercises, while another group completed strength exercises.

All trials considered participants' abilities, tolerance, or perceived exertion. However, the extent to which participants had control over the nature of the exercises varied. In six trials, the exercise modality and intensity were the same for all participants (236,241,244,248–250). Four studies prescribed exercises based on personal preferences and individual conditions (238,240,245,246), and one study partially took them into account (242). In one trial, participants in the intervention group were randomised to different intensity levels, resulting in changes in exercise modalities (243).

Most studies conducted supervised onsite exercise sessions (236,237,239,242–245,248–250), while four studies included both partially supervised sessions and unsupervised home-based exercise (240,241,246,247). Thirteen trials specified the professionals responsible for supervised exercise programs, including exercise therapists (242,245), a trained nurse (240), a physical activity facilitator (246), fitness instructors (239,241,243,244,247), researchers (238,249,250), and mental health professionals (248).

Outcomes

There was heterogeneity in the instruments used to assess outcomes.

Assessment of functioning and quality of life

Six studies assessed functioning using the SF-36 (236,237,240,244,248–250), while four studies utilized its 12-item version, the SF-12 (239,245–247). Additionally, two studies

employed the Global Assessment of Function (GAF) (241,242). Other assessments included the Social Adjustment Self-Report Questionnaire (SAS) (248) and the Outcome Questionnaire-45 (OQ-45) (243). In terms of quality of life, four trials conducted additional assessments using the Quality of Life in Depression Scale (QLDS) (245), EQ-5D (246), World Health Organization Quality of Life Brief Version (WHOQOL-BREF) (238), and the Diabetes Quality of Life measure (DQOL) (247).

Assessment of depressive symptoms

Measures of depressive symptoms varied across studies. The most commonly used tools were the BDI and BDI-II (237,241,245,247,249,250), followed by the HAM-D (236,238,241,248,249). Four studies reported scores on the GDS (236,240,244,249). Danielsson et al. (2014) and the authors of the REGASSA study (251) reported MADRS scores. Additional scales included the Edinburgh Postnatal Depression Scale (246) and the Centre for Epidemiological Studies Depression Scale (239).

Other outcomes

Twelve trials reported adherence to the exercise intervention, considering session attendance and goal completion. Klein et al. (1984) noted that 57% of participants completed the intervention, though 'completion' was not explicitly defined. Another study labeled all exercise group participants as completers, but did not provide adherence rates (250). Singh et al. (1997) reported a median adherence of 9%, while Callaghan et al. (2011) found attendance rates of 66%. In one trial, adherence to sessions ranged from 95%–100% for high intensity and 99%–100% for low intensity (236). Another study calculated adherence via accelerometer data, reporting a 91% adherence rate, defined as completing at least 50% of walks per week (241).

Kerse et al. (2010) measured adherence by exercise units and frequency: during the first 6 months, one-third of participants completed the recommended units at least 3 times weekly, and two-thirds completed them at least twice weekly. By 12 months, 55% met the twice-weekly target, 25% exercised 3 times weekly, and one-third walked at least 3 times weekly. Danielsson et al. (2014) defined adherence as attending >50% of sessions and not initiating other treatments, which was fulfilled by 85% of participants. In the REGASSA study (243,252), participants completed an average of one session per week, resulting in 33% adherence. Schuch et al. (2015) reported 90.72% adherence overall.

Huang et al. (2015) observed a decline in adherence after the initial prescription: 100% of participants completed exercise logs initially, but rates dropped to 63% at 3 months and 47% at 6 months. Conversely, Daley et al. (2015) reported that participants completed 69.4% of the recommended logs, with exercise levels increasing from 161.1 to 245 minutes weekly by the intervention's end.

Adverse events

Few studies (236,240,242,249) reported adverse events, which included musculoskeletal symptoms as the most common issue. Visits to health professionals and minor physical illnesses were also reported.

Costs

Detailed information concerning costs was not reported by any study.

Timing of outcome measures

All trials conducted baseline and end-of-intervention measurements. Three trials included long-term follow-up assessments, ranging from 1 to 9 months (241,243,248).

Risk of bias in included studies

The quality and risk of bias varied among the studies, ranging from low to high. Only three studies (238,240,242) met the low-risk criteria for all factors, with one additional study (247) having an overall low risk. Eight studies had some concerns (237,239,241,244–246,249,249), and three studies were deemed high risk (243,248,250). More than half of the included studies also had small sample sizes, limiting the robustness of their results.

For studies with an overall assessment of ‘some concerns’ or ‘high’ risk of bias, the reasons included insufficient information regarding the randomisation process (241,244,245,248,249) or allocation concealment (239,250), issues with handling missing data (243,248), unblinded or half-blinded assessments (241,246,248–250), and a lack of published protocols or trial registration to confirm the pre-specified analysis plan (236,237,241,244,248,249). Some inconsistencies in reported results were also noted (266, 273). Figures 5 and 6 provide a summary and graphical representation of the risk of bias.

Figure 5 Risk of bias graph for included studies displaying each domain presented as percentages

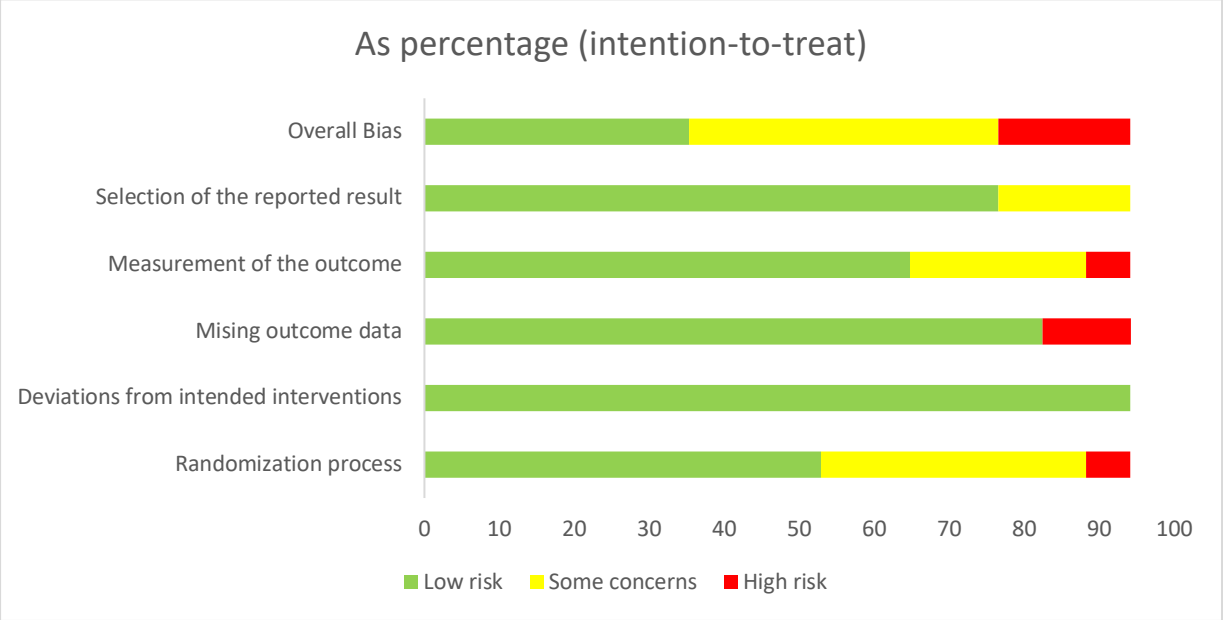


Figure 6 Tabular representation of risk of bias in individual studies

Primary outcome measures

General functioning

Most studies reported the effects of interventions on functioning, except for Schuch et al. (2015) who primarily focused on assessing depression and quality of life. Due to the diverse assessment methods used, changes were observed in various aspects depending on the specific instruments and study objectives. The SF-36 and SF-12 were frequently used by different authors to measure functioning, although some reported it as a measure of quality of life. Since this questionnaire specifically evaluates health-related limitations, we categorised it as a measure of functioning and included the results originally reported as quality of life outcomes.

Seven studies reported significant improvements in functioning after exercise interventions. Singh et al. (1997) observed improved functioning measures, specifically in the subscales of Vitality ($p = .002$), Bodily Pain ($p = .001$), Role Emotional ($p = .02$), and Social Functioning ($p = .008$) compared to the CG. In a subsequent study, Singh et al. (2005) examined the impact of different intensity levels on functioning. Across all groups, functioning improved in most SF-36 subdomains (p values ranging from $<.0001$ to $<.04$). The high intensity intervention showed superior improvement compared to the low intensity and usual care groups, specifically on the Vitality subscale ($p = .048$).

Similarly, Mota-Pereira et al. (2011) reported improved functioning compared to baseline values. At the 8- and 12-week follow-ups, the exercise group showed significantly higher functioning parameters than the CG ($p = .006$), although participants in the exercise group had lower baseline functioning scores than the CG ($p = .003$). Abrahão et al. (2016) found significant improvements in functioning across multiple SF-36 subscales in the cardiovascular training group, including Role Physical, Vitality, and Role Emotional, compared to the resistance training group. The cardiovascular training group also achieved significantly higher scores in the Role Physical and Vitality subscales compared to the resistance training group, with no significant improvements observed in the control group.

Huang et al. (2015) found that only the exercise group showed improved functioning ($p < .001$), with significantly higher SF-36 scores immediately post-intervention compared to baseline. This improvement was not observed in participants who received CBT or TAU. Strid et al. (2016) reported significant improvements in psychological functioning within both the exercise group ($p < .001$) and the iCBT group ($p < .001$) compared to the CG at 3 months ($p < .001$),

with no significant differences between iCBT and exercise ($p = .683$). Effect sizes favouring both exercise ($d = 0.20$) and iCBT (Cohen's $d = 0.35$) compared to the CG were reported. Lok et al. (2017) noted positive effects of exercise on functioning, with improvements in all eight SF-36 subscales in the EG ($p < .05$). However, no significant differences were found in the CG after the exercise programme.

In contrast, seven studies reported mixed results, with improvements observed in some areas but not all, following exercise interventions. For example, Klein et al. (1984) compared exercise, meditation, and group therapy, finding a reduction in social and leisure impairment among exercise ($p < .01$) and meditation ($p < .05$) participants. However, significant improvement in overall social functioning was only observed in the meditation group ($p < .01$). Kerse et al. (2010) compared changes between groups at baseline and 6 months post-intervention but found no differential effects ($p = .06$), although both groups showed improvements in mental health over time ($p < .001$), with no changes in physical health ($p = .76$). Similarly, Danielsson et al. (2014) found no differences in global functional capacity among participants receiving aerobic exercise, basic body awareness therapy, or advice on physical activity.

In Daley et al.'s study (2015), the exercise-based intervention did not yield significant differences in the SF-12 total score or any of its domains at the 6-month follow-up (PCS: $p = .50$; MCS: $p = .11$). Pibernik-Okanović et al. (2015) observed significant improvements in the MCS score of the SF-12 for all patients at the 12-month follow-up ($F = 16.87$, $p < .001$, $\eta^2 = 0.09$). However, the PCS score did not change after any interventions ($p = .71$), and while self-reported exercise increased across all groups ($F = 5.14$, $p = .008$, $\eta^2 = 0.03$), no significant differences were found between groups in any assessed domains at the 12-month follow-up.

De Groot et al. (2019) found significantly higher SF-12 PCS post-intervention in both the exercise ($p = .047$) and the exercise + CBT groups ($p = .001$) compared to the TAU group. The CBT-only group showed no significant difference For the Mental Component Score (MCS), no significant differences were found in any group compared to TAU (CBT: $p = .06$; CBT + exercise: $p = .27$; exercise: $p = .10$).

Callaghan et al. (2011) reported no difference in the change in functioning (mean SF-12 score) between the exercise intervention group with prescribed intensity and the group with preferred

intensity (p = .08). Without conducting within-group statistical tests, it remains unclear whether exercise led to improvements in functioning. Klein et al. (1984) noted effects on functioning at the 9-month follow-up, particularly in the meditation group (p < .01). The improvement in social impairment observed post-treatment did not persist during follow-up assessments, and treatment differences became more evident at follow-up, suggesting that the effects of exercise and meditation may be more enduring.

In Daley et al. (2015), there were also no significant improvements in SF-12 domain scales, including PCS (p = .77) and MCS scores (p = .64), when comparing exercise and TAU at the 12-month follow-up. Finally, Huang et al. (2015) observed no significant changes in functioning from baseline at three and six months post-intervention for participants in the exercise, CBT, and TAU groups. Strid et al. (2016) reported that the advantages observed at 3 months for both the exercise and iCBT groups (p = .001 and p = .005, respectively) over the TAU group persisted at 12 months but again, no difference was observed between iCBT and exercise (p = .612).

Quality of life

Callaghan et al. (2011) reported significant improvements in quality of life, as measured by the QLDS, for participants exercising at their preferred intensity compared to those following a prescribed intensity (p = .032). Daley et al. (2015), however, found no significant differences between the exercise and TAU groups at 6- and 12-month follow-ups using the EQ-5D instrument (p = .12 and p = .22, respectively). Schuch et al. (2015) observed improvements in the physical and psychological domains of quality of life among exercise participants, measured with the WHOQOL-BREF. For the physical domain, differences between groups were more pronounced at the second-week assessment (p = .002) than at discharge (p = .001), while for the psychological domain, the difference was smaller at the second week (p = .025) than at discharge (p = .01). De Groot et al. (2019) found significantly higher scores on the DQOL for both the exercise (p = .001) and exercise + CBT groups (p < .001) compared to TAU, with no significant difference between the CBT-only group and TAU (p = .06).

Secondary outcome measures

Depressive symptoms

Most studies showed a reduction in depressive symptoms after exercise interventions, with many reporting significant post-treatment improvements. For instance, Singh et al. (1997)

found that 59% in the exercise group achieved a clinically significant response (50% reduction in HAM-D score) compared to 26% in the CG ($p = .06$), with intensity identified as a key predictor of improvement ($p = .0002$). In a later study, Singh et al. (2005) confirmed that over 60% of high-intensity participants showed clinically significant improvements, outperforming both low-intensity (nearly 30%) and CG (over 20%) ($p = .03$). Similarly, Lok et al. (2017) reported a significant decrease in BDI scores for the exercise group compared to controls ($p = .005$). Meanwhile, Callaghan et al. (2011) observed that individuals exercising at their preferred intensity reported lower depression scores than those following prescribed intensities ($p = .006$).

Other studies reported significant reductions in depressive symptoms following exercise interventions, though they did not outperform CGs. For example, Kerse et al. (2010) observed a decrease in depression scores across all groups at six months, with no significant advantage for the exercise intervention over social visits ($p = .91$). The REGASSA study showed that both exercise and internet-based CBT (iCBT) improved depressive symptoms significantly compared to controls ($p < .001$), with similar outcomes across the two active treatment groups (243). In the same line, Pibernik-Okanović et al. (2015) reported a significant reduction in depressive symptoms post-treatment across all groups, but no significant differences were found between them. Huang et al. (2015) found significant, lasting decreases in depression scores for the exercise group from post-treatment ($p = .003$) through 3-month ($p = .012$) and 6-month follow-ups ($p = .037$). Although CBT and exercise initially showed similar improvements, exercise effects persisted longer. Symptom reductions were seen across all groups, with no significant differences between exercise and control. De Groot et al. (2019) further supported these findings, showing significant reductions in BDI-II scores for all interventions compared to usual care (exercise: $p = .021$, CBT + exercise: $p < .001$, CBT: $p = .011$), with the highest remission rates observed in the exercise group (72%) and the lowest in the TAU group (32%).

Further consistency in improvement across treatment groups has been observed, with Mota-Pereira et al. (2011) demonstrating significant reductions in depression scores within the exercise group using HAM-D ($p = .014$), BDI ($p = .016$), and the Clinical Global Impression Scale-Severity (CGI-S) ($p = .033$), compared to controls. However, participants in the exercise group had greater depression severity than the CG at baseline ($p < .05$). Danielsson et al. (2014) also found notable improvements in the EG over the advice group ($p = .048$), while Daley et

al. (2015) reported significantly lower depression scores in the EG only after adjusting for baseline depression and demographic variables ($p = .03$). Schuch et al. (2015) reported lower depression scores in the exercise group compared to TAU ($p = .005$), though remission and response rates did not differ significantly.

Age and intensity further influenced the effectiveness of exercise interventions. In the REGASSA study, a stratified analysis by age indicated that exercise and iCBT were more effective among older participants ($p < .001$), with non-significant group differences in younger participants aged 18–34 ($p = .40$) (243,251). Additionally, Singh et al. (2005) found that high-intensity exercise led to the greatest improvement in depression scores ($p < .006$).

Not all studies, however, found exercise to be effective. Abrahão et al. (2016), for example, observed no significant effect of cardiovascular or resistance training on depression, with BDI scores remaining unchanged. Long-term follow-up studies also provided mixed results; Daley et al. (2015) and Kerse et al. (2010) both reported no significant differences between groups at 6- and 12-month follow-ups.

4.2 Study 2: Association between physical health and functioning parameters in transdiagnostic depressive symptoms

Descriptive results

A total of 121 participants were included in the study (87 women, 34 men). Their average age was 51 years (SD = 10.4, range 19 – 65 years). Most participants self-identified as Caucasian (81.8%), followed by Hispanic (15.7%), Asian (1.7%), and Roma (0.8%). A noteworthy proportion of participants were on disability leave (45.5%), either temporary (28.1%) or permanent (17.4%), with the majority having attained secondary (58.7%) or graduate-level education (18.2%). Regarding marital status, 52.9% were married or partnered, 24% were single, 18.2% were separated or divorced, and 5% were widowed. Living arrangements varied, with 28.9% living with a partner and children, 23.1% living with a partner, and 14.9% living alone. Further sociodemographic details are provided in Table 8.

Regarding clinical and health characteristics, the mean BMI was 27.56, indicating that participants were, on average, overweight. Rheumatoid disease (28.9%), anxiety disorders (15.7%), and cardiovascular disease (17.4%) were the most common comorbidities. Psychopharmacological treatment was the norm, with 81% using antidepressants, 36.4% using antipsychotics, 32.2% using anxiolytics, 20.7% using anticonvulsants and 4.1% using mood stabilisers. Alcohol use varied, with 55.5% being non-drinkers and 35% having low consumption. Tobacco use was prevalent among 35.5% as smokers, 30.6% as past smokers, and 33.9% as never smokers. The mean MADRS score was 26.3 (SD = 6.1). Table 9 presents the clinical and health characteristics of the EG, CG and total sample at baseline, including the absolute frequencies and percentages.

No significant baseline differences were found between the groups in terms of sociodemographic, clinical, and health characteristics (Tables 8 and 9), except for minor imbalances in living arrangements ($p = .01$) and endocrine disease ($p = .01$), likely due to randomisation. The groups were well balanced regarding baseline depressive symptoms, with BMI showing a borderline significant difference ($p = .05$), but overall group comparability was preserved.

Table 8 Sociodemographic characteristics of the experimental, control, and total sample groups

Characteristic	EG (n=59)		CG (n=62)		Total sample (N=121)		P-value
	n	%	n	%	n	%	
Sex, female	43	72.9	44	71	87	71.9	.82
Ethnicity							.50
Caucasian	51	86.4	48	77.4	99	81.8	
Hispanic	7	11.9	12	19.4	19	15.7	
Asian	1	1.7	1	1.6	2	1.7	
Roma	0	0	1	1.6	1	0.8	
Age (mean), SD	51.6	9.5	50.6	11.2	51.1	10.4	.60
Marital status							.75
Single	12	20.3	17	27.4	29	24	
Married/ Partnership	34	57.6	30	48.4	64	52.9	
Separated/Divorced	10	16.9	12	19.4	22	18.2	
Widowed	3	5.1	3	4.8	6	5	
Education level							.55
No Formal Education	1	1.7	2	3.2	3	2.5	
Primary education	9	15.3	8	12.9	17	14	
Secondary education	33	55.9	38	61.3	71	58.7	
Bachelor's Degree	12	20.3	10	16.1	22	18.2	
Master's/Doctoral Degree	4	6.8	4	6.5	8	6.6	
Employment status							.29
Unemployed	9	15.3	13	21	22	18.1	
Student	0	0	1	1.6	1	0.8	
Employed	21	35.6	18	29	39	32.2	
Retired	1	1.7	3	4.8	4	3.3	
Temporary disability leave	18	30.5	16	25.8	34	28.1	
Permanent disability leave	10	16.9	11	17.7	21	17.4	
Living arrangement							.01
Alone	8	13.6	10	16.1	18	14.9	
With relatives	3	5.1	12	19.4	15	12.4	
With children	14	23.7	8	12.9	22	18.2	
With partner/spouse	12	20.3	16	25.8	28	23.1	
With partner/spouse and children	20	33.9	15	24.2	35	28.9	
With roommates/ friends	2	3.4	1	1.6	3	2.5	

***Note**. EG = experimental group; CG = control group; SD = standard deviation*

Table 9 Clinical and health characteristics of the experimental, control, and total sample groups

Characteristics	EG (n=59)		CG (n=62)		Total sample (N=121)		P-value
	n	%	n	%	n	%	
BMI mean, SD	28.7	5.9	26.4	5.4	27.6	5.8	.05
Menopausal and postmenopausal (female)	24	55.8	28	63.6	52	59.8	.45
Comorbidity [a]							
Anxiety disorders	7	11.9	12	19.4	19	15.7	.33
PTSD	0	0	2	3.2	2	1.7	.16
ADHD	1	1.7	0	0	1	0.8	.30
Personality disorders	0	0	2	3.2	2	1.7	.16
Eating disorder	3	5.1	0	0	3	2.5	.07
Rheumatoid disease	13	22	22	35.5	35	28.9	.10
Cardiovascular disease	9	15.3	12	19.4	21	17.4	.55
Respiratory disease	8	13.6	7	11.3	15	12.4	.71
Neurological disease	4	6.8	10	16.1	14	11.6	.11
Endocrine disease	11	18.6	2	3.2	13	10.7	.01
Hepato-gastrointestinal disease	6	10.2	6	9.7	12	9.9	.93
Oncology disease	0	0	6	9.7	6	5	.01
Other*	8	13.6	11	17.7	19	15.7	.71
Psychopharmacological treatment							
Antidepressant	50	84.7	48	77.4	98	81	.31
Antipsychotic	21	35.6	23	37.1	44	36.4	.86
Anxiolytic	15	25.4	24	38.7	39	32.2	.12
Mood stabilizer	2	3.4	3	4.8	5	4.1	.69
Anticonvulsant	9	15.3	16	25.8	25	20.7	.15
Current exercise practice	4	6.9	11	17.7	15	12.5	.07
Alcohol use [a]	27	46.6	26	42.6	53	44.5	.67
Non-Drinker	31	53.4	35	57.4	66	55.5	
Low (≤1-2 SDU/week)	22	37.9	19	31.2	41	34.5	
Moderate (3-6 SDU/week)	5	8.6	5	8.2	10	8.3	
High (≥7 SDU/week)	0	0	2	3.28	2	1.7	
Tobacco use							.48
Past smoker	21	35.4	16	25.8	37	30.6	
Current smoker	21	35.4	22	35.5	43	35.5	
MADRS mean, SD	25.7	6.2	26.9	6.1	26.3	6.1	.28

Note. *[a] N = 119 (58 = EG, 61 = CG). EG = experimental group; CG = control group; SD = standard deviation; BMI = Body Mass Index; PTSD = Post Traumatic Stress Disorder; ADHD = Attention-Deficit/Hyperactivity Disorder; SDU = standard drink unit; MADRS = Montgomery- Åsberg Depression Rating Scale*

**Urologic, infectious, autoimmune, gynecologic, and other unspecified conditions*

Associations between study variables

The FAST Total score showed significant negative correlations with 1MSTS ($r = -.36$, $p < .01$), HGST ($r = -.31$, $p < .01$), and 6MWT ($r = -.37$, $p < .01$), while the SF-36 PCS demonstrated positive associations with 1MSTS ($r = .46$, $p < .01$), HGST ($r = .30$, $p < .01$), and 6MWT ($r = .51$, $p < .01$). In contrast, the SF-36 MCS did not show any significant correlations with the physical performance scores. Due to missing data from some participants, the number of observations varied across variables. Table 10 presents these associations, and Figure 7 provides scatter plots, showing no non-linear relationships or outliers.

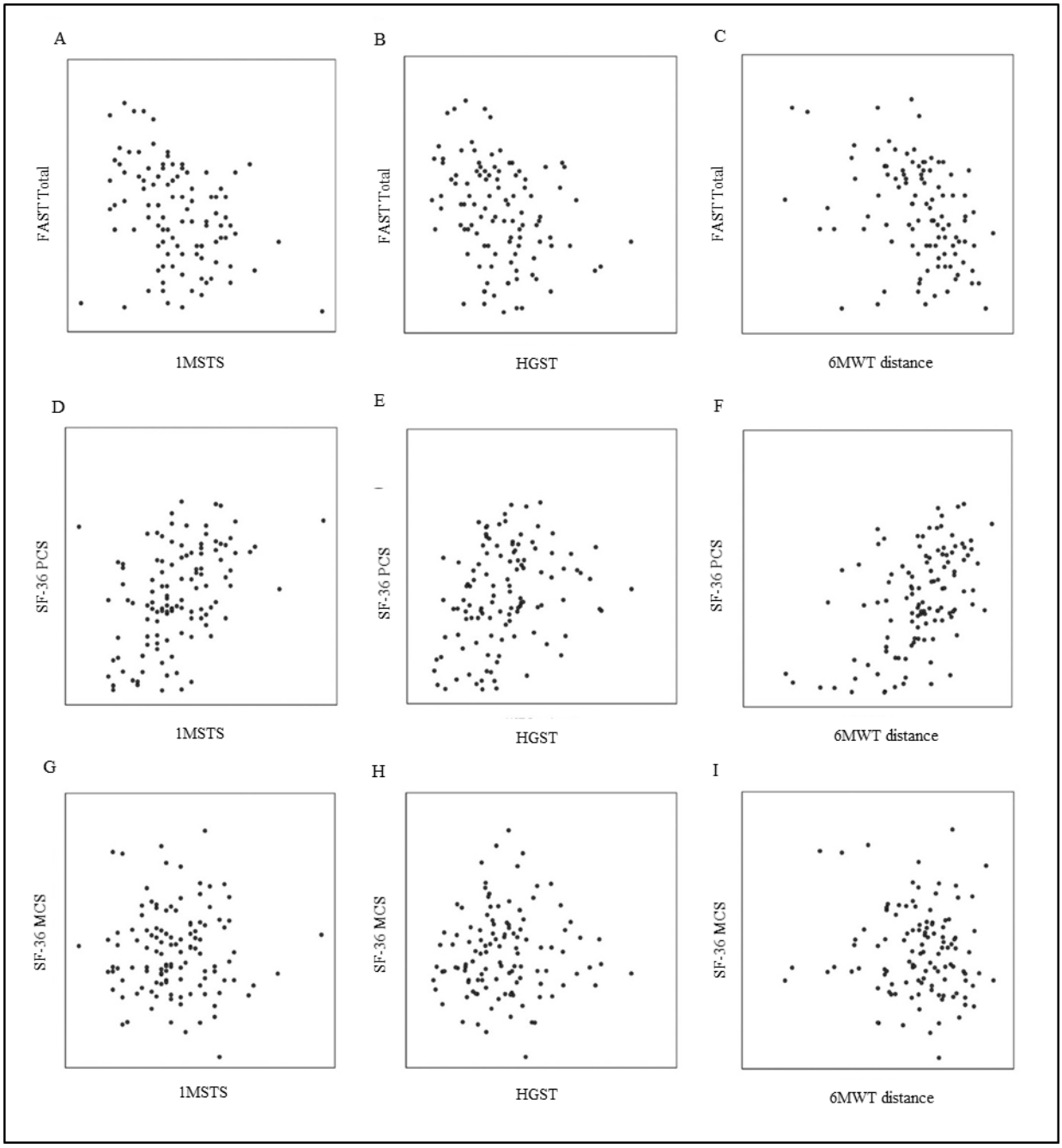
Table 10 Correlation coefficients between functioning and physical health parameters in subjects with transdiagnostic depressive symptoms

Variable	1MSTS	HGST (dominant hand)	6MWT Distance
FAST Total score	-.36**[a]	-.31**[b]	-.37**[c]
SF-36 PCS	.46**[d]	.30**[e]	.51**[f]
SF-36 MCS	-.01[d]	.04[e]	-.07[f]

Note. *[a] n = 107. [b] n = 106. [c] n = 104. [d] N = 116. [e] n = 115. [f] n = 114. 6MWT= 6-minute walking test; HGST= Handgrip strength test; 1MSTS= 1-minute sit to stand test; SF-36= 36-Item Short Form Health Survey; PCS= Physical Component Summary; MCS= Mental Component Summary.*

** p < .05 ; **p < .01*

Figure 7 Scatter plots illustrating the relationships between physical performance and functioning variables



Note. *6MWT= 6-minute walking test; HGST= Handgrip strength test;1MSTS= 1-minute sit to stand test; SF-36= 36-Item Short Form Health Survey; PCS= Physical Component Summary; MCS= Mental Component Summary.*

Exploring relationships while controlling for covariates

Further partial correlation analyses suggest various associations between functioning measures and physical health indicators while accounting for the influence of covariates such as age, BMI, tobacco use, and menopause status. These results are presented in Tables 11-14.

Controlling for age, significant negative correlations were found between general functioning and all three physical health parameters. Specifically, the FAST total score was negatively correlated with the 1MSTS ($r = -0.33$, $p < 0.01$), HGST ($r = -0.30$, $p < 0.01$), and 6MWT ($r = -0.35$, $p < 0.01$). Additionally, a significant negative correlation was observed between SF-36 PCS and 1MSTS ($r = -0.20$, $p < 0.05$), though no significant correlations were found with the other measures of physical health. For the SF-36 MCS, no significant correlations were observed with any of the physical tests.

Table 11 Partial correlation coefficients between functioning and physical health parameters controlling for age

Variable	1MSTS	HGST (dominant hand)	6MWT Distance
FAST Total score	-.33**[a]	-.30**[b]	-.35**[c]
SF-36 PCS	-.20*[d]	-.03[e]	-.08[f]
SF-36 MCS	-.10[d]	-.12[e]	-.12[f]

Note. *[a] n = 107 (df = 104). [b] n = 106 (df = 103). [c] n = 104 (df = 101). [d] n = 119 (df = 116). [e] n = 118 (df = 115). [f] n = 116 (df = 113). 6MWT= 6-minute walking test; HGST= Handgrip strength test; 1MSTS= 1-minute sit to stand test; SF-36= 36-Item Short Form Health Survey; PCS= Physical Component Summary; MCS= Mental Component Summary*

** p < .05; ** p < .01*

When controlling for BMI, significant negative correlations were again observed between the FAST total score and the physical health indicators. The correlations were as follows: 1MSTS ($r = -0.38$, $p < 0.01$), HGST ($r = -0.31$, $p < 0.01$), and 6MWT ($r = -0.40$, $p < 0.01$). However, there were no significant correlations between the SF-36 PCS and MCS scores and any of the physical tests.

Table 12 Partial correlation coefficients between functioning and physical health parameters controlling for body mass index

Variable	1MSTS	HGST (dominant hand)	6MWT Distance
FAST Total score	-.38**[a]	-.31**[b]	-.40**[c]
SF-36 PCS	-.16[d]	-.04[e]	-.05[f]
SF-36 MCS	-.14[d]	-.13[e]	-.16[f]

Note. *[a] n = 107 (df = 104). [b] n = 106 (df = 103). [c] n = 104 (df = 101). [d] n = 119 (df = 116). [e] n = 118 (df = 115). [f] n = 116 (df = 113). 6MWT= 6-minute walking test; HGST= Handgrip strength test; 1MSTS= 1-minute sit to stand test; SF-36= 36-Item Short Form Health Survey; PCS= Physical Component Summary; MCS= Mental Component Summary*

** p < .05; **p < .01.*

.

Controlling for tobacco use, the FAST total score remained significantly and negatively correlated with all three physical health measures: 1MSTS (r = -0.32, p < 0.01), HGST (r = -0.32, p < 0.01), and 6MWT (r = -0.40, p < 0.01). No significant relationships were found between SF-36 PCS and MCS scores and the physical tests.

Table 13 Partial correlation coefficients between functioning and physical health parameters controlling for tobacco use

Variable	1MSTS	HGST (dominant hand)	6MWT Distance
FAST Total score	-.32**	-.32**	-.40**
SF-36 PCS	-.17	.00	-.08
SF-36 MCS	-.06	-.09	-.17

Note. *n = 102 (df = 99). 6MWT= 6-minute walking test; HGST= Handgrip strength test; 1MSTS= 1-minute sit to stand test; SF-36= 36-Item Short Form Health Survey; PCS= Physical Component Summary; MCS= Mental Component Summary*

** p < .05; **p < .01*

When controlling for menopause status, the FAST total score remained significantly negatively correlated with the HGST (r = -0.39, p < 0.01) and 6MWT (r = -0.33, p < 0.01), but not with 1MSTS. Interestingly, no significant correlations were found between the SF-36 PCS or MCS and any of the physical parameters in this subgroup.

Table 14 Partial correlation coefficients between functioning and physical health parameters controlling for menopause

Variable	1MSTS	HGST (dominant hand)	6MWT Distance
FAST Total score	-.20	-.39**	-.33**
SF-36 PCS	.17	.11	.13
SF-36 MCS	.16	.09	-.11

***Note**. n = 75 (df = 72). 6MWT= 6-minute walking test; HGST= Handgrip strength test; 1MSTS= 1-minute sit to stand test; SF-36= 36-Item Short Form Health Survey; PCS= Physical Component Summary; MCS= Mental Component Summary*
** p < .05; **p < .01*

In sum, across all covariates, the FAST total score consistently showed significant negative correlations with physical health measures, especially with the 6MWT and HGST. In contrast, the SF-36 PCS and MCS generally did not show significant relationships with physical health measures, except for an isolated case when controlling for age.

4.3 Study 3 The IDEA trial: A single-blind randomised controlled study of a personalised exercise-based intervention for transdiagnostic depressive symptoms

Participant flow

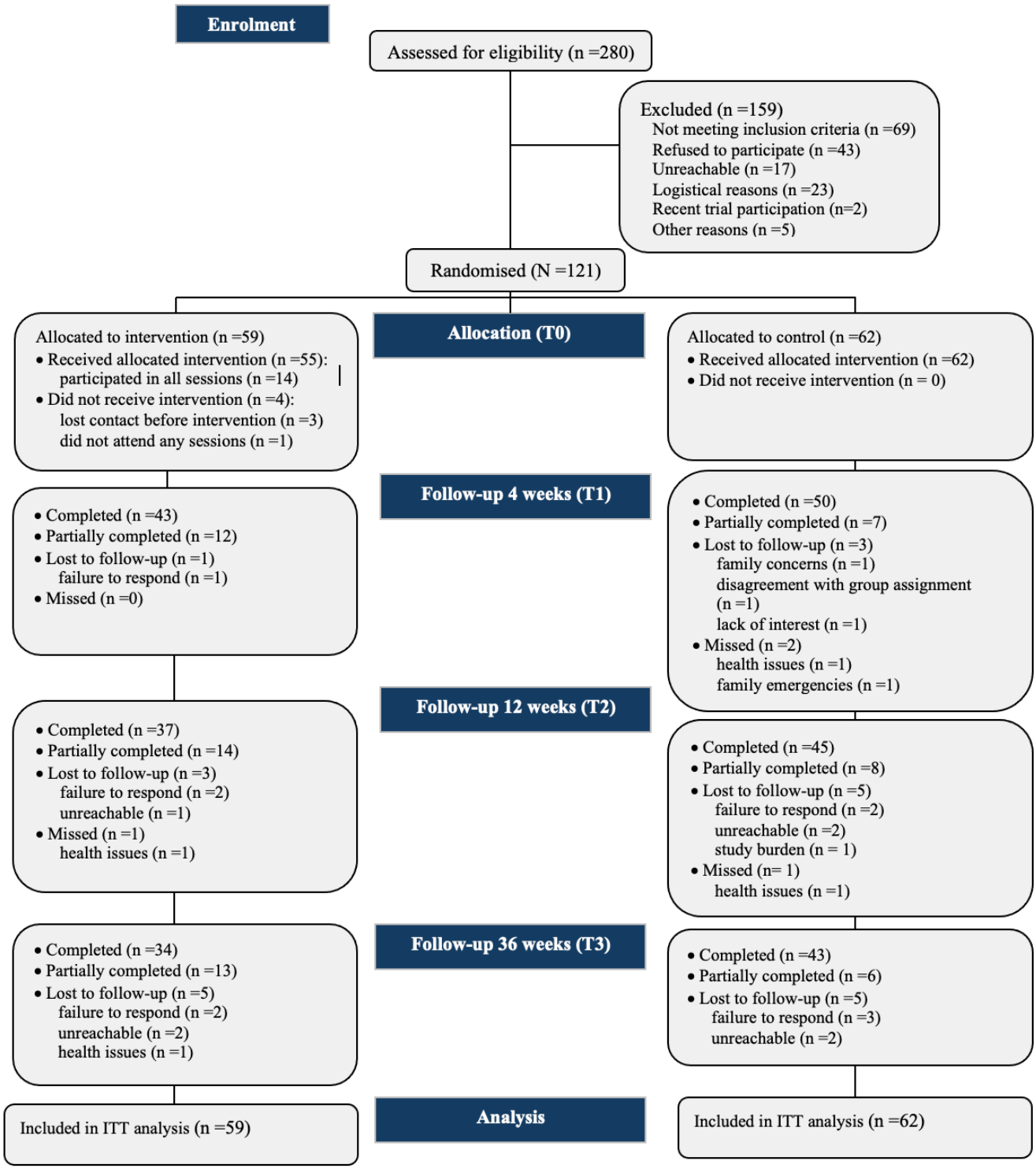
Out of 280 individuals screened for eligibility, 159 were excluded due to various reasons, including not meeting inclusion criteria (n = 69), refusal to participate (n = 43), being unreachable (n = 17), logistical reasons (n = 23), recent trial participation (n = 2), and other reasons (n = 5). The remaining 121 were enrolled in the study and randomly assigned to two groups. In the intervention group (n = 59), 55 participants received the intervention, while 4 did not, mainly due to being lost to contact before it began (n = 3). In the CG (n = 62), all participants received the allocated intervention.

At the 4-week follow-up, 1 participant in the EG was lost to follow-up (i.e., did not complete the study assessments), and in the CG, 3 participants were lost to follow-up, and 2 missed it (i.e., did not complete a specific assessment). At the 12-week follow-up (T2), the EG had 3 participants lost to follow-up (2 due to failure to respond and 1 as unreachable) and 1 missed due to health issues. In the CG, 5 participants were lost to follow-up (2 due to failure to respond, 2 as unreachable, and 1 due to study burden) and 1 was missed due to health issues. At the final 36-week follow-up (T3), the EG had 5 participants lost to follow-up (2 due to failure to respond, 2 as unreachable, and 1 due to health issues). In the CG, 5 participants were lost to follow-up (3 due to failure to respond and 2 as unreachable). See CONSORT diagram in Figure 7 for details.

Participation rate

After excluding the three participants in the EG who were lost to contact before the intervention, participation rates were calculated from a sample of 56 individuals. Among them, 25% attended all six sessions, 19.6% attended five sessions, 21.4% attended four sessions, 25% attended three sessions, 5.4% attended two sessions, 1.8% attended one session, and 1.8% did not attend any sessions. The mean number of sessions attended by participants was 4.21, with a standard deviation of 1.45, and the mean attendance rate was 70.24%. The proportion of participants who completed the study was similar for both arms, with approximately 91.5% of participants in the intervention group and around 91.9% in the control condition.

Figure 8 CONSORT diagram of participant flow for the IDEA study



Note. *T1 = 4-week assessment; T2 = 12-week assessment; T3 = 36-week final assessment; ITT = Intention-to-treat. Participants classified as 'partially completed' in the follow-up stages (e.g., T1, T2 and T3) are those who completed some, but not all, of the required assessments at that time point. These participants were not considered fully lost to follow-up but are included in the analysis for the assessments they completed. Participants labelled as 'lost to follow-up' did not complete any assessments for that follow-up time point. Participants categorised as 'missed' did not complete a specific assessment.*

Descriptive results

The sociodemographic, clinical and health characteristics of the study sample have been previously reported in the results of Study 2. In brief, the sample consisted of 121 participants (87 women, 34 men) with an average age of 51.1 years (SD = 10.4). Common comorbidities included rheumatoid disease (28.9%), anxiety (15.7%), and cardiovascular disease (17.4%), and 45.5% were on disability leave. Psychopharmacological treatment was widespread, with 81% using antidepressants. Alcohol use was low, with 55.5% being non-drinkers, and 35.5% were smokers. The mean MADRS score was 26.3 (SD = 6.1). For a detailed account of the descriptive statistics, including demographic information and relevant clinical variables, refer to the aforementioned section. Table 15 presents descriptive statistics for baseline functioning, depressive symptoms, and well-being variables for the EG, CG, and total sample. The mean scores for most variables were similar between the two study arms. However, small differences can be observed in specific areas of functioning (e.g., autonomy, occupational functioning), where the CG shows marginally higher scores. Additionally, the CG had slightly lower well-being scores (WHO-5).

Table 15 Baseline functioning, depressive symptoms, and well-being for experimental, control, and total sample groups

Variables	EG (n=59)		CG (n=62)		Total sample (N=121)	
	Mean	SD	Mean	SD	Mean	SD
Functioning						
FAST Autonomy	3.04	2.48	3.92	2.75	3.49	2.65
FAST Occupational functioning	7.2	4.91	8.78	5.65	8.01	5.34
FAST Cognitive functioning	5.84	2.93	6.80	3	6.33	2.99
FAST Financial issues	0.7	1.02	0.83	1.1	0.77	1.06
FAST Interpersonal relationships	5.76	2.47	6.28	3.1	6.03	2.81
FAST Leisure time	4.16	1.34	4.13	1.57	4.15	1.46
FAST Total score	26.7	10.81	30.75	11.76	28.77	11.44
SF-36 General Health	12.52	4.13	12.03	3.99	12.27	4.05
SF-36 Physical Functioning	22.93	5.09	21.32	4.81	22.11	4.99
SF-36 Role-Physical	11.68	5.52	10.76	5.4	11.21	5.46
SF-36 Role-Emotional	7.22	3.25	6.71	2.79	6.96	3.02
SF-36 Social Functioning	4.86	2.23	4.12	1.56	4.48	1.94
SF-36 Bodily Pain	6.87	2.77	5.88	2.88	6.36	2.86
SF-36 Mental Health	12.34	2.89	12.17	3.04	12.25	2.95
SF-36 Vitality	8.31	2.86	7.83	2.65	8.06	2.75
SF-36 PCS	43.29	9.20	40.08	10.02	41.64	9.73
SF-36 MCS	23.74	9.27	23.01	7.71	23.37	8.48
Depressive symptoms						
PHQ-9	15.58	5.54	15.99	5.13	15.79	5.32
Well-being						
WHO-5	24.81	16.92	21.69	16.54	23.22	16.73

***Note**. EG = experimental group; CG = control group; SD = standard deviation; FAST = Functional Assessment Short Test; SF-36 = 36-item Short-Form Health Survey; PCS = Physical Component Score; MCS = Mental Component Score; PHQ-9 = Patient Health Questionnaire-9; = WHO-5 = World Health Organisation- Five Well-Being Index*

Primary outcome

Mauchly's test of sphericity indicated a violation of the assumption ($W = 0.74$, $\chi^2(5) = 35.58$, $p < .001$), thus the Greenhouse-Geisser correction was applied for the main effect of time (T) and the interaction (G x T). Levene's test confirmed homoscedasticity was met at all time points ($p \geq .05$). These results are presented in Tables 16 and 17.

Table 16 Mauchly's test of sphericity for FAST total scores over time

Mauchly's W	Approx. χ^2	*df*	*p*
0.74	35.58	5	<.001

Note. *df = degrees of freedom; p = significance level*

Table 17 Levene's test of homoscedasticity for FAST total scores across time points

	Levene's test	*p*
T0	1.06	.30
T1	0.79	.37
T2	3.48	.06
T3	0.07	.79

Note. *Degrees of freedom for Levene's test are (1,119); p= significance level*

Table 18 presents the means, standard deviations, and ANOVA results for FAST total scores across the EG and CG at four time points (T0 to T3). Table 19 presents the within-group comparisons of total FAST scores across time for both the EG and CG, as well as between-group differences at each time point. The group-time interaction in the mixed factorial ANOVA did not reach significance (F(2.46, 292.67) = 2.43, p = .078). However, the p-value was below the 10% threshold, thus proximal to significance, warranting further investigation. Subsequent simple effects analyses revealed statistically significant between-gorup differences favouring the EG at T1 (p = .008), T2 (p = .003), and T3 (p = .006), whereas no significant difference was observed at T0 (p = .20). Within-group comparisons showed that the EG experienced a significant improvement over time, with a statistically significant difference from T0 to T2 (p = .010); however, this improvement was not maintained at T3. In contrast, the CG exhibited no significant changes compared to baseline at any time point (p > .05). Figure 9 illustrates the trajectory of FAST total scores, depicting changes in marginal means across time for both groups.

Table 18 Means, standard deviations, and mixed factorial ANOVA results for FAST total scores

Time	Experimental Mean (SD)	Control Mean (SD)	ANOVA		
			Effect	*F* Ratio (df)	η²
T0	26.7 (10.81)	30.75 (11.76)	G	11.09 (1,119) **	.09
T1	24.04 (10.93)	30.7 (12.25)	T	1.52 (2.46, 292.67) [a]	.01
T2	23.16 (11.21)	31.2 (14.02)	G x T	2.43(2.46, 292.67) [a]	.02
T3	23.9 (12.52)	31.28 (12.39)			

Note. *N = 121 (n = 59 for the experimental group and n = 62 for the control group); ANOVA = analysis of variance; G = group; T = time; SD = standard deviation; df = degrees of freedom*

** *p < .01*

[a] *Greenhouse-Geisser correction applied*

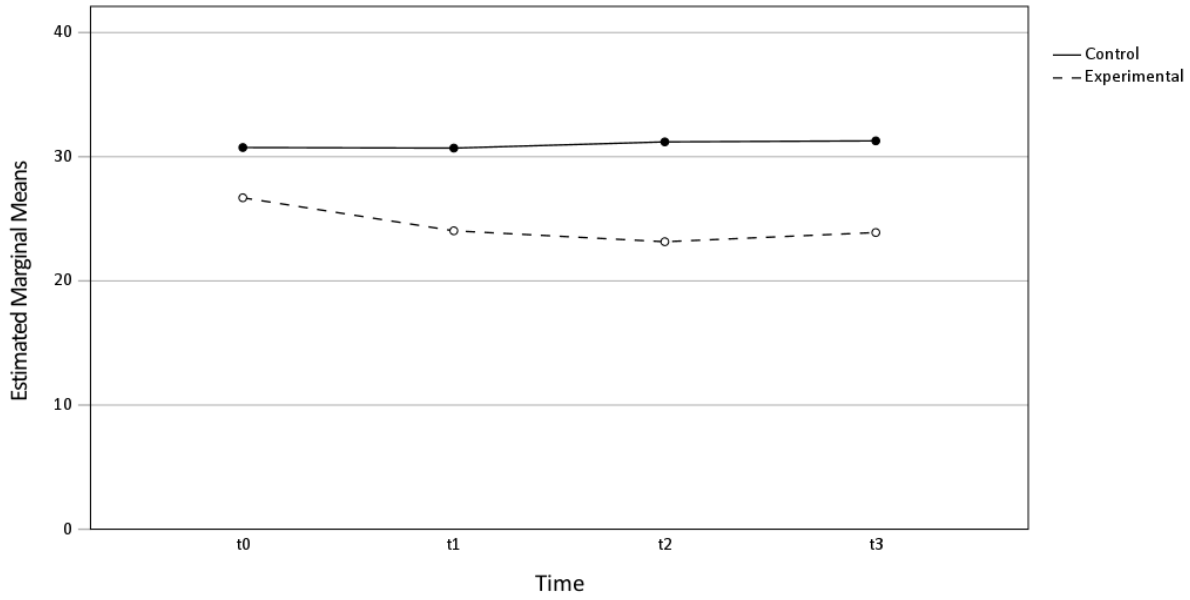
Table 19 Changes in FAST total scores over time within groups and between groups at each time point

Comparison	Difference	*SE*	95% CI[a]		*p*[a]
			LL	*UL*	
Experimental group					
T0-T1	2.66	0.98	-0.01	5.33	.05
T0-T2	3.54	1.07	0.62	6.46	.010
T0-T3	2.8	1.41	-1.04	6.64	.30
Control group					
T0-T1	0.05	0.9	-2.39	2.49	1
T0-T2	-0.45	1.16	-3.62	2.72	1
T0-T3	-0.54	1.24	-3.93	2.86	1
Experimental-Control					
T0	-4.05	2.06	-8.12	0.03	.20
T1	-6.66	2.11	-10.85	-2.47	.008
T2	-8.04	2.31	-12.62	-3.46	.003
T3	-7.38	2.27	-11.87	-2.90	.006

Note. *T0 = baseline; T1 = post-intervention; T2 = 12 weeks post-randomisation; T3 = 36 weeks post-randomisation; SE = standard error; CI = confidence interval; LL = lower limit; UL = upper limit*

[a] *p-values were adjusted using the Bonferroni correction for multiple comparisons*

Figure 9 Estimated marginal means of FAST total scores for the experimental and control groups across time points



As for the FAST subdomains scores, while the group-time interaction did not reach statistical significance in most subdomains, it was observed in Leisure Time ($F(3, 357) = 8.26$, $p < .01$ and Interpersonal Relationships ($F(2.77, 329.22) = 3.66$, $p < .05$). Subsequent simple effects analyses revealed that, over time, significant between-group differences that were not present at T0 ($p \geq .05$) emerged at multiple time points, favouring the EG: at T1 ($p = .004$), T2 ($p = .017$) and T3 ($p = .042$) in Autonomy; at T3 in Cognitive Functioning ($p = .004$); at T1 in Leisure Time ($p < .001$); at T2 in Financial Issues ($p = .037$); at T2 in Occupational Functioning ($p = .042$); and at T2 in Interpersonal Relationships ($p < .001$). Within-group analyses in the EG showed statistically significant improvements compared to baseline, particularly in Autonomy (T0-T2, $p = .013$) and Leisure Time (T0-T1, T0-T2, and T0-T3; all $p < .001$). In contrast, the CG showed minimal changes, with the only significant improvement observed in Leisure Time at T2 ($p = .032$). Table 20 presents the means, standard deviations, and mixed factorial ANOVA results. Table 21 presents the differences in FAST subdomains scores within-group and between-group across time points (T0, T1, T2, and T3).

Table 20 Means, standard deviations, and mixed factorial ANOVA results for FAST subdomains scores

Subdomain	Time	Experimental		Control		ANOVA			
		Mean	SD	Mean	SD	Effect	*F* ratio	*df*	η^2
Autonomy	T0	3.04	2.48	3.92	2.75	G	8.99**	1, 119	.07
	T1	2.94	2.31	4.47	2.61	T	1.17[a]	2.46, 293.22	.01
	T2	2.76	2.66	4.22	2.82	G x T	1.39[a]	2.46, 293.22	.01
	T3	2.76	2.64	4.02	2.67				
Occupational Functioning	T0	7.2	4.91	8.78	5.65	G	4.83*	1, 119	.04
	T1	7.04	5.16	8.32	5.64	T	1.92[a]	2.36, 281.12	.02
	T2	6.28	4.95	8.88	6.04	G x T	1.22[a]	2.36, 281.12	.01
	T3	7.3	5.54	9.55	5.8				
Cognitive Functioning	T0	5.84	2.93	6.80	3	G	6.06*	1, 119	.05
	T1	5.9	2.74	6.90	2.83	T	0.74[a]	2.83, 337.22	.01
	T2	5.82	3.01	6.77	3.28	G x T	2.21[a]	2.83, 337.22	.02
	T3	5.2	2.77	7.02	3.12				
Financial Issues	T0	0.7	1.02	0.83	1.10	G	3.51	1, 119	0.03
	T1	0.6	0.87	0.92	1.27	T	1.83[a]	2.69, 320.37	0.02
	T2	0.42	0.98	1.05	1.57	G x T	2.45[a]	2.69, 320.37	0.02
	T3	0.48	1.19	0.63	0.96				
Interpersonal Relationships	T0	5.76	2.47	6.28	3.1	G	8.05**	1, 119	.06
	T1	5.18	2.4	6.27	3.15	T	1.05[a]	2.77, 329.22	.01
	T2	4.8	2.44	6.83	3.13	G x T	3.66[a]*	2.77, 329.22	.03
	T3	4.96	3.06	6.3	3.05				
Leisure Time	T0	4.16	1.34	4.13	1.57	G	7.44**	1, 119	.06
	T1	2.38	1.56	3.83	1.69	T	17.68[a]**	3, 357	.13
	T2	3.08	1.44	3.45	1.78	G x T	8.26[a]**	3, 357	.06
	T3	3.2	1.56	3.77	1.62				

Note. *N = 121 (n = 59 for the experimental group and n = 62 for the control group). ANOVA = analysis of variance; df = degrees of freedom; G =* main effect of *group;* G x T = group × time interaction; *SD = standard deviation; T =* main effect of *time; T0 = baseline; T1 = post-intervention; T2 = 12 weeks post-randomisation; T3 = 36 weeks post-randomisation*

[a] *Greenhouse-Geisser correction applied.*

*p < .05, **p < .01

Table 21 Differences in FAST subdomains scores within groups over time and between groups at each time point

Subdomain		Difference EG and CG[a]				Difference EG[b]			Difference CG[b]		
		T0	T1	T2	T3	T0-T1	T0-T2	T0-T3	T0-T1	T0-T2	T0-T3
Autonomy	MD	-0.88	-1.53	-1.46	-1.26	0.10	0.28	0.28	-0.55	-0.30	-0.10
	p-value	.274	.004[c]	.017	.042	1.000	1.000	1.000	.124	1.000	1.000
Occupational Functioning	MD	-1.58	-1.28	-2.60	-2.25	0.16	0.92	-0.10	0.47	-0.10	-0.77
	p-value	.409[c]	.789	.042[c]	.125	1.000	.306	1.000	1.000	1.000	1.000
Cognitive Functioning	MD	-0.96	-1.00	-0.95	-1.82	-0.06	0.02	0.64	-0.10	0.03	-0.22
	p-value	.315	.204	.404	.004	1.000	1.000	.258	1.000	1.000	1.000
Financial Issues	MD	-0.13	-0.32	-0.63	-0.15	0.10	0.28	0.22	-0.08	-0.22	0.20
	p-value	1.000	.446[c]	.037[c]	1.000	1.000	.455	1.000	1.000	1.000	.804
Interpersonal Relationships	MD	-0.52	-1.09	-2.03	-1.34	0.58	0.96	0.80	0.02	-0.55	-0.02
	p-value	1.000	.138[c]	<.001[c]	.070	.330	.013	.215	1.000	.806	1.000
Leisure Time	MD	0.03	-1.45	-0.37	-0.57	1.78	1.08	0.96	0.30	0.68	0.37
	p-value	1.000	<.001	.838[c]	.212	<.001	<.001	.001	.903	.032	.576

Note. *N = 121 (n = 59 for the experimental group and n = 62 for the control group). CG = control group; EG = experimental group; MD = mean difference; T0 = baseline; T1 = post-intervention; T2 = 12 weeks post-randomisation; T3 = 36 weeks post-randomisation*

[a] *Adjusted using the Bonferroni correction for multiple comparisons*

[b] *Adjusted using the Bonferroni correction for multiple comparisons within EG and CG.*

[c] *Welch correction applied.*

Secondary efficacy outcomes

Functional status

Significant group-time interactions were found for several SF-36 subscales, including General Health ($F(3, 357) = 2.96$, $p < .05$, $\eta^2 = .02$) and Mental Health ($F(2.58, 307.19) = 4.06$, $p < .05$, $\eta^2 = .03$),), as well as for one of the two main components of functional status, the MCS ($F(3, 357) = 3.94$, $p < .01$, $\eta^2 = .03$). Subsequent simple effects analyses revealed significant between-group differences favouring the EG at T3 in General Health ($p = .048$), Mental Health ($p = .010$), Role-Emotional ($p = .008$), Social Functioning ($p = .001$), and Vitality ($p = .011$). These group differences were not present at baseline, as both groups were equivalent across SF-36 subscales and summary components, with no statistically significant differences observed ($p \geq .05$). Within-group analyses in the EG showed significant improvements from T0 to T3 in General Health ($p = .011$), Vitality ($p = .001$), Social Functioning ($p = .006$) and Role-Emotional ($p = .021$). Additionally, Mental Health improved significantly from T0 to T1 ($p = .013$) and T0 to T3 ($p = .001$). Similarly, a significant between-group difference in MCS at T3

(p = .003) favoured the EG, along with a significant within-group improvement in the EG from T0 to T3 (p = .001). In contrast, Physical Functioning and the PCS did not show significant overall differences. (p >.05). The CG exhibited no significant within-group improvements, except for a deterioration in Bodily Pain at T2 (p = .042) rather than an improvement. Table 22 presents the means, standard deviations, and mixed factorial ANOVA results for SF-36 scores, while Table 23 details between-group differences across time points (T0, T1, T2, and T3).

Table 22 Means, standard deviations, and mixed factorial ANOVA results for SF-36 scores

Subscale	Time	Experimental		Control		ANOVA			
		Mean	SD	Mean	SD	Effect	*F* ratio	*df*	η^2
General health	T0	12.52	4.13	12.03	3.99	G	4.92*	1, 119	.04
	T1	13.37	4.35	11.75	3.77	T	2.76*	3, 357	.02
	T2	13.57	4.67	11.72	3.87	G x T	2.96*	3, 357	.02
	T3	14.16	5.03	12.05	4.04				
Physical functioning	T0	22.93	5.09	21.32	4.81	G	5.18*	1, 119	.04
	T1	23.19	4.85	21.56	4.73	T	0.59[a]	2.53, 301.51	.00
	T2	23.71	5.1	21.02	5.18	G x T	1.27[a]	2.53, 301.51	.01
	T3	23.41	5.53	21.73	5.53				
Role - Physical	T0	11.68	5.52	10.76	5.4	G	8.46**	1, 119	.07
	T1	12.22	5.19	9.66	4.59	T	0.3[a]	2.35, 279.18	.00
	T2	12.59	5.32	9.53	4.93	G x T	2.37[a]	2.35, 279.18	.02
	T3	12.59	5.51	10.03	5.01				
Bodily pain	T0	6.87	2.77	5.88	2.88	G	8.78**	1, 119	.07
	T1	6.74	2.38	5.24	2.54	T	2.7[a]	2.79, 331.67	.02
	T2	6.64	2.44	5.17	2.87	G x T	0.87[a]	2.79, 331.67	.01
	T3	6.81	2.57	5.65	2.94				
Vitality	T0	8.31	2.86	7.83	2.65	G	5.65*	1, 119	.05
	T1	8.85	3.04	7.95	2.84	T	6.39**	3, 357	.05
	T2	9.22	3.4	8.09	2.89	G x T	2.43	3, 357	.02
	T3	10.05	3.4	8.24	3.09				
Social functioning	T0	4.86	2.23	4.12	1.56	G	11.03**	1, 119	.08
	T1	5.29	2.19	4.59	2.03	T	5.11[a]**	3, 357	.04
	T2	5.56	2.37	4.58	2.04	G x T	2.38[a]	3, 357	.02
	T3	6.03	2.59	4.41	1.96				

Table 22 (continued) Means, standard deviations, and mixed factorial ANOVA results for SF-36 scores

Subscale	Time	Experimental		Control		ANOVA			
		Mean	SD	Mean	SD	Effect	*F* ratio	*df*	η^2
Role - Emotional	T0	7.22	3.25	6.71	2.79	G	6.82*	1, 119	.05
	T1	7.92	3.12	6.98	2.98	T	2.86[a]*	2.75, 327.29	.02
	T2	7.93	3.59	6.54	2.94	G x T	2.37[a]	2.75, 327.29	.02
	T3	8.78	3.91	6.80	2.92				
Mental health	T0	12.34	2.89	12.17	3.04	G	6.2*	1, 119	.05
	T1	13.44	3.10	12.12	2.95	T	4.19[a]**	2.58, 307.19	.03
	T2	13.46	4.07	12.20	3.40	G x T	4.06[a]*	2.58, 307.19	.03
	T3	14.53	4.5	12.19	3.77				
PCS	T0	43.29	9.2	40.08	10.02	G	7.99**	1, 119	.06
	T1	43.39	9.02	38.59	9.03	T	0.7[a]	2.77, 330.11	.01
	T2	44.16	9.25	38.19	9.67	G x T	2.11[a]	2.77, 330.11	.02
	T3	43.58	9.88	39.72	10.05				
MCS	T0	23.74	9.27	23.01	7.71	G	4.41*	1, 119	.04
	T1	26.48	9.28	24.68	8.87	T	6.19**	3, 357	.05
	T2	26.79	10.86	24.52	8.80	G x T	3.94**	3, 357	.03
	T3	30.25	11.07	23.93	8.68				

Note. *N = 121 (n = 59 for the experimental group and n = 62 for the control group). ANOVA = analysis of variance; df = degrees of freedom; G =* main effect of *group;* G x T = group × time interaction; MCS = Mental component summary; PCS = Physical component summary; *SD = standard deviation; T =* main effect of *time; T0 = baseline; T1 = post-intervention; T2 = 12 weeks post-randomisation; T3 = 36 weeks post-randomisation*

[a] *Greenhouse-Geisser correction applied.*

*p < .05, **p < .01.

Table 23 Differences in SF-36 subscales scores within groups over time and between groups at each time point

Subscale		Difference EG and CG[a]				Difference EG[b]			Difference CG[b]		
		T0	T1	T2	T3	T0-T1	T0-T2	T0-T3	T0-T1	T0-T2	T0-T3
General health	MD	0.48	1.61	1.85	2.11	-0.85	-1.06	-1.64	0.28	0.31	-0.02
	P value	1.000	.124	.076	.048	.248	.179	.011	1.000	1.000	1.000
Physical functioning	MD	1.61	1.63	2.70	1.68	-0.25	-0.78	-0.47	-0.24	0.31	-0.41
	P value	.305	.257	.019	.391	1.000	.913	1.000	1.000	1.000	1.000
Role - Physical	MD	0.92	2.56	3.07	2.56	-0.54	-0.92	-0.92	1.10	1.24	0.73
	P value	1.000	.019	.005	.034	1.000	1.000	1.000	.390	.546	1.000
Bodily pain	MD	0.99	1.50	1.48	1.16	0.13	0.23	0.06	0.63	0.71	0.23
	P value	.223	.005	.012	.089	1.000	1.000	1.000	.162	.042	1.000
Vitality	MD	0.48	0.90	1.14	1.81	-0.54	-0.92	-1.75	-0.12	-0.25	-0.41
	P value	1.000	.380	.200	.011	.640	.262	.001	1.000	1.000	1.000
Social functioning	MD	0.75	0.69	0.98	1.63	-0.42	-0.69	-1.17	-0.47	-0.46	-0.29
	P value	.145[c]	.291	.063	.001[c]	1.000	.336	.006	.124	.315	1.000
Role - Emotional	MD	0.51	0.93	1.39	1.98	-0.69	-0.71	-1.56	-0.27	0.17	-0.08
	P value	1.000	.381	.085	.008[c]	.467	.685	.021	1.000	1.000	1.000
Mental health	MD	0.17	1.32	1.25	2.34	-1.10	-1.12	-2.19	0.05	-0.03	-0.02
	P value	1.000	.072	.271	.010	.013	.136	.001	1.000	1.000	1.000
PCS	MD	3.21	4.80	5.97	3.85	-0.10	-0.87	-0.28	1.49	1.88	0.35
	P value	.276	.016	.003	.143	1.000	1.000	1.000	.477	.155	1.000
MCS	MD	0.73	1.80	2.28	6.32	-2.74	-3.05	-6.61	-1.66	-1.50	-0.92
	P value	1.000	1.000	.825	.003[c]	.162	.345	.001	.651	1.000	1.000

***Note**. N = 121 (n = 59 for the experimental group and n = 62 for the control group). CG = control group; EG = experimental group; MCS = Mental component summary; MD = mean difference; PCS = Physical component summary; T0 = baseline; T1 = post-intervention; T2 = 12 weeks post-randomisation; T3 = 36 weeks post-randomisation*

[a] Adjusted using the Bonferroni correction for multiple comparisons

[b] Adjusted using the Bonferroni correction for multiple comparisons within EG and CG.

[c] Adjusted using the Welch correction

Depressive symptoms

The mixed factorial ANOVA revealed a statistically significant group-time interaction ($F(2.76, 328.98) = 5.35$, $p < .01$, $\eta^2 = .04$), suggesting that the intervention influenced depressive symptoms over time. Between-group comparisons showed significant differences at T1 ($p = .038$) and T3 ($p = .002$), favouring the EG, while no differences were observed at baseline ($p \geq .05$). Within-group analyses indicated significant improvements in the EG over time, with PHQ-9 scores significantly decreased between T0 and T1 ($p = .002$), T0 and T2 ($p = .002$), and T0 and T3 ($p < .001$). In contrast, no significant within-group differences were detected in the CG at any time point. The intervention's impact on depressive symptoms, as measured by PHQ-

9 scores, is illustrated in Table 24, while Table 25 provides a detailed summary of within-group and between-group differences over time. Figure 10 illustrates the estimated marginal means of PHQ-9 scores across time points for both groups.

Table 24 Means, standard deviations, and mixed factorial ANOVA results for PHQ-9 scores

Time	Experimental		Control		ANOVA			
	Mean	SD	Mean	SD	Effect	*F* ratio	*df*	η^2
T0	15.58	5.54	15.99	5.13	G	7.32**	1,119	.06
T1	12.97	6.37	15.77	5.31	T	7.96[a]**	2.76,328.98	.06
T2	12.73	6.50	15.07	5.60	G x T	5.35[a]**	2.76,328.98	.04
T3	11.42	7.16	15.72	6.11				

Note. *N = 121 (n = 59 for the experimental group and n = 62 for the control group). ANOVA = analysis of variance; G = group; T = time; T0 = baseline; T1 = post-intervention, or 4 weeks after allocation for the control group; T2 = 12 weeks post-randomisation; T3 = 36 weeks post- randomisation; SD = standard deviation; df = degrees of freedom*

[a] *Greenhouse-Geisser correction applied*

** *p < .01*

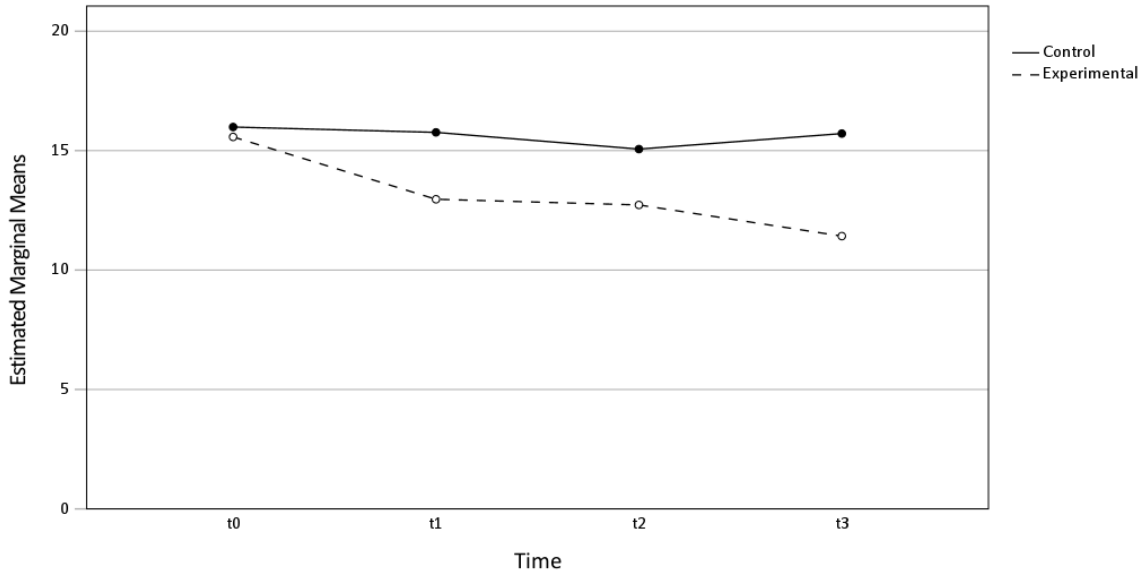
Table 25 Differences in PHQ-9 scores within groups over time and between groups at each time point

Comparison	Difference	*SE*	95% CI[a]		*p*[a]
			LL	*UL*	
Experimental group					
T0-T1	2.61	0.68	0.74	4.48	.002
T0-T2	2.85	0.75	0.80	4.89	.002
T0-T3	4.15	0.84	1.85	6.46	<.001
Control group					
T0-T1	0.22	0.49	-1.11	1.56	1
T0-T2	0.92	0.54	-0.54	2.38	.54
T0-T3	0.27	0.74	-1.75	2.30	1
Experimental-Control					
T0	-0.41	0.97	-2.33	1.51	1
T1	-2.8	1.06	-4.91	-0.69	.038
T2	-2.34	1.1	-4.52	-0.16	.14
T3	-4.29	1.21	-6.68	-1.90	.002

Note. *T0 = baseline; T1 = post-intervention, or 4 weeks after allocation for the control group; T2 = 12 weeks post-randomisation; T3 = 36 weeks post- randomisation; SE = standard error; CI = confidence interval; LL = lower limit; UL = upper limit*

[a] *Bonferroni adjustment was applied for multiple comparisons*

Figure 10 Estimated marginal means of PHQ-9 scores for the experimental and control groups across time points



Well-being

The group-time interaction effect did not reach statistical significance ($F(2.66, 316.89) = 2.63$, $p = .06$, $\eta^2 = .02$); however, the p-value fell just below the 10% threshold. Subsequent between-group comparisons revealed a significant difference favouring the EG at T3 ($p = .010$), which was not present at baseline ($p \geq .05$). In contrast, no significant differences were observed at T1 ($p = .29$) or T2 ($p = .80$).Within-group analyses showed a significant improvement in the EG from T0 to T3 ($p = .002$), whereas no significant changes were observed within the EG at T1 ($p = .12$) or T2 ($p = .25$). Similarly, the CG exhibited no significant within-group differences at any time point. Table 25 presents the means, standard deviations, and mixed factorial ANOVA results for WHO-5 WBI scores. Table 27 summarizes the within-group and between-group differences over time, while Figure 11 illustrates the estimated marginal means of WHO-5 WBI scores across time points for both groups.

Table 26 Means, standard deviations, and mixed factorial ANOVA results for WHO-5 WBI scores

Time	Experimental		Control		ANOVA			
	Mean	SD	Mean	SD	Effect	*F* ratio	*df*	η²
T0	24.81	16.92	21.69	16.54	G	5.21*	1, 119	.04
T1	30.17	19.59	24.2	16.55	T	6.99a**	2.66, 316.89	.06
T2	30.64	21.48	25.9	19.04	G x T	2.63a	2.66, 316.89	.02
T3	36.75	22.96	24.81	19.55				

Note. *N = 121 (n = 59 for the experimental group and n = 62 for the control group). ANOVA = analysis of variance; G = group; T = time; T0 = baseline; T1 = post-intervention, or 4 weeks after allocation for the control group; T2 = 12 weeks post-randomisation; T3 = 36 weeks post- randomisation; SD = standard deviation; df = degrees of freedom*

[a] Greenhouse-Geisser correction applied.

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

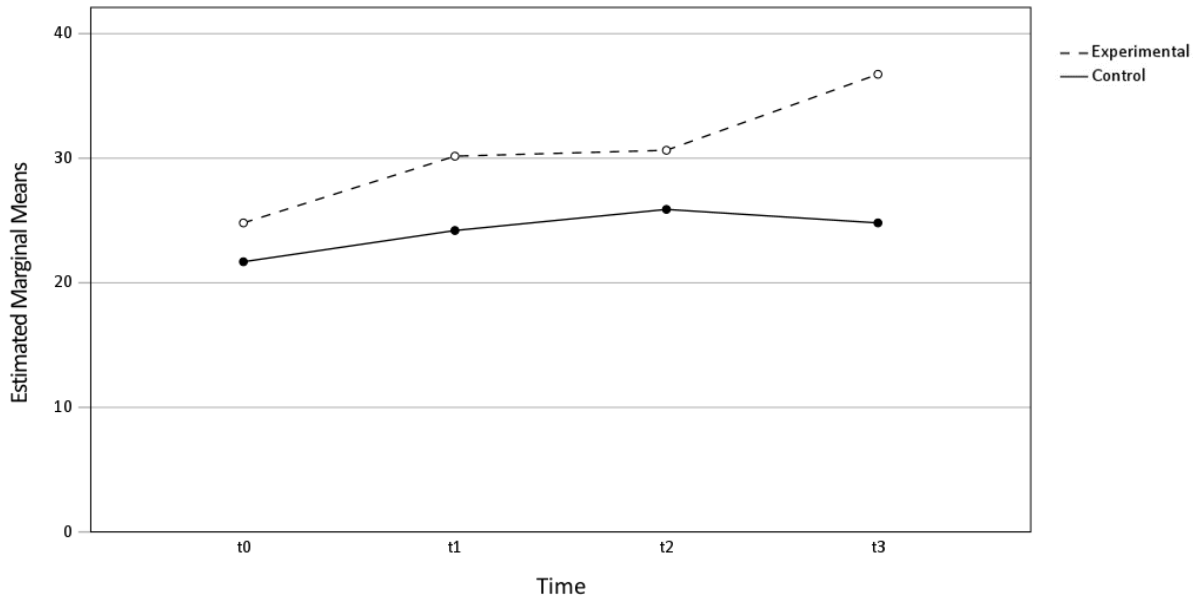
Table 27 Differences in WHO-5 WBI scores within groups over time and between groups at each time point

Comparison	Difference	*SE*	95% CI[a]		*p*[a]
			LL	*UL*	
Experimental group					
T0-T1	-5.36	2.25	-11.5	0.79	.12
T0-T2	-5.83	2.8	-13.47	1.81	.25
T0-T3	-11.93	3.07	-20.32	-3.54	.002
Control group					
T0-T1	-2.51	1.47	-6.51	1.5	.55
T0-T2	-4.2	1.81	-9.13	0.73	.14
T0-T3	-3.12	1.97	-8.5	2.26	.71
Experimental-Control					
T0	3.12	3.04	-2.9	9.14	1
T1	5.97	3.29	-0.55	12.48	.29
T2	4.75	3.69	-2.55	12.05	.80
T3	11.93	3.87	4.27	19.6	.010

Note. *T0 = baseline; T1 = post-intervention, or 4 weeks after allocation for the control group; T2 = 12 weeks post-randomisation; T3 = 36 weeks post- randomisation; SE = standard error; CI = confidence interval; LL = lower limit; UL = upper limit*

[a] *Bonferroni adjustment was applied for multiple comparisons*

Figure 11 Estimated marginal means of WHO 5 WBI scores for the experimental and control groups across time points



Chapter 5. Discussion

5.1 Summary of main findings

Through three interconnected studies using different methodological approaches, this thesis aimed to develop a comprehensive understanding of the effects of exercise-based interventions on general functioning among individuals with transdiagnostic depressive symptoms. Each study addresses a different but complementary aspect of this topic, creating a logical progression from broader evidence to deeper exploration of associations and, finally, to experimental validation. Study 1 (systematic review) set the foundation by synthesizing existing research on exercise-based interventions for this population and identified gaps in the literature. Study 2 (cross-sectional study) explored the relationship between functional impairment and physical health in this population. Study 3 (RCT) directly tested the IDEA intervention, an ultra-brief, personalised, group-based exercise intervention adjunct to TAU, assessing its effects on functioning, depressive symptoms, and well-being over time. The main findings of this thesis were as follows:

1. Study 1 was the first evidence targeting exercise interventions and functioning as a main outcome from a symptom-based perspective, and found that these interventions can significantly improve general functioning in individuals with depressive symptoms regardless diagnosis, though results varied based on intensity, duration, and study design. While multiple studies reported benefits, others found mixed or non-significant changes. Although physical exercise can improve functioning, many studies often treated it as a secondary outcome, lacked long-term follow-ups or did not standardize intervention parameters.

2. Study 2 found that poorer functioning was significantly and consistently associated with lower physical performance across multiple tests, even after controlling for covariates. Physical health also showed positive associations with performance measures and remained stable across covariates, whereas mental health scores exhibited no significant correlations with physical performance. Age and BMI influenced some of these associations.

3. Study 3 demonstrated positive effects of the IDEA intervention on general functioning (FAST total scores), the primary outcome, with significant between-group differences at T1, T2, and T3, despite the group-time interaction not reaching statistical significance

but approaching it. Within-group improvements were observed in the experimental group (EG) from T0 to T2. Specific aspects of functioning, including Leisure Time and Interpersonal Relationships (FAST subdomains), also improved in the EG. For secondary outcomes, the intervention led to significant improvements in mental health-related functioning (SF-36 General Health, Mental Health, and MCS summary scores), with effects becoming more pronounced at T3, while physical health-related functioning remained unchanged. Depressive symptoms (PHQ-9) were significantly reduced in the EG, with effects emerging early (T1) and strengthening over time (T3). Well-being (WHO-5) while showed between-group differences favouring the EG later (T3), though without evidence of a group-time interaction effect. Overall, the CG showed minimal significant changes across outcomes.

5.2 Interpretation of findings

Functional improvements in context

The systematic review conducted in this thesis anticipated positive effects on functional outcomes and reductions in depressive symptoms post-intervention in the target population. These effects, while influenced by individual and methodological differences, were supported by the findings of the IDEA trial.

There was no a statistically significant group-time interaction in general functioning scores at $\alpha = .05$, though it approached significance at the 10% level ($p < .10$), indicating a trend toward significance. However, significant between-group differences were observed at multiple time points (T1, T2, T3) that were not present at baseline, consistently favoring the EG. Additionally, within-group improvement in the EG from T0 to T2 suggests an intervention effect. While the significant within-group improvement in the EG at T2 was not maintained at T3, the EG continued to show significantly better functioning than the CG at T3, suggesting suggesting potential but attenuated effect beyond the active intervention period. Graphical analyses further support the functional improvement in the EG and provide additional evidence of the effectiveness of the IDEA programme. However, these findings should be interpreted with caution.

Additionally, the findings suggest that the intervention had specific benefits in the Leisure Time and Interpersonal Relationships subdomains of the FAST measure. The significant group-time interaction effects observed in these areas indicate that the intervention may have

contributed to improvements in social and recreational functioning. When comparing the two groups over time, the EG showed significantly greater improvements in Leisure Time at T1 and Interpersonal Relationships at T2, suggesting that the intervention's impact in these areas became evident at different time points. The continued within-group improvements in Leisure Time at all post-baseline assessments further reinforce the intervention's positive effects on this domain, indicating that participants in the EG were able to sustain engagement in leisure activities over time. In contrast, the CG exhibited minimal changes across subdomains.

The SF-36 results suggest that the IDEA intervention contributed to improvements in several aspects of functional status over time, particularly in mental health-related subscales (General Health and Mental Health) and the MCS summary score. The significant group-time interactions observed in these subscales and the MCS indicate that participants in the EG experienced improvements in these areas compared to the CG. These effects became particularly evident at T3, while the CG showed minimal change, suggesting that the intervention's positive impact on psychological functioning strengthened over time. Within-group analyses further support these findings, with the EG demonstrating sustained improvements in Mental Health from T0 to T3. Notably, the significant improvements in MCS at T3, both within the EG and in comparison to the CG, suggest that the intervention was effective in enhancing overall mental well-being perception.

In contrast, no significant changes were observed in Physical Functioning or the PCS, indicating that the intervention may have primarily influenced mental health and psychosocial dimensions rather than physical health outcomes. This finding suggests that while the intervention supported mental health, additional strategies may be needed to address physical health-related aspects of functioning.

These SF-36 results are broadly consistent with the Study 1 findings, particularly regarding mental health-related improvements, yet they contrast with some RCTs that have reported improvements in PCS (254). However, Study 3 showed stronger and more sustained between-group differences, suggesting a potential long-term benefit of the intervention.

Overall, these findings highlight the potential of exercise-based interventions to address functional impairment, an important yet sometimes underexplored aspect of depression treatment (253).There are multiple indications that IDEA was beneficial in this regard.

Depressive symptoms and well-being in context

The findings suggest that the IDEA programme significantly reduced depressive symptoms. The significant group-time interaction and the between-group differences favouring the EG at T1 and T3 indicate that the intervention contributed to clinical benefits, with effects emerging early and becoming more pronounced over time. The within-group improvements in the EG, observed at multiple time points (T0 to T1, T2, and T3), further suggest that the intervention provided progressive and sustained benefits for depressive symptoms.

In addition, the absence of significant changes in the CG over time suggests that, without this personalised active intervention, participants did not experience symptom improvement. This is somewhat concerning, given that all participants were receiving TAU. Since the intervention was adjunct to standard treatment, some level of symptom improvement might have been expected in both groups over time. The fact that only the EG demonstrated significant within-group reductions in depressive symptoms suggests that TAU alone may not have been sufficient to drive meaningful symptom changes in this population. This underscores the potential value of integrating personalised exercise-based interventions alongside standard treatment to enhance mood regulation and overall clinical outcomes.

While these results align with Study 1 and previous research highlighting the role of exercise-based interventions in reducing depressive symptoms (208), it is important to acknowledge that this was a secondary outcome. Thus, these findings should be interpreted with caution.

Regarding well-being, although the group-time interaction for WHO-5 WBI scores did not reach statistical significance, the p-value fell just below the 10% threshold, indicating a trend toward significance. This suggests a potential intervention effect on well-being that did not meet conventional significance criteria but warrants consideration, particularly given the observed between-group differences at T3. The significant between-group difference favouring the EG at T3, which was not present at baseline, suggests that the intervention may have contributed to improvements in well-being over time. However, the lack of significant differences at previous time points suggests that these benefits emerged gradually, rather than immediately after the intervention. Within-group comparisons further support this pattern, as the EG showed a significant improvement in well-being from T0 to T3, but not at earlier time points. This finding suggests that the positive effects of the intervention on well-being became

more apparent over time, possibly due to cumulative benefits of continued participation. In contrast, the CG showed no significant within-group improvements at any time point.

These findings align with improvements observed in mental health-related SF-36 aspects, supporting the intervention's gradual psychological impact. However, again, they should be interpreted with caution, as well-being was a secondary outcome and the group-time interaction did not reach statistical significance at conventional thresholds. While the trend toward significance and the between-group differences at T3 suggest potential benefits, they do not provide definitive evidence of an intervention effect on well-being. Nonetheless, these results align with the idea that personalised exercise-based interventions may play a role in enhancing psychological well-being, but their effects may take time to fully manifest. The delayed emergence of significant between-group differences highlights the potential importance of sustained engagement in such interventions to achieve notable improvements.

The IDEA intervention offers a promising approach to managing depressive symptoms by reducing their severity and maintaining improvements over time. These findings align with the principle that early and targeted interventions can support long-term symptom management, in line with ICD-based clinical practice and ICF's focus on maintaining and improving functioning (255). While further research is needed to determine its impact on relapse prevention, the sustained improvements observed suggest its potential applicability for managing mild to moderate symptoms across diverse conditions.

Physical health associations

Study 2 provides partial support for the idea that increased general functioning impairment (as measured by FAST total scores) increases, is associated with a trend towards worsening of physical health indicators, suggesting a link between performance health and overall functioning. In contrast, SF-36 PCS exhibited significant but weaker correlations with physical performance, which diminished after controlling for a few covariates. SF-36 MCS, however, did not show significant correlations with physical health parameters, indicating that mental health-related aspects of functioning are not directly linked to physical performance.

The covariates examined in Study 2 accounted for minimal variance, further evidencing the relatively robust link between functional impairment and physical health. Notably, age and

BMI had the greatest impact on the association between physical health parameters and SF-36 PCS, highlighting their importance in understanding these relationships and their potential moderating effects.

Prior research has explored the relationship between physical performance measures, such as gait speed, and depressive symptoms, finding that slower gait speed is associated with higher depressive symptoms (256). Even individuals with subthreshold levels of depression tend to display slower gait speed, hinting at potential future declines in physical performance. While sociodemographic, clinical, and lifestyle factors partly explain this connection, the association between gait speed and elevated depressive symptoms was fully clarified after adjustments. Additionally, Veronese et al. (2017) suggested that low physical performance is an independent predictor of depression over the long term (257).

The IDEA trial builds on these findings, highlighting the multifaceted nature of these relationships and providing evidence that tailored interventions addressing individual characteristics may be more effective for both physical health and overall functioning. This results are consistent with similar studies (208) and bring up the need for multidisciplinary approaches and teams in exercise-based treatments that target both physical and mental health. Overall, these findings underscore the importance of maintaining physical activity to uphold various aspects of general functioning.

Sample characteristics and their influence on findings

The IDEA study sample was notable for its complexity, particularly regarding gender, comorbidities, and health profiles. A high percentage of women (59.77%) were menopausal or postmenopausal, a group known to experience physiological changes that can affect exercise responses and limit physical functioning improvements (258,259). Moreover, 70.25% had comorbid conditions, reflecting the presence of complex health profiles that could complicate the benefits of exercise, particularly for physical functioning. Anxiety disorders were the most common psychiatric comorbidity, consistent with their high prevalence in individuals with depressive symptoms (260,261).

Rheumatoid disease was also notably prevalent in the sample, affecting 28.9% of participants. Mild and moderate depressive symptoms are common among individuals with rheumatoid disease, with prevalence rates often exceeding 50% for mild symptoms and ranging between

18-33% for moderate symptoms (261). These rates vary depending on the methodology used and the population examined, but they are significantly higher than those observed in the general population (262,39). This may explain the notable prevalence of rheumatoid disease (28.9%) in our sample. Depression in patients with rheumatoid disease is linked to worse disease outcomes, including increased functional disability (263,264). This association may partially explain why, despite the IDEA intervention having a positive short-term effect on general functioning, no significant improvement was observed at the 8-month mid-term follow-up.

As previously discussed in this work, there is a well-documented association between depressive symptoms and various physical health conditions. The recruitment strategy of the IDEA study, which focused on transdiagnostic depressive symptoms rather than exclusive depression diagnoses, naturally contributed to the diversity of comorbidities observed in the sample. Additionally, the involvement of diverse outpatient services in recruitment, including mental health, neurology and physical rehabilitation, general practice, and a post-COVID-19 unit, likely amplified this heterogeneity.

Participants were, on average, overweight or obese, which is often linked to metabolic issues that may reduce exercise tolerance and influence both mental and physical health (265). However, those with higher BMIs may have experienced additional psychological benefits from the intervention, such as enhanced self-esteem and body satisfaction, which could have amplified its positive mental health impact.

Adherence

Session attendance averaged around 70%, with 25% attending all six sessions, showing varied engagement levels. Despite this, effectiveness was likely unaffected, as participants may have stayed active by following programme recommendations outside sessions. Written summaries for missed sessions helped maintain engagement, minimising any disconnect. This suggests that adherence encompasses more than just session attendance, supporting the intervention's effectiveness even with lower session participation. These attendance rates align with the average found in our systematic review (approximately 72.8%). Furthermore, the average dropout rate was low at 8.27%, contrasting sharply with the typical 18.1% in exercise-for-depression trials (210). While adherence to these interventions remains challenging—particularly for individuals with higher baseline depressive symptoms— these rates highlight

the influence of differential factors such as specialist-led interventions with support and tailored prescriptions, which likely enhanced engagement and outcomes (151,177,197).

Comparison with previous literature

The transdiagnostic nature of depressive symptoms presents a unique challenge and is a notable strength, barely seen in exercise trials. An exception is a study from the University of Tübingen, which tested a supervised exercise-based intervention combined with behaviour change techniques in patients with various psychiatric disorders, achieving positive outcomes in behaviour change and global symptom severity (266). Since depressive symptoms are common in a plethora of mental and physical conditions, traditional therapeutic strategies fall short of fully addressing them. The IDEA trial proved the enhanced benefits of incorporating this exercise-based intervention as a complement to traditional treatments, effectively addressing the complex nature of depressive symptoms and the diverse needs of individuals experiencing them.

Similar works have reported substantial heterogeneity in exercise recommendations (208), and debates about the optimal exercise dose for mental health continue. However, current evidence suggests that even modest amounts of exercise can confer mental health benefits, with the greatest gains seen when individuals transition from inactivity to any level of activity (185,207). While moderate exercise is often advised under the principle of ‘the more, the better’, a values-based approach that encourages engagement in meaningful activities may yield better outcomes as proved in the IDEA study. Consistency and appropriate intensity, rather than simply increasing duration, appear to be the most crucial factors for maximizing benefits (211).

While 12–16 week interventions are common in exercise studies, we tested a shorter, six-session programme over four weeks to evaluate its potential for sustained benefits. This brief, tailored approach, featuring small groups of 4–6 participants, enhanced integration and allowed for better identification of individual needs. Research shows that even short bouts of exercise, such as 30 minutes of treadmill walking for 10 consecutive days, can lead to clinically significant reductions in depression (267). Furthermore, lower-than-recommended exercise doses can still positively impact depressive symptoms and comorbid conditions (268).

Other personalised interventions, such as that by Keller-Varady et al. (269), combined motivational interviewing with tailored physical activities. Although both studies aimed to promote exercise modifications, the IDEA RCT relied on group supervision with a physiotherapist, while the German study featured individualised sessions with a sports therapist. Both included a practical component, guiding participants through specific exercises. However, the German study did not yield significant clinical benefits, likely due to its small sample size (N=31), whereas our study demonstrated improvements beyond clinical outcomes. The IDEA RCT also involved input from specialists in developing the structure of the exercise programmes, enhancing its value over standardised protocols (230).

5.3 Summary of findings by hypothesis

The findings of this thesis are summarised below in relation to each hypothesis.

Hypothesis 1:Individuals experiencing transdiagnostic depressive symptoms will demonstrate greater functional capabilities and an enhanced quality of life after participating in exercise-based treatments compared to those receiving TAU or other active interventions (Study 1).

Findings: Exercise-based interventions can enhance functioning in individuals with depressive symptoms, though effects vary by intensity, duration, and study design. While some studies reported benefits, results were mixed across studies, often due to secondary outcome focus, lack of long-term follow-ups, or inconsistent intervention parameters.

This hypothesis is partially supported, as moderate evidence supports the effectiveness of exercise-based interventions in improving functioning and quality of life, but inconsistencies exist across studies.

Hypothesis 2: Functional impairment (FAST and SF-36 summary scores) will be associated with worse physical health indicators in a population with transdiagnostic depressive symptoms (Study 2).

Findings: Greater functional impairment, as measured by the FAST, was significantly correlated with poorer physical performance across all parameters. SF-36 PCS scores showed significant positive correlations with all physical performance measures, suggesting that better physical functioning was linked to higher physical performance. SF-36 MCS did not show any significant associations with physical health indicators.

This hypothesis is partially supported, as FAST and SF-36 PCS showed consistent associations with physical health indicators, but the mental health-related aspects of functioning (SF-36) did not correlate with any of them.

Hypothesis 3: Sociodemographic and health variables (age, BMI, tobacco use and menopause status) will influence the relationship between physical health parameters and general functioning (FAST and SF-36 summary scores) in a population presenting with transdiagnostic depressive symptoms (Study 2).
Findings: Some variables, particularly BMI and age, influenced the association between physical health parameters and SF-36 PCS by weakening it, while FAST remained significant after adjusting for them. Menopause status and tobacco use did not significantly modify these associations.

This hypothesis is only partially supported, as some sociodemographic factors influenced functional outcomes, but their overall contribution was limited.

Hypothesis 4: Participation in IDEA will improve general functioning (FAST total scores), from baseline to weeks 4, 12 and 36, compared to CG (Study 3).
Findings: Significant between-group differences favouring the EG were observed at T1, T2, and T3, whereas no such differences were present at T0, suggesting that the intervention had a positive impact on general functioning. However, the group-time interaction for FAST total scores was not statistically significant at $\alpha = .05$, though it approached significance at the 10% level ($p < .10$). Additionally, the CG showed no improvement over time.

The hypothesis is partially supported, as the treatment appears to be effective based on the simple effects analyses, despite the interaction effect not reaching statistical significance at $\alpha = .05$. Descriptive and graphical analyses further suggest a greater improvement in the EG, culminating in a significant difference between groups at T3 that was not present at baseline.

Hypothesis 5: Participation in IDEA will improve perceived functional status (SF-36 scores), from baseline to weeks 4, 12 and 36, compared to CG (Study 3).
Findings: Group-time interactions were observed for some SF-36 subscales (e.g., General Health, Mental Health) and the MCS summary score, suggesting that the EG experienced improvements in these areas compared to the CG. Significant between-group differences at T3

were found for these SF-36 subscales and the MCS, suggesting sustained intervention effects. Within-group improvements in the EG from T0 to T3 were observed in Mental Health, reinforcing some positive sustained effects. In contrast, no changes were found in Physical Functioning or the PCS. The CG showed minimal changes.

This hypothesis is partially supported, as the IDEA intervention contributed to improvements in mental health-related areas of functioning over time. However, no effects were observed on the physical health-related aspects of functional status, leading to partial support for the hypothesis.

Hypothesis 6: Participation in IDEA will improve depression severity (PHQ-9 scores), from baseline to weeks 4, 12 and 36, compared to CG (Study 3).
Findings: The IDEA intervention led to a significant group-time interaction, indicating that the paths or patterns of the groups were different. Between group comparisons revealed reductions in depressive symptoms at T1 and T3 favouring the EG. Also, the EG showed a significant reduction of symptoms at all follow-ups (T1, T2 and T3) compared to baseline. In contrast, the CG showed no significant improvements at any time point.

This hypothesis is fully supported, as participation in the IDEA programme effectively reduced depressive symptoms, with sustained improvements observed at T3.

Hypothesis 7: Participation in IDEA will improve well-being (WHO 5 WBI scores), from baseline to weeks 4, 12 and 36, compared to CG (Study 3).
Findings: Between-group comparisons showed a significant difference favouring the EG overtime (T3), which was not present at baseline. Within-group comparisons showed a significant improvement in the EG from T0 to T3, whereas no significant changes were observed within the EG at earlier time points Additionally, no significant changes were observed in the CG over time.

This hypothesis is partially supported, as the treatment appears to enhance well-being based on the simple effects analyses, despite the interaction effect not reaching statistical significance at $\alpha = .05$. Descriptive and graphical analyses further suggest a greater improvement in the EG compared to CG, culminating in a significant difference between groups at T3 that was not present at baseline, and within-group improvements in the EG from T0 to T3.

Table 28 Summary of hypothesis testing

	Hypothesis	Study	Findings	Support level
1.	Exercise- based treatments improve functioning and quality of life	1	Mixed evidence; some strong effects, but inconsistencies	Partially supported
2.	Functional impairment is linked to physical health	2	Consistent correlations found between FAST and SF-36 PCS with physical health indicators, but SF-36 MCS showed no associations	Partially supported
3.	Sociodemographic factors influence functioning outcomes	2	FAST maintained significant correlations with physical health indicators after controlling for BMI/age, while SF-36 PCS associations weakened. No effect for tobacco/menopause	Partially supported
4.	IDEA improves general functioning	3	No significant group-time interaction. EG showed significant between-group differences at T1, T2, and T3, outperforming CG at T3. CG showed no significant improvement	Partially supported
5.	IDEA improves functional status	3	Significant group-time interactions in Mental Health, General Health, and MCS. EG improved over time in mental health-related areas, with strongest effects at T3. Minimal changes in CG. No significant effects on physical health-related areas	Partially supported
6.	IDEA reduces depressive symptoms	3	Significant group-time interaction. EG showed reduced depressive symptoms at T1 and T3. Within-group improvements in EG from T0 to T1, T2, and T3. CG showed no improvement	Supported
7.	IDEA enhances well-being	3	No significant group-time interaction. EG showed significant between-group differences at T3. Within-group improvements in EG from T0 to T3. No significant changes in CG	Partially supported

Note. *CG= Control group; EG= Control group; FAST= Functional Assessment Short Test; MCS=SF-36 Mental Component Summary; SF-36 = 36-items Short-form Health Survey; PHQ-9 = Patient Health Questionnaire; T1 = post-intervention, or 4 weeks after allocation for the control group; T2 = 12 weeks post-randomisation; T3 = 36 weeks post- randomisation; WHO-5 WBI = World Health Organization Well-being Index*

5.4 Implications of findings

Theoretical implications

These results reinforce the growing body of evidence supporting physical activity as an integral component of treatment within mental health frameworks. While traditional approaches typically focus on pharmacological and psychotherapeutic treatments, the findings suggest that the IDEA programme may serve as a useful adjunct, particularly for individuals with mild to moderate depressive symptoms, by providing benefits for both mental and physical health. This aligns with the biopsychosocial model, which advocates a holistic approach to health (272).

In addition, the ICF (255) offers a complementary perspective for understanding the IDEA programme's impact. The ICF categorizes health and disability into components such as body functions, activities, and participation, allowing for a broader evaluation of functioning beyond symptom reduction alone. This framework can help contextualize how interventions like IDEA contribute to overall well-being and key functional domains such as mobility, self-care, and social participation.

These findings also align with theories on behavioural change, such as Self-Determination Theory and Behavioural Activation. The former emphasises autonomy, competence, and relatedness—factors supported in IDEA through personalised exercise prescriptions and group sessions— which can contribute to long-term adherence (273). Behavioural Activation, in turn, promotes engagement in meaningful activities, with supervision playing a role in maintaining motivation and participation (118). This suggests that personalised and supervised exercise interventions can enhance motivation and engagement while also fitting within the ICF framework's emphasis on activity and participation, further informing the need for tailored approaches in contemporary models of treatment.

The psychological component of the IDEA programme reflects an integrated approach. Grounded in CBT, it incorporates Behavioural Activation and Self-Determination Theory, , with an emphasis on autonomy, competence, and relatedness as key drivers of behavioural change. Additionally, self-compassion and values-based strategies were included to promote long-term engagement. By illustrating how psychological and physical components can complement each other, these results reinforce the relevance of holistic intervention models. However, the intervention's limited impact on physical health aspects suggests that while

mental health improvements can occur independently, targeted strategies may be needed to achieve sustained physical health benefits.

Practical implications

The findings from this research have practical applications across clinical and public health settings, offering insights for mental health professionals, physiotherapists, and other healthcare providers.

Clinical applications

Healthcare professionals, including mental health clinicians and physiotherapists, may consider integrating exercise-based interventions into routine care for individuals with transdiagnostic depressive symptoms. The IDEA programme, , as an adjunct to conventional treatments such as medication or psychotherapy, highlights the potential for a more holistic approach that considers both mental and physical health. In addition to the physiological benefits and improved sleep regulation that exercise naturally offers, may facilitate social interaction and peer support, which could enhance therapeutic outcomes.

This intervention also supports the potential of transdiagnostic approaches in addressing comorbidities, providing an alternative to disorder-specific treatments that primarily target a single diagnosis.

These results also underscore the role of physical health professionals, such as physiotherapists, kinesiologists, exercise physiologists, and specialists in Physical Medicine and Rehabilitation, in delivering structured exercise interventions for individuals with depressive symptoms. Within the IDEA programme, physiotherapists played a key role in leading group sessions, monitoring exercises, and ensuring participant safety through gradual progression and supervision. Their expertise allows for individualised adaptations based on physical health status, comorbid conditions, and exercise tolerance, ensuring both safety and feasibility in clinical applications. Unlike generalised exercise recommendations, a tailored approach guided by these professionals may optimise outcomes by addressing the unique needs of each participant.

This research supports the importance of a multidisciplinary team—combining mental health professionals with physical activity experts—in creating comprehensive, personalised

treatment plans that address both physical and psychological needs. Such collaboration optimises exercise-based interventions for safety, effectiveness, and sustained adherence. While physical health professionals are not typically primary providers in mental health care, their involvement supports a holistic approach, as exemplified by the IDEA trial, which tailored activities to individual abilities and preferences for a more integrated, impactful treatment experience. Therefore, establishing routine referral methods and providing individualised support for behavioural activation through physical activity can further enhance patient care, ensuring that a comprehensive approach to manage depressive symptoms and other mental health conditions.

Public health initiatives

Findings show the importance of integrating physical activity into mental health strategies, especially for populations struggling with depressive symptoms. Public health institutions could promote exercise-based programmes specifically designed for this population to enhance overall functioning, reduce symptoms, and improve well-being and quality of life, ultimately leading to better outcomes. This could be especially useful in community-based settings, where access to comprehensive mental health services may be limited, offering a more accessible and cost-effective intervention.

The IDEA programme stands out for its broad applicability, short duration, and low cost, making it more scalable and easier to implement than traditional psychotherapies. This is crucial for lower-income populations, like those in the Hospital del Mar area, where income is below the average. Designed for clarity and ease of use, the IDEA programme encourages adherence by minimising travel and accessibility barriers, making it a viable option for individuals with limited time and financial resources.

Group interventions, like the IDEA programme, can further optimise the use of available resources, especially in light of the high demands of primary healthcare and mental health services in Spain. Small group sessions promote patient integration, enable professionals to address individual needs, and offer an efficient alternative to traditional one-on-one therapies.

In line with this work, initiatives of other countries provide models for incorporating exercise into healthcare systems. For example, in Australia, ‘Lifestyle Clinics’ in hospitals involve exercise physiologists working alongside mental health professionals to prescribe

tailored exercise programmes. In the Netherlands, ‘Running Therapy’ has been developed as a specific exercise intervention for depression, offered by trained professionals.

Policy implications

One of the major challenges facing modern societies is to provide efficacious evidence-based mental health care. However, in the SNS, the estimated workforce of clinical psychologists is limited, with only around 2,600 to 2,800 psychologists, resulting in a ratio of about 5.58 per 100,000 inhabitants. (262). This indicates an urgent need for resources that can reduce the time psychologists spend with each patient without compromising treatment efficacy. The IDEA intervention has shown potential to meet this need.

In parallel, Spain is among the countries with the highest consumption of psychopharmacology in the world, particularly benzodiazepines, and the consumption of antidepressant drugs has increased by 208% between 2000 and 2020 (110). These alarming figures suggest that the current mental healthcare model may not be fully addressing patients' needs, signaling the necessity for change.

In the Hospital del Mar catchment area, where this research took place, the per capita household income is below the Barcelona average, with some neighbourhoods ranking among the lowest income areas (274). This further underscores the need for innovative solutions to improve access to treatments and promote multidisciplinary approaches in managing mental health conditions.

Currently, the mental healthcare model in Spain primarily focuses on specialised services, which may be well-suited for severe mental disorders. However, there is a rising prevalence of other mental disorders in their mild and moderate forms, such as depression, anxiety, and sleep disorders. These conditions could benefit more from highly accessible interventions. In terms of prevention, exercise-based interventions present a viable option. While these interventions may have smaller effect sizes compared to ‘gold standard’ treatments, their scalability and broad reach have the potential to create a greater overall public health impact (9).Implementing transdiagnostic group treatments like the IDEA programme on a larger scale could address these needs. Such approaches reduce training costs for therapists and increase access to evidence-based treatments, highlighting the importance of policy support for broader implementation.

With an aging population, along with high levels of obesity and sedentary behaviour across all age groups—especially among mental health service users—incorporating exercise programmes into healthcare services should be a strategic priority. However, not all forms of exercise are equally effective. Factors such as dosage, personalised prescriptions, and the level of supervision play a critical role in ensuring proper treatment outcomes. Therefore, it is essential to involve qualified professionals and to improve access to the necessary facilities and resources to implement these programmes effectively.

The current effort in Spain to incorporate exercise as a form of treatment for symptoms of depression reflects part of the wider trend toward more comprehensive and integrated approaches to mental health interventions. While increasingly recognised for its benefits, the extent and the way it is applied varies greatly between regions and healthcare providers. The main initiatives and approaches that have been introduced to integrate physical activity and exercise into healthcare services include the following: 1) National health guidelines established by Spanish health authorities incorporate physical activity as a component of depression management (275), 2) In primary care, general practitioners (GPs) are recommended to integrate exercise prescriptions into depression treatment regimens, with the government offering grants to provide training courses on 'exercise prescription' to healthcare staff, enabling tailored physical activity across regions (276), 3) Spain has established community-based initiatives such as walking groups, yoga classes, and collective exercise sessions aimed at individuals experiencing depression, 4) Public health campaigns raising awareness about the mental health benefits of exercise by educating the public on its role in managing depression, 5) Within the context of mental health services, some of them have included exercise in their treatment options, 6) The rise of digital health solutions such as apps and online platforms supports exercise as part of mental health care, and have the potential to offer routines, track progress, and motivation. While these strategies reflect progress in embracing evolving mental health treatments in Spain, they fall short of incorporating exercise as a routine treatment within healthcare services. Currently, the SNS lacks a formal referral system for exercise interventions for mental health patients, and exercise has yet to be systematically introduced as a treatment for depressive symptoms.

The mental health benefits of exercise are well-documented, yet its consistent integration into mental healthcare remains limited. Expanding national access to exercise-based interventions

through structured implementation and policy support could enhance their role in routine care. This presents an opportunity to develop policies that enable healthcare professionals to incorporate exercise prescriptions more systematically within mental health services.

Currently, no scientifically evaluated and pragmatic exercise and activity support programme for individuals with depressive symptoms is widely available within the SNS. The IDEA intervention demonstrated improvements in clinical and functional outcomes without requiring additional investment in staff, making it a feasible option within existing SNS services, particularly given ongoing resource constraints.

This brief intervention promotes a flexible approach that values incremental increases in physical activity as meaningful steps toward improved well-being. Rather than emphasizing high-intensity exercise as the goal, it encourages sustainable engagement by reinforcing that even small amounts of activity can be beneficial. A more inclusive and adaptable approach to promoting physical activity—both in clinical practice and policy—could support greater long-term adherence and accessibility for individuals with depressive symptoms (277).

The introduction of exercise-based interventions, such as the IDEA programme, into services as a treatment for depressive symptoms, needs to be accompanied by the implementation of supportive economic policies. For instance, in the UK, exercise has been integrated into services as a treatment for depression through exercise prescription schemes, where patients receive vouchers from their GP to use at local gyms or community centres (245). In Spain there has been a longstanding demand for applying a reduced Value Added Tax (VAT) rate on fitness centers and exercise services intended for both general and clinical population, as well as the deduction of expenses on physical activity in all Autonomous Communities on income tax returns to encourage the increase in physical activity.

5.5 Limitations

When interpreting the results of the studies in this thesis, it is important to consider the following limitations, both methodological and technical.

A key limitation of our systematic review is the exclusion of trials specifically addressing depressive symptoms in BD through exercise-based interventions, leaving gaps in understanding the impact of different BD polarities on functioning. Additionally, there is an underrepresentation of studies focused on somatic diseases compared to psychiatric conditions, which limits insights into exercise interventions across varied health contexts. Furthermore, only 8 of the 15 trials were registered, raising concerns about transparency and potential bias. Addressing these gaps, alongside reducing bias risks in RCTs, is essential for strengthening the evidence on exercise as a treatment for depressive symptoms.

Only 2 of the 15 trials in Study 1 focused primarily on functional outcomes, while the majority treated them as secondary objectives. This limited emphasis restricts comparisons with current results and hinders understanding of how exercise-based interventions have historically impacted these patients' daily lives beyond symptom reduction. Although this systematic review provides a comprehensive synthesis of the evidence, the heterogeneity in study designs, populations, and outcomes necessitated a narrative approach rather than a formal meta-analysis.

The IDEA trial addressed gaps in previous research by prioritising functional outcomes. While initially using the SF-36 as the primary outcome measure, it was later replaced with the FAST to improve sensitivity to functional changes. This adjustment resulted in the first 11 participants missing the FAST assessment and was reflected in the revised trial registration at ClinicalTrials.gov. While this change might appear as a limitation at first glance, it actually demonstrates the study's responsiveness and commitment to capturing meaningful outcomes. This adaptive approach, which could not have been ascertained in the systematic review, strengthened the main study's design and potential impact.

Although the IDEA intervention demonstrated some significant effects, the sample size was 29.65% smaller than planned, which may have reduced statistical power. It is possible that a larger sample size could have resulted in a statistically significant group-time interaction effect

on FAST total scores, warranting further investigation in future studies. This limitation was primarily due to COVID-19-related delays in recruitment and human resource constraints in the early stages of the research. Additional factors included overestimated recruitment targets, resource shortages that persisted for several years, and concurrent trials targeting the same population, which conflicted with routine clinical practice. Furthermore, the lack of funding for extended recruitment hindered progress. Despite these challenges, approximately 70.35% of the original target was achieved, which remains sufficient to meet the thesis' objectives without compromising publication potential. The heterogeneity of the sample may help mitigate these limitations, enhancing the applicability of the results to a broader population.

A further constraint in our main study arises from the inclusion of participants with adjustment disorders. These disorders often resolve naturally over time and are influenced by cultural factors, potentially confounding the effects of the exercise intervention. This could mean that some observed improvements in functioning may partly reflect the natural course of recovery rather than the specific impact of the intervention itself. Distinguishing between spontaneous recovery and intervention-related improvements can be challenging in such cases. If spontaneous recovery a major factor, we would expect the CG to improve on its own. However, the CG did not show significant within-group improvements at any time point. In addition, if spontaneous recovery were driving the results, both groups would have improved similarly, leading to non-significant between-group differences. Instead, the EG showed greater improvements, reinforcing the role of the intervention. This weakens the argument that the improvements in the EG were due to a natural symptom fluctuation rather than the intervention itself.

There is also a gender imbalance in the sample, with 71.9% of participants being women. While this reflects the real-world higher prevalence of depressive episodes in women, it may limit the generalizability of the findings to men, whose experiences with depressive symptoms may differ. This imbalance could have influenced the results related to functioning, as women may respond to exercise interventions differently than men. For example, hormonal differences, particularly in menopausal and postmenopausal women, could impact physical performance and functional outcomes.

In the same vein, some participants had a history of regular exercise prior to the study, which could act as a confounding factor. Although 85.7% of the sample reported no exercise at

baseline, those with prior exercise habits may have had higher baseline fitness levels, influencing their response to the intervention.

Lastly, despite strong participation rates and follow-up completion, session attendance data suggest that not all participants were fully engaged in the intervention. This variation in adherence highlights challenges in maintaining involvement over time, an area that needs future improvement. Overweight and obese participants, in particular, may have faced more barriers to consistent participation in physical activity, including discomfort or lack of motivation, which could have affected adherence to the exercise programme.

5.6 Future directions and challenges

Given the extensive data collection from participants in the IDEA RCT at multiple time points, several subanalyses are planned following the publication of the main results. For instance, adherence to physical activity and exercise among individuals with depressive symptoms is typically low, highlighting the critical role of motivation. Identifying individual barriers and motivations that align with a person's needs and interests can help them find meaning in the IDEA intervention. Personalising exercise interventions based on these factors makes the programme more tailored and impactful. Addressing barriers in a personalised context allows for practical solutions, while motivation should be directed towards achieving goals that are closely tied to the individual's daily life. In the IDEA study, this approach was already integrated by identifying participants' motivations and barriers, although this was not a focus of the current thesis. The next step will be to investigate whether having specific barriers or motivations influenced adherence to the programme and improved treatment outcomes. Future research should focus on conducting detailed subanalyses to determine if personalised motivation strategies were key to better engagement and sustained exercise adherence. Understanding how individualised motivation impacts adherence could not only improve exercise interventions for depressive symptoms, regardless of diagnosis, but also inform more targeted approaches in broader mental health treatments.

It would be valuable to explore whether sociodemographic, clinical, or health-related variables in the study act as confounding factors in the effect of the exercise-based treatment on the main and secondary outcomes. To assess this, multiple linear regression analyses could be conducted to examine the influence of these variables on improvements in functional status, depressive

symptoms, and well-being in the EG from baseline to the 36-week follow-up. The goal would be to develop a regression model that includes only those variables significantly contributing to improvements. This approach would reinforce the internal validity of the findings and demonstrate the robustness of both the RCT design and the analyses performed.

Conducting subanalyses of changes in sedentarism and physical activity levels post-intervention could enhance our understanding of its impacts on behavioural changes while helping to identify specific patterns and behaviours that the IDEA programme most effectively targets. Additionally, these analyses could serve as a foundation for larger studies. This insight is critical, as reducing sedentary time while increasing physical activity is essential for improving overall health outcomes, particularly in populations with depressive symptoms. Analysing how individuals shift from sedentary to more active lifestyles can lead to more personalised exercise prescriptions, enhancing adherence and contributing to sustained activity levels.

A key area for future research is establishing a clear and standardised definition of completion and engagement in the IDEA programme. As previously mentioned, session attendance averaged around 70%, with 25% of participants completing all six sessions; however, adherence extended beyond attendance. Future studies should consider defining completion as attending a specific proportion of sessions, such as setting a threshold (e.g., at least 75% or 4 out of 6 sessions), and/or fulfilling home exercise requirements. Additionally, engagement metrics could incorporate both participation in supervised sessions and adherence to unsupervised or home-based activities. These definitions would allow for better evaluation of the relationship between different levels of engagement and intervention outcomes, helping refine strategies to optimise adherence and maximise benefits.

Considering that most participants in our main study were women with a mean age of 51, subanalyses focused on menopausal women would be valuable. Menopause brings increased disease risk due to changes like higher fat mass, reduced lean mass, and lower bone density, raising the likelihood of conditions like osteoporosis (278). These physiological shifts also affect exercise responses. Research suggests that multicomponent exercise for postmenopausal women is most beneficial for maintaining muscle mass and bone density caused by hormonal changes (279). Therefore, the IDEA intervention may have unique benefits for this group compared to non-menopausal women.

Given the results of correlation analyses, analyses of mediation and moderation for sociodemographic and health-related factors would enhance the validity of findings and help to understand complex relationships between general functioning measures and physical performance in this population. Exploring the mediating effects of covariates can provide insights into the underlying mechanisms. Likewise, investigating whether the strength or direction of the relationship between functional status and physical performance varies by these covariates can reveal interactions. For instance, does the relationship between general functioning and physical performance differ significantly between younger and older individuals with transdiagnostic depressive symptoms or between those with different BMI levels? Understanding how these factors interact can help identify which groups may benefit more from specific interventions. Such analyses could uncover new research questions as well as have significant implications for clinical practice, leading to more personalised approaches in intervention strategies based on the potentially identified moderators and mediators.

Another area for future research is to explore the acceptability of the IDEA intervention, which involves assessing participants' reactions to the programme and determining which sessions were the most impactful and useful. Evaluating the perceived usefulness of the content can provide insights into which aspects of the intervention resonate most with participants. This ultra-brief programme that includes practical, personalised exercise sessions with clear and concise prescriptions has proven effective. Thus, it is likely that sessions focusing on exercise practice under the supervision of a physiotherapist were particularly key in delivering results. These sessions may have provided essential guidance and support, ensuring participants' safety and engagement. This suggests that while some sessions may hold more value than others, missed sessions have not significantly undermine the overall outcomes.

In addition to the planned subanalyses, future iterations of interventions like IDEA could expand on the existing maintenance strategies introduced in the final session of the programme. Although the IDEA intervention included a session on exercise maintenance, focusing on individual adherence strategies, the results suggest that the intervention's positive effects on general functioning diminished over time without ongoing support. This highlights an opportunity to integrate additional components, such as booster sessions and long-term follow-up plans, to reinforce adherence and motivation.

These booster sessions could provide a structured opportunity for participants to revisit and refine their adherence strategies, address new barriers, and stay engaged in physical activity. Similar to psychological therapies that emphasize future-oriented behavioural strategies (e.g., "becoming your own therapist") (280), a more intense maintenance plan could also empower participants to sustain exercise benefits independently (281,282). For instance, incorporating periodic peer support, reminders, or check-ins could foster accountability and engagement, ensuring that improvements in functional status, and mental health are maintained long after the formal intervention concludes. Such adaptations would build upon the existing foundation of the IDEA programme and potentially extend its long-term impact.

As a final point, testing the IDEA intervention on other populations would allow us to explore the underlying mechanisms of change across various contexts. This could lead to valuable insights into how different factors, such as or co-occurring conditions or sociodemographic factors, influence the efficacy of exercise-based programmes. For example, the strategies that resonate with younger populations may differ from those that are effective with older adults. Insights gained from these adaptations could enhance the intervention's effectiveness and appeal.

Chapter 6. Conclusions

Based on the findings from this work, the following conclusions are drawn:

1. Findings highlight the potential of exercise-based interventions to address functional impairment in individuals with transdiagnostic depressive symptoms —an important yet sometimes underexplored aspect of treatment. The IDEA intervention appeared to contribute to improvements in general functioning (FAST total scores), as indicated by significant between-group differences at all follow-up time points, which were not present at baseline. Further supporting this effect, within-group improvements in the EG were observed with the most pronounced effects occurring from baseline to week 12. Thus, there are multiple indicators that IDEA was beneficial in this regard. These findings provide preliminary evidence of effectiveness for general functioning, with the caveat that the non-significant interaction effect may be attributed to limited statistical power. Additionally, the results suggest that the intervention had a specific positive impact on social and recreational functioning (Leisure Time and Interpersonal Relationships subdomains).

2. The IDEA intervention had a positive impact on secondary outcomes, including improvements in mental health-related areas of functioning (SF-36) over time. In contrast, the lack of improvements in physical health-related aspects of functioning (e.g., SF-36 PCS and Physical Functioning) suggest that the intervention's impact on physical health may require additional support or longer follow-up.

3. The IDEA intervention led to significant and sustained reductions in depressive symptoms, with early improvements observed post-intervention, maintained at 12 weeks, and further increasing by week 36, reinforcing its clinical benefits. In contrast, well-being improvements appeared to emerge later, becoming significant at 36 weeks, without evidence of a group-time interaction effect.

4. Findings stress the complex relationship between functional impairment and physical health, with greater impairment correlating with poorer physical performance. This supports the need for integrated interventions addressing both aspects.

5. Targeted exercise-based interventions may enhance both functioning and mental health in individuals with transdiagnostic depressive symptoms. However, sociodemographic and health factors should be considered to maximise effectiveness.

6. The IDEA intervention reinforces the potential role of personalised exercise as a complement to standard care for depressive symptoms, regardless diagnosis, though further research with larger sample sizes is needed.

7. Further exploration and replication of these findings could inform the refinement of exercise-based interventions for clinical practice, the development of personalised treatment strategies, and the implementation of public health initiatives.

The collective findings support the integration of structured, personalised exercise-based interventions as a complementary approach to standard care for individuals with transdiagnostic depressive symptoms. Future research with larger sample sizes should validate these findings, optimise adherence, establish more conclusive evidence regarding the interaction effects, and evaluate scalability across diverse clinical and community settings.

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Appendix

Appendix A. Improving Depressive Symptoms through Personalised Exercise and Activation (IDEA): Study protocol for a randomised controlled trial

Reference: **García-Estela, A.**, Angarita-Osorio, N., Alonso, S., Polo, M., Roldán-Berengué, M., Messaggi-Sartor, M., Mur-Mila, E., Vargas-Puertolas, L., Pérez, V., Duarte, E. & Colom, F. (2021). Improving depressive symptoms through personalised exercise and activation (Idea): Study protocol for a randomised controlled trial. *International journal of environmental research and public health*, *18*(12), 6306.
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Study Protocol

Improving Depressive Symptoms through Personalised Exercise and Activation (IDEA): Study Protocol for a Randomised Controlled Trial

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Abstract: Individuals who suffer from depressive symptoms experience a substantial impact on psychosocial functioning, physical health, mortality, and quality of life. In the search for therapeutic strategies, exercise has been found to play a relevant part in its treatment. However, the promotion of exercise entails adherence difficulties that arose out of the tendency towards sedentarism led by symptomatology. Personalised exercise plans on top of usual care have the potential to enhance behavioural changes and mental health. The present study aims at evaluating the changes in functioning deriving from a blended intervention merging a psychological intervention with a personalised exercise programme based on medical assessment. We will conduct a three-arm randomised controlled trial in which 172 participants suffering from mild–moderate depressive symptoms will be allocated to Intervention A (personalised exercise group programme + app with motivational messages), B (personalised exercise group programme + app with no motivational messages) or control group (app with no motivational messages). Data regarding global functioning, well-being, symptoms, physical activity, and exercise capacity will be collected at baseline, 4, 12, and 36 weeks. The results of this trial will provide information about whether this physical activity support programme may be efficient for improving mental and physical health outcomes. Trial registration: ClinicalTrials.gov NCT04857944 (accessed on 15 April 2021). Registered April 2021.

Keywords: depressive symptoms; exercise; personalised medicine; blended intervention; transdisciplinary

1. Introduction

Major depressive disorder (MDD) was reported as the third leading cause of years lived with disability in the world and the third leading cause in the areas with the highest sociodemographic index by the Global Burden of Disease [1]. Individuals presenting

depressive symptomatology experience, regardless of their diagnoses, a significant impact on social and work functioning, physical health and mortality.

Moreover, despite the wide range of effective treatments licensed for depression, MDD is the first worldwide leading cause of impairment and it is globally suffered by over 300 million people [2]. This is partly due to undertreatment being the rule rather than the exception for depressed patients. In high-income countries, only one in five depressed individuals receives systematically minimally adequate treatment [3].

A symptom-based, dimensional view of mental health disorders has the practical advantage of genuinely respecting individual differences. By lacking rigid nosotaxis, professionals are free to enrich each patient clinical case description and their derived needs. One-size-fits-all categorical descriptions lead too often to guideline/algorithm diagnostic-driven therapeutic recommendations which most of the time may not cover patient needs and will not consider patient-already-existing capabilities. In other words, diagnostic-driven treatment algorithms too often become a Procrustes bed: nobody ever fits therapeutic recommendations, which usually end up becoming impractical.

Conversely, the very intrinsic nature of symptom-based approaches—per se respecting individual differences—enhances personalised medicine. The symptom-based mental-health paradigm becomes, by definition, transdiagnostic, a word that describes most daily clinical jobs. The path to precision medicine in mental health is being built and various transdiagnostic treatment programmes for affective disorders are being designed [4,5].

A solid body of scientific evidence supports the regular practise of exercise and validates the many benefits it brings for people with mental disorders, among which are the reductions of depressive symptoms, a positive anxiolytic effect and better quality of life [6]. In support of this, structured and limited in time exercise programmes are particularly recommended as treatments for people with mild to moderate depression or with persistent subthreshold depressive symptoms [7].

However, the effective promotion of this lifestyle entails a challenge, essentially due to adherence difficulties arising out of the tendency towards sedentarism usually led by symptomatology (apathy, fatigue, low motivation, anxiety, etc.). People with MDD engage in high levels of sedentary behaviour and low levels of physical activity [8], which are predictors of mortality. Moreover, higher levels of symptoms of anxiety are associated with higher levels of sedentary behaviour [9].

Here, special consideration must be given to what seems the most important factor associated with the performance of regular exercise among the population suffering from mood disorders: the delivery of advice or indications by health professionals [10]. Personalised medicine stresses a practical need for transdisciplinary effort.

Physical Medicine and Rehabilitation Therapy can have a positive impact on patients with depressive symptoms. Specialists in this field are uniquely positioned to evaluate a patient's current physical capabilities and limitations, design and discuss a personalised treatment plan and prescribe tailored exercise routines to effectively cope with depressive symptoms in a realistic approach.

Group exercise sessions have specifically shown great benefits [11], and beyond physiological changes and the regulation of sleep produced by physical activity per se, this modality represents added value as it boosts social contact, mirroring, interaction and facilitates the support of other people. Furthermore, the implementation of group interventions is proposed as an alternative to maximizing the optimisation of the use of available resources and services.

A multidisciplinary-based approach merging Physical Medicine and Rehabilitation care with psychological interventions focusing on needs and capabilities, and tailored exercise routines should have an impact on motivation to increase physical activity—including both aerobic and anaerobic exercises—and enhance behavioural changes towards a healthier lifestyle.

We hypothesized that participation in a brief app-blended group intervention promoting personalised exercise and activity, as an add-on to treatment-as-usual, will improve

functioning and well-being. Both efficacy measures would result in a lesser impact of depressive symptomatology in life.

The main objective of this research is to evaluate the changes in functioning deriving from a blended intervention merging psychological intervention aimed at increasing activity and exercise with a personalised exercise programme based on medical assessment on subjects suffering from mild to moderate depressive symptoms.

2. Materials and Methods

2.1. Study Design

We will conduct a 3-arm randomised controlled clinical trial in which 172 eligible participants will be allocated to one of the following conditions:

- Intervention A (N = 48): Personalised exercise group programme + smart band + IDEApp (Mass Factory Urban Accessible Mobility S.L, Barcelona, Spain) with motivational messages: After study entry and baseline assessments, subjects will attend the one-month IDEA group sessions aimed at promoting physical activity and exercise. Participants randomly assigned to this study arm will use the smart band and IDEApp with the motivation set enabled, allowing participants to receive the messages according to their compliance and adherence to the personalised prescriptions. After group sessions, study subjects will start receiving the messages in Week 4, and up until the end of the trial. Intervention A study subjects will be expected to continue using the smart band and IDEApp for 8 consecutive months.
- Intervention B (N = 48): Personalised exercise group programme + smart band + IDEApp without motivational messages: Subjects will follow the same procedure as Intervention A, with the difference that the IDEApp will have the motivation set disabled and therefore will not receive any messages regarding their compliance. After group sessions, study subjects will be expected to continue using the smart band and IDEApp for 8 consecutive months.
- Control Group (N = 76): smart band + IDEApp without motivational messages: After study entry and baseline assessments, all patients assigned to the control group will receive both the IDEApp and the smart band, but the motivation set will be disabled. Study subjects will be expected to use the smart band and IDEApp for 8 consecutive months.

All participants, regardless of their treatment condition, will be read a short text about the benefits of regular exercise on mood during the initial clinical interview, in order to make sure that they have listened to this unspecific advice at least once.

All participants will continue receiving naturalistic pharmacological and/or psychological treatment, without any research-related disruption. A schematic diagram including the schedule of enrolment, assessments, and visits for participants is available in Figure 1.

We hereby propose a seminal project on the efficacy of personalised exercise plans and psychological advice leading to a regular activity increase on top of the usual treatment regime of subjects presenting with depressive symptomatology: The IDEA (acronym standing for "Improving Depression through Exercise and Activity") programme. Moreover, the proposal also introduces the advantages of e-mental health to maximise the results. The inclusion of a digital platform app format as a mobile support 'companion' tool and a smart band in the project has the potential to prolong motivation and exercise performance and maintain the benefits in the long term. At the same time, it allows for a non-invasive and fine-tuning measuring of variables and changes related to the activity.

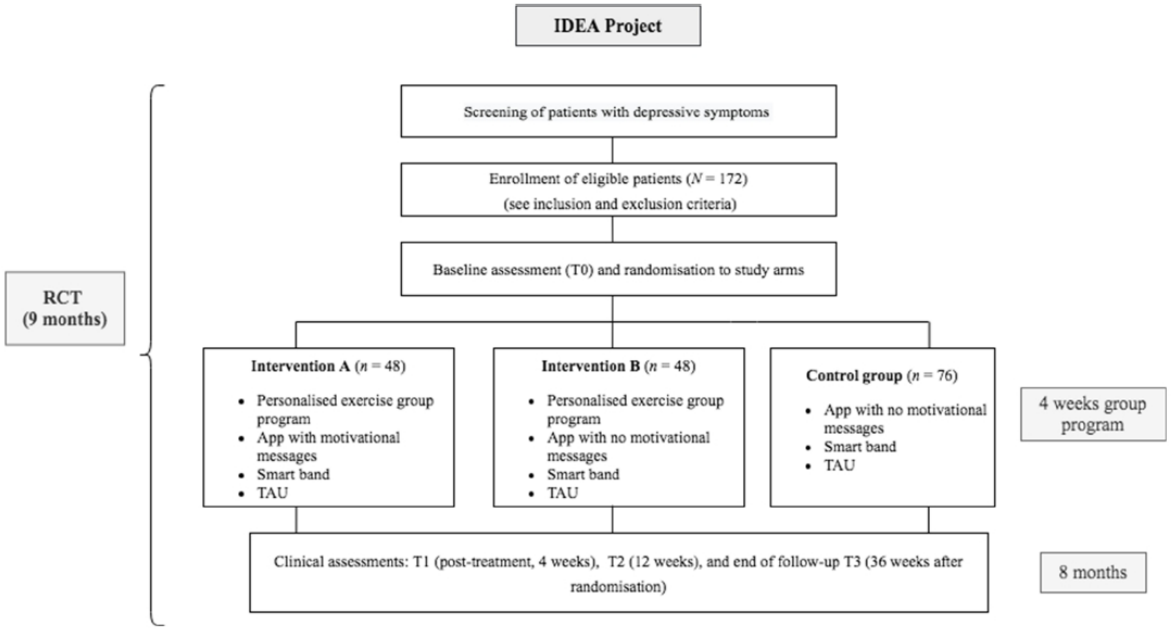

Figure 1. Flowchart of the IDEA Project. IDEA: Improving Depression through Exercise and Activity; RCT: randomised controlled trial; TAU = treatment as usual; T1 = 4-week assessment; T2 = 12-week assessment; T3 = 36-week final assessment.

2.2. Study Setting

The research setting will be outpatient mental health centres and General Practice surgeries belonging to the healthcare network of Parc de Salut Mar in Barcelona, Spain, which covers a catchment area of over 700,000 people for mental health. The available Gross Domestic Product of this area is below average when compared to other districts of Barcelona city. In addition, this area includes some of the neighbourhoods with the lowest incomes in the city [12].

2.3. Eligibility Criteria

All participants will meet the following inclusion criteria: aged 18–65 years, presenting mild to moderate depressive symptoms according to the Montgomery–Asberg Depression Rating Scale (MADRS score > 16 and <34), currently owning an Android-compatible smartphone, fluent in Spanish language, basic knowledge and skills using a smartphone, and able to provide written informed consent to participate. Potential participants will be excluded as per the following exclusion criteria: severe cognitive and/or physical impairment; cognitive deficit or developmental disorder; current psychotic, melancholic or catatonic futures; drug or alcohol dependence; modification of drug treatment (or its dose) in the last month; beginning of psychological treatment in the last month; beginning of biophysical treatment in the last month; BMI > 40; physical disability. Any general practitioner, nurse, psychologist or psychiatrist treating the patient will make the referral.

Group sessions will be facilitated by a psychologist (Psychology BSc, MSc) and a physiotherapist (Physiotherapy BSc, MSc) with accredited experience who will receive a brief therapy training.

Before any study procedures occur, participants will be informed about the study characteristics, they will be provided with a study information leaflet and a written informed consent form must be signed by them. After signing the informed consent, an experienced (more than five years of regular clinical practise since specialisation) clinical psychologist or a psychiatrist will confirm or disregard depressive symptomatology, administer the

MADRS and judge that the subjects fulfil all the inclusion criteria items and none of the exclusion criteria requirements.

2.4. Interventions

2.4.1. Intervention Description

The main goal of the intervention is to personalise exercise prescription and enhance motivation towards being physically active. To fulfil our objectives, a collaborative team of 4 psychologists, 2 Physical Medicine and Rehabilitation specialists (one medical doctor specialised in the field and one physiotherapist), and 1 psychiatrist designed a brief group intervention—the IDEA programme.

The programme will consist of six 90 min group sessions composed of four to six participants as working with small groups facilitates the patient's integration and allows professionals to better detect their needs. These short intervention sessions will be distributed in one month, with a frequency of once or twice a week depending on the week of the programme. Group sessions will take place in the therapy room of Centre Fòrum–Parc de Salut Mar, which provides rehabilitation, sociosanitary and mental health services. In the exercise-oriented sessions, participants will be asked to wear sports clothes to practise the individualised exercise prescription on-site and will receive an individual brochure with indications and photographs of their prescription.

For the implementation of the sessions, we created a guide for the professionals where the content of each session and its dynamics were outlined. In the case of the individualised exercise prescription, a pool of exercises was created in order to standardise the potential exercises that will be chosen individually for each participant. Table 1 presents an overview of the IDEA programme. Detailed information regarding the content of the group sessions is available in Table S1 as Supplementary Material.

Table 1. Description of the content of the IDEA group sessions.

Session
1 Depression and exercise
2 Motivation towards exercise
3 Introduction to the exercise prescription
4 Barriers to exercise
5 Review of the exercise on prescription
6 What now? Exercise maintenance

The exercise prescription will be personalised in terms of intensity and amount of time. Therefore, all participants will perform four types of exercise: stretching, aerobic, strength and relaxation. We have designed three types of programmes covering low, moderate and high intensity. Participants with higher levels of sedentarism will be prescribed 45 min sessions twice a week, while participants with lower levels will do 60 min sessions three times a week.

Participants will choose the type of aerobic exercise according to their preferences and possibilities (i.e., having easy access and knowing how to perform the exercise). Options can include—but are not limited to—walking, running, water aerobics, biking or dancing.

The intensity of the aerobic exercise will be based on the maximum age-related heart rate estimated by subtracting the age of participants from 220. All participants will receive instructions on how to keep track of their heart rate. In the low and moderate intensity programmes, participants should keep their heart rate between 45 and 54% of their maximum heart rate, while participants receiving the high-intensity programme should keep a heart between 70 and 89%. Further information regarding the personalised exercise prescription is detailed in Table S2 contained in the Supplementary Material.

As a result of the COVID-19 pandemic, we are currently facing many uncertainties around this rapidly evolving situation and the governmental measures responding to it. The IDEA trial will be conducted undertaking risk assessments and adapting trial processes

when necessary. The intervention will be delivered ensuring participants and professionals' safety by following the advice of local public health authorities (e.g., mandatory use of hygienic or surgical masks, participants will be encouraged to maintain physical distance, fitness material used will not be shared during group sessions and will be properly disinfected before and after the sessions, doors will remain open and alcohol-based hand rub will be at participants' disposal).

2.4.2. Application Development

Simultaneously, the same working group that designed the intervention designed the application describing the characteristics of an app meant both to store activity and sleep data and able to send motivational messages to the user whenever an activity decline or sleep problem was identified. The group designed the algorithms thought to classify adherence or lack of it regarding physiotherapist prescriptions. After putting the software development out to tender—a must, as the project is receiving public funding—the selected app developer software company (Mass Factory Urban Accessible Mobility S.L., Barcelona, Spain) was contacted and the team started a co-creative process including several software engineers and designers to create an ad-hoc-made app both to register and store the participants' physical activity, exercise compliance and sleep patterns and to send the already mentioned motivational messages when needed.

The result of this process was a user-friendly smartphone application—IDEApp—that can be synchronised to a smart band. The smart band will register, store data regarding physical activity (i.e., heart rate) and sleep patterns, as well as provide information about daily exercise practice. IDEApp will collect two types of data: objective and self-informed. Objective data will include the number of daily steps, aerobic exercise—including minutes, distance in metres, and maximum, minimum and average heart rate—and sleep structure, including duration in a 24-h period, and deep and light sleep discrimination. On the other hand, self-reported data will require participants to simply indicate on IDEApp whether they have performed one of three exercise options: (1) relaxation, (2) stretching, or (3) strength and endurance.

When non-compliance with the exercise prescription, physical activity decreases, or altered sleep patterns are detected, the system will trigger motivational or awareness messages through the app. The motivational messages were classified according to 12 potential situations following an algorithm based on the percentage of exercise prescription performed and the number of hours of sleep. A pool of more than 50 motivational messages was created for each category. Detailed information about the algorithm and type of messages is displayed in Table S3 presented in Supplementary Material. Accessibility options of IDEApp include features relating to language (Spanish or Catalan) and text size. Screenshots of IDEApp running can be found in Figure 2. Messages' function will be "on" for only one of the trial arms and "off" for the rest of subjects. The app was named "IDEApp" for obvious reasons.

2.4.3. Criteria for Discontinuing or Modifying Allocated Interventions

Participants may withdraw from the study for any reason at any time. The investigators also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures (i.e., health care providers notice a serious adverse event including hypomania or mixed features).

2.4.4. Strategies to Improve Adherence to Interventions

The inclusion of a mobile support tool (IDEApp) that delivers motivational messages and a smart band in the trial is not a core part of the intervention but, rather, a way to monitor activity and sleep patterns, and a strategy to improve adherence to the intervention, which has the potential to prolong motivation and exercise performance in the long term. All participants will benefit from monitoring their exercise physical activity and sleep patterns, regardless of their allocation to study condition. In addition, IDEApp will

deliver motivational messages to participants allocated to Intervention A when the smart band detects activity decrease, non-compliance with the exercise prescription or strange sleep patterns.

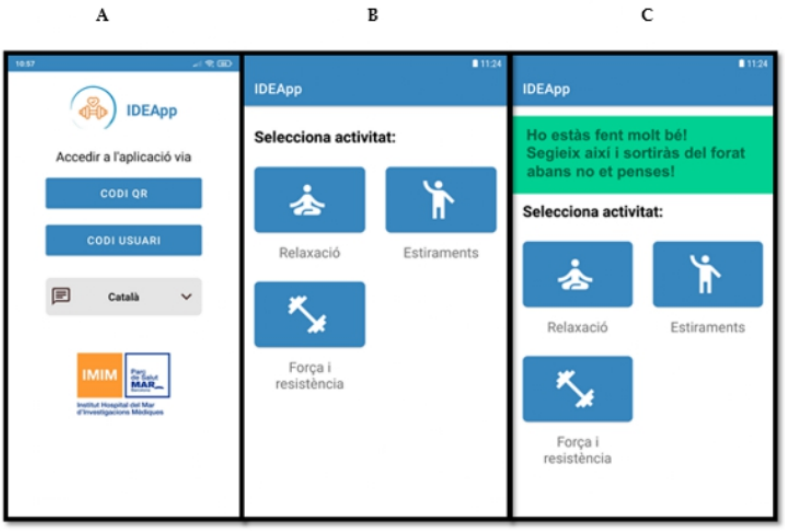

Figure 2. Screenshots of IDEApp running on a smartphone (messages in Catalan). (**A**)—login and register screen; (**B**)—home Screen without notification; (**C**)—home screen with motivational notification.

2.4.5. Relevant Concomitant Care Permitted or Prohibited during the Trial

This study seeks to investigate the effects of personalised exercise in addition to standard of care. It tests a trans-paradigmatic intervention that does not require therapist—or user—to strongly adhere to—or renounce—ideological models of mental health. It is fully compatible with other psychological therapies. All concomitant care and interventions are permitted if they were implemented more than a month before study entry.

2.5. Outcomes

2.5.1. Primary Outcome Measure

Given the great heterogeneity expected in the sample of patients, the intervention is aimed at improving global functioning in the first place. The functional impairment will be assessed using the 36-item Short-Form Health Survey (SF-36v2, Quality Metric Inc., Lincoln, NE, USA) [13,14]. As the main target of the trial is to learn about the efficacy of personalised exercise prescription, the main outcome comparison will be (Intervention A + Intervention B) vs. Control, being the comparison of A vs. B vs. C considered as secondary.

2.5.2. Secondary Outcome Measures

All the Secondary outcomes will compare both (A + B) vs. C and A vs. B vs. C.

- Depressive symptoms using the Patient Health Questionnaire (PHQ-9) [15,16].
- Well-being measured by the World Health Organization Well-Being Index (WHO-5 WBI) [17,18].
- Motivation for exercise using the Spanish validation of the Exercise Motivations Inventory (EMI-2) [19,20].
- To identify their physical needs and capabilities, we will measure:
- Current physical activity using the Simple Physical Activity Questionnaire (SIM-PAQ) [21].

- Functional exercise capacity using the 6 min walking test (6MWT) [22]. The change in the distance walked in the 6MWT after completion of the programme will be used to trace the natural history of change in exercise capacity over time. Before the test, a finger pulse oximeter will be attached to participants to record baseline and final heart rate and oxygen saturation. For the evaluation of perceived exertion, the short Borg CR 10 Scale [23] will be used before and after the test. This modified Borg scale has a score range from 0 to 10 and seems more appropriate than the longer Borg 15 Graded Category Scale, which requires a greater differentiation capacity. The Borg CR 10 Scale showed moderate reliability for patients with depressive and anxiety disorders [24].
- Functional exercise capacities using the 1 min sit-to-stand test [25].
- Isometric muscle strength of the hand and the forearm using the handgrip strength test [26]. The equipment used will be a digital hand dynamometer (JAMAR®, Nottinghamshire, UK) [27], and grip strength will be measured 3 times per hand in the 2-handle position.

For all the questionnaires, we will be using the validated versions in the Spanish language.

2.6. Sample Size

Initially, we computed a sample size of 152, given a power of 0.8, an alpha level of 0.05 and inferring functioning according to clinical remission data [28]. To our knowledge, functioning as a main outcome for physical exercise in depression has not set a precedent to guide our calculations. Thus, we computed a Cohen's d effect size of 0.5 to make estimations more reliable. An expected drop-out rate of 20% was set, which resulted according to the initial design in two arms of 76 subjects each. However, during the cocreative process of the intervention, it was discussed whether motivational messages of the app would mask the effect of the group sessions on the outcomes of the study. Therefore, it was decided to include a third study arm to assess the intervention without motivational elements triggered by the app. We increased the sample size by adding 20 participants, which will be distributed into the two experimental groups, leaving us with a sample size of 172.

2.7. Recruitment

The recruitment period will extend over 12 months and all participants will be given a smart band that will be free to use together with free access to the app after study completion.

The resources and strategies for identifying and recruiting potential subjects will include: (1) Sending a monthly newsletter to clinical staff in adult inpatient and outpatient wards to keep IDEA in mind. (2) Attending regular clinic meetings. (3) Posting leaflets or posters with a brief overview of IDEA in each clinic room at the trust. (4) Keeping in close contact with clinicians in the trust (outpatient, inpatient, and primary services) to make sure everyone has ongoing awareness and knowledge of the process. (5) Giving an incentive for trainee clinicians such as research 'tokens' for psychiatry training portfolio depending on the number of patients referred.

2.8. Assignment of Interventions: Allocation

During the baseline assessment, participants will be registered individually in the IDEApp web-based platform, which will randomly assign them to one of the three conditions while maintaining the following distribution:

- Intervention A: participants receiving the intervention and motivational messages (48 participants; 27.9% of the sample).
- Intervention B: participants receiving the intervention and no motivational messages (48 participants; 27.9% of the sample).
- Control group: using the smart band without motivational messages (76 participants; 44.2% of the sample).

When subjects enter the study, they will be allocated to whichever condition is furthest from the expected percentage of subjects allocated. This allocation system will allow us to guarantee that all groups will have an even distribution at baseline irrespective of the number of participants.

All participants will be identified with a computer-generated random number that will be paired with a 9-digit identification number.

2.9. Concealment Mechanism

Allocation will be concealed through the IDEApp web-based system and will be accessible only by request. In order to maintain allocation concealment, only one of the researchers in charge of the evaluation will be able to see the allocation placement. The allocation information will enlighten whether participants have been allocated to the control or intervention condition, but this study researcher will not know which of the experimental conditions (A or B) participants have been allocated to. The purpose of knowing the placement of participants is to inform them whether they must attend the IDEA group sessions or not.

2.10. Implementation

Allocation and intervention assignment will be automatically generated by the IDEApp web-based platform once participants are registered in the system by study staff. A study psychologist will enrol participants in the trial after baseline assessment.

2.11. Blinding

For logistics purposes, after assignment to study conditions, trial participants will know whether they have been allocated to experimental or control conditions, but the specific experimental intervention (A or B) will not be revealed. Unfortunately, it is hardly achievable to blind therapists and physiotherapists delivering the group sessions. Evaluators blind to treatment condition will carry out baseline assessments. To avoid assessment bias, an independent evaluator blinded to group allocation will complete follow-up assessments. Other care providers (i.e., clinicians), statisticians and principal investigators will be blind to randomisation procedure and group allocation.

Due to ethical considerations, the blinding process will be interrupted if a risk situation is detected during any phase of the study. In this case, the subject will be identified, and their clinician will be informed immediately. Cessation of participation will be discussed depending on the circumstances.

2.12. Data Collection and Management

2.12.1. Plans for Assessment and Collection of Outcomes

A trained psychologist (Psychology BSc, MSc) and a physiotherapist (Physiotherapy BSc, MSc) will carry out the assessments. Evaluation instruments have been described in the Outcomes section, and time points and assessment tools are outlined in Table 2.

Following referral, participants will attend the study entry clinical interview and baseline assessment, followed by an evaluation with a physiotherapist to identify their physical needs and capabilities. Such assessments will allow for the subsequent prescription of tailored exercise to the intervention groups. After baseline assessment, the study staff will install IDEApp on the smartphone of all participants and provide them with the smart band. Instructions on how to use both will be provided, alongside written information with basic information and contact information (e.g., help phone or email) where technical issues regarding device use will be resolved. In the first week after study entry, all subjects will effectively start using the devices and IDEApp, which will provide estimates of their baseline physical activity and exercise, and up until the end of the trial by implementing ecological momentary assessment methods (EMA). This monitoring system using a wearable band and a mobile phone-based EMA includes objective measures of physical activity and health variables, such as heart rate, walking and sleep patterns, and is intended to

be minimally invasive to the users and their mobile phone usage. The EMA methods are expected to provide with accurate data on activity changes that will allow for adapting motivational messages according to the activity states.

After completion of the group sessions (or after 1 month for Control Group), every participant will be followed-up for eight months. Post-allocation assessments following the intervention at 4 weeks (T1) and 12 weeks (T2) will be carried out by telephone in order to ease the burden of participants. These assessments will last 30 min and will be performed from the facilities of the Centre Fòrum in order to guarantee data safety. The final assessment at 36 weeks (T3) will be carried out face-to-face and will follow a similar outline as the baseline assessment, and again will be carried out by a psychologist and a physiotherapist.

Table 2. SPIRIT diagram of the IDEA trial.

	Study Period					
	Enrolment	**Allocation**	**Post-Allocation**			**Close-Out**
Time point	$-t_1$	t_0	4 Week group sessions	t_1	t_2	t_3
Enrolment:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Interventions:						
Intervention A			X	X	X	X
Intervention B			X	X	X	X
Control group				X	X	X
Assessments:						
Sociodemographic data		X				
Health habits and clinical data		X				
SF-36		X		X	X	X
WHO-5 WBI		X		X	X	X
PHQ-9		X		X	X	X
SIMPAQ		X		X	X	X
6 min walking test		X				X
1 min STS test		X				X
Hand grip strength test		X				X
EMI-2		X				
Activity and sleep monitoring		X	X	X	X	X
Delivery of motivational messages				X	X	X

SPIRIT = Standard Protocol items: Recommendations for Interventional Trials [29].; t_1 = pre-allocation; t_0 = baseline assessment; t_1 = post-allocation assessment at 4 weeks; t_2 = post-allocation assessment at 12 weeks; t_3 = final assessment at 36 weeks; SF-36 = 36-item short-form health survey; WHO-5 WBI = world health organization well-being index; PHQ-9 = patient health questionnaire; SIMPAQ = simple physical activity questionnaire; STS = sit-to-stand; EMI-2 = exercise motivations inventory.

2.12.2. Plans to Promote Participant Retention and Complete Follow-Up

The plans to promote participant retention and complete follow-up include: (1) delivering hand-outs with highlights at the end of each session; (2) contacting participants when no records of the smart band are detected by the IDEApp web-based platform; (3) contacting participants to remind them about the upcoming appointments and let them know what to expect from them and the estimated time frame; (4) availability and flexibility of study stuff to arrange assessment visits at convenient times; (5) developing good therapist–client alliance.

2.12.3. Data Management

Study data will be collected, entered, and managed using REDCap electronic data capture tools hosted at IMIM [30], which offer a free and secure method of robust data collection. More specifically, data will be collected offline in the REDCap mobile app on

an Android tablet and then will be sync back to the project on the REDCap server. A password system will be utilised to control access to data and the activity that researchers may undertake is regulated by the privileges associated with their user identification code.

Original study consent forms will be entered, stored in numerical order and kept on file in locked cabinets at the site for a period of 5 years after completion of the study. Access to the study files will be restricted.

2.12.4. Confidentiality

In order to ensure participants' confidentiality during the study and the transmission of personal data, we will set a security protocol in accordance with the local Spanish laws. A 9-digit identification number (IDN) will be generated for all the participants throughout all the phases of the study. The cross-reference of this identification number and the patient identity will be encrypted and stored in a database file kept in a computer without access to the Internet (neither by wire nor Wi-Fi). Patients will be identified by the IDN, and a random number assigned by the app, which will be the user code to access the application too. Study participants will be requested by a user or QR code when signing into the app. Personal information will not be collected by IDEApp.

All data collected by the smart band and IDEApp will be processed applying technical and organisational security measures established by the current legislation (Organic Law 3/2018, of 5th December, on Protection of Personal Data and guarantee of digital rights). The database will be stored in a physical server kept in the IMIM-Parc de Salut Mar facilities. This information will be used solely and exclusively to carry out analyses related to the objectives of the study and will be stored anonymously in a database during and after the trial.

3. Statistical Methods

3.1. Statistical Methods for Primary and Secondary Outcomes

Statistical analysis will be performed using the software SPSS Statistics 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics will be used to analyse the distribution of socio-demographic and clinical characteristics among groups at baseline. Continuous variables with a normal distribution will be analysed performing an ANOVA. Where the premises of normalcy are not met, the Wilcoxon test will be used. The differences between groups on the categorical and mail clinical variables will be evaluated by using a Chi-square test. Those variables that are statistically significant may be used as covariates for a logistic or linear regression study of the factors associated with the magnitude of the effect, and determine which variables are better predictors of functioning. The effect size index will be estimated in case of correlation indexes for each of the performed analyses. To analyse efficacy, we will perform intention to treat analysis. Analysis will be two-tailed and the significance set a $p < 0.05$.

3.2. Methods in Analysis to Handle Protocol Non-Adherence and Any Statistical Methods to Handle Missing Data

Last Observation Carried Forward analysis will be used to handle and minimise missing data on the clinical variables.

4. Ethics and Dissemination

All the procedures and assessments will follow the accordance of the 1964 Helsinki declaration and its following amendments (64th WMA General Assembly, Fortaleza, Brazil, October 2013). Before any procedure, all the participants will be informed about the study characteristics, and all will be provided with a study information leaflet and written informed consent will be signed. The project has been approved by the IMIM Drug Research Ethical Committee (2019/8816/I).

The study will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines [31] to describe, report and publish the results. The moment the trial is completed, results will be published in international peer-reviewed journals.

5. Trial Status

At the time of the elaboration of this manuscript, the development and testing phase of the IDEApp was finalised after being carried out intensively by three software engineers, three psychologists and one physical medicine specialist. Moreover, the test of the smart band was completed, as well as the co-creation of group contents. In order to be timely aware of improvable issues regarding the programme contents and duration, and to identify IDEApp mistakes and bugs, we are running a pilot with subjects who suffer depressive symptoms. Conclusions from this pilot will be used to fine-tune the programme final version and a "Work in progress" manual will be written to ensure research falsifiability.

6. Discussion and Conclusions

This project is subject to some limitations. First, participants who exercise regularly prior to the study inclusion may result in a confounding factor. Second, the physical assessment includes Body Mass Index as a measure of obesity to ensure that the morbidly obese are not put at risk by exercising. However, this does not exclude sarcopenic obesity, which includes normal weight, hence normal BMI but low muscle mass percentage. The usage of a body fat calliper and asking for a blood count looking for cholesterol levels would help make sure that people with sarcopenic obesity are not put at risk. Third, we assume that our sample will include subjects with adjustment disorders, including complicated grief where both time from the event and cultural issues play a sensible role regarding improvement. This may emerge as a confounding factor, and we should trust random assignment to handle it. Finally, introducing a new technology such as a wearable device can alter participants' default behaviour; thus, the measurements may not accurately reflect the activity that they would normally perform under non-experimental conditions.

On the other hand, we introduce novel highlights such as using a transdisciplinary approach, performing the recruitment based on symptoms; the inclusion of personalised medicine, guaranteeing that every participant will receive a tailored prescription of exercise; a transdisciplinary team, joining mental health professionals with physical medicine and rehabilitation specialists; the creation of a brief intervention, comprised of one month to promote adherence; a blended therapy, combining a group intervention with IDEApp and the use of a smart band and promoting a behavioural change that might last longer, and finally evaluating functionality outcomes, providing us with more reliable and ecological outcomes.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/ijerph18126306/s1, Table S1: Description of the IDEA group sessions, Table S2: Personalised exercise prescription programmes, Table S3: Algorithm and type of messages of IDEApp.

Author Contributions: Conceptualization, F.C., E.D.; methodology, F.C., E.D., A.G.-E., N.A.-O., S.A., M.M.-S.; writing—original draft preparation, A.G.-E., N.A.-O., S.A.; writing—review and editing, M.P., M.R.-B., E.M.-M., L.V.-P.; supervision, F.C., E.D., V.P.; funding acquisition, E.D., F.C. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study will be conducted according to the guidelines of the Declaration of Helsinki and was approved by the IMIM Drug Research Ethical Committee (Protocol code: 2019/8816/I and date of approval 12 April 2019).

Informed Consent Statement: Before any study procedures occur, informed consent will be obtained from all subjects involved in the study.

Data Availability Statement: Data sharing not applicable. No new data were created or analysed in this study. Data sharing is not applicable to this article.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the writing of the manuscript, or in the decision to publish the protocol.

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Appendix B. Evaluating the effect of exercise-based interventions on functioning in people with transdiagnostic depressive symptoms: A systematic review of randomised controlled trials

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Review Article

Evaluating the effect of exercise-based interventions on functioning in people with transdiagnostic depressive symptoms: A systematic review of randomised controlled trials

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ABSTRACT

Background: Depressive symptoms are associated with various conditions and can exacerbate the outcome of somatic diseases. Transdiagnostic symptom-based approaches provide treatment flexibility, and exercise has demonstrated benefits beyond clinical symptoms. This work aimed to synthesise and establish the effects of exercise-based interventions on global functioning and quality of life in adults with transdiagnostic depressive symptoms, as well as their impact on clinical symptoms.

Methods: A systematic review was conducted following PRISMA guidelines. PubMed, Scopus and PsycINFO databases were searched from inception to April 2023. Eligibility criteria included randomised controlled trials involving adults with transdiagnostic depressive symptoms who received exercise-based interventions and provided details of the interventions. Comparators included treatment as usual or other active control groups. The Cochrane quality assessment tool was used for quality assessment.

Results: Fifteen articles involving 2064 participants were included. Data on study design, sample, intervention characteristics, and outcomes were extracted. Several trials demonstrated the expected positive effects of exercise on functioning (7/15). Most results supported the benefits of adjunctive exercise interventions on illness outcomes.

Limitations: The studies had methodological limitations, including small sample sizes and an underrepresentation of somatic diseases.

Conclusions: The functional consequences of exercise-based interventions targeting depressive symptoms are often understudied. Incorporating exercise routinely as an add-on treatment for transdiagnostic depressive symptoms could improve overall functioning, quality of life, and symptom severity. There is a need to expand the focus of exercise-based interventions to incorporate functional outcomes. Future research should address the methodological limitations and include a wider range of participants, including those with somatic diseases.

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1. Background

Among mental disorders, depression has been associated with most disability-adjusted life years and depressive symptoms are a major contributor to worldwide disease burden with >264 million people affected (James et al., 2018). Even mild episodes can negatively affect quality of life and are associated with functional impairment, an increase in mortality and risk of worsening to severe depression and suicidal behaviour (Gotlib et al., 1995; Judd et al., 1997; Bachmann, 2018).

Depressive symptoms can be present in several disorders, conditions, and illnesses. In some of these, they play a primary role, constituting a more or less stable category of diagnosis known as depressive or affective disorders. However, "secondary" depressive symptomatology can be present in virtually every psychiatric disorder and may worsen the outcome of somatic diseases –from cardiovascular conditions to respiratory problems, from neurodegenerative disorders or Parkinson to cancer (Hirschfeld, 2001; Häfner et al., 2005; Riglin et al., 2021; Lai et al., 2015; Krishnan et al., 2002; Steffen et al., 2020; Krebber et al., 2014).

The prevalence of current depressive disorder has been estimated at 6.4 % of the population (Arias-de la Torre et al., 2021). Depressive disorders are particularly prevalent in primary care settings; about 3.2 % to 27.2 % of primary care outpatients are likely to meet the criteria for major depressive disorder (Craven and Bland, 2013; Mitchell et al., 2009). Beside the impact on people's well-being, depression also constitutes a substantial economic burden in Europe, being among the costliest of brain conditions (Gustavsson et al., 2011).

Also, individuals with bipolar disorder (BD) spend an average of 47.3 % of their time unwell long-term, whose symptomatic course is dominated by depressive symptoms and accounts for one-third of their lives (Judd et al., 2002; Judd et al., 2003).

All of the above are major psychiatric conditions in which depressive symptoms are a core and constitutional ingredient. The same applies to other less severe affective conditions such as adjustment disorder. Following with this chronic but mild-moderate depressive symptomatology, current classifications describe persistent depressive disorder, previously consolidated under the umbrella term dysthymic disorder (American Psychiatric Association, 2013), whose lifetime prevalence ranges between 3.3 and 15.2 % (Vandeleur et al., 2017). Individuals with persistent depressive disorder can experience significant job productivity loss and tend to have less stable work histories when compared with controls (Adler et al., 2004).

However, depressive symptoms are even more prevalent, and worsen the clinical and functional outcomes, when they are present as a secondary symptom to another major condition. Severity of depressive symptoms was strongly associated with having more medical conditions that worsen some conditions such as heart disease, migraine, and eyesight difficulties (Niles et al., 2015). A recent systematic review with >100,000 participants concluded that there is a strong -and bidirectional- relationship between depressive symptoms and unfavourable cardiovascular health (Ogunmoroti et al., 2022). Depressive symptoms are also more prevalent among people suffering epilepsy (Scott et al., 2020), Parkinson's disease -with up to one of three sufferers presenting depressive symptomatology as well (Reijnders et al., 2008), dementia (Savva et al., 2009) and cancer (Hartung et al., 2017). Moreover, participants underreporting depressive symptoms is one of the biggest issues researchers face when dealing with them (Tam et al., 2020).

Transdiagnostic symptom-based approaches study the underlying cognitive and behavioural processes and/or common maintaining mechanisms in different disorders and are often suggested as a solution to the limitations of disorder-specific treatments, providing more adaptable interventions. These transcend categorical models and seek integration with dimensions, which is the axis of the functional treatment approach. Furthermore, transdiagnostic approaches synthesise the underlying theoretical constructs and view cognitive and behavioural processes as a base and/or common maintenance for mental disorders. For example, the National Institute of Mental Health has shifted its interest towards Research Domain Criteria, assuming that mental health comprehension should be led by biology and symptoms and acknowledging that dimensions can occur across disorders (Cuthbert and Insel, 2013). This approach makes room for more flexibility regarding treatment options, as it does not target specific diagnoses and allows individual differences to be respected.

Despite the wide range of existing effective treatment options, there is a gap in access to mental health services (Thornicroft et al., 2017). Barriers including mental healthcare staff shortages, high out-of-pocket cost, and stigma (Clement et al., 2015; World Health Organization, 2022; National Alliance on Mental Illness, 2021) contribute to this gap. In the search for new therapeutic strategies, physical activity- any form of movement that requires energy expenditure- has a large and significant effect on depressed subjects' physical health, improving cardiorespiratory capacity and decreasing the risk of metabolic disorders (Schuch et al., 2016), which are substantially prevalent among them. Physical activity also modulates the body's response to stress and optimises its antioxidant capacity. Since the relationship between mood disorders and inflammation is well supported (Valkanova et al., 2013; Serafini et al., 2013), the anti-inflammatory effects of exercise may play a relevant role (Kucyi et al., 2010). In line with this, recent research suggested a link between physical activity and a higher risk of mental disorders such as depression and bipolar disorder (Firth et al., 2020).

Exercise- a subset of physical activity typically structured, planned, and repetitive - has proven to have a positive anxiolytic effect and may even reduce depressive symptoms and suicidal ideation (Vancampfort et al., 2018; Rosenbaum et al., 2014). Furthermore, exercise represents an outstanding opportunity for efficiently reducing the high incidence of cardio-metabolic health problems associated with depressive symptomatology, which is a leading contributor to the premature mortality gap in people with depression compared to the general population (Walker et al., 2015).

At the biological level, several studies have documented that moderate exercise programs positively influence mood by increasing levels of neurotransmitters, cortisol, beta-endorphins, and neurotrophic factors such as brain-derived neurotrophic factor (Phillips, 2017). Interaction between these mechanisms explains how exercise reduces symptoms of mood disorders and the recurrence rates, thereby improving the quality of life in patients (Melo et al., 2016). Even the effect of exercise has been suggested to be comparable to antidepressant medication and psychotherapy for mild to moderate depression, whereas for severe depression exercise seems to be a beneficial adjunctive therapy to treatment as usual (Knapen et al., 2015). Exercise is associated with a greater reduction in depression symptoms compared with no treatment, placebo, or active control interventions (Cooney et al., 2013). However, analysis of high-quality studies alone suggests only small benefits.

While symptom reduction is an important goal, it is equally crucial to examine whether treatment improvements translate into meaningful changes in an individual's daily functioning and quality of life, as mental health is not solely about symptom reduction but also encompasses broader aspects of life. Given the substantial effect that depressive symptoms have on function and their association with high levels of suffering, the need to entirely understand their impact and treatment effects on overall functioning - understood as the difficulties experienced in participating in and maintaining daily or social activities- is noteworthy (Greer et al., 2010). That is, are people who experience depressive symptoms more functionally capable after exercise-based treatment? This efficacy measure would result in a lesser impact of depressive symptomatology in life and reflects a more holistic approach to its treatment. Therefore, the present systematic review aims to synthesise the effect of exercise-based interventions on global functioning and quality of life in the adult population with transdiagnostic depressive symptoms. Secondarily, it will synthesise the impact of exercise on clinical symptoms.

2. Methods

We registered the review in PROSPERO (CRD42020186480) and followed the procedures outlined in the Preferred Reporting items for Systematic Reviews and Meta-Analysis guidelines (Page et al., 2021) (Appendix A).

2.1. Search strategy

We performed the literature search in PubMed, Scopus and PsycInfo for records from database inception through April 2023. We used the following query to conduct the search: (((depressive symptoms) OR (depression) OR (depressive disorders) OR (major depressive disorders)) AND ((exercise) OR (physical activity) OR (physical exercise)) AND (randomised controlled trial) AND ((therapy) OR (treatment))).

2.2. Eligibility criteria

We searched for randomised controlled trials focusing on exercise-based interventions for adults (aged ≥18 years) with depressive symptoms at study entry. Interventions included aerobic, anaerobic, or a combination of both activities in at least one study arm. Detailed information on activity type, intensity, duration, and frequency was required. Comparators included treatment as usual or any other active control group. Outcome measures of interest were quantitative data on psychosocial and occupational functioning, and/or quality of life. Additionally, we included depressive symptoms as a secondary outcome. Validated questionnaires were used to measure these outcomes. We excluded observational, qualitative, quasi-experimental, and single-case studies, as well as pilot or preliminary results, unpublished articles, and trials focusing solely on pharmacological treatment. We included original studies published in peer-reviewed journals in the following languages: English, Spanish, Catalan, French, Italian, Portuguese, and German.

2.3. Study selection and data extraction

Using the inclusion and exclusion criteria, two authors (A. G-E and N. A-O) independently screened titles and abstracts of potential studies. Relevant full-text articles were retrieved for further review and examined by the same authors. Discrepancies were resolved by consensus with a third researcher (M.C.H). Results were tracked using Mendeley Desktop reference management software (version 1.19.4, Elsevier) and imported into Rayyan (Ouzzani et al., 2016). For the selected studies, two reviewers (A. G-E and N. A-O) independently extracted relevant information, including sample characteristics, intervention details, comparator group, assessment instruments, and main findings.

2.4. Risk of bias

Two reviewers (A. G-E and N. A-O) independently assessed the risk of bias, with a third reviewer (J. M-S) resolving discrepancies. The Cochrane Collaboration's Risk of Bias Tool for randomised trials (Sterne et al., 2019) and the RoB2 Excel tool were used to evaluate methodological quality (see Figs. 2 and 3). The effect of the assignment to interventions was evaluated as the "intention-to-treat effect." Bias was categorised as "low" (−), "high" (+), or unclear (?) when details were insufficient.

3. Results

3.1. Results of the search

Out of 6024 records initially identified, 37 full articles were screened after removing duplicates. Among these, 22 articles were excluded due to reporting irrelevant outcomes (6 articles), not meeting eligibility criteria (4 articles), irrelevant study type (8 articles) or publication (3 articles), and 1 article with a duplicated sample. Ultimately, 15 studies were included in this review (Klein et al., 1984; Singh et al., 1997; Singh et al., 2005; Kerse et al., 2010; Callaghan et al., 2011; Mota-Pereira et al., 2011; Danielsson et al., 2014; Daley et al., 2015; Schuch et al., 2015; Huang et al., 2015; Pibernik-Okanović et al., 2015; Abrahão et al., 2016; Strid et al., 2016; Lok et al., 2017; De Groot et al., 2019). Fig. 1 shows the flowchart of the selection process.

3.2. Included studies

A total of 2064 participants were included in the studies, which were conducted in Australia (Singh et al., 2005), Brazil (Schuch et al., 2015; Abrahão et al., 2016), Croatia (Pibernik-Okanović et al., 2015), New Zealand (Kerse et al., 2010), Portugal (Mota-Pereira et al., 2011), Sweden (Danielsson et al., 2014; Strid et al., 2016), Taiwan (Huang et al., 2015), the United Kingdom (Callaghan et al., 2011; Daley et al., 2015), the USA (Klein et al., 1984; Singh et al., 1997; De Groot et al., 2019), and Turkey (Lok et al., 2017).

3.3. Design

All studies had a randomised controlled trial design. Among them, 46.7 % had two arms (Singh et al., 1997; Kerse et al., 2010; Callaghan et al., 2011; Mota-Pereira et al., 2011; Daley et al., 2015; Schuch et al., 2015; Lok et al., 2017), 46.7 % had three arms (Klein et al., 1984; Singh et al., 2005; Danielsson et al., 2014; Huang et al., 2015; Pibernik-Okanović et al., 2015; Abrahão et al., 2016; Strid et al., 2016), and 6.7 % had four arms (De Groot et al., 2019). The intervention designs varied, with the most common being exercise combined with treatment as usual versus treatment as usual alone (Singh et al., 2005; Daley et al., 2015; Schuch et al., 2015; Huang et al., 2015; Lok et al., 2017). The choice of 'active' comparator interventions also varied, with cognitive-behavioural therapy (CBT) and health/disease education being the most frequently selected (Singh et al., 1997; Huang et al., 2015; Pibernik-Okanović et al., 2015; Abrahão et al., 2016; Strid et al., 2016; De Groot et al., 2019). See Table 1 for details on the characteristics of the included studies.

3.4. Participants

Seven studies included participants from non-clinical settings (Klein et al., 1984; Singh et al., 1997; Singh et al., 2005; Danielsson et al., 2014; Schuch et al., 2015; Huang et al., 2015; De Groot et al., 2019), seven included participants from clinical settings (outpatients from mental health services, primary care, a diabetes clinic, and a rheumatology clinic) (Kerse et al., 2010; Callaghan et al., 2011; Mota-Pereira et al., 2011; Daley et al., 2015; Pibernik-Okanović et al., 2015; Abrahão et al., 2016; Strid et al., 2016), and one study included participants from a mixed setting (volunteers from a nursing home) (Lok et al., 2017).

All studies included participants with depressive symptoms, which were assessed using various instruments. The inclusion criteria varied across studies. For example, Klein et al. (1984) used Research Diagnostic Criteria (RDC) and the Symptom Checklist-90-Revised (SCL-90-R) for psychiatric outpatients. Callaghan et al. (2011) included participants receiving treatment for depression but did not employ symptom severity cut-points. Some studies relied on either DSM-IV, DSM-IV TR, or ICD-10 for Major Depressive Disorder (MDD) criteria (Mota-Pereira et al., 2011; Danielsson et al., 2014; Daley et al., 2015; De Groot et al., 2019) or risk of depression (Kerse et al., 2010). Other studies used instruments such as the Beck Depression Inventory (BDI) (Singh et al., 1997; Lok et al., 2017), the Geriatric Depression Scale (GDS) (Singh et al., 2005; Huang et al., 2015), the Patient Health Questionnaire (PHQ-9 and PHQ-2) (Pibernik-Okanović et al., 2015; Strid et al., 2016), and the Hamilton Scale for Depression (HAM-D) (Schuch et al., 2015), along with specific DSM-IV diagnostic criteria for MDD, minor depression, or dysthymia.

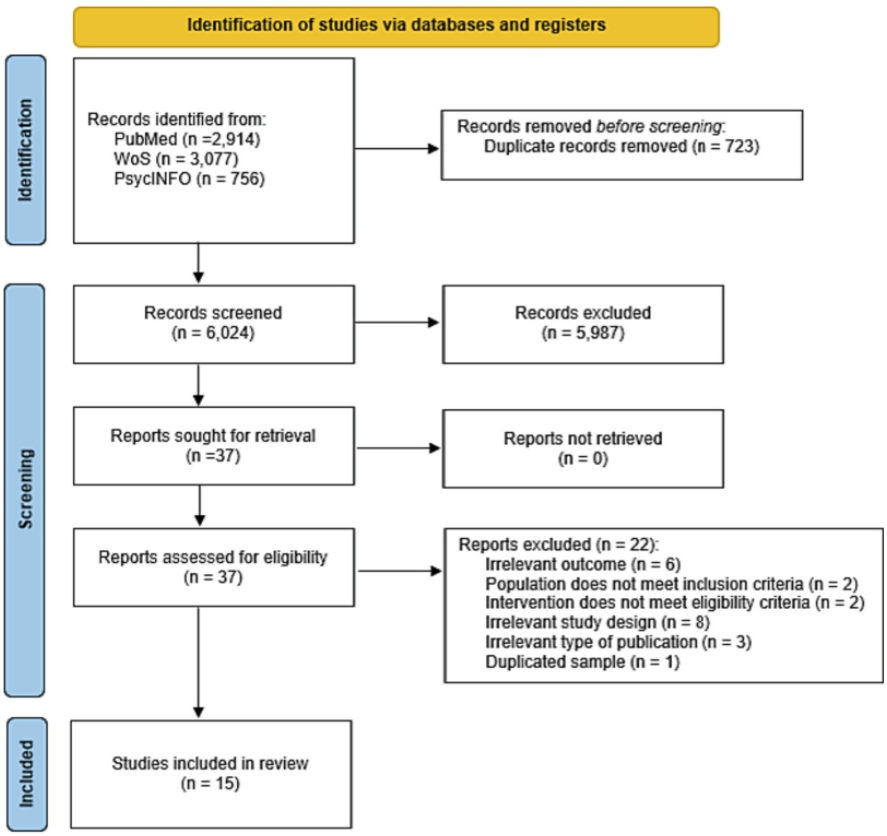

Fig. 1. Flow diagram describing the identification, selection, and the systematic review of the studies. The selection process followed the recommendations of the PRISMA.

Only one study did not employ screening measures for symptom severity or cut-off points (Abrahão et al., 2016).

The age of participants ranged from 30 to 81 years, with a majority being female (70.25 %) (see Table 2).

3.5. Interventions

The interventions lasted for an average of 11.6 weeks (2–26), with 3 sessions per week (2–5), each lasting between 30 and 90 min. One trial did not mention duration and only indicated that assessments were conducted at discharge (Schuch et al., 2015). Seven trials conducted group sessions (Singh et al., 1997; Singh et al., 2005; Callaghan et al., 2011; Huang et al., 2015; Pibernik-Okanović et al., 2015; Lok et al., 2017; De Groot et al., 2019), five conducted individual sessions (Klein et al., 1984; Kerse et al., 2010; Mota-Pereira et al., 2011; Daley et al., 2015; Schuch et al., 2015), two studies used a combination of group and individual consultations (Danielsson et al., 2014; Strid et al., 2016), and one trial did not specify the format (Abrahão et al., 2016).

The most common type of exercise was aerobic, which was provided in ten trials (Klein et al., 1984; Callaghan et al., 2011; Mota-Pereira et al., 2011; Danielsson et al., 2014; Daley et al., 2015; Schuch et al., 2015; Pibernik-Okanović et al., 2015; Strid et al., 2016; Lok et al., 2017; De Groot et al., 2019). Two trials focused on strength exercises (Singh et al., 1997; Singh et al., 2005), while two others offered a combination of aerobic and strength exercise (Kerse et al., 2010; Huang et al., 2015). In Abrahão et al. (2016), one group performed aerobic exercises, while another group completed strength exercises.

All trials considered participants' abilities, tolerance, or perceived exertion. However, the extent to which participants had control over the nature of the exercises varied. In six trials, the exercise modality and intensity were the same for all participants (Klein et al., 1984; Singh et al., 1997; Singh et al., 2005; Mota-Pereira et al., 2011; Huang et al., 2015; Lok et al., 2017). Four studies prescribed exercises based on personal preferences and individual conditions (Kerse et al., 2010; Callaghan et al., 2011; Daley et al., 2015; Schuch et al., 2015), and one study partially took them into account (Danielsson et al., 2014). In one trial, participants in the intervention group were randomised to different intensity levels, resulting in changes in exercise modalities (Strid et al., 2016).

Most studies conducted supervised onsite exercise sessions (Klein et al., 1984; Singh et al., 1997; Singh et al., 2005; Callaghan et al., 2011; Danielsson et al., 2014; Huang et al., 2015; Pibernik-Okanović et al., 2015; Abrahão et al., 2016; Strid et al., 2016; Lok et al., 2017), while four studies included both partially supervised sessions and unsupervised home-based exercises (Kerse et al., 2010; Mota-Pereira et al., 2011; Daley et al., 2015; De Groot et al., 2019). Thirteen trials specified the professionals responsible for supervised exercise programs, including exercise therapists (Callaghan et al., 2011; Danielsson et al., 2014), a trained nurse (Kerse et al., 2010), a physical activity facilitator (Daley et al., 2015), fitness instructors (Mota-Pereira et al., 2011; Huang et al., 2015; Pibernik-Okanović et al., 2015; Strid et al., 2016; De Groot et al., 2019), researchers (Singh et al., 1997; Schuch et al., 2015; Lok et al., 2017), and mental health professionals (Klein et al., 1984).

Table 1
Characteristics of the included studies.

Study	Intervention				
	Type	Setting and format	Length and frequency	Intensity	Comparator
Klein et al. (1984) (Klein et al., 1984)	Aerobic	Home-based and individual	12 w, 2 times/w, 45′ sessions	Tailored	1. Meditation 2. Interpersonal and cognitive therapy
Singh et al. (1997) (Singh et al., 1997)	Strength	Onsite and group	10 w, 3 times/w, 50′ sessions	Vigorous	Health education
Singh et al. (2005) (Singh et al., 2005)	Strength + TAU	Onsite and group	8 w, 3 times/w, sessions of 65'sessions	Arm 1: Vigorous Arm 2: Light	TAU
Kerse et al. (2010) (Kerse et al., 2010)	Aerobic, balance and strength + TAU	Home-based and individual	24 w, 3 times/w, at least 30′ sessions	Tailored	Social visits + TAU
Callaghan et al. (2011) (Callaghan et al., 2011)	Aerobic + Psychosocial support + TAU	Onsite and group	4 w, 3 times/w	Tailored	Prescribed exercise + Psychosocial support + TAU
Mota-Pereira et al. (2011) (Mota-Pereira et al., 2011)	Aerobic + Usual pharmacotherapy + Accelerometer	Home-based and individual	12 w, 5 times/w, 30–45′ sessions	Moderate	Usual pharmacotherapy + Accelerometer
Danielsson et al. (2014) (Danielsson et al., 2014)	Aerobic + Usual pharmacotherapy	Onsite and mixed	10 w, 2 times/w, 50–60′ sessions	Moderate/ vigorous	1. Body awareness + Usual pharmacotherapy 2. Advice + Usual pharmacotherapy
Daley et al. (2015) (Daley et al., 2015)	Aerobic + TAU	Home-based and individual	6 m, 3–5 times/w, final goal of 30′ sessions	Moderate	TAU
Schuch et al. (2015) (Schuch et al., 2015)	Aerobic + TAU	Onsite and individual	2 w, 3 times/w	Tailored	TAU
Huang et al. (2015) (Huang et al., 2015)	Aerobic and strength + TAU	Onsite and group	12 w, 3 times/w, 50′ sessions	Moderate	1. CBT + TAU 2. TAU
Pibernik-Okanović et al. (2015) (Pibernik-Okanović et al., 2015)	Strength + flexibility	Onsite and group	6w, once/w, 90′ sessions	Light/medium	1.Psychoeducation + diabetes TAU 2. Diabetes education + TAU
Abrahão et al. (2016) (Abrahão et al., 2016)	Arm 1: Aerobic + TAU Arm 2: Strength + TAU	Onsite and not reported	12 w, 3 times/w, 50′ sessions	Moderate/ vigorous	Lupus education + TAU
Strid et al. (REGASSA study, 2015–2016)* (Strid et al., 2016)	Aerobic, strength, or flexibility + Usual pharmacotherapy	Offsite and individual	12 w, 3 h/w, 60′ sessions	Low, moderate, or high	1. Internet-based CBT + Usual pharmacotherapy 2. TAU
Lok et al. (2017) (Lok et al., 2017)	Aerobic + TAU	Onsite and group	10 w, 4 times/w, 40′ sessions	Not reported	TAU
de Groot et al. (2019) (De Groot et al., 2019)	Aerobic + Usual pharmacotherapy	Offsite and group	12 w, 6 monitored sessions, final goal of 150′/w	Moderate	1. CBT + Usual pharmacotherapy 2. CBT + Exercise + Usual pharmacotherapy 3. TAU

CBT Cognitive-behavioural therapy, *HRR* heart rate reserve, *1RM* one-repetition maximum, *TAU* treatment as usual, *W* week(s).

3.6. Outcomes

There was heterogeneity in the instruments used to assess outcomes.

3.6.1. Assessment of functioning and quality of life

For the assessment of functioning, six studies used the 36-Item Short Form Health Survey (SF-36) (Klein et al., 1984; Singh et al., 1997; Singh et al., 2005; Kerse et al., 2010; Huang et al., 2015; Abrahão et al., 2016; Lok et al., 2017), while four studies used its 12-Item version (SF-12) (Callaghan et al., 2011; Daley et al., 2015; Pibernik-Okanović et al., 2015; De Groot et al., 2019). Two studies used the Global Assessment of Function (GAF) (Mota-Pereira et al., 2011; Danielsson et al., 2014). Other assessments included the Social Adjustment Self-Report Questionnaire (SAS) (Klein et al., 1984) and the Outcome Questionnaire-45 (OQ-45) (Strid et al., 2016).

Four trials conducted additional assessments on quality of life using the Quality of Life in Depression Scale (QLDS) (Callaghan et al., 2011), the EQ-5D (Daley et al., 2015), the WHOQOL-BREF (Schuch et al., 2015), and the Diabetes Quality of Life measure (DQOL) (De Groot et al., 2019).

3.6.2. Assessment of depression

Depression measures varied across studies. The most commonly used tools were the BDI and BDI-II (Singh et al., 1997; Callaghan et al., 2011; Mota-Pereira et al., 2011; Abrahão et al., 2016; Lok et al., 2017; De Groot et al., 2019), followed by the HDRS (Klein et al., 1984; Singh et al., 1997; Singh et al., 2005; Mota-Pereira et al., 2011; Schuch et al., 2015). Four studies reported scores on the GDS (Singh et al., 1997; Singh et al., 2005; Kerse et al., 2010; Huang et al., 2015). Danielsson et al. (2014) and the authors of the REGASSA study (Hallgren et al., 2015) reported Montgomery-Åsberg Depression Rating Scale MADRS scores. Additional scales included the Edinburgh Postnatal Depression Scale (EPDS) (Daley et al., 2015) and the Centre for Epidemiological Studies Depression Scale (CES-D) (Pibernik-Okanović et al., 2015).

3.6.3. Other outcomes

Twelve trials reported adherence to the exercise intervention, considering session attendance and/or completion of predefined goals. Klein et al. (1984) reported that 57 % of participants completed the intervention, without explicitly defining the term "completion". Similarly, one study labelled all exercise group participants as completers, but adherence characteristics and rates were not provided (Lok et al., 2017). Singh et al. (1997) reported a median adherence of 93 %, while Callaghan et al. (2011) focused on attendance and found rates of 66 %. In one trial, adherence rates to exercise sessions were 95 %–100 % for high intensity and 99–100 % for low intensity (Singh et al., 2005).

One study reported a 91 % adherence rate, calculated through accelerometer data, defined as completing at least 50 % of the walks per week during the program (Mota-Pereira et al., 2011). Kerse et al. (2010) measured adherence by recording exercise units and frequency. During the first 6 months, one-third of participants completed the recommended units at least 3 times weekly, two-thirds completed them at least twice a week. At 12 months, 55 % completed the recommended training at least twice a week, 25 % exercised at least 3 times a week, and one-

Table 2
Sample characteristics.

Study	Sample				Depressive symptoms screening	Functioning and/or Quality of life assessment
	N	Type	Mean age	% female		
Klein et al. (1984) (Klein et al., 1984) USA	74	Volunteers from community	30.02	71.62	> 60th percentile SCL-90-R score for psychiatric outpatients + RDC	SF-36, SAS
Singh et al. (1997) (Singh et al., 1997) USA	32	Volunteers from community	71.3	60.71	DSM-IV criteria for MDD, minor depression, or dysthymia + BDI score > 12	SF-36
Singh et al. (2005) (Singh et al., 2005) Australia	60	Volunteers from community	69	55	DSM-IV criteria for MDD, minor depression or dysthymia + GDS score ≥ 14	SF-36
Kerse et al. (2010) (Kerse et al., 2010) New Zealand	193	Outpatients from primary healthcare service	81	59	DSM-IV or ICD-10 for MDD or risk of depression + 3-question depression screen	SF-36
Callaghan et al. (2011) (Callaghan et al., 2011) UK	38	Outpatients from mental health service	53.7	100	Under monitoring or treatment for depression. No symptom severity assessment	SF-12, QLDS
Mota-Pereira et al. (2011) (Mota-Pereira et al., 2011) Portugal	33	Outpatients from mental health service	47.52	57.57	DSM-IV criteria for MDD for >9–15 months	GAF
Danielsson et al. (2014) (Danielsson et al., 2014) Sweden	62	Volunteers from community	45.4	77.4	DSM-IV criteria for MDD evaluated with the MINI	GAF
Daley et al. (2015) (Daley et al., 2015) UK	94	Outpatients from primary healthcare service	30.5	100	ICD-10 criteria for MDD	SF-12, EQ-5D
Schuch et al. (2015) (Schuch et al., 2015) Brazil	50	Inpatients from a hospital unit	40.3	74	DSM-IV criteria for MDD evaluated with the MINI + HAM-D score ≥ 25	WHOQOL-BREF
Huang et al. (2015) (Huang et al., 2015) Taiwan	57	Volunteers from community	76.53	52.6	GDS-15 with scores ≥5	SF-36
Pibernik-Okanović et al. (2015) (Pibernik-Okanović et al., 2015) Croatia	209	Outpatients from Diabetes clinic	58.1	54	Subsyndromal depression according to PHQ-2 + subjective need of professional help	SF-12
Abrahão et al. (2016) (Abrahão et al., 2016) Brazil	63	Outpatients from Rheumatology clinic	42.9	96.8	No symptom severity assessment	SF-36
Strid et al. (REGASSA study, 2015–2016) * (Strid et al., 2016) Sweden	879	Outpatients from primary healthcare service	43	73	PHQ-9 score ≥ 10 + interview using the MINI	OQ-45
Lok et al. (2017) (Lok et al., 2017) Turkey	80	Nursing home	Not reported	45	BDI score ≥ 10	SF-36
de Groot et al. (2019) (De Groot et al., 2019) USA	140	Volunteers from community	56	77	DSM-IV TR criteria for MDD	SF-12, DQOL

BDI Beck Depression Inventory, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders 4th edition, *DSM-IV TR* Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision, *GDS* Geriatric Depression Scale, *GDS-15* 15-item Geriatric Depression Scale, *HAM-D* Hamilton Depression Scale, *ICD-10* International Classification of Diseases-10, *MDD* Major depressive disorder, *MINI* Mini-International Neuropsychiatric Interview, *PHQ-2* Patient Health Questionnaire-2, *PHQ-9* Patient Health Questionnaire-9, *RDC* Research Diagnostic Criteria, *SCL-90-R* Symptom Checklist-90-Revised, *SF-36* 36-Item Short Form Health Survey, *SAS* Social Adjustment Self-Report Questionnaire, *SF-12* 12-Item Short Form Health Survey, *QLDS* Quality of Life in Depression Scale, *GAF* Global Assessment of Function, *EQ-5D* European Quality of Life 5 Dimensions, *WHOQOL-BREF* World Health Organization Quality of Life Brief Version, *OQ-45* Outcome Questionnaire-45, *DQOL* Diabetes Quality of Life.

third walked at least 3 times a week during the same period. Danielsson et al. (2014) defined adherence as attendance at >50 % of exercise sessions and not initiating another healthcare treatment, which was fulfilled by 85 % of participants.

In the REGASSA study (Strid et al., 2016; Hallgren et al., 2015), participants completed an average of one exercise session per week, resulting in a 33 % adherence rate. Schuch et al. (2015) reported that participants performed 90.72 % of exercise sessions overall.

Huang et al. (2015) found a decrease in exercise uptake over time after the initial prescription. Initially, all participants completed 100 % of the recommended exercise logs. However, adherence rates decreased to 63 % and 47 % at 3 and 6 months after the intervention, respectively. In contrast, Daley et al. (2015) reported that subjects completed 69.4 % of the recommended training logs and showed increased levels of exercise throughout the intervention, ranging from 161.1 to 245 min weekly by the end.

3.7. Adverse events

Few studies (Singh et al., 1997; Singh et al., 2005; Kerse et al., 2010; Danielsson et al., 2014) reported self-reported adverse events, which included musculoskeletal symptoms as the most common issue. Visits to health professionals and minor physical illnesses were also reported.

3.8. Costs

Detailed information concerning costs was not reported by any study.

3.9. Timing of outcome measures

All trials conducted baseline and end-of-intervention measurements. Three trials included long-term follow-up assessments, ranging from 1 to 9 months (Klein et al., 1984; Mota-Pereira et al., 2011; Strid et al., 2016).

3.10. Risk of bias in included studies

The quality and risk of bias varied among the studies, with risk classified from low to high. Only three studies (Kerse et al., 2010; Danielsson et al., 2014; Schuch et al., 2015) met the low-risk criteria for all factors, and one study (De Groot et al., 2019) had an overall low risk. Eight studies had some concerns (Singh et al., 1997; Singh et al., 2005; Callaghan et al., 2011; Mota-Pereira et al., 2011; Daley et al., 2015; Huang et al., 2015; Pibernik-Okanović et al., 2015; Abrahão et al., 2016), and three studies were deemed high risk (Klein et al., 1984; Strid et al., 2016; Lok et al., 2017). In addition, more than half of the included studies had small sample sizes, limiting results robustness.

Among studies with an overall assessment of "some concerns" or "high" risk of bias, reasons included a lack of information regarding the randomisation process (Klein et al., 1984; Singh et al., 1997; Callaghan et al., 2011; Mota-Pereira et al., 2011; Huang et al., 2015) or allocation concealment (Pibernik-Okanović et al., 2015; Lok et al., 2017), treatment of missing data (Klein et al., 1984; Strid et al., 2016), unblinded or half-blinded assessments (Klein et al., 1984; Singh et al., 1997; Mota-Pereira et al., 2011; Daley et al., 2015; Lok et al., 2017), and the inability to identify or confirm the pre-specified analysis plan due to lack of published protocols or trials registry (Klein et al., 1984; Singh et al., 1997; Singh et al., 2005; Mota-Pereira et al., 2011; Huang et al., 2015; Abrahão et al., 2016) or inconsistencies in the reported results (Strid et al., 2016; Lok et al., 2017).

Figs. 2 and 3 depict the summary and graphical representation of the risk of bias.

3.11. Primary outcome measures

3.11.1. General functioning

Most studies reported the effects of interventions on functioning, except for Schuch et al. (2015) who primarily focused on assessing depression and quality of life. Due to the diverse assessment methods used, changes were observed in various aspects depending on the specific instruments and study objectives. The Short Form Health Survey (SF-36 and SF-12) was frequently used by different authors to measure functioning, although some reported it a measure of quality of life. Since this questionnaire specifically evaluates health-related limitations, we categorised it as a measure of functioning and included the results originally reported as quality of life outcomes.

Seven studies reported significant improvements in functioning after exercise interventions. Singh et al. (1997) observed improved functioning measures, specifically in the subscales of Vitality ($p = .002$), Bodily Pain ($p = .001$), Role Emotional ($p = .02$), and Social Functioning ($p = .008$) compared to the control group.

In a subsequent study, Singh et al. (2005) examined the impact of different intensity levels on functioning. Across all groups, functioning improved in most SF-36 subdomains (p values ranging from <0.0001 to <0.04). The high intensity intervention showed superior improvement compared to the low intensity and usual care groups, specifically on the Vitality subscale ($p = .048$).

The exercise intervention conducted by Mota-Pereira et al. (2011) led to improved functioning compared to baseline values. Furthermore, at 8- and 12-week follow-ups, the exercise group demonstrated higher functioning parameters than the control group ($p = .006$). However, it is worth noting that participants in the exercise group had lower functioning scores than the control group at baseline ($p = .003$).

Abrahão et al. (2016) found significant improvements in functioning after cardiovascular training and resistance training interventions. These improvements were observed in all SF-36 subscales (except for Vitality in the cardiovascular training group) and were not present in the control group. Participants in the cardiovascular training group achieved significantly higher scores in the Role Physical and Vitality subscales compared to the other groups. Additionally, they had significantly higher values in the Role Emotional subscale compared to the resistance training group.

Huang et al. (2015) found that only the exercise group showed improved functioning ($p < .001$), with significantly higher SF-36 scores immediately after the intervention compared to baseline. This effect was not observed in participants who received CBT or TAU.

Strid et al. (2016) reported positive changes in psychological functioning. The exercise group achieved larger improvements than the control group ($p < .001$), as did the active comparator group (iCBT). Effect sizes favoured exercise ($d = 0.20$) and iCBT (Cohen's $d = 0.35$) compared to the control group.

Lok et al. (2017) found that exercise had a positive effect on functioning. In the intervention group, the SF-36 scores of the 8 subscales (Physical Health, Physical Role, Bodily Pain, General Health Perception, Vitality, Mental Health, Emotional Role, and Social Function) improved ($p < .05$). However, no significant difference was observed in the control group after the exercise program period. The two component summary scores reflecting physical and mental health were not presented.

Seven studies reported mixed results, with improvements observed in some areas but not all, following exercise interventions. Klein et al. (1984) compared exercise, meditation, and group therapy and found a reduction in social and leisure impairment among exercise ($p < .01$) and

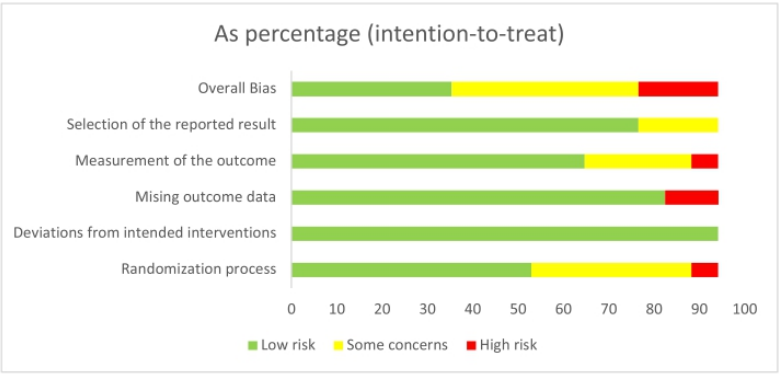

Fig. 2. Risk of bias graph for included studies displaying each domain presented as percentages.

Fig. 3. Tabular representation of risk of bias in individual studies.

meditation ($p < .05$) subjects after the intervention. However, significant improvement in overall social functioning was only observed among participants in the meditation group ($p < .01$).

Kerse et al. (2010) compared changes between groups at baseline and six months after the intervention but did not find a differential effect.

Danielsson et al. (2014) compared functioning among participants receiving aerobic exercise intervention, basic body awareness therapy (BBAT), or advice on physical activity. However, no differences were observed between the groups in global functional capacity.

In Daley et al.'s study (2015) the exercise-based intervention did not result in significant differences in the SF-12 total score, any of its domains, or in the component analyses at the 6-month follow-up: Physical Component ($p = .50$) and Mental Component summaries ($p = .11$).

Pibernik-Okanović et al. (2015) observed a significant improvement in diabetes-related distress and the mental health component score of the SF-12 for all patients at the 12-month follow-up ($F = 16.87$, $p < .001$, $\eta 2 = 0.09$; $F = 18.13$, $p < .001$, $\eta 2 = 0.09$). However, the Physical Component score did not change after any of the interventions ($p = .711$) and self-reported exercise increased in all groups ($F = 5.14$, $p = .008$, $\eta 2 = 0.03$). No significant differences were found between groups in any of the assessed domains after the 12-month follow-up.

De Groot et al. (2019) found partial evidence supporting a positive effect of exercise on functioning. The Physical Component score of the SF-12 was significantly higher at post-intervention in the exercise group ($p = .047$) and the exercise + CBT group ($p = .001$) compared to the TAU group. Patients who received only CBT did not differ in their health-related quality of life from the usual care group (Physical Component score: $p = .147$, Mental Component score: $p = .069$). However, there were no significant differences in the Mental Component score of the SF-12 for any of the groups compared to the usual care group (CBT group $p = .069$, CBT + exercise group $p = .270$, exercise group $p = .109$).

In a study by Callaghan et al. (2011), the change in functioning (mean SF-12 score) did not differ between the exercise intervention group with prescribed intensity and the group with preferred intensity ($p = .08$). However, participants who chose their intensity level had significantly increased General Health Questionnaire scores ($p = .001$). As both groups received an exercise intervention and no within-group statistical tests were conducted, it is unclear whether exercise led to an improvement in functioning or not.

Klein et al. (1984) observed effects on functioning at 9-month follow-up, specifically in the meditation group ($p < .01$). The improvement in social impairment seen post-treatment did not persist in the follow-up assessment. Treatment differences were more evident during follow-up, indicating that the effects of exercise and meditation treatments may be more enduring and general.

Kerse et al. (2010) found a significant decline in functional status for all patients ($p < .003$) over time. Nevertheless, both groups showed improvement in mental health ($p < .001$), and there were no changes in physical health for all participants ($p = .761$). No significant differences were observed between the groups ($p = .068$).

Daley et al. (2015) found no significant improvements in SF-12 domain scales, including Physical Component ($p = .77$) and Mental Component summary scores ($p = .64$), when comparing exercise and TAU at 12-month follow-up.

In the study by Huang et al. (2015), functioning did not significantly change from baseline at 3- and 6-months post-intervention for participants in the exercise, CBT, and TAU groups.

Strid et al. (2016) reported larger proportions of participants in the exercise and active comparator groups achieving recovery (OQ-45 score < 64) compared to the control condition ($p = .014$ and $p < .001$, respectively) at 12-month post-intervention, but no significant differences were found between the exercise and active comparator groups.

3.11.2. Quality of life

Callaghan et al. (2011) found significant improvements in the group that exercised in their preferred intensity measured with the Quality of Life in Depression Scale (QLDS) ($p = .0325$) compared with the pre-described intensity group after the interventions.

Daley et al. (2015) did not report significant differences between the exercise and TAU groups at 6- and 12-month follow-ups ($p = .12$ and $p = .22$ respectively), as measured with the EQ-5D instrument.

Schuch et al. (2015) assessed quality of life with the WHOQOL-BREF and described improvements in the physical and psychological domains of quality of life for exercise participants. In the physical domain, the difference between groups was greater at the second week assessment ($p = .002$) than at discharge ($p = .001$); conversely, this difference for the psychological domain was smaller at the second week ($p = .025$) than at discharge ($p = .01$).

De Groot et al. (2019) found significantly higher scores in the Diabetes Quality of Life Measure (DQOL) for both the exercise ($p = .001$) and exercise + CBT groups ($p < .001$) compared to TAU. There was no significant difference between the CBT-only group and TAU ($p = .061$).

3.12. Secondary outcome measure

3.12.1. Depressive symptoms

Most studies effectively reduced depressive symptoms. Post-treatment assessments showed that 9 out of 14 studies observed a reduction in depressive symptoms after exercise interventions. Singh et al. (1997) found that 59 % of the exercise group had a clinically meaningful response (50 % reduction in HRSD score) compared to 26 % of controls ($p = .067$). Depressive symptoms significantly decreased after the intervention in the exercise group, with a 2–3 times greater improvement compared to controls. Intensity of training was identified as an independent predictor of depression score reduction ($p = .0002$).

In a subsequent study, Singh et al. (2005) observed that over 60 % of participants in the high-intensity exercise group achieved a clinically meaningful response, compared to nearly 30 % in the low-intensity and over 20 % in the control group ($p = .03$). Higher intensity exercise led to the greatest improvement ($p < .006$), indicating that high-intensity training was the most effective treatment.

After a 6-month follow-up, Kerse et al. (2010) reported a decrease in depression scores for all participants compared to baseline ($p < .001$). However, the exercise intervention did not significantly reduce depressive symptoms more than social visits ($p = .916$).

One trial (Mota-Pereira et al., 2011) reported an improvement in all depression parameters for the exercise group compared to baseline ($p < .05$). A post-treatment comparison between the exercise and control groups showed significantly lower scores in HDRS ($p = .014$), BDI ($p = .016$), and CGI-S ($p = .033$) for the exercise group. However, participants in the exercise group had greater depression severity than the control group at baseline ($p < .05$).

Callaghan et al. (2011) found that participants in the exercise of preferred intensity group had lower depression scores ($p = .006$) compared to the exercise 'as usual' group.

Danielsson et al. (2014) observed improvements in symptom scores for the exercise group ($p = .038$). Additionally, the exercise group showed a significant improvement compared to the advice group ($p = .048$), and self-rated depression outcomes favoured exercise ($p = .036$).

Daley et al. (2015) found that the exercise-based intervention resulted in lower depression scores compared to TAU, but the difference between the groups was not significant ($p = .053$) until adjusted for baseline EPDS score and demographic variables ($p = .03$). The intervention led to a higher proportion of recovered participants (46.5 % vs. 23.8 %) when defined as a ≥ 4 points reduction and < 13 score in EPDS.

Huang et al. (2015) observed a reduction in depressive symptoms for all groups post-treatment, with 57.9 % of subjects in the exercise group, 61.1 % in the CBT group, and 30.0 % in the control group showing no longer depressive symptoms. However, the exercise group did not show significant superiority over the control or CBT group.

Pibernik-Okanović et al. (2015) reported a significant reduction in depressive symptoms post-treatment across all intervention groups (exercise, psychoeducation, and diabetes education), but no significant differences were found between the groups.

Schuch et al. (2015) found significantly lower depression scores in the exercise group compared to usual care after the intervention ($p = .005$). However, there were no significant differences in remission ($p = .248$) or response rates ($p = .114$) between the groups at post-treatment.

In the REGASSA study (Strid et al., 2016), both the exercise and active comparator groups showed larger improvements in depressive symptoms compared to controls ($p < .001$), with clinically significant improvements in all three treatment groups from baseline to post-treatment. The treatment effect of exercise and iCBT was similar. Stratified analysis by age favoured exercise and iCBT ($p < .001$), except among younger participants (aged 18–34 years) where the group differences were not statistically significant ($p = .40$).

Lok et al. (2017) found that the exercise group showed a significant decrease in BDI scores after the intervention compared to controls ($p = .005$).

De Groot et al. (2019) reported a significant reduction in BDI-II depression scores after all three interventions compared to usual care (exercise group: $p = .021$, CBT + exercise group: $p < .001$, CBT: $p = .011$). Post-treatment, remission rates varied from 72 % in the exercise group, 71 % in the CBT + exercise group, 66 % in the CBT group, and 32 % in the usual care group. Participants in the intervention groups also reported greater improvement in negative automatic thoughts compared to the TAU group (exercise $p = .006$, exercise + CBT $p = .010$, CBT $p = .018$).

In contrast, Abrahão et al. (2016) found no positive influence on depression for either the cardiovascular or resistance training intervention. BDI scores did not change over time and did not significantly differ between the exercise and control groups after the intervention.

In the long-term follow-up assessment, Daley et al. (2015) found no significant differences in depression scores between participants who received the 6-month exercise intervention and those treated as usual.

Huang et al. (2015) reported decreased depression scores in the exercise group compared to baseline at post-treatment ($p = .003$), 3-month ($p = .012$), and 6-month follow-up ($p = .037$). Both the CBT and exercise groups had fewer participants with depressive symptoms than the control group at the 6-month follow-up. While the decrease in GDS scores immediately after treatment was non-significant between the exercise and CBT groups, the effect of exercise lasted longer as the CBT group did not show significantly decreased symptoms at 3 or 6-month follow-up.

After a 12-month follow-up, Kerse et al. (2010) found no differences between groups regarding depressive symptoms ($p = .269$). However, the number of participants with GDS-15 scores suggesting depression (>4) decreased from 29 % to 18 % ($p = .015$).

4. Discussion

In this systematic review, we found that the success of exercise-based interventions on functioning in people with transdiagnostic depressive symptoms when compared with any other active control group or TAU depends on factors such as baseline functional status, intervention intensity, supervision during exercise, and delivery method (15 trials, 2064 participants). Some trials demonstrated the expected beneficial effects of exercise on functioning (7/15) (Singh et al., 1997; Singh et al., 2005; Mota-Pereira et al., 2011; Huang et al., 2015; Abrahão et al., 2016; Strid et al., 2016; Lok et al., 2017).

Recently, there has been a surge in reviews examining the effects of exercise interventions on depressive symptoms. Over 80 reviews in the past five years have evaluated different forms of exercise in randomised clinical trials for their effectiveness in treating depressive symptoms. However, most of these reviews primarily focused on standard clinical measures, with only a few assessing functioning parameters as primary outcomes. In fact, <5 % of the clinical trials measure and report functional outcomes (McKnight and Kashdan, 2009).

Long-term studies on the impact of exercise-based interventions on functioning were limited in this review. None of the included trials assessed outcomes beyond 9 months after the interventions. Only five trials examined long-term follow-up changes (Klein et al., 1984; Kerse et al., 2010; Daley et al., 2015; Huang et al., 2015; Strid et al., 2016), indicating that the benefits may be relatively short-lived. Among these trials, no significant differences were found between exercise and comparator groups. However, one trial indicated that both exercise (various modalities and intensities) and iCBT were more effective than TAU in reducing psychological functioning impairment during long-term follow-up (Strid et al., 2016).

Most studies support the benefits of adjunctive exercise interventions on illness outcomes, despite variations in intervention format, duration,

settings, comparison groups, and participant conditions. The interventions that showed the most significant improvement in functioning lasted 8–12 weeks, with frequencies ranging from 3 h to four days per week. Though it is challenging to establish a generic prescription due to the unclear dose-response relationship between activity and depression, even minimal physical activity below major public health recommendations build up on its benefits (Pearce et al., 2022). Similar to this study, other research has also noted substantial heterogeneity in prescriptions (Xie et al., 2021), making it difficult to determine the "ideal treatment" dose.

The ideal dose of physical activity remains uncertain due to high variability among studies. Recent data (Pearce et al., 2022; Hallgren et al., 2016) suggest that even small amounts of physical activity can benefit mental health, with the greatest impact observed when transitioning from inactivity to any level of activity. Additionally, a cohort study revealed that reducing time spent in moderate and vigorous physical activity negatively affects cognitive scores, implying that every minute of exercise provides benefits (Mitchell et al., 1978). While moderate exercise can be recommended with the principle of "the more, the better," it is important to consider a values-based approach to behavioural activation, encouraging individuals to engage in meaningful behaviours that promote long-term adherence to both physical and mental activities.

Adherence to exercise-based interventions is a major challenge. Tailoring exercise prescriptions to individual needs, abilities, limitations, and preferences is crucial (Knapen et al., 2015). Mental health benefits have been observed even below public health recommendations (Pearce et al., 2022). Delivery of interventions by qualified professionals, such as physiotherapists or physiatrists, enhances benefits and adherence (Stubbs et al., 2016). Inclusion of specialists enables adaptation of interventions to individual preferences, goals, and abilities, increasing adherence and maintenance of exercise (Firth et al., 2019). Multidisciplinary teams can provide clearer advice and training. Personalisation can be achieved by offering participants options for activity selection and recommending exercise plans based on their abilities and limitations, as suggested in the IDEA ongoing trial (García-Estela et al., 2021).

Functional assessment tools often overlap with indicators of quality of life, creating confusion and ambiguity in their conceptualisation. Both terms are frequently blended or interchanged with one another. The term "quality of life" is subjective and multidimensional, influenced by personal, social, and cultural factors (World Health Organization, 1996). Overall functioning encompasses physiological functions, activities, participation, and environmental factors. Some measurement tools provide dual outcomes, which is acceptable when outcomes belong to different domains. However, overlapping outcomes in quality of life and functioning domains can be problematic. This review identified studies (Singh et al., 1997; Singh et al., 2005; Kerse et al., 2010; Callaghan et al., 2011; Huang et al., 2015; Pibernik-Okanović et al., 2015; Abrahão et al., 2016) that reported quality of life outcomes using overall functioning measures, highlighting the conceptualisation gap.

4.1. Strengths and limitations

This review assesses exercise-based treatments for transdiagnostic depressive symptoms, focusing on improving functional outcomes/quality of life as the primary outcome. The included studies encompassed a range of symptom severities, including minor and major depression as well as subclinical symptomatology (Singh et al., 2005; Pibernik-Okanović et al., 2015). Although the sample heterogeneity might appear inconsistent, it enhances external validity as comorbid depressive symptoms are prevalent in a plethora of diseases.

Functional outcomes are crucial for assessing treatment response and understanding the impact of depressive symptoms. However, this review highlights that general functional outcomes are rarely used as primary measures in the treatment of depressive symptoms, with only two trials including them as such (Kerse et al., 2010; Abrahão et al., 2016). In most studies, functional outcomes are designated as secondary measures, potentially indicating inadequate statistical power to determine their effect size.

One limitation of this review is that it did not include trials of exercise-based interventions specifically targeting depressive symptoms in bipolar disorder. The available evidence does not differentiate between the impact of each polarity of bipolar disorder on functioning, which hinders a comprehensive understanding of the effect of exercise-based treatments on functioning outcomes. Additionally, there was an underrepresentation of studies focusing on somatic diseases compared to psychiatric illnesses. Overcoming these limitations is important for addressing functioning concerns in bipolar depression and expanding research on exercise interventions in somatic diseases.

Also, the selected studies in this review included adult and older adult populations, excluding children and youth due to not meeting the search criteria.

Unfortunately, the included articles did not systematically report side effects of exercise-based prescriptions using treatment-related side effects inventories. Therefore, there is a lack of evidence-based information on potential long-term problems associated with exercise in treating depressive symptoms. Future exercise-controlled trials should prioritise the estimation of side effects to address this gap.

Finally, a significant number (7/15) of the trials included in this review were not registered at their inception or retrospectively. This lack of transparency and incomplete reporting of the evidence raises concerns regarding bias and the authors' perception of physical exercise as a valid treatment for depressive symptoms. It is important to address this issue and ensure unbiased reporting in future studies.

5. Conclusions

Including exercise as a routine add-on treatment for individuals with transdiagnostic depressive symptoms, including subthreshold cases, can improve functioning/quality of life and symptom severity. Given the extensive evidence supporting the physical health benefits of exercise, it should be considered standard clinical practice to recommend exercise. To enhance effectiveness and adherence, two strategies should be considered: 1) evaluate individuals' abilities, limitations, and needs to create personalised exercise prescriptions with the help of qualified professionals, and 2) consider individuals' preferences and explore meaningful activities when designing exercise-based treatment plans. Even small doses of physical activity can have mental health benefits, particularly for those who have not previously engaged in exercise. However, the functional consequences of exercise-based treatments for depressive symptoms are often understudied, and existing RCTs have important methodological limitations. It is crucial for both researchers and healthcare professionals to expand their focus to include the functional outcomes of exercise interventions. Lastly, the development of exercise-based treatments that specifically target improvements in functional impairment is warranted.

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CRediT authorship contribution statement

Aitana García-Estela: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Natalia Angarita-Osorio:** Data curation, Formal analysis, Methodology, Resources, Writing – original draft, Writing – review & editing. **Marlene Charlotte Holzhausen:** Data curation, Methodology. **Javier Mora-Salgueiro:** Formal analysis. **Víctor Pérez:** Supervision, Validation. **Esther Duarte:** Resources, Validation. **Guy Faulkner:** Supervision, Validation, Visualization. **Francesc Colom:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

Availability of data and material

The data are available from the corresponding author upon reasonable request (e.g., wanting to reproduce the review, data validation, or addressing limitations).

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Appendix. Supplementary data

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Appendix C. Prescription for participants in the IDEA study

PRESCRIPCIÓN PARA PARTICIPANTES ESTUDIO IDEA

1. RECOMENDACIONES GENERALES SOBRE ACTIVIDAD FÍSICA

- Utiliza varios momentos del día para moverte: estiramientos, tareas de limpieza del hogar, ordenar armarios.
- No permanezcas más de dos horas seguidas sentado/a.
- Al salir a la calle, siempre que sea posible, utiliza medios de movilidad activos (por ejemplo, caminar, bicicleta) y las escaleras en lugar del ascensor.
- Sustituye el transporte motorizado (coche, autobús, metro) por transporte activo (por ejemplo, caminar, bicicleta).
- Limita el "tiempo delante de la pantalla" (televisión, ordenador, teléfonos móviles, tabletas, consolas de videojuegos, etc.) ya que se considera un tiempo sedentario, en el que se utiliza muy poca energía.

2. PROGRAMA PERSONALIZADO DE EJERCICIOS

En las siguientes tablas se describen los ejercicios con imágenes para facilitar la comprensión y correcta realización de estos. Recuerda:

- Realiza **únicamente** los ejercicios que te haya indicado la fisioterapeuta, siguiendo la intensidad y frecuencia cardiaca prescritas.
- Las **imágenes son orientativas**. Realiza los ejercicios siguiendo las indicaciones y adaptaciones que hayas trabajado en las sesiones presenciales.
- Todas las sesiones de ejercicio (tanto las que se realizan en casa como las aeróbicas) deben empezar con aproximadamente 10 minutos de estiramientos, continuar con los ejercicios de fuerza y/o aeróbicos y finalizar con aproximadamente 10 minutos de ejercicios de relajación.

3. TIPO DE PROGRAMA: MODERADO

EJERCICIO PARA HACER EN CASA		
Tipo de Ejercicio	**Frecuencia/Tiempo**	**Intensidad**
Estiramientos	3 veces x semana 10 min	
Ejercicios de fuerza	3 veces x semana 2-3 series (según tolerancia) de 10 - 15 repeticiones y descansa entre 30 y 60 segundos (según tu capacidad de recuperación) entre series de ejercicio 15 min	Escala de BORG: 3-4 Frecuencia cardiaca: 45-54% máxima
Ejercicios de relajación	3 veces x semana 10 min	

EJERCICIO AERÓBICO		
Tipo de Ejercicio	**Frecuencia/Tiempo**	**Intensidad**
Inserta el ejercicio aeróbico de tu preferencia: _____	Diario 30 min	Escala de BORG: 5-6 Frecuencia cardiaca: 55%-69% máxima

La escala de Borg: es una manera de medir el esfuerzo físico que estamos realizando durante la práctica del ejercicio aeróbico, y también es una herramienta que nos ayuda a comprender las sensaciones que experimentamos al hacer ejercicio.

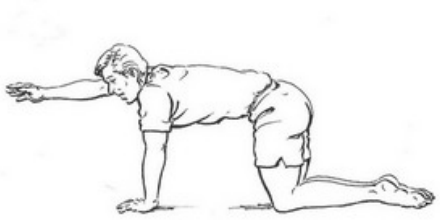
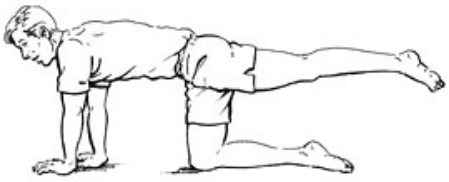
ESCALA DE ESFUERZO BORG	
0	Reposo total
1	Esfuerzo muy suave
2	Suave
3	Esfuerzo moderado
4	Un poco duro
5	Duro
6	
7	Muy duro
8	
9	
10	Esfuerzo máximo

Referencia: Dunbar, C. C., Robertson, R. J., Baun, R., Blandin, M. F., Metz, K., Burdett, R., & Goss, F. L. (1992). The validity of regulating exercise intensity by ratings of perceived exertion. *Medicine and science in sports and exercise*, *24*(1), 94-99.

4. EJERCICIOS DE ESTIRAMIENTO

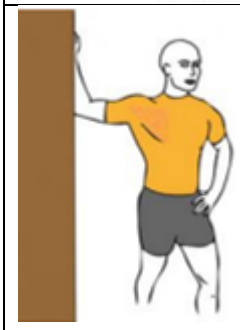
Para estos ejercicios, se debe i**nhalar por la nariz** y **exhalar lentamente por la boca**. Es importante mantener una respiración regular durante todo el ejercicio y **NO forzar** el estiramiento hasta sentir dolor.

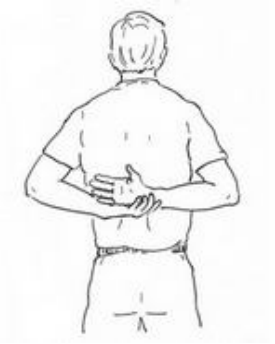
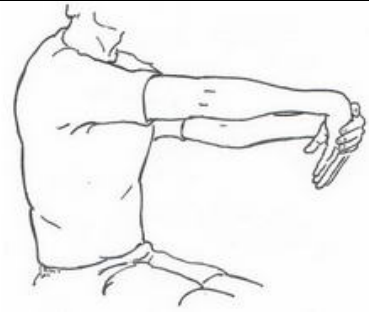
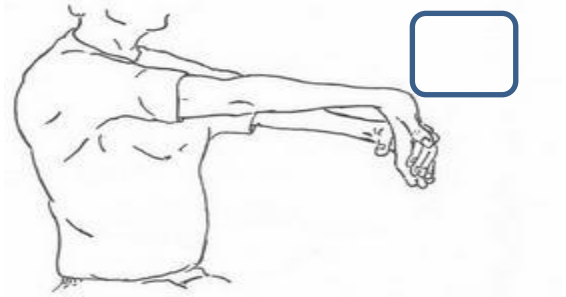
Estiramientos miembros inferiores

	**1. <u>Estiramiento Isquiotibiales</u>** Inclina el cuerpo hacia delante evitando que la rodilla se doble y mantén la columna lumbar recta. Mantén la posición 20 segundos. Repite con la otra pierna.
	**2. <u>Estiramiento de psoas y flexores de cadera</u>** Da un paso un poco largo, dejando atrás la pierna que quieras estirar. El pie debe mirar hacia delante. Lleva hacia atrás la espalda, de forma que quede recta y mantén la posición 20 segundos.
 	**3. <u>Elevación brazo-pierna alternativa</u>** En posición de cuatro patas, estira el brazo derecho y mantén 5s. Vuelve a la posición inicial. Eleva la pierna izquierda y mantén 5s. Vuelve a la posición inicial. Repite con el brazo y la pierna contrarios.

	**4. <u>Estiramiento cuádriceps de pie</u>** Flexiona la rodilla hasta alcanzar con la mano el empeine del pie. Sin arquear la columna lumbar, llevar pasivamente el talón en dirección a los glúteos. Mantén 20 segundos y vuelve a la posición inicial. Repite con la otra pierna.
	**5. <u>Estiramiento tríceps sural</u>** Inclínate hacia delante apoyado/a en una pared con la pierna derecha flexionada y la izquierda estirada, apoyando totalmente las plantas de ambos pies en el suelo. Flexiona los codos, la cadera y la rodilla de la pierna derecha sin mover la otra ni despegar el talón del suelo. Mantén 20 segundos y repite con la otra pierna.
	**6. <u>Estiramiento musculatura glútea/piramidal</u>** El pie del lado afectado se coloca encima de la rodilla contralateral. Tirar con las manos de la rodilla del lado afectado en dirección al hombro contralateral. Mantener 20 segundos y volver a la posición inicial.

Estiramientos miembros superiores

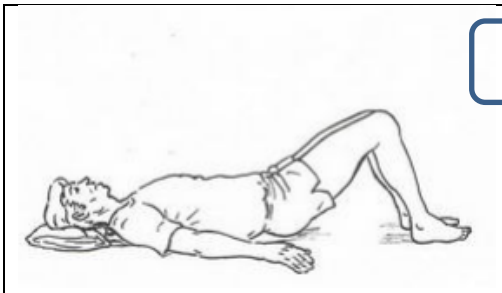
	**7. <u>Estiramiento hombro posterior</u>** Sube el brazo a 90º, dobla el codo y pon la mano en el hombro contrario. Con la otra mano empuja el codo hacia atrás mientras expulsas el aire lentamente. Mantén la posición 20 segundos y repite con el otro brazo.
	**8. <u>Estiramiento hombro anterior</u>** Frente a un rincón con las palmas de las manos sobre ambas paredes, a la altura de los hombros. Aproxima el pecho al rincón hasta notar tirantez en el pecho y cara anterior del hombro. Mantén la posición 20 segundos, mientras exhalas el aire lentamente.
	**9. <u>Estiramiento pectoral</u>** Con el brazo flexionado y apoyado girar el cuerpo ligeramente hasta notar estiramiento en la zona pectoral. Mantén la posición 20 segundos y cambia de brazo.

	**10. <u>Rotación interna autopasiva</u>** Desplaza una mano con ayuda de la mano contraria hasta la altura de la espalda que puedas tolerar. Mantén la posición final 10 segundos y repite con el brazo contrario.
	**11. <u>Estiramientos epicondíleos</u>** Empuja con la mano contralateral para aumentar al máximo la flexión hasta notar una sensación de tirantez o tensión. Mantén la posición final 20 segundos y repite con la mano contraria.
	**12. <u>Estiramientos epitrocleares</u>** Empuja con la mano contralateral para aumentar al máximo la flexión hasta notar una sensación de tirantez o tensión. Mantén la posición final 20 segundos y repite con el brazo contrario.

Estiramientos de columna

	**13. <u>Estiramiento en flexión con rotación</u>** Con una mano apoyada en la silla, realiza una flexión máxima y rotación del cuello hacia el otro lado. Mantén la posición 20 segundos, exhala lentamente y vuelve a la posición inicial. Y repite rotando la cabeza hacia el lado contrario.

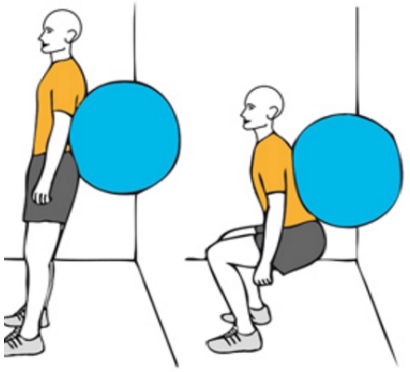
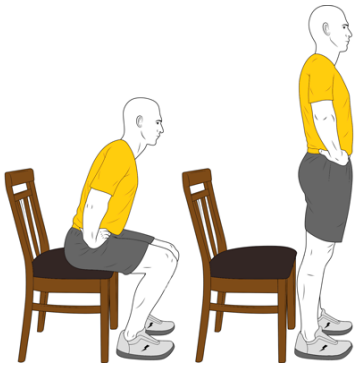
	**14. <u>Estiramiento de extensores de cuello</u>** Con ambas manos en los muslos realiza una flexión máxima del cuello. Mantén la posición 20 segundos, exhala lentamente y vuelve a la posición inicial.
 	**15. <u>Estiramiento lumbosacro tumbado</u>** Túmbate y dobla de forma simultánea la cadera y las rodillas de ambas piernas. Empuja las rodillas hacia el pecho. Mantén la posición 20 segundos, exhala lentamente y vuelve a la posición inicial.
	**16. <u>Estiramiento lumbosacro en silla</u>** Dobla hacia adelante el cuello y el tronco, e intenta llevar las manos hacia los pies. Mantén 20 segundos, exhala lentamente y vuelve a la posición inicial.

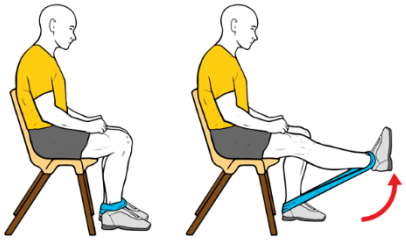
 	**17. <u>Estiramiento de isquiotibiales tumbado</u>** Túmbate y flexiona la cadera dejando los pies apoyados en el suelo. Con ayuda de las manos detrás del muslo eleva la pierna derecha, estírala hacia el techo lo más que puedas. Mantén 20 segundos, exhala lentamente y repite con la otra pierna.
	**18. <u>Estiramiento paravertebrales y dorsales</u>** Entrelaza los dedos, estira los brazos por encima de la cabeza y llévalos ligeramente hacia atrás. Mantén 20 segundos y repite.
	**19. <u>Estiramiento lumbar en rotación</u>** Estírate de lado, con las dos piernas dobladas, y gira el tronco hacia el otro lado estirando los brazos. Relájate y mantén la posición 20 segundos por lado.

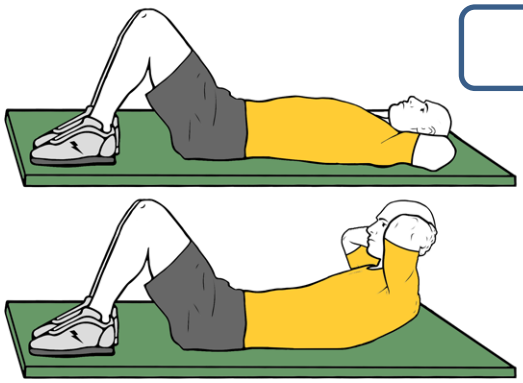
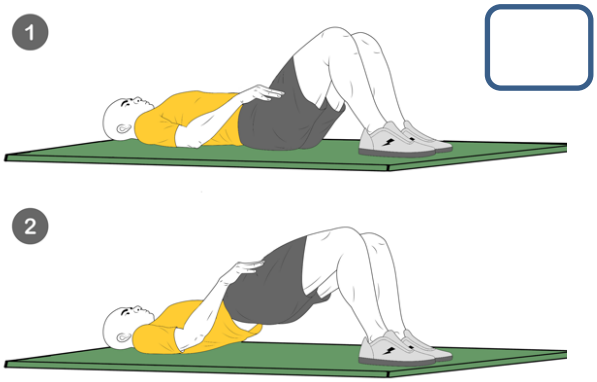
Estiramientos adaptados de la Sociedad Española de Rehabilitación y Medicina Física (SERMEF), 2020. Utilizado con autorización expresa de la Junta Directiva. https://ejercicios.sermef.es/#/.

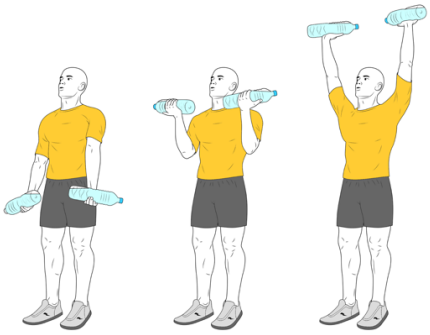
5. EJERCICIOS DE FUERZA

- Realiza todos los movimientos de cada ejercicio de forma lenta y controlada.
- Controla tu respiración: inhala por la nariz al hacer fuerza y exhala lentamente por la boca al relajar.
- Material necesario: dos botellas llenas con una capacidad de 33cl, una pelota de goma o plástico de unos 30-40 cm, una toalla pequeña y una banda o goma elástica.

	**1. <u>Sentadilla</u>** Pon la pelota entre tu espalda y la pared. Apoya el cuerpo en la pelota y separa los pies al ancho de los hombros. Dobla las rodillas y mueve tu trasero hacia atrás, flexiona las piernas hasta que los muslos queden paralelos al suelo mientras inhalas. En un movimiento rápido, regresa a la posición inicial extendiendo las rodillas y exhalando. Repite 10 veces.
	**2. <u>Sedestación-bipedestación</u>** Siéntate en una silla y coloca tus pies a la anchura de los hombros. Empujando principalmente desde los talones, ponte de pie mientras exhalas. Dobla las rodillas y mueve tu trasero hacia atrás, bajando las piernas hasta que te sientes de nuevo mientras inhalas. Concéntrate en tener siempre tu peso en toda la planta de los pies. La cabeza y pecho siempre deben mirar hacia delante.

	**3. <u>Extensión de cadera de pie con apoyo</u>** Colócate de pie con los pies a la anchura de los hombros frente a una silla. Coge la silla con ambas manos. Extiende la cadera derecha moviendo el talón hacia atrás con la pierna recta. Exhala durante el movimiento. Vuelve a la posición inicial con un suave movimiento mientras inhalas. Repite el movimiento 10 veces con cada pierna.
	**4. <u>Flexión de rodilla de pie</u>** Flexionar la rodilla llevando el pie hacia la nalga. Mantener 3 segundos y volver a la posición inicial.
	**5. <u>Extensión de rodilla con banda elástica</u>** Siéntate en una silla con respaldo y coloca los pies en el suelo. Coloca una banda elástica alrededor de los tobillos. Extiende una de las piernas hasta intentar alinearla con la cadera. Mantén 5 segundos y vuelve a la posición inicial. Repite el ejercicio 5 veces con cada pierna**.**
	**6. <u>Abductores con banda elástica</u>** Haz un nudo a la banda elástica enrollándola alrededor de las rodillas. Ábrelas con fuerza y vuelve a la posición inicial frenando la vuelta. Repite 10 veces.

	**7. <u>Abdominales superiores</u>** Túmbate boca arriba con los pies apoyados en el suelo. Las rodillas deben estar a 90º. Coloca las manos a ambos lados de la cabeza. Eleva la parte superior del tronco unos 25 cm. Mantén durante 3 segundos y vuelve a la posición inicial mientras exhalas el aire lentamente. No separes la espalda baja del suelo cuando hagas el ejercicio. Repite 10 veces.
	**8. <u>Puente de glúteos</u>** Túmbate boca arriba con los pies apoyados en el suelo. Las rodillas deben estar a 90º, los pies deben estar separados al ancho de los hombros. Coloca las manos en las caderas. Eleva la pelvis y mantén la posición durante 5 segundos. Vuelve a la posición inicial con un suave movimiento. Repite 10 veces.

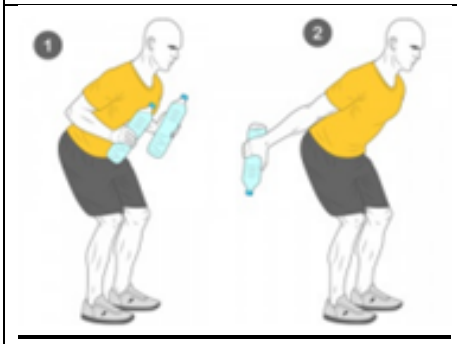


9. <u>Elevación de brazos con botellas</u>

Colócate de pie con los pies separados al ancho de los hombros, sosteniendo una botella en cada mano y a la altura de las caderas.

Contrae los bíceps y dobla los codos completamente mientras exhalas. Extiende los brazos para empujar las botellas hacia arriba hasta que los codos estén extendidos. Las palmas deben mirar hacia delante. Baja lentamente el peso hasta que tus manos estén justo por encima de los hombros, y luego regresa a la posición inicial.

Repite 10 veces.



10. <u>Extensión de tríceps con botellas</u>

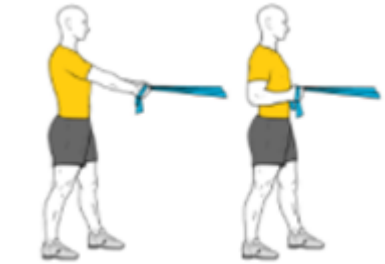
En una posición semiflexionada de piernas, y con el cuerpo recto pero hacia delante, estira los codos hacia atrás y ligeramente hacia arriba.

Repite 10 veces.

11. <u>*Curl* y excéntrico de bíceps con banda elástica</u>

Pisa la banda elástica con el pie asegurándote que no se escapa. Con un extremo en cada mano, dobla los codos hacia arriba y baja frenando la fuerza de la banda.

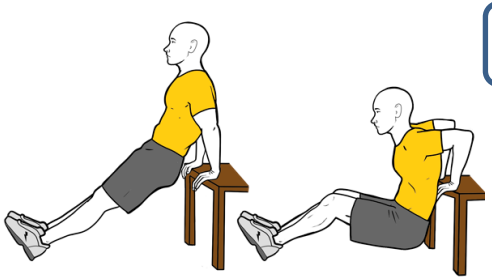
Repite 10 veces.



12. <u>Remo de pie con banda elástica</u>

Con la banda elástica atada en un lugar seguro, sujétala con ambas manos y estira hacia ti doblando los codos, manteniendo los brazos pegados al cuerpo.

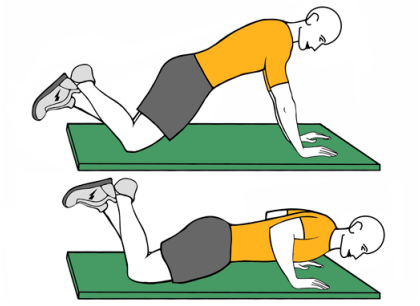
Haz dos series de 10 repeticiones.



13. <u>Extensión de brazos apoyados en silla</u>

Coloca una silla o banco detrás de tu espalda. Pon las manos sobre la silla, cos dedos mirando hacia delante (en dirección a la espalda). Extiende los codos y las piernas mientras tu trasero está cerca del banco. Retrae tus omoplatos elevando el pecho hacia arriba.

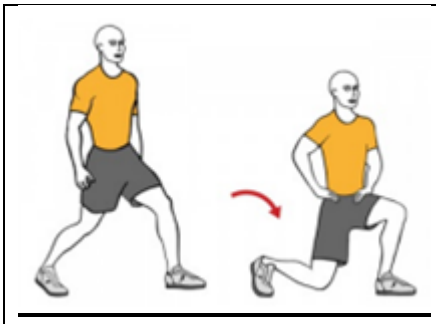
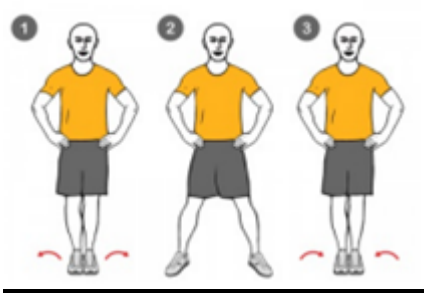
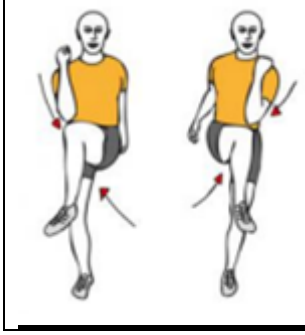
Empieza a bajar doblando los codos hasta que estén a 90º mientras inhalas. Contrae los tríceps y empuja el torso hacia la posición inicial apretando el resto del cuerpo mientras exhalas. Repite 10 veces



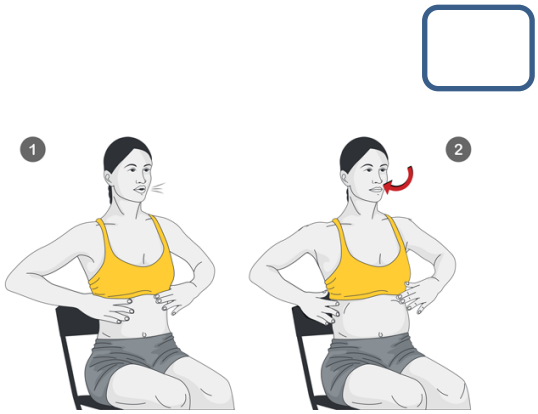
14. <u>Flexiones de brazos con rodillas apoyadas</u>

Colócate apoyado en las rodillas, con los brazos extendidos y las manos un poco más separadas que el ancho de los hombros. Las piernas deben formar un ángulo de 45º. Durante el ejercicio, mantén los hombros alejados de las orejas. Inhala y flexiona los codos hasta que el pecho esté cerca del suelo. Exhala y, haciendo fuerza con los brazos, eleva el torso hasta la posición inicial. Asegúrate de mantener las escápulas retraídas durante todo el ejercicio.

Repite 10 veces.

	**15. <u>Zancada frontal</u>** Con las manos en la cintura, da una zancada larga de forma que puedas flexionar la rodilla de la pierna de atrás y llevarla casi hasta el suelo. La rodilla de la pierna delantera no debe sobrepasar la altura del pie. Vuelve a la posición inicial y repite 10 veces.
	**16. <u>Zancada lateral</u>** Da un paso lateral abriendo las piernas y dobla la pierna con la que has hecho el paso. Vuelve a la posición inicial, repite 10 veces.
	**17. <u>Medio jumping Jack</u>** Abre y cierra las piernas saltando suave, 10 veces.
	**18. <u>Flexión de caderas alternas hacia el codo contrario</u>** Levanta una pierna haciendo que se toque la rodilla con el codo contrario. Haz 10 repeticiones con cada pierna.

6. EJERCICIOS DE RELAJACIÓN



1. <u>Respiración costo-diafragmática. Posición sentada</u>

Siéntate en una silla y coloca tus manos sobre tus costillas.

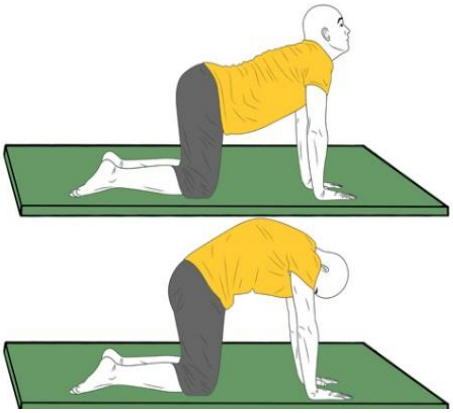
Inhala lentamente por la nariz, mientras inhalas intenta respirar llenando abdomen y la caja torácica. Exhala lentamente por la boca.

Repite 10 veces.

2. <u>Inclinaciones laterales del cuello</u>

Siéntate en una silla con los pies apoyados en el suelo a la anchura de los hombros y las manos en las caderas.

Inclina la cabeza hacia el lado izquierdo. Asegúrate de que tus ojos estén siempre mirando hacia adelante. Vuelve a la posición inicial con un suave movimiento. Repite el ejercicio 5 veces a cada lado lentamente.

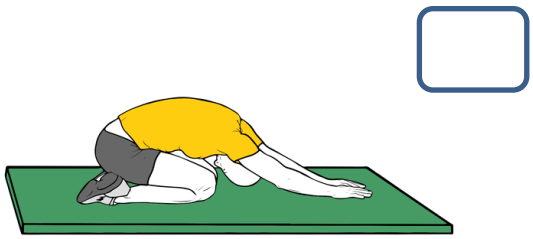


3. <u>El gato-vaca</u>

Colócate en cuadrupedia. Tus rodillas deben estar separadas al ancho de las caderas y debajo de las caderas, las manos debajo de los hombros. Tu cabeza debe mirar hacia el suelo.

Al inhalar abrir el pecho, extender la columna y elevar la mirada. Con la exhalación redondear/flexionar la espalda como un gato, dejar caer la cabeza y llevar la mirada hacia el ombligo.

Repite 10 veces.

	**4. <u>Estiramiento lumbar de rodillas</u>** Colócate en cuadrupedia sobre una colchoneta. Tus rodillas deben estar debajo de las caderas (si es necesario las rodillas pueden estar separadas todo lo que sea necesario para sentirte cómodo/a durante el ejercicio) y las manos debajo de los hombros. Mueve lentamente el trasero hacia atrás doblando la columna hasta que sientas el estiramiento en los músculos de la espalda. Mantén el estiramiento durante 30 segundos.

Programa de ejercicios del Col·legi de Fisioterapeutes de Catalunya, 2020. Utilizado con autorización expresa de la Junta de Govern.

Appendix D. Control group - General health recommendations

D.1 Original version

INFORMACIÓN BÁSICA

¿QUIÉN NECESITA HACER ACTIVIDAD FÍSICA O EJERCICIO?

Cualquier persona, ya que un estilo de vida físicamente activo reduce el sedentarismo y minimiza el impacto de los factores que ponen en riesgo nuestra salud.

La encuesta nacional de salud de 2017 de España, indica que entre los 15 - 69 años, un 35% de las personas no alcanza el nivel de actividad física recomendado.

¿ACTIVIDAD FÍSICA, EJERCICIO O DEPORTE? ¿QUÉ HAGO?

Hay que aclarar algunos conceptos:

ACTIVIDAD FÍSICA
Cualquier movimiento corporal que realizamos con los músculos y que generan un gasto de energía, como ir andando al trabajo.

EJERCICIO
Es una actividad física planeada, estructurada y repetitiva, su objetivo es mejorar o mantener la salud, por ejemplo salir a correr con el objetivo de 10 km.

DEPORTE
Es una actividad física reglamentada y competitiva, con el objetivo de obtener una victoria o conseguir un record, por ejemplo el fútbol.

FORMA/CONDICIÓN FÍSICA
Es el nivel de energía y vitalidad que nos permite realizar tareas de la vida diaria sin una fatiga excesiva, por ejemplo caminar deprisa sin cansarse.

MOTIVACIONES Y BARRERAS PARA LA PRÁCTICA DE EJERCICIO

Al iniciar una práctica de ejercicio hay factores que facilitan o que dificultan que se lleve a cabo la actividad, destacan:

MOTIVOS

- Divertirse y sentirse bien.
- Evitar problemas de salud y mantener una buena salud.
- Controlar la ansiedad y el estrés.
- Relacionarse con otros.
- Mejorar la condición física.

BARRERAS

- Tener vergüenza de enseñar el cuerpo en público.
- Tener pereza.
- No disponer de tiempo suficiente.
- No disponer de instalaciones cercanas o de fácil acceso.

EN CONCLUSIÓN:

- El sedentarismo es un riesgo para la salud porque aumenta la presencia de algunos problemas de salud.
- Dejar de ser sedentario reduce la posibilidad de tener problemas de salud.
- El estilo de vida activo es saludable y reduce la probabilidad de que aparezcan problemas de salud.
- Un estilo de vida activo genera beneficios para la salud.

IDEA PROJECT: HEALTHY PHYSICAL ACTIVITY

Hospital del Mar Research Institute
Barcelona

What should we know about physical activity?

1. Physical activity reduces the risk of conditions such as heart disease, stroke, hypertension, diabetes, and breast and colon cancer.

2. It helps to keep us healthy by improving muscle function, enhancing bone health, reducing the risk of heart disease and falls, and helping to maintain a healthy weight.

3. Some physical activity is better than none! You can start with small amounts and gradually increase the duration, frequency, and intensity over time.

4. Physical activity is especially beneficial when done at moderate (e.g., brisk walking) or vigorous (e.g., running) intensity levels.

5.Adults (up to 64 years old) should aim for at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity activity per week.

6.Unless there are medical contraindications, all adults should aim to meet these activity levels.

Illnesses are caused by multiple factors, and to prevent them, we should aim to reduce the associated risk factors. Physical inactivity is a known risk factor for several conditions, including cardiovascular disease, hypertension, osteoporosis, weight gain, anxiety, and depression.

Benefits and risks of physical activity

Benefits

- Improves cardiorespiratory fitness and reduces the risk of heart disease.
- Enhances memory and overall brain function.
- Helps maintain a healthy weight, reducing the risks associated with obesity (such as diabetes and hypertension).
- Lowers the risk of type 2 diabetes.
- Reduces the likelihood of age-related physical limitations, such as difficulty climbing stairs.
- Boosts overall wellbeing by lowering the risk of depression and cognitive decline associated with ageing.

Risks

- The benefits of physical activity outweigh the potential adverse effects if done correctly and in accordance with recommendations.
- If there are no prior injuries or health conditions, physical activity should not pose any risks. It is advisable to consult a healthcare or exercise professional who can provide guidance tailored to your needs.
- To avoid risks:
  - Plan your activity: include stretching exercises and a proper warm-up.
  - Start at a low intensity and gradually increase it over time.
  - Stay properly hydrated and avoid eating immediately before exercising.
  - Be mindful of weather conditions, especially extreme temperatures (whether too hot or too cold).

BASIC INFORMATION

Who needs to do physical activity or exercise?

Anyone, as a physically active lifestyle reduces sedentary behaviour and minimises the impact of factors that put our health at risk.

The 2017 National Health Survey of Spain indicated that 35% of the population aged between 15 and 69 did not meet the recommended level of physical activity.

Physical activity, exercise, or sport? What should I do?

Some concepts need to be clarified:

PHYSICAL ACTIVITY
Any bodily movement we perform using our muscles that expends energy, such as walking to work, is considered physical activity.

SPORT
Sport is a regulated and competitive form of physical activity, with the aim of achieving victory or setting a record, such as football.

EXERCISE
Exercise is planned, structured, and repetitive physical activity with the aim of improving or maintaining health, such as running with the goal of completing 10 km.

PHYSICAL FITNESS
Physical fitness refers to the level of energy and vitality that allows us to perform daily tasks without excessive fatigue, such as brisk walking without getting tired.

Motivations and barriers to exercising

When starting an exercise routine, there are factors that either facilitate or hinder the activity, including:

Motivations

- Having fun and feeling good
- Avoiding health problems and maintaining good health
- Managing anxiety and stress
- Socialising
- Improving physical fitness

Barriers

- Feeling embarrassed to show one's body in public
- Feeling lazy
- Not having enough time
- Lacking nearby or easily accessible facilities

Conclusion

- Sedentary behaviour is a health risk because it increases the likelihood of certain health problems.
- Becoming more active reduces the risk of developing health issues.
- An active lifestyle is healthy and decreases the chance of health problems arising.
- An active lifestyle provides health benefits.