Trials

STUDY PROTOCOL

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Treatment with combined exercise in patients with resistant major depression (TRACE-RMD): study protocol for a randomised controlled trial

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Abstract

Background Around 40% of people with major depressive disorder (MDD) experience moderate remission, with the remainder meeting the criteria for resistant major depression (RMD). It has been shown that exercise has a low-to-moderate effect on MDD, but there is a lack of evidence on exercise interventions in RMD patients. The primary purpose of the proposed study will be to investigate the effect of a 12-week supervised combined exercise program on depressive symptoms in people with RMD compared to a treatment-as-usual (TAU) group.

Method This randomised, single-blind, controlled experimental trial will include 70 adults (≥ 18 years old) with RMD. Participants randomised to an exercise intervention, or a TAU group will be assessed at baseline and after a three-month intervention period. The primary variable will be participants' depressive symptoms measured with the Montgomery-Asberg Depression Rating Scale. Secondary outcome variables will include cardiorespiratory fitness (peak oxygen uptake through peak cardiopulmonary exercise test), body composition (bioimpedance and anthropometric variables), physical activity level (the International Physical Activity Questionnaire), health-related quality of life (the Short Form-36 Health Survey), functional outcome (the Sheehan Disability Scale and Quality of Life in Depression Scale), overall disease severity (the Clinical Global Impression Scale-Severity of Illness), and biochemical variables (a fasting blood sample).

Discussion This study will try to answer whether a supervised co-adjuvant combined (aerobic and resistance training) exercise program will help the prognosis of this population with RMD.

Trial registration ClinicalTrials.gov NCT05136027. Last public release on 12/13/2023.

Keywords Randomised controlled trial, Resistant major depression, Exercise, Quality of life, Combined training

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Introduction

Major depressive disorder (MDD) is one of the most prevalent mental disorders worldwide and one of the most disabling, affecting more than 300 million people globally [1]. Thus, MDD is a complex multifactorial condition that includes complex pathophysiology and creates neural and neurotransmitter inflammation [1, 2].

In addition to depressive symptoms, people with MDD tend to lead an unhealthy lifestyle, including a lack of physical activity, sedentary behaviour, smoking, abuse of alcohol, and poor diet, resulting in various cardiovascular-related diseases (e.g. coronary heart disease, obesity, diabetes mellitus type 2, and stroke) [3]. Physiologically, people suffering from MDD are associated with increased immune system activation, leukocyte function, and release of proinflammatory cytokines such as interleukins (IL) 1, 2, and 6 [1]. Therefore, the combination of pharmacological treatment (i.e. a variety of antidepressants) and psychological therapies for the treatment of MDD is insufficient. In this sense, around 40% of people with MDD experience moderate remission, with the remainder meeting the criteria for resistant major depression (RMD) [4].

The typical treatment for this population consists of a pharmacological intervention using first- and second-generation antidepressant drugs that act on the brain synapse to increase the bioavailability of amines (i.e. serotonin, noradrenaline, and dopamine) [5]. However, only one-third of people achieve remission after initial treatment [5]. Hence, RMD is defined as an inadequate response to at least two different antidepressants of appropriate dose and duration [6]. Given this bleak outlook, several non-pharmacological strategies have been considered as possible co-adjuvant interventions to help improve the prognosis and remission rates of RMD, such as neurosurgical intervention, somatic therapies, electroconvulsive therapy, or even adjunctive strategies, among which exercise is one of the most important [7]. It has been shown that exercise has a low-to-moderate amelioration effect on MDD, with response rates comparable to mainstream therapies like antidepressant medication and cognitive behavioural therapy [1, 8].

The latest World Health Organization guidelines on physical activity and sedentary behaviour include evidence-based public health recommendations for people living with chronic conditions like mental disorders. Thus, adults should perform 150–300 min per week of moderate-intensity physical activity and two days of muscle-strengthening activity [9]. However, controversy still exists about the FITT (frequency, intensity, time, and type) principle and the latest scientific advances in exercise training for people with RMD.

In most studies conducted with this population, the exercise interventions included 1 h per session, two days per week, and more than 10 weeks of endurance intervention [10, 11], performed on a cycle ergometer or treadmill [10, 12]. Only one study conducted a combined intervention, including endurance and resistance training [12]. Previous studies have shown that low-to-moderate intensity training is an efficient method to improve different outcomes like cardiorespiratory fitness (CRF) and body mass index (BMI) in adult populations with chronic diseases, especially for individuals with a low initial level of aerobic fitness [13, 14].

Considering the above, here we propose the TRACE-RMD study to investigate the effects of a 12-week supervised combined exercise program (i.e. aerobic and resistance exercises in the same session) for people with RMD in comparison with a treatment-as-usual (TAU) control group doing occupational activity sessions with the same frequency and duration as the exercise group. Thus, the main aim of this randomised controlled trial will be to analyse the effects of a combined exercise program on depressive symptoms compared to a TAU group. The secondary objectives will be (1) to analyse the program's effects on CRF, body composition, and biochemical levels and (2) to determine changes in the functional outcome, overall disease severity, and quality of life of participants.

Methods

Study design, ethical approval, and registration

The TRACE-RMD study will be a randomised, single-blind (i.e. medical specialists will evaluate the psychiatric variables) controlled experimental trial with two parallel groups, superiority trial [15]. The study protocol was written per the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [16] and the updated SPIRIT 2024 and CONSORT 2024 reporting guidelines [17], aiming to improve the quality of the intended randomised clinical trial. This project is funded by the "III Convocatoria Intramural de la Fundación Vital Fundazioa – IIS BIOARABA" and the Mental Health Network of Álava, with a single purpose of financial assistance.

Participants: recruitment and selection criteria

Specialised psychiatrists from the Resistant Depression Unit of the Álava Psychiatric Hospital and Álava Mental Health Network (Basque Country, Spain) will recruit 70 adults with RMD, which provides psychiatric care to the population living in the community and encourage participation by explaining the benefits of exercise as an adjuvant programme in their treatment. Before accepting written informed consent from all eligible participants,

psychiatrists and specialised nurses will be approached for questions. The inclusion and exclusion criteria for the TRACE-RMD study are shown in Table 1.

Participants will be free to withdraw from the study at any time. The participant may not continue in the study for the following reasons: (1) failure to maintain 80% compliance with training sessions (minimum 19 sessions); (2) missing more than two consecutive training sessions; (3) the participant's condition or disease progresses; (4) the participant experiences a severe adverse event (e.g. angina, dyspnoea, dizziness) that requires discontinuation or withdrawal from the study in accordance with the study protocol; or (5) pregnancy.

Randomisation

After the informed consent is accepted and signed, the participants will be included in the trial by being given a trial-specific anonymous identification (i.e. TRACE-01) number (ID) to ensure confidentiality and facilitate possible prospective meta-analyses. Allocation consignment will be performed by a technician from Bioaraba Health Research Institute (http://aleatorizacion.bioaraba.org/) using the technique of stratified randomisation (1:1) by sex (men/women) and depressive symptoms. The participants will be randomised to one of the two intervention groups: (1) the exercise (EX) group and (2) the TAU group. Exercise physiologists will be responsible for informing each participant of the group in which they will participate. Figure 1 presents a flow diagram of the study process.

Outcomes and measurements

Data collection will be based on an assessment protocol for gathering data on physical, clinical, and biochemical variables. Assessments used in the protocol will be evaluated before (T0) and after a 12-week intervention period (T1). Experienced specialists in psychiatry and nursing from the Psychiatric Hospital of Álava will assess and collect clinical data. The physical, physiological and functional variables will be evaluated and recorded by physical sports educators with over 20 years of experience who will train their doctoral, undergraduate, and postgraduate students. Participants from the two groups will be assessed concurrently. Sociodemographic data (including participant sex, age, state of convivence, professional status, drug and smoking status, age of onset of illness, number of hospitalisations, date of last hospitalisation, medication intake, and treatment duration) will be collected before the baseline assessment. Measurements will be performed in three separate visits according to the sequence:

- Visit 1: functional outcome and quality of life with questionnaires.
- Visit 2: anthropometry, body composition and cardiopulmonary exercise test (CPET).
- Visit 3: fasting blood sample.

The primary outcome (depressive symptoms) will be measured with the Montgomery-Asberg Depression Rating Scale (MADRS) using the validated Spanish version [18]. Secondary outcome variables will include CRF, body composition, biochemical and functional outcomes, and quality of life. The SPIRIT figure showing the time points for assessments and intervention is shown in Fig. 2.

The MADRS is a clinical interview with extended phrased questions about symptoms of depression and anxiety. The questionnaire has ten different items about depression. Adding up scores can be obtained between

Table 1 Inclusion and exclusion criteria for the TRACE-RMD study

Inclusion criteria
- ≥ 18 years old
- Patients living in the community or hospitalised patients. In the two cases, the RMD diagnosis is defined as the person who receives the treatment does not have a remission, with a poor or unsatisfactory response to at least two adequate (i.e. optimal dosage and duration) different antidepressants. However, previous research studies have demonstrated the lack of consensus criteria in defining RMD [6].
- Treatment-resistant depression is defined as resistance to two or more antidepressants
- Written informed consent has been signed
Exclusion criteria
- Schizophrenia or other psychoses
- Presence of imminent suicidal risk
- Unstable or inadequately controlled medical illnesses (in acute pathology situations)
- Active substance use disorder
- Comorbidity with other psychiatric pathologies constitutes the main focus of treatment
- Cognitive impairment anchored by the Montreal Cognitive Assessment scale < 26/30
- Inability to perform exercise secondary to osteoarticular, cardiovascular or metabolic difficulties
- Performing exercise continuously as a regular practice

≥ greater than or equal to, *RMD* resistant mayor depression

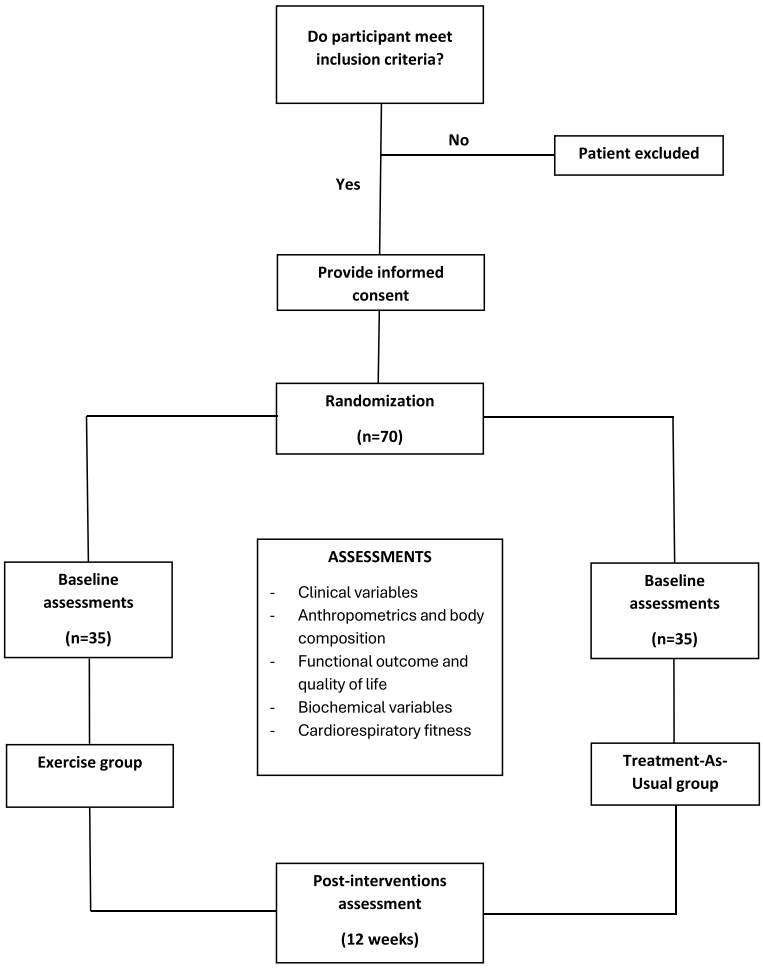

Fig. 1 Flow diagram of the TRACE-RMD study

0 (zero; absence of depression) and 60 (major level of depression) [18].

For evaluating functionality, the Sheehan Disability Scale (SDS) [19] and the Spanish version of the Quality of Life in Depression Scale (QLDS) [20] will be used. The copyright license agreement for the SDS was obtained through Dr. David V. Sheehan, and it included a Spanish linguistic validation. The SDS is a subjective scale with three items (social, family, and work) evaluating the incapacity or depression [21], and the QLDS is a depression-specific quality of life scale based on the possibility and capacity of the individual to satisfy the particular needs [20]. The overall disease severity will be measured using the Clinical Global Impression Scale-Severity of Illness (CGI-SI). The CGI-SI is a descriptive, hetero-applied scale that provides qualitative information on the severity of the clinical condition and the change experienced by the patient concerning the baseline condition in three different measures (i.e. illness severity, global improvement, and efficacy index) [22].

Anthropometry will include stature (SECA 213, Hamburg, Germany), total body mass (SECA 869, Hamburg, Germany), BMI calculated as total body mass (kg)/stature (m^2), and waist and hip circumferences calculated with waist-to-hip ratio (SECA 200, Hamburg, Germany). All measurements follow the International Society for the Advancement of Kinanthropometry guidelines [23]. Furthermore, bioelectrical impedance analysis will estimate fat-free mass, total body water, and fat mass (Tanita, BF 350, and Tanita, BC-418 MA, Amsterdam, the Netherlands).

The International Physical Activity Questionnaire (IPAQ) will assess physical activity level and sedentary behaviour. This questionnaire has seven items, and the participant should respond on their own basis over the prior 7 days [24]. The Spanish version of the Short Form-36 Health Survey (SF-36) will assess participants' health-related quality of life. The SF-36 is a short questionnaire with 36 items of eight dimensions of items, including physical functioning, social functioning, role limitations

Activity/Assessment	Study period		
	Baseline	Pre-intervention	Post-intervention (12 weeks)
TIMEPOINT	T-1	T0	T1
Eligibility screen	X		
Informed consent	X		
Clinical and physical examination	X		
Randomization		X	
INTERVENTIONS			
Treatment-As-Usual group (TAU)			← →
Exercise group (EX)			← →
ASSESSMENTS			
Anthropometry: Stature, body mass, waist/hip ratio, fat-free mass, fat mass, total body water		X	X
Functional outcome and quality of life		X	X
Fasting blood sample		X	X
Cardiopulmonary Exercise Test		X	X

Fig. 2 The SPIRIT figure shows an overview of the assessment schedule at baseline and follow-up in the TRACE-RMD study

attributed to physical problems, role limitations attributed to emotional issues, mental health, vitality, pain, and general health perception [25].

The CRF assessment will involve a symptom-limited CPET on a bike ergometer (Lode Excalibur, Groningen, the Netherlands). The protocol will commence at 40 W, with gradual increments of 10 W per minute until exhaustion while continuously monitoring an electrocardiogram. The gas analyser (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) will undergo calibration before each test. Peak oxygen uptake (VO_{2peak}) will be defined as the highest oxygen consumption value achieved after the test. Peak effort will be acknowledged when meeting at least two or more of the following criteria: participant fatigue (Borg scale > 18), respiratory exchange ≥ 1.1, attainment of > 85% of predicted maximum heart rate (HR), and no increase in VO_2 and/or HR with escalating workload [26].

After each minute, the subjective sensation of exertion will be documented using the original Borg scale [27]. Blood pressure (BP) will be assessed at two-minute intervals throughout the test. Ventilatory thresholds (VTs) will be evaluated through standardised methodologies employing V-slope and ventilatory equivalents (EqV). The first ventilatory threshold (VT_1) will be determined when the inflexion point in the carbon dioxide production (VCO2) *versus* VO2 slope transitions from less than 1 to greater than 1. Alternatively, it can be identified as the nadir in the EqV ratio of VO_2 *versus* workload. The second ventilatory threshold (VT_2) will be pinpointed as the nadir in the EqV/VCO_2 ratio *versus* workload [26]. After completing the test, the participant will rest on the bicycle for an additional 5 min to record recovery variables. All absolute and relative criteria for concluding the test will be duly considered. The intensity ranges will be individually tailored based on HR to establish light (ranging from a resting HR value to an HR value of the VT_1) and moderate (HR value between VT_1 and VT_2) intensity categories: specifically, R1—light to moderate intensity with HR values below VT_1; R2—moderate-to-high intensity with HR values between VT_1 and VT_2; and R3—intense-to-severe intensity with HR values above VT_2 up to peak HR.

Biochemical profiles will be determined with a fasting blood sample (10 mL) collected at the hospital for each participant after an overnight fast, including

the following parameters: haemoglobin, haematocrit, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, insulin, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, C-reactive protein, uric acid, creatinine, sodium, potassium, and albumin. HOMA-IR will be used to evaluate insulin resistance (i.e. fasting serum insulin [μU/mL] × fasting plasma glucose [mg/dL]/405) [28]. Moreover, cytokine levels in IL-1, IL-6, and IL-10 plasma levels will be measured via enzyme immunoassays.

Study intervention

The participants enrolled in the EX group will undergo a 12-week exercise program (two non-consecutive days per week) under the supervision of exercise specialists at out-of-hospital facilities (i.e. the Physical Activity for Health Research Center). All sessions will start and end with BP measurements, and exercise intensity will be monitored by HR monitors (Polar Electro, Kempele, Finland) and through the original Borg scale (6–20). Each session will include a 10 min warm-up and a 10 min cool-down with stretching. The main part of the session will consist of a four-part circuit of 10 min each: (1) a low-volume and low-intensity interval training (LV-LIIT) exercise on the bicycle (Table 2); (2) strength-resistance exercises (elastic bands, own body weight, dumbbells (Additional file 1)); (3) an LV-LIIT exercise on the bicycle (Table 2); and (4) lumbopelvic strengthening exercises (Additional file 1). During the sessions, the power and speed of the bike will be adjusted to achieve the target HR. In the LV-LIIT exercise, participants will warm up for 2 min and then engage in six intervals of 15 s at R2 interspersed with 1-min intervals at R1, finishing with 2 min of cool-down at R1 (Table 2). In the resistance workout, the participants will perform a time-based circuit (30 s per exercise, with 30 s rest) of 10 strength-resistance exercises, including both upper and lower body, covering the main muscle groups and coordinated with breathing. In the lumbopelvic strengthening workout, the participants will carry out six exercises (20 repetitions with 20 s of rest between each exercise), including the anterior and posterior musculature (Additional file 1). Some strategies will be used to achieve adherence, such as individualised attention while exercising and telephone calls following missed sessions. The TAU group will conduct a standard practice and continue with their regular treatment plus occupational activities (inpatient) for the same duration as the intervention in the EX group. Due to RMD, it is not necessary to instruct participants not to engage in any other activity involving exercise because the difficulty is to involve them in the project. To promote retention in the project, after completion of the post-intervention assessments, all participants are offered an exercise programme within the hospital (unrelated to the research).

In case of adverse events will be recorded and reported to the corresponding Ethics Committee.

Table 2 Exercise intervention through low-intensity interval training on a cycle ergometer

Protocol					
Moderate-intensity interval training			Low-intensity interval training		
Weeks	Volume (min)	Intensity (%HR_{res})	Weeks	Volume (min)	Intensity (%HR_{res})
1–4	3	60	1–4	17	50
5–8	3	65	5–8	17	55
9–12	3	70	9–12	17	60

Data management

Data management will comply with the regulations of the Bioaraba Health Research Institute. All data recording will be carried out by the lead research psychiatrist (NIY) and the persons responsible for the exercise programme (JEO and MTE) with a paper-based registry. The paper-based database will be coded, registered, and stored in a cloud platform, and only the persons responsible for the research will have access to it. Communication among specialists (psychiatry, nursing, and sports physical educators) will be constant to ensure that once the psychiatrist recruits, the nurse will carry out the questionnaires the following week, and the sports physical educators will assess the physical and physiological conditions. Both groups (hospital and university) will meet every three months to identify possible errors and evaluate the study's progress. The ethical committee will ask for a memory report once a year.

Upon completion of the study, the results will be published and presented to social media, academics, and clinical institutions. Likewise, research articles will be submitted to peer-reviewed journals and presented at relevant scientific conferences. The data will be available by publishing on open data repositories. We have no contractual agreements that limit investigators' access.

Sample size estimation

We have conducted a previous pilot study with 18 participants diagnosed with RMD in a single supervised exercise group (12 weeks, 2 days/week). Following the intervention (data not yet published), no significant changes ($P > 0.05$) were found in the body composition, main CRF physiological variables, and biochemical profile. However, regarding clinical symptoms, MADRS

(Δ = −27.2%; P=0.021), CGI-S (Δ = −25.3%; P=0.006), and SDS (Δ = −22%; P=0.046) values decreased; and the domains of health-related QoL, general health (Δ=50.5%; P=0.017), vitality (Δ=41.4%; P=0.045), social functioning (Δ=76.5%; P=0.008), and mental component summary (Δ=24.9%; P=0.024) values increased. Thus, based on this previous pilot study with the same population, to achieve a power of 80% where differences in depressive symptoms (measured by the MADRS) are detected after the exercise intervention, having a significance of 5%, a reference mean of 29.13 ± 12.2 units, an experimental group mean of 22.23 units, a standard deviation between both groups of 9.61, and an expected difference of 2.5 units, 31 patients per group will be needed. If we assume a 10% loss rate, 35 patients per group will be required, with a total sample of 70 participants.

Statistical analysis

A general descriptive analysis of the sample will be performed to assess baseline homogeneity. The Kolmogorov–Smirnov test will determine the normality of quantitative variables, and results will be expressed as means and standard deviations or as median values and interquartile ranges in the case of non-normal distributions. Qualitative variables will be expressed as frequencies and percentages. Student's *t*-test for related samples will be carried out to assess the impact of the intervention on quantitative variables. A nonparametric analogue Wilcoxon will be chosen if it does not meet normality criteria. A covariate analysis (ANCOVA) will evaluate change after the intervention, considering the two EX and TAU groups (i.e. independent variable). The magnitude of the differences will be assessed using 95% confidence intervals and Hedges's *g* effect sizes.

During the development of the study, deviations from the protocol may arise. In that case, the sponsor will inform the funder using a breach report form, and the corresponding changes will be performed in the clinical trial registry. The statistical analysis will be performed via intention-to-treat and protocol to manage these situations within the study.

The TRACE-RMD study does not have a data monitoring committee, and the Ethical Committee does not require it, given the project is under constant review by the psychiatry specialists.

No interim analyses are planned.

Discussion

This study will be the first clinical trial to explore the efficacy of a combined exercise intervention as a potential co-adjuvant to pharmacological treatment in patients with an RMD diagnosis. Recent meta-analyses have shown that different types and dose-responses of exercises like walking, aerobic training, Yoga, Qigong, resistance training, and Tai Chi have effectively alleviated depressive symptoms in older adults [29], and adults in general [30]. Therefore, since RMD populations can be resistant to two or more antidepressants [6], exercise interventions should be considered an effective adjuvant program in the treatment of RMD.

In this sense, the appropriate FITT principle of exercise interventions remains unclear, and controversy exists [31, 32]. Moreover, although a significant percentage of interventions are aerobically oriented, a recent meta-analysis revealed moderate antidepressant effects of strength training in people with a diagnosis of depression or depressive symptoms [33]. Therefore, combined training (i.e. aerobic + resistance training in the same session) could be considered a powerful option to investigate in people with RMD. Thus, previous studies have implemented and analysed exercise interventions in people with RMD [11, 10, 34, 12]. While these interventions have shown improvements in psychiatric variables, enhancing psychopathological symptoms like depression, functionality, and even quality of life, none has implemented a combined exercise training intervention or analysed potential physical, objective physiological, and biochemical improvements in this population. In this regard, given that the improvement in CRF through exercise training has led to enhanced health and reduced mortality in people with severe mental illness [35], to analyse this variable is crucial.

Furthermore, the biochemical analysis will provide the opportunity to examine IL-6 and IL-1, which have been associated with the onset of proinflammatory inflammation and are particularly relevant in the brain [36–38]. In line with this, peripheral cytokines can cross the blood–brain barrier and reach the central nervous system, provoking neuroinflammation, which might trigger psychiatric disorders such as depression [39]. Therefore, analysing these ILs will be pertinent, as exercise interventions have been shown to decrease IL-6 levels [40]. Overall, this research will provide further information and build upon previous findings regarding a co-adjunctive strategy (combined exercise training) in individuals diagnosed with RMD.

Trial status

The trial was initially released as a pilot study (no clinical trial) on 24th November 2021 (version 1). The present manuscript is based on the 18th December 2023 trial protocol (version 2). Recruitment of participants started in January 2024 and is estimated to be completed up to December 2025.

Abbreviations

BMI Body mass index

BP	Blood pressure
CGI-SI	Clinical Global Impression Scale-Severity of Illness
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness
EqV	Ventilatory equivalent
EX	Exercise
FITT	Frequency, intensity, time, and type
HR	Heart rate
IL	Interleukin
IPAQ	International Physical Activity Questionnaire
LV-LIIT	Low-volume and low-intensity interval training
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
QLDS	Quality of Life in Depression Scale
RMD	Resistant major depression
SDS	Sheehan Disability Scale
SF-36	Short Form-36 Health Survey
TAU	Treatment as usual
VCO_2	Carbon dioxide production
VO_{2peak}	Peak oxygen uptake
VT	Ventilatory threshold

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08685-7.

Additional file 1. Resistance training program.

Additional file 2. SPIRIT Checklist.

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Trial sponsor
Osakidetza Basque Health Service. Araba Mental Health Network, Psychiatric Hospital of Alava, Vitoria-Gasteiz, Spain. Araba Kalea, 43, 01007 Vitoria-Gasteiz, Araba/Álava, Basque Country, Spain.

Role of sponsor
Recruitment, management, and interpretation of data.

Role of funders
Only financial support.

Responsibilities
The study will be conducted by the Psychiatric Hospital of Álava in collaboration with the University of the Basque Country (UPV/EHU). The hospital has a team of psychiatry specialists responsible for recruitment and signing the informed consent form. They, together with the hospital's nursing services, will carry out the questionnaires related to the study. The UPV/EHU researchers will be responsible for the physical and physiological assessment before and after the intervention and the exercise programme (design and supervision). Both groups (hospital and university) will meet every three months to identify possible errors and evaluate the study's progress.

Authors' contributions
All authors read and approved the final manuscript. Conception of the project (NIY, JEO, CPN, MTE, PMSG, SMM, EEZ). Design of the work and methodology (NIY, JEO, CPN, MTE, PMSG, SMM, ABYE, EEZ).

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Data availability
The data will be available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The design of the study conforms to the principles outlined in the Declaration of Helsinki, and the protocol, together with the informed consent procedures of the TRACE-RMD study, were approved by the Ethics Committee of Investigation of the local Hospital (11 May 2023, Certificate No. 2023–008). The protocol was registered with the United States National Library of Medicine (ClinicalTrials.gov ID no. NCT05136027). Participants will be fully informed of the aims and procedures of the research before collecting their informed consent and before the clinical and physiological examination. Each participant will be allowed to ask questions about the investigation. No identifying images or other personal or clinical details of participants will be presented in reports of the trial results. The participant information materials and informed consent forms are available from the corresponding author on request.

Consent for publication
Not applicable.

Competing interest
The authors declare that they have no competing interests.

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