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Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial

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TITLE OF MANUSCRIPT: Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial

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Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial

Abstract

Introduction: Numerous studies support the practice of different physical exercise modalities as an effective treatment to address the different problems associated with schizophrenia, reporting that they result in significant improvements in patient symptoms and quality of life. Given the lack of studies comparing different types of training in controlled environments, the aim of this proposed study will be to compare the effects of three physical exercise programs (strength, aerobic, and mixed) on the symptoms, body composition, level of physical activity, and health-related quality of life of patients with schizophrenia.

Methods and analysis: A multicentric, parallel-group, single-blinded (evaluator), randomised (ratio 1:1:1) clinical trial will be conducted with 84 patients recruited from different psychosocial care centres. The participants will be randomised into three 16-week training groups comprising 48 sessions lasting one hour each. The groups will complete aerobic, strength, or mixed (aerobic + strength) training. All the participants will be assessed before, immediately after, and 6 months after the end of the intervention. The study variables will include positive symptomatology, negative symptomatology, and general symptomology (using the *Positive and Negative Syndrome Scale)* as the primary outcome; as secondary outcome: body composition (by assessing body mass index, body fat mass and waist circumference), physical activity levels (*International Physical Activity Questionnaire-Short Form*), and quality of life (abbreviated *World Health Organization Quality of Life* questionnaire).

Ethics and dissemination: This study was approved by the ethics committees of the participating institutions. Participants will be fully informed of the purpose and procedures of

the study, and written informed consent will be obtained from every participant. The results from this study will be published in peer-reviewed journals and presented in scientific conferences.

Trial registration number: NCT03953664.

Strengths and limitations of this study

- To the best of our knowledge, this is the first randomised controlled trial to analyse and compare the effects of three different physical exercise programs on the symptomatology, health-related quality of life, and anthropometric variables of schizophrenic patients.
- The design of this this study incorporates a series of improvements with respect to previously published work examining the effects of strength training in patients with schizophrenia: this will be a multicentre study, with a larger sample size, and a follow-up assessment carried out 6 months after the end of the intervention.
- The outcomes of this study will help to improve the prescription of different training types to each patient to help them better manage their disease in the future.
- Possible limitations of this study are the lack of some records such as the dietary intake of the participants. In addition, some data will be self-reported, which may be affected by participants' personal perceptions.

Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial

Introduction

Schizophrenia is a serious chronic mental illness that, according to Word Health Organization (WHO) data [1], affects 21 million people worldwide. This disease is characterised by a combination of positive symptoms (hallucinations, delusions, thoughts, and/or movement disorders), negative symptoms (associability, anhedonia, abolition, affective flattening, and alogia), and cognitive symptoms (problems with operational memory, executive functioning, and concentration) [2, 3]. In addition, schizophrenia is accompanied by a huge individual and social burden [4, 5] and is the eighth leading cause of disability-adjusted life years in 15 to 44-year-olds [6].

Schizophrenia is related to a sedentary lifestyle [7–9] and is associated with cardiovascular diseases, coronary heart disease [10], diabetes, obesity, dyslipidemia, and metabolic syndrome, among other comorbidities [11, 12]. Some of these pathologies are a consequence of the antipsychotic drugs that these patients receive to treat their disease [13], but there are also studies that postulate that the metabolic alterations present in these individuals are inherent to the schizophrenic disease they suffer [14]. All of the above means that, compared to the general population, people suffering from this disease have a 40% to 60% higher probability of premature death and a 20% lower life expectancy [15].

On the other hand, there is evidence that the quality of life perceived by patients with schizophrenia is lower than in the rest of the population in every domain studied [16]. The intensity of the symptoms of this disease, its treatment, and the comorbidities associated with it strongly impact the quality of life of patients affected by it, which is further jeopardised by the social stigma and low self-esteem that it entails [17, 18]. Of note, some studies have shown that physical activity positively contributes to the quality of life of these patients [19].

Without a doubt, physical activity is an important factor in preserving the general health and preventing chronic diseases such as diabetes, dyslipidemia, obesity, and cardiovascular diseases in individuals with schizophrenia. Indeed, in schizophrenic patients, exercise is inversely correlated with morbidity and mortality as a result of these diseases [20]. Specifically, significant results in terms of quality of life [21], positive and negative symptoms [22–24], improvement in sleep quality [25, 26], and cardiopulmonary function [27-29] were found in studies that used physical activity as an intervention in populations affected by schizophrenia. In addition, physical activity reduces the general care burden of these patients [30].

Therefore, the prescription of physical exercise is a practice validated by doctors for improving the symptoms of schizophrenia and to help prevent the diseases associated with it. However, to the best of our knowledge, there are still significant gaps in the evidence indicating what types of training might be most effective at improving the symptoms of these patients [21, 31–33]. Most work studying the effects of physical activity in patients suffering from schizophrenia has focused on aerobic or mixed physical exercise programs [12, 23, 26, 28–30, 34]. In fact, even though strength training exercise interventions have obtained very good results such as anxiolytic and antidepressant effects in diseases such as depression and anxiety [24, 35], only two studies have used this type of training in schizophrenic patients [36]. Nonetheless, these studies found that strength training programs reduced the psychopathology [24] and improved the maximum strength and walking performance of these patients [24, 35].

Based on all the above, and considering that we were unable to identify any studies that simultaneously evaluated different types of intervention in patients with schizophrenia, the main objective of this proposed work will be to analyse and compare the effects of three different physical exercise programs (strength, aerobic, or mixed) on the symptomatology (positive and negative), health-related quality of life, and anthropometric variables of schizophrenic patients enrolled in a psychosocial rehabilitation program.

Methods and analysise

Study design

This will be a three-armed, multi centre, single-blinded, randomised clinical trial (RCT), comparing three conditions: strength training, aerobic training, and mixed training (strength + aerobic). The participants will be assessed at baseline, post-treatment, and at a 6-month follow-up. A flowchart showing the proposed progression of the participants through the study is shown in figure 1. The work will adhere to the CONSORT standards for randomised trials [37–39] as well as the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and on Line Tele Health) [40], the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines (Additional file 1) and the World Health Organization trial registration data set criteria (Additional file 2) [41]. This current protocol was registered at ClinicalTrial.gov with reference number NCT03953664.

Figure 1. Flowchart representing the movement of the participants through the study.

Patient involvement

Patients will be involved at several stages of the trial, including the design, management, and conduct of the trial. We will receive input from patients who are living with schizophrenia in the design of the trial materials and management oversight through membership of the trial steering committee. We carefully will assess the burden of the trial interventions on patients. We intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

Study population, recruitment, and eligibility criteria

This RCT will be conducted from six psychosocial care centres for people with severe mental illness located in different parts of Spain: the Fundación Agustín Serrate (Huesca), Fundación Rey Ardid (Zaragoza), Fundación SASM (Valencia), Fundación Els Tres Turons (Barcelona), CREAP (Valencia), and Asociación Acova (Valencia). The participants will be recruited by the health staff working in the different centres.

The researchers who manage the study will go to the different psychosocial care centres to explain the study and eligibility criteria to the health staff, and will give them an information sheet containing the study characteristics. The health staff at those institutions will then distribute the information to interested and suitable candidates directly via an interview in which the study will be explained in detail and the patient's participation in it will be requested. If they wish to participate, these patients will be asked to sign the informed consent document (Additional file 3) and will be instructed to maintain their usual treatments and appointments with mental health professionals.

To be included, the participants must fulfil all the inclusion criteria and none of the exclusion criteria. The inclusion criteria will be as follows: (1) age between 18–65 years; (2) Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of schizophrenia; and (3) able to read and understand the Spanish language. The exclusion criteria will be: (1) acute suicidality; (2) representing an acute danger to others; (3) other psychiatric diagnoses or acute psychiatric illnesses; (4) motor or behavioural pathologies that prevent the person from completing the exercise training; (5) participation in similar programs or interventions at the time of enrolment.

Randomisation and blinding

An independent researcher unaware of the study characteristics will perform the randomisation process. In order to randomly allocate the participants to one of the three conditions (aerobic, strength, or mixed), a computer-generated random number sequence [42] will be used (applying a simple allocation strategy). The allocation ratio will be 1:1:1. This sequence will be recorded in a password-protected spreadsheet table and concealed to other researchers during the study. Because the different exercise interventions significantly vary, it will be impossible to mask the group allocation to the physical therapists or the participants. However, the outcome evaluators and data analysts will be blinded to treatment allocations. To avoid inter-observer variability bias, the measurements in each of the groups will always be completed by the same investigator.

Sample size

A power analysis with G-Power software version 3.1.9.2 [43] showed that a target sample size of 69 participants would be required to detect a medium-sized effect ($f = 0.2$) for the positive symptoms of schizophrenia in an ANCOVA analysis with $\alpha = 0.05$ and a power of 0.90. Thus, anticipating a dropout rate of 20%, the necessary sample size would be approximately 28 participants per study arm ($n = 84$).

Interventions

The intervention will consist of a total of 48 sessions (3 weekly sessions lasting one hour each for 16 weeks) and will be carried out at each of the psychosocial care centres. The total number of training sessions and duration of each session will be the same for the three training groups. These groups will be led by a professional physical education specialist from each psychosocial care centre who will also be responsible for recording each participant's degree of compliance with the intervention.

Strength training: Each strength training session will begin with a set of gentle stretching exercises lasting 10 minutes, designed to target the major muscle groups. This will be followed by two sets of 8 strength training exercises with 1 minute of recovery programmed between each one. An elastic resistance band (Thera-band) will be used in 4 of the 8 strength exercises. Finally, the training will end with 10 minutes of gentle stretching of the major muscle groups as a cool-down (Figure 2).

Figure 2. Strength training.

Legend of figure 2: RPE: Borg Rating of Perceived Exertion

The training intensity will increase over the 16 weeks of this intervention; the intensity of exercises completed without an elastic band will be amplified by increasing the number of repetitions the participants perform. For exercises performed with an elastic band, the intensity increase will be achieved by using the Borg Scale [44]. This scale measures the effort an

individual perceives when exercising and creates criteria to adjust the intensity of the programmed exercise.

In order to adequately use the Borg scale, the participants assigned to the strength training group must learn to use Thera-band resistance bands on the first day and to easily identify, for each exercise, which gripping point on the band is equivalent to an effort that is moderate, intermediate, hard, or very hard according to the Borg scale. In addition, to facilitate the progression in the effort intensity required for the exercises with the elastic band, from the eighth week of training the Silver Thera-band will be changed for the Gold one which produces greater resistance.

Aerobic training: Each session will begin with 10 minutes of stretching of the major muscle groups. Subsequently, participants will complete 4 series of brisk walking for 10 minutes followed by 1 minute of recovery. To ensure that the intensity of the exercise progresses from moderate to vigorous, we will monitor the heart rate (HR) of each participant. The progression in exercise intensity will be achieved by increasing the participant's target HR every 2 weeks. Thus, using the formula published by Tanaka et al. to calculate the maximum HR (MHR) [45], the intensity of the exercise will be progressively increased as follows: weeks 1–2: 55% MHR; weeks 3–4: 58% MHR; weeks 5–6: 61% MHR; weeks 7–8: 64% MHR; weeks 9–10: 67% MHR; weeks 11–12: 70% MHR; weeks 13–14: 73% MHR; and weeks 15–16: 76% MHR. The session will end with a 10-minute session of gentle stretching exercises targeting the major muscle groups (Figure 3).

Figure 3. Aerobic training.

Legend of figure 3: HR: Heart Rate

Mixed training: As in the previous two groups, each training session will begin with 10 minutes of stretching of the major muscle groups. The main part of each mixed session will consist of two parts. First, similar to the strength training group, the participants will perform a single circuit of 8 strength exercises interspersed with 1 minute of recovery for each strength exercise. Second, as in the aerobic training group, the participants will perform 2 sets brisk walking for 10

minutes followed by 1 minute of recovery, following the same exercise intensity progression as described for the aerobic training group. Finally, these sessions will also end with a 10-minute session of gentle stretching exercises targeting the major muscle groups.

Instruments

The participants will be assessed at three different times. First, before beginning the intervention; second, immediately after the end of the intervention; and third, six months after the end of the intervention (6-month follow-up). All the assessments will be performed in one single session and will be scheduled between 10 a.m. and 12 p.m. to minimise variability. Variables and evaluation times are summarized in Table 1.

Table 1. Study variables and assessment points

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		**Close-out**
TIMEPOINT**	**$-t_1$**	**0**	***t_1*** *baseline*	***t_2*** *Post-treatment*	***t_3*** *6 month follow-up*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
[Strength training]			←	→	
[Aerobic training]			←	→	
[Mixed training]			←	→	
ASSESSMENTS:					
Positive psychotic symptoms			X	X	X
Negative psychotic symptoms			X	X	X
General psychopathology			X	X	X

Body mass index			X	X	X
Body fat mass			X	X	X
Waist circumference			X	X	X
Quality of life			X	X	X
Level of physical activity			X	X	X

Metrics

The psychometric attributes of all the measurement tools used in this project, such as the reliability and validity, are psychometrically sound.

Primary outcome

The *Positive and Negative Syndrome Scale* (PANSS) is a semi-structured interview which assesses the positive (PANSS-P: 7 items, range 7–49), negative (PANSS-N: 7 items, range 7–49), and general (PANSS-G: 16 items, range 16–112) symptoms of psychosis experienced by patients in the week prior to the test on a 7-point Likert-type scale (from 1, 'none', to 7, 'extreme') [46]. We will analyse the three subscales separately and the positive-symptom factor will serve as the primary outcome of this study. The subscales of the Spanish version are strongly associated with those of the original version ($r = 0.92$ for PANSS-P and $r = 0.83$ for PANSS-N), with item correlations ranging from $r = 0.64$ to $r = 0.97$, and with high inter-rater reliability ($r = 0.81$) [47].

Secondary outcomes

Anthropometric and body composition variables: The body mass index (BMI), calculated as the patient weight in kilograms divided by their height in squared meters, will be calculated using a SECA® 780 electronic balance scale with a mechanical telescopic stadiometer. Body fat mass (BFM) will be determined using a TANITA® TBF-410 M body-fat analyser. Waist circumference (WC) will be measured to the nearest centimetre using a flexible tape measure at the level half-way between the lower rib margin and the iliac crest.

Physical activity (PA) levels: PA levels will be assessed using the *International Physical Activity Questionnaire-Short Form* (IPAQ-SF) [48]. Using seven items, this self-reported questionnaire collects data on the patients' PA in the 7 days prior to the test. The total number of days and minutes of PA will be calculated by adding all PA category scores performed over the seven days. Data from the IPAQ-SF will be converted into metabolic equivalent minutes per week (METs-min/week), using the formula published by Ainsworth et al. [11].

Specifically, the IPAQ-SF questionnaire records activity at four intensity levels: (1) vigorous activity such as aerobics; (2) moderate activity such as leisure cycling; (3) walking; and (4) sitting. This makes it possible to classify the PA levels of the participants as 'high' (> 1,500 METs), 'moderate' (600–1,500 METs), or 'low' (< 600 METs). The IPAQ has been validated in 12 countries [49] and showed adequate psychometric properties and the short version (the IPAQ-SF) has shown acceptable validity in an adult Spanish population [50].

The abbreviated *World Health Organization Quality of Life Assessment (WHO-QoL-BREF)* [51]: This survey comprises 26 items with five Likert-type responses each, and is a standard questionnaire used to measure patient quality of life. It assesses patients under four health domains: physical, psychological, social, and environmental. In this study we will analyse the sum of the four dimensions, with higher scores indicating a better quality of life. This scale has been validated for Spanish and the instrument has a good internal consistency with a Cronbach alpha of 0.88 for the overall scale and a range of 0.70 to 0.79 for its dimensions [52].

Sociodemographic metrics

Age, gender, marital status, education level, job status, and institutionalisation regime will be encoded.

Clinical metrics

The duration of patient psychoses and history of hospitalisations since the first episode will be recorded. Other pharmacological and non-pharmacological interventions, as well as current medication and psychosocial care will also be checked.

Adherence

Specialists will direct all 48 sessions in each of the three training groups, registering each participant's attendance for each session, and adverse or unintended effects. Specialist will promote participant retention and complete follow-up. Sessions will be marked as finished when at least 75% of the training was completed.

Statistical data analysis

Based on an intention-to-treat sample, two-way mixed ANCOVA tests will be used to compare how the study interventions affect the primary and secondary outcomes, using time (baseline, post-intervention, and 6-month follow-up) as the within-group factor and group (aerobic, strength, or mixed) as the between-group factor. The analysis will be adjusted for sex, age, and antipsychotic medications. Effect sizes will be estimated using the partial eta squared formula ($\eta 2p$) and interpreted following the Cohen guidelines [53] for small effect sizes ($\eta 2p = 0.01$), moderate effect sizes ($\eta 2p = 0.06$), and large effect sizes ($\eta 2p = 0.14$). The significance level will be set at 5% (two-tailed analyses) and the data will be analysed using SPSS software, version 24.0 (IBM Corp., Armonk, NY.).

Data monitoring

The data monitoring committee will comprise at least two independent members that will periodically check the progression of the trial. After randomising the participants, the committee will meet every 6 weeks to review a report submitted by the researchers for the purpose of monitoring the progress of recruitment and data collection. The data monitoring committee will do an interim analyses immediately after the end of the intervention, in order to decide to finish the trial. If any important modifications are made to the protocol, these will be communicated to the Ethics Committee at once.

Data confidentiality

After the measurements are recorded, the collected data will be transferred to a database on a password-locked stand-alone desktop computer which will be kept in a locked research room at

the Department of Medicine in the Faculty of Health Sciences at the University CEU-Cardenal Herrera of Valencia. The collected data will be saved as traceable anonymous data with sequentially allocated numbers which the researchers will be able to access.

Ethics and dissemination

This study will be conducted according to the principles established in the Declaration of Helsinki, the Convention on Human Rights and Biomedicine (Oviedo Convention), and the UNESCO Universal Declaration on the human genome research and human rights. This project was approved by the Ethics Committee for Biomedical Research at the CEU Cardenal Herrera University of Valencia in Spain (reference number: CEI18/215) (Additional file 4); the ethics approval applies to all participating centres.

All the participants will be informed about the length and characteristics of the study and the voluntary nature of their participation in it. After explaining the project in detail, we will answer any questions potential participants might have about it and then they will be provided with an informed consent document that they will have to sign should they wish to participate in the study. In turn, we will provide them with the contact details for the principal investigator of the project so participants will be able to communicate with them at any time.

Participants will also be informed that all the data collected during the investigation will be treated confidentially in accordance with current regulations on the protection of personal data, Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, and European Union regulation 2016/679 of the European Parliament and Council, of April 27, 2016, regarding the protection of natural persons with regard to the processing of personal data and the free circulation of this data. Additionally, the study is registered at ClinicalTrials.gov (NCT03953664).

The findings of this study will be published in peer reviewed indexed (JCR) journals. We will also present the results and findings at related research conferences. Furthermore, we will also make the full study report available to the relevant health authorities.

Discussion

The greatest strength of this study is that, to the best of our knowledge, it will be the first RCT to compare the effects of three types of training program (aerobic, strength, or mixed) on improving the symptoms of psychosis.

Many studies have been published that demonstrate the benefits that performing physical exercise has on the population affected by schizophrenia [12, 13, 29, 35, 54], and therefore this type of non-pharmacological therapeutic strategy should be one of the standard treatments prescribed to these patients. Some studies have examined the benefits of aerobic training [13, 23, 54], others have focused on mixed training interventions [12, 34], and still others have compared these strategies or implemented more sedentary activities such as occupational therapy [29]. Some work has also evaluated the effects of practicing yoga [23], dance [55, 56], or football [22]. However, only two studies have evaluated the effectiveness of strength training in patients with schizophrenia [24, 35].

The work by Heggelund et al. [35] evaluated the effects that training the maximum lower-limb strength for 8 weeks had on the net mechanical efficiency of walking, the symptoms of schizophrenia, and patient quality of life, and compared these outcomes with the effects of a sedentary activity such as self-entertainment with video games. Their results suggested that this type of strength training improved the maximum lower-limb strength of these patients as well as their walking performance, however, they found no alterations in the overall PANNS or SF-36 (*36-Item Short Form Health Survey*) scores.

In contrast, the study by Silva et al. [24] assessed the differences between the effects of 20 weeks of strength training versus mixed training on the symptoms of psychosis or depression, quality of life, and serum concentrations of Insuline Growth Factor-1, Insuline Growth Factor Binding Protein, and a neurotrophic factor derived from brain Brain-Derived Neurotrophic Factor in patients with schizophrenia. This group found statistically significant improvements for both the strength and the mixed training groups in the overall PANNS scale score, positive

symptomatology, and maximum strength in the arm-extension test. Statistically significant improvements in the negative symptomatology and maximum strength in the chest-press test were only found in the strength training group. Although the results of these two publications are encouraging, further investigation will be required because the sample size in both these studies was small, with a maximum of only 13 participants per group, and neither of them collected data from a follow-up phase. In addition, one of these studies did not use a randomised sampling strategy [35].

Strength training has also obtained good results in other lines of research enquiry. For example, Cassilhas et al. concluded that intensive strength training conducted in an elderly population improved their mood, anxiety, and strength [57]. Similarly, Stanton et al. reviewed the benefits of aerobic and strength training in patients with depression and found that the latter was able to improve the mood and symptoms of depression in these patients [58]. However, these results strongly differ from those from a meta-analysis carried out by Gordon et al. which concluded that strength training significantly reduced the symptoms of depression [36].

Finally, Subramaniapillai et al. conducted a descriptive study with 113 patients diagnosed with schizophrenia and 60 patients with bipolar disorder to determine their physical activity preferences, and 67.6% of the respondents subsequently stated that they would like incorporate strength training into their exercise programs [59].

Considering all the above, and given that so far no studies have identified which training types are most beneficial to patients affected by schizophrenia, the study plan described here aims to analyse and compare the effects of strength training, aerobic training, and mixed training interventions on the symptomatology, health-related quality of life, and anthropometric variables of these patients. The design of this study incorporates a series of improvements with respect to previously published work examining the effects of strength training in patients with schizophrenia: this will be a multicentre study, with a larger sample size (n = 84), and a follow-up assessment carried out 6 months after the end of the intervention. Finally, we will be able to

compare the benefits of each of the main types of training because we will include three intervention groups.

Nevertheless, this study will have some limitations. We do not plan to record the dietary intake of the participants and so it will be impossible to independently assess the impact of physical exercise on anthropometric parameters and body composition. In addition, the questionnaire data (level of physical activity and quality of life) will be self-reported, which may be affected by participants' personal perceptions.

The results of this project will allow us to separately understand the effects of each of the training interventions and identify if any of them are more beneficial to these patients with schizophrenia in terms of the different variables we plan to analyse. This knowledge will help to improve the prescription of different training types to each patient to help them better manage their disease in the future.

Trial Status

Protocol version number: NCT03953664

Protocol version date: May 16, 2019

Date recruitment began: Jan 14, 2020

Approximate date when recruitment will be completed: January 2021

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Authors' contributions

LGG: Conceived the study and wrote the draft for the manuscript. LGG, SLC, YCM, MISL, JFL, DMA and LPG contributed to the development of the design. SLC and LPG contributed to the literature search. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Competing interests

The authors declare they have no competing interests.

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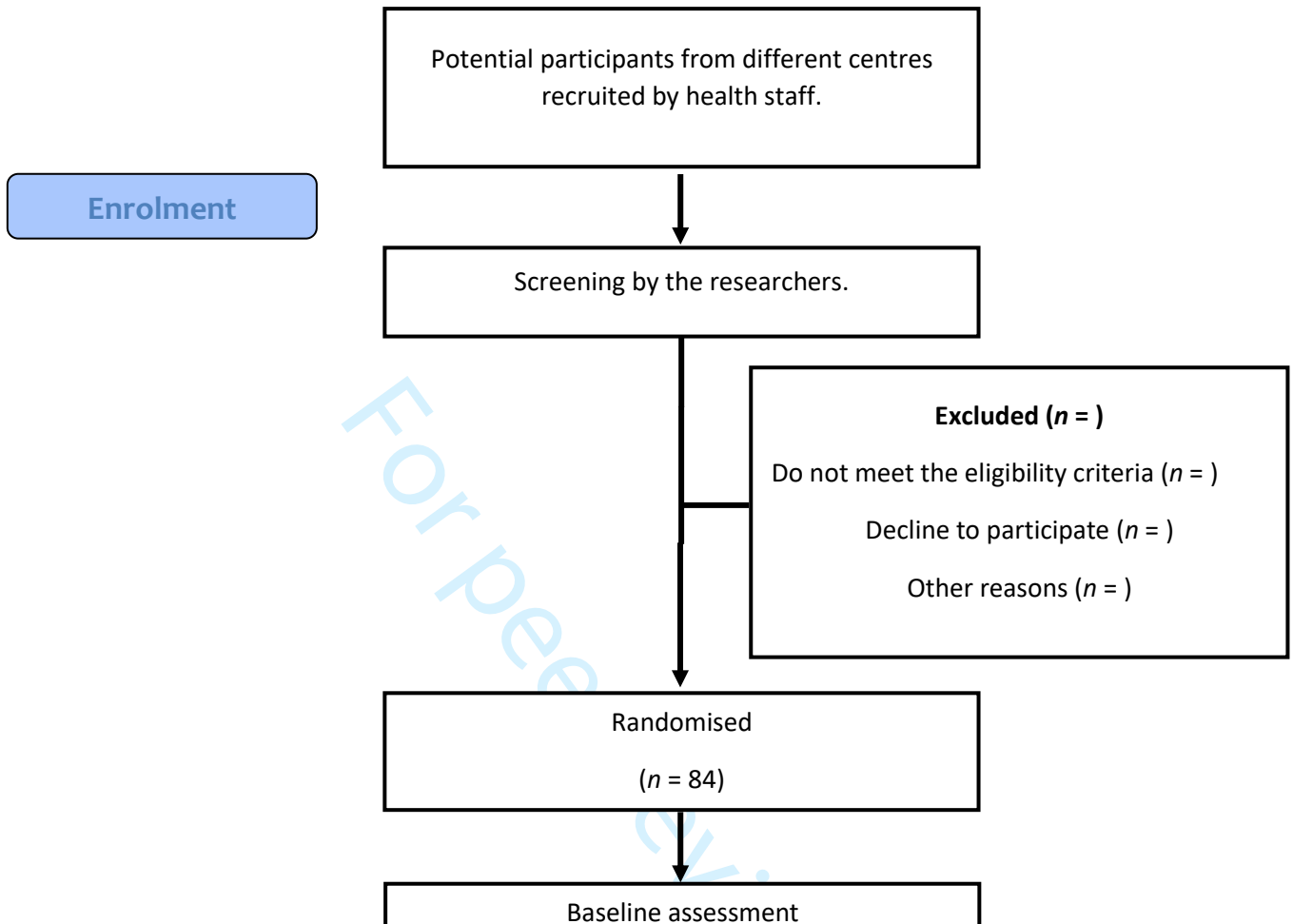
Abbreviations

BMI: Body Mass Index; CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and on Line Tele Health; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; IPAQ-SF: Physical Activity Questionnaire-Short Form; METs-min/week: Minutes Per Week; PA: Physical Activity; PANSS: Positive and Negative Syndrome Scale; PANSS-G: General symptoms of Syndrome Scale; PANSS-N: Negative Syndrome Scale; PANSS-P: Positive Syndrome Scale; RCT: Randomised Clinical Trial; SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials; WHO: Word Health Organization; WHO-QoL-BREF: World Health Organization Quality of Life Assessment



STRENGTH TRAINING PROGRAM

	1 WEEK	2 WEEK	3 WEEK	4 WEEK	5 WEEK	6 WEEK	7 WEEK	8 WEEK	9 WEEK	10 WEEK	11 WEEK	12 WEEK	13 WEEK	14 WEEK	15 WEEK	16 WEEK
WARM-UP	**10 mins of stretching the major muscle groups**															
	15 rep.	15 rep.	15 rep.	15 rep.	20 rep.	20 rep.	20 rep.	20 rep.	25 rep.	25 rep.	25 rep.	25 rep.	30 rep.	30 rep.	30 rep.	30 rep.
Recovery	**1 mins of gentle stretching**															
	15 rep.	15 rep.	15 rep.	15 rep.	20 rep.	20 rep.	20 rep.	20 rep.	25 rep.	25 rep.	25 rep.	25 rep.	30 rep.	30 rep.	30 rep.	30 rep.
Recovery	**1 mins of gentle stretching**															
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	**1 mins of gentle stretching**															
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	**1 mins of gentle stretching**															

	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	**1 mins of gentle stretching**														
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	**1 mins of gentle stretching**														
	15 rep.	15 rep.	15 rep.	15 rep.	18 rep.	18 rep.	18 rep.	18 rep.	20 rep.	20 rep.	20 rep.	20 rep.	22 rep.	22 rep.	22 rep.	22 rep.
Recovery	**1 mins of gentle stretching**														
	15 rep.	15 rep.	15 rep.	15 rep.	18 rep.	18 rep.	18 rep.	18 rep.	20 rep.	20 rep.	20 rep.	20 rep.	22 rep.	22 rep.	22 rep.	22 rep.
Recovery	**1 min of gentle stretching**														
The entire circuit is repeated following the same indications															
COOL-DOWN	**10 mins of stretching the major muscle groups**														

AEROBIC TRAINING PROGRAM																
PROGRAM	**1 WEEK**	**2 WEEK**	**3 WEEK**	**4 WEEK**	**5 WEEK**	**6 WEEK**	**7 WEEK**	**8 WEEK**	**9 WEEK**	**10 WEEK**	**11 WEEK**	**12 WEEK**	**13 WEEK**	**14 WEEK**	**15 WEEK**	**16 WEEK**
WARM-UP	**10 mins of stretching the major muscle groups**															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
COOL-DOWN	**At the end of the second set: 10 mins of stretching the major muscle groups**															

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Title of manuscript: *Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial*

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	*Manuscript page*
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	*Page 2*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	*Page 2*
	2b	All items from the World Health Organization Trial Registration Data Set	*Included in the additional file 2*
Protocol version	3	Date and version identifier	*22 Oct, 2020*
Funding	4	Sources and types of financial, material, and other support	*The study is not funded*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	*Page 23*
	5b	Name and contact information for the trial sponsor	*The study is not funded*
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	*The study is not funded, and it has no sponsors*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	*There are no coordinating centre or steering committee*

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	*Pages 3-4*
	6b	Explanation for choice of comparators	*Pages 5,7-9*
Objectives	7	Specific objectives or hypotheses	*Page 4*
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	*Page 5*
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	*Page 5*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	*Page 6*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	*Pages 7-9*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	*There are no criteria for discontinuing or modifying allocated interventions for a given trial participant*
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	*Page 12*
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	*Page 6*

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	*Pages 10-11*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	*Pages 5, 6 and table 1*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	*Page 7*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	*Page 6*
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	*Page 6*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	*Page 6*
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	*Page 6-7*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	*Page 6*

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	*The study will be blinded during all the research*
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	*Pages 10-13*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	*Page 12*
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	*Page 12-13*
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	*Page 12*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	*Page 12*
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	*We are not going to do this analyses; we'll do only an intention-to-treat sample*
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	*Page 12*

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	*Page 12*
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	*Page 12*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	*Page 12*
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	*Page 13*
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	*Page 12*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	*Page 6*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	*Not applicable: the model consent include all the information of the study*
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	*Page 12-13*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	*Page 23*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	*Page 12-13*

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	*None of the interventions affects the health and integrity of the participants. The exercises proposed for each type of training will be adapted to the physical condition of each participant to avoid any type of injury typical of performing physical exercise.*
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	*Page 13*
	31b	Authorship eligibility guidelines and any intended use of professional writers	*Page 23*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	*Page 13*
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	*Yes*
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	*No biological specimens are collected as part of this trial*

ALL ITEMS FROM THE WORLD HEALTH ORGANIZATION TRIAL REGISTRATION DATA SET

Data category	Information
Primary registry and trial identifying number	*ClinicalTrials.gov NCT03953664*
Date of registration in primary registry	*16 May, 2019*
Secondary identifying numbers	-
Source(s) of monetary or material support	*The study is not funded*
Primary sponsor	*The study is not funded*
Secondary sponsor(s)	*The study is not funded*
Contact for public queries	-
Contact for scientific queries	-
Public title	*Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial*
Scientific title	*Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial*
Countries of recruitment	*Spain*
Health condition(s) or problem(s) studied	*Exercise training; Schizophrenia*

Data category	Information
Intervention(s)	*Three physical exercise programs: strength, aerobic, and mixed (strength and aerobic)*
Key inclusion and exclusion criteria	*Inclusion criteria: (1) age between 18–65 years; (2) Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of schizophrenia; and (3) able to read and understand the Spanish language.* *Exclusion criteria: (1) acute suicidality; (2) representing an acute danger to others; (3) other psychiatric diagnoses or acute psychiatric illnesses; (4) motor or behavioural pathologies that prevent the person from completing the exercise training; (5) participation in similar programs or interventions at the time of enrolment.*
Study type	*Interventional* *Allocation: randomized* *Intervention model: simple allocation strategy* *Masking: single-blinded (evaluator)* *Primary purpose: prevention* *Phase III*
Date of first enrolment	*January 2020*
Target sample size	*84*
Recruitment status	*Recruiting*
Primary outcome(s)	*Positive symptomatology, negative symptomatology, and general symptomology (using the Positive and Negative Syndrome Scale)*
Key secondary outcomes	*body composition (by assessing body mass index, body fat mass and waist circumference), physical activity levels (International Physical Activity Questionnaire-Short Form), and quality of life (abbreviated World Health Organization Quality of Life questionnaire).*

BMJ Open

Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial

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Primary Subject Heading:	Mental health
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TITLE OF MANUSCRIPT: Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial

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Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial

Abstract

Introduction: Numerous studies support the practice of different physical exercise modalities as an effective treatment to address the different problems associated with schizophrenia, reporting that they result in significant improvements in patient symptoms and quality of life. Given the lack of studies comparing different types of training in controlled environments, the aim of this proposed study will be to compare the effects of three physical exercise programs (strength, aerobic, and mixed) on the symptoms, body composition, level of physical activity, and health-related quality of life of patients with schizophrenia.

Methods and analysis: A multicentre, parallel-group, single-blinded (evaluator), randomised (ratio 1:1:1) clinical trial will be conducted with 102 patients recruited from different psychosocial care centres. The participants will be randomised into three 16-week training groups comprising 48 sessions lasting one hour each. The groups will complete aerobic, strength, or mixed (aerobic + strength) training. All the participants will be assessed before, immediately after, and 6 months after the end of the intervention. The study variables will include positive symptomatology, negative symptomatology, and general symptomology (using the *Positive and Negative Syndrome Scale)* as the primary outcome; as secondary outcome: body composition (by assessing body mass index, body fat mass and waist circumference), physical activity levels (*International Physical Activity Questionnaire-Short Form*), and quality of life (abbreviated *World Health Organization Quality of Life* questionnaire).

Ethics and dissemination: This study was approved by the ethics committees for Biomedical Research at the CEU Cardenal Herrera University of Valencia in Spain (reference number:

CEI18/215). Participants will be fully informed of the purpose and procedures of the study, and written informed consent will be obtained from every participant. The results from this study will be published in peer-reviewed journals and presented in scientific conferences.

Trial registration number: NCT03953664.

Strengths and limitations of this study

- This is the first prospective randomised clinical trial to compare the effects of three different physical exercise programs (aerobic, strength, and mixed) in individuals with schizophrenia.
- This study assesses positive and negative psychotic symptoms, health-related quality of life, and body composition.
- The statistical power is based on the primary objective to evaluate effects of physical exercise programs on symptomatology.
- The nature of the physical exercise programs (types of exercise, frequency, session duration, program duration, intensity, progression, and training settings) and the 6-month follow-up assessment are strengths of the study design.
- The study is limited by the absence of daily food records.

Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial

Introduction

Schizophrenia is a serious chronic mental illness that, according to World Health Organization (WHO) data [1], affects 21 million people worldwide. This disease is characterised by a combination of positive symptoms (hallucinations, delusions, thoughts, and/or movement disorders), negative symptoms (associability, anhedonia, abolition, affective flattening, and alogia), and cognitive symptoms (problems with operational memory, executive functioning, and concentration) [2, 3]. In addition, schizophrenia is accompanied by a huge individual and social burden [4, 5] and is the eighth leading cause of disability-adjusted life years in 15 to 44-year-olds [6].

Schizophrenia is related to a sedentary lifestyle [7–9] and is associated with cardiovascular diseases, coronary heart disease [10], diabetes, obesity, dyslipidemia, and metabolic syndrome, among other comorbidities [11, 12]. Some of these pathologies are a consequence of the antipsychotic drugs that these patients receive to treat their disease [13], but there are also studies that postulate that the metabolic alterations present in these individuals are inherent to the schizophrenic disease they suffer [14]. All of the above means that, compared to the general population, people suffering from this disease have a 40% to 60% higher probability of premature death and a 20% lower life expectancy [15].

On the other hand, there is evidence that the quality of life perceived by patients with schizophrenia is lower than in the rest of the population in every domain studied [16]. The intensity of the symptoms of this disease, its treatment, and the comorbidities associated with it strongly impact the quality of life of patients affected by it, which is further jeopardised by the social stigma and low self-esteem that it entails [17, 18]. Of note, some studies have shown that physical activity positively contributes to the quality of life of these patients [19].

Without a doubt, physical activity is an important factor in preserving the general health and preventing chronic diseases such as diabetes, dyslipidemia, obesity, and cardiovascular diseases in individuals with schizophrenia. Indeed, in individuals with schizophrenia, exercise is inversely correlated with morbidity and mortality as a result of these diseases [20]. Specifically, significant results in terms of quality of life [21], positive and negative symptoms [22-24], cognitive functioning [25-28] improvement in sleep quality [29, 30], and cardiopulmonary function [31-33] were found in studies that used physical activity as an intervention in populations affected by schizophrenia. In addition, physical activity reduces the general care burden of these patients [34].

Therefore, the prescription of physical exercise is a practice validated for improving the symptoms of schizophrenia and to help prevent the diseases associated with it. However, to the best of our knowledge, there are still significant gaps in the evidence indicating what types of training might be most effective at improving the symptoms of these patients [21, 35–37]. Most work studying the effects of physical activity in patients diagnosed with schizophrenia has focused on aerobic or mixed physical exercise programs [12, 23, 30, 32–34, 38]. In fact, even though strength training exercise interventions have shown improvements in diseases such as depression and anxiety [24, 39], only two studies have used this type of training in patients with schizophrenia [40]. Nonetheless, these studies found that strength training programs reduced the psychopathology [24] and improved the maximum strength and walking performance of these patients [24, 39].

Based on all the above, the main objective of this proposed work will be to analyse and compare the effects of three different physical exercise programs (strength, aerobic, or mixed) on the symptomatology (positive and negative), health-related quality of life, and anthropometric variables of patients with schizophrenia enrolled in a psychosocial rehabilitation program.

Methods and analysis

Study design

This will be a three-armed, multi centre, single-blinded, randomised clinical trial (RCT), comparing three conditions: strength training, aerobic training, and mixed training (strength + aerobic). The participants will be assessed at baseline, post-treatment, and at a 6-month follow-up. A flowchart showing the proposed progression of the participants through the study is shown in figure 1. The work will adhere to the CONSORT standards for randomised trials [41-43] as well as the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and on Line Tele Health) [44], the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines (Additional file 1) and the World Health Organization trial registration data set criteria (Additional file 2) [45]. This current protocol was registered at ClinicalTrial.gov with reference number NCT03953664.

Figure 1. Flowchart representing the movement of the participants through the study.

Patient involvement

Patients will be involved at several stages of the trial, including the design, management, and conduct of the trial. We will receive input from patients who are living with schizophrenia in the design of the trial materials and management oversight through membership of the trial steering committee. We carefully will assess the adverse events of the trial interventions on patients. We intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

Study population, recruitment, and eligibility criteria

This RCT will be conducted from six psychosocial care centres for people with severe mental illness located in different parts of Spain: the Fundación Agustín Serrate (Huesca), Fundación Rey Ardid (Zaragoza), Fundación SASM (Valencia), Fundación Els Tres Turons (Barcelona), CREAP (Valencia), and Asociación Acova (Valencia). The participants will be recruited by the health staff working in the different centres.

The researchers who manage the study will go to the different psychosocial care centres to explain the study and eligibility criteria to the health staff, and will give them an information

sheet containing the study characteristics. The health staff at those institutions will then distribute the information to interested and suitable candidates directly via an interview in which the study will be explained in detail and they will be asked if they want to participate in the study. If they wish to participate, these patients will be asked to sign the informed consent document (Additional file 3) and will be instructed to maintain their usual treatments and appointments with mental health professionals.

To be included, the participants must fulfil all the inclusion criteria and none of the exclusion criteria. The inclusion criteria will be as follows: (1) age between 18–65 years; (2) Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of schizophrenia; and (3) able to read and understand the Spanish language. The exclusion criteria will be: (1) acute suicidality; (2) representing an acute danger to others; (3) other psychiatric diagnoses or acute psychiatric illnesses; (4) other disorders that could prevent the person from completing the exercise training; (5) participation in similar programs or interventions at the time of enrolment.

Randomisation and blinding

An independent researcher unaware of the study characteristics will perform the randomisation process. In order to randomly allocate the participants to one of the three conditions (aerobic, strength, or mixed), a computer-generated random number sequence [46] will be used (applying a simple allocation strategy). The randomisation will occur before baseline measures are taken and the allocation ratio (1:1:1) will be counter-balanced in each center. This sequence will be recorded in a password-protected spreadsheet table and concealed to other researchers during the study.

Because the different exercise interventions significantly vary, it will be impossible to mask the group allocation to the physical therapists or the participants. However, the outcome evaluators and data analysts will be blinded to treatment allocations; outcome assessors and data analysts will be not involved in participant recruitment, treatment assignment, and treatment administration (interventions). Participants will be instructed not to tell outcome assessors of

the intervention they received. The success of blinding will be measured and reported using a blinding questionnaire. To avoid inter-observer variability bias, the measurements in each of the groups will always be completed by the same investigator.

Sample size

Sample size calculation was conducted using G*Power software version 3.1.9.2 [47] based on data collected from a similar study by Silva et al [24]. The effect size (ηp^2) for the difference in the positive symptoms of schizophrenia at the end of 10-weeks in the study was 0.229. To achieve 90% power, with an α level of 0.05, the total sample size needed is 78 (26 participant in each group). Thus, anticipating a dropout rate of 30% according to Vancampfort et al. [48], the necessary sample size would be 34 participants per study arm (n = 102).

Interventions

The intervention will consist of a total of 48 sessions (3 weekly group-based sessions lasting one hour each for 16 weeks) and will be carried out at the gymnasium or the sports courts of each of the psychosocial care centres. To make the comparison fair, the total number of training sessions and duration of each session will be the same for the three training groups. These groups will be led by a professional physical education specialist from each psychosocial care centre who will also be responsible for recording each participant's degree of compliance with the intervention. The exercise dosing patters will be based on current recommendations for individuals with schizophrenia [49-51]. The progression of the intensity of each training session will be a motivational strategy for the participants. To describe interventions, we have used the Consensus on Exercise Reporting Template (CERT) (Additional file 4).

Strength training: Each strength training session will begin with a set of gentle stretching exercises lasting 10 minutes, designed to target the major muscle groups. This will be followed by two sets of 8 strength training exercises with 1 minute of recovery programmed between each one. An elastic resistance band (Thera-band) will be used in 4 of the 8 strength exercises.

Finally, the training will end with 10 minutes of gentle stretching of the major muscle groups as a cool-down (Figure 2).

Figure 2. Strength training.

Legend of figure 2: RPE: Borg Rating of Perceived Exertion

The training intensity will increase over the 16 weeks of this intervention; the intensity of exercises completed without an elastic band will be amplified by increasing the number of repetitions the participants perform. For exercises performed with an elastic band, the intensity increase will be achieved by using the Borg Scale [52]. This scale measures the effort an individual perceives when exercising and creates criteria to adjust the intensity of the programmed exercise.

In order to adequately use the Borg scale, the participants assigned to the strength training group must learn to use Thera-band resistance bands on the first day and to easily identify, for each exercise, which gripping point on the band is equivalent to an effort that is moderate, intermediate, hard, or very hard according to the Borg scale. In addition, to facilitate the progression in the effort intensity required for the exercises with the elastic band, from the eighth week of training the Silver Thera-band will be changed for the Gold one which produces greater resistance.

Aerobic training: Each session will begin with 10 minutes of stretching of the major muscle groups. Subsequently, participants will complete 4 series of brisk walking for 10 minutes followed by 1 minute of recovery. To ensure that the intensity of the exercise progresses from moderate to vigorous, we will monitor the heart rate (HR) of each participant. The progression in exercise intensity will be achieved by increasing the participant's target HR every 2 weeks. Thus, using the formula published by Tanaka et al. to calculate the maximum HR (MHR) (208 – 0.7 * age) [53], the intensity of the exercise will be progressively increased as follows: weeks 1–2: 55% MHR; weeks 3–4: 58% MHR; weeks 5–6: 61% MHR; weeks 7–8: 64% MHR; weeks 9–10: 67% MHR; weeks 11–12: 70% MHR; weeks 13–14: 73% MHR; and weeks 15–16: 76% MHR.

The session will end with a 10-minute session of gentle stretching exercises targeting the major muscle groups (Figure 3).

Figure 3. Aerobic training.

Legend of figure 3: HR: Heart Rate

Mixed training: As in the previous two groups, each training session will begin with 10 minutes of stretching of the major muscle groups. The main part of each mixed session will consist of two parts. First, similar to the strength training group, the participants will perform a single circuit of 8 strength exercises interspersed with 1 minute of recovery for each strength exercise. Second, as in the aerobic training group, the participants will perform 2 sets brisk walking for 10 minutes followed by 1 minute of recovery, following the same exercise intensity progression as described for the aerobic training group. Finally, these sessions will also end with a 10-minute session of gentle stretching exercises targeting the major muscle groups.

Instruments

The participants will be assessed at three different times. First, before beginning the intervention; second, immediately after the end of the intervention; and third, six months after the end of the intervention (6-month follow-up). All the assessments will be performed in one single session and will be scheduled between 10 a.m. and 12 p.m. to minimise variability.

Variables and evaluation times are summarized in Table 1.

Table 1. Study variables and assessment points

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		**Close-out**
TIMEPOINT**	**$-t_1$**	**0**	**t_1** *baseline*	**t_2** *Post-treatment*	**t_3** *6 month follow-up*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			

INTERVENTIONS:					
[Strength training]			←	→	
[Aerobic training]			←	→	
[Mixed training]			←	→	
ASSESSMENTS:					
Positive psychotic symptoms			X	X	X
Negative psychotic symptoms			X	X	X
General psychopathology			X	X	X
Body mass index			X	X	X
Body fat mass			X	X	X
Waist circumference			X	X	X
Quality of life			X	X	X
Level of physical activity			X	X	X

Metrics

The psychometric attributes of all the measurement tools used in this project, such as the reliability and validity, are psychometrically sound.

Primary outcome

The *Positive and Negative Syndrome Scale* (PANSS) is a semi-structured interview which assesses the positive (PANSS-P: 7 items, range 7–49), negative (PANSS-N: 7 items, range 7–49), and general (PANSS-G: 16 items, range 16–112) symptoms of psychosis experienced by patients in the week prior to the test on a 7-point Likert-type scale (from 1, 'none', to 7, 'extreme') [54]. We will analyse the three subscales separately and the positive-symptom factor will serve as the primary outcome of this study. The subscales of the Spanish version are strongly associated with those of the original version ($r = 0.92$ for PANSS-P and $r = 0.83$ for PANSS-N), with item correlations ranging from $r = 0.64$ to $r = 0.97$, and with high inter-rater reliability ($r = 0.81$) [55].

Secondary outcomes

Anthropometric and body composition variables: The body mass index (BMI), calculated as the patient weight in kilograms divided by their height in squared meters, will be calculated using a SECA® 780 electronic balance scale with a mechanical telescopic stadiometer. Body fat mass (BFM) will be determined using a TANITA® TBF-410 M body-fat analyser. Waist circumference (WC) will be measured to the nearest centimetre using a flexible tape measure at the level half-way between the lower rib margin and the iliac crest.

Physical activity (PA) levels: PA levels will be assessed using the *International Physical Activity Questionnaire-Short Form* (IPAQ-SF) [56]. Using seven items, this self-reported questionnaire collects data on the patients' PA in the 7 days prior to the test. The total number of days and minutes of PA will be calculated by adding all PA category scores performed over the seven days. Specifically, the IPAQ-SF questionnaire records activity at four intensity levels: (1) vigorous activity such as aerobics; (2) moderate activity such as leisure cycling; (3) walking; and (4) sitting. This makes it possible to classify the PA levels of the participants as 'high', 'moderate, or 'low' [57]. The IPAQ has been validated in 12 countries [58] and showed adequate psychometric properties and the short version (the IPAQ-SF) has shown acceptable validity in an adult Spanish population [59].

The abbreviated *World Health Organization Quality of Life Assessment (WHO-QoL-BREF)* [60]: This survey comprises 26 items with five Likert-type responses each, and is a standard questionnaire used to measure patient quality of life. It assesses patients under four health domains: physical, psychological, social, and environmental. In this study we will analyse the sum of the four dimensions, with higher scores indicating a better quality of life. This scale has been validated for Spanish and the instrument has a good internal consistency with a Cronbach alpha of 0.88 for the overall scale and a range of 0.70 to 0.79 for its dimensions [61].

Sociodemographic metrics

Age, gender, marital status, education level, job status, and institutionalisation regime will be encoded.

Clinical metrics

The duration of patient psychoses and history of hospitalisations since the first episode will be recorded. Other pharmacological and non-pharmacological interventions, as well as current medication and psychosocial care will also be checked. Adverse events to the interventions will be also registered.

Adherence

Specialists will direct all 48 sessions in each of the three training groups, registering each participant's attendance for each session, and adverse or unintended effects. Specialist will promote participant retention and complete follow-up. Sessions will be marked as finished when at least 75% of the training was completed. Participants will be instructed not to perform other rehabilitation interventions programs outside of the intervention for the entire duration of the study.

Statistical data analysis

Based on an intention-to-treat sample, two-way mixed ANCOVA tests will be used to compare how the study interventions affect the primary and secondary outcomes, using time (baseline, post-intervention -primary end point-, and 6-month follow-up) as the within-group factor and group (aerobic, strength, or mixed) as the between-group factor. The analysis will be adjusted for sex, age, adherence, and antipsychotic medications. Effect sizes will be estimated using the partial eta squared formula ($\eta 2p$) and interpreted following the Cohen guidelines [62] for small effect sizes ($\eta 2p = 0.01$), moderate effect sizes ($\eta 2p = 0.06$), and large effect sizes ($\eta 2p = 0.14$). Chi-squared test will be used to statistically assess success of blinding. The significance level will be set at 5% (two-tailed analyses) and the data will be analysed using SPSS software, version 24.0 (IBM Corp., Armonk, NY.).

Data monitoring

The data monitoring committee will comprise at least two independent members that will periodically check the progression of the trial. After randomising the participants, the committee will meet every 6 weeks to review a report submitted by the researchers for the purpose of monitoring the progress of recruitment and data collection. The data monitoring committee will do an interim analysis immediately after the end of the intervention, in order to decide to finish the trial. If any important modifications are made to the protocol, these will be communicated to the Ethics Committee at once.

Data confidentiality

After the measurements are recorded, the collected data will be transferred to a database on a password-locked stand-alone desktop computer which will be kept in a locked research room at the Department of Medicine in the Faculty of Health Sciences at the University CEU-Cardenal Herrera of Valencia. The collected data will be saved as traceable anonymous data with sequentially allocated numbers which the researchers will be able to access.

Ethics and dissemination

This study will be conducted according to the principles established in the Declaration of Helsinki, the Convention on Human Rights and Biomedicine (Oviedo Convention), and the UNESCO Universal Declaration on the human genome research and human rights. This project was approved by the Ethics Committee for Biomedical Research at the CEU Cardenal Herrera University of Valencia in Spain (reference number: CEI18/215) (Additional file 5); the ethics approval applies to all participating centres.

All the participants will be informed about the length and characteristics of the study and the voluntary nature of their participation in it. After explaining the project in detail, we will answer any questions potential participants might have about it and then they will be provided with an informed consent document that they will have to sign should they wish to participate in the study. In turn, we will provide them with the contact details for the principal investigator of the project so participants will be able to communicate with them at any time.

Participants will also be informed that all the data collected during the investigation will be treated confidentially in accordance with current regulations on the protection of personal data, Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, and European Union regulation 2016/679 of the European Parliament and Council, of April 27, 2016, regarding the protection of natural persons with regard to the processing of personal data and the free circulation of this data. Additionally, the study is registered at ClinicalTrials.gov (NCT03953664).

The findings of this study will be published in peer reviewed indexed (JCR) journals. We will also present the results and findings at related research conferences. Furthermore, we will also make the full study report available to the relevant health authorities.

Discussion

The greatest strength of this study is that, to the best of our knowledge, it will be the first RCT to compare the effects of three types of training program (aerobic, strength, or mixed) on improving the symptoms of psychosis.

Many studies have been published that demonstrate the benefits that performing physical exercise has on the population affected by schizophrenia [12, 13, 33, 39, 63], and therefore this type of non-pharmacological therapeutic strategy should be one of the standard treatments prescribed to these patients. Some studies have examined the benefits of aerobic training [13, 23, 63], others have focused on mixed training interventions [12, 38], and still others have compared these strategies or implemented more sedentary activities such as occupational therapy [33]. Some work has also evaluated the effects of practicing yoga [23], dance [64, 65], or football [22]. However, only two studies have evaluated the effectiveness of strength training in patients with schizophrenia [24, 39].

The work by Heggelund et al. [39] evaluated the effects that training the maximum lower-limb strength for 8 weeks had on the net mechanical efficiency of walking, the symptoms of schizophrenia, and patient quality of life, and compared these outcomes with the effects of a

sedentary activity such as self-entertainment with video games. Their results suggested that this type of strength training improved the maximum lower-limb strength of these patients as well as their walking performance, however, they found no alterations in the overall PANSS or SF-36 (*36-Item Short Form Health Survey*) scores.

In contrast, the study by Silva et al. [24] assessed the differences between the effects of 20 weeks of strength training versus mixed training on the symptoms of psychosis or depression, quality of life, and serum concentrations of Insuline Growth Factor-1, Insuline Growth Factor Binding Protein, and a neurotrophic factor derived from brain Brain-Derived Neurotrophic Factor in patients with schizophrenia. This group found statistically significant improvements for both the strength and the mixed training groups in the overall PANSS scale score, positive symptomatology, and maximum strength in the arm-extension test. Statistically significant improvements in the negative symptomatology and maximum strength in the chest-press test were only found in the strength training group. Although the results of these two publications are encouraging, further investigation will be required because the sample size in both these studies was small, with a maximum of only 13 participants per group, and neither of them collected data from a follow-up phase. In addition, one of these studies did not use a randomised sampling strategy [39].

Strength training has also obtained good results in other lines of research enquiry. For example, Cassilhas et al. [66] concluded that intensive strength training conducted in an elderly population improved their mood, anxiety, and strength. Similarly, Stanton et al. reviewed the benefits of aerobic and strength training in patients with depression and found that the latter was able to improve the mood and symptoms of depression in these patients [67]. However, these results strongly differ from those from a meta-analysis carried out by Gordon et al. which concluded that strength training significantly reduced the symptoms of depression [40].

A cross-sectional study concluded that patients with schizophrenia showed lower hand grip strength scores compared to healthy controls, and that hand grip strength scores correlated

positively with cognitive functions [68]. A more recent study concluded that higher hand grip strength was associated with greater left and right hippocampal volume and reduced white matter hyperintensities in major depressive disorder (MDD). These authors considered that interventions targeting strength fitness could improve brain health and reduce the neurocognitive abnormalities associated with MDD [69]. Finally, Subramaniapillai et al. [70] conducted a descriptive study with 113 patients diagnosed with schizophrenia and 60 patients with bipolar disorder to determine their physical activity preferences, and 67.6% of the respondents subsequently stated that they would like incorporate strength training into their exercise programs.

While the mechanisms by which the different exercise interventions may influence the symptoms and cognition of our patients will extend beyond the scope of this study, several mechanisms have been proposed in the scientific literature. The most frequently cited are neuroprotective mechanisms such as decreased inflammation, increased neurogenesis and neuroplasticity via brain-derived neurotrophic factor, and remyelination of white matter tracts [71,72].

Considering all the above, and given that so far no studies have identified which training types are most beneficial to patients affected by schizophrenia, the study plan described here aims to analyse and compare the effects of strength training, aerobic training, and mixed training interventions on the symptomatology, health-related quality of life, and anthropometric variables of these patients. The design of this study incorporates a series of improvements with respect to previously published work examining the effects of strength training in patients with schizophrenia: this will be a multicentre study, adequately powered (n = 102), and a follow-up assessment carried out 6 months after the end of the intervention. Finally, we will be able to compare the benefits of each of the main types of training because we will include three intervention groups, and we will report of all the exercise training programs information (types

of exercise, frequency, session duration, program duration, intensity, progression, training settings [i.e., supervised or group sessions]).

Nevertheless, this study will have some limitations. We do not plan to record the dietary intake of the participants and so it will be impossible to independently assess the impact of physical exercise on anthropometric parameters and body composition. In addition, the questionnaire data (level of physical activity and quality of life) will be self-reported, which may be affected by participants' personal perceptions.

The results of this project will allow us to separately understand the effects of each of the training interventions and identify if any of them are more beneficial to these patients with schizophrenia in terms of the different variables we plan to analyse. This knowledge will help to improve the prescription of different training types to each patient to help them maintain good control of symptoms of the disease.

Trial Status

Protocol version number: NCT03953664

Protocol version date: May 16, 2019

Date recruitment began: Jan 14, 2020

Approximate date when recruitment will be completed: April 2021

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Authors' contributions

LGG: Conceived the study and wrote the draft for the manuscript. LGG, SLC, YCM, MISL, JFL, DMA and LPG contributed to the development of the design. SLC and LPG contributed to the literature search. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Competing interests

The authors declare they have no competing interests.

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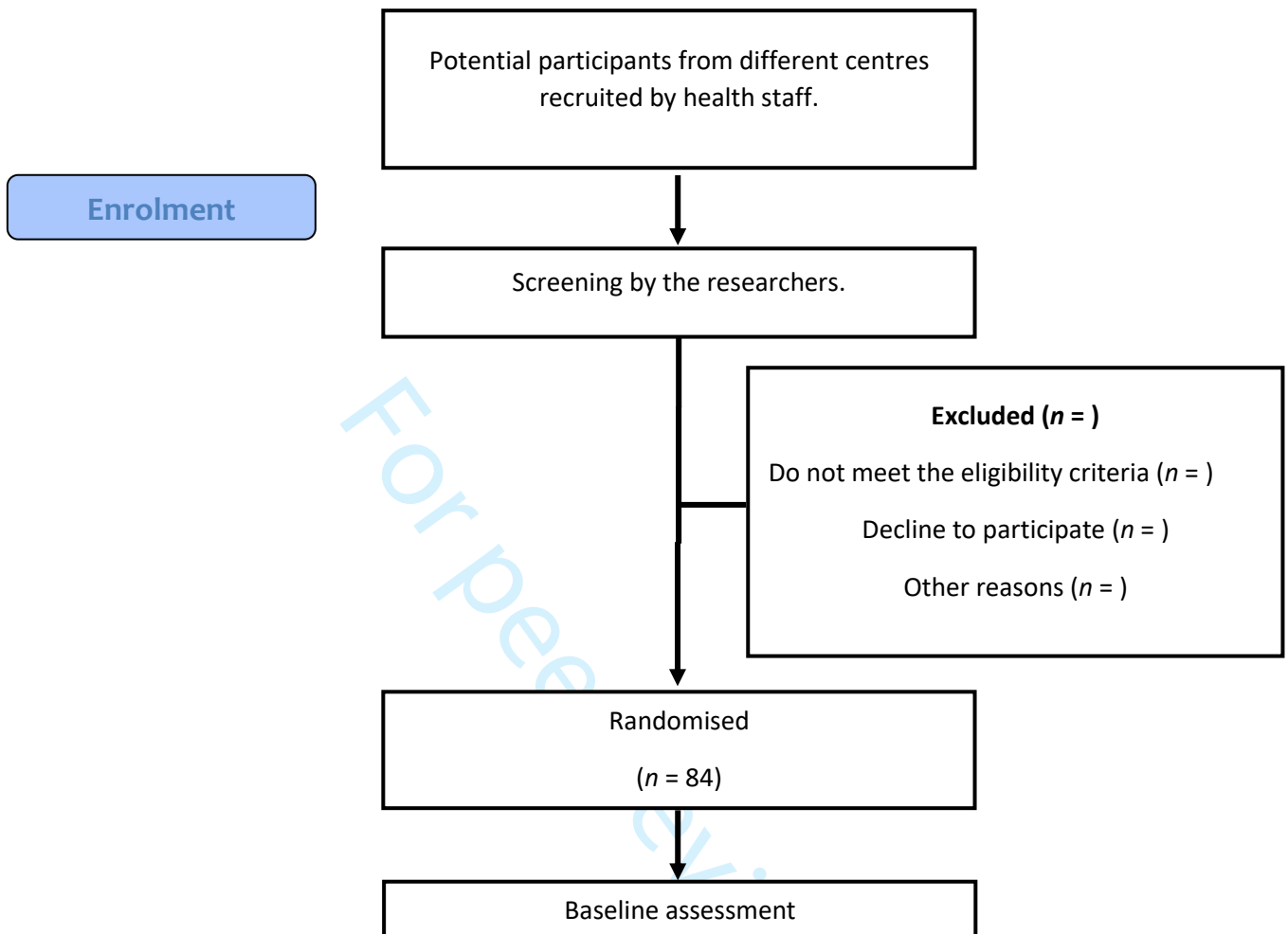
Abbreviations

BMI: Body Mass Index; CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and on Line Tele Health; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; IPAQ-SF: Physical Activity Questionnaire-Short Form; METs-min/week: Minutes Per Week; PA: Physical Activity; PANSS: Positive and Negative Syndrome Scale; PANSS-G: General symptoms of Syndrome Scale; PANSS-N: Negative

643 Syndrome Scale; PANSS-P: Positive Syndrome Scale; RCT: Randomised Clinical Trial; SPIRIT:
644 Standard Protocol Items: Recommendations for Intervention Trials; WHO: World Health
645 Organization; WHO-QoL-BREF: World Health Organization Quality of Life Assessment



STRENGTH TRAINING PROGRAM

	1 WEEK	2 WEEK	3 WEEK	4 WEEK	5 WEEK	6 WEEK	7 WEEK	8 WEEK	9 WEEK	10 WEEK	11 WEEK	12 WEEK	13 WEEK	14 WEEK	15 WEEK	16 WEEK
WARM-UP	**10 mins of stretching the major muscle groups**															
	15 rep.	15 rep.	15 rep.	15 rep.	20 rep.	20 rep.	20 rep.	20 rep.	25 rep.	25 rep.	25 rep.	25 rep.	30 rep.	30 rep.	30 rep.	30 rep.
Recovery	**1 mins of gentle stretching**															
	15 rep.	15 rep.	15 rep.	15 rep.	20 rep.	20 rep.	20 rep.	20 rep.	25 rep.	25 rep.	25 rep.	25 rep.	30 rep.	30 rep.	30 rep.	30 rep.
Recovery	**1 mins of gentle stretching**															
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	**1 mins of gentle stretching**															
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	**1 mins of gentle stretching**															

	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	**1 mins of gentle stretching**														
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	**1 mins of gentle stretching**														
	15 rep.	15 rep.	15 rep.	15 rep.	18 rep.	18 rep.	18 rep.	18 rep.	20 rep.	20 rep.	20 rep.	20 rep.	22 rep.	22 rep.	22 rep.	22 rep.
Recovery	**1 mins of gentle stretching**														
	15 rep.	15 rep.	15 rep.	15 rep.	18 rep.	18 rep.	18 rep.	18 rep.	20 rep.	20 rep.	20 rep.	20 rep.	22 rep.	22 rep.	22 rep.	22 rep.
Recovery	**1 min of gentle stretching**														
The entire circuit is repeated following the same indications															
COOL-DOWN	**10 mins of stretching the major muscle groups**														

AEROBIC TRAINING PROGRAM																
PROGRAM	**1 WEEK**	**2 WEEK**	**3 WEEK**	**4 WEEK**	**5 WEEK**	**6 WEEK**	**7 WEEK**	**8 WEEK**	**9 WEEK**	**10 WEEK**	**11 WEEK**	**12 WEEK**	**13 WEEK**	**14 WEEK**	**15 WEEK**	**16 WEEK**
WARM-UP	**10 mins of stretching the major muscle groups**															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
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AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
COOL-DOWN	**At the end of the second set: 10 mins of stretching the major muscle groups**															

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Title of manuscript: *Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial*

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	**Item No**	**Description**	***Manuscript page***
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	*Page 1*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	*Page 2*
	2b	All items from the World Health Organization Trial Registration Data Set	*Included in the additional file 2*
Protocol version	3	Date and version identifier	*22 March, 2021*
Funding	4	Sources and types of financial, material, and other support	*The study is not funded*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	*Page 26*
	5b	Name and contact information for the trial sponsor	*The study is not funded*
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	*The study is not funded, and it has no sponsors*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	*There are no coordinating centre or steering committee*

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	*Pages 3-4*
	6b	Explanation for choice of comparators	*Pages 5,7-9*
Objectives	7	Specific objectives or hypotheses	*Page 4*
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	*Page 5*
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	*Page 5*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	*Page 6*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	*Pages 7-9*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	*There are no criteria for discontinuing or modifying allocated interventions for a given trial participant*
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	*Page 12*
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	*Page 12*

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	*Pages 10-12*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	*Pages 5-9 and table 1*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	*Page 7*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	*Pages 5-6*
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	*Page 6*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	*Page 6*
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	*Page 6-7*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	*Pages 6-7*

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	*The study will be blinded during all the research*
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	*Pages 9-10; 12*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	*Page 12*
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	*Page 13*
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	*Page 12*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	*Page 12*
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	*We are not going to do this analyses; we'll do only an intention-to-treat sample*
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	*Page 12-13*

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	*Page 13*
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	*Page 12*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	*Page 13*
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	*Page 13*
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	*Page 13*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	*Pages 5-6*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	*Not applicable: the model consent include all the information of the study*
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	*Page 13*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	*Page 26*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	*Page 13*

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	*None of the interventions affects the health and integrity of the participants. The exercises proposed for each type of training will be adapted to the physical condition of each participant to avoid any type of injury typical of performing physical exercise.*
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	*Page 14*
	31b	Authorship eligibility guidelines and any intended use of professional writers	*Page 26*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	*Page 14*
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	*Yes*
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	*No biological specimens are collected as part of this trial*

ALL ITEMS FROM THE WORLD HEALTH ORGANIZATION TRIAL REGISTRATION DATA SET

Data category	Information
Primary registry and trial identifying number	*ClinicalTrials.gov NCT03953664*
Date of registration in primary registry	*16 May, 2019*
Secondary identifying numbers	-
Source(s) of monetary or material support	*The study is not funded*
Primary sponsor	*The study is not funded*
Secondary sponsor(s)	*The study is not funded*
Contact for public queries	-
Contact for scientific queries	-
Public title	*Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial*
Scientific title	*Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial*
Countries of recruitment	*Spain*
Health condition(s) or problem(s) studied	*Exercise training; Schizophrenia*

Data category	Information
Intervention(s)	*Three physical exercise programs: strength, aerobic, and mixed (strength and aerobic)*
Key inclusion and exclusion criteria	*Inclusion criteria: (1) age between 18–65 years; (2) Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of schizophrenia; and (3) able to read and understand the Spanish language.* *Exclusion criteria: (1) acute suicidality; (2) representing an acute danger to others; (3) other psychiatric diagnoses or acute psychiatric illnesses; (4) other disorders that could prevent the person from completing the exercise training; (5) participation in similar programs or interventions at the time of enrolment.*
Study type	*Interventional* *Allocation: randomized* *Intervention model: simple allocation strategy* *Masking: single-blinded (evaluator)* *Primary purpose: prevention* *Phase III*
Date of first enrolment	*January 2020*
Target sample size	*102*
Recruitment status	*Recruiting*
Primary outcome(s)	*Positive symptomatology, negative symptomatology, and general symptomology (using the Positive and Negative Syndrome Scale)*
Key secondary outcomes	*Body composition (by assessing body mass index, body fat mass and waist circumference), physical activity levels (International Physical Activity Questionnaire-Short Form), and quality of life (abbreviated World Health Organization Quality of Life questionnaire).*

RESEARCH ON STRENGTH TRAINING IN PATIENTS WITH SEVERE MENTAL DISORDER

INFORMED CONSENT document for Mr. / Mrs._____

_____

This Informed Consent Form is aimed at men and women who are cared for in one of the following centers: State Reference Center for Psychosocial Care (CREAP), Santos Andrés, Santiago y Miguel Foundation (SASM), ACOVA Association and Rey Ardid Foundation. These people are invited to participate in research on the impact of physical exercise on people with severe mental disorder.

Main researchers: Sergio Lacamara Cano (Responsible for Knowledge Management CREAP) and **Loreto Peyró Gregori** (Professor and researcher at the Faculty of Health Sciences of the CEU-Cardenal Herrera University).

The CEU - Cardenal Herrera University, in collaboration with the CREAP, SASM, ACOVA and Rey Ardid centers, are investigating the possible benefits of different forms of physical exercise in people with severe mental disorders. I am going to give you information and invite you to participate in this research. You do not have to decide today whether or not to participate in this research. Before deciding, you can discuss the research with someone you feel comfortable with and trust. There may be some words that you don't understand. Please do not hesitate to interrupt me to ask any questions or words you do not understand, and if you have questions later, you can ask me or the researchers conducting the study, whenever you want.

PURPOSE OF THE STUDY

There are many studies that support the practice of physical exercise as an effective treatment to address different problems related to the disease you suffer, especially it has significant effects on the quality of life and the symptoms of these people. For this reason, an investigation will be carried out in order to assess the effectiveness of different types of training to improve the symptoms and quality of life of these people.

The investigation will last for about 3 months, during which you will participate in a training plan led by a professional at the facilities of the center to which you belong and within the schedule contemplated in your comprehensive rehabilitation plan, so that you participate in This study will not take longer than the usual time. In addition, three researchers from the CEU - Cardenal Herrera University (Alfara del Patriarca, Valencia) will visit their center to carry out a small assessment of each participant that will be repeated three times, before starting the physical exercise sessions, at the end and six months later for this intervention to end. This assessment

does not contain any invasive techniques, it is not annoying, nor does it pose any risk to your health and well-being. The three evaluations will be identical and carried out by the same people. In order to study the effects of the different forms of physical exercise, we will do three different groups, each one with a different training. The allocation to each group is random, that is, neither we nor you can choose which group to be in since the allocation is done randomly, as if we were tossing a coin.

RISKS OR SIDE EFFECTS

None of the physical exercises carried out throughout the study will put the health and integrity of the person at risk. The exercises proposed for each type of training will be adapted to the physical condition of each participant to avoid any type of injury typical of physical exercise.

BENEFITS

If you participate in this research, you will get the following benefits:

- It will improve your physical condition
- It will improve your cardiovascular and cardiorespiratory health
- It will improve your body composition
- You will have a fun time with the rest of the participants

CONFIDENTIALITY

The information we collect during this research project will be kept confidential. Any information about you will have a number instead of your name, so only investigators will know what your number is, and the information will not be shared or released to anyone outside of the investigation team.

TO REFUSE OR WITHDRAW

Your participation in this research is completely voluntary. You can choose to participate or not. Whether you choose to participate or decide not to, all the services you receive at your center will continue as normal. You can change your mind later and stop participating at any time even if you have previously stated that you do.

If you have any questions, you can ask them now or later, even after the study has started. If you have questions later, you can contact the following person: **Sergio Lacamara Cano** (963403520 / slacamara@reyardid.org) and **Loreto Peyró Gregori** (96 136 90 00 - 64311 / lpeyro@uchceu.es).

This proposal has been reviewed and approved by the CEU - Cardenal Herrera University Ethical Evaluation Committee, which is a Committee whose task is to ensure that research participants are protected from harm.

INFORMED CONSENT SHEET

I have been invited to participate in **research on the effects of strength training in patients with severe mental disorders**. I have been informed about the purpose of the study, the risks, and the possible benefits.

I have read the information provided or it has been read to me. I have had the opportunity to ask about it and the questions I have asked have been answered satisfactorily. I voluntarily consent to participate in this research as a participant and understand that I have the right to withdraw from the research at any time without being affected in any way by the medical and psychosocial care I am receiving.

Participant Name: ____

Participant Signature: ____

Date (day / month): ____

Table 1. Proforma CERT assessment form					
Author and year					
Title: Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised clinical trial					
Journal: BMJ Open					
Study Location: Spain					
Reviewer and date					
Item	Description	Data extraction details	Location (pg, URL, etc)	Yes, No	
1	Detailed description of the type of exercise equipment		Pages 7-9, rows 175-216		
2	Detailed description of the qualifications, expertise and/or training		Pages 7-9, Rows 164-216 Fig 1 and Fig 2		
3	Describe whether exercises are performed individually or in a group		Page 7, Row 166		
4	Describe whether exercises are supervised or unsupervised; how they are delivered		Page 7, Rows 168-171 Page 12, Row 270-273		
5	Detailed description of how adherence to exercise is measured and reported		Page 7, Rows 170-171 Page 12, Row 269-273		
6	Detailed description of motivation strategies		Page 7, Rows 172-173 Page 12, Row 270-272		
7a	Detailed description of the decision rule(s) for determining exercise progression		Pages 7-9, Rows 175-216 Fig 1 and Fig 2		
7b	Detailed description of how the exercise program was progressed		Pages 7-9, Rows 175-216 Fig 1 and Fig 2		
8	Detailed description of each exercise to enable replication		Pages 7-9, Rows 175-216 Fig 1 and Fig 2		
9	Detailed description of any home programme component		Does not apply		
10	Describe whether there are any non-exercise components		Does not apply		
11	Describe the type and number of adverse events that occurduring exercise		Does not apply		
12	Describe the setting in which the exercises are performed		Page 7, Row 166		

13	Detailed description of the exercise intervention		Pages 7-9, Rows 164-216 Fig 1 and Fig 2		
14a	Describe whether the exercises are generic (one size fits all) or tailored		Page 8, Rows 185-188 Page 8, Rows 199-204		
14b	Detailed description of how exercises are tailored to the individual		Page 8, Rows 185-188 Page 8, Rows 199-204		
15	Describe the decision rule for determining the starting level		Page 7, Rows 171-172		
16a	Describe how adherence or fidelity is assessed/measured		Page 7, Rows 170-171 Page 12, Rows 269-273		
16b	Describe the extent to which the intervention was delivered as planned		Pages 7-9, Rows 165-216 Fig 1 and Fig 2		

CEU Universidad Cardenal Herrera

Vicerrectorado de Investigación
Comité de Ética para la Investigación Biomédica

INFORME CEI18/215

TÍTULO DEL PROYECTO: **Effects of three different types of physical training improving symptomatology adn quality of individuals with schizophrenia in psychosocial rehabilitation program. A multi-centre, single blind, randomized trial**.

INVESTIGADOR PRINCIPAL: **Dra. Dña. Loreto Peyró Gregori**

El Comité de Ética para la Investigación Biomédica de la Universidad CEU-Cardenal Herrera, reunido en sesión presencial con fecha del 10 de enero de 2019 ha revisado dicho proyecto y considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y las molestias previsibles para el sujeto.

Por lo que acepta que dicho estudio sea realizado.

REPORT IEC18 / 215

PROJECT TITLE: **Effects of three different types of physical training that improve the symptomatology and quality of people with schizophrenia in the psychosocial rehabilitation program. A multicenter trial, simple blind, randomized.**

PRINCIPAL INVESTIGATOR: **Dr. Loreto Peyró Gregori**

The Ethics Committee for Biomedical Research at the CEU Cardenal Herrera University, in a meeting dated January 10, 2019, has reviewed the project and considers that:

The necessary requirements for the suitability of the protocol in relation to the objectives of the study are met and the foreseeable risks and inconveniences for the subject are justified.

So The Ethics Committe accept the study to be conducted.

Ignacio Pérez Roger

President of the Ethics Committee for Biomedical Research

BMJ Open

Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised wait-list controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046216.R2
Article Type:	Protocol
Date Submitted by the Author:	04-Aug-2021
Complete List of Authors:	García-Garcés, Laura; Universidad CEU Cardenal Herrera Facultad de Ciencias de la Salud, Department of Nursing, Faculty of Health Sciences Lacamara Cano, Sergio; Socio-sanitary Attention State Reference Centre for People with Severe Mental Disorders of Valencia Cebolla Meliá, Yago; Socio-sanitary Attention State Reference Centre for People with Severe Mental Disorders of Valencia Sánchez-López, María ; Universidad CEU Cardenal Herrera Facultad de Ciencias de la Salud, Department of Nursing, Faculty of Health Sciences Marqués Azcona, David; Universidad CEU Cardenal Herrera Facultad de Ciencias de la Salud, Department of Nursing Lisón, J.F. ; Universidad CEU Cardenal Herrera Facultad de Ciencias de la Salud, Department of Biomedical Science; Carlos III Health Institute, Centre of Networked Biomedical Research in the Physiopathology of Obesity and Nutrition (CIBERobn), CB06/03 Peyró-Gregori, Loreto; Universidad CEU Cardenal Herrera Facultad de Ciencias de la Salud, Department of Nursing, Faculty of Health Sciences
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Adult psychiatry < PSYCHIATRY, EDUCATION & TRAINING (see Medical Education & Training), Clinical trials < THERAPEUTICS, Schizophrenia & psychotic disorders < PSYCHIATRY

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TITLE OF MANUSCRIPT: Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised wait-list controlled trial

AUTHORS:

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CORRESPONDING AUTHOR: Laura García-Garcés lauragarciagarcesphd@gmail.com

Keywords: schizophrenia; psychiatric symptoms; resistance training; endurance training; quality of life; clinical trial
Word count (excluding titel page, abstract, tables, references and figures): 4573 words

Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised wait-list controlled trial

Abstract

Introduction: Numerous studies support the practice of different physical exercise modalities as an effective treatment to address the problems associated with schizophrenia, reporting that they result in improvements in patient symptoms and quality of life. Given the lack of studies comparing different types of training in controlled environments, the aim of this proposed study will be to compare the effects of three physical exercise programs (strength, aerobic, and mixed) on the symptoms, body composition, level of physical activity, and health-related quality of life of patients with schizophrenia.

Methods and analysis: A multicentre, single-blinded (evaluator), randomised, wait-list controlled (ratio 2:2:2:1) trial will be conducted with 105 patients recruited from different psychosocial care centres. The participants will be randomised into three 16-week training groups comprising 48 sessions lasting one hour each, or to the wait-list control group. The training groups will complete aerobic, strength, or mixed (aerobic + strength) training. The participants will be assessed before, immediately after, and 6 months after the end of the intervention. The patients in the wait-list control group (n=15) will receive one of the three trainings immediately after the intervention. The study variables will include positive, negative, and general symptomology *(Positive and Negative Syndrome Scale)* as the primary outcome; as secondary outcome: body composition (by assessing body mass index, body fat mass and waist circumference), physical activity levels (*International Physical Activity Questionnaire-Short Form*), and quality of life (abbreviated *World Health Organization Quality of Life* questionnaire).

Ethics and dissemination: This study was approved by the ethics committees for Biomedical Research at the CEU Cardenal Herrera University of Valencia, Spain (CEI18/215). Participants will be fully informed of the purpose and procedures of the study, and written informed consent will be obtained. The results from this study will be published in peer-reviewed journals and presented in scientific conferences.

Trial registration number: NCT04987151

Strengths and limitations of this study

- This is the first prospective randomised wait-list controlled trial to compare the effects of three different physical exercise programs (aerobic, strength, and mixed) in individuals with schizophrenia.
- This study assesses positive and negative psychotic symptoms, health-related quality of life, and body composition.
- The statistical power is based on the primary objective to evaluate effects of physical exercise programs on symptomatology.
- The nature of the physical exercise programs (types of exercise, frequency, session duration, program duration, intensity, progression, and training settings) and the 6-month follow-up assessment are strengths of the study design.
- The study is limited by the absence of daily food records and for the lack of a control group for the analysis at 6 months.

Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised wait-list controlled trial

Introduction

Schizophrenia is a serious chronic mental illness that, according to Word Health Organization (WHO) data [1], affects 21 million people worldwide. This disease is characterised by a combination of positive symptoms (hallucinations, delusions, thoughts, and/or movement disorders), negative symptoms (associability, anhedonia, abolition, affective flattening, and alogia), and cognitive symptoms (problems with operational memory, executive functioning, and concentration) [2, 3]. In addition, schizophrenia is accompanied by a huge individual and social burden [4, 5] and is the eighth leading cause of disability-adjusted life years in 15 to 44-year-olds [6].

Schizophrenia is related to a sedentary lifestyle [7–9] and is associated with cardiovascular diseases, coronary heart disease [10], diabetes, obesity, dyslipidemia, and metabolic syndrome, among other comorbidities [11, 12]. Some of these pathologies are a consequence of the antipsychotic drugs that these patients receive to treat their disease [13], but there are also studies that postulate that the metabolic alterations present in these individuals are inherent to the schizophrenic disease they suffer [14]. All of the above means that, compared to the general population, people suffering from this disease have a 40% to 60% higher probability of premature death and a 20% lower life expectancy [15].

On the other hand, there is evidence that the quality of life perceived by patients with schizophrenia is lower than in the rest of the population in every domain studied [16]. The intensity of the symptoms of this disease, its treatment, and the comorbidities associated with it strongly impact the quality of life of patients affected by it, which is further jeopardised by the

social stigma and low self-esteem that it entails [17, 18]. Of note, some studies have shown that physical activity positively contributes to the quality of life of these patients [19].

Without a doubt, physical activity is an important factor in preserving the general health and preventing chronic diseases such as diabetes, dyslipidemia, obesity, and cardiovascular diseases in individuals with schizophrenia. Indeed, in individuals with schizophrenia, exercise is inversely correlated with morbidity and mortality as a result of these diseases [20]. Specifically, significant results in terms of quality of life [21], positive and negative symptoms [22-24], cognitive functioning [25-28] improvement in sleep quality [29, 30], and cardiopulmonary function [31-33] were found in studies that used physical activity as an intervention in populations affected by schizophrenia. In addition, physical activity reduces the general care burden of these patients [34].

Therefore, the prescription of physical exercise is a practice validated for improving the symptoms of schizophrenia and to help prevent the diseases associated with it. However, to the best of our knowledge, there are still significant gaps in the evidence indicating what types of training might be most effective at improving the symptoms of these patients [21, 35–37]. Most work studying the effects of physical activity in patients diagnosed with schizophrenia has focused on aerobic or mixed physical exercise programs [12, 23, 30, 32–34, 38]. In fact, even though strength training exercise interventions have shown improvements in diseases such as depression and anxiety [24, 39], only two studies have used this type of training in patients with schizophrenia [40]. Nonetheless, these studies found that strength training programs reduced the psychopathology [24] and improved the maximum strength and walking performance of these patients [24, 39].

Based on all the above, the main objective of this proposed work will be to analyse and compare the effects of three different physical exercise programs (strength, aerobic, or mixed) on the symptomatology (positive and negative), health-related quality of life, and anthropometric variables of patients with schizophrenia enrolled in a psychosocial rehabilitation program.

Methods and analysis

Study design

This will be a four-armed, multi centre, single-blinded, randomised, wait-list controlled trial (RCT), comparing four conditions: strength training, aerobic training, mixed training (strength + aerobic), and wait-list control group. The participants will be assessed at baseline, post-treatment, and at a 6-month follow-up. All the patients in the wait-list control group will receive one of the three trainings immediately after the intervention, and will not be assessed at the 6-month follow-up. A flowchart showing the proposed progression of the participants through the study is shown in figure 1. The work will adhere to the CONSORT standards for randomised trials [41-43] as well as the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and on Line Tele Health) [44], the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines (Additional file 1) and the World Health Organization trial registration data set criteria (Additional file 2) [45]. This current protocol was registered at ClinicalTrial.gov with reference number NCT04987151.

Figure 1. Flowchart representing the movement of the participants through the study.

Patient involvement

Patients will be involved at several stages of the trial, including the design, management, and conduct of the trial. We will receive input from patients who are living with schizophrenia in the design of the trial materials and management oversight through membership of the trial steering committee. We carefully will assess the adverse events of the trial interventions on patients. We intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

Study population, recruitment, and eligibility criteria

This RCT will be conducted from six psychosocial care centres for people with severe mental illness located in different parts of Spain: the Fundación Agustín Serrate (Huesca), Fundación Rey Ardid (Zaragoza), Fundación SASM (Valencia), Fundación Els Tres Turons (Barcelona), CREAP

(Valencia), and Asociación ACOVA (Valencia). The participants will be recruited by the health staff working in the different centres.

The researchers who manage the study will go to the different psychosocial care centres to explain the study and eligibility criteria to the health staff, and will give them an information dossier containing the study characteristics and a detailed audiovisual manual with the description of each exercise intervention. The health staff at those institutions will then distribute the information to interested and suitable candidates directly via an interview in which the study will be explained in detail and they will be asked if they want to participate in the study. If they wish to participate, these patients will be asked to sign the informed consent document (Additional file 3) and will be instructed to maintain their usual treatments and appointments with mental health professionals.

To be included, the participants must fulfil all the inclusion criteria and none of the exclusion criteria. The inclusion criteria will be as follows: (1) age between 18–65 years; (2) Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of schizophrenia; and (3) able to read and understand the Spanish language. The exclusion criteria will be: (1) acute suicidality; (2) representing an acute danger to others; (3) other psychiatric diagnoses or acute psychiatric illnesses; (4) other disorders that could prevent the person from completing the exercise training; (5) participation in similar programs or interventions at the time of enrolment.

Randomisation and blinding

An independent researcher unaware of the study characteristics will perform the randomisation process. In order to randomly allocate the participants to one of the four conditions (aerobic, strength, mixed, or wait-list control group), a computer-generated random number sequence [46] will be used (applying a simple allocation strategy). The randomisation will occur after baseline measures are taken and the allocation ratio (2:2:2:1) will be counter-balanced in each center. This sequence will be recorded in a password-protected spreadsheet table and concealed to other researchers during the study.

Because the different exercise interventions significantly vary, it will be impossible to mask the group allocation to the physical therapists or the participants. However, the outcome evaluators and data analysts will be blinded to treatment allocations; outcome assessors and data analysts will be not involved in participant recruitment, treatment assignment, and treatment administration (interventions). Participants will be instructed not to tell outcome assessors of the intervention they received. The success of blinding will be measured and reported using a blinding questionnaire. To avoid inter-observer variability bias, the measurements in each of the groups will always be completed by the same investigator.

Sample size

Sample size calculation was conducted using G*Power software version 3.1.9.2 [47] based on data collected from a similar study by Silva et al [24]. The effect size (ηp^2) for the time by-group interaction in the positive symptoms of schizophrenia was 0.229. To achieve 90% power, with an α level of 0.05, the total sample size needed is 80. Thus, anticipating a dropout rate of 30% according to Vancampfort et al. [48], the necessary total sample size would be (n = 105).

Interventions

The intervention will consist of a total of 48 sessions (3 weekly group-based sessions lasting one hour each for 16 weeks) and will be carried out at the gymnasium or the sports courts of each of the psychosocial care centres. To make the comparison fair, the total number of training sessions and duration of each session will be the same for the three training groups. These groups will be led by certified and experienced physical trainers (average experience of 5-10 years) from each psychosocial care centre who will also be responsible for recording each participant's degree of compliance with the intervention. The exercise dosing patters will be based on current recommendations for individuals with schizophrenia [49-51]. The progression of the intensity of each training session will be a motivational strategy for the participants. To describe interventions, we have used the Consensus on Exercise Reporting Template (CERT) (Additional file 4).

Strength training: Each strength training session will begin with a set of gentle stretching exercises lasting 10 minutes, designed to target the major muscle groups. This will be followed by two sets of 8 strength training exercises with 1 minute of recovery programmed between each one. An elastic resistance band (Thera-band) will be used in 4 of the 8 strength exercises. Finally, the training will end with 10 minutes of gentle stretching of the major muscle groups as a cool-down (Figure 2).

Figure 2. Strength training.

Legend of figure 2: RPE: Borg Rating of Perceived Exertion

The training intensity will increase over the 16 weeks of this intervention; the intensity of exercises completed without an elastic band will be amplified by increasing the number of repetitions the participants perform. For exercises performed with an elastic band, the intensity increase will be achieved by using the Borg Scale [52]. This scale measures the effort an individual perceives when exercising and creates criteria to adjust the intensity of the programmed exercise.

In order to adequately use the Borg scale, the participants assigned to the strength training group must learn to use Thera-band resistance bands on the first day and to easily identify, for each exercise, which gripping point on the band is equivalent to an effort that is moderate, intermediate, hard, or very hard according to the Borg scale.

Aerobic training: Each session will begin with 10 minutes of stretching of the major muscle groups. Subsequently, participants will complete 4 series of brisk walking for 10 minutes followed by 1 minute of recovery. To ensure that the intensity of the exercise progresses from moderate to vigorous, we will monitor the heart rate (HR) of each participant. The progression in exercise intensity will be achieved by increasing the participant's target HR every 2 weeks. Thus, using the formula published by Tanaka et al. to calculate the maximum HR (MHR) (208 – 0.7 * age) [53], the intensity of the exercise will be progressively increased as follows: weeks 1–2: 55% MHR; weeks 3–4: 58% MHR; weeks 5–6: 61% MHR; weeks 7–8: 64% MHR; weeks 9–

10: 67% MHR; weeks 11–12: 70% MHR; weeks 13–14: 73% MHR; and weeks 15–16: 76% MHR. The session will end with a 10-minute session of gentle stretching exercises targeting the major muscle groups (Figure 3).

Figure 3. Aerobic training.

Legend of figure 3: HR: Heart Rate

Mixed training: As in the previous two groups, each training session will begin with 10 minutes of stretching of the major muscle groups. The main part of each mixed session will consist of two parts. First, similar to the strength training group, the participants will perform a single circuit of 8 strength exercises interspersed with 1 minute of recovery for each strength exercise. Second, as in the aerobic training group, the participants will perform 2 sets brisk walking for 10 minutes followed by 1 minute of recovery, following the same exercise intensity progression as described for the aerobic training group. Finally, these sessions will also end with a 10-minute session of gentle stretching exercises targeting the major muscle groups.

Instruments

The participants will be assessed at three different times. First, before beginning the intervention; second, immediately after the end of the intervention; and third, six months after the end of the intervention (6-month follow-up). All the assessments will be performed in one single session and will be scheduled between 10 a.m. and 12 p.m. to minimise variability.

Variables and evaluation times are summarized in Table 1.

Table 1. Study variables and assessment points

	STUDY PERIOD				
	Enrolment		**Allocation**	**Post-allocation**	**Close-out**
TIMEPOINT**	***-t_1***	***t_1*** *baseline*	***0***	***t_2*** *Post-treatment*	***t_3*** *6 month follow-up*
ENROLMENT:					
Eligibility screen	X				

Informed consent	X				
Allocation			X		
INTERVENTIONS:					
[Strength training]		◆——	——	——◆	
[Aerobic training]		◆——	——	——◆	
[Mixed training]		◆——	——	——◆	
[Control group]					
ASSESSMENTS:					
Positive psychotic symptoms		X		X	X
Negative psychotic symptoms		X		X	X
General psychopathology		X		X	X
Body mass index		X		X	X
Body fat mass		X		X	X
Waist circumference		X		X	X
Quality of life		X		X	X
Level of physical activity		X		X	X

Metrics

The psychometric attributes of all the measurement tools used in this project, such as the reliability and validity, are psychometrically sound.

Primary outcome

The *Positive and Negative Syndrome Scale* (PANSS) is a semi-structured interview which assesses the positive (PANSS-P: 7 items, range 7–49), negative (PANSS-N: 7 items, range 7–49), and general (PANSS-G: 16 items, range 16–112) symptoms of psychosis experienced by patients in the week prior to the test on a 7-point Likert-type scale (from 1, 'none', to 7, 'extreme') [54].

We will analyse the three subscales separately and the positive-symptom factor will serve as the primary outcome of this study. The subscales of the Spanish version are strongly associated with those of the original version ($r = 0.92$ for PANSS-P and $r = 0.83$ for PANSS-N), with item correlations ranging from $r = 0.64$ to $r = 0.97$, and with high inter-rater reliability ($r = 0.81$) [55].

Secondary outcomes

Anthropometric and body composition variables: The body mass index (BMI), calculated as the patient weight in kilograms divided by their height in squared meters, will be calculated using a SECA® 780 electronic balance scale with a mechanical telescopic stadiometer. Body fat mass (BFM) will be determined using a TANITA® TBF-410 M body-fat analyser. Waist circumference (WC) will be measured to the nearest centimetre using a flexible tape measure at the level half-way between the lower rib margin and the iliac crest.

Physical activity (PA) levels: PA levels will be assessed using the *International Physical Activity Questionnaire-Short Form* (IPAQ-SF) [56]. Using seven items, this self-reported questionnaire collects data on the patients' PA in the 7 days prior to the test. The total number of days and minutes of PA will be calculated by adding all PA category scores performed over the seven days. Specifically, the IPAQ-SF questionnaire records activity at four intensity levels: (1) vigorous activity such as aerobics; (2) moderate activity such as leisure cycling; (3) walking; and (4) sitting. This makes it possible to classify the PA levels of the participants as 'high', 'moderate, or 'low' [57]. The IPAQ has been validated in 12 countries [58] and showed adequate psychometric properties and the short version (the IPAQ-SF) has shown acceptable validity in an adult Spanish population [59].

The abbreviated *World Health Organization Quality of Life Assessment (WHO-QoL-BREF)* [60]: This survey comprises 26 items with five Likert-type responses each, and is a standard questionnaire used to measure patient quality of life. It assesses patients under four health domains: physical, psychological, social, and environmental. In this study we will analyse the sum of the four dimensions, with higher scores indicating a better quality of life. This scale has

been validated for Spanish and the instrument has a good internal consistency with a Cronbach alpha of 0.88 for the overall scale and a range of 0.70 to 0.79 for its dimensions [61].

Sociodemographic metrics

Age, gender, marital status, education level, job status, and institutionalisation regime will be encoded.

Clinical metrics

The duration of patient psychoses and history of hospitalisations since the first episode will be recorded. Other pharmacological and non-pharmacological interventions, as well as current medication and psychosocial care will also be checked. Adverse events to the interventions will be also registered.

Adherence

Specialists will direct all 48 sessions in each of the three training groups, registering each participant's attendance for each session, and adverse or unintended effects. Specialist will promote participant retention and complete follow-up. Sessions will be marked as finished when at least 75% of the training was completed. Participants will be instructed not to perform other rehabilitation interventions programs outside of the intervention for the entire duration of the study.

Statistical data analysis

Based on an intention-to-treat sample, two-way mixed ANCOVA (2x4) tests will be used to compare how the study interventions affect the primary and secondary outcomes, using time (baseline, and post-intervention -primary end point-) as the within-group factor and group (aerobic, strength, mixed, or wait-list control) as the between-group factor. Two-way mixed ANCOVA (3x3) tests will also be used to compare how the study interventions affect the outcomes, using time (baseline, post-intervention, and 6-month follow-up) as the within-group factor and group (aerobic, strength, or mixed) as the between-group factor. The analysis will be adjusted for sex, age, adherence, and antipsychotic medications. Effect sizes will be estimated

using the partial eta squared formula (η2p) and interpreted following the Cohen guidelines [62] for small effect sizes (η2p = 0.01), moderate effect sizes (η2p = 0.06), and large effect sizes (η2p = 0.14). Chi-squared test will be used to statistically assess success of blinding. The significance level will be set at 5% (two-tailed analyses) and the data will be analysed using SPSS software, version 24.0 (IBM Corp., Armonk, NY.).

Data monitoring

The data monitoring committee will comprise at least two independent members that will periodically check the progression of the trial in the six psychosocial care centres. After randomising the participants, the committee will meet every 6 weeks to review a report submitted by the researchers for the purpose of monitoring the progress of recruitment and data collection. The data monitoring committee will do an interim analysis immediately after the end of the intervention, in order to decide to finish the trial. If any important modifications are made to the protocol, these will be communicated to the Ethics Committee at once.

Data confidentiality

After the measurements are recorded, the collected data will be transferred to a database on a password-locked stand-alone desktop computer which will be kept in a locked research room at the Department of Medicine in the Faculty of Health Sciences at the University CEU-Cardenal Herrera of Valencia. The collected data will be saved as traceable anonymous data with sequentially allocated numbers which the researchers will be able to access.

Ethics and dissemination

This study will be conducted according to the principles established in the Declaration of Helsinki, the Convention on Human Rights and Biomedicine (Oviedo Convention), and the UNESCO Universal Declaration on the human genome research and human rights. This project was approved by the Ethics Committee for Biomedical Research at the CEU Cardenal Herrera University of Valencia in Spain (reference number: CEI18/215) (Additional file 5); the ethics approval applies to all participating centres.

All the participants will be informed about the length and characteristics of the study and the voluntary nature of their participation in it. After explaining the project in detail, we will answer any questions potential participants might have about it and then they will be provided with an informed consent document that they will have to sign should they wish to participate in the study. In turn, we will provide them with the contact details for the principal investigator of the project so participants will be able to communicate with them at any time.

Participants will also be informed that all the data collected during the investigation will be treated confidentially in accordance with current regulations on the protection of personal data, Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, and European Union regulation 2016/679 of the European Parliament and Council, of April 27, 2016, regarding the protection of natural persons with regard to the processing of personal data and the free circulation of this data. Additionally, the study is registered at ClinicalTrials.gov (NCT04987151).

The findings of this study will be published in peer reviewed indexed (JCR) journals. We will also present the results and findings at related research conferences. Furthermore, we will also make the full study report available to the relevant health authorities.

Discussion

The greatest strength of this study is that, to the best of our knowledge, it will be the first RCT to compare the effects of three types of training program (aerobic, strength, or mixed) on improving the symptoms of psychosis.

Many studies have been published that demonstrate the benefits that performing physical exercise has on the population affected by schizophrenia [12, 13, 33, 39, 63], and therefore this type of non-pharmacological therapeutic strategy should be one of the standard treatments prescribed to these patients. Some studies have examined the benefits of aerobic training [13, 23, 63], others have focused on mixed training interventions [12, 38], and still others have compared these strategies or implemented more sedentary activities such as occupational

therapy [33]. Some work has also evaluated the effects of practicing yoga [23], dance [64, 65], or football [22]. However, only two studies have evaluated the effectiveness of strength training in patients with schizophrenia [24, 39].

The work by Heggelund et al. [39] evaluated the effects that training the maximum lower-limb strength for 8 weeks had on the net mechanical efficiency of walking, the symptoms of schizophrenia, and patient quality of life, and compared these outcomes with the effects of a sedentary activity such as self-entertainment with video games. Their results suggested that this type of strength training improved the maximum lower-limb strength of these patients as well as their walking performance, however, they found no alterations in the overall PANSS or SF-36 (*36-Item Short Form Health Survey*) scores.

In contrast, the study by Silva et al. [24] assessed the differences between the effects of 20 weeks of strength training versus mixed training on the symptoms of psychosis or depression, quality of life, and serum concentrations of Insuline Growth Factor-1, Insuline Growth Factor Binding Protein, and a neurotrophic factor derived from brain Brain-Derived Neurotrophic Factor in patients with schizophrenia. This group found statistically significant improvements for both the strength and the mixed training groups in the overall PANSS scale score, positive symptomatology, and maximum strength in the arm-extension test. Statistically significant improvements in the negative symptomatology and maximum strength in the chest-press test were only found in the strength training group. Although the results of these two publications are encouraging, further investigation will be required because the sample size in both these studies was small, with a maximum of only 13 participants per group, and neither of them collected data from a follow-up phase. In addition, one of these studies did not use a randomised sampling strategy [39].

Strength training has also obtained good results in other lines of research enquiry. For example, Cassilhas et al. [66] concluded that intensive strength training conducted in an elderly population improved their mood, anxiety, and strength. Similarly, Stanton et al. reviewed the

benefits of aerobic and strength training in patients with depression and found that the latter was able to improve the mood and symptoms of depression in these patients [67]. However, these results strongly differ from those from a meta-analysis carried out by Gordon et al. which concluded that strength training significantly reduced the symptoms of depression [40].

A cross-sectional study concluded that patients with schizophrenia showed lower hand grip strength scores compared to healthy controls, and that hand grip strength scores correlated positively with cognitive functions [68]. A more recent study concluded that higher hand grip strength was associated with greater left and right hippocampal volume and reduced white matter hyperintensities in major depressive disorder (MDD). These authors considered that interventions targeting strength fitness could improve brain health and reduce the neurocognitive abnormalities associated with MDD [69]. Finally, Subramaniapillai et al. [70] conducted a descriptive study with 113 patients diagnosed with schizophrenia and 60 patients with bipolar disorder to determine their physical activity preferences, and 67.6% of the respondents subsequently stated that they would like incorporate strength training into their exercise programs.

While the mechanisms by which the different exercise interventions may influence the symptoms and cognition of our patients will extend beyond the scope of this study, several mechanisms have been proposed in the scientific literature. The most frequently cited are neuroprotective mechanisms such as decreased inflammation, increased neurogenesis and neuroplasticity via brain-derived neurotrophic factor, and remyelination of white matter tracts [71,72].

Considering all the above, and given that so far no studies have identified which training types are most beneficial to patients affected by schizophrenia, the study plan described here aims to analyse and compare the effects of strength training, aerobic training, and mixed training interventions on the symptomatology, health-related quality of life, and anthropometric variables of these patients. The design of this wait-list controlled study incorporates a series of

improvements with respect to previously published work examining the effects of strength training in patients with schizophrenia: this will be a multicentre study, adequately powered (*n* = 105), and a follow-up assessment carried out 6 months after the end of the intervention. Finally, we will be able to compare the benefits of each of the main types of training because we will include three intervention groups, and we will report of all the exercise training programs information (types of exercise, frequency, session duration, program duration, intensity, progression, training settings [i.e., supervised or group sessions]).

Nevertheless, this study will have some limitations. First, we do not plan to record the dietary intake of the participants and so it will be impossible to independently assess the impact of physical exercise on anthropometric parameters and body composition. Second, the questionnaire data (level of physical activity and quality of life) will be self-reported, which may be affected by participants' personal perceptions. Third, it should be noted -when interpreting the results- that the combined exercise type group (aerobic + strength) will not include a full dose of either of the treatments alone. Finally, the lack of a control group for the analysis at 6 months should be considered when interpreting the results at this point.

The results of this project will allow us to separately understand the effects of each of the training interventions and identify if any of them are more beneficial to these patients with schizophrenia in terms of the different variables we plan to analyse. This knowledge will help to improve the prescription of different training types to each patient to help them maintain good control of symptoms of the disease.

Trial Status

Protocol version number: NCT04987151

Protocol version date: July 26, 2021

Date recruitment began: Oct, 2021

Approximate date when recruitment will be completed: Jan, 2022

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Authors' contributions

LGG: Conceived the study and wrote the draft for the manuscript. LGG, SLC, YCM, MISL, JFL, DMA and LPG contributed to the development of the design. SLC and LPG contributed to the literature search. All authors contributed to refinement of the study protocol and approved the final manuscript.

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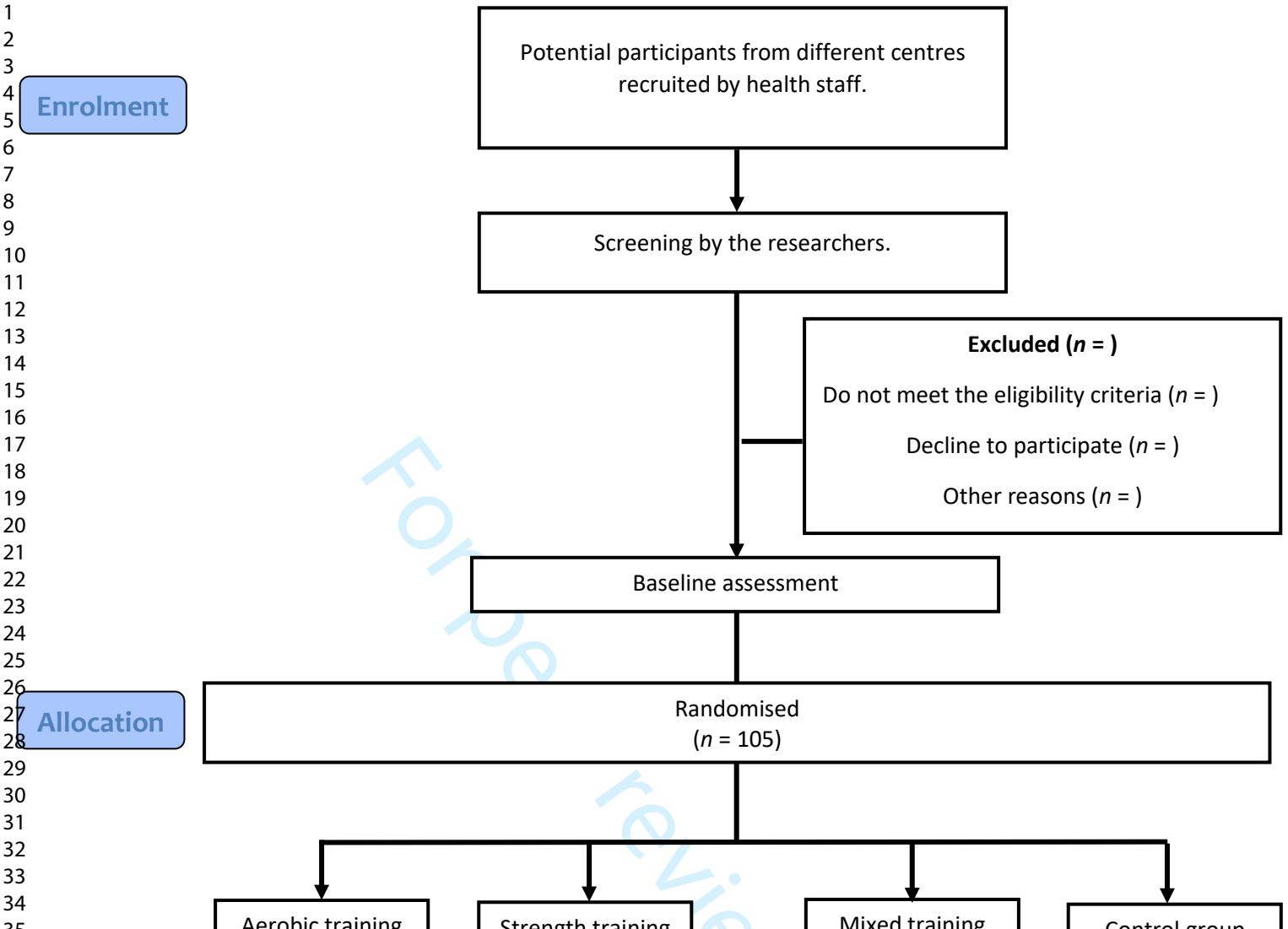
Competing interests

The authors declare they have no competing interests.

Word count (not including abstract, tables and references)**:** 4573 words

Abbreviations

BMI: Body Mass Index; CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and on Line Tele Health; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; IPAQ-SF: Physical Activity Questionnaire-Short Form; METs-min/week: Minutes Per Week; PA: Physical Activity; PANSS: Positive and Negative Syndrome Scale; PANSS-G: General symptoms of Syndrome Scale; PANSS-N: Negative Syndrome Scale; PANSS-P: Positive Syndrome Scale; RCT: Randomised Clinical Trial; SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials; WHO: Word Health Organization; WHO-QoL-BREF: World Health Organization Quality of Life Assessment



	STRENGTH TRAINING PROGRAM															
	1 WEEK	2 WEEK	3 WEEK	4 WEEK	5 WEEK	6 WEEK	7 WEEK	8 WEEK	9 WEEK	10 WEEK	11 WEEK	12 WEEK	13 WEEK	14 WEEK	15 WEEK	16 WEEK
WARM-UP	10 mins of stretching the major muscle groups															
	15 rep.	15 rep.	15 rep.	15 rep.	20 rep.	20 rep.	20 rep.	20 rep.	25 rep.	25 rep.	25 rep.	25 rep.	30 rep.	30 rep.	30 rep.	30 rep.
Recovery	1 mins of gentle stretching															
	15 rep.	15 rep.	15 rep.	15 rep.	20 rep.	20 rep.	20 rep.	20 rep.	25 rep.	25 rep.	25 rep.	25 rep.	30 rep.	30 rep.	30 rep.	30 rep.
Recovery	1 mins of gentle stretching															
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	1 mins of gentle stretching															
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	1 mins of gentle stretching															
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	1 mins of gentle stretching															
	RPE = 3	RPE = 3	RPE = 4	RPE = 4	RPE = 5	RPE = 5	RPE = 6	RPE = 6	RPE = 7	RPE = 7	RPE = 7	RPE = 7	RPE = 8	RPE = 8	RPE = 8	RPE = 8
Recovery	1 mins of gentle stretching															
	15 rep.	15 rep.	15 rep.	15 rep.	18 rep.	18 rep.	18 rep.	18 rep.	20 rep.	20 rep.	20 rep.	20 rep.	22 rep.	22 rep.	22 rep.	22 rep.
Recovery	1 mins of gentle stretching															
	15 rep.	15 rep.	15 rep.	15 rep.	18 rep.	18 rep.	18 rep.	18 rep.	20 rep.	20 rep.	20 rep.	20 rep.	22 rep.	22 rep.	22 rep.	22 rep.
Recovery	1 min of gentle stretching															
The entire circuit is repeated following the same indications																
COOL-DOWN	10 mins of stretching the major muscle groups															

AEROBIC TRAINING PROGRAM																
PROGRAM	**1 WEEK**	**2 WEEK**	**3 WEEK**	**4 WEEK**	**5 WEEK**	**6 WEEK**	**7 WEEK**	**8 WEEK**	**9 WEEK**	**10 WEEK**	**11 WEEK**	**12 WEEK**	**13 WEEK**	**14 WEEK**	**15 WEEK**	**16 WEEK**
WARM-UP	**10 mins of stretching the major muscle groups**															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
AEROBIC TRAINING	**10 minutes of brisk walking**. The exercise intensity should be moderate. We will control it by monitoring the heart rate (HR). Any patients who cannot use their HR as a reference because of their medical treatments should perform the exercise at an intensity which makes it difficult but not impossible for them to speak while performing it.															
HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
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HR MEASUREMENT	See the proposed HR table created based on the patient age and the training program exercise week															
COOL-DOWN	**At the end of the second set: 10 mins of stretching the major muscle groups**															

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Title of manuscript: *Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised wait-list controlled trial*

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	*Manuscript page*
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	*Page 1*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	*Page 2*
	2b	All items from the World Health Organization Trial Registration Data Set	*Included in the additional file 2*
Protocol version	3	Date and version identifier	*July 26, 2021*
Funding	4	Sources and types of financial, material, and other support	*The study is not funded*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	*Page 26*
	5b	Name and contact information for the trial sponsor	*The study is not funded*
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	*The study is not funded, and it has no sponsors*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	*There are no coordinating centre or steering committee*

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	*Pages 3-4*
	6b	Explanation for choice of comparators	*Pages 5,7-9*
Objectives	7	Specific objectives or hypotheses	*Page 4*
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	*Page 5*
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	*Page 5*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	*Page 6*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	*Pages 7-9*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	*There are no criteria for discontinuing or modifying allocated interventions for a given trial participant*
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	*Page 12*
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	*Page 12*

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	*Pages 10-12*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	*Pages 5-9 and table 1*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	*Page 7*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	*Pages 5-6*
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	*Page 6*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	*Page 6*
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	*Pages 6-7*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	*Pages 6-7*

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	*The study will be blinded during all the research*
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	*Pages 9-10; 12*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	*Page 12*
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	*Page 13*
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	*Pages 12-13*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	*Pages 12-13*
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	*We are not going to do this analyses; we'll do only an intention-to-treat sample*
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	*Page 13*

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	*Page 13*
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	*Page 13*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	*Page 13*
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	*Page 13*
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	*Page 13*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	*Page 6*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	*Not applicable: the model consent include all the information of the study*
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	*Page 13*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	*Page 26*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	*Page 13*

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	*None of the interventions affects the health and integrity of the participants. The exercises proposed for each type of training will be adapted to the physical condition of each participant to avoid any type of injury typical of performing physical exercise.*
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	*Page 14*
	31b	Authorship eligibility guidelines and any intended use of professional writers	*Page 26*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	*Page 14*
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	*Yes*
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	*No biological specimens are collected as part of this trial*

ALL ITEMS FROM THE WORLD HEALTH ORGANIZATION TRIAL REGISTRATION DATA SET

Data category	Information
Primary registry and trial identifying number	*ClinicalTrials.gov* *NCT04987151*
Date of registration in primary registry	*July 26, 2021*
Secondary identifying numbers	-
Source(s) of monetary or material support	*The study is not funded*
Primary sponsor	*The study is not funded*
Secondary sponsor(s)	*The study is not funded*
Contact for public queries	-
Contact for scientific queries	-
Public title	*Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised wait-list controlled trial*
Scientific title	*Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised wait-list controlled trial*
Countries of recruitment	*Spain*
Health condition(s) or problem(s) studied	*Exercise training; Schizophrenia*

Data category	Information
Intervention(s)	*Three physical exercise programs: strength, aerobic, and mixed (strength and aerobic)*
Key inclusion and exclusion criteria	*Inclusion criteria: (1) age between 18–65 years; (2) Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of schizophrenia; and (3) able to read and understand the Spanish language.* *Exclusion criteria: (1) acute suicidality; (2) representing an acute danger to others; (3) other psychiatric diagnoses or acute psychiatric illnesses; (4) other disorders that could prevent the person from completing the exercise training; (5) participation in similar programs or interventions at the time of enrolment.*
Study type	*Interventional* *Allocation: randomized* *Intervention model: simple allocation strategy* *Masking: single-blinded (evaluator)* *Primary purpose: prevention* *Phase III*
Date of first enrolment	*October 2021*
Target sample size	*105*
Recruitment status	*Not recruiting*
Primary outcome(s)	*Positive symptomatology, negative symptomatology, and general symptomology (using the Positive and Negative Syndrome Scale)*
Key secondary outcomes	*Body composition (by assessing body mass index, body fat mass and waist circumference), physical activity levels (International Physical Activity Questionnaire-Short Form), and quality of life (abbreviated World Health Organization Quality of Life questionnaire).*

RESEARCH ON STRENGTH TRAINING IN PATIENTS WITH SEVERE MENTAL DISORDER

INFORMED CONSENT document for Mr. / Mrs._____

_____

This Informed Consent Form is aimed at men and women who are cared for in one of the following centers: State Reference Center for Psychosocial Care (CREAP), Santos Andrés, Santiago y Miguel Foundation (SASM), ACOVA Association and Rey Ardid Foundation. These people are invited to participate in research on the impact of physical exercise on people with severe mental disorder.

Main researchers: Sergio Lacamara Cano (Responsible for Knowledge Management CREAP) and **Loreto Peyró Gregori** (Professor and researcher at the Faculty of Health Sciences of the CEU-Cardenal Herrera University).

The CEU - Cardenal Herrera University, in collaboration with the CREAP, SASM, ACOVA and Rey Ardid centers, are investigating the possible benefits of different forms of physical exercise in people with severe mental disorders. I am going to give you information and invite you to participate in this research. You do not have to decide today whether or not to participate in this research. Before deciding, you can discuss the research with someone you feel comfortable with and trust. There may be some words that you don't understand. Please do not hesitate to interrupt me to ask any questions or words you do not understand, and if you have questions later, you can ask me or the researchers conducting the study, whenever you want.

PURPOSE OF THE STUDY

There are many studies that support the practice of physical exercise as an effective treatment to address different problems related to the disease you suffer, especially it has significant effects on the quality of life and the symptoms of these people. For this reason, an investigation will be carried out in order to assess the effectiveness of different types of training to improve the symptoms and quality of life of these people.

The investigation will last for about 3 months, during which you will participate in a training plan led by a professional at the facilities of the center to which you belong and within the schedule contemplated in your comprehensive rehabilitation plan, so that you participate in this study will not take longer than the usual time. In addition, three researchers from the CEU - Cardenal Herrera University (Alfara del Patriarca, Valencia) will visit their center to carry out a small assessment of each participant that will be repeated three times, before starting the physical exercise sessions, at the end and six months later for this intervention to end. This assessment

does not contain any invasive techniques, it is not annoying, nor does it pose any risk to your health and well-being. The three evaluations will be identical and carried out by the same people. In order to study the effects of the different forms of physical exercise, we will do four different groups, three of them with a different training, and the fourth will be the control group. The allocation to each group is random, that is, neither we nor you can choose which group to be in since the allocation is done randomly, as if we were tossing a coin.

RISKS OR SIDE EFFECTS

None of the physical exercises carried out throughout the study will put the health and integrity of the person at risk. The exercises proposed for each type of training will be adapted to the physical condition of each participant to avoid any type of injury typical of physical exercise.

BENEFITS

If you participate in this research, you will get the following benefits:

- It will improve your physical condition
- It will improve your cardiovascular and cardiorespiratory health
- It will improve your body composition
- You will have a fun time with the rest of the participants

CONFIDENTIALITY

The information we collect during this research project will be kept confidential. Any information about you will have a number instead of your name, so only investigators will know what your number is, and the information will not be shared or released to anyone outside of the investigation team.

TO REFUSE OR WITHDRAW

Your participation in this research is completely voluntary. You can choose to participate or not. Whether you choose to participate or decide not to, all the services you receive at your center will continue as normal. You can change your mind later and stop participating at any time even if you have previously stated that you do.

If you have any questions, you can ask them now or later, even after the study has started. If you have questions later, you can contact the following person: **Sergio Lacamara Cano** (963403520 / slacamara@reyardid.org) and **Loreto Peyró Gregori** (96 136 90 00 - 64311 / lpeyro@uchceu.es).

This proposal has been reviewed and approved by the CEU - Cardenal Herrera University Ethical Evaluation Committee, which is a Committee whose task is to ensure that research participants are protected from harm.


INFORMED CONSENT SHEET

I have been invited to participate in **research on the effects of strength training in patients with severe mental disorders**. I have been informed about the purpose of the study, the risks, and the possible benefits.

I have read the information provided or it has been read to me. I have had the opportunity to ask about it and the questions I have asked have been answered satisfactorily. I voluntarily consent to participate in this research as a participant and understand that I have the right to withdraw from the research at any time without being affected in any way by the medical and psychosocial care I am receiving.

Participant Name: _____

Participant Signature: _____

Date (day / month): _____

Table 1. Proforma CERT assessment form					
Author and year					
Title: Comparison of three different exercise training modalities (aerobic, strength, and mixed) in patients with schizophrenia: study protocol for a multi-centre randomised wait-list clinical trial					
Journal: BMJ Open					
Study Location: Spain					
Reviewer and date					
Item	Description	Data extraction details	Location (pg, URL, etc)	Yes, No	
1	Detailed description of the type of exercise equipment		Pages 8-9, rows 180-218		
2	Detailed description of the qualifications, expertise and/or training		Pages 7, Row 173-174		
3	Describe whether exercises are performed individually or in a group		Page 7, Row 169, 172		
4	Describe whether exercises are supervised or unsupervised; how they are delivered		Page 7, Rows 172-175 Page 12, Rows 272-275		
5	Detailed description of how adherence to exercise is measured and reported		Page 7, Rows 174-175 Page 12, Rows 272-275		
6	Detailed description of motivation strategies		Page 7-8, Rows 176-177 Page 12, Rows 272-274		
7a	Detailed description of the decision rule(s) for determining exercise progression		Pages 8-9, rows 180-218 Fig 1 and Fig 2		
7b	Detailed description of how the exercise program was progressed		Pages 8-9, rows 180-218 Fig 1 and Fig 2		
8	Detailed description of each exercise to enable replication		Pages 8-9, rows 180-218 Fig 1 and Fig 2		
9	Detailed description of any home programme component		Does not apply		
10	Describe whether there are any non-exercise components		Does not apply		
11	Describe the type and number of adverse events that occurduring exercise		Does not apply		
12	Describe the setting in which the exercises are performed		Page 7, Row 170-171		
13	Detailed description of the exercise intervention		Pages 8-9, rows 180-218		

			Fig 1 and Fig 2		
14a	Describe whether the exercises are generic (one size fits all) or tailored		Page 8, Rows 188-191 Page 8-9, Rows 200-208		
14b	Detailed description of how exercises are tailored to the individual		Page 8, Rows 188-191 Page 8-9, Rows 200-208		
15	Describe the decision rule for determining the starting level		Page 8, Rows 188-193 Pages 8-9, Rows 200-206 Page 9 219-227 Fig 2 and Fig 3		
16a	Describe how adherence or fidelity is assessed/measured		**Adherence** Page 7, Rows 174-175 Page 12, Rows 272-275 **Fidelity** Page 6, Rows 130-133 Page 13, Rows 293-299		
16b	Describe the extent to which the intervention was delivered as planned		Pages 8-9, rows 180-218 Fig 1 and Fig 2		

CEU Universidad Cardenal Herrera

Vicerrectorado de Investigación
Comité de Ética para la Investigación Biomédica

INFORME CEI18/215

TÍTULO DEL PROYECTO: **Effects of three different types of physical training improving symptomatology adn quality of individuals with schizophrenia in psychosocial rehabilitation program. A multi-centre, single blind, randomized trial**.

INVESTIGADOR PRINCIPAL: **Dra. Dña. Loreto Peyró Gregori**

El Comité de Ética para la Investigación Biomédica de la Universidad CEU-Cardenal Herrera, reunido en sesión presencial con fecha del 10 de enero de 2019 ha revisado dicho proyecto y considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y las molestias previsibles para el sujeto.

Por lo que acepta que dicho estudio sea realizado.

REPORT IEC18 / 215

PROJECT TITLE: **Effects of three different types of physical training that improve the symptomatology and quality of people with schizophrenia in the psychosocial rehabilitation program. A multicenter trial, simple blind, randomized.**

PRINCIPAL INVESTIGATOR: **Dr. Loreto Peyró Gregori**

The Ethics Committee for Biomedical Research at the CEU Cardenal Herrera University, in a meeting dated January 10, 2019, has reviewed the project and considers that:

The necessary requirements for the suitability of the protocol in relation to the objectives of the study are met and the foreseeable risks and inconveniences for the subject are justified.

So The Ethics Committe accept the study to be conducted.

Ignacio Pérez Roger

President of the Ethics Committee for Biomedical Research