Trials

STUDY PROTOCOL

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Physical Activity in young female outpatients with BORderline personality Disorder (PABORD): a study protocol for a randomized controlled trial (RCT)

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Abstract

Background Current treatments for mental disorders, like pharmacotherapy or psychological approaches, do not lead to full remission in all individuals. Physical activity (PA) is effective at improving psycho-physical health in major depressive and anxiety disorders. However, the efficacy of PA as an adjunctive treatment for borderline personality disorder (BPD) has not been studied. To date, there are no approved pharmacological treatments for this severe condition and limited accessibility to effective psychotherapeutic interventions. This study tests the efficacy of a structured PA programme as an additional treatment for BPD outpatients.

Methods The PABORD is a randomised controlled trial for female outpatients (18–40 years) with a BPD diagnosis. The intervention group ($n=32$) will participate in a 12-week structured PA programme supervised by a sport medicine physician and preceded by three psychoeducation sessions on healthy eating habits. The control group ($n=32$) will receive a 12-week psychoeducation programme on PA, diet, and health risks of a sedentary lifestyle for a total of 8 sessions. The study aims to determine if the PA intervention is superior to the control in reducing BPD symptoms. Secondary aims include improving PA levels and physical and psychological health. Assessments will be conducted at baseline, post-intervention, and 3 months post-intervention.

Discussion The structured PA programme is expected to outperform the control group in terms of health and PA outcomes at the end of the intervention. Repeated assessments will also help to identify psychosocial factors that influence PA maintenance. Findings will support the potential widespread implementation of PA programmes for BPD treatment.

Trial registration ClinicalTrials.gov NCT06461104. Registered on 6 June 2024 {2a}.

Keywords Physical activity, Borderline personality disorder, Experience sampling method, Female outpatients, General functioning, Accelerometer, Physical activity motivation, Premenstrual symptoms

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Administrative information

Note: the numbers in brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items. (see http://www.equator-network.org/reporting-guidelines/spirit2013-statement-defning-standard-protocol-items-forclinical-trials/).

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Introduction

Background and rationale {6a}

Treatments for major mental disorders consist primarily of pharmacotherapy or psychological approaches, which have small-to-moderate effect sizes. Although these treatments are effective for many, they do not lead to full remission in all individuals. Furthermore, even those who respond well to conventional treatments may still experience residual symptoms and remain at risk of future relapses. Additionally, pharmacological and psychological treatments do not adequately address physical health issues common among those with serious mental disorders, such as metabolic disorders and cardiovascular diseases. Therefore, there is a need for additional, adjunctive treatments that target both physical and mental health of individuals living with a mental disorder.

Physical activity (PA) is a promising adjunctive option to fill these gaps. PA, defined as any bodily movement produced by skeletal muscles that requires energy expenditure, is particularly effective at improving physical health in the general population. For instance, a recent meta-analysis reported that exercise, a structured form of PA, has effects on systolic blood pressure in hypertensive individuals comparable to common pharmacological treatments [1]. In addition, PA can preserve cognition and brain health, improve sleep, and contribute to healthy ageing [2, 3]. Furthermore, extensive research has shown that higher levels of PA can reduce the risk of developing depression, anxiety, and stress-related disorders and can significantly improve remission odds in individuals with these conditions [4, 5].

There is a growing interest in the potential role of PA as a transdiagnostic treatment across mental health disorders, including major depressive disorder [6], pre- and postnatal depression [7, 8], anxiety and stress-related disorders [9], post-traumatic stress disorder [10], schizophrenia [11], substance use disorder [12], and bipolar disorder [13]. However, despite the well-established benefits of PA, individuals with mental disorders engage in significantly less PA compared to healthy controls [14].

Borderline personality disorder (BPD) is a severe disorder characterised by significant psychosocial dysfunction, high risk of suicide, and a substantial burden on family members and mental health staff. It is characterised by a wide range of psychopathological features, including chronic emptiness, emotional instability, fear of abandonment, identity disturbance, impulsivity, intense anger, unstable relationships, self-harm, and occasional paranoid ideation or severe dissociative symptoms. The prevalence of BPD is estimated to range between 0.7 and 2.7% in adults, and between about 2 and 3% in adolescents aged 12 to 17 years, being 2.6 times more common among females than males (72.0% vs 28.0%) in psychiatric

outpatient settings [15]. To date, there are no approved pharmacological treatments for BPD, although evidence highlights that psychosocial interventions are effective [16]. However, delivering of psychosocial treatments requires intensively trained staff, which may limit their widespread use in mental health services [17]. Surprisingly, no studies to date have evaluated the efficacy of structured PA as an adjunctive treatment option for people with BPD.

Objectives {7}

The aim of this randomised controlled trial (RCT) is to investigate the effects of a 3-month structured PA programme, followed by a 3-month follow-up, on the clinical state of female outpatients who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria for BPD [18]. The primary objective is to evaluate the efficacy of the PA intervention (combined with psychoeducation focusing solely on healthy eating habits) in reducing clinical symptoms and enhancing PA-related parameters compared to a psychoeducation intervention alone focused on different aspects of healthy lifestyles, by using real-time evaluations of PA levels with a wearable biosensor (accelerometer), and of psychological domains using experience sampling method (ESM). We hypothesise that BPD symptoms will improve more significantly with the PA intervention than with psychoeducation delivered independently. Specifically, we expect improvements in:

(1) Psychological variables: BPD symptoms and related symptomatology such as mood, anxiety levels, impulsivity and global functioning;
(2) Physical and physiological components: muscle strength, endurance and movement;
(3) Motivational and psychological factors related to PA: motivation to engage (long-term maintenance) in PA, self-esteem, and optimism; and
(4) PA-related biomarker levels: brain-derived neurotrophic factor (BDNF), kynurenine, cortisol, dehydroepiandrosterone (DHEA), agrin, neurofilament light chain (Nf-L), plasma extracellular vesicles (EVs), blood glucose, and lipid profile.

Trial design {8}

PABORD is a RCT with a parallel assignment model and a superiority framework, aiming to evaluate the effectiveness and superiority of a structured PA programme compared to a psychoeducation programme in reducing symptoms of BPD. Participants will be randomly allocated to either the intervention group or the control group (comparator), with a 1:1 ratio. In both arms, participants will receive different treatments over a period of 12 weeks. Follow-up data for both groups will be collected 3 months after the end of the intervention.

This trial adheres to the Declaration of Helsinki and has received ethical approval (protocol number: 0027604/24).

Methods: participants, interventions, and outcomes

Study setting {9}

The study will be conducted at the IRCCS Fatebenefratelli in Brescia (Italy). Participants will be recruited at the site centre as well as at other local treatment centres, such as the local Department of Mental Health, private mental health professionals (e.g. psychiatrists and clinical psychologists), and family associations with a family member suffering from BPD. The PA intervention will take place at a sports centre nearby the research site centre, while the psychoeducation sessions will be conducted at the site centre. All assessments and examinations, including collection of blood samples, will be carried out at the site centre, except for saliva samples, which will be collected at home by the participants themselves.

Eligibility criteria {10}

The following eligibility criteria will be applied in the selection of the study population:

i. Female sex
ii. Age between 18 and 40 years;
iii. Primary diagnosis of BPD according to DSM-5-TR diagnostic criteria [18];
iv. Receiving treatment as outpatients at any treatment facility (public, private, residential); and
v. Ability to provide written Informed Consent Form (ICF), a good understanding of the Italian language, and proficiency in smartphone usage.

The presence of ongoing pharmacological and/or psychotherapeutic treatments will not be grounds for exclusion, and participants will continue their current treatments throughout the study.

Patients who meet the following criteria will be excluded from the study:

i. Those who are currently pregnant (or planning a pregnancy within the next 6 months);
ii. Those who exhibit acute psychotic symptoms or comorbidities with eating disorders, substance use disorders, or bipolar disorder [18]; and
iii. Participants showing absolute contraindications to physical exercise, subject to verification by the sports physician during the initial screening visit

(medical conditions that could interfere with their ability to perform exercise—e.g. orthopaedic and/or neurological conditions—or affect their physiological response to exercise tests—e.g. use of beta-adrenergic blocking agents).

Who will take informed consent? {26a}

A written and signed ICF from all participants will be collected by research assistants before the eligibility screening. Participants may withdraw their consent to participate in the research at any time, with no consequences.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Consent for the collection and use of biological material will be part of the single ICF collected before the eligibility screening.

Interventions

Explanation for the choice of comparators {6b}

Current treatments for BPD typically involve manual-based psychotherapies and/or psychoeducation [16, 19]. Thus, the control group in this study will participate in an eight-session psychoeducation programme focused on promoting healthy diet and lifestyle choices, emphasising the benefits of PA, and highlighting the risks of sedentary behaviour. This choice is informed by several factors: (i) previous research demonstrates the effectiveness of psychoeducation groups in improving outcomes for patients with BPD [19]; (ii) focusing on healthy lifestyle habits aligns with the study goal of enhancing overall well-being in patients with BPD. This ensures that the control group receives a meaningful intervention; (iii) while the PA intervention group is expected to directly benefit from increased PA, the control group will benefit from greater motivation to healthier lifestyles.

Intervention description {11a}

The two groups will receive two different treatments running concurrently over 3 months, from baseline (T0) to the end of the intervention (T3). The interventions are structured as follows:

1) Experimental group (structured PA intervention). Participants will receive structured PA sessions monitored by a personal trainer at a sports centre in Brescia (Italy), near the trial research site. A sports physician will design an individualised PA plan based on participants' clinical profile, characteristics, physical limitations, and needs during the initial screening visit (baseline). The intervention will consist of three 60-min sessions of structured PA per week, over a 12-week period, for a total of 36 sessions. The PA sessions will be conducted in groups of up to three participants, with groups organised based on the participants' objectives and remaining skills. Make-up PA sessions will be offered to those who miss any of the scheduled sessions. The personal trainer will record participants' attendance at each session and will maintain regular contacts with the research team to coordinate treatment progress and provide feedback.
2) Control group (Psychoeducation Intervention). Participants will attend eight 60-min sessions of psychoeducation divided into three modules:
    i. Module 1: methods for and benefits of following a healthy diet (total of three sessions conducted by a nutritionist)
    ii. Module 2: psychological and physical risks related to a sedentary lifestyle (total of three sessions conducted by two clinical psychologists).
    iii. Module 3: benefits of PA (total of three sessions conducted by two clinical psychologists).

In addition, participants in the experimental group will also participate in three 60-min psychoeducation sessions on healthy eating style (common Module 1) which will be held together with the control group. Furthermore, participants in the control group will be given the opportunity to participate at no cost in a PA programme at the same sports centre immediately after the end of the trial.

Criteria for discontinuing or modifying allocated interventions {11b}

The study is deemed at minimal risk, and no harm is expected from the intervention. Unusual muscular exercise may cause transient pain in participants ("exercise-induced muscle damage", EIMD) [20]. This side effect is expected to subside gradually within 48 h and will not be considered a significant adverse event (AE) that would result in the exclusion of participants from the trial. Participants will be informed about this transient discomfort and advised on ways to mitigate it, such as undertaking low-intensity aerobic exercise for approximately 10–30 min. However, the following specific discontinuation criteria will be applied: occurrence of intolerable and/or unexpected undesirable side effects and other safety concerns during the PA sessions; medical request or advice; occurrence of any of the exclusion criteria during the 6 months of the study; violation of the study protocol; other circumstances that would pose the health of the participant at risk; participant request/withdraw of consent.

Strategies to improve adherence to interventions {11c}

Adherence to the intervention will be prompted as follows: (i) research personnel (psychologists) will be available by phone, should participants require any assistance; (ii) participants will receive reminder calls/text messages 1 week and 1 day prior to each sport session; (iii) sessions at the sports centre will be led by a personal trainer, who will track participant attendance and provide feedback on intervention progress to the research staff after each session; (iv) participants will be given the opportunity to make up any missed PA sessions; (v) furthermore, all participants will be provided with a fitness tracker at the end of the 3-month intervention.

Relevant concomitant care permitted or prohibited during the trial {11d}

Throughout their participation in the study, patients will continue any ongoing drug and/or psychotherapeutic treatments. Any relevant change in medication usage, including psychotropic medications and others, during the study period will be accurately recorded and documented.

Provisions for post-trial care {30}

Given that the risk for participants is deemed low and no long-term adverse effects are expected from the intervention, no specific provisions for post-trial care have been established. Insurances from both the sports centre and the coordinating centre will cover compensations for any harms resulting from participation in the trial.

Outcomes {12}

The *primary outcome* measure is the Italian validated version of the *Zanarini Rating Scale for BPD* (ZAN-BPD) [21] evaluated at baseline (T0), at the end of treatment (T3) and at follow-up (T6) assessments. The ZAN-BPD is considered a valid and reliable tool for assessing the severity of BPD symptoms, making it suitable for both research and clinical use [22]. It consists of nine items ranging from 0 (no symptoms) to 4 (severe symptoms). Based on findings from prior studies [22, 23], a reduction of at least 3.5 points in the ZAN-BPD rating is expected to be clinically significant as indicative of improvement in BPD symptoms following structured PA intervention in comparison to psychoeducation alone.

Additionally, the study includes the following *secondary outcomes*:

Physical activity is measured by wearable devices for daily continuous monitoring. This evaluation aims to provide insights into the intervention efficacy in fostering sustained engagement in exercise, thereby potentially contributing to overall health enhancements. Movement and sleep–wake patterns over 7-day periods will be obtained with a wrist-worn accelerometer (*Actigraph GT9X*); data will be analysed to calculate parameters such as movement, objective quantity of PA, sleep–wake patterns, step counts, and energy expenditure.

Motivation and regulation to engage in PA is measured with the Italian validated version of the *Behavioural Regulation in Exercise Questionnaire-3* (BREQ-3) [24]. Based on the Self-Determination Theory (SDT), the BREQ-3 explores various motivational types along a continuum from external regulation to intrinsic motivation. It consists of 18 items measured on a five-point Likert scale, encompassing subscales such as external regulation, introjected regulation, identified regulation, integrated regulation, intrinsic motivation, and amotivation. The *Positivity scale* (P-scale) [25] will measure the disposition toward experiencing positive emotions, reflecting optimism, and maintaining a positive attitude in life. It includes eight items assessing connections with self-esteem, life satisfaction, and optimism. The P-scale is used to assess motivational components related to PA, showing strong associations with affectivity and depression. The Italian validated version [26] of the *Rosenberg Self-Esteem Scale* (RSES) will be used to assess self-perception and emotional well-being. It consists of 10 items measured on a four-point Likert scale, reflecting facets of self-esteem and self-worth. The RSES captures feelings about oneself and plays a crucial role in initiating and sustaining PA behaviour. Additionally, a *Paper-based PA diary* will be completed by the personal trainer at the sports centre to monitor participants' adherence to the treatment, and subsequently by the participants themselves to monitor their independent engagement in PA during follow-up.

Physical health status is measured by muscle strength, cardiorespiratory fitness (CRF), blood pressure, and body composition (e.g. BMI). Muscular strength will be assessed using a hand-grip dynamometer (Vald). Additionally, upper and lower limb strength will be measured with ballistic push-ups and five-sit-to-stand tests, respectively. Core strength will be evaluated using a timed plank test. These assessments will be conducted throughout the study to determine baseline strength levels, track training benefits, and tailor individualised training programmes. Walking gait parameters, including speed, cadence, step length, contact time, flight time, symmetry, and variability, will be measured at self-selected speed using optical sensors (*Optogait).* Assessments will occur periodically throughout the study to assess the impact of training. Blood pressure will be measured with a sphygmomanometer (medical device, CE certified: 0476) by a trained sports physician, at rest and during CRF tests. These measurements will inform intervention adjustments and track training outcomes throughout the study.

Furthermore, *Anthropometric Measures* such as BMI, body composition (body fat measured by plicometry), and waist-hip-abdominal circumference will be obtained to provide insights into participants' physical changes over the course of the study.

Biological markers, such as BDNF, kynurenine, cortisol, DHEA, specific biomarkers of muscle function (agrin) and synaptic function (Nf-L), plasma EVs concentration and size, fasting blood glucose, and basic haematochemistry (complete blood count and lipid profile), are measured at each assessment. This evaluation aims to elucidate the neurobiological effects and underlying mechanisms of the intervention.

Psychological variables, such as mood, anxiety levels, impulsivity and daily functioning. This evaluation seeks to examine the impact of the PA intervention on enhancing overall mental well-being and functioning among individuals with BPD. Specifically, the Italian validated version of the following instruments will be employed: (i) the *Beck Depression Inventory short form* (BDI-13) [27], a self-administered questionnaire with 13 items ranging from 0 (none) to 3 (severe), of proved validity and reliability in assessing the presence and severity of depressive symptoms; (ii) the *State-Trait Anxiety Inventory* (STAI-Y) [28], a state form comprising 40 items rated on a 1–4 scale, where 1 (not at all) to 4 (very much) indicates anxiety levels. The total score ranges from 20 to 80, with higher scores indicating higher anxiety levels. The STAI-Y is widely recognised for its validity and reliability in assessing anxiety; (iii) the *UPPS-P Impulsive Behaviour Scale* [29], which includes 20 items, rated on a scale from 0 (not at all) to 4 (very much), representing four subdimensions of impulsivity (Premeditation, Urgency, Sensation Seeking, and Perseverance). The scale is recognised for its validity and reliability in assessing impulsivity levels; (iv) the *World Health Organization Disability Assessment Schedule* (WHODAS 2.0), interview version, developed by the WHO (1985) [30] to assesses the impact of health conditions on daily functioning across six domains: Cognition, Mobility, Self-care, Getting along, Life activities, and Participation. Each item is rated on a five-point Likert scale, ranging from "None" (no difficulty = 1) to "Extreme/Cannot do" (complete inability = 5); (v) *Objective sleep quantity* will be assessed with actigraphy activity measures: time of falling asleep; wake-up time; sleep onset time; total sleep time (TST); sleep efficiency (time asleep during the night); waking after sleep onset (WASO); sleep fragmentation; vi) the *ESM* will be used to assess real-time mood, daily activities and social interactions, with participants receiving eight daily notifications over 1 week period via a custom-built app for the project; vii) additionally, participants will complete an app-based food diary (*Myfood24*) on Thursdays, Fridays, and Sundays following the week of actigraphy monitoring at baseline and at the end of treatment (T3).

Premenstrual symptoms are measured by the Italian version of the Premenstrual Symptoms Screening Tool (PSST) [31] score. The PSST is a self-reported 19-item questionnaire to assess the presence, severity, and change of premenstrual symptoms. It covers psychological, physical, and behavioural symptoms related to the premenstrual syndrome, each rated on a 4-point Likert scale (0 = not at all to 3 = severe), and it evaluates how these symptoms interfere with normal activities in work, family, relationships, social activities, and home responsibilities. This assessment aims to pinpoint the potential broader benefits of the intervention.

Participant timeline {13}

Socio-demographic characteristics (i.e. age, gender, education level, socio-economic and civil status), obstetric history (i.e. number of pregnancies, number of miscarriages/abortions, any contraceptive drug treatments, hormonal therapies), clinical data (i.e. age at disease onset, medications, adherence to medication, and substance use disorders), and lifestyle habits (e.g. smoking, alcohol and drug use, PA, sleep hours, and diet) will be collected at the eligibility screening of all patients who have accepted to participate. Subsequent assessments will be conducted at baseline (T0) and at the conclusion of the intervention (T3). A final set of assessments will occur at the follow-up (T6), 3 months after the conclusion of the treatment phase. Table 1 illustrates the phases of administering the instruments and conducting the assessments, while Table 2 shows the assessment tools employed across the trial phases.

Sample size {14}

The sample size was computed via simulation assuming a longitudinal design with three time points for each treatment arm and a normal distribution for the main outcome (ZAN-BPD). As an RCT, we set a common mean value for baseline (T0) measurements in both arms following Zanarini et al. [21] (mean = 14) and residual standard deviation (sd = 6.8), with no variation in following visits in the control arm, and a 4 points reduction both at T3 and T6. This scenario corresponds to a reduction of at least 4 points in ZAN-BPD in the experimental group compared to the control group at T3, and a stabilisation of the difference until T6. The simulation assumed a within-subjects first-order autoregressive (AR1) correlation structure with rho set to 0.4, being the lower bound value suggested by Walters et al. [32]. We adopted an ANCOVA model in the simulations, testing a time-treatment interaction considering T3 and T6 measurements and adjusting for baseline value. Assuming a two-sided

5% significance level, a sample size of 32 patients in each group allowed to achieve a power of at least 88% ($B = 200$ simulations) for the comparison at T3, and a power of at least 80% for a simultaneous comparison at T3 and T6.

Recruitment {15}

Participants will be recruited from outpatients receiving treatment at the coordinating centre in Brescia, and via advertisements at mental health departments of local hospitals, university departments, mental health associations, and private psychotherapy centres. The research team will actively contact treating psychologists, psychotherapists, and psychiatrists at these centres. Treating professionals will appropriately inform and invite female individuals who meet the DSM-5-TR diagnostic criteria for BPD—*thus ensuring a confirmed diagnosis*—to participate in the trial. The recruitment is intended to continue for a maximum of 12 months and to be concluded before the baseline assessment (T0) and initiation of the treatment phase. In the event of participant drop-out or exclusion from the trial, no further recruitment will be performed, unless the drop-out occurs within the first 15 days from inclusion in the project.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be allocated to the two groups (intervention group versus control group) with a 1:1 ratio according to a computer-generated random list generated using a permuted blocks algorithm with random block size [33]. The recruitment process will occur gradually over time, i.e. participants may be recruited intermittently rather than all at once. This approach ensures that the allocation remains unpredictable and upholds the integrity of the randomisation process.

Concealment mechanism {16b}

All data will be collected, managed, and stored by the Data Controller in accordance with the most appropriate technical and organisational measures to prevent theft, loss, destruction (including accidental destruction), or unlawful transfer to third parties. To identify each patient the Case Report Forms (CRFs) will randomly generate unique codes. This security measure ensures that patients are not directly identified by those processing personal data. Only professionals authorised by the Promoter will be able to link the code to the patients' personal data. Moreover, separate projects will be created through CRFs to ensure that personal identifiers are not stored alongside clinical data, maintaining the required data protection standards.

The identification of the subjects using a code will be possible only for the time necessary for the study.

Implementation {16c}

Two assistant psychologists, alongside the Principal Investigator (PI) of the study, will recruit participants who have been initially diagnosed with BPD and are currently receiving treatment at the coordinating centre. For participants recruited from external centres, referrals will be made by the healthcare professionals who are currently managing their care, to safeguard participants' well-being. Allocation to the treatment arm will be centrally performed by the coordinating centre following the randomisation list.

Assignment of interventions: blinding

Who will be blinded {17a}

An experienced data systems analyst, as part of the research team involved in the project, will provide Data Management and will be responsible for the blinding, randomisation, and pseudonymisation procedures for the participants.

Due to the nature of the interventions, the staff delivering the intervention and control procedures, as well as the participants, will not be blinded. Outcome assessments will be conducted and analysed with blinding to the group assignments.

Procedure for unblinding if needed {17b}

There are no reasons for which unblinding would be required.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Multidimensional assessments (physical and physiological, psychological, and biological) will be conducted at three time points (see Figs. 1 and 2 for more details): baseline (T0), 3 months (end of treatment, T3), and 3 months post-treatment (follow-up, T6). Before starting the interventions, interviewers will gather background information. At T0 and at T3 a sports physician will conduct physiological and physical assessments. At T0, T3, and T6 participants will wear a wrist accelerometer continuously for 7 days; during the same weeks, according to the ESM procedure, they will be asked to respond to eight daily notifications about sleep quality, mood and social interactions via a smartphone app. Voluntary PA levels will be additionally assessed (i) throughout the duration of the PA intervention (from T0 to T3) with a paper diary completed by a personal trainer at the sports centre and (ii) at T6 using a weekly self-reported paper diary for participants in both groups. Blood and saliva samples will be collected at each assessment (T0, T3 and T6). Standardised tools will be used to assess BPD symptoms, mood, anxiety,

Table 1 Time schedule showing the main protocol phases: from recruitment procedure to follow-up

	Ethical approval	Enrolment	Eligibility screen	Allocation	Post- Allocation			Follow-up
TIMEPOINTS	$-t_3$	$-t_2$	$-t_1$	0	T_0		T_3	T_6
APPROVAL:								
Protocol drafting	X							
Documents submission	X							
Tools renting	X							
ENROLMENT:								
Informed consent		X						
Data collection form and Obstetric anamnesis			X					
Allocation				X				
INTERVENTIONS:								
1. Psychoeducation Group					═══	═══	═══	
2. Structured PA Group					═══	═══	═══	
3. Shared treatment (3 psychoeducational sessions on diet)					- - - - - - - - - -		- - -	
ASSESSMENTS:								
Physical examination					X		X	X
1-week Actigraph + ESM					X		X	X
Blood sampling					X*		X*	X*
Saliva sampling					X		X	X
Resting Blood Glucose					X		X	X
ZAN-BPD					X		X	X
BDI-13					X		X	
STAI-Y					X		X	
UPPS-P					X		X	
WHODAS 2.0					X		X	
Myfood24					X		X	
PSST					X		X	
PA diary					- - - - - - - -	- - - - - - - -	- - - - - - - -	
P-scale					X		X	X
BREQ-3					X		X	X
RSES					X		X	X

Abbreviations: *PA* physical activity, *ESM* experience sampling method, *ZAN-BPD* Zanarini Rating Scale for Borderline Personality Disorder, *BDI-13* Beck Depression Inventory short form, *STAI* State-Trait Anxiety Inventory, *UPPS-P* Impulsive Behaviour Scale, *WHODAS 2.0* World Health Organization Disability Assessment Schedule, *PSST* Premenstrual Symptom Screening Tool, *P-scale* Positivity scale, *BREQ-3* Behavioural Regulation Exercise Questionnaire-3, *RSES* Rosenberg Self-Esteem Scale

* At T0, T3, and T6 sampling will include the following analyses: brain-derived neurotrophic factor (BDNF); kynurenine; cortisol; DHEA; analysis of specific biomarkers: of muscle function (agrin) and synaptic function (neurofilament light chain protein, Nf-L); analysis of novel biomarkers: concentration and size of plasma extracellular vesicles (EVs); resting blood glucose; basic haematochemistry: complete blood count and lipid profile

impulsivity, general functioning, premenstrual symptoms, emotional well-being, as well as motivation to exercise, self-esteem, and positivity across the study period, as detailed in Fig. 2 and Table 2. Additionally, on Thursday, Friday, and Sunday during the week following each actigraph period, participants will complete a food diary. A detailed list and description of the diagnostic interviews, questionnaires, and assessment schedule is reported under SPIRIT Item 12, as well as in Tables 1 and 2.

Self-reported or interview-based data will be recorded into CRFs using REDCap (Research Electronic Data Capture) [34]. PA, ESM and food-diary data will be collected with digital tools, such as accelerometers and smartphone-specific apps. Data collected through digital tools will be further integrated into the centralised electronic database. Blood samples will be drawn at the site centre; saliva samples will be collected at home by the participants themselves.

All personnel collecting data will be properly trained; the accuracy of the data will be periodically reviewed by the investigators.

Plans to promote participant retention and complete follow-up {18b}

All participants will be notified by phone and sent a reminder text message a week before and the day before each evaluation, respectively. A personal trainer will oversee the PA programme of the participants of the intervention group, keeping a paper record of sports centre visits and session durations to ensure adherence to the 60-min PA plan, which will be tailored to each participant's needs. At the end of the 3-month intervention, all participants will receive a fitness tracker (i.e., a PA monitoring device) to encourage PA continuation during the 3-month

Table 2 Complete overview and description of the assessment tools and schedule shared by both groups

Tool	Measure	Assessment site	T_0	T_3	T_6
Psychopathological assessment					
Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) ([21]	Severity of BPD symptoms	Site centre	x	x	x
Beck Depression Inventory short form (BDI-13) [27]	Mood status; presence and severity of depressive symptoms	Site centre	x	x	
State-Trait Anxiety Inventory (STAI) [28]	Anxiety levels	Site centre	x	x	
Impulsive Behavior Scale (UPPS-P) [29]	Impulsiveness levels (premeditation, urgency, sensation seeking, perseverance)	Site centre	x	x	
World Health Organization Disability Assessment Schedule (WHODAS 2.0) [30]	General functioning; impact of health conditions on daily functioning (cognition, mobility, self-care, getting alone, life activities, participation)	Site centre	x	x	
Premenstrual Symptom Screening Tool (PSST) [31]	Presence, severity and change of premenstrual symptoms; psychological, physical and behavioural symptoms and their interference with normal activities in various functional areas	Site centre	x	x	
MyFood24 (food diary)	Nutrition data	Home	x	x	
Experience sampling method (ESM)	Real-time assessment of mood and psychosocial variables (e.g. social interactions)	Home	x	x	x
Physical and physiological testing Conducted in line with the instructions contained in the ICH E6 (R2) GCP					
Dynamometer	Muscular strength (hand-grip test); strength of the upper limbs (ballistic push-up test); strength of the lower limbs (five-sit-to-stand test); core strength (timed plank test)	Site centre	x	x	x
Step-ramp-step test on a cycloergometer	Cardiorespiratory Fitness (CRF), gas exchange, and ventilation (Ventilatory thresholds and VO2max)	Site centre	x	x	x
Self-selected speed with optical sensors (Optogait)	Walking gait: detection of the relevant space and time parameters (i.e. speed, cadence, step length, contact time and flight time, symmetry, and variability)	Site centre	x	x	x
Sphigmomanometer (medical device, CE certified: 0476)	Blood pressure	Site centre	x	x	x
Plicometer	Anthropometric measures: body mass index (BMI), abdomen/hip/waist circumference	Site centre	x	x	x
Actigraph (GT9X) (7 days at each time-point)	Level of PA (intensity-sedentary, light PA, moderate-to-vigorous PA-, step count, energy expenditure), objective sleep quantity (sleep–wake rhythms)	Home	x	x	x
Motivation to practice PA					
Behavioural Regulation in Exercise Questionnaire-3 (BREQ-3) [24]	Motivation and Regulation to engage in PA (external regulation, introjected regulation, identified regulation, integrated regulation, intrinsic motivation, and amotivation)	Site centre	x	x	x
Positivity scale (P-scale) [25]	Disposition toward experiencing positive emotions	Site centre	x	x	x
Rosenberg Self-Esteem Scale (RSES) [26]	Self-perception and emotional well-being (feelings -positive or negative- about oneself)	Site centre	x	x	x
PA diary	Monitoring adherence to the PA programme and maintenance of PA	Sport centre (personal trainer's monitoring for the PA group)	x	x	
		Home (self-monitoring for both groups)			x

Table 2 (continued)

Tool	Measure	Assessment site	T_0	T_3	T_6
Biological sampling					
Saliva sampling (salivary drools)	Cortisol, Dehydroepiandrosterone (DHEA)	Home	x	x	x
Blood (venous) sampling	Biomarkers analyses: brain-derived neurotrophic factor (BDNF), kynurenine, cortisol, DHEA, agrin, neurofilament light chain (Nf-L), plasma extracellular vesicles (EVs)	Site centre	x	x	x
	Basic haematochemistry (blood count and blood lipid profile)	External laboratory	x	x	x
Ear prick test kit	Resting blood glucose	Site centre	x	x	x

follow-up. Participants can request results of their evaluations, and withdraw from the study at any time; any withdrawals will be promptly recorded in the CRFs.

Data management {19}

Diagnostic interview and self-report data assessed at baseline (T0), 3 months (T3), and 6 months (T6) will be collected using REDCap [34]. REDCap is a secure web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, and automated export procedures for seamless data downloads to common statistical packages. Similarly, data collected via digital tools such as accelerometer and ESM is collected by establishing a link between the data and the identification code of the study participants. Data obtained from the devices during the survey period is initially stored locally on the device itself. The data loaded onto the device are then downloaded using the dedicated software and integrated into the electronic database specifically created for the project, and subsequently analysed. The same procedure is applied to the data collected via smartphone through the myFood24 app. Regular backups of the data will be performed weekly, and the database will only be accessed through password-protected direct access, with authorisation limited to authorised Internet Protocol (IP) addresses via Secure Shell (SSH) connection to the server. Authentication and authorisation for a SSH connection will require a private key.

Blood and saliva samples collected before analyses will be stored, after pseudonymisation, for short-term storage (months) in a − 80 °C or − 20 °C freezer in secured laboratory rooms accessible only to authorised in-house laboratory staff. Storage of the samples for future use is not planned.

Confidentiality {27}

All data will be treated with strict confidentiality in accordance with the General Data Protection Regulation (GDPR) [Regulation (EU) 2016/679]. Upon inclusion in the study, each participant will be assigned a unique trial identification number, which will serve as a personal identifier across all CRFs and related documents. This unique code will not contain any direct identifying information. The link between real identities and pseudonymised IDs (a correspondence table) will be kept as hard copies, stored separately from other data, encrypted, and securely archived in a locked cupboard under the local PI responsibility. Only authorised members of the research team will have access to these identification tables.

Upon completion of data collection and after thorough quality control, the entire pseudonymised dataset will be deposited in the public repository Zenodo. Five years after the conclusion of the project, all patient identities and related information stored at the recruiting site will be deleted, fully anonymising the data in the repository.

Participants will be informed that their pseudonymised data may be shared with other researchers. They will also be informed of their rights under the European Data Protection Regulation (EU-DSGVO).

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Molecular analyses in this RCT refer to both salivary and blood samples. Healthcare personnel will supervise blood sampling, while participants will provide saliva samples themselves according to the study design described above. After pseudonymisation, blood vials and saliva drops will be stored in secure rooms in a freezer (at − 80 °C or − 20 °C, for temporary storage—several months). All saliva and blood samples will be analysed for biological markers by biochemists. Biological samples will not be further stored for future use in ancillary studies.

Statistical methods

Statistical methods for primary and secondary endpoints {20a}

The analysis of this RCT will adhere to the intention-tot-Treat analysis (ITT).

The primary objective, specifically addressing the variation of BPD symptoms as evaluated by the ZAN-BPD scale, will be investigated using a random intercept linear mixed model with a time-treatment interaction term, addressing the main hypothesis of a differential variation of BPD symptoms along time in the two treatment arms. The model will account for baseline BPD values (a so-called ANCOVA model) as well as other potential confounding variables such as baseline PA level, obstetric history (e.g. complications during pregnancy, number of pregnancies), psychiatric comorbidities, pharmacological and psychotherapeutic treatment, sleep quality, and participants motivation levels for both treatments. More complex random effects structures (random slopes) will be evaluated.

Linear regression models will be employed to explore the effect on psychiatric severity/functional levels (as measured by ZAN-BPD, PSST, and other rating scales) of levels of PA (vector magnitude, VM) and emotions in patients with BPD. For variables measured at multiple time points (T0, T3, T6), longitudinal models will be used. These models will adjust for age, medication, disability level, smoking, and seasonality. For variables assessed only at T0 and T3, ordinary least squares (OLS) regression will be applied, adjusting for baseline outcome values.

Positive and negative emotions, assessed using the ESM methodology, will be computed by averaging ratings of positive (happy, relaxed, quiet, and full of energy) and negative (sad, tired, and nervous) emotions, respectively. These will be synthesised as daily averages on a 0–100 scale. Emotion ratings will be compared between treatment arms using a random intercept linear mixed model adjusting for smoking and seasonality.

The impact of the intervention on anthropometric measures such as BMI, actigraph data, dynamometer measurements, and biological markers, will be evaluated using random intercept linear mixed models, with time-treatment interaction.

Sensitivity analyses will be conducted on stratified samples to confirm the role of covariates and confounding factors. All statistical tests will be two-sided and evaluated at a 5% significance level. All results will be presented as estimated effects with corresponding 95% confidence intervals. The analyses will be performed using the R software system version 4.4.1 or above.

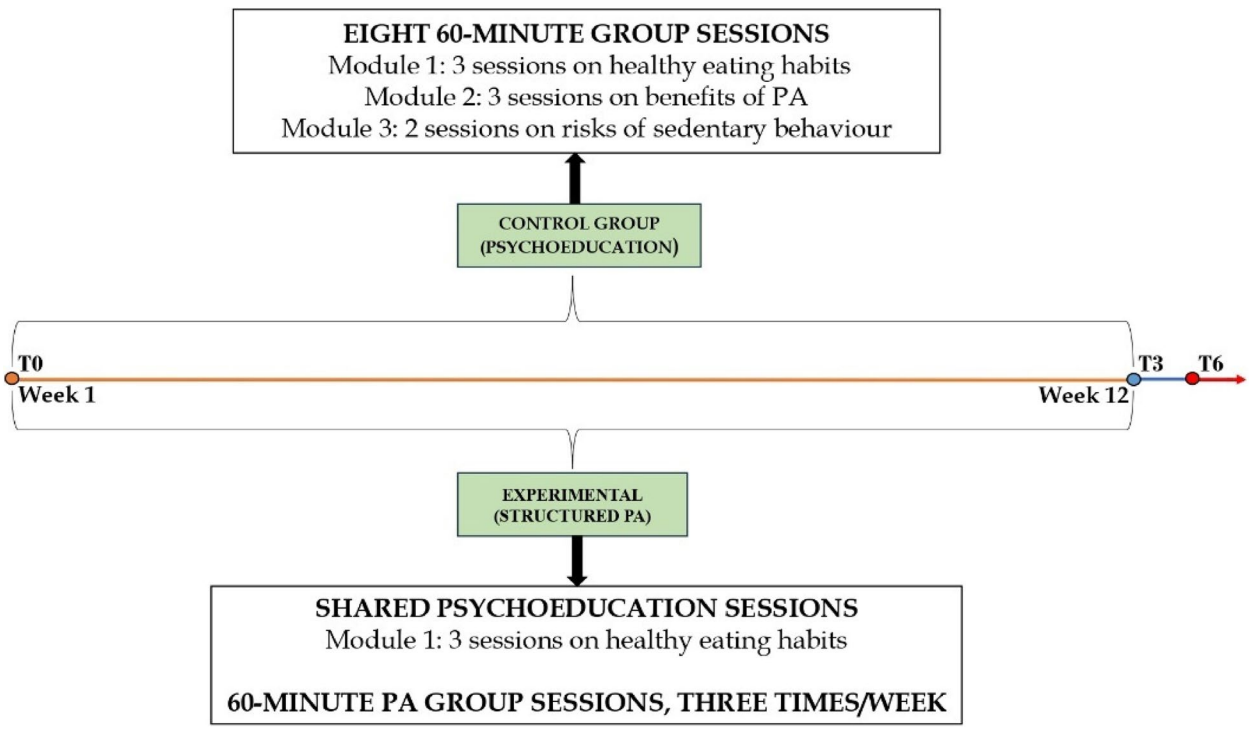

Fig. 1 Timeline showing intervention and control procedures for female BPD outpatients during the 12-week trial period. The orange line represents the 3-month period during which the two treatments take place; the blue line represents the follow-up of a further 3 months; and the red line is for all the following analyses. The top box indicates the treatment schedule for the control group; the box below the timeline represents the treatment schedule for the experimental group

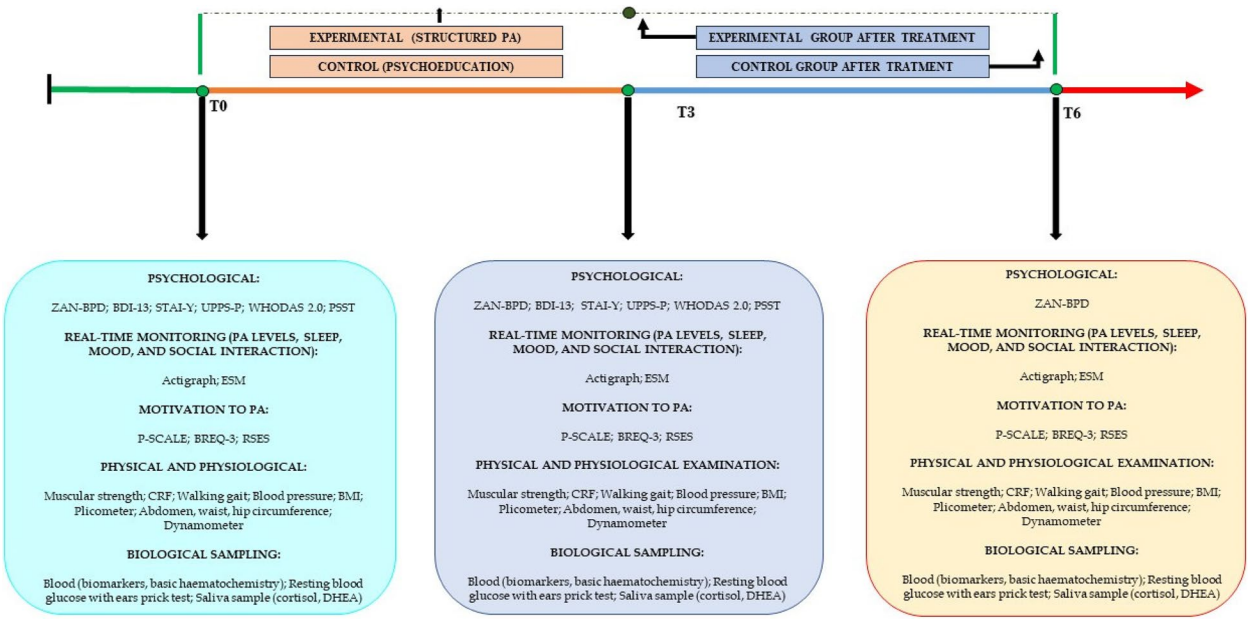

Fig. 2 Planned overview of the assessment timeline for both the experimental and control groups. The experimental and control groups share the same assessment plan; the green line represents all the phases preceding the baseline assessment (T_0), corresponding to the enrolment and allocation of participants; the orange line is for the two different treatment phases, each of a 3-month duration; the blue line represents the 3 months of follow-up; the red line is for the final phase of analysis and dissemination of results. The arrows indicate the exact time point for the assessments

Processing of accelerometer data

Individual Actigraph GT9X files will be processed using the GGIR package [35] to estimate VM [36] using a 60-s epoch and default settings (calibration, no data imputation). VM captures the total movement as a combination of accelerations along the three axes. Each patient must have at least four valid monitoring days, with each day containing at least 10 valid hours of wearing time.

Interim analyses {21b}

There are no interim analyses planned.

Methods for additional analyses (e.g. subgroup analyses) {20b}

To confirm the role of covariates and confounding factors we will run a sensitivity analysis on stratified samples. For example, a stratifying strategy may be based on menstrual cycle phases. However, the findings from subgroup analyses will be handled cautiously and employed exclusively for generating hypotheses.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

A minimal amount of missing data is expected. Therefore, no multiple imputations will be performed. The analysis will be conducted on only available data.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

The study protocol is accessible online on the trial registration website. The PI will provide every detail (including the complete version of the protocol, pseudonymised data, and statistical code) upon specific and justified request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The trial management group is chaired by the PI of the project. Day-to-day organisation and coordination of the study are managed by a research team composed of the PI and several sub-investigators. They supervise the study and coordinate all aspects of the project, connecting the intervention and evaluation staff. The research team will hold weekly meetings to discuss new developments, make decisions regarding changes to the research protocol or specific activities, and address any additional intervening issues. Additional meetings will be convened as needed to clarify urgent questions. Meetings with the larger research team, including consultants, are scheduled to coincide with the baseline, 3-month, and 6-month assessments, and then every 3 months thereafter, to discuss the study progress, possible changes to procedures, planning of the analyses, and preparation of the

manuscripts. There is no Stakeholder and Public Involvement Group (SPIG).

A Trial Steering Committee (TSC) will ensure that the trial is conducted in compliance with the approved protocol, ethical standards, and regulatory requirements. The TSC will provide independent oversight and guidance to the trial management team. Its responsibilities include reviewing and approving the trial protocol, as well as monitoring the progress of the trial to ensure adherence to the protocol. The TSC will include the project PI and at least two experienced clinicians or trial methodologists, who will provide specialised knowledge and oversight.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Data Monitoring Committee will include professionals from various disciplines including psychiatry, biology, and statistics, ensuring a comprehensive oversight of trial proceedings. It will safeguard participant safety and will maintain the integrity of trial data. To achieve this, the committee will monitor the safety and efficacy of the data throughout the trial duration, review adverse events, assess trial progress to ensure sustained scientific validity and data integrity and assess the validity and rigour of final data.

Adverse event reporting and harms {22}

The study is considered to be of minimal risk. Nevertheless, in order to minimise the risk of AEs, an initial assessment by a sports medicine specialist will ensure the selection of the most appropriate type, intensity, and volume of physical exercise for each individual. A PA intervention may cause a transitory, moderate pain and swelling of the muscles involved in the activity. No other unexplained AEs or long-term harms are expected. However, the onset of any unforeseen physical difficulties and the levels of adaptation to the proposed exercises will be continuously monitored by a personal trainer. The research team will monitor continuously the occurrence of any unanticipated problems potentially causing risk to the participants. The PI will record any such events electronically in the trial-specific CRFs, REDcap [34]. Any adverse experiences, whether psychological or physical, will be classified as AEs and immediately reported to the PI of the study. The PI's research team will maintain regular communication with the participants to discuss the progress of the treatment and any issues that may impact their health. Suspected Unexpected Serious Adverse Reactions (SUSAR), such as significant health risks including cardiac issues, muscle or tendon rupture, respiratory or renal problems, or worsening of psychiatric symptoms, will be reported within 3 days. In the case of a serious adverse event (SAE), such as an injury resulting from PA or a worsening of psychiatric symptoms, the PI or a qualified medical delegate will swiftly fill out an SAE form. This form will provide an evaluation of the causality (i.e. its relation to the PA intervention) and severity of the event. The research team will meet weekly to review trial progress and events and discuss potential AEs and necessary protocol amendments.

To minimise the likelihood of any form of risk, especially those impacting mental health, interventions will be customised to address the specific needs of each participant. Throughout the study, participants will receive support in a compassionate and empathetic environment provided by qualified professionals, including psychologists, psychiatrists, nursing staff, personal trainers, and a sports physician. As outlined in the ethical guidelines, the participants' well-being will have the highest priority. Participants will also retain the right to withdraw from the study at any time without any repercussions.

Frequency and plans for auditing trial conduct {23}

Compliance with the study procedures and other quality checks will be conducted every 3 months, in order to verify that all personal identifying information, medical records and consent forms are secured. The audit process operates independently from the researchers and the sponsor. The PI along with the research team are responsible for the monitoring procedures.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Potential amendments to the study protocol will be submitted for approval to the competent Ethics Committee and then uploaded into the clinical trial registry.

Dissemination plans {31a}

All trial results will be presented according to the guidelines outlined by the Consolidated Standards of Reporting Trials (CONSORT) (www.consort-statement.org). All participants will be informed of the trial results, which will be published in peer-reviewed scientific journals, with open-access journals being prioritised. Additionally, findings will be presented at national and international scientific conferences and disseminated to healthcare professionals via seminars. Results will also be disseminated to the study participants via finding summaries and individual reports, and to the general public via press and social media.

Discussion

PA not only significantly improves physical health [1], but has proven as an effective adjunctive therapy for many psychiatric conditions, such as major depressive and anxiety disorders (6, 9). BPD is a common disorder characterised by severe impairment of psychological, social and general functioning, along with high suicidal risk. In spite of a lack of approved effective pharmacological treatments, and limited availability of psychological treatments for patients with BPD within the public health system, little is known on the potential efficacy of PA for alleviating BPD symptoms.

This trial is the first to examine the effects of a structured, 3-month PA programme for young women with BPD. If the results provide evidence for the effective contribution of PA to significantly reduce BPD symptoms compared to traditional psychoeducation interventions, PA recommendations, promotion and possibly active sessions could be easily implemented as part of everyday clinical practice for patients with BPD.

Moreover, given the employment of multifaceted assessment tools, including self-report questionnaires, objective accelerometer and dynamometric measures, app-recorded measurements, along with biological samples, this project will provide a comprehensive overview of PA effects on the multiple dimensions affected by the BPD. Additionally, the inclusion of repeated measures throughout and over the intervention period will allow examination of dynamic changes in both, somatic and psychological symptoms, and PA levels, along with identification of factors involved in motivational aspects of long-term PA. In particular, a better understanding of the factors contributing to initiating and maintaining PA over time, along with identification of exercise barriers, will allow individualised interventions aimed at improving positive attitudes towards PA and reducing sedentary behaviour in patients with BPD.

Possible limitations of the study include difficulties with recruiting an adequate sample size and retention of patients in the study. However, given the relative easiness and feasibility of the proposed intervention, we are confident that patient adherence will be satisfactory.

Thus, our study will contribute to filling in an important gap in public health and clinical practice, by promoting broadly reaching interventions with potential for large-scale, cost-effective implementation.

Trial status

This trial is registered with ClinicalTrials.gov (Trial Registration number: NCT06461104; Protocol Version: 1, date: 04.09.2024) and posted on 6th June 2024. This trial is not yet recruiting. The anticipated start date for recruitment is 1st October 2024, while recruitment is expected to be completed by 1st April 2025.

Abbreviations

AEs	Adverse events
AR1	First-order autoregressive
BDI-13:	Beck Depression Inventory short form
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BPD	Borderline personality disorder
BREQ-3	Behavioural Regulation in Exercise Questionnaire-3
CONSORT	Consolidated Standards of Reporting Trials
CRF	Cardiorespiratory Fitness
CRFs	Case Report Forms
DHEA	Dehydroepiandrosterone
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text revision
EIMD	Exercise-induced muscle damage
ESM	Experience sampling method
EU-DSGVO	European Data Protection Regulation
EVs	Plasma extracellular vesicles
GDPR	General Data Protection Regulation
ICF	Informed consent form
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice;
IP	Internet Protocol
IRCCS	Istituto Centro San Giovanni di Dio Fatebenefratelli
ITT	Intention-to-treat analysis
Nf-L	Neurofilament light chain
OLS	Ordinary least squares
P-scale	Positivity scale
PA	Physical activity
PI	Principal Investigator
PSST	Premenstrual Symptom Screening Tool
RCT	Randomised controlled trial
REDCap	Research electronic data capture
RSES	Rosenberg Self-Esteem Scale
SAE	Serious adverse event
SDT	Self-determination theory
SPIG	Stakeholder and Public Involvement Group
SSH	Secure Shell
STAI	State-Trait Anxiety Inventory
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSC	Trial Steering Committee
TST	Total sleep time
UPPS-P	Impulsive Behaviour Scale
VM	Vector magnitude
WASO	Wake after sleep onset
WHODAS 2.0	World Health Organization Disability Assessment Schedule
ZAN-BPD	Zanarini Rating Scale for Borderline Personality Disorder

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08525-8.

Additional file 1: {2b} Trial registration data. The WHO Trial Registration Data Set [37].

Additional file 2: {24} a. Duplicate of the original ethical approval document. b English translation of the original ethical approval document.

Additional file 3: {4} a Duplicate of the original document detailing received funds, 5x1000. b English translation of the original document detailing received funds, 5x1000.

Additional file 4. GANTT CHART.

Additional file 5. {4} a Duplicate of the original document detailing received funds, Banca d'Italia. b English translation of the original document detailing received funds, Banca d'Italia.

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personal trainer of the sports centre, and all the nurses who will assist the patients during the treatment phases. We also thank the valuable work of Drs. Manuel Zamparini and Giulia Moncalieri, who have contributed to the initial stages of this research project with great dedication.

Authors' contributions {31b}
All authors contributed to the design of the study, reviewed drafts of the report and gave technical support throughout the trial. GdG was responsible for the conception of the trial, the overall supervision, and obtained funding. GdG, SL, MD and ET performed the literature research. SL, MD, ET, RR, SP, and AM participated in the first drafting of the protocol. SL and MD will manage data gathering and data entry. SP will conduct sports medical examinations for the participants and will be responsible for screening to include participants with BPD as potential members of the PA group. DM and DM provided expertise in the implementation of statistical analysis and will perform the data analyses. SC and MC will perform data processing of the accelerometer. RR, SM, GBT and AM participated in the design of the study and will provide expertise in the intervention for BPD. RG, AC, SB, CS, AL, EM, and NC will conduct biological analyses. GdG, SL, ET, and MD were responsible for the subsequent collation of inputs and redrafting. All authors read and approved the final protocol.

Funding {4}
The trial is funded by the Ministero della Salute (grant number 10128) through the "5 × mille" contribution for the year 2021, with funding allocated on March 8, 2023. Additional funding has been received by the Banca d'Italia "Voluntary contribution January–February 2024". Both funders have the role of providing financial support, covering various aspects of the trial such as research staff salaries, participant compensation, materials, and other operational costs. They also promote public health research and maintain oversight to ensure the proper use of funds. However, they do not have a direct influence on the research, as they do not interfere with the scientific or operational aspects of the study.

Data availability {29}
Upon completion of the trial, all data and materials will be deposited in Zenodo and made available. Please note that the link will direct to a placeholder until the data is uploaded. Additionally, it will be made available upon formal request, subject to the PI's approval.

Declarations

Ethics approval and consent to participate {24}
This Trial has been approved by the competent Ethical Committee (Comitato Etico Territoriale Lombardia 6—C.E. Fondazione IRCCS Policlinico San Matteo di Pavia, ASST Ospedale Papa Giovanni XXIII di Bergamo e ASST degli Spedali Civili di Brescia, Viale Camillo Golgi 19, 27100 Pavia) on 17 May 2024 (Protocol number: 0027604/24). The study will be conducted according to the Declaration of Helsinki (2013) and consistent with Good Clinical Practice (2016 ICH-GCP) and all applicable regulatory requirements. All participants voluntarily confirming their willingness to participate in this trial will provide a written, signed and dated ICF.

Consent for publication {32}
No details, images, or videos relating to any individual person are included in this study protocol. However, biological samples will be collected, and participants will be asked to provide a written and signed ICF and Privacy Information Form. Informed consent materials are attached as supplementary materials.

Competing interests {28}
The authors declare they have no competing interests.

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