PLOS ONE

RESEARCH ARTICLE

Clinical outcomes and anti-inflammatory mechanisms predict maximum heart rate improvement after physical activity training in individuals with psychiatric disorders and comorbid obesity

Pau Soldevila-Matías[1,2,3☯], Joan Vicent Sánchez-Ortí[1,2,4,5☯], Patricia Correa-Ghisays[1,2,4,5☯]*, Vicent Balanzá-Martínez[2,4,5,6,7], Gabriel Selva-Vera[2,4,5,6], Roberto Sanchis-Sanchis[8], Néstor Iglesias-García[9], Manuel Monfort-Pañego[9], Pilar Tomás-Martínez[10], Víctor M. Victor[2,11,12,13], Benedicto Crespo-Facorro[5,14], Constanza San Martin Valenzuela[2,4,5,15], José Antonio Climent-Sánchez[16], Rosana Corral-Márquez[16], Inmaculada Fuentes-Durá[1,2,4,5], Rafael Tabarés-Seisdedos[2,4,5,6]*

1 Faculty of Psychology, University of Valencia, Valencia, Spain, **2** INCLIVA—Health Research Institute, Valencia, Spain, **3** Department of Psychology, Faculty of Health Sciences, European University of Valencia, Valencia, Spain, **4** TMAP—Evaluation Unit in Personal Autonomy, Dependency and Serious Mental Disorders, University of Valencia, Valencia, Spain, **5** Center for Biomedical Research in Mental Health Network (CIBERSAM), Health Institute Carlos III, Madrid, Spain, **6** Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Valencia, Spain, **7** VALSME (VALencia Salut Mental i Estigma) Research Group, University of Valencia, Valencia, Spain, **8** Department of Physical Education and Sports, University of Valencia, Valencia, Spain, **9** Department of Didactics of Physical, Artistic and Music Education, University of Valencia, Valencia, Spain, **10** Mental Health Unit of Xàtiva, Lluís Alcanys Hospital, Valencia, Spain, **11** Service of Endocrinology and Nutrition, University Hospital Dr. Peset, Valencia, Spain, **12** Foundation for the Promotion of Health and Biomedical Research in the Valencian Region (FISABIO), Valencia, Spain, **13** Department of Physiology, University of Valencia, Valencia, Spain, **14** Department of Psychiatry, University Hospital Virgen Del Rocio, IBIS-CSIC, University of Sevilla, Seville, Spain, **15** Department of Physiotherapy, University of Valencia, Valencia, Spain, **16** Mental Health Unit of Sagunto, Valencia, Spain

☯ These authors contributed equally to this work.
* rafael.tabares@uv.es (RTS); patricia.correa@uv.es (PCG)

Citation: Soldevila-Matías P, Sánchez-Ortí JV, Correa-Ghisays P, Balanzá-Martínez V, Selva-Vera G, Sanchis-Sanchis R, et al. (2025) Clinical outcomes and anti-inflammatory mechanisms predict maximum heart rate improvement after physical activity training in individuals with psychiatric disorders and comorbid obesity. PLoS ONE 20(1): e0313759. https://doi.org/10.1371/journal.pone.0313759

Editor: Marina De Rui, University Hospital of Padova, ITALY

Received: June 29, 2024

Accepted: October 10, 2024

Published: January 3, 2025

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: Rafael Tabares-Seisdedos has been supported by the State Research Agency (SRA), European Regional Development Fund (ERDF), EU (PID2021-129099OB-I00), and Generalitat Valenciana, Spain (PROMETEO/CIPROM/2022/58).

Abstract

Introduction

This study aimed to evaluate the predictive validity and discriminatory ability of clinical outcomes, inflammatory activity, oxidative and vascular damage, and metabolic mechanisms for detecting significant improve maximum heart rate after physical activity training in individuals with psychiatric disorders and obesity comorbid using a longitudinal design and trans-diagnostic perspective.

Methods

Patients with major depressive disorder, bipolar disorder and, schizophrenia and with comorbid obesity (n = 29) were assigned to a 12-week structured physical exercise program. Peripheral blood biomarkers of inflammation, oxidative stress, vascular mechanisms,

Víctor M Victor has been supported by the Generalitat Valenciana, Spain (PROMETEO/CIPROM/2022/32), Spanish Ministry of Science and Innovation (CIBERehd CB06/04/0071) and, ISCIII (PI22/00424).

Competing interests: The authors have declared that no competing interests exist.

and metabolic activity, as well as neurocognitive and functional performance were assessed twice, before and after intervention. Maximum heart rate was considered a marker of effectiveness of physical activity. Mixed one-way analysis of variance and linear regression analyses were performed.

Results

Individuals with psychiatric disorders and comorbid obesity exhibited an improvement in cognition, mood symptoms and body mass index, increase anti-inflammatory activity together with enhancement of the oxidative and cardiovascular mechanisms after physical activity training ($p<0.05$ to 0.0001; $d = 0.47$ to 1.63). A better clinical outcomes along with regulation of inflammatory, oxidative, and cardiovascular mechanisms were critical for predicting significant maximum heart rate variation over time ($\chi^2 = 32.2$ to 39.0, $p < 0.0001$).

Conclusions

The regulation of the anti-inflammatory mechanisms may be essential for maintained of healthy physical activity across psychiatric disorders and obesity. Likewise, inflammatory activity, oxidative stress, vascular and cardio-metabolic mechanisms may be a useful to identify individuals at greater risk of multi-comorbidity.

Introduction

Physical inactivity and sedentary behavior are significant risk factors for the development and maintained cardiovascular problems in individuals with obesity (OB) and psychiatric disorders [1, 2]. In individuals with major depressive disorder (MDD), aerobic exercise training is significantly associated with a reduction in depressive symptoms and has a positive impact on neurocognitive performance and cardiovascular health [3, 4]. Moreover, physical activity sustained over time can be an effective adjunctive treatment for the development of metabolic complications [5]. Similarly, healthier lifestyles and increased physical activity have been associated with cardiovascular gain in individuals with schizophrenia spectrum disorders and mood disorders [6, 7]. Furthermore, a prospective study also showed that physical activity is a key prognostic factor for positive trajectory bipolar disorder (BD), which reinforces its potential translation into clinical practice [8]. In individuals with schizophrenia (SZ), systematic evidence also supports this relationship [9].

A prospective study highlights that weight loss combined with high-frequency aerobic exercise has a positive impact on cardio-metabolic parameters [10]. Inflammation, oxidative damage, vascular and endothelial dysfunction are recognized as contributing factors in the common pathophysiology of OB and psychiatric disorders [11]. Likewise, chronic low-grade inflammation contributes to insulin resistance, cardiovascular risk, and joint pain, affecting healthy lifestyles and quality of life [12]. Neurocognitive and functional performance has been also linked to poorer cardio-metabolic condition. In individuals with schizophrenia and mood disorders, cognitive deficits and physical limitations may be exacerbated by vascular issues [13, 14]. Inflammatory and vascular markers contribute to decreased social and occupational functioning and diminished psychological well-being in individuals with psychiatric disorders [11]. In obesity, endothelial dysfunction contributes to reduced exercise capacity and increased fatigue, impacting functional performance [15]. Obesity, with its associated inflammation and

vascular impairments, adds to physical discomfort, emotional distress, and reduced participation in social and recreational activities [12].

These molecular mechanisms play a crucial role in understanding the relationship between physical activity and cardiovascular health. Recent studies showed that blood biomarkers have been used to predict health status in individuals with psychiatric disorders and OB, including the interleukins (IL-6, IL-10), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) [16, 17]. Inflammation was correlated with poorer functional performance and unhealthy lifestyles [18]. Moreover, it seems that there is a close relationship between the oxidative stress and physical activity [19]. The changes in the levels of glutathione (GSH), reactive oxygen species (ROS), mitochondrial reactive oxygen species (mROS), superoxide dismutase (SOD), and mitochondrial membrane potential ($\Delta\Psi m$) were associated with an unhealthy phenotype [20]. Likewise, emerging evidence suggests that endothelial dysfunction and vascular damage are associated with an increased risk of cardiovascular events in individuals with psychiatric disorder [21] and OB [22]. Fluctuations in the levels of the following cellular adhesion molecules (CAM); inter (ICAM) and vascular (VCAM) and polymorphonuclear cells (PMN); leukocyte-endothelium adhesion (LEPMN), rolling (RPMN), rolling velocity (RVPMN), pselectin (PSEL), and myeloperoxidase (MPO) were correlated with the presence of poorer physical activity [23]. Moreover, waist circumference (WC), triglycerides (TG), high- and low-density lipoprotein (HDL and LDL) blood pressure (BP), and fasting plasma glucose (FPG) could play an important role in the induction of changes in the cardiovascular health [24]. It has been suggested that a deregulations of these molecular mechanisms may be related to the cardiovascular impairment and poorer healthy status in individuals with psychiatric and OB.

In recent years, the relationship between biomarkers, clinical outcomes, inflammatory activity, oxidative and vascular damage, metabolic mechanisms, and their predictive validity for maximum heart rate has become a subject of growing interest, particularly in the context of OB and psychiatric disorders. These conditions present unique challenges, each affecting individuals' mental health, physical well-being, and overall quality of life. Understanding how these biomarkers impact maximum heart rate can provide valuable insights for better patient care and tailored interventions. This study aims to evaluate the predictive validity of clinical outcomes, inflammatory activity, oxidative and vascular damage, and metabolic mechanisms for maximum heart rate in individuals with schizophrenia, major depression, bipolar disorder, and obesity.

Materials and methods

The original description of the methods was elaborated by our research group [GIUV2016-312, CB/07/09/0021].

Study design and ethical considerations

This article is part of a project aimed at finding and validating peripheral biomarkers for neurocognitive deficits in MDD, BD, SZ and T2DM carried out by Group 24 CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental) / TMAP-UV (Unidad Autonomía Personal, Dependencia y Trastorno Mental Grave—Universitat de València). This prospective and comparative cohort project was conducted between April 2015 and January 2018 to investigate the association and evolution of certain peripheral blood biomarkers and neurocognitive impairments in a unique longitudinal cohort of individuals with somatic and psychiatric disorders. Demographic and clinical data, neurocognitive and functional data, and biomarkers of peripheral blood were collected at baseline (T1) and after one year (T2). Individuals with

psychiatric disorders were recruited from mental health units (MHUs) in several towns in the province of Valencia, Spain (Gandía, Foios, Catarroja, Paterna, and Sagunto); the psychiatry outpatient clinic and endocrinology department of the University Hospital Dr. Peset; and the Miguel Servet MHU in Valencia City. HCs were residents of the same areas as the individuals with psychiatric disorders. Participants were demographically matched. All participants provided informed consent after the study procedures were fully explained. The ethics committees or institutional review boards at each participating center approved the study protocol, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. For this article, only those variables related to the present study aims were included in the analyses. This study is part of the randomized controlled trial (RCT) registered by ClinicalTrials.gov (number: NCT06069739).

Participants

MDD, BD and SZ were diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders—DSM-5 [25]. Participants with MDD and BD should meet the remission criteria [26] of an acute affective episode, defined as Young Mania Rating Scale (YMRS) score ≤ 6 and Hamilton Rating Scale for Depression (HRSD) score ≤ 8, and individuals with SZ had to be clinically stable, defined as Positive and Negative Syndrome Scale (PANSS) score ≤ 36 [27]. The comorbid OB diagnosis was based on World Health Organization (WHO) criteria [28, 29]. For recruitment as HC, the absence of physical illness, pharmacological treatments, and family history of psychiatric disorders in first-degree relatives were required. Ability to understand study procedures and willingness to give written consent was required for participation. General exclusion criteria for all groups included: current hospitalization, documented cognitive impairment not secondary to psychiatric disorder (intellectual disability or major neurocognitive disorder, i.e. dementia), disability or inability that prevented understanding of the protocol, current substance use disorders (except for nicotine), pregnancy, intake of steroids, corticosteroids, antioxidants, antibiotics, and immunologic therapies, fever over 38˚C, and history of vaccination within 4 weeks of the evaluation, medical contraindications for exercise, body mass index ≥ 40, diastolic/systolic blood pressure $\geq 140/90$, resting heart rate ≥ 100. The same inclusion and exclusion criteria were used at T1 and T2.

Intervention procedure in physical exercise

Participants were assigned to a 12-week structured physical exercise program. All treatment sessions were conducted from March to June 2016. To maintain the rigor of the research, possible risks that could question the internal and external validity of the study results were identified and strategies were proposed to eliminate them, following the indications proposed by Creswell [30].

Participants were required to attend three on-site sessions by week over 12 weeks and autonomous exercise was monitored offside the sessions through a series of weekly checkpoints. It was provided with brief healthy lifestyle counseling at baseline. To achieve the European guidelines of 150 minutes by week of moderate intensity physical activity [31], participants were prescribed three 60 minutes exercise sessions (five minutes of warm-up and five minutes of cool-down for a total of sixty minutes per session). Exercise consisted of brisk walking in urban and rural open spaces during which heart rate monitors were worn and participants were instructed to stay within their moderate intensity range (64–76% maximum heart rate (MHR) [32]. Participants gradually progressed to the target intensity and duration over the course of the first few sessions according to a gradual progression adapted to their development and personal characteristics. The standard progression was to work the first few

weeks at 40–50% of MHR, increasing the intensity of the work from 50–60% MHR to 60–70% MHR in the next six weeks according to their personal development and trying to reach 70% MHR in the last weeks attending their personal level. The professional researchers followed up the sessions by conducting the initial and final phase of each session and accompanying the patients during the rest of the session in order to attend to any needs or doubts and to follow up on the fulfillment of the planned work.

Clinical and neuropsychological assessments

The assessments were conducted by the same experienced psychologists and psychiatrists of the research group (G24 CIBERSAM/TMAP-UV). Sociodemographic data, including sex, age, years of education, premorbid Intelligence Quotient (IQ), which was calculated using the WAIS-III Vocabulary subtest, considered a classical measure of the level of intelligence before the onset of a mental disorder [33], dependent and occupational status, motor laterality (defined as manual, ocular and crural dominance), tobacco consumption, and Godin-Shephard leisure-time physical activity questionnaire (GSLTPAQ) [34], were collected.

Clinical evaluations were conducted using the following instruments: (i) the Clinical Global Impression (CGI) scale [35], (ii) 17-item Hamilton Rating Scale for Depression [36], (iii) Young Mania Rating Scale [37], (iv) Positive and Negative Syndrome Scale [38], (v) Kaplan-Feinstein Scale (KFS) [39], (vi) Charlson Comorbidity Index (CCI) [40]. The age of onset, illness duration, body mass index (BMI), total number of prescribed psychopharmacological medications and other medications were also registered.

Cognitive performance was evaluated using a comprehensive battery of neuropsychological tests and subtests previously used by our group [41–51]. Six cognitive domains were assessed: (i) *verbal learning and memory*: Complutense Verbal Learning Test (TAVEC) total immediate recall, short-term free recall and long-term free recall variables [52]; (ii) *cognitive flexibility*: Stroop Color and Word test (SCWT) color/word subtest [53] and Wisconsin Card Sorting Test (WCST) categories completed and perseverative errors [54]; (iii) *verbal fluency*: FAS and animal naming test for phonemic and semantic fluency, respectively [55]; (iv) *working memory*: Trail Making Test (TMT) Part B [55] and Wechsler Adult Intelligence Scale III edition (WAIS-III) digit span backwards [56]; (v) *short-term memory*: TAVEC immediate recall of the first learning trial and immediate recall of the interference list [52] and WAIS-III digit span forward [56]; (vi) *visual memory*: Rey-Osterrieth Complex Figure Test (ROCFT) figure two minutes after the copy (fRey2) and 20 minutes after the copy (fRey20) [57]; and (vii) *processing speed*: finger tapping test (FTT) left unimanual, right unimanual, left bimanual, right bimanual and average four scores [55, 58], WAIS-III digit symbol coding subtest [56], SCWT color and word subtests [53] and TMT Part A [55]. A global cognitive score (GCS) was calculated by averaging the seven cognitive domain scores.

Functional performance was evaluated using: (i) the Functional Assessment Short Test (FAST) [59], (ii) the Short Form-36 Health Survey questionnaire (SF-36) [60], and (iii) the World Health Organization Quality of Life brief scale (WHO-QoL-Bref) [61]. A global functional score (GFS) was calculated by averaging the total scores on the three scales.

Determination of biomarkers in peripheral blood

Venesection was performed, and serum and plasma samples were stored in a freezer at –80˚C.

(i) Inflammatory markers

Serum cytokine concentrations were determined using Luminex® X-MAP technology (Luminex Corp., Austin, TX, USA) based on flow cytometry. The following cytokines were analyzed:

interleukins (IL-6 and IL-10), and tumor necrosis factor alpha (TNF-α). Sample processing and data analysis were performed according to the manufacturer's instructions. C-reactive protein (CRP) levels were determined using an immunonephelometric assay (Behring Nephelometer II, Dade Behring, Inc., Newark, DE, USA).

(ii) Oxidative stress markers

Oxidative stress in leukocytes was evaluated using fluorimetry techniques with a fluoroscan (Synergy MX). In total, 100 000 cells were plated in each well of 96-well plates and incubated for 30 min at 37˚C with the corresponding fluorochromes, as follows: dichlorofluorescein diacetate to measure reactive oxygen species (ROS) production (485 nm excitation, 535 nm emission), MitoSOX to measure mitochondrial ROS (mROS) (510 nm excitation, 580 nm emission), tetramethylrodamin methyl ester to assess mitochondrial membrane potential (ΔΨm) (552 nm excitation, 574 nm emission), superoxide dismutase (SOD) (total SOD/ T-SOD Activity Assay Kit–Colorimetric—from NOVUS), and 5-chloromethylfluorescein diacetate to measure intracellular glutathione (GSH) (492 nm excitation, 517 nm emission). The monocyte cell line U-937 was used as an internal control to avoid potential fluctuations in fluorescence over time.

(iii) Adhesion molecules

Serum lipid peroxidation levels were measured using a commercial thiobarbituric acid reactive substances (TBARS) kit according to the manufacturer's instructions (Olympus, Hamburg, Germany). A Luminex 200 flow analyzer system (Austin, TX, USA) was employed to analyze cellular adhesion molecules (CAM) in serum. To measure immunological markers, citrated blood samples were incubated with dextran (3%) for 45 min to isolate human polymorphonuclear leukocytes (PMNs). The supernatant was layered over Ficoll-Hypaque (GE Healthcare, Barcelona, Spain) and centrifuged for 25 min at room temperature at 650g. Lysis buffer was added to the remaining erythrocytes in the pellet, which were incubated at room temperature for 5 min and then spun at 240g for 5 min. PMNs were rinsed twice and resuspended at 37˚ in Hanks' balanced salt solution (Sigma Aldrich, MO). Scepter 2.0 cell counters (Millipore, MA, USA) was employed to count cells.

PMNs were isolated as previously described. 56 A 1.2-mL aliquot of PMNs was obtained from the peripheral blood of HCs and patients at a density of 106 cells/mL in complete RPMI (RPMI 1640 medium supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin, 1% glutamine, and 1% sodium pyruvate). Prior to this, primary cultures of human umbilical cord endothelial cells (HUVECs) were established. HUVECs were isolated as previously reported. On the day of experimentation, PMNs were monitored through the endothelial monolayer at a speed of 0.3 mL/min over a 5-min period. Activity was recorded, and the number, velocity, and adhesion to the endothelial monolayer of rolling PMNs were determined. The number of rolling PMNs was measured as those rolling for 1 minute. Velocity was assessed by determining the time in which 15 rolling PMNs covered 100 μm. Adhesion was analyzed by counting the number of PMNs adhering to the endothelium for at least 30 s in five fields.

(iv) Cardio-metabolic markers

The following cardio-metabolic markers were collected as follows: waist circumference (WC) (cm), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), systolic blood pressure (SBP) / diastolic blood pressure (DBP) (mmHg), fasting plasma glucose (FPG) and maximum heart rate (MHR). The MHR was measured with a watch-shaped device that was worn on the wrist and captured the beats per minute. Body weight, height, and WC

were measured by calibrated scales. WC was measured in the standing position at the end of normal expiration and at the midway between the inferior costal margin and the superior border of the iliac crest. BP was measured on the right arm using an automatic sphygmomanometer with participants in the sitting position after resting for 5 minutes. Average SBP and DBP values of at least two repeated measurements were calculated. Under aseptic conditions, fasting venous blood samples were collected between 8 and 9 am to measure TG, LDL, HDL and FPG levels. Individuals with diseases followed the prescribed pharmacological treatment throughout the study.

Statistical analyses

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 26.0 for Windows [62]. The sample size was calculated using Ene 2.0 software, which estimated that twenty-nine individuals were sufficient to ensure the representativeness [63]. Descriptive analyses were expressed as mean (standard deviation) for continuous variables and total number (percentage) for categorical variables. Normality was assumed for all continuous variables because the sample was statistically verified using Shapiro-Wilk test. This fact guarantees that the variables were distributed in a normalized way. The differences between times for clinical characteristics and biomarkers were assessed using a t-test for dependent samples. To test predictive capacity the clinical outcomes and biomarkers at T1 to explain the variance of change maximum heart rate before and after of the physical activity training, a linear regression analysis was performed using a predictive model that included all variables that were significant. To test the ability of clinical outcomes and biomarkers at T1 to discriminate between individuals with improve maximum heart rate, a discriminant analysis was performed used all baseline variables. Subsequently, a single model using only significant clinical characteristic and biomarkers was tested. For all analyses, $p < 0.05$ was considered statistically significant. The effect size was calculated with Cohen's d (d) and the following values were taken as reference: small ≈ 0.20; moderate ≈ 0.50; large ≈ 0.80.

Results

Sample description

At T1, the sample consisted of 29 persons with psychiatric disorders, including 17 with SZ, 6 with BD, and 6 with MDD, and comorbid diagnosis of obesity (OB). None participants were lost to follow-up at T2 (retention rate: 100%).

Females represented 31% of the total sample. The mean age was 47.3 (SD: 10.2) years and 10.0 (SD: 3.7) years of education of the whole sample. It was characterized by IQ standard values 96.2 (SD: 15.5) and moderately active physical condition 41.6 (SD: 39.4). The entire sample was unemployed (100%) and less than half were dependent (38%). Moreover, the great majority of the sample was right-handed (90%) and approximately half of the individuals used tobacco (52%).

Between-group comparison of clinical outcomes and biomarkers

Clinical characteristics at both times are shown in **Table 1**. The individuals had an age of illness onset close to 25 years and mean illness duration of 22 years. Concerning to mental health outcomes, individuals showed significant improvement in cognition ($p < 0.0001$; $d = 0.87$) and mood symptoms ($p < 0.01$; $d = 0.53$) after the physical activity training was performed. Likewise, with regard to physical health outcomes, a decrease in BMI was observed over time ($p < 0.01$; $d = 0.64$). In all cases, the effect size was from moderate to large.

Table 1. Clinical characteristics.

Variables[a]	T1	T2	*Statistical analyses*	
	T1 (*n* = 29)	T2 (*n* = 29)	t(*p*)[f]	*d*[g]
Mental health outcomes				
Age of onset[b]	25.6(8.6)	-		
Illness duration[b]	22.2(10.9)	-		
CGI[c]	4.5(1.1)	4.3(1.3)	.24	
HRSD[c]	9.7(5.4)	9.8(6.3)	.93	
YMRS[c]	6.1(5.3)	3.5(4.4)	.01	.53
PANSS-P[c]	12.1(6.3)	11.1(6.6)	.11	
PANSS-N[c]	16.5(10.5)	17.2(10.2)	.52	
PANSS-G[c]	33.6(14.7)	33.0(15.7)	.68	
Psychiatric medicines[d]	4.7(2.3)	4.8(2.2)	.76	
GCS	238.3(166.8)	350.2(165.6)	< .0001	.87
Physical health outcomes				
BMI	32.0(4.0)	31.6(4.1)	.01	.64
KFS	0.6(1.0)	0.5(0.8)	.16	
CCI	0.5(0.9)	0.4(0.6)	.29	
Tobacco[e]	10(34.5)	10(34.5)	.32	
General medicines[d]	5.0(2.3)	5.1(2.2)	.65	
GFS	2247.5(533.4)	2105.7(664.3)	.12	

[a] Expressed as mean (standard deviation) except when indicated

[b] years

[c] lower scores represent a better outcome

[d] number

[e] yes n (%)

[f] paired t-test for dependent samples

[g] Cohen's d. Abbreviations: T1 = time 1, T2 = time 2, CGI = clinical global impression, HRSD = Hamilton rating scale for depression, YMRS = Young mania rating scale, PANSS = positive and negative syndrome scale, P = positive, N = negative, G = general, GCS = global cognitive score, BMI = body mass index, KFS = Kaplan-Feinstein scale, CCI = Charlson comorbidity index, GFS = global functional score. Effect size (*d*: small ≈ 0.20; moderate ≈ 0.50; large ≈ 0.80).

https://doi.org/10.1371/journal.pone.0313759.t001

Peripheral serum markers at both times are shown in Table 2. Regarding the inflammatory state, anti-inflammatory biomarker IL-10 had significantly increased after the physical activity training was carried out ($p < 0.05$; $d = 0.47$). Similarly, for oxidative stress markers, ROS had significantly higher concentrations after of the physical activity training was observed ($p < 0.01$; $d = 1.63$) and, by contrast, mROS had significantly lower concentrations after of the physical activity training ($p < 0.01$; $d = 0.56$). Moreover, LEPMN marker significantly decreased ($p < 0.01$; $d = 0.46$) and insulin sensitivity had significantly higher levels after the physical activity training ($p < 0.01$; $d = 0.56$). It should be noted that MHR significantly decreased after the physical activity training ($p < 0.01$; $d = 0.49$). In all cases, the effect size was from moderate to large.

Predictive capacity of clinical outcomes and biomarkers at T1 of change maximum heart rate before and after the physical activity training

The results of the relative contributions of clinical outcomes and biomarkers at T1 to explain the variation of MHR were shown in Table 3. The combination of clinical outcomes (age of onset and illness duration), anti-inflammatory activity (IL-10), mitochondrial membrane

Table 2. Biomarkers.

Variables[a]	T1	T2	*Statistical analyses*	
	(*n* = 29)	(*n* = 29)	t(*p*)[b]	*d*[c]
Inflammatory markers				
IL-6	2.8(2.0)	2.6(2.6)	.52	
IL-10	45.6(42.3)	60.1(49.2)	.02	.47
TNF-α	9.0(2.6)	9.6(4.7)	.31	
CRP	4.7(4.8)	7.3(9.3)	.16	
Oxidative stress markers				
GSH	166.3(106.5)	173.4(74.7)	.76	
ROS	106.2(26.0)	161.8(88.8)	.002	1.63
mROS	187.6(81.7)	131.0(26.0)	.003	.56
SOD	102.8(17.3)	96.7(14.9)	.11	
ΔΨm	40.3(22.1)	44.1(17.3)	.48	
Adhesion molecules				
ICAM	118.0(45.7)	123.4(58.6)	.59	
VCAM	591.9(126.3)	603.5(142.0)	.56	
LEPMN	11.1(8.0)	6.0(2.8)	.003	.46
RPMN	231.3(105.4)	208.1(65.9)	.24	
RVPMN	411.1(134.9)	431.2(98.3)	.46	
PSEL	132.3(28.8)	135.7(38.9)	.64	
MPO	725.6(427.8)	755.4(418.2)	.62	
Cardio-metabolic markers				
WC	109.0(12.1)	108.3(10.4)	.44	
TG	178.2(62.2)	179.4(80.6)	.91	
HDL	43.6(11.7)	43.9(12.4)	.79	
LDL	116.6(43.5)	114.9(30.0)	.72	
SBP	121.9(12.8)	123.0(11.5)	.54	
DBP	78.3(10.1)	79.3(9.4)	.23	
FPG	97.8(18.3)	97.3(18.7)	.76	
Insulin	16.4(10.4)	22.2(13.5)	.01	.56
Physical exercise effectiveness marker				
MHR	184.9(23.7)	172.5(10.2)	.004	.49

[a] Expressed as mean (standard deviation)

[b] paired t-test for dependent sample

[c] Cohen's d. Abbreviations: T1 = time 1, T2 = time 2, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumor necrosis factor alpha, CRP = c-reactive protein, GSH = glutathione, ROS = reactive oxygen species, mROS = mitochondrial reactive oxygen species, SOD = superoxide dismutase, ΔΨm = mitochondrial membrane potential, CAM = cellular adhesion molecule, PMN = polymorphonuclear cells, I = inter, V = vascular, LE = leukocyte-endothelium adhesion, R = rolling, RV = rolling velocity, PSEL = pselectin, MPO = myeloperoxidase, WC = waist circumference, TG = triglycerides, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, MHR = maximum heart rate. Effect size (*d*: small ≈ 0.20; moderate ≈ 0.50; large ≈ 0.80).

https://doi.org/10.1371/journal.pone.0313759.t002

potential (ΔΨm), and cardio-metabolic parameter (FPG) significantly predicted MHR over time and explained 41.2% of the variance. Similarly, the combination of clinical outcomes (PANSS-N), anti-inflammatory activity (IL-10), oxidative stress (ROS), leukocyte-endothelium interactions (rolling polymorphonuclear cells [RPMN]), and pselectin [PSEL]) significantly predicted MHR over time and explained 48.0% of the variance. Clinical outcomes

Table 3. Predictive clinical outcomes and biomarkers at T1 of change maximum heart rate.

Dependent variables at T2	Predictors at T1	*β*	95% CI	*p*	Percent of variance explained (adjusted R^2)
MHR (T2-T1)	**Age of onset**	-.70	-2.79 to -.67	.003	41.2
	Illness duration	-.60	-2.04 to -.30	.01	
	IL-10	.39	.04 to .35	.01	
	ΔΨm	-.52	-.86 to -.14	.008	
	FPG	.38	.02 to .87	.03	
	PANSS-N	-.58	-1.82 to -.53	.001	48.0
	IL-10	.33	.01 to .31	.03	
	ROS	-.27	-.46 to .02	.07	
	RPMN	.40	.01 to .14	.01	
	PSEL	.35	.04 to .48	.02	
	HRSD	-.61	-3.58 to -1.19	< .0001	59.1
	GFS	-.32	-.02 to -.001	.04	
	ICAM	.27	.001 to .25	.04	
	RVPMN	-.52	-.12 to -.03	.001	
	HRSD	-.49	-2.8 to -1.0	< .0001	67.7
	SOD	-.46	-.89 to -.25	.001	
	VCAM	.28	.008 to .08	.02	
	LEPMN	-.32	-1.48 to -.22	.01	
	RVPMN	-.65	-.14 to -.06	< .0001	
	PANSS-G	-.53	-1.09 to -.46	< .0001	72.1
	CRP	-.23	.10 to 1.97	.03	
	ROS	-.33	-.44 to -.10	.003	
	LEPMN	-.26	-1.26 to -.12	.01	
	RVPMN	-.47	-.10 to -.04	< .0001	

Abbreviations: T1 = time 1, T2 = time 2, MHR = maximum heart rate, IL-10 = interleukin-10, CRP = c-reactive protein, ROS = reactive oxygen species, SOD = superoxide dismutase, ΔΨm = mitochondrial membrane potential, CAM = cellular adhesion molecule, PMN = polymorphonuclear cells, I = inter, V = vascular, LE = leukocyte-endothelium adhesion, R = rolling, RV = rolling velocity, PSEL = pselectin, FPG = fasting plasma glucose, GFS = global functional score, HRSD = Hamilton rating scale for depression, PANSS = positive and negative syndrome scale, N = negative, G = general.

https://doi.org/10.1371/journal.pone.0313759.t003

(HRSD), GFS, and adhesion molecules also significantly predicted MHR over time and explained 59.1% of the variance. Moreover, clinical outcomes (HRSD), oxidative stress biomarker (SOD), and adhesion molecules (vascular cellular adhesion molecule [VCAM], leukocyte-endothelium polymorphonuclear cells [LEPMN] and rolling velocity polymorphonuclear cells [RVPMN]) significantly predicted MHR over time and explained 67.7% of the variance. Lastly, the combination of clinical outcomes (PANSS-G), inflammatory activity (CRP), oxidative stress (ROS), and adhesion molecules (LEPMN and RVPMN) significantly predicted MHR over time and explained 72.1% of the variance. There was a negative relationship between clinical outcomes ($p < 0.01$ –$p < 0.0001$), oxidative stress ($p < 0.05$ –$p < 0.0001$), vascular damage ($p < 0.01$ –$p < 0.0001$), GFS ($p < 0.05$), and pro-inflammatory activity ($p < 0.05$), whereas a positive correlation with anti-inflammatory mechanisms ($p < 0.05$ – $p < 0.01$) associated with MHR variation for all predictive models.

Discriminatory ability of clinical outcomes and biomarkers on improvements in maximum heart rate

The results regarding the discriminatory ability of clinical outcomes and serum peripheral markers showed that the combination of PANSS-G, IL-10, RVPMN, ΔΨm was the

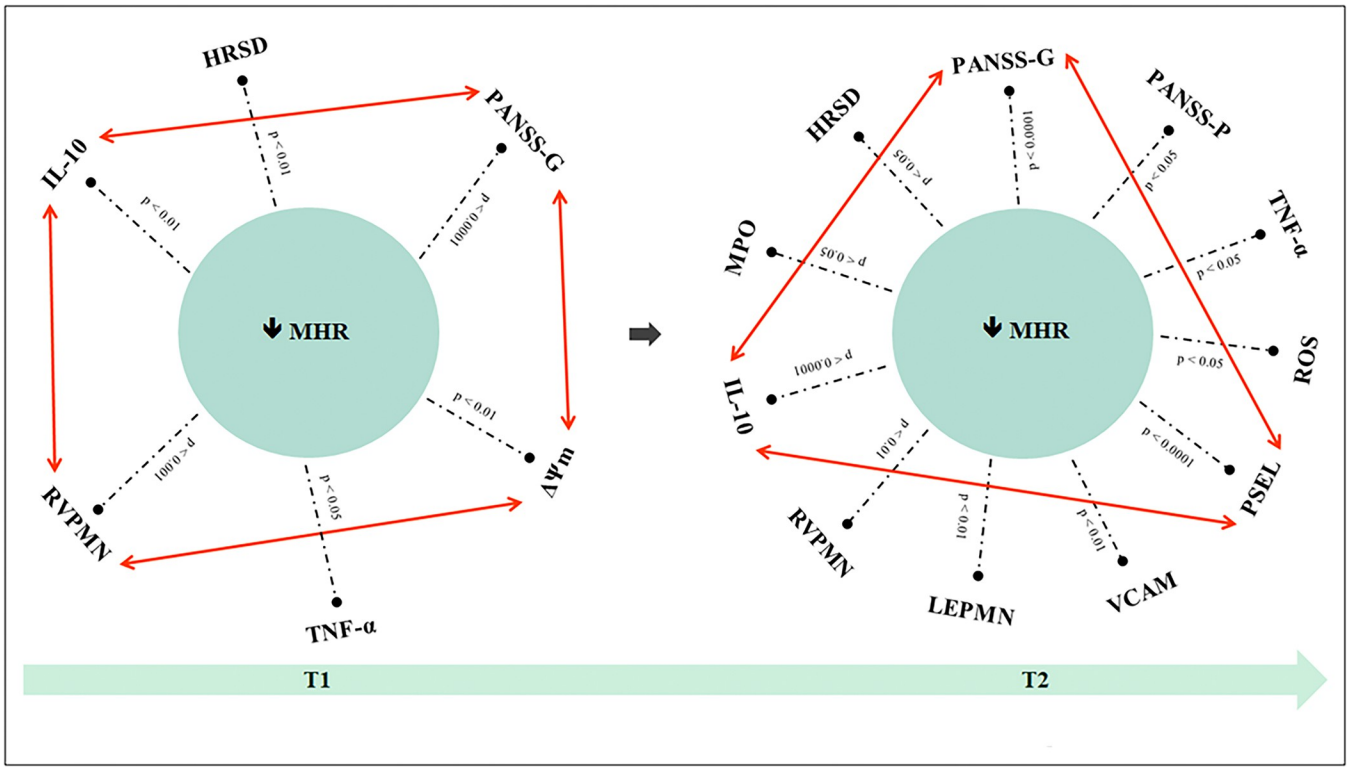

Fig 1. Discriminatory capacity of the clinical outcomes and biomarkers to differentiate to the individuals with improved MHR. MHR: maximum heart rate, HRSD: Hamilton rating scale for depression, PANSS-P: positive and negative syndrome scale (positive subscale), PANSS-G: positive and negative syndrome scale (general subscale), IL-10: interleukin 10, TNF-α: tumor necrosis factor alpha, ROS: reactive oxygen species; ΔΨm: mitochondrial membrane potential, VCAM: vascular cellular adhesion molecule, LEPMN: leukocyte-endothelium adhesion polymorphonuclear, RVPMN: rolling velocity polymorphonuclear cells, PSEL: P-selectin; MPO: myeloperoxidase.

https://doi.org/10.1371/journal.pone.0313759.g001

transdiagnostic model that best discriminated between individuals with improved maximum heart rate at T1 ($\chi^2 = 32.2$, $p < 0.0001$). Likewise, the combination of PANSS-G, IL-10, PSEL was the transdiagnostic model that best discriminated between individuals with improved MHR at T2 ($\chi^2 = 39.0$, $p < 0.0001$) (Fig 1). According to the models, individuals with improved MHR were characterized by more severe general psychopathology, increased rolling velocity, and larger mitochondrial membrane potential, while lower anti-inflammatory activity at T1. In contrast, these same individuals were characterized by lower general psychopathology, and better anti-inflammatory mechanisms at T2.

Discussion

To the best of our knowledge, this study is the first to examine the predictive validity of clinical outcomes such as inflammatory activity, oxidative and vascular damage, and metabolic mechanisms concerning maximum heart rate as a marker for physical activity effectiveness. Additionally, we evaluated their ability to discriminate significant improvements in maximum heart rate following physical activity training in individuals with psychiatric disorders and comorbid obesity. Our study employs a longitudinal design and adopts a transdiagnostic perspective.

The present results show that individuals with psychiatric disorders and OB comorbid exhibited an improvement in cognition, mood symptoms, BMI, and increased anti-inflammatory activity together with enhancement of the oxidative and cardiovascular mechanisms after

physical activity training. Indeed, better clinical outcomes (age of onset and illness duration, HRSD, and PANSS) along with regulation of inflammatory (IL-10 and CRP), oxidative ($\Delta\Psi m$, ROS, and SOD) and cardiovascular (i.e. LEPMN, RPMN, and RVPMN) mechanisms were critical for predicting significant MHR variation over time. Moreover, the discriminant analysis showed that general psychopathology and anti-inflammatory activity were able to distinguish individuals with improved MHR.

Our findings are in accordance with previous evidence suggesting that physical activity sustained over time improves neurocognitive performance and mood symptoms across psychiatric disorders [64]. In individuals with OB, meta-analytic evidence also supports this relationship [65]. Likewise, having an established physical exercise routine has favorable effects on BMI and other weight parameters in these individuals [66, 67]. Recent findings suggest that exercise induces an anti-inflammatory effect, which positively impacts the immune system response [68]. Specifically, IL-10´s anti-inflammatory action has been postulated as potential common therapeutic avenue linked to physical exercise, as it promotes stabilization of inflammatory parameters across chronic pathologies [69]. Our results indicate that oxidative stress is involved in the beneficial effects of exercise, aligning with findings from recent studies [70]. Moderate levels of exercise-induced ROS production play an essential role in promoting physiological benefits, such as enhancing immunological function [19]. Additionally, improved mitochondrial ROS capacity provides a beneficial adaptive effect on the cellular antioxidant system, potentially preventing neurodegenerative diseases associated with impaired mitochondrial recycling [71]. Moreover, improvement of cardio-metabolic parameters is directly related to increased physical activity. Growing evidence supports that leukocyte-endothelium adhesion is significantly reduced with the continued practice of physical exercise and was strongly related to improving healthy lifestyles [72]. Exercise also improves insulin sensitivity through the reduction of cytokines, inflammatory and oxidative stress responses [73]. Likewise, exercise decreases nicotine consumption in individuals with psychiatric disorders and promotes a toxic-free environment that is conducive to a healthy lifestyle. In fact, reducing nicotine levels has a positive impact on inflammation and reduces cardiovascular risk [74].

Consider removing and promote a toxic-free environment that is conducive to a healthy lifestyle.

Exercise has been identified as a promising intervention to improve physical and mental health outcomes in individuals with comorbidities, positioning itself as a key element in reducing cardiovascular risk [75]. In accordance with our findings, existing evidence indicates a strong relationship between the severity of mood and psychotic symptoms and cardiovascular activity. This connection is thought to be mediated by underlying biological mechanisms related to the increase of inflammatory markers and autonomic nervous system dysregulation [76, 77]. Similarly, our findings align with existing evidence demonstrating a critical link between inflammatory activity and heart rate performance. We postulate that cardiovascular activity may adaptively regulate inflammatory processes [78]. Our results converge also with previous findings suggesting that ROS and mROS generation mediate the relationship between clinical severity and HR performance, and it is associated with poorer outcomes in physical activity [79]. Similarly, endothelial dysfunction is associated with worse prognosis and higher rate of cardiovascular events [80]. Thus, a better understanding of the mitochondrial and vascular endothelial adaptations to exercise can shed light on the mechanisms of exercise-induced cardiovascular protection and provide new tools to orient precise exercise therapies for mental and physical health [81, 82]. Indeed, recent studies show that HR monitoring could be used as a clinical marker to identify increased risk of developing inflammation and cardiovascular damage in people with OB [83] and that vagal stimulation and anti-inflammatory treatments can be key factors for support the pharmacological therapy in individuals with MDD [84]. In

fact, it has been observed that heart rate can be a potentially powerful transdiagnostic biobehavioral change mechanism associated with several psychiatric disorders [85] and OB [86]. It should be noted that advanced understanding of this relationship may be useful to maximize the benefits of regular exercise on psychopathology and functional impairment [87] and promote and promote the importance of clinicians being aware of the benefits of exercise for these conditions [88].

Our study has several limitations and strengths. Firstly, the sample was relatively small and was composed of individuals with psychiatric disorders and OB comorbid only; however, the multicenter design of the study may increase the external validity of the results and compensate for such limitation. Second, it is a prospective study from which data was gathered over two times, allowing for more robust cause-effect relationships to be established between clinical variables, biomarkers and heart rate. It should be noted that retention rate was at a maximum. Third, while we included many molecular parameters thought to affect heart rate, there may be additional variables not included in our study that may show an association. Moreover, inflammatory biomarkers interact in a complex manner with other parameters, such as oxidative stress, vascular activity, and cardio-metabolic mechanisms to mediate inflammation which limits the interpretation of our findings. However, we believe that the variables we included are the most common serum parameters that have clinical relevance. Fourth, our analysis may come with potential biases including ascertainment, disease classification, and sample selection bias, which may affect overall internal validity. However, we did controlee the significant sociodemographic variables that could affect to internal validity, making this issue less outstanding. Fifthly, while brief counseling on healthy lifestyle was provided at baseline, we did not assess lifestyle behaviors beyond physical activity in this study [89, 90]. Factors such as hydration, nutritional intake, sleep patterns, and pre-workout preparation could also influence maximum heart rate and overall cardiovascular performance, warranting further investigation. Lastly, it is important to mention that peripheral blood biomarkers among the individuals with psychiatric disorders and comorbid OB can be fluctuate depending on the stage of the mental disorder or BMI, as well as pharmacological and lifestyle interventions [91].

Conclusion

In conclusion, this study emphasizes the key role of molecular mechanisms in the exercise across several disorders. Our findings suggest that maintaining good mental health and properly regulating inflammatory, oxidative, and cardiovascular mechanisms are essential for sustaining healthy physical activity levels. This interplay underscores the importance of exercise in enhancing mental health and modulating biological systems. Specifically, our findings support that biomarker-based model can be considered as a potential pathway for discerning those individuals with the greatest potential to benefit from physical exercise across pathologies. If confirmed by future studies, this model could facilitate a more personalized application of exercise that will implement the benefits of physical activity from early stages and enhance healthy lifestyles in order to prevent future complications linked to the course of the disease. Therefore, our study highlights the potential of using biomarkers as predictors for personalized exercise interventions in individuals with psychiatric disorders and comorbid obesity. By leveraging these insights, clinicians can develop tailored exercise programs to maximize heart rate improvements, ultimately contributing to enhanced physical and mental health outcomes. The results support the use of specific biomarkers as valuable tools for predicting the effectiveness of exercise interventions, thereby guiding personalized treatment strategies. It will enable us to move forward in our understanding of the impact of molecular mechanisms and psychopathology on physical exercise in individuals with comorbidities from a transdiagnostic perspective.

Supporting information

S1 Data.
(XLSX)

Acknowledgments

We would like to thank the research participants and staff members of the mental health units in Foios, Catarroja, Paterna, Sagunto, and Gandía towns, and the psychiatry outpatient clinic of the University Hospital Dr. Peset and mental health center Miguel Servet, Valencia City.

Author Contributions

Data curation: Pau Soldevila-Matías, Joan Vicent Sánchez-Ortí, Patricia Correa-Ghisays.

Formal analysis: Pau Soldevila-Matías, Joan Vicent Sánchez-Ortí, Patricia Correa-Ghisays.

Investigation: Pau Soldevila-Matías, Joan Vicent Sánchez-Ortí, Patricia Correa-Ghisays, Gabriel Selva-Vera, Roberto Sanchis-Sanchis, Néstor Iglesias-García, Manuel Monfort-Pañego, Pilar Tomás-Martínez, Víctor M. Victor, Benedicto Crespo-Facorro, Constanza San Martin Valenzuela, José Antonio Climent-Sánchez, Rosana Corral-Márquez, Inmaculada Fuentes-Durá.

Methodology: Pau Soldevila-Matías, Joan Vicent Sánchez-Ortí, Patricia Correa-Ghisays, Gabriel Selva-Vera, Roberto Sanchis-Sanchis, Néstor Iglesias-García, Manuel Monfort-Pañego, Pilar Tomás-Martínez, Víctor M. Victor, Benedicto Crespo-Facorro, Constanza San Martin Valenzuela, José Antonio Climent-Sánchez, Rosana Corral-Márquez, Inmaculada Fuentes-Durá.

Project administration: Vicent Balanzá-Martínez, Rafael Tabarés-Seisdedos.

Resources: Vicent Balanzá-Martínez, Gabriel Selva-Vera, Roberto Sanchis-Sanchis, Néstor Iglesias-García, Manuel Monfort-Pañego, Pilar Tomás-Martínez, Víctor M. Victor, Benedicto Crespo-Facorro, Constanza San Martin Valenzuela, José Antonio Climent-Sánchez, Rosana Corral-Márquez, Inmaculada Fuentes-Durá, Rafael Tabarés-Seisdedos.

Supervision: Vicent Balanzá-Martínez, Rafael Tabarés-Seisdedos.

Writing – original draft: Pau Soldevila-Matías, Joan Vicent Sánchez-Ortí, Patricia Correa-Ghisays.

Writing – review & editing: Vicent Balanzá-Martínez, Gabriel Selva-Vera, Roberto Sanchis-Sanchis, Néstor Iglesias-García, Manuel Monfort-Pañego, Pilar Tomás-Martínez, Víctor M. Victor, Benedicto Crespo-Facorro, Constanza San Martin Valenzuela, José Antonio Climent-Sánchez, Rosana Corral-Márquez, Inmaculada Fuentes-Durá, Rafael Tabarés-Seisdedos.

References

1. Martins LB, Monteze NM, Calarge C, Ferreira AVM, Teixeira AL. Pathways linking obesity to neuropsychiatric disorders. *Nutrition*. 2019; 66: 16–21. https://doi.org/10.1016/j.nut.2019.03.017 PMID: 31200298
2. Minhas S, Patel JR, Malik M, Hana D, Hassan F, Khouzam RN. Mind-Body connection: Cardiovascular sequelae of psychiatric illness. *Current problems in cardiology*. 2022; 47: 100–959. https://doi.org/10.1016/j.cpcardiol.2021.100959 PMID: 34358587

3. Berk M, Köhler-Forsberg O, Turner M, et al. Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. *World psychiatry*. 2023; 22: 366–387. https://doi.org/10.1002/wps.21110 PMID: 37713568
4. Meyer JD, Murray TM, Brower CS, et al. Magnitude, timing and duration of mood state and cognitive effects of acute moderate exercise in major depressive disorder. *Psychology of Sport and Exercise*. 2022; 61: 2–22.
5. Heinzel S, Schwefel M, Sanchez A, et al. Physical exercise training as preceding treatment to cognitive behavioral therapy in mild to moderate major depressive disorder: A randomized controlled trial. *Journal of affective disorders*. 2022; 319: 90–98. https://doi.org/10.1016/j.jad.2022.09.024 PMID: 36113693
6. Ringin E, Dunstan DW, McIntyre RS, et al. Differential associations of mentally-active and passive sedentary behaviours and physical activity with putative cognitive decline in healthy individuals and those with bipolar disorder: Findings from the UK Biobank cohort. *Mental Health and Physical Activity*. 2023; 24: 100–151.
7. Fernández-Abascal B, Suárez-Pinilla P, Cobo-Corrales C, et al. In- and outpatient lifestyle interventions on diet and exercise and their effect on physical and psychological health: a systematic review and meta-analysis of randomised controlled trials in patients with schizophrenia spectrum disorders and first episode of psychosis. *Neurosci Biobehav Rev*. 2021; 125: 535–568. https://doi.org/10.1016/j.neubiorev.2021.01.005 PMID: 33503476
8. Melo MCA, Garcia RF, de Araújo CFC, Rangel DM, de Bruin PFC, de Bruin VMS. Physical activity as prognostic factor for bipolar disorder: An 18-month prospective study. *Journal of affective disorders*. 2019; 251: 100–106. https://doi.org/10.1016/j.jad.2019.03.061 PMID: 30921592
9. Nyboe L, Lemcke S, Møller AV, Stubbs B. Non-pharmacological interventions for preventing weight gain in patients with first episode schizophrenia or bipolar disorder: A systematic review. *Psychiatry research*. 2019; 281: 112–556. https://doi.org/10.1016/j.psychres.2019.112556 PMID: 31521840
10. Peven JC, Jakicic JM, Rogers RJ, et al. The effects of a 12-month weight loss intervention on cognitive outcomes in adults with overweight and obesity. *Nutrients*. 2020; 12: 29–88. https://doi.org/10.3390/nu12102988 PMID: 33003548
11. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. *Molecular Psychiatry*. 2021; 26: 4–18.
12. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006; 444: 860–867. https://doi.org/10.1038/nature05485 PMID: 17167474
13. Liou YJ, Chen MH, Hsu JW, et al. Circulating endothelial progenitor cell dysfunction in patients with bipolar disorder. *European archives of psychiatry and clinical neuroscience*. 2023; 273: 1255–1265. https://doi.org/10.1007/s00406-022-01530-5 PMID: 36527490
14. Shimada T, Ito S, Makabe A, et al. Aerobic exercise and cognitive functioning in schizophrenia: An updated systematic review and meta-analysis. *Psychiatry research*. 2022; 314: 114–165. https://doi.org/10.1016/j.psychres.2022.114656 PMID: 35659670
15. Boateng SY, Olfert IM, Chantler PD. Role of perivascular adipose tissue and exercise on arterial function with obesity. *Exercise and sport sciences reviews*. 2021; 49: 188–196. https://doi.org/10.1249/JES.0000000000000251 PMID: 33831902
16. Chen X, Yao T, Cai J, et al. Systemic inflammatory regulators and 7 major psychiatric disorders: A two-sample Mendelian randomization study. *Progress in neuro-psychopharmacology & biological psychiatry*. 2022; 116: 110–153. https://doi.org/10.1016/j.pnpbp.2022.110534 PMID: 35150783
17. McNeill JN, Lau ES, Zern EK, et al. Association of obesity-related inflammatory pathways with lung function and exercise capacity. *Respiratory medicine*. 2021; 183: 106–143. https://doi.org/10.1016/j.rmed.2021.106434 PMID: 33964816
18. Hillari L, Frank P, Cadar D. Systemic inflammation, lifestyle behaviours and dementia: A 10-year follow-up investigation. *Brain, behavior, & immunity–health*. 2024; 38: 100–177. https://doi.org/10.1016/j.bbih.2024.100776 PMID: 38706574
19. Powers SK, Deminice R, Ozdemir M, Yoshihara T, Bomkamp MP, Hyatt H. Exercise-induced oxidative stress: Friend or foe?. *J Sport Health Sci*. 2020; 9: 415–425. https://doi.org/10.1016/j.jshs.2020.04.001 PMID: 32380253
20. Sharifi-Rad M, Anil Kumar NV, Zucca P, et al. Lifestyle, Oxidative stress, and antioxidants: Back and forth in the pathophysiology of chronic diseases. *Frontiers in physiology*. 2020; 11: 694–710. https://doi.org/10.3389/fphys.2020.00694 PMID: 32714204
21. Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S, Howes OD. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. *JAMA Psychiatry*. 2017; 74: 261–269. https://doi.org/10.1001/jamapsychiatry.2016.3803 PMID: 28097367

22. Martínez-Martínez E, Souza-Neto FV, Jiménez-González S, et al. Oxidative stress and vascular damage in the context of obesity: The hidden guest. *Antioxidants*. 2021; 10: 406–416. https://doi.org/10.3390/antiox10030406 PMID: 33800427

23. Lee J, Hong J, Umetani M, et al. Vascular protection by exercise in obesity: Inflammasome-associated mechanisms. *Medicine and science in sports and exercise*. 2020; 52: 2538–2545. https://doi.org/10.1249/MSS.0000000000002419 PMID: 32555019

24. Silveira-Rossi JL, Barbalho SM, Reverete de Araujo R, et al. Metabolic syndrome and cardiovascular diseases: Going beyond traditional risk factors. *Diabetes/metabolism research and reviews*. 2022; 38: 350–342. https://doi.org/10.1002/dmrr.3502 PMID: 34614543

25. American Psychiatric Association. 2014. Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM 5). Quinta edición. Madrid: Editorial Médica Panamericana.

26. Tohen M, Frank E, Bowden CL, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord*. 2009; 11: 453–473. https://doi.org/10.1111/j.1399-5618.2009.00726.x PMID: 19624385

27. Andreasen NC, William T, Carpenter J, et al. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am. J. Psychiatry*. 2005; 162: 441–449. https://doi.org/10.1176/appi.ajp.162.3.441 PMID: 15741458

28. Pasquali R, Casaneuva F, Haluzik M, et al. European Society of Endocrinology Clinical Practice. Guideline: Endocrine work-up in obesity. Eur. J. Endocrinology. 2020; 182: 1–32

29. World Health Organization. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2016. 2018. World Health Organization, Geneva, Switzerland.

30. Creswell J. Research Design: qualitative, quantitative, and mixed method approaches. 2003. California. Sage Publications.

31. USDHHS. 2018. Physical activity guidelines for americans (2nd ed.). USDHHS.

32. American College of Sports Medicine. 2010. Acsm's guidelines for exercise testing and prescription (8th ed.). Lippincott, Williams, & Wilkins.

33. Krull KR, Scott JG, Sherer M. Estimation of premorbid intelligence from combined performance and demographic variables. *Clin. Neuropsychol*. 1995; 9: 83–88.

34. Godin G, Shephard R. A Simple Method to Assess Exercise Behavior in the Community. *Canadian journal of applied sport sciences*. 1985; 10: 141–146 PMID: 4053261

35. Guy W. ECDEU Assessment Manual for Psychopharmacology. 1996. US Department of Health, Rockville, Maryland. Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration.

36. Ramos-Brieva JA, Cordero-Villafáfila AA. Validation of the Castillian version of the Hamilton Rating Scale for Depression. *Actas Luso Esp Neurol Psiquiatr Cienc Afines*. 1996; 14: 324–334.

37. Colom F, Vieta E, Martínez-Arán A, et al. Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale. *Med Clin*. 2002; 119: 366–371.

38. Peralta V, Cuesta MJ. Validación de la escala de síntomas positivos y negativos (PANSS) en una muestra de esquizofrénicos españoles. *Actas Luso Esp Neurol Psiquiatr*. 1994; 4: 44–50.

39. Rosas-Carrasco O, González-Flores E, Brito-Carrera AM, Vázquez-Valdez OE, Peschard-Sáenz E, Gutiérrez-Robledo LM. Evaluación de la comorbilidad en el adulto mayor. *Revista Médica del Instituto Mexicano del Seguro Social*. 2011; 49: 153–162.

40. Rius C, Pérez G, Martínez JM, et al. An adaptation of Charlson comorbidity index predicted subsequent mortality in a health survey. *J. Clin. Epidemiol*. 2004; 57: 403–408. https://doi.org/10.1016/j.jclinepi.2003.09.016 PMID: 15135843

41. Aliño-Dies M, Sánchez-Ortí JV, Correa-Ghisays P et al. Grip strength, neurocognition, and social functioning in people with Type-2 diabetes mellitus, major depressive disorder, bipolar disorder, and schizophrenia. *Front. Psychol*. 2020; 11: 525–231.

42. Correa-Ghisays P, Balanzá-Martínez V, Selva-Vera G, et al. Manual motor speed dysfunction as a neurocognitive endophenotype in euthymic bipolar disorder patients and their healthy relatives. Evidence from a 5-year follow-up study. *J. Affect. Disord*. 2017; 215: 156–162. https://doi.org/10.1016/j.jad.2017.03.041 PMID: 28334676

43. Correa-Ghisays P, Sánchez-Ortí JV, Ayesa-Arriola R, et al. Visual memory dysfunction as a neurocognitive endophenotype in bipolar disorder patients and their unaffected relatives. Evidence from a 5-year follow-up Valencia study. *J. Affect. Disord*. 2019; 257: 31–37. https://doi.org/10.1016/j.jad.2019.06.059 PMID: 31299402

44. Correa-Ghisays P, Sánchez-Ortí JV, Balanzá-Martínez V, et al. Transdiagnostic neurocognitive deficits in patients with type 2 diabetes mellitus, major depressive disorder, bipolar disorder, and schizophrenia:

A 1-year follow-up study. *Journal of affective disorders*. 2022; 300: 99–108. https://doi.org/10.1016/j.jad.2021.12.074 PMID: 34965401

45. Garés-Caballer M, Sánchez-Ortí JV, Correa-Ghisays P, et al. Immune-inflammatory biomarkers predict cognition and social functioning in patients with type 2 diabetes mellitus, major depressive disorder, bipolar disorder, and schizophrenia: A 1-year follow-up study. *Front. Neurol*. 2022; 13: 883–927. https://doi.org/10.3389/fneur.2022.883927 PMID: 35720107

46. Luperdi SC, Correa-Ghisays P, Vila-Francés J, et al. Is processing speed a valid neurocognitive endophenotype in bipolar disorder? Evidence from a longitudinal, family study. *Journal of psychiatric research*. 2021; 141: 241–247. https://doi.org/10.1016/j.jpsychires.2021.07.008 PMID: 34256275

47. San Martín-Valenzuela C., Borras-Barrachina A, Gallego JJ, et al. Motor and cognitive performance in patients with liver cirrhosis with minimal hepatic encephalopathy. *J. Clin. Med*. 2020; 8: 21–54. https://doi.org/10.3390/jcm9072154 PMID: 32650464

48. Sánchez-Ortí JV, Balanzá-Martínez V, Correa-Ghisays P, et al. Specific metabolic syndrome components predict cognition and social functioning in people with type 2 diabetes mellitus and severe mental disorders. *Acta Psychiatr. Scand*. 2022; 146: 215–226. https://doi.org/10.1111/acps.13433 PMID: 35359023

49. Sánchez-Ortí JV, Correa-Ghisays P, Balanzá-Martínez V, et al. Inflammation and lipid metabolism as potential biomarkers of memory impairment across type 2 diabetes mellitus and severe mental disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2023; 127: 110–181. https://doi.org/10.1016/j.pnpbp.2023.110817 PMID: 37327846

50. Selva-Vera G, Balanzá-Martínez V, Salazar-Fraile J, et al. The switch from conventional to atypical antipsychotic treatment should not be based exclusively on the presence of cognitive deficits. A pilot study in individuals with schizophrenia. *BMC*. 2010; 10: 47–57.

51. Tabarés-Seisdedos R, Balanzá-Martínez V, Sánchez-Moreno J, et al. Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *J. Affect. Disord*. 2008; 109: 286–299. https://doi.org/10.1016/j.jad.2007.12.234 PMID: 18289698

52. Benedet MJ, Alejandre MA. TAVEC. Test de Aprendizaje Verbal España-Complutense. 2014. Madrid: TEA Ediciones.

53. Golden CJ. Test de Colores y palabras Stroop Manual. 2001. Madrid: TEA ediciones.

54. Grant DA, Berg EA. Test de clasificación de tarjetas Wisconsin Manual. 2001. Madrid: TEA ediciones.

55. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. 1985. Tucson, Arizona: Neuropsychology Press.

56. Weschler D. Weschler Memory Scale—Third Edition. Escala de Inteligencia Wechsler para adultos-III. 1999. Madrid: TEA Ediciones.

57. Rey A. Test de Copia y de Reproducción de Memoria de Figuras Geométricas Complejas. 1999. Madrid: TEA ediciones S.A. 7ª edición.

58. Tabarés-Seisdedos R, Salazar J, Selva G, et al. Abnormal motor asymmetry only during bimanual coordination in schizophrenic patients compared to healthy subjects. *Schizophrenia Research*. 2003; 61: 245–253.

59. Rosa AR, Sánchez-Moreno J, Martinez-Aran A, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clin. Pract. Epidemiol. Ment. Health*. 2007; 3: 5–16. https://doi.org/10.1186/1745-0179-3-5 PMID: 17555558

60. Alonso J, Prieto L, Antó JM. The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results. *Med. Clin*. 1995; 104: 771–776.

61. Bobes J, Portilla MP, Bascarán MT, Saiz PA, Bousoño M. Banco de instrumentos básicos para la práctica de la psiquiatría clínica; 3ª edición. 2004. Ars Médica, Barcelona.

62. IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

63. Pedromingo-Marino A. Cálculo del tamaño muestral con el programa Ene 2.0; manual del programa, documentación y ejemplos; Llorenç Badiella Busquets. 2005. Madrid.

64. Ashdown-Franks G, Firth J, Carney R, et al. Exercise as medicine for mental and substance use disorders: A meta-review of the benefits for neuropsychiatric and cognitive outcomes. *Sports medicine*. 2020; 50: 151–170. https://doi.org/10.1007/s40279-019-01187-6 PMID: 31541410

65. De Sousa RAL, Santos LG, Lopes PM, et al. Physical exercise consequences on memory in obesity: A systematic review. *Obesity reviews*. 2021; 22: 132–198. https://doi.org/10.1111/obr.13298 PMID: 34105227

66. Bradley T, Campbell E, Dray J, et al. Systematic review of lifestyle interventions to improve weight, physical activity and diet among people with a mental health condition. *Systematic reviews*. 2022; 11: 198–211. https://doi.org/10.1186/s13643-022-02067-3 PMID: 36085250

67. Lee HS, Lee J. Effects of exercise interventions on weight, body mass index, lean body mass and accumulated visceral fat in overweight and obese individuals: A systematic review and meta-analysis of randomized controlled trials. *International journal of environmental research and public health*. 2021; 18: 26–35. https://doi.org/10.3390/ijerph18052635 PMID: 33807939

68. Scheffer DDL, Latini A. Exercise-induced immune system response: Anti-inflammatory status on peripheral and central organs. *Molecular basis of disease*. 2020; 18: 165–182. https://doi.org/10.1016/j.bbadis.2020.165823 PMID: 32360589

69. Islam H, Neudorf H, Mui AL, Little JP. Interpreting 'anti-inflammatory' cytokine responses to exercise: focus on interleukin-10. *The Journal of physiology*. 2021; 599: 5163–5177. https://doi.org/10.1113/JP281356 PMID: 34647335

70. Thirupathi A, Gu Y, Pinho RA. Exercise Cuts Both Ways with ROS in Remodifying Innate and Adaptive Responses: Rewiring the Redox Mechanism of the Immune System during Exercise. *Antioxidants*. 2021; 10: 18–46. https://doi.org/10.3390/antiox10111846 PMID: 34829717

71. Kolodziej F, O'Halloran KD. Re-Evaluating the Oxidative Phenotype: Can Endurance Exercise Save the Western World? *Antioxidants*, 2021; 10: 609. https://doi.org/10.3390/antiox10040609 PMID: 33921022

72. Brahmer A, Neuberger E, Esch-Heisser L, et al. Platelets, endothelial cells and leukocytes contribute to the exercise-triggered release of extracellular vesicles into the circulation. *Journal of extracellular vesicles*. 2019; 8: 161–182.

73. Yaribeygi H, Atkin SL, Simental-Mendía LE, Sahebkar A. Molecular mechanisms by which aerobic exercise induces insulin sensitivity. *Journal of cellular physiology*. 2019; 234: 12385–12392. https://doi.org/10.1002/jcp.28066 PMID: 30605232

74. Bao K, Zheng K, Zhou X, et al. The effects of nicotine withdrawal on exercise-related physical ability and sports performance in nicotine addicts: a systematic review and meta-analysis. *Journal of the International Society of Sports Nutrition*. 2024; 21: 230–238. https://doi.org/10.1080/15502783.2024.2302383 PMID: 38213003

75. Dekker J, Buurman BM, van der Leeden M. Exercise in people with comorbidity or multimorbidity. *Health Psychol*. 2019; 38: 822–830. https://doi.org/10.1037/hea0000750 PMID: 31021125

76. Benjamin BR, Valstad M, Elvsåshagen T, et al. Heart rate variability is associated with disease severity in psychosis spectrum disorders. *Progress in neuro-psychopharmacology & biological psychiatry*. 2021; 111: 110–108. https://doi.org/10.1016/j.pnpbp.2020.110108 PMID: 32946948

77. Lesnewich LM, Conway FN, Buckman JF, et al. Associations of depression severity with heart rate and heart rate variability in young adults across normative and clinical populations. *International journal of psychophysiology*. 2019; 142: 57–65. https://doi.org/10.1016/j.ijpsycho.2019.06.005 PMID: 31195066

78. Williams DP, Koenig J, Carnevali L, et al. Heart rate variability and inflammation: A meta-analysis of human studies. *Brain*, *behavior*, *and immunity*. 2019; 80: 219–226. https://doi.org/10.1016/j.bbi.2019.03.009 PMID: 30872091

79. Shirakawa R, Yokota T, Nakajima T, et al. Mitochondrial reactive oxygen species generation in blood cells is associated with disease severity and exercise intolerance in heart failure patients. *Sci Rep*. 2019; 9: 147–159.

80. Zuchi C, Tritto I, Carluccio E, et al. Role of endothelial dysfunction in heart failure. *Heart Fail Rev*. 2020; 25: 21–30. https://doi.org/10.1007/s10741-019-09881-3 PMID: 31686283

81. Streese L, Lona G, Wagner J, et al. Microvascular endothelial dysfunction in heart failure patients: An indication for exercise treatment?. *Microvascular research*. 2022; 142: 104–134. https://doi.org/10.1016/j.mvr.2022.104345 PMID: 35182579

82. Zhang X, Gao F. Exercise improves vascular health: Role of mitochondria. *Free radical biology & medicine*. 2021; 177: 347–359. https://doi.org/10.1016/j.freeradbiomed.2021.11.002 PMID: 34748911

83. Al-Rashed F, Sindhu S, Al Madhoun A et al. Elevated resting heart rate as a predictor of inflammation and cardiovascular risk in healthy obese individuals. *Scientific reports* 2021; 11: 138–183.

84. Buchmann A, Ritter C, Müller ST, et al. Associations between heart rate variability, peripheral inflammatory markers and major depressive disorder. *Journal of affective disorders*. 2022; 304: 93–101. https://doi.org/10.1016/j.jad.2022.02.017 PMID: 35196535

85. Heiss S, Vaschillo B, Vaschillo EG, Timko CA, Hormes JM. Heart rate variability as a biobehavioral marker of diverse psychopathologies: A review and argument for an "ideal range". *Neuroscience and biobehavioral reviews*. 2021; 121: 144–155. https://doi.org/10.1016/j.neubiorev.2020.12.004 PMID: 33309905

86. Höchsmann C, Dorling JL, Apolzan JW, et al. Effect of different doses of supervised aerobic exercise on heart rate recovery in inactive adults who are overweight or obese: results from E-MECHANIC.

European journal of applied physiology. 2019; 119: 2095–2103. https://doi.org/10.1007/s00421-019-04198-3 PMID: 31367909

87. Fisher E, Wood SJ, Upthegrove R, Aldred S. Designing a feasible exercise intervention in first-episode psychosis: Exercise quality, engagement and effect. *Psychiatry research*. 2020; 286: 112–184. https://doi.org/10.1016/j.psychres.2020.112840 PMID: 32062521

88. Pizzoli SFM, Marzorati C, Gatti D, et al. A meta-analysis on heart rate variability biofeedback and depressive symptoms. *Sci Rep*. 2021; 11: 66–50.

89. Balanzá-Martínez V, Kapczinski F, de Azevedo Cardoso T, et al. The assessment of lifestyle changes during the COVID-19 pandemic using a multidimensional scale. *Revista de psiquiatría y salud mental*. 2021; 14: 16–26.

90. Simjanoski M, Patel S, Boni R, et al. Lifestyle interventions for bipolar disorders: A systematic review and meta-analysis. *Neuroscience and biobehavioral reviews*. 2023; 152: 105–125. https://doi.org/10.1016/j.neubiorev.2023.105257 PMID: 37263531

91. Ribera C, Sánchez-Ortí JV, Clarke G, Marx W, Mörkl S, Balanzá-Martínez V. Probiotic, prebiotic, synbiotic and fermented food supplementation in psychiatric disorders: A systematic review of clinical trials. *Neuroscience and biobehavioral reviews*. 2024; 10: 55–71. https://doi.org/10.1016/j.neubiorev.2024.105561 PMID: 38280441