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# As We Were and As We Should Be, Combined Exercise Training in Adults With Schizophrenia: CORTEX-SP Study Part II

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**Keywords:** combined training | mental health | physical health | SF-36 questionnaire | sleep quality

## ABSTRACT

**Objective:** To determine the changes in health-related quality of life (HRQoL) and sleep quality following a supervised combined exercise (EX) program compared to a Treatment-As-Usual (TAU) and to analyze the relationship between the differences in cardiorespiratory fitness (CRF) and HRQoL domains in people with schizophrenia (SZ).

**Methods:** The SZ ( $n = 112$ ,  $41.3 \pm 10.4$  year) was randomly assigned into a TAU control group ( $n = 53$ ) or EX-group ( $n = 59$ , 3 days/week). The 36-item Short-Form Health Survey questionnaire assessed HRQoL and the sleep quality analysis (accelerometry).

**Results:** After the intervention (20 weeks), physical functioning ( $\Delta = 12.9\%$ ), general health ( $\Delta = 15.3\%$ ), mental health ( $\Delta = 8.3\%$ ), physical component summary (PCS) ( $\Delta = 5.1\%$ ), and sleep efficiency ( $\Delta = 1.9\%$ ) increased ( $p < 0.05$ ) in the EX, with no significant changes in the TAU for any domains studied. There were significant differences between groups whose EX showed improvements ( $p < 0.05$ ) compared to TAU in physical functioning, general health, PCS, and sleep efficiency. A greater CRF was associated with better values in physical functioning, role-physical, bodily pain, general health, vitality, and PCS after the exercise program in SZ.

**Conclusions:** A 20-week supervised combined exercise intervention program for SZ increased sleep efficiency and physical functioning, general and mental health, and PCS scores. This could lead to a critical HRQoL change from how they were to how they should be.

**Trial Registration:** ClinicalTrials.gov identifier: NCT03509597

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## 1 | Introduction

Quality of life (QoL), a subjective evaluation embedded in an environmental, cultural, and social context [1], has gained increasing acceptance in psychiatric research and traditional clinical outcomes assessments. In recent times, the relationship between QoL and severe mental illness has been extensively studied, where QoL is considered an essential indicator of the impact of disease in people with serious mental illness. Perceived stigma and lack of treatment adherence negatively affect the QoL of people with serious mental illness, which in turn affects relapse rates, ability to perform and/or enjoy occupational and social activities, prospects, medical problems, and treatment adherence [2]. In people with schizophrenia (SZ), psychosocial (i.e., decreased self-esteem and social stigma) and psychopathological factors (i.e., negative and positive symptoms), as well as an unhealthy lifestyle, negatively influence the health-related QoL (HRQoL) [3]. Thus, people with SZ generally reported more significant disability and lower physical and mental QoL scores than healthy control people in HRQoL [4, 5]. In this sense, after logistic-regression analysis, it has been suggested that physical and emotional functioning and body pain assessed by the 36-item Short-Form Health Survey questionnaire (SF-36) were the best predictors of a poorer HRQoL in the SZ group compared to healthy controls [6].

In addition to the above, it has already been stated that poor sleep quality plays a vital role in the lower HRQoL maintained in people with SZ [7]. Further, this association appears to occur independently and synergistically with an increased risk of suicidality [8], symptoms of depression and distress, and the side effects of medications [9]. Similarly, studies with large samples found an independent association between insomnia and QoL in patients with SZ [10, 11], and sleep impairment was associated with lower life satisfaction [12]. Likewise, SZ patients with more sleep disturbances show a poor exercise pattern and lighter exercise intensity than the healthy control population [8].

Previous meta-analyses have shown that exercise improves QoL and clinical symptoms in people with SZ [13], improving global functioning [14]. Similarly, regular exercise is associated with better sleep quality assessed through the Pittsburgh Sleep Quality Index in SZ patients, showing that the higher the attendance in moderate-intensity group sessions, the better sleep quality [15]. Therefore, international organizations recommend lifestyle programs, including exercise, for people living with disabilities in general [16], and with SZ in particular [17]. Thus, although light-intensity exercise has health benefits, adults with SZ should aim to do more than the recommended levels of moderate-to-vigorous physical activity, including muscle-strengthening activities on two or more days a week [16]. Further, low-volume high-intensity interval training (HIIT) (i.e., 10 min or less of short bouts of high-intensity exercise separated by periods of recovery at a lower intensity) has been postulated as a more time-efficient method of improving cardiorespiratory fitness (CRF) compared to continuous training at moderate-intensity [18]. Hence, knowing that a higher CRF is an independent significant predictor of physical HRQoL in people with SZ [19], how can this benefit be denied in this population?

Therefore, given the current physical activity recommendations by the World Health Organization for people with mental disorders and the lack of research investigating the effects of combined training on QoL in adults diagnosed with SZ, the primary purposes of this study were: (1) to determine changes in HRQoL and sleep quality following a 20 week combined (low-volume HIIT+resistance training) supervised exercise program (EX) compared to a Treatment-As-Usual control (TAU) group in the studied SZ population, and (2) to analyze the relationship between the changes achieved through the exercise program in CRF and different domains of HRQoL.

## 2 | Materials and Methods

### 2.1 | Study Design

The CORTEX-SP study is a randomized, single-blind (medical staff) controlled experimental trial ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier, NCT03509597). The study protocol was approved by the Clinical Research Ethics Committee of the Autonomous Region of the Basque Country (PI2017044), and all participants provided written informed consent before any data collection. After baseline measurements, participants were randomized ([www.randomization.com](https://www.randomization.com)) to two intervention groups: TAU or supervised EX.

### 2.2 | Study Participants

One hundred and twelve non-Hispanic white participants ( $41.3 \pm 10.4$  years old,  $n=87$  men, and  $n=25$  women) were enrolled in the study from May 2018 to July 2021 in Vitoria-Gasteiz (Basque Country, Spain). All participants were recruited from the Psychiatric Hospital of Alava and the Mental Health Network in Alava, Basque Country. Patients from the study met the diagnostic criteria for SZ according to DSM-5 [20]. The participants included were inpatients (46.3%) and outpatients (53.7%). The former was hospitalized at a psychiatric rehabilitation unit with imminent discharge to the community setting. The inclusion and exclusion criteria of the study have been previously published [21].

### 2.3 | Measurements

The measurements for the study were taken pre (T0) and post (T1) 20 week intervention period.

Age, sex, and cigarette smoking status were assessed by self-report. All medications prescribed to participants were recorded and transformed into chlorpromazine-equivalents using the defined daily dose method [22, 23].

Body composition, CRF, and sleep quality analysis measurements have been previously explained [21]. Participants' CRF, defined as peak oxygen uptake ( $\dot{V}O_{2peak}$ ), was assessed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). Initial power was 40 W, increasing in 10 W increments every minute until exhaustion. Peak oxygen uptake was determined using a commercially available

metabolic cart (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) calibrated before each test with a standard gas of known concentration and volume. Sleep quality analysis was objectively and continuously assessed through a triaxial accelerometer (ActiGraph GT3X+, Pensacola, Florida, USA). Participants always wore a triaxial on their non-dominant wrist with a Velcro strap for eight consecutive days (24h), except during water-based activities. The following sleep variables were derived from ActiGraph data: total sleep time, bedtime, wakefulness after sleep onset, and sleep efficiency.

The psychometric properties of scores from the SF-36 questionnaire have been validated in the population with SZ [24]. Hence, HRQoL was assessed using the Spanish version of the SF-36 questionnaire [25]. The items of the questionnaire report both positive and negative states of “physical component summary (PCS)” and “mental component summary”, identifying eight dimensions of health: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. For each dimension of the SF-36, the items are coded, added, and transformed into a scale with a path from 0 to 100 (higher scores indicating higher levels of HRQoL) using the algorithms and indications that the scoring and interpretation manual of the questionnaire offers [26].

## 2.4 | Intervention

Detailed descriptions of the exercise intervention procedure have already been reported [27]. Briefly, the participants in the EX-group took part in exercise sessions 3 days per week for 5 months under the supervision of exercise specialists at out-of-hospital facilities of the Vitoria-Gasteiz City Council (i.e., the Physical Activity for Health Research Center).

Combined exercise training was performed in the central part of each session (40 min). Each training session consisted of a low-volume HIIT exercise (i.e., a total volume of 20 min with less than 10 min of high-intensity time per session), cycling on a stationary bike, and a resistance circuit-training program (20 min). The intensity on the bike was individually tailored to each participant’s heart rate at moderate (R2) or vigorous (R3) intensities. The resistance-circuit training was conducted with three circuits, one for each week’s workout, with 10 different exercises.

The TAU conducted occupational activity sessions with the same frequency and duration as the EX.

No adverse events were reported during the exercise intervention, and mean exercise adherence reached higher than 85% of the 60 scheduled sessions.

## 2.5 | Statistical Analysis

Descriptive statistics were calculated for all variables. Data are expressed as mean  $\pm$  standard deviations and the range. Analysis of variance was used to determine if there were significant pre-intervention between-group differences. The comparison of frequencies in categorical variables among groups was performed using the chi-squared test. A Student’s *t*-test with

repeated measures was used to determine whether there was a significant difference in the recorded data between pre-and post-intervention within each group. Analysis of Covariance was used to examine the delta ( $\Delta$ ) score for each group (TAU and EX), adjusting for age and sex. Bonferroni correction is an adjustment to *p* values when several dependent or independent statistical tests are performed simultaneously on a single data set. Pearson’s *r* correlations were performed between  $\Delta$  domains of health-related QoL and  $\Delta$ CRF variables. Data were analyzed according to the intention-to-treat principle. Statistical significance was set at  $p < 0.05$ . All statistical analyses were performed with the SPSS version 25.0.

In the present study, a priori power analysis was performed through G\*Power 3 software (ver. 3.1.9.7; Heinrich-Heine Universität Düsseldorf, Germany) to calculate the sample size [28, 29]. A sample size of 106 participants (53 in each group) was estimated to obtain an effect size of  $d = 0.64$  to observe inter-group differences, with 90% power and a 5% significance level.

## 3 | Results

Baseline characteristics (Table 1) have been previously published, including the analysis of sleep quality from actigraphy comparing inter-group (SZ vs. healthy control) and SZ sample subgroups (EX vs. TAU) [21]. Adding to that, after analyzing the domains and component summaries of HRQoL through SF-36, there were no significant differences between SZ subgroups ( $p > 0.05$ ), except for the diastolic blood pressure ( $p = 0.007$ ) and PCS ( $p = 0.008$ ).

After the 20-week intervention period (Table 2, Figure 1), on the one hand, the analysis of the domains of HRQoL changes showed that physical functioning (change,  $\Delta = 12.9\%$ ;  $p = 0.001$ ), general health ( $\Delta = 15.3\%$ ;  $p < 0.001$ ), mental health ( $\Delta = 8.3\%$ ;  $p = 0.024$ ), and PCS ( $\Delta = 5.1\%$ ;  $p = 0.043$ ), increased in EX-group with no significant changes in the TAU group. Following the Bonferroni correction, the EX-group showed improvements (i.e., higher values,  $p < 0.05$ ) compared with the TAU group in physical functioning (mean difference = 14.3; 95% CI, 5.8–22.8), general health (mean difference = 11.7; 95% CI, 5.0–18.5), and PCS (mean difference = 4.6; 95% CI, 1.1–8.2), and no significant between-group differences were found in any other domains. On the other hand, the sleep quality changes showed that sleep efficiency increased ( $\Delta = 1.9\%$ ;  $p = 0.004$ ) in the EX-group, with no significant changes in the TAU group for any of the variables studied. Following the Bonferroni correction, the EX-group showed improvements (i.e., higher values,  $p = 0.027$ ) compared with the TAU group in sleep efficiency (mean difference = 1.6; 95% CI, 0.2–3.0). However, after a deeper analysis of the reliability measures within-subject variation using the typical error affecting the precision of estimates of change in the sleep quality variable, a 2.6% typical error was calculated, higher than the systematic mean change (1.9 vs. 2.6%) [30].

Pearson correlation coefficients demonstrated relationships between the  $\Delta\dot{V}O_{2peak}$  ( $L \cdot \text{min}^{-1}$  and  $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively) with  $\Delta$ physical functioning ( $R = 0.295$ ,  $p = 0.007$ ;  $R = 0.342$ ,  $p = 0.002$ ),  $\Delta$ role-physical ( $R = 0.262$ ,  $p = 0.018$ ;  $R = 0.248$ ,  $p = 0.026$ ),  $\Delta$ bodily pain ( $R = 0.261$ ,  $p = 0.019$ ;  $R = 0.263$ ,  $p = 0.018$ ),

**TABLE 1** | Characteristics of the studied population and mean (SD) scores and sample sizes for eight variables of SF-36 by group and subgroups at baseline.

Variables	SZ (N=112)	SZ subgroups		
		TAU (N=53)	EX (N=59)	p
Age (years)	41.3 ± 10.5	42.5 ± 9.9	40.1 ± 10.9	0.224
Body mass (kg)	85.0 ± 16.8	85.5 ± 17.6	84.6 ± 16.2	0.782
BMI (kg/m <sup>2</sup> )	29.3 ± 5.4	29.5 ± 5.5	29.2 ± 5.4	0.831
Waist (cm)	99.1 ± 14.8	99.8 ± 16.1	98.4 ± 13.7	0.622
SBP (mmHg)	117.7 ± 13.7	121.8 ± 15.0	114.5 ± 11.6	0.006
DBP (mmHg)	71.3 ± 8.7	73.8 ± 8.8	69.3 ± 8.1	0.007
$\dot{V}O_{2peak}$ (mL kg <sup>-1</sup> min <sup>-1</sup> )	22.0 ± 6.4	22.0 ± 6.1	22.0 ± 6.7	0.968
<b>HRQoL SF-36</b>				
Physical functioning	80.3 ± 19.9	84.2 ± 17.0	77.4 ± 21.5	0.085
Role—physical	78.6 ± 31.6	80.1 ± 33.1	77.5 ± 30.7	0.685
Bodily pain	73.4 ± 25.0	78.3 ± 25.4	69.7 ± 24.3	0.083
General health	59.3 ± 22.5	63.0 ± 22.3	56.6 ± 22.4	0.150
Vitality	50.4 ± 16.5	52.0 ± 14.2	49.2 ± 18.0	0.395
Social functioning	69.3 ± 24.4	70.7 ± 23.2	68.2 ± 25.5	0.607
Role—emotional	70.5 ± 39.4	70.5 ± 40.2	70.6 ± 39.2	0.983
Mental health	66.5 ± 17.0	65.5 ± 16.7	67.2 ± 17.3	0.630
Physical component summary	48.6 ± 7.1	50.8 ± 6.7	47.0 ± 7.0	0.008
Mental component summary	44.1 ± 10.1	43.5 ± 10.2	44.6 ± 10.1	0.610
<b>Sleep quality</b>				
Efficiency (%)	91.5 ± 4.4	91.0 ± 4.5	92.0 ± 4.3	0.250
Bedtime (min/day)	568.8 ± 104.7	552.4 ± 97.7	580.6 ± 108.9	0.185
TST (min/day)	523.0 ± 105.1	503.2 ± 95.6	537.4 ± 110.1	0.109
WASO	44.7 ± 22.4	48.3 ± 23.8	42.1 ± 21.2	0.176

Note: Values are mean ± SD or number.  $p < 0.05$ .

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; EX, exercise group; SBP, systolic blood pressure; TAU, Treatment-As-Usual; TST, total sleep time;  $\dot{V}O_{2peak}$ , peak oxygen uptake; WASO, wake after sleep onset.

Δgeneral health ( $R=0.309$ ,  $p=0.005$ ;  $R=0.338$ ,  $p=0.002$ ), Δvitality ( $R=0.264$ ,  $p=0.017$ ;  $R=0.241$ ,  $p=0.030$ ), and ΔPhysical Component Summary ( $R=0.399$ ,  $p<0.001$ ;  $R=0.432$ ,  $p<0.001$ , Table 3).

#### 4 | Discussion

To our knowledge, this is the most extensive study to date in adults diagnosed with SZ investigating the effects of a highly demanding and supervised 20 weeks combined exercise training program (low-volume HIIT + resistance training) compared to a TAU group only conducting occupational activity sessions on domains of HRQoL and sleep quality variables. The main findings of the study were: (1) after a 20 week intervention period, both some of the HRQoL domains (“physical functioning,” “general health,” “mental health,” and “physical component summary” scores) and the sleep efficiency

improved in the supervised EX with no changes in TAU group; and (2) a greater CRF was associated with better values in “physical functioning,” “role-Physical,” “bodily pain,” “general health,” “vitality,” and “physical component summary” from the SF-36 questionnaire, after 20 week of combined exercise program in SZ participants (Figure 1). Our results re-emphasize prior publication and confirm this kind of training as a safe and efficient modality for patients with SZ [27], as participants did not report any significant adverse effects during or after exercise sessions.

To know how the studied population is doing, we must go beyond traditional clinical endpoints to represent the implications of the disease and the pharmacological treatment regarding how they feel and how it affects their daily lives. Compared with the general population, people with SZ are dissatisfied with their QoL, and it confirmed that they could have additional needs due to the remarkable role of psychosocial factors, such as stigma

**TABLE 2** | Health-related quality of life outcomes before and after the 20-week intervention program. Mean  $\pm$  SD.

	<b>TAU (N=38)</b>	<b>EX (N=51)</b>	<b>p</b>	<b>F value</b>	<b>%Variance</b>
SF-36					
Physical functioning					
T0	83.8 $\pm$ 18.4	76.5 $\pm$ 21.9			
T1	79.4 $\pm$ 24.7	86.4 $\pm$ 17.7**	0.001	11.262	0.123
Role—physical					
T0	81.8 $\pm$ 33.2	76.0 $\pm$ 31.4			
T1	72.0 $\pm$ 24.7	73.5 $\pm$ 34.4	0.473	0.520	0.006
Bodily pain					
T0	77.9 $\pm$ 26.2	70.3 $\pm$ 24.1			
T1	77.0 $\pm$ 29.0	75.6 $\pm$ 26.4	0.275	1.211	0.015
General health					
T0	61.8 $\pm$ 20.0	57.4 $\pm$ 23.2			
T1	58.8 $\pm$ 25.1	66.2 $\pm$ 22.2***	0.001	12.021	0.131
Vitality					
T0	52.6 $\pm$ 15.3	49.0 $\pm$ 18.9			
T1	51.2 $\pm$ 19.8	51.9 $\pm$ 18.8	0.312	1.034	0.013
Social functioning					
T0	70.5 $\pm$ 23.8	70.7 $\pm$ 25.7			
T1	68.6 $\pm$ 26.5	73.5 $\pm$ 28.2	0.486	0.490	0.006
Role—emotional					
T0	70.7 $\pm$ 39.7	72.8 $\pm$ 38.9			
T1	65.6 $\pm$ 41.2	78.2 $\pm$ 37.6	0.217	1.549	0.019
Mental health					
T0	65.1 $\pm$ 17.6	67.5 $\pm$ 17.9			
T1	66.8 $\pm$ 17.1	73.1 $\pm$ 17.1*	0.293	1.121	0.014
Physical component summary					
T0	50.7 $\pm$ 6.8	46.7 $\pm$ 7.3			
T1	48.4 $\pm$ 10.4	49.1 $\pm$ 7.0*	0.011	6.851	0.079
Mental component summary					
T0	43.5 $\pm$ 10.1	45.3 $\pm$ 9.9			
T1	43.7 $\pm$ 10.3	47.0 $\pm$ 9.0	0.511	0.435	0.005
Sleep quality					
Efficiency (%)					
T0	91.1 $\pm$ 4.2	91.6 $\pm$ 4.6			
T1	91.1 $\pm$ 4.8	93.3 $\pm$ 2.9**	0.027	5.101	0.061
Bedtime (min/day)					
T0	564.5 $\pm$ 92.9	588.8 $\pm$ 109.4			
T1	558.9 $\pm$ 121.1	596.6 $\pm$ 97.7	0.516	0.425	0.005

(Continues)

TABLE 2 | (Continued)

	TAU (N=38)	EX (N=51)	p	F value	%Variance
TST (min/day)					
T0	514.9 ± 91.1	544.0 ± 112.8			
T1	512.0 ± 121.4	554.2 ± 96.4	0.512	0.434	0.006
WASO					
T0	48.7 ± 23.6	43.8 ± 22.4			
T1	45.8 ± 24.4	41.5 ± 19.3	0.903	0.015	0.000

Note: Values are mean ± SD or number.

Abbreviations: EX, exercise group; TAU, Treatment-As-Usual; TST, total sleep time; WASO, wake after sleep onset.

\* $p < 0.05$  between T0 and T1.

\*\* $p < 0.01$ .

\*\*\* $p < 0.001$ .

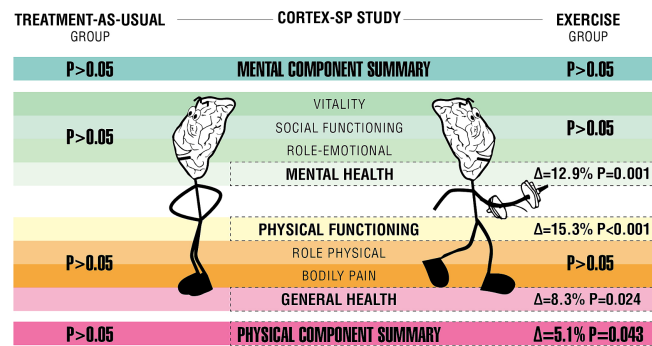


FIGURE 1 | Health-related quality of life after a 20-week intervention program in people with schizophrenia.

TABLE 3 | Correlations between the  $\Delta$  domains of health-related quality of life and physical fitness variables.

Variables	$\Delta \dot{V}O_{2peak}$ ( $L \cdot min^{-1}$ )	$\Delta \dot{V}O_{2peak}$ ( $mL \cdot kg^{-1} \cdot min^{-1}$ )
$\Delta$ Physical functioning	0.295**	0.342**
$\Delta$ Role—physical	0.262*	0.248*
$\Delta$ Bodily pain	0.261*	0.263*
$\Delta$ General health	0.309**	0.338**
$\Delta$ Vitality	0.264*	0.241*
$\Delta$ Social functioning	0.149	0.178
$\Delta$ Role—emotional	0.144	0.101
$\Delta$ Mental health	0.147	0.141
$\Delta$ Physical component summary	0.399***	0.432***
$\Delta$ Mental component summary	0.116	0.089

Abbreviation:  $\dot{V}O_{2peak}$ , peak oxygen uptake.

\* $p < 0.05$ .

\*\* $p < 0.01$ .

\*\*\* $p < 0.001$ .

dilemma and psychopathological factors, mainly self-reported depressive symptoms [3]. In this sense, it has been shown that QoL among people with SZ is negatively associated with positive and negative symptoms and general psychopathology [31].

In the present study, “vitality” and “general health” dimensions showed the lowest values ( $59.3 \pm 22.5$  and  $50.4 \pm 16.5$ , respectively, Table 1), meaning that the participants felt tired most of the day, with a lack of vitality, and reflected poor health. Therefore, the well-being assessment in the medical practice helps promote alternative treatments such as exercise programs.

In the current investigation, after a 20-week intervention program in the SZ population, no significant differences were found, without benefits of HRQoL domains, in the TAU group; however, the EX-group did demonstrate improvements in the physical area (i.e.,  $\uparrow 12.9\%$  in physical functioning and  $\uparrow 15.3\%$  in general health) resulting in significant differences concerning TAU group. Furthermore, while in a previous meta-analysis, total ( $p < 0.001$ ) and physical ( $p < 0.05$ ) QoL experienced several improvements, with no significant ( $p = 0.09$ ) changes in mental QoL [13], in our study, after analyzing the health-related mental domain, the EX-group improved the “mental health” ( $\uparrow 8.3\%$ ) dimension at follow-up (Figure 1). Recent investigations have shown excellent physical and mental health results in patients with SZ after different exercise programs, including HIIT [32, 33]. The subjective feeling of recovery may also benefit each individual's HRQoL [34], where exercise may be helpful. In line with these results and knowing that the quality of sleep has a profound impact on both the perception of QoL and the ability to cope with stressful situations in people with SZ [7], in the present study, after 20 weeks of combined exercise training, including HIIT and resistance training, only EX participants improved ( $\Delta = 1.9\%$ ) the sleep efficiency (i.e., the ratio between the time a person spends asleep, and the total time dedicated to sleep) reaching values of 93.3%.

Although it could be suggested that the change was not clinically relevant after an analysis of within-subject variation using the typical error, with a lower result than the calculated (i.e., 2.6%), the minor changes could be significant in this population.

There are two types of strategies for improving sleep in people with SZ: (1) Among pharmacological approaches, some sedative antipsychotics may improve sleep through antihistaminic action [35]; and (2) among non-pharmacological methods, regular exercise under supervision and education about a healthy lifestyle is taking a prominent place [36].

In this regard, during the last few years, there has been much evidence on brain and skeletal muscle communication through exercise to achieve better mental health, advocating for exercise as a relevant adjuvant program for brain disease. The endocrine communication with molecules derived from the myokinome that can effectively cross the blood–brain barrier and display neuroactive roles is still under investigation [37]. However, HIIT has been considered relevant for brain health due to the effects of high-intensity work along with its responses and adaptations [38]. In this line, the potential positive effects of exercise on dopamine synthesis and its impact on mental health have already been presented knowing the regulation of other neurotransmitters (i.e., noradrenaline and serotonin) [39], and the possible beneficial effect on the dopaminergic system dysfunction in people with SZ [40]. Further, HIIT seems to increase melatonin secretion and better control patients' internal circadian clock and the loop between sleep and dopamine irregularities [8].

Considering the exercise-associated benefits and the importance of improving CRF for general health [41], the current study went one step further by analyzing the associations between the  $\Delta$ CRF and  $\Delta$  domains of HRQoL after 20 weeks of intensive combined training 3 days per week. Thus, very important results were observed indicating that the higher the CRF, the better were the values of “physical functioning” and “role-physical” (i.e., a lesser degree of limitation of physical activity in daily life at moderate-to-high intensity), “bodily pain” (i.e., a lower degree of pain intensity and its effect on usual work, outside, and inside the home), “general health” (i.e., an improved personal assessment of health, including future health prospects), “vitality” (i.e., a better feeling of energy and vitality as opposed to feeling tired and exhausted), and “PCS” (Table 3). In a previous study with SZ patients, CRF was also associated with some QoL domains assessed by SF-36 (physical functioning, role-physical, bodily pain, and general health) [19]. However, in the current study, more significant relationships were observed, likely because our analysis was performed after the intensive training program, and our CRF assessment was maximal, with objective maximum oxygen uptake. Therefore, the data observed in the improvement of QoL related to physical condition join the previously published objective improvements in CRF [27].

The strengths of this study include the use of low-volume HIIT and resistance training protocols in the same session with such a large sample of people with SZ. Nevertheless, this study was limited by: (1) the patients were treated with a heterogeneous sample of antipsychotics reflecting the usual clinical practice in

the province of Álava (Basque Country). Further, it is a heterogeneous sample, in the state and evolution of the disease, and the personal and social aspects; (2) the current study does not represent a division by equal sex (i.e., 22.3% women), which the perspective between the sexes could be different when highlighting the questionnaire since women usually present lower values in all multi-items compared to men [26], and (3) as the SF-36 is a subjective questionnaire, it is difficult to assess all its results accurately.

## 5 | Conclusions

A 20-week supervised combined exercise intervention program for SZ individuals effectively increased sleep efficiency and physical functioning, general health, mental health, and PCS scores. This could lead to a critical HRQoL change from how they were to how they should be. Hence, these results highlight the vital role of supervised exercise in improving physical and psychological health.

## 6 | Perspective

The results of the present study show the continuation of the analysis of an intervention with exercise as an adjuvant program in people diagnosed with schizophrenia. Thus, a combined supervised exercise program, including low-volume HIIT and resistance training, demonstrated a real impact, on the one hand, on the maintenance of body composition and the improvement of CRF and cardiometabolic profile [27] and, on the other hand, observable benefits in sleep quality and essential aspects of QoL. In addition, the subjective experiences of participants with sz underscore the proper perspective of supporting out-of-hospital exercise programs as an adjunct to standard treatment to achieve holistic improvements [42].

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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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