European Journal of Sport Science

WILEY

ORIGINAL PAPER OPEN ACCESS

Differential Responsiveness to Exercise and Cognitive Remediation in Physical Health in People With Schizophrenia: Results From the CORTEX-SP Study

Mikel Tous-Espelosin[1,2] | Nagore Iriarte-Yoller[3,4,5] | Agurne Sampedro[6] | Iker Lasa-Sagaseta[1] | Cristóbal Pavon[3,4,5] | Natalia Ojeda[6] | Pedro Sanchez[3,4,5] | Javier Peña[6] | Sara Maldonado-Martín[1,2]

[1]Society, Sports, and Physical Exercise Research Group (GIKAFIT), Department of Physical Education and Sport, Faculty of Education and Sport-Physical Activity and Sport Sciences Section, University of the Basque Country (EHU), Vitoria-Gasteiz, Araba/Álava, Spain | [2]Physical Activity, Exercise, and Health Group, Bioaraba Health Research Institute, Vitoria-Gasteiz, Spain | [3]New Therapies in Mental Health Group, Bioaraba Health Research Institute, Vitoria-Gasteiz, Spain | [4]Osakidetza Basque Health Service, Araba Mental Health Network, Psychiatric Hospital of Alava, Vitoria-Gasteiz, Spain | [5]Department of Medicine, Faculty of Health Sciences, University of Deusto, Bilbao, Spain | [6]Department of Psychology, Faculty of Health and Sciences, University of Deusto, Bilbao, Spain

Correspondence: Mikel Tous-Espelosin (mikel.tous@ehu.eus)

Received: 21 October 2025 | **Revised:** 21 April 2026 | **Accepted:** 27 April 2026

Keywords: body composition | cardiorespiratory fitness | responder | sleep efficiency

ABSTRACT

Non-pharmacological interventions, such as exercise and cognitive remediation, have been widely investigated in people with schizophrenia (SZ), showing beneficial effects and supporting their role as complementary approaches to pharmacological treatment. Moving towards precision medicine, it is important to consider variability in individual responses. Thus, this study aimed to analyse the prevalence of responders regarding body composition, cardiorespiratory fitness (CRF), and sleep quality in people with SZ following exercise or cognitive remediation programmes. A total of 159 participants with SZ (41 ± 10 years) were randomly assigned to the treatment-as-usual (TAU, $n = 53$), exercise (EX, $n = 59$), or cognitive remediation programme (REHACOP, $n = 47$) groups. Anthropometric outcomes, CRF, and sleep efficiency were assessed pre- and post-intervention using standardised methodologies. The typical error (TE) was calculated to identify responders. The EX group showed the highest prevalence of responders in body mass index (21.2%) and fat mass percentage (20%). There were significant improvements in CRF in the EX group ($\Delta = 21.0\%$, $p < 0.001$), with a significantly higher prevalence of responders compared with the REHACOP and TAU groups ($p < 0.001$). Sleep efficiency also improved significantly in the EX group ($\Delta = 1.75\%$, $p = 0.004$), again with the highest prevalence of responders (27.7%) in this group. These findings suggest that exercise is a particularly effective strategy for enhancing physical health outcomes in people with SZ. However, cognitive remediation may still play a complementary role by supporting the cognitive resources required to maintain exercise engagement and healthy lifestyle changes.

1 | Introduction

Schizophrenia (SZ) is a chronic and disabling mental illness associated with markedly elevated rates of premature mortality, primarily driven by cardiovascular disease (Correll et al. 2022; Goldfarb et al. 2022). Despite advances in pharmacological treatment, antipsychotic medication alone is insufficient to address the full spectrum of physical impairments observed in this population. Robust scientific evidence now supports the

Highlights

- Exercise training significantly improved cardiorespiratory fitness and sleep efficiency in people with schizophrenia, with a higher prevalence of responders compared with cognitive remediation or treatment as usual.
- The findings highlight the importance of exercise as a robust intervention for enhancing physical health in people with schizophrenia within a precision medicine framework.
- The findings highlight the need for integrated, multimodal interventions and precision-based approaches to optimise both mental and physical health in individuals with schizophrenia.

efficacy of exercise (Bull et al. 2020; Stubbs et al. 2018) and cognitive remediation (Barlati et al. 2025; Sampedro et al. 2025; Taylor et al. 2025) as adjunctive treatments for SZ. Exercise has been shown to improve physical outcomes, especially cardiorespiratory fitness (CRF), a strong predictor of cardiovascular health, while also reducing cardiometabolic risk factors (Firth et al. 2020). Despite receiving equivalent exercise doses, individual responses to exercise vary widely. This phenomenon highlights the need for a precision medicine approach and a better understanding of responder profiles in this population (Bouchard et al. 2011; Ross et al. 2019).

Alongside exercise, cognitive remediation has emerged as another evidence-based non-pharmacological strategy aimed at ameliorating the cognitive deficits that are characteristic of SZ (Vita et al. 2024). These deficits, particularly in attention, memory, and executive function, are closely linked to long-term disability and poor functional outcomes (Vita et al. 2021). The findings from recent meta-analyses underscore the efficacy of cognitive remediation in improving cognitive performance, supporting its integration into clinical guidelines for SZ treatment (Buonocore et al. 2018; Shu et al. 2024). This approach is especially relevant given the strong association between cognitive improvements and gains in functional capacity, autonomy, and quality of life (Martini et al. 2024; McGuiness et al. 2025). Enhancing domains such as attention, memory, and executive functioning facilitates greater engagement in activities of daily living and social participation, thereby reducing functional disability (Tulliani et al. 2022). Moreover, better cognitive functioning may promote healthier lifestyle behaviours, such as increased adherence to physical activity and reduced sedentary behaviour, which are critical for preventing cardiometabolic complications and supporting cardiovascular health (Qi et al. 2023). These findings represent a notable departure from earlier conclusions that questioned the clinical utility of cognitive remediation, reflecting methodological advances in both intervention design and outcome assessment (McGrath and Hayes 2000).

In summary, the current literature indicates that exercise and cognitive remediation programmes can exert beneficial effects on physical health in individuals with SZ. Even though the available studies have reported average improvements, substantial inter-individual variability has been documented across different exercise interventions (Gallardo-Gómez et al. 2023; Rahmati et al. 2025). This variability suggests the presence of distinct response patterns, with some individuals demonstrating meaningful positive adaptations ('responders'), while others exhibit minimal or no improvements, and in some cases even negative responses ('non-responders'). Environmental and genetic factors have been proposed as key contributors to inter-individual variability; however, the influence of antipsychotic medication and unhealthy lifestyle behaviours—both of which are highly prevalent in this population—remains unclear (Mann et al. 2014). Traditional statistical approaches, which focus on average variability, are limited in their ability to capture the proper individual responsiveness to interventions, resulting in relevant interpretive gaps (Bouchard et al. 2011). In contrast, emerging statistical methods, such as the use of standard deviation, control group comparisons, and typical error (TE), provide more robust tools for assessing inter-individual responses to a standardised exercise dose (Atkinson et al. 2019). Despite their potential, these methods have not yet been widely applied to people with SZ. Therefore, the present study aimed to analyse both the effects of intervention programmes (supervised exercise [EX], cognitive remediation [REHACOP], and treatment as usual [TAU]) and the prevalence of responders regarding body composition, CRF, and sleep quality in people with SZ. Based on previous evidence, we hypothesised that the EX group would show greater improvements in CRF, body composition, and sleep efficiency compared with the REHACOP and TAU groups; the prevalence of responders would be higher in the EX group, particularly for CRF; and substantial inter-individual variability would be observed across all intervention groups, supporting the need for a precision medicine framework.

2 | Materials and Methods

2.1 | Study Design

The CORTEX-SP study is a randomised, single-blind (medical specialists who evaluated the psychiatric variables) controlled experimental trial (Clinical Trials.gov identifier). The study was approved by the Clinical Research Ethics Committee of the Autonomous Region of the (PI2017044), and written informed consent was obtained from all participants prior to data collection. After baseline measurements, the participants were randomised (www.randomization.com) to one of the three intervention groups: the TAU control group, the EX group, or the REHACOP group.

2.2 | Study Participants

One hundred and fifty-nine non-Hispanic white participants (41 ± 10 years old, n = 128 men and n = 31 women) were enrolled in the study from May 2018 to July 2021. Figure 1 presents a flow diagram of the study process. All participants were recruited from the Mental Health Network, which provides psychiatric care to the population living in the community. Patients from the study met the diagnostic criteria for SZ according to the *Diagnostic and Statistical Manual of Mental Disorders* (fifth ed.; DSM-5; American Psychiatric Association 2013). Additional clinical characteristics, including illness duration, symptom severity, pharmacological treatment profiles,

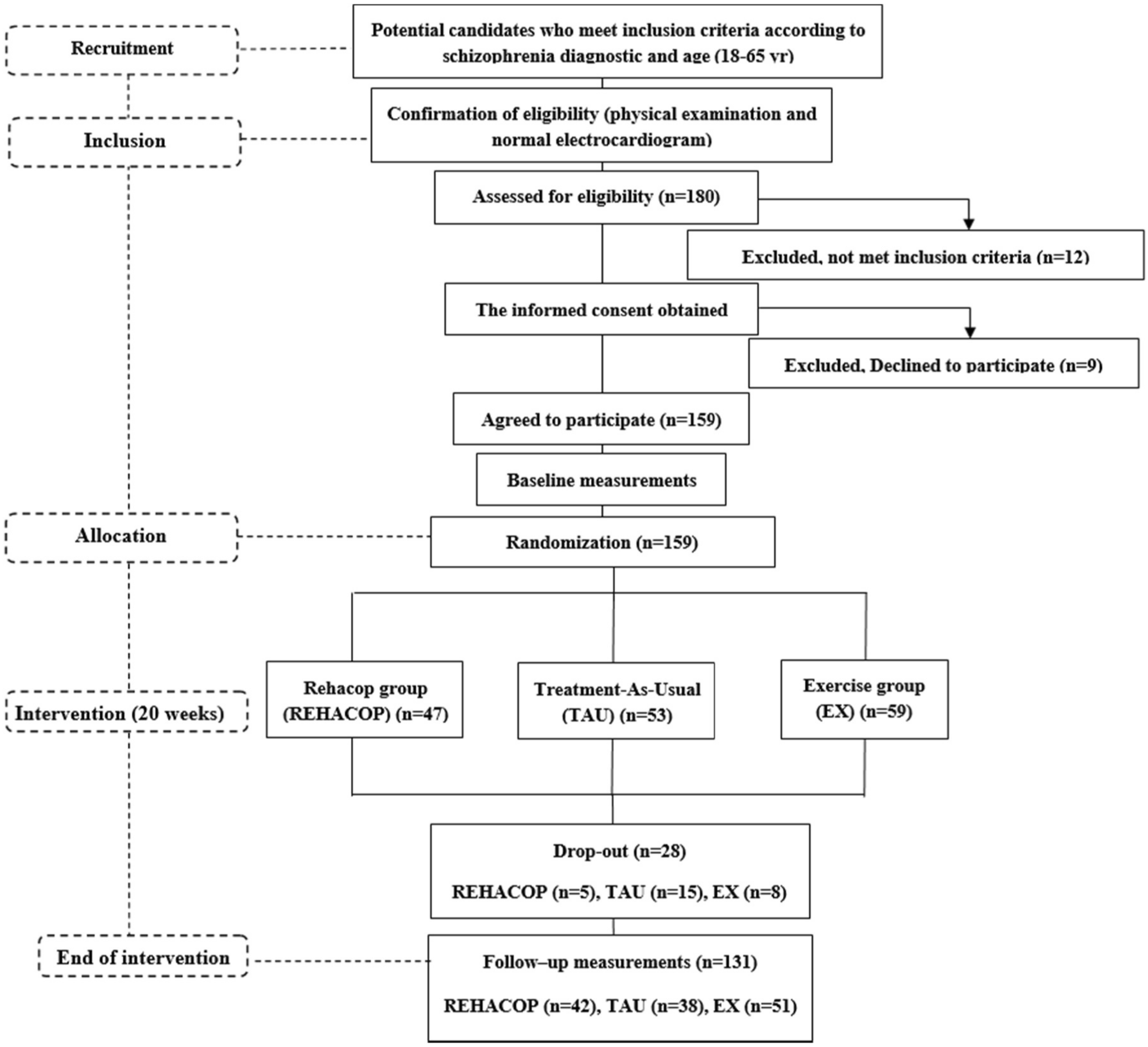

FIGURE 1 | Flow diagram of the CORTEX-SP study from recruitment to the end of the intervention.

and clinical settings, were collected as part of the CORTEX-SP study and are reported in detail elsewhere (Tous-Espelosin et al. 2021). All medications prescribed to participants were recorded and classified according to antipsychotic type (e.g., aripiprazole, clozapine, paliperidone, olanzapine, quetiapine, haloperidol, risperidone, ziprasidone, levomepromazine, perphenazine, and lurasidone) (Tous-Espelosin et al. 2021). Additionally, medication dosages were standardised using chlorpromazine equivalents based on the defined daily dose method (Tous-Espelosin et al. 2023). These variables were considered in the present analyses as potential modulators of responsiveness. The participants included both inpatients (46.3%) and outpatients (53.7%). The inpatients were hospitalised at a psychiatric rehabilitation unit with an imminent hospital discharge to the community setting. The inclusion and exclusion criteria of the study have been previously published (Tous-Espelosin et al. 2021).

2.3 | Measurements

The measurements for the study were taken before (T0) and after (T1) the 20-week intervention period. The procedures used to assess body composition, CRF, and sleep efficiency have been detailed in previous publications (Tous-Espelosin et al. 2021). Briefly, body composition, specifically the fat mass percentage (FM%), was evaluated using bioelectrical impedance analysis (Tanita BF 350, Arlington Heights, IL, USA). CRF was assessed via a symptom-limited cardiopulmonary exercise test followed by a progressive, ramp protocol starting at 40 W and increasing 10 W per minute, conducted on an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, the Netherlands) to determine the peak metabolic equivalent of task (MET_{peak}). Finally, sleep efficiency was assessed objectively and continuously through a triaxial accelerometer (ActiGraph GT3X+, ActiGraph LLC, Pensacola, FL, USA). The participants wore a triaxial on their non-dominant wrist with a Velcro strap for eight consecutive days (24 h a day), except during water-based activities.

2.4 | Intervention

A comprehensive description of the exercise intervention protocol (used for the EX group) has been previously published (Tous-Espelosin et al. 2023). In brief, the participants engaged in supervised training sessions 3 times per week for 20 weeks. Qualified exercise professionals at community-based facilities conducted these sessions. Each session included a 40-min central block of combined training consisting of a low-volume and high-intensity interval training segment, approximately 20 min in total, with less than 10 min at high intensity, using a stationary bike, followed by 20 min of resistance-based circuit training. The cycling portion was customised to each participant's heart rate, targeting moderate-to-vigorous-intensity zones. The resistance component followed a rotating 3-week circuit system, incorporating 10 distinct exercises per circuit.

A comprehensive description of the intervention protocol followed by the REHACOP group has also been published (Sampedro et al. 2023). The participants were distributed into 9 subgroups, each consisting of 4–8 patients. The clinical team administering the intervention was trained in the REHACOP methodology, ensuring consistency in the materials and procedures used across all groups. The sessions lasted 60 min and were conducted 3 times per week for 20 weeks. During the REHACOP intervention, the following modules were delivered: attention, learning and memory, language, executive functions, social cognition, social skills, and functional skills units. Additionally, processing speed was trained throughout the first four units. No additional cognitive interventions were administered to participants during the course of the programme.

The participants in the TAU group attended occupational activities sessions with the same frequency and duration as the other two groups.

Inter-individual variability in response to the EX, REHACOP, and TAU interventions was analysed by categorising the participants as responders or non-responders based on the TE. The TE was calculated for the following variables: body mass index (BMI), FM%, MET_{peak}, and sleep efficiency. The following equation was used for the calculation:

$$TE = SD_{diff}/\sqrt{2},$$

where SD_{diff} is the variance (standard deviation) of the difference between the two results (post-intervention minus pre-intervention value) from the control group (i.e., TAU; Hopkins 2000). A responder is defined as an individual who achieves a clinically meaningful benefit from a treatment or intervention, demonstrating a desirable change in their condition or symptoms. In the context of this study, a responder showed an increase in MET_{peak} and sleep efficiency (i.e., $MET_{peak} \uparrow + 1.01$, and sleep efficiency $\uparrow + 2.2\%$), and a decrease in BMI and FM% (i.e., BMI $\downarrow - 1.4$ kg m^{-2}, FM% $\downarrow - 2.6\%$). A change exceeding the TE suggests a high likelihood (i.e., 6:1 odds) that the observed response represents a genuine physiological adaptation, rather than an outcome attributable to technical error or inherent biological variability (Hopkins 2000).

2.5 | Statistical Analysis

Descriptive statistics were calculated for all variables. The data are presented as the mean ± standard deviation and range. A one-way analysis of variance (ANOVA) was conducted to assess potential baseline differences between the groups. The chi-square test was used to compare frequency distributions of categorical variables across groups. To evaluate within-group differences from pre-to post-intervention, paired-samples *t*-tests were performed. Analysis of covariance (ANCOVA) was employed to examine delta (Δ) scores for each group (EX, REHACOP, and TAU), with adjustments for age and sex. Additionally, relevant sociodemographic and clinical variables, including illness duration, baseline physical fitness, symptom severity, and pharmacological treatment, were explored as potential covariates in relation to responder status.

The Bonferroni correction was applied to adjust the *p*-values for multiple comparisons conducted within a single dataset, regardless of whether the tests were dependent or independent. Additionally, the TE was calculated to assess individual variability in response. Group differences in the proportion of responders and non-responders were analysed using the Kruskal–Wallis test. Statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

3 | Results

Sociodemographic and clinical variables were examined as potential covariates of responder status at the beginning of the analyses. However, none of these variables demonstrated a significant association with responsiveness across any of the outcomes evaluated.

3.1 | Follow-Up

No adverse events were reported during the interventions, and the mean intervention adherence was > 85% of the 60 scheduled sessions. None of the participants changed their medication during the intervention period unless psychiatric instability was present. Eight participants in the EX group, five in the REHACOP group, and 15 in the TAU group were lost to follow-up ($n = 28$). There were no significant differences between intervention dropouts and completers in any of the measured variables across the study groups. Thus, 131 participants with SZ completed the 20-week intervention and were included in the final analysis (Figure 1).

3.2 | Baseline

The baseline characteristics of the participants have been previously published (Tous-Espelosin et al. 2021). There were no significant between-group differences in the anthropometric variables, CRF, and sleep efficiency. The published data classified the participants as metabolically unhealthy, with overweight (27.6 ± 7.4 kg m^{-2}), a high FM% (26.5% ± 10.4%), low CRF (MET_{peak} = 6.4 ± 2.7), and optimal sleep efficiency (91.5% ± 5.4%).

3.3 | Pre-Post Changes and the Prevalence of Responders Regarding the Anthropometric Variables

While the EX group did not demonstrate significant changes in the anthropometric variables, the REHACOP group showed significant increases in BMI (Δ = 2.55%, $p = 0.002$, Figure 2A) and FM% (Δ = 4.65%, $p = 0.002$, Figure 2C). There were no significant differences between the groups after applying the

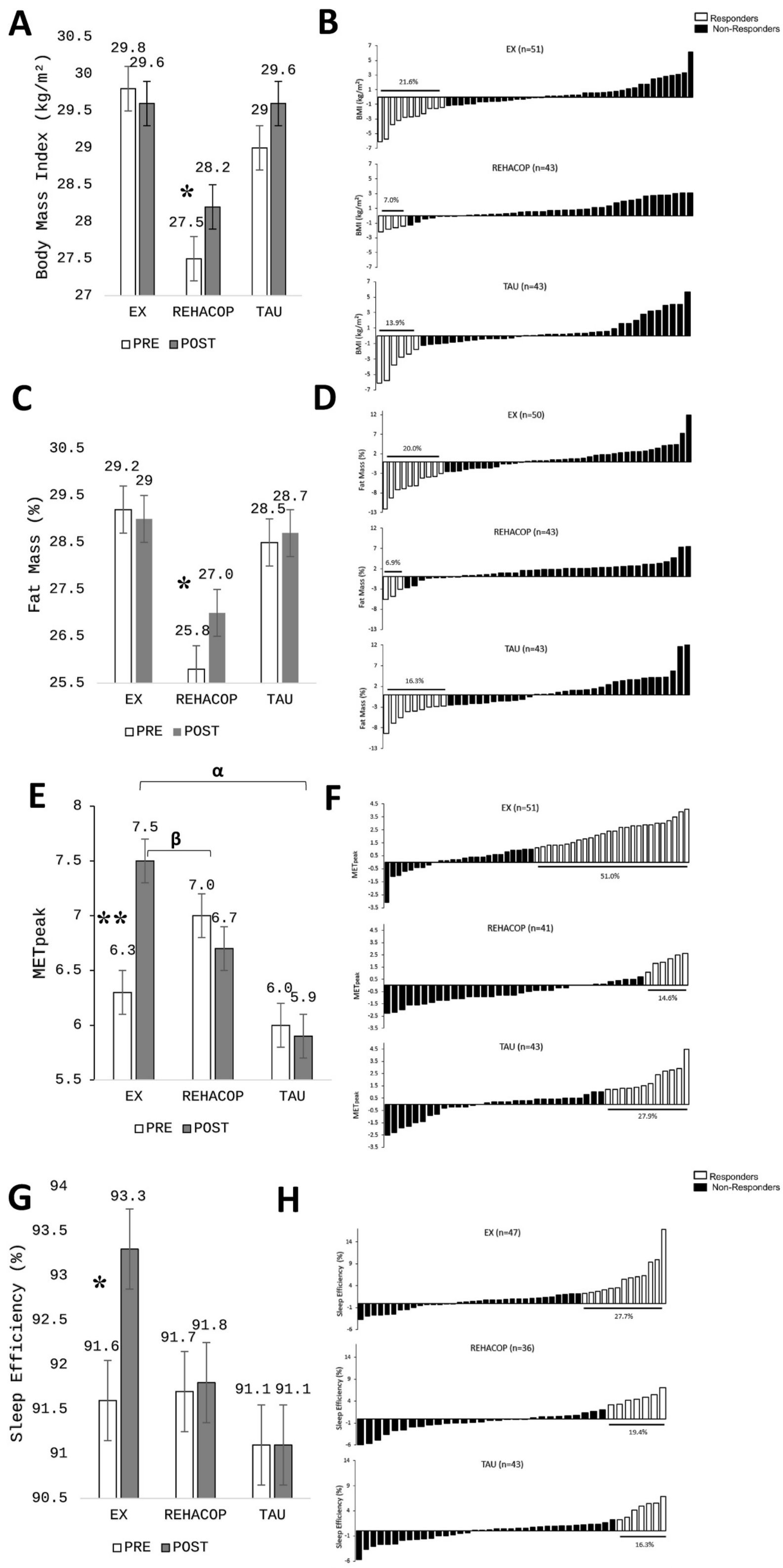

FIGURE 2 | Body mass index (A and B), fat mass percentage (C and D), MET_{peak} (E and F), and sleep efficiency (G and H) in individuals with schizophrenia: mean changes and 'responder' prevalence after 20 weeks of interventions. BMI, body mass index; FM%, fat mass percentage; MET_{peak}, metabolic equivalent of task. Intragroup $^*p < 0.05$; $^{**}p < 0.01$; $^*p < 0.001$. Intergroup EX versus TAU, $^{\alpha}p < 0.001$; EX versus REHACOP, $^{\beta}p < 0.001$.

Bonferroni correction ($p > 0.05$). The EX group had the highest prevalence of responders for BMI (EX: 21.2% vs. REHACOP: 7.0% vs. TAU: 13.9%) and FM% (EX: 20.0% vs. REHACOP: 6.9% vs. TAU: 16.3%; Figure 2B,D). However, based on the Kruskal–Wallis test, neither BMI (p = 0.187) nor FM% (p = 0.148) differed significantly among the groups.

3.4 | Pre-Post Changes and the Prevalence of Responders Regarding CRF

MET_{peak} increased significantly in the EX group ($\Delta = 21.0\%$, $p < 0.001$). After applying the Bonferroni correction, there were significant between-group differences: the EX group showed a greater increase ($p < 0.001$) compared with the REHACOP group (mean difference = −1.501, 95% confidence interval [CI]: −2.209 to 0.793) and the TAU group (mean difference = −1.618, 95% CI: −2.324 to 0.912, Figure 2E). However, there was no significant difference between the REHACOP and TAU groups ($p > 0.05$). The EX group also showed a much higher percentage of responders (51.0%) compared with the REHACOP (14.6%) and TAU (27.9%) groups (Figure 2F). The Kruskal–Wallis test confirmed a significant difference in the prevalence of responders between EX group with REHACOP and TAU groups ($H = 16.120$, $p < 0.001$).

3.5 | Pre-Post Changes and the Prevalence of Responders Regarding Sleep Efficiency

Sleep efficiency increased significantly in the EX group ($\Delta = 1.75\%$, $p = 0.004$), but not in the other two groups. After applying the Bonferroni correction, the EX group presented a significant increase compared with the TAU group (mean difference = −2.228, 95% CI: −3.865 to 0.591, $p = 0.004$, Figure 2G). However, there was no difference between the EX and REHACOP groups ($p = 0.067$) or between the TAU and REHACOP groups ($p > 0.05$). The EX group showed a higher prevalence of responders (27.7%) compared with the REHACOP (19.4%) and TAU (16.3%) (Figure 2H). However, the Kruskal–Wallis test revealed that the difference among the groups was not significant ($p = 0.365$).

4 | Discussion

The present study investigated the differential responsiveness to exercise and cognitive remediation on physical health outcomes in individuals with SZ. The main findings are the significant improvements in the EX group in both CRF (i.e., an increase in MET_{peak}) and sleep efficiency, along with a higher prevalence of responders in the EX group compared with the REHACOP and TAU groups (Figure 3). Although there were no between-group differences in the anthropometric variables, the EX group showed the highest proportion of responders for both BMI and FM%. In contrast, cognitive remediation alone was associated with increases in both BMI and FM%, suggesting that without simultaneous lifestyle modification or physical activity intervention, cognitive remediation may not confer direct physical health benefits.

The effects of the CORTEX-SP trial on the four health-related variables within the EX group have been previously reported (Tous-Espelosin et al. 2023, 2024). The findings are consistent with prior evidence highlighting exercise as a highly effective intervention for enhancing physical health and reducing cardiometabolic risk in people with SZ (Firth et al. 2020; Vancampfort, Wampers, et al. 2013). After the 20-week intervention, there were no between-group differences in the anthropometric variables, and no statistically significant positive effects. Several factors may account for these findings when considering the specific characteristics of individuals with SZ: first, pharmacological treatment must be considered, as second-generation antipsychotics inhibit lipid oxidation and thus prevent lipolysis (Halstead et al. 2025; Perez-Cruzado et al. 2018). As a result, people with SZ often experience difficulties in reducing FM%, which may partly explain the low prevalence of responders in the present study. Second, it is well established that individuals with SZ engage in high levels of sedentary behaviour (Firth et al. 2020), and low physical activity levels directly limit total daily energy expenditure, thereby hindering reductions in FM%. Therefore, exercise interventions alone may be insufficient in this population, and broader strategies aimed at promoting healthier and more active lifestyles are also required (Sethi et al. 2024; Teasdale et al. 2025). Despite these barriers, evidence from previous studies as well as the findings from this study indicate that structured exercise programmes do have positive effects on anthropometric variables. Indeed, the EX group had a higher prevalence of responders regarding both BMI and FM% compared with the other two groups.

CRF is a well-known and relevant health endpoint, as it is one of the strongest predictors of cardiovascular health and premature mortality in patients with SZ (Correll et al. 2022). The prevalence of responders regarding CRF in the EX group (51%) further supports the idea that supervised combined exercise training is a potent stimulus to improve physical health in people with SZ (Ross et al. 2019). Consistent with prior work (Atkinson et al. 2019; Bouchard et al. 2011), in the present study, there was substantial heterogeneity in the outcomes, even among the participants exposed to the same standardised exercise programme. An important conceptual question is whether responsiveness to behavioural interventions represents a stable individual trait. Although the parallel-group design of the present study does not allow this hypothesis to be directly tested, the substantial inter-individual variability observed supports this possibility. Emerging evidence from exercise science suggests that variability in adaptation may, in part, reflect inherent biological characteristics, including genetic predisposition and physiological adaptability (Ross et al. 2019). In SZ, this question is particularly relevant given the marked heterogeneity of the disorder. Longitudinal and crossover designs are needed to determine whether individuals consistently respond (or fail to respond) across different types of interventions, which would have important implications for precision medicine approaches (Ross et al. 2019). While approximately half of the participants in the EX group were classified as responders regarding CRF, others demonstrated minimal or no improvements, underscoring the importance of precision medicine approaches in this field. Several factors may help to explain these results: first, pharmacological treatment (particularly antipsychotics) is associated with cardiometabolic side effects (e.g., weight gain, sedation, impaired autonomic regulation) that can blunt exercise adaptations (De Hert et al. 2011; Pillinger et al. 2020). Second, negative symptoms such as anhedonia, avolition, or cognitive impairment, may reduce engagement during sessions, leading to a lower training intensity and limited stimulus for adaptation (Firth et al. 2015; Vancampfort, Probst, et al. 2013). Thus, some participants may have been unable to perform maximally during the post-intervention CRF assessment (Mann et al. 2014). Finally, the heterogeneity of SZ itself, with high interindividual variability in symptom severity, lifestyle behaviours, and comorbidities, likely contributes to the

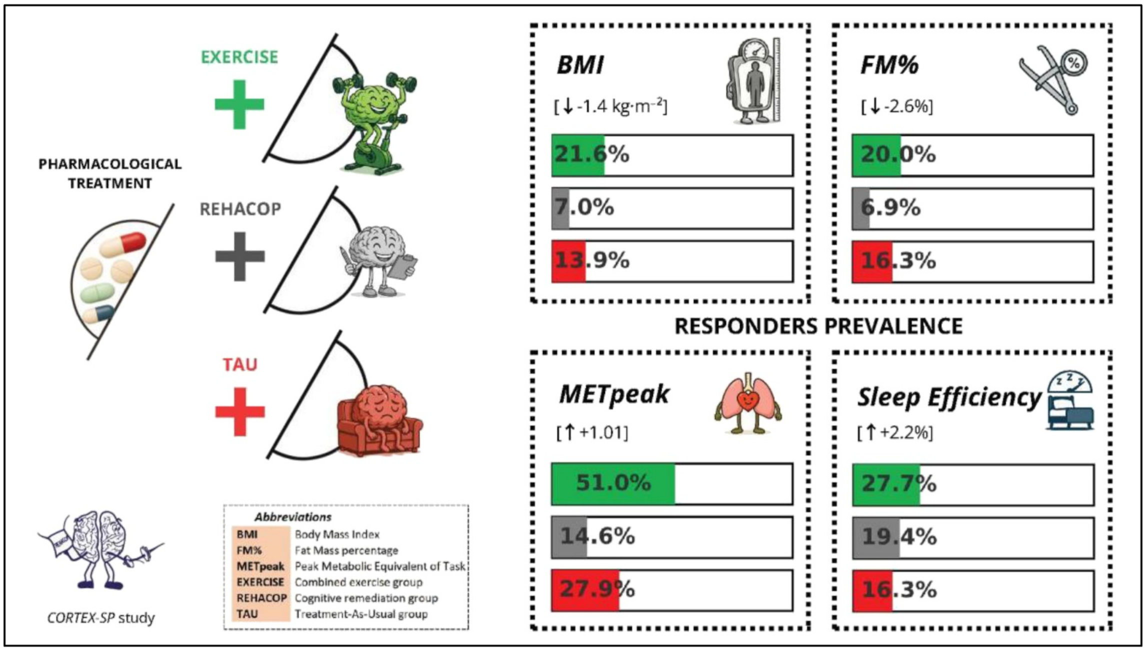

FIGURE 3 | Responders' prevalence after 20-week different intervention programs in people with schizophrenia. 'Responder' was defined as an individual who achieves a clinically meaningful benefit from a treatment or intervention, demonstrating a desirable change in their condition or symptoms [described in brackets].

observed differences in exercise responsiveness (Stubbs et al. 2016; Vancampfort et al. 2017). Importantly, this inter-individual variability is likely influenced by multiple patient-specific factors, including illness duration, baseline physical fitness, symptom severity, pharmacological treatment, and clinical setting. In the present study, however, these variables were explored as potential covariates, and none showed a significant association with responder status. This finding suggests that commonly assessed clinical and demographic factors may not be sufficient on their own to explain variability in intervention response in SZ (Ross et al. 2019).

There was a low prevalence of responders regarding sleep quality in all groups: 27.7% in the EX group, 19.4% in the REHACOP groups, and 16.3% in the TAU group. Importantly, the improvements in sleep efficiency observed in the EX group complement previous reports indicating that exercise positively influences sleep quality, which in turn is a critical determinant of mental and physical health in SZ (Subotnik et al. 2023). Several factors may help explain the relatively low prevalence of responders across groups. First, the participants in the CORTEX-SP trial already presented optimal baseline sleep efficiency (> 85%), and meta-analytic evidence indicates that the magnitude of improvement in sleep outcomes is inversely correlated with baseline levels (Hasan et al. 2022). Indeed, individuals with poorer initial sleep efficiency tend to exhibit greater intervention-related gains, whereas those with relatively high baseline values show limited change due to a 'ceiling effect' (i.e., when already near the upper range, further improvements are unlikely; Hasan et al. 2022). Second, the second-generation antipsychotics are known to improve sleep efficiency, potentially masking the specific contributions of behavioural interventions such as exercise or cognitive remediation (Monti and Monti 2004). Despite these limiting factors, the EX group demonstrated a significant improvement and had the highest prevalence of responders among the three groups (Tous-Espelosin et al. 2023), reinforcing prior evidence that physical activity interventions can effectively enhance sleep quality in individuals with mental disorders (Lederman et al. 2019).

The REHACOP intervention has been shown to improve cognitive outcomes, providing evidence that integrative cognitive remediation has positive effects on primary negative symptoms, creativity, and cognitive variables (Sampedro et al. 2021). In the present study, however, the participants in the REHACOP group did not show improvements in CRF or sleep efficiency, and they exhibited an increase in BMI and FM%. These results may reflect the absence of direct metabolic stimulation from physical activity and highlight that while cognitive remediation is effective for improving neurocognition and functional outcomes (Martini et al. 2024; McGuiness et al. 2025), it does not appear to translate into short-term changes in physical health when delivered in isolation. Nevertheless, it remains plausible that improvements in cognitive domains such as planning, attention, and executive functioning could enhance adherence to physical activity and healthy lifestyle choices over more extended periods (Qi et al. 2023; Tulliani et al. 2022). Thus, the integration of cognitive remediation with exercise interventions may provide synergistic benefits, enabling individuals to sustain their engagement with physical training and maximise improvements in cardiometabolic health. Taken together, these findings reinforce the need for future studies to incorporate a broader range of determinants—including genetic, physiological, behavioural, environmental, and pharmacological factors—to better identify responder profiles and advance precision exercise medicine in this population (Teasdale et al. 2025).

This study has several strengths, including the relatively large sample size ($n = 159$), the application of rigorous methods to assess responder prevalence beyond average group effects, and the high adherence rates (> 85%). The adherence rate observed in the present study is notably higher than that reported in many previous exercise interventions for SZ, which typically range from 60% to 80% (Firth et al. 2015). This high adherence may reflect the supervised nature of the intervention and the integration within community-based mental health services. However, some limitations should be acknowledged: first, this study lacked an intervention group that integrated cognitive remediation and exercise training. Second, the absence of significant group differences in anthropometric measures may be partially explained by the medication side effects or dietary factors which were not controlled in this study. Additionally, although several clinical and pharmacological variables were explored, the study may have been underpowered to detect small-to-moderate associations with responder status. Finally, the higher dropout rate in the TAU group may have influenced between-group comparisons.

5 | Conclusions

This study provides evidence that exercise training is a robust intervention for improving CRF, sleep efficiency, and body composition responsiveness in people with SZ. In contrast, cognitive remediation alone does not directly impact physical health outcomes. Nonetheless, cognitive remediation may serve an important complementary role by enhancing the cognitive capacities necessary for sustaining exercise engagement and lifestyle changes. Together, these findings highlight the need for integrated, multimodal interventions and precision-based approaches to optimise both mental and physical health in individuals with SZ.

Acknowledgements

Our special thanks to Amaia Ortiz de Zarate for all her excellent work in the recruitment and management of the participants. Last but not least, thanks to all the participants for their willingness to engage in this research—which has made this project possible—and to all the undergraduate students who collaborated on this project.

Funding

This study was supported by the Spanish Ministry of Economy and Competitiveness, 'Fondo de Investigación Sanitaria del Instituto de Salud Carlos III' (PI16/01022). The University of the Basque Country supported MT-E with a predoctoral grant (UPV/EHU, PIF19/40). The Council of Vitoria-Gasteiz provides the facilities of the Physical Activity and Health Research Centre for exercise intervention.

Ethics Statement

The study was approved by the Clinical Research Ethics Committee of the Autonomous Region of the Basque Country (PI2017044). The CORTEX-SP study is a randomized, single-blind (medical specialists who evaluated the psychiatric variables) controlled experimental trial (Clinical Trials.gov identifier, NCT03509597).

Consent

Written informed consent was obtained from all participants before any data collection.

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.

References

American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing, Inc.

Atkinson, G., P. Williamson, and A. M. Batterham. 2019. "Issues in the Determination of 'Responders' and 'Non-Responders' in Physiological Research." *Experimental Physiology* 104, no. 8: 1215–1225. https://doi.org/10.1113/EP087712.

Barlati, S., G. Nibbio, A. Bellomo, et al. 2025. "Effectiveness of Cognitive Remediation in Subjects With Major Depressive Disorder: A Multicenter Randomised Controlled Study in a Real-World Setting." *European Psychiatry* 68, no. 1: e106. https://doi.org/10.1192/j.eurpsy.2025.10073.

Bouchard, C., M. A. Sarzynski, T. K. Rice, et al. 2011. "Genomic Predictors of the Maximal O_2 Uptake Response to Standardised Exercise Training Programs." *Journal of Applied Physiology* 110, no. 5: 1160–1170. https://doi.org/10.1152/japplphysiol.00973.2010.

Bull, F. C., S. S. Al-Ansari, S. Biddle, et al. 2020. "World Health Organization 2020 Guidelines on Physical Activity and Sedentary Behaviour." *British Journal of Sports Medicine* 54, no. 24: 1451–1462. https://doi.org/10.1136/bjsports-2020-102955.

Buonocore, M., M. Spangaro, M. Bechi, et al. 2018. "Integrated Cognitive Remediation and Standard Rehabilitation Therapy in Patients of Schizophrenia: Persistence After 5 Years." *Schizophrenia Research* 192: 335–339. https://doi.org/10.1016/j.schres.2017.05.022.

Correll, C. U., M. Solmi, G. Croatto, et al. 2022. "Mortality in People With Schizophrenia: A Systematic Review and Meta-Analysis of Relative Risk and Aggravating or Attenuating Factors." *World Psychiatry* 21, no. 2: 248–271. https://doi.org/10.1002/wps.20994.

De Hert, M., J. Detraux, R. van Winkel, W. Yu, and C. U. Correll. 2011. "Metabolic and Cardiovascular Adverse Effects Associated With Antipsychotic Drugs." *Nature Reviews Endocrinology* 8, no. 2: 114–126. https://doi.org/10.1038/nrendo.2011.156.

Firth, J., J. Cotter, R. Elliott, P. French, and A. R. Yung. 2015. "A Systematic Review and Meta-Analysis of Exercise Interventions in Schizophrenia Patients." *Psychological Medicine* 45, no. 7: 1343–1361. https://doi.org/10.1017/S0033291714003110.

Firth, J., M. Solmi, R. E. Wootton, et al. 2020. "A Meta-Review of 'Lifestyle Psychiatry': The Role of Exercise, Smoking, Diet and Sleep in the Prevention and Treatment of Mental Disorders." *World Psychiatry*19, no. 3: 360–380. https://doi.org/10.1002/wps.20773.

Gallardo-Gómez, D., M. Noetel, F. Álvarez-Barbosa, et al. 2023. "Exercise to Treat Psychopathology and Other Clinical Outcomes in Schizophrenia: A Systematic Review and Meta-Analysis." *European Psychiatry* 66, no. 1: e40. https://doi.org/10.1192/j.eurpsy.2023.24.

Goldfarb, M., M. De Hert, J. Detraux, et al. 2022. "Severe Mental Illness and Cardiovascular Disease: JACC State-of-the-Art Review." *Journal of the American College of Cardiology* 80, no. 9: 918–933. https://doi.org/10.1016/j.jacc.2022.06.017.

Halstead, S., C. X. Yap, N. Warren, et al. 2025. "Holistic Prevention and Management of Physical Health Side-Effects of Psychotropic Medication: Second Report of the Lancet Psychiatry Physical Health Commission." *Lancet Psychiatry* 12, no. 9: 673–699. https://doi.org/10.1016/S2215-0366(25)00162-2.

Hasan, F., Y. Tu, C. Lin, et al. 2022. "Comparative Efficacy of Exercise Regimens on Sleep Quality in Older Adults: A Systematic Review and Network Meta-Analysis." *Sleep Medicine Reviews* 65: 101673. https://doi.org/10.1016/j.smrv.2022.101673.

Hopkins, W. G. 2000. "Measures of Reliability in Sports Medicine and Science." *Sports Medicine* 30, no. 1: 1–15. https://doi.org/10.2165/00007256-200030010-00001.

Lederman, O., P. B. Ward, J. Firth, et al. 2019. "Does Exercise Improve Sleep Quality in Individuals With Mental Illness? A Systematic Review and Meta-Analysis." *Journal of Psychiatric Research* 109: 96–106. https://doi.org/10.1016/j.jpsychires.2018.11.004.

Mann, T. N., R. P. Lamberts, and M. I. Lambert. 2014. "High Responders and Low Responders: Factors Associated With Individual Variation in Response to Standardised Training." *Sports Medicine* 44, no. 8: 1113–1124. https://doi.org/10.1007/s40279-014-0197-3.

Martini, F., M. Spangaro, M. Bechi, et al. 2024. "Improving Outcome of Treatment-Resistant Schizophrenia: Effects of Cognitive Remediation Therapy." *European Archives of Psychiatry and Clinical Neuroscience* 274, no. 6: 1473–1481. https://doi.org/10.1007/s00406-023-01731-6.

McGrath, J., and R. L. Hayes. 2000. "Cognitive Rehabilitation for People With Schizophrenia and Related Conditions." *Cochrane Database of Systematic Reviews* 2000, no. 3: CD000968. https://doi.org/10.1002/14651858.CD000968.

McGuiness, A., L. Travethan, K. Irvin, et al. 2025. "The Potential of Cognitive Remediation Therapy for Improving the Communication Capabilities of Adults With Schizophrenia and Other Psychotic Spectrum Disorders." *International Journal of Language & Communication Disorders* 60, no. 1: e13141. https://doi.org/10.1111/1460-6984.13141.

Monti, J. M., and D. Monti. 2004. "Sleep in Schizophrenia Patients and the Effects of Antipsychotic Drugs." *Sleep Medicine Reviews* 8, no. 2: 133–148. https://doi.org/10.1016/S1087-0792(02)00158-2.

Perez-Cruzado, D., A. Cuesta-Vargas, E. Vera-Garcia, and F. Mayoral-Cleries. 2018. "Medication and Physical Activity and Physical Fitness in Severe Mental Illness." *Psychiatry Research* 267: 19–24. https://doi.org/10.1016/j.psychres.2018.05.055.

Pillinger, T., R. A. McCutcheon, L. Vano, et al. 2020. "Comparative Effects of 18 Antipsychotics on Metabolic Function in Patients With Schizophrenia, Predictors of Metabolic Dysregulation, and Association With Psychopathology: A Systematic Review and Network Meta-Analysis." *Lancet Psychiatry* 7, no. 1: 64–77. https://doi.org/10.1016/S2215-0366(19)30416-X.

Qi, Y., Z. Zhang, X. Fu, et al. 2023. "Adherence to a Healthy Lifestyle and Its Association With Cognitive Impairment in Community-Dwelling Older Adults in Shanghai." *Frontiers in Public Health* 11: 1291458. https://doi.org/10.3389/fpubh.2023.1291458.

Rahmati, M., H. Lee, H. Lee, et al. 2025. "Associations Between Exercise Training, Physical Activity, Sedentary Behaviour and Mortality: An Umbrella Review of Meta-Analyses." *Journal of Cachexia, Sarcopenia and Muscle* 16, no. 2: e13772. https://doi.org/10.1002/jcsm.13772.

Ross, R., B. H. Goodpaster, L. G. Koch, et al. 2019. "Precision Exercise Medicine: Understanding Exercise Response Variability." *British Journal of Sports Medicine* 53, no. 18: 1141–1153. https://doi.org/10.1136/bjsports-2018-100328.

Sampedro, A., N. Ibarretxe-Bilbao, J. Peña, et al. 2023. "Analysing Structural and Functional Brain Changes Related to an Integrative Cognitive Remediation Program for Schizophrenia: A Randomised Controlled Trial." *Schizophrenia Research* 255: 82–92. https://doi.org/10.1016/j.schres.2023.03.021.

Sampedro, A., J. Peña, P. Sánchez, et al. 2021. "Cognitive, Creative, Functional, and Clinical Symptom Improvements in Schizophrenia After an Integrative Cognitive Remediation Program: A Randomised Controlled Trial." *NPJ Schizophrenia* 7, no. 1: 52. https://doi.org/10.1038/s41537-021-00181-0.

Sampedro, A., J. Peña, P. Sánchez, et al. 2025. "Theory-of-Mind Improvement in Schizophrenia After Integrative Cognitive Remediation: Which Patients Benefit More?" *Schizophrenia Research: Cognition* 42: 100380. https://doi.org/10.1016/j.scog.2025.100380.

Sethi, S., D. Wakeham, T. Ketter, et al. 2024. "Ketogenic Diet Intervention on Metabolic and Psychiatric Health in Bipolar and Schizophrenia: A Pilot Trial." *Psychiatry Research* 335: 115866. https://doi.org/10.1016/j.psychres.2024.115866.

Shu, X., Y. Dai, J. Tang, Y. Huang, R. Hu, and Y. Lin. 2024. "Cognitive Rehabilitation in Schizophrenia Research: A Bibliometric and Visualisation Analysis." *Frontiers in Psychiatry* 15: 1509539. https://doi.org/10.3389/fpsyt.2024.1509539.

Stubbs, B., J. Firth, A. Berry, et al. 2016. "How Much Physical Activity Do People With Schizophrenia Engage In? A Systematic Review, Comparative Meta-Analysis and Meta-Regression." *Schizophrenia Research* 176, no. 2–3: 431–440, S0920-9964(16)30241-9 [pii]. https://doi.org/10.1016/j.schres.2016.05.017.

Stubbs, B., D. Vancampfort, M. Hallgren, et al. 2018. "EPA Guidance on Physical Activity as a Treatment for Severe Mental Illness: A Meta-Review of the Evidence and Position Statement From the European Psychiatric Association (EPA), Supported by the International Organization of Physical Therapists in Mental Health (IOPTMH)." *European Psychiatry* 54: 124–144. https://doi.org/10.1016/j.eurpsy.2018.07.004.

Subotnik, K. L., S. C. McEwen, J. Ventura, et al. 2023. "Exercise Predicts a Good Night's Sleep: Preliminary Findings From a UCLA Study of First-Episode Schizophrenia." *Behavioral Sciences* 13, no. 2: 88. https://doi.org/10.3390/bs13020088.

Taylor, R., M. Cella, and T. Wykes. 2025. "Cognitive Remediation Is an Evidence-Based Psychological Therapy: Isn't It Time It Was Treated Like One?" *Behavior Modification* 49, no. 5–6: 1454455251343303. https://doi.org/10.1177/01454455251343303.

Teasdale, S. B., K. K. Machaczek, W. Marx, et al. 2025. "Implementing Lifestyle Interventions in Mental Health Care: Third Report of the Lancet Psychiatry Physical Health Commission." *Lancet Psychiatry* 12, no. 9: 700–722. https://doi.org/10.1016/S2215-0366(25)00170-1.

Tous-Espelosin, M., S. R. de Azua, N. Iriarte-Yoller, et al. 2021. "Clinical, Physical, Physiological, and Cardiovascular Risk Patterns of Adults With Schizophrenia: CORTEX-SP Study: Characterisation of Adults With Schizophrenia." *Psychiatry Research* 295: 113580, S0165-1781(20)33241-8 [pii]. https://doi.org/10.1016/j.psychres.2020.113580.

Tous-Espelosin, M., C. Pavon, E. Elizagarate, A. Sampedro, and S. Maldonado-Martín. 2024. "As We Were and as We Should be, Combined Exercise Training in Adults With Schizophrenia: CORTEX-SP Study Part II." *Scandinavian Journal of Medicine & Science in Sports* 34, no. 8: e14707. https://doi.org/10.1111/sms.14707.

Tous-Espelosin, M., S. Ruiz de Azua, N. Iriarte-Yoller, P. M. Sanchez, E. Elizagarate, and S. Maldonado-Martín. 2023. "As We Were and as We Should be, Combined Exercise Training in Adults With Schizophrenia: CORTEX-SP Study Part I." *Medicine & Science in Sports & Exercise* 56, no. 1: 73–81. https://doi.org/10.1249/MSS.0000000000003284.

Tulliani, N., M. Bissett, P. Fahey, R. Bye, and K. P. Y. Liu. 2022. "Efficacy of Cognitive Remediation on Activities of Daily Living in Individuals With Mild Cognitive Impairment or Early-Stage Dementia: A Systematic Review and Meta-Analysis." *Systematic Reviews* 11, no. 1: 156. https://doi.org/10.1186/s13643-022-02032-0.

Vancampfort, D., M. Probst, T. Scheewe, et al. 2013. "Relationships Between Physical Fitness, Physical Activity, Smoking and Metabolic and Mental Health Parameters in People With Schizophrenia." *Psychiatry Research* 207, no. 1–2: 25–32. https://doi.org/10.1016/j.psychres.2012.09.026.

Vancampfort, D., S. Rosenbaum, F. Schuch, et al. 2017. "Cardiorespiratory Fitness in Severe Mental Illness: A Systematic Review and Meta-

Analysis." *Sports Medicine* 47, no. 2: 343–352. https://doi.org/10.1007/s40279-016-0574-1.

Vancampfort, D., M. Wampers, A. J. Mitchell, et al. 2013. "A Meta-Analysis of Cardio-Metabolic Abnormalities in Drug Naïve, First-Episode and Multi-Episode Patients With Schizophrenia Versus General Population Controls." *World Psychiatry* 12, no. 3: 240–250. https://doi.org/10.1002/wps.20069.

Vita, A., S. Barlati, A. Ceraso, et al. 2021. "Effectiveness, Core Elements, and Moderators of Response of Cognitive Remediation for Schizophrenia: A Systematic Review and Meta-Analysis of Randomised Clinical Trials." *JAMA Psychiatry* 78, no. 8: 848–858. https://doi.org/10.1001/jamapsychiatry.2021.0620.

Vita, A., S. Barlati, A. Ceraso, et al. 2024. "Durability of Effects of Cognitive Remediation on Cognition and Psychosocial Functioning in Schizophrenia: A Systematic Review and Meta-Analysis of Randomised Clinical Trials." *American Journal of Psychiatry* 181, no. 6: 520–531. https://doi.org/10.1176/appi.ajp.20230396.