

Does higher cardiorespiratory fitness impact the clinical symptoms in individuals with schizophrenia? A tertiary analysis of the CORTEX-SP study

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Published online: July 31, 2023

(Accepted for publication July 15, 2023)

DOI:10.7752/jpes.2023.07204

Abstract:

Problem statement and purpose: Cardiorespiratory fitness (CRF) is recognized as a modifiable risk factor that can help reduce the risk of non-communicable diseases, and as such, it serves as a crucial reference for vital signs. Moreover, it has been found to have a negative association with clinical symptoms. Nevertheless, the specific impact of each variable on the clinical symptoms of schizophrenia (SP) remains unclear. Therefore, the objective of this study was to examine the predictive significance of CRF and body composition concerning clinical symptom factors in the population with SP. **Approach:** Body composition, specifically body mass index (BMI), and CRF, measured as peak oxygen uptake from the cardiopulmonary exercise test, were evaluated in all participants (n = 122, 41.6 ± 10.3 years old, 16.7% women). The psychopathology of the participants was assessed using the Brief Negative Symptom Scale and the Positive and Negative Syndrome Scale. Correlations, including Spearman's Rho and Pearson's *r*, were conducted to examine the relationships between sociodemographic factors, symptoms, and BMI. Stepwise Multiple Regression analyses were then employed to identify the variables that can predict CRF. **Results:** The correlations revealed a negative association between negative symptoms and peak oxygen uptake ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) ($B = -0.252$; $P < 0.001$). The regression analysis showed that lower peak oxygen uptake ($\text{L} \cdot \text{min}^{-1}$) ($P < 0.001$) and higher BMI ($P = 0.019$) were predictors of negative symptoms, explaining 22.8% of the variance ($R^2 = 22.8\%$; $F = 8.067$; $P < 0.001$). Additionally, lower peak oxygen uptake ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) ($P = 0.016$) predicted general symptoms ($R^2 = 12.3\%$; $F = 5.135$; $P = 0.002$), and lower peak oxygen uptake ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) ($P = 0.001$) predicted total symptoms ($R^2 = 17.8\%$; $F = 7.928$; $P < 0.001$). **Conclusions:** Given the significant associations observed between CRF and BMI with negative symptoms, and CRF with general and total symptoms, it becomes evident that enhancing physical health through exercise and adopting a healthy diet may serve as crucial adjunctive treatments for managing SP disorder.

Keywords: negative, physical fitness, prediction, exercise

Introduction

Schizophrenia (SP) is a severe mental disorder characterized by the presence of positive symptoms (*i.e.*, hallucinations and delusions) and negative symptoms (*i.e.*, affect flattening, poverty of speech, lack of motivation, and social withdrawal). Additionally, individuals with SP often experience neurocognitive deficits in perception, memory, and attention, which contributes to SP being one of the leading causes of disability (Strassnig et al., 2015). Individuals with SP have a reduced life expectancy, with a mortality rate 2–3-fold higher than that for the general population (Laursen et al., 2012). Cardiovascular disease is the most common illness in this population, and there is also an increased rate of suicide (Olfson et al., 2015). Unhealthy lifestyle habits, including physical inactivity (Stubbs et al., 2016), unhealthy diet, smoking, alcohol and/or caffeine abuse (Ratliff et al., 2012), contribute significantly to the presence of cardiovascular risk factors such as obesity and low cardiorespiratory fitness (CRF) (Tous-Espelosin et al., 2021). These factors, along with the adverse effects of

medications (Mukundan et al., 2010) and socioeconomic factors such as access to healthcare (Correll et al., 2014), exacerbate the health challenges faced by individuals with SP.

According to different clinical guidelines, it is recommended to control and assess cardiovascular risk in patients with SP (American Diabetes Association et al., 2004; De Hert et al., 2009; Saiz Ruiz et al., 2008). In addition to traditional parameters, CRF (*i.e.* the ability of the cardiorespiratory system to transport oxygen to the muscles) measured as peak oxygen uptake ($\dot{V}O_{2peak}$) is considered a modifiable risk factor to reduce the risk of non-communicable diseases and is already recognized as an important health indicator (Despres, 2016; Kaminsky et al., 2019). Poor CRF levels have been linked to an increased mortality risk independently of other clinical risk factors (Despres, 2016). Moreover, previous studies have identified CRF as a critical factor influencing cognitive function (España-Irla et al., 2021). Several qualitative (Johnstone et al., 2009; McDevitt et al., 2006) and quantitative (Vancampfort et al., 2012) reviews have examined the benefits of physical activity in relation to psychiatric symptoms, highlighting the need for further research in prospective studies and interventions to improve modifiable variables. It appears that negative symptoms, such as anhedonia and avolition, significantly contribute to physical inactivity in patients with SP. Therefore, special attention should be given not only to the presence of cardiometabolic comorbidities but also to negative symptoms (Vancampfort et al., 2012). However, other potential factors derived from theories and models should be evaluated to better explain CRF in patients with SP.

In a study conducted with individuals diagnosed with SP, a backward linear regression analysis was performed to predict $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). The results revealed that a low CRF level was associated with the severity of negative symptoms and higher BMI. This suggests a bidirectional relationship, indicating that interventions aimed at increasing CRF and decreasing BMI may also lead to a reduction in negative symptoms (Rimes et al., 2015; Scheewe et al., 2019) and ultimately improve the overall quality of life (Pavlova et al., 2017). However, despite these findings, the specific influence of each variable on the clinical symptoms of this pathology is not yet fully understood. Therefore, the primary objective of this study was to analyze and assess the predictive value of CRF and BMI on clinical symptom factors in the SP population.

Materials and methods

Participants

Data for the baseline-tertiary analysis in the CORTEX-SP study were collected between May 2018 and March 2021 in Vitoria-Gasteiz (Basque Country, Spain). All participants ($n = 122$, 41.6 ± 10.3 years old, 16.7% women) were recruited from the Psychiatric Hospital of Alava and the Mental Health Network located in Alava, Basque Country, Spain. The patients in the study met the diagnostic criteria for SP according to DSM-5 (American Psychiatric Association, 2013). The inclusion and exclusion criteria of the study have been previously published (Sampedro et al., 2020; Tous-Espelosin et al., 2021).

The Research Ethics Committee of the Basque Country (PI2017044) approved this study, and all participants signed the informed consent before any data collection commenced (Clinical Trials.gov identifier, NCT03509597).

Measures

Age, sex, and cigarette smoking status were collected through self-report from the participants. All medications prescribed to the participants were documented and converted into chlorpromazine-equivalents using the defined daily dose method (Leucht et al., 2016; Rothe et al., 2018).

Stature and body mass measurements were taken, and BMI was calculated by dividing the total body mass by the square of the height (kg/m^2).

For CRF measurement, a symptom-limited cardiopulmonary exercise test was conducted using an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, Netherlands). The detailed protocol and procedures for this assessment have been previously published in the first baseline paper, providing an initial characterization of the sample (Tous-Espelosin et al., 2021).

Clinical symptoms were assessed using two scales: the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011). The PANSS scale comprises 30 items, with seven items related to positive (psychotic) symptoms, seven items to negative symptoms (*i.e.*, blunted affect and abstract thinking), and 16 items to general psychopathology. Each item is rated on a scale from 1 (none) to 7 (extremely severe), with higher scores indicating greater symptom severity. The sum of the ratings for each item is calculated to obtain the score for each subscale, ranging from 7 to 49 for positive and negative subscales, and from 16 to 112 for the general psychopathology subscale (Peralta & Cuesta, 1994). The BNSS is used to assess the severity of negative symptoms (Marder et al., 1997). It consists of 13 items, rated on a seven-point scale from 0 (normal) to 6 (extremely severe). The items are further categorized into six subscales: anhedonia, distress, asociality, avolition, blunted affect, and alogia. The ratings are based on a semi-structured interview. The Spanish version of the BNSS has been validated (Mane et al., 2014), and the total knowledge of mental disorder score was obtained through the three general items of the scale (*i.e.*, awareness of the mental disorder, awareness of the effects of medication, and awareness of the social consequences of the disorder).

Total symptoms (*i.e.*, the sum of positive, negative, and general symptoms), general symptoms, and positive symptoms were derived from the PANSS scale. To assess negative symptoms, the BNSS was utilized instead of the negative PANSS subscale, following the recommendation of the NIMH-MATRICES Consensus Statement on Negative Symptoms (Carpenter et al., 2016; Kirkpatrick et al., 2006).

Statistical analysis

Statistical analysis involved performing the Shapiro–Wilk test to determine normality. It was observed that, except for the PANSS positive subscale and $\dot{V}O_{2peak}$, all other variables were normally distributed. Spearman's Rho and Pearson's r correlations were conducted to explore the relationships between sociodemographic factors, symptoms, and BMI variables. Additionally, Stepwise Multiple Regression analyses were performed to identify the variables predicting CRF. To assess multicollinearity in the regression analyses, variance inflation factor and tolerance statistics were used. According to Kleinbaum et al. (1988), a variance inflation factor ≥ 10 and tolerance ≤ 0.10 would indicate collinearity problems (Kleinbaum et al., 1988). No multicollinearity (based on tolerance and variance inflation factor statistics) among measures was found. The significance level was set at 0.05. All tests were two-tailed.

Results

The characterization of the sample, including clinical, physical, and physiological variables along with descriptive data (Table 1), has been previously presented (Tous-Espelosin et al., 2021).

Table 1. Characteristics of the studied population. The values are presented as means $\pm$ standard deviation or percentages (%)

Variables	n = 122
Age (yrs)	41.7 $\pm$ 10.3
Cigarette smoking/day	11.6 $\pm$ 12.1
Medication dosage (mg/day)	483.3 $\pm$ 287.2
Total PANSS	73.9 $\pm$ 18.5
General PANSS	36.4 $\pm$ 10.6
Positive PANSS	15.3 $\pm$ 6.0
Negative PANSS	22.2 $\pm$ 6.6
BNSS	31.8 $\pm$ 14.6
BMI (kg/m ²)	28.7 $\pm$ 5.3
$\dot{V}O_{2peak}$ (mL·kg ⁻¹ ·min ⁻¹)	23.6 $\pm$ 7.4
$\dot{V}O_{2peak}$ (L·min ⁻¹)	1.97 $\pm$ 0.62

Note. BMI = body mass index, BNSS = brief negative symptom scale, PANSS = positive and negative syndrome scale, $\dot{V}O_{2peak}$ = peak oxygen uptake

Correlation analyses were conducted between clinical symptoms, BMI, and CRF (Table 2). Spearman's rho correlation coefficients showed an inverse relationship between negative symptoms and $\dot{V}O_{2peak}$ (mL·kg⁻¹·min⁻¹) ($B = -0.252$; $P < 0.001$). However, no significant correlation coefficients were found with total, general, and positive symptoms.

Table 2. Correlations between clinical symptoms, body composition, and cardiorespiratory fitness

Variables	Total symptoms	General symptoms	Positive symptoms	Negative symptoms
$\dot{V}O_{2peak}$ (L·min ⁻¹)	-.134	-.106	-.108	-.181
$\dot{V}O_{2peak}$ (mL·kg ⁻¹ ·min ⁻¹)	-.134	-.081	-.067	-.252**
BMI	.033	-.033	-.050	.154

Note. BMI, body mass index; $\dot{V}O_{2peak}$, peak oxygen uptake. Values * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Regression analyses were performed, including only those BMI and CRF variables that negatively and significantly correlated with each clinical symptom (Table 3), while controlling for sociodemographic variables (age and sex). Lower $\dot{V}O_{2peak}$ (L·min⁻¹) ($P < 0.001$) and higher BMI ($P = 0.019$) predicted negative symptoms ($R^2 = 22.8\%$; $F = 8.067$; $P < 0.001$). No variables predicted positive symptoms ($F = 2.151$; $P = 0.121$). Lower $\dot{V}O_{2peak}$ (mL·kg⁻¹·min⁻¹) ($P = 0.016$) predicted general symptoms ($R^2 = 12.3\%$; $F = 5.135$; $P = 0.002$), and lower $\dot{V}O_{2peak}$ (mL·kg⁻¹·min⁻¹) ($P = 0.001$) predicted total symptoms ($R^2 = 17.8\%$; $F = 7.928$; $P < 0.001$).

Table 3. Regression models for the prediction of clinical symptoms

Variable	R^2	R^2_{change}	B	t	P	Predictors
Negative symptoms	22.8%	11.1% 4%	-.373 .202	-4.086 2.384	<0.001 0.019	$\dot{V}O_{2peak}$ (L·min ⁻¹) BMI
Positive symptoms	19.3%	2%				x
General symptoms	12.3%	4.8%	-.232	-2.454	0.016	$\dot{V}O_{2peak}$ (mL·kg ⁻¹ ·min ⁻¹)
Total symptoms	17.8%	8.9%	-.315	-3.455	0.001	$\dot{V}O_{2peak}$ (mL·kg ⁻¹ ·min ⁻¹)

Note. BMI = body mass index, $\dot{V}O_{2peak}$ = peak oxygen uptake, R^2 = coefficient of determination

Discussion

Although the population in this study has been previously characterized (Tous-Espelosin et al., 2021), to our knowledge, this is the first study to examine the predictive value of CRF and BMI on clinical symptom factors in a cohort of individuals with SP. The main findings from this study were as follows: 1) individuals with lower CRF also exhibited a higher presence of negative symptoms; 2) after regression analysis, CRF emerged as the best predictor of negative symptoms, indicating that SP patients with higher CRF were less likely to experience severe negative symptoms; 3) the BMI variable also contributed to predicting negative symptoms in conjunction with CRF. The participants in this study demonstrated overweight values as assessed by BMI ($>25 \text{ kg/m}^2$) (Khan et al., 2018), low levels of $\dot{V}O_{2\text{peak}}$ ($<25 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) (Kaminsky et al., 2017) attributed to a predominantly unhealthy lifestyle (Correll et al., 2014; Ratliff et al., 2012; Stubbs et al., 2016), and adverse drug effects (*i.e.*, body mass gain and metabolic syndrome) (Mukundan et al., 2010).

Treatment with antipsychotic drugs, applied as first-line therapy, typically leads to a reduction of positive symptoms with minimal impact on negative and cognitive symptoms (Gold, 2004). Therefore, the question addressed in this study was whether higher physical fitness positively affects clinical symptoms in individuals with SP. Previous research has indicated a strong association between reduced CRF in SP patients and negative and cognitive symptoms (Vancampfort et al., 2012; Vancampfort et al., 2013). The findings of this study align with previous research (Scheewe et al., 2013; Scheewe et al., 2019) because individuals with higher relative $\dot{V}O_{2\text{peak}}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) displayed lower total scores ($P = 0.001$) and general subscale scores ($P = 0.016$) in the PANSS. Additionally, those with higher absolute $\dot{V}O_{2\text{peak}}$ ($\text{L}\cdot\text{min}^{-1}$) exhibited lower negative symptom scores ($P > 0.001$). This suggests that exercise interventions that increase CRF, such as aerobic high-intensity interval training (Andersen et al., 2020; Brobakken et al., 2020; Heggelund et al., 2011), may be highly relevant as adjuvant programs for individuals with SP. However, it is crucial to exercise caution in this assertion since improvements in negative symptoms through pharmacological treatment may also lead to increased CRF because individuals become more active, engaged, and motivated to participate in physical activity programs.

In this study, $\dot{V}O_{2\text{peak}}$ ($\text{L}\cdot\text{min}^{-1}$) and BMI significantly explained 11.1% ($P < 0.001$) and 4% ($P = 0.019$) of the variance in negative symptoms, respectively, resulting in a total prediction of 22.8%. Furthermore, $\dot{V}O_{2\text{peak}}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) explained 12.3% and 17.8% of the variance in general and total symptoms, respectively. While the range of 11.1–17.8% may appear modest in the prediction of clinical symptoms through CRF, particularly with the gold standard parameter ($\dot{V}O_{2\text{peak}}$), the influence of this variable should not be underestimated. Previous studies in people with SP have shown a potential bidirectional association between CRF and state-sensitive cognitive functions (Holmen et al., 2018), PANSS symptomatology (Curcic et al., 2017), and the severity of negative symptoms (Scheewe et al., 2019; Vancampfort et al., 2012). Although the design of this study does not permit establishing causal pathways between CRF and cognition or symptomatology, there is promising evidence on the endocrine crosstalk between skeletal muscle and the brain through exercise (Delezie & Handschin, 2018; Huang et al., 2021; Isaac et al., 2021). Recent investigations have revealed biological and molecular pathways affected by exercise in individuals with SP, shedding light on the underlying mechanisms of anhedonia, one of the main negative symptoms of this disorder (Vallejo-Curto et al., 2021). The physical activity program in SP patients appeared to regulate the ubiquitin–proteasome system, including proteins involved in neuronal and neuroinflammatory regulation, as well as cytoskeleton proteins of cells (Vallejo-Curto et al., 2021).

Previous research in individuals with SP has demonstrated an association between higher BMI and lower CRF (Scheewe et al., 2019). In our current study, BMI provided an additional 4% contribution to predicting negative symptoms, along with CRF. This underscores the importance of improving physical health, as seen by the decrease in the combination of overweight/obesity with low CRF, highlighting the need for lifestyle changes, such as adopting a healthy diet and engaging in regular physical activity, to better manage clinical symptoms in this population. Given the aforementioned findings, it is crucial to consider CRF for both assessing the physical condition status of people with SP and implementing exercise interventions aimed at increasing CRF, which may lead to a likely improvement in disease symptoms.

This study has several strengths. Despite the challenges in recruiting participants with a mental dysfunction, we managed to assemble a relatively large and highly representative sample ($n = 122$) of the SP population, with most patients recruited from community mental health centers in the same city. The results can be a valuable tool for understanding which variables have the most significant influence on clinical symptoms in individuals with SP. However, we should acknowledge certain limitations: 1) symptoms can affect each individual differently, and their direct relationship during the exercise test evaluation may vary, and 2) the cross-sectional nature of the study limits the establishment of causal relationships between the studied variables.

Conclusions

Individuals with lower CRF demonstrated a higher presence of negative symptoms. CRF emerged as the most potent predictor of negative symptoms, indicating that SP patients with higher CRF were less likely to experience severe negative symptoms. Additionally, the BMI variable contributed to predicting negative symptoms along with CRF. Considering the remarkable association of CRF and BMI with negative symptoms, and CRF with general and total symptoms, improving physical health through exercise and a healthy diet could

serve as an essential adjuvant treatment for managing SP disorder. These findings hold the potential to enhance comprehensive treatment strategies for individuals with SP.

Acknowledgments

Special thanks are extended to Amaia Ortiz de Zarate for her exceptional work in participant recruitment and management, as well as to Dr. Iñaki Arratibel-Imaz for his invaluable assistance and professionalism in conducting the laboratory testing. We would also like to express our gratitude to the Vitoria-Gasteiz City Council for providing essential facilities at the Physical Activity and Health Research Center for conducting the exercise intervention. We thank all of the participants whose willingness made this project possible, the undergraduate students who collaborated on this project, and IJB7 for his selfless friendship.

Declaration of Interest statement

The authors have no conflicts of interest to declare.

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