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EJERCICIO FÍSICO COMBINADO EN PERSONAS CON ESQUIZOFRENIA: ESTUDIO CORTEX-SP

COMBINED EXERCISE IN PEOPLE WITH SCHIZOPHRENIA: CORTEX-SP STUDY

Mikel Tous Espelosín

Dra. Sara Maldonado Martín
Dra. Sonia Ruiz de Azua

A Pedro, Gabina, Anne, Xabi y familia,
por haberme hecho quien soy.

A Imanol,
por seguir volando juntos.

A la kuadrilla, amigos y amigas,
la familia que volvería a elegir.

A Sara,
por haber confiado en mí.

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AUTHOR

MIKEL TOUS ESPELOSIN

SUPERVISORS

Sara Maldonado-Martín Ph.D.

Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), University of the Basque Country

Sonia Ruiz de Azua Ph.D.

Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), University of the Basque Country

DEPARTMENT

Department of Physical Education and Sport

Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), University of the Basque Country

"No importa lo lento que vayas mientras no pares, y si te encuentras con una curva, acelera."

Anónimo

"La satisfacción radica en el esfuerzo, no en el logro. El esfuerzo es la victoria."

Mahatma Gandhi

"La mejor red social siempre fue un café."

Anónimo

"Todo largo camino requiere de esfuerzo y sacrificio que serán tus fieles compañeros, y aunque la distancia nos separe, siempre encontrarás apoyo en aquellos que admiramos tu dedicación."

Anónimo

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DECLARACIÓN

El autor de esta tesis doctoral ha participado en todo el proceso de investigación, desde el diseño hasta el producto final en forma de publicaciones y contribuciones en congresos. Para ello, ha revisado la bibliografía existente, participado en el diseño de las intervenciones y en su puesta en práctica, así como en las distintas valoraciones y en la obtención y análisis de datos, y ha tratado de hacer una buena discusión tras haber interpretado los resultados en profundidad. Por otro lado, ha sido responsable, junto con las directoras de la tesis doctoral, del proceso de divulgación en forma de publicación de artículos en revistas científicas.

Este trabajo no podría haberse llevado a cabo sin la supervisión de la tutora y directoras del mismo, quienes han sido parte activa durante todo el proceso, y han contado con la participación de alumnado de grado en prácticas obligatorias y de posgrado, así como de colaboradores externos que han participado en la valoración de las personas participantes para su inclusión en el estudio.

La investigación se ha llevado a cabo en instalaciones y con recursos de la Universidad del País Vasco/ Euskal Herriko Unibertsitatea (UPV/EHU), Facultad de Educación y Deporte (Sección Ciencias de la Actividad Física y del Deporte) y del Departamento de Educación Física y Deportiva de la UPV/EHU. Además, la intervención con el ejercicio físico se realizó en las instalaciones del Centro de Investigación en Actividad Física y Salud cedido por el Ayuntamiento de Vitoria-Gasteiz a la UPV/EHU. Las becas de la Universidad del País Vasco (UPV/EHU, PIF19/40) así como el "Fondo de Investigación Sanitaria del Instituto de Salud Carlos III" (PI16/01022) del Ministerio de Economía y Competitividad de España han ayudado en la financiación de la investigación. El Instituto de Investigación Biosanitaria de Bioaraba, ha colaborado durante el proyecto en el análisis de datos estadísticos y difusión de resultados.

No ha existido conflicto de interés alguno a la hora de realizar esta investigación, y las becas y ayudas no han repercutido en los resultados obtenidos y presentados.

RECOMENDACIONES PARA LA LECTURA

La presente tesis doctoral se ha realizado en formato de "*tesis por compendio de artículos científicos*". Por ello, quiero destacar que a pesar de que las publicaciones estén adjuntas en modo de anexos en el último apartado del presente trabajo (debido a las especificaciones de formato requeridas por la universidad), estas son la parte central y principal sobre la que se sustenta la tesis.

Para seguir el hilo de los contenidos que forman este trabajo, es necesario seguir el orden que se describe a continuacion. Se debe partir de la introducción y marco teórico, presentes en el primer capítulo, que sirven como justificación de la necesidad de este proyecto, dan unión y cohesion a los apartados siguientes y establecen el estado de la cuestión referente a la temática tratada.

A continuación, se seguirá con el segundo capítulo en el que se presentan los objetivos e hipótesis de la tesis doctoral, para así pasar al tercer capítulo en el que se abordan las herramientas metodológicas utilizadas.

Llegados a este punto, se debe complementar el cuarto capítulo, donde se resumen los resultados obtenidos y la discusión de cada artículo, con el séptimo capítulo, en el cual se encuentran las publicaciones completas en su fomato original y se expone de manera más específica, tanto la metodología utilizada, como los resultados de cada estudio de manera completa.

Tal y como indica la estructura que ordena la universidad, en el quinto capítulo se muestran las referencias bibliográficas utilizadas a los largo de todo el texto, y en el sexto capítulo se presentan las conclusiones de la tesis doctoral.

Se trata de una tesis internacional, por lo que a lo largo de este documento, el texto se va a encontrar escrito en dos lenguas, castellano e inglés. A continuación, se podrán leer dos listas de abreviaciones, una para los acrónimos utilizados en los apartados escritos en castellano y otra para los utilizados en inglés**.**

ABREVIACIONES

AF: actividad física

CCR: capacidad cardiorrespiratoria

CdV: calidad de vida

CPET: del inglés, cardiopulmonary exercise test

CT: colesterol total

DLP: dislipidemia

DM: diabetes mellitus

DSM: del inglés, Diagnostic and Statistical Manual of Mental Disorders

ECV: enfermedad cardiovascular

EF: ejercicio físico

EV: edad vascular

GEF: grupo de ejercicio físico

FITT: frecuencia, intensidad, tipo y tiempo

FC: frecuencia cardiaca

FHS: del inglés, Framingham Heart Study

HC: muestra de personas sanas

HDL-C: colesterol de lipoproteínas de alta densidad

HIIT: entrenamiento interválico de alta intensidad

HTA: hipertensión arterial

IMC: índice de masa corporal

JCR: del inglés, Journal Citation Reports

LDL-C: colesterol de lipoproteínas de baja densidad

LV-HIIT: entrenamiento interválico de alta intensidad y bajo volumen

MET: equivalente metabólico

MSWT: del inglés, Modified Shuttle Walk Test

ObME: obesidad metabólicamente enferma

ObMS: obesidad metabólicamente sana

OMS: Organización Mundial de la Salid

TA: tensión arterial

TAD: tensión arterial diastólica

TAS: tensión arterial sistólica

TH: tratamiento habitual

RCV: riesgo cardiovascular

SCORE2: del inglés, Systematic Coronary Risk Estimation

SF-36: del inglés, Short-Form Health Survey de 36 ítems

SobME: sobrepeso metabólicamente enfermo

SobMS: sobrepeso metabólicamente sano

SZ: esquizofrenia

$\dot{V}CO_2$: producción de dióxido de carbono

$\dot{V}O_2$: consumo de oxígeno

$\dot{V}O_{2pico}$: consumo de oxígeno pico

ABBREVIATIONS

BMI: body mass index

BNSS: Brief Negative Symptom Scale

BP: blood pressure

CPET: cardiopulmonary exercise test

CRF: cardiorespiratory fitness

CVR: cardiovascular risk

DSM: Diagnostic and Statistical Manual of Mental Disorders

EX: exercise group

HC: healthy control

FHS: Framingham Heart Study

HIIT: high-intensity interval training

HR: heart rate

HRR: heart rate reserve

LV-HIIT: low-volume high-intensity interval training

MUO: metabolically unhealthy overweight or obesity

PA: physical activity

PANSS: Positive and Negative Syndrome Scale

TAU: treatment-as-usual

SCORE2: Systematic Coronary Risk Estimation

SZ: schizophrenia

VA: vascular age

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

VT1: ventilatory threshold 1

VT2: ventilatory threshold 2

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Resumen

Objetivos: los objetivos principales de esta tesis doctoral en personas con esquizofrenia (SZ) fueron: 1) determinar algunos marcadores físicos, fisiológicos y bioquímicos clave del estado de salud, incluida la calidad del sueño, así como estimar el riesgo cardiovascular (RCV) y la edad vascular a través de diferentes métodos en personas adultas con SZ en comparación con una muestra de personas sanas (HC) antes de iniciar una intervención adyuvante con ejercicio físico (EF); 2) validar la ecuación presentada en el estudio original de Singh *et al*. para evaluar la relación entre la prueba *Modified Shuttle Walk Test* (MSWT) y el consumo pico de oxígeno ($\dot{V}O_{2pico}$) en personas adultas con SZ, desarrollar una nueva ecuación desde la MSWT para predecir el $\dot{V}O_{2pico}$ y validar la nueva ecuación; 3) analizar el valor predictivo de la capacidad cardiorrespiratoria (CCR) y el índice de masa corporal (IMC) sobre los factores sintomáticos clínicos en población con SZ; 4) determinar los cambios en la composición corporal, la CCR y las variables bioquímicas tras 20 semanas de entrenamiento combinado en personas adultas con SZ caracterizadas al inicio como metabólicamente no sanas, con sobrepeso/obesidad y baja CCR; y 5) dar a conocer las voces de las personas con SZ y sus experiencias subjetivas de un programa de EF combinado diseñado para mejorar tanto su salud física como mental, a través de la participación.

Métodos: personas con SZ (N = 112) participantes en el estudio CORTEX-SP, se aleatorizaron a uno de los dos grupos de intervención, tratamiento habitual (TH, N = 53) y grupo de ejercicio físico (GEF, N=59). Antes y después de la intervención, se evaluó a cada participante con pruebas que incluían mediciones antropométricas, tensión arterial, CCR, calidad del sueño y entrevistas. Además, se reclutó una muestra HC (N = 30) para la comparación antes de la intervención.

Resultados: 1) las personas con SZ mostraron un perfil de RCV que incluía sobrepeso metabólicamente no sano, baja CCR y pobre eficiencia ventilatoria. Aunque las personas con SZ presentaron más horas de sueño nocturno en comparación con el grupo HC, ambos grupos mostraban una eficiencia del sueño similar, pero con niveles significativamente más altos de vigilia tras el inicio del sueño por parte del grupo con SZ. La evaluación del RCV reveló valores significativamente más altos en las personas con SZ (riesgo moderado) en comparación con HC (riesgo bajo), independientemente del sistema de estimación; 2) una nueva ecuación que incorpora la frecuencia cardíaca (FC) en reposo, el IMC y la distancia de MSWT (R^2 = 0,617; R^2 ajustado= 0,60; P < 0,001) presenta una mejor estimación del $\dot{V}O_{2pico}$ que la ecuación de Singh *et al.* (R^2 = 0,57; R^2 ajustado= 0,57; P < 0,001) en la población estudiada. El método de validación cruzada a posteriori confirmó la estabilidad del modelo (R^2 = 0,617 *vs*. 0,626); 3) las correlaciones revelaron una asociación negativa entre los síntomas negativos y el $\dot{V}O_{2pico}$ ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) (B = -0,252; P < 0,001). El análisis de regresión mostró que valores bajos de $\dot{V}O_{2pico}$ ($L{\cdot}min^{-1}$) (P < 0,001) y altos de IMC (P = 0,019) eran predictores de la sintomatología negativa, explicando

el 22,8% de la varianza (R^2 = 22,8%; F = 8,067; P < 0,001). Además, un menor $\dot{V}O_{2pico}$ (mL·kg^{-1}·min^{-1}) (P = 0,016) predijo tanto los síntomas generales (R^2 = 12,3%; F = 5,135; P = 0,002), como (P = 0,001) los síntomas totales (R^2 = 17,8%; F = 7,928; P < 0,001); 4) tras la intervención, el GEF mostró aumentos en la CCR (P < 0,001) a través del $\dot{V}O_{2pico}$ (L·min^{-1}; Δ = 17,6%; mL·kg^{-1}·min^{-1}, Δ = 19,6%) y el equivalente metabólico (Δ = 19%), sin cambios significativos (P > 0,05) en la composición corporal y las variables bioquímicas. Sin embargo, el grupo TH no mostró ningún cambio significativo en las variables de estudio (P > 0,05). Tras la intervención, se observaron diferencias significativas entre grupos (P ≤ 0,05) en la CCR, primer umbral ventilatorio y FC pico que favorecieron al GEF; y 5) seis temas surgieron del análisis cualitativo. Las relaciones entre los temas se presentan en un marco conceptual. Así, las entrevistas previas a la intervención determinaron los temas "expectativas sobre la participación" y "actitud hacia el EF, el programa y el estilo de vida en general" pareciendo influir en las personas para participar en el programa de EF. Las entrevistas posteriores a la intervención definieron el hecho de participar (y los factores asociados) conduciendo posteriormente a los "resultados percibidos" y los "planes a futuro".

Conclusiones: 1) la identificación de perfiles específicos del RCV clínico, físico y fisiológico en la enfermedad de SZ en comparación con personas sanas sugiere firmemente que dirigir un enfoque integral que incluya intervenciones no farmacológicas, como el EF y/o la rehabilitación cognitiva, podría ser eficaz y beneficioso en la evolución de la enfermedad; 2) los hallazgos de este estudio respaldan la validez de una nueva ecuación de regresión que incorpora la FC en reposo, el IMC y la distancia de la MSWT prediciendo el $\dot{V}O_{2pico}$ para la evaluación de la CCR en personas con SZ. Sin embargo, cuando se requiere una determinación precisa de la capacidad funcional para el diagnóstico, la investigación clínica y el diseño del EF, la medición directa del $\dot{V}O_{2pico}$ y umbrales ventilatorios seguirán siendo el "patrón oro"; 3) teniendo en cuenta la notable asociación de la CCR y el IMC con los síntomas negativos, y la CCR con los síntomas generales y totales, la mejora de la salud física a través del EF y una dieta saludable podría servir como tratamiento adyuvante esencial para controlar el trastorno de SZ. Estos hallazgos tienen el potencial de mejorar las estrategias de tratamiento integral para la población con SZ; 4) un programa de EF combinado supervisado en personas con SZ ayuda a mejorar los niveles de CCR. Esto podría conducir a un cambio clínico importante en la caracterización de la muestra como sobrepeso/obesidad metabólicamente no sana ("*lo que era*") a una población metabólicamente sana con sobrepeso u obesidad ("*lo que debería ser*"). De ahí que el EF deba considerarse un programa adyuvante en el tratamiento de la población con SZ; y 5) el EF como estrategia en el tratamiento y mantenimiento de la salud integral de las personas con SZ. La creación de un plan de continuación de la participación también es imprescindible para garantizar una participación sostenible y a largo plazo en dichos programas. Parece importante tener en cuenta la ubicación del programa (es decir, fuera del hospital), así como la constitución del grupo, el tipo de personas y el propio programa de EF. Para las personas que participaban, el programa no sólo funciona como una intervención para la mejora física y mental, sino que también tiene el potencial de aportar beneficios holísticos para la salud, como el bienestar.

Abstract

Objectives: the main objectives of this doctoral thesis in people with schizophrenia (SZ) were: 1) to determine some key physical, physiological and biochemical markers of health status, including sleep quality, and to estimate cardiovascular risk (CVR) and vascular age through different methods in adults with SZ compared to a healthy control (HC) population before starting an adjuvant exercise program; 2) to validate the equation presented in the original study by Singh *et al.* for evaluating the relationship between Modified Shuttle Walk Test (MSWT) with peak oxygen uptake ($\dot{V}O_{2peak}$) in adults with SZ, to develop a new equation for the MSWT to predict $\dot{V}O_{2peak}$, and to validate the new equation; 3) to analyze the predictive value of cardiorespiratory fitness (CRF) and body mass index (BMI) on clinical symptom factors in SZ population; 4) to determine changes in body composition, CRF, and biochemical variables following 20-week combined exercise training in adults with SZ characterized at baseline as metabolically unhealthy overweight/obesity with low CRF; and 5) to provide the voices of people with SZ and their subjective experiences of a combined exercise program designed to improve both their physical and mental health, through participation.

Methods: people diagnosed with SZ (N=112) participated in the CORTEX-SP study. They were randomized to one of the two intervention groups, treatment-as-usual (TAU) and exercise group (EX). Each participant was assessed before and after the intervention, including anthropometric measurements, blood pressure, CRF, sleep quality, and interviews. Further, an HC sample (n = 30) was recruited for comparison before the intervention.

Results: 1) participants with SZ showed a CVR profile including “overweight metabolically unhealthy”, low CRF, and impairment of ventilatory efficiency. Although participants with SZ slept more compared to HC, similar sleep efficiency was shown by both groups, but with significantly higher levels of wake after sleep onset by SZ. The assessment of CVR revealed significantly higher values in SZ (moderate risk) compared to HC (low risk) regardless of the estimation system; 2) a new equation incorporating resting heart rate, BMI, and distance from MSWT ($R^2 = 0.617$; adjusted $R^2 = 0.60$; $P < 0.001$) performs better than the Singh *et al.* equation ($R^2 = 0.57$; adjusted $R^2 = 0.57$; $P < 0.001$) to estimate $\dot{V}O_{2peak}$ for the studied population. A posteriori cross-validation method confirmed the model’s stability ($R^2 = 0.617$ vs. 0.626); 3) the correlations revealed a negative association between negative symptoms and $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) ($B = -0.252$; $P < 0.001$). The regression analysis showed that lower $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$) ($P < 0.001$) 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 $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) ($P = 0.016$) predicted both general symptoms ($R^2 = 12.3\%$; $F = 5.135$; $P = 0.002$), and predicted total symptoms ($R^2 = 17.8\%$; $F = 7.928$; $P < 0.001$); 4) Following the intervention, participants from the EX showed increases

in CRF (P<0.001) through $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$; Δ = 17.6%; $mL \cdot kg^{-1} \cdot min^{-1}$, Δ = 19.6%) and the metabolic equivalent of task (Δ=19%), with no significant changes (P > 0.05) in body composition and biochemical variables. However, the TAU group (n=38) did not show any significant change in the study variables (P > 0.05). Between-group significant differences (P ≤ 0.05) were observed in CRF, first ventilatory threshold, and heart rate peak after the intervention period, favoring the EX group; and 5) six themes emerged from the analysis. The relationships among the themes are presented in a conceptual framework. Thus, the themes "expectations about taking part" and "attitude to exercise, the program, and general lifestyle" appeared to influence participants to take part and are pre-intervention interviews. The act (and factors associated with "taking part") then led to subsequent "perceived outcomes" and "plans" should be considered post-intervention interviews.

Conclusions: 1) the identification of specific clinical, physical, and physiological cardiovascular risk profiles in SZ illness compared to healthy people strongly suggests that targeting a comprehensive approach, including non-pharmacological interventions, such as exercise or cognitive rehabilitation, or both, could be effective and beneficial in the evolution of the disease; 2) the findings of this study support the validity of a new regression equation incorporating resting heart rate, BMI, and distance from MSWT to predict $\dot{V}O_{2peak}$ for assessment of CRF in people with SZ. However, when an accurate determination of functional capacity is required for diagnosis, clinical research, and exercise design, the direct measurement of $\dot{V}O_{2peak}$ and ventilatory thresholds will continue to be the “gold standard”; 3) 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 SZ disorder. These findings can enhance comprehensive treatment strategies for people with SZ; 4) a supervised combined exercise program in people with SZ helps improve CRF levels. This result could lead to an important clinical change in the characterization from metabolically unhealthy overweight/obesity (they were) to a metabolically healthy population with overweight or obesity (they should be). Hence, exercise should be considered an adjuvant program in treating the population with SZ; and 5) exercise as a strategy in treating and maintaining holistic health for people with SZ. A continuation plan for participation is also imperative to ensure sustainable and longer-term involvement in such programs. The program's location appears important (*i.e.*, out-of-hospital), as does the group's constitution, the type of people, and the exercise program itself. For these participants, the program serves as an intervention for physical and mental improvement. It has the potential for holistic health benefits, such as well-being and essential opportunities for social interaction for this clinical group.

Capítulo 1 / Chapter 1

Síntesis/Synthesis

1. INTRODUCCIÓN / Introduction

1.1. Consecuencias del estilo de vida actual

En los últimos años, el sedentarismo ha emergido como uno de los principales problemas de salud en todo el mundo.[1] Con los avances tecnológicos y cambios en el estilo de vida, cada vez más personas se encuentran atrapadas en una falta de actividad física (AF) significativa en el día a día, es decir, una disminución en el gasto energético y una mayor propensión a desarrollar enfermedades crónicas.[2]

En la actualidad, en algunas ocasiones los términos inactividad física y sedentarismo se utilizan como sinónimos. Al respecto cabe mencionar que, si bien estos términos están fuertemente relacionados entre sí, no son lo mismo. El sedentarismo o el comportamiento sedentario, se define como cualquier comportamiento de vigilia caracterizado por un gasto energético inferior a 1,5 equivalentes metabólicos (MET), es decir, pasar mucho tiempo en actividades de bajo costo energético (*i.e.,* estar en posición sentada, reclinada o tumbada).[3,4] Hoy en día existe gran evidencia que muestra al sedentarismo como un factor de riesgo independiente en el desarrollo de múltiples problemas de salud y patologías.[5]

En cambio, si bien la revolución tecnológica ha traído grandes beneficios para las personas, también ha conllevado el aumento de la inactividad física, que se define como la falta de cumplimiento de las recomendaciones internacionales de AF.[6] Estas recomendaciones son actualmente, según la Organización Mundial de la Salud (OMS), realizar al menos 150 minutos de AF aeróbica a intensidad moderada o 75 minutos a intensidad vigorosa, o una combinación equivalente de AF moderada y vigorosa a lo largo de la semana incluyendo, al menos dos veces por semana, actividades de fortalecimiento que ejerciten los principales grupos musculares.[7] Por lo tanto, es importante no confundir ambos términos, ya que una persona puede cumplir con las recomendaciones de AF, pero destinar la mayor parte del día a comportamientos sedentarios. Datos epidemiológicos indican que comportamientos sedentarios tienen efectos cardiovasculares y metabólicos nocivos que son independientes de que las personas cumplan o no las recomendaciones generales de AF.[8] En resumen, son diferentes las consecuencias de "estar demasiado tiempo sentado" al de "realizar insuficiente AF".[8] Por ello, las nuevas guías incluyen la necesidad de alentar a las personas a romper los períodos de comportamiento sedentario, introduciendo en tramos intermitentes actividades diarias no ejercitantes,[7,9] o de intensidad ligera.[7,10]

A nivel mundial, cerca del 27,5% de las personas adultas no cumplen las recomendaciones mundiales de la OMS de 2010 sobre AF, y casi no se ha registrado mejora alguna en los últimos 10 años.[7]

Asimismo, todavía puede agravarse porque existen desigualdades notables: (1) los datos demuestran que en casi todos los países las niñas y las mujeres son menos activas que los niños y los hombres, a nivel mundial el 23% de los hombres son inactivos, por el 32% de las mujeres.[11] En España los datos se igualan un poco más, el 25% de los hombres, por el 30% de las mujeres;[11] y (2) los niveles de AF varían enormemente entre los grupos económicos de mayor y menor nivel y en función del país y la región. Este problema se acentúa en los países con economías avanzadas, que superan en más del doble a los países con economías en vías de desarrollo en los porcentajes de inactividad física (37% *vs.* 16%), respectivamente.[11] Según la OMS, la inactividad física es el cuarto factor de riesgo de mortalidad más importante, a él se le atribuye 5,5% del total de las muertes a nivel mundial, llegando a la cifra de 32 millones de muertes anuales.[12]

En el Plan de acción mundial sobre AF 2018-2030 se ha fijado la meta de reducir los niveles de inactividad física en un 15% para 2030, recomendando 20 medidas normativas, así como una serie de intervenciones, ya que cada año podrían evitarse entre cuatro y cinco millones de muertes si toda la población se mantuviera más activa físicamente.[13] Por lo que la AF y el ejercicio físico (EF) son componentes esenciales para mantener un estilo de vida saludable y activo reduciendo la mortalidad. Estas dos prácticas complementarias están diseñadas para promover la vitalidad y el bienestar general, mejorando la salud física y mental. Aun así, como con los términos de inactividad física y sedentarismo, algo parecido suele ocurrir con los términos de AF y EF, ya que están fuertemente relacionados entre sí, pero tampoco son lo mismo.

La AF se considera cualquier movimiento corporal producido por el sistema musculo-esquelético que tenga como resultado un gasto energético superior a los valores basales (*i.e.,* caminar, subir escaleras, hacer tareas domésticas, entre otros).[14] Incluso pequeñas acciones cotidianas pueden marcar una gran diferencia en la salud y deben ser consideradas en la lucha contra el sedentarismo. Por otro lado, el EF es una AF planificada, estructurada y repetitiva que busca un objetivo claro, tratando de mejorar o mantener uno o varios de los componentes físicos (*i.e.,* correr, nadar, practicar deportes o entrenar en el gimnasio), y diseñada a diferentes intensidades (ligera, moderada o vigorosa).[14] Así, las recomendaciones generales de la OMS aconsejan intercalar intensidades moderadas y vigorosas porque se pueden llegar a conseguir mayores beneficios para la salud.[7]

La AF regular es un importante factor de protección para la prevención y el tratamiento de enfermedades no transmisibles como las enfermedades cardiovasculares (ECV), la diabetes mellitus (DM) tipo 2 y varios tipos de cáncer.[15] La AF es beneficiosa para mejorar la calidad de vida (CdV) de las personas y por lo tanto contribuye al bienestar general, tanto a nivel físico, como también en la salud mental.[7] Sin embargo, en los últimos años, el estilo de vida moderno y los cambios socioculturales han influido significativamente en la disminución de la AF y el aumento de las enfermedades mentales.[16]

1.2. Enfermedad mental: la esquizofrenia

Las enfermedades mentales, también conocidas como trastornos mentales graves, son un conjunto diverso de condiciones que afectan el pensamiento, las emociones, el comportamiento y el bienestar emocional de las personas.[17] Estos trastornos pueden manifestarse de diferentes maneras, desde cambios sutiles en la forma de pensar y sentir, hasta alteraciones significativas en el funcionamiento diario y en las relaciones sociales. En 2019, una de cada ocho personas en el mundo padecía un trastorno mental, pero las cifras siguen aumentando año tras año.[16]

Una de las clasificaciones más utilizadas para el diagnóstico de las enfermedades mentales es el *Diagnostic and Statistical Manual of Mental Disorders* (DSM).[17] Con el objetivo de unificar y mejorar los criterios diagnósticos se han publicado cinco ediciones, siendo la herramienta actual los criterios del DSM-5.[18] Hasta 1980, año en el que se publicó el DSM-III, a gran parte de las personas con desordenes psicóticos, se les consideraba personas cuyo funcionamiento mental estaba tan deteriorado que interfería en su capacidad para ejecutar las necesidades cotidianas de la vida diaria.[18] La esquizofrenia (SZ) que afecta en torno al 1% de la población,[19] es una enfermedad que aparece a temprana edad, entre la segunda y tercera década de la vida, y en la mayoría de los casos sigue un curso crónico.[20] En esta enfermedad, aparecen una serie de síntomas, como síntomas positivos (delirios y alucinaciones, mayoritariamente auditivas), síntomas negativos (pérdida de motivación, expresión emocional limitada y dificultad para llevar a cabo actividades cotidianas) y dificultades cognitivas (comportamiento psicomotor anormal y pensamiento desorganizado),[17] que afectan de manera distinta a cada persona, finalmente deteriorándola. Cuando esta sintomatología aparece se llama primer episodio de psicosis o trastorno esquizofreniforme, sin embargo, si los síntomas vuelven a aparecer o se mantienen en el tiempo (*i.e.,* durante más de seis meses), se diagnostica la SZ.[18]

La SZ es una enfermedad de origen multifactorial y probablemente involucra una combinación de factores genéticos, neurobiológicos, ambientales y sociales. Por un lado, el componente genético es indudable, con una prevalencia en la población general del 0,1-1% aumentando exponencialmente en las familias con una persona afectada por esta enfermedad. Por ello, cuanto mayor grado de asociación familiar, mayor carga genética y mayor posibilidad de desarrollar la enfermedad.[21] Por el otro lado, en esta población prevalece un ambiente tóxico, con un estilo de vida insano que incluye hábitos de sedentarismo,[22] dieta pobre,[23] y tabaquismo.[24]

La farmacología es el principal tratamiento de la SZ, donde los medicamentos antipsicóticos son una opción terapéutica muy importante. Tras la aparición de la Clorpromacina, fueron surgiendo los llamados medicamentos antipsicóticos de primera generación (*i.e.,* típicos), los cuales resultaban efectivos sobre todo en la sintomatología positiva del trastorno pero con gran predominio de efectos secundarios extrapiramidales (acatisia, distonía, pseudoparkinsonismo o/y discinesia tardía).[25] Posteriormente, aparecieron medicamentos antipsicóticos de segunda generación (*i.e.,* atípicos), resultando un avance importante en el tratamiento, ya que pueden llegar a tener una eficacia superior en los síntomas negativos, mejorar el estado de ánimo y la cognición y prevenir recaídas, además de un riesgo significativamente menor de discinesia tardía y efectos secundarios extrapiramidales. Sin embargo, algunos medicamentos antipsicóticos de segunda generación están más asociados con un riesgo significativo de alteraciones en el metabolismo de la glucosa y lipídico, provocando un aumento de la masa corporal,[26] obesidad abdominal, DM tipo 2, hipercolesterolemia, hipertrigliceridemia y tener niveles bajos de colesterol de lipoproteína de alta densidad (HDL-C).[27] Por ello, la combinación de los fármacos con otros métodos no farmacológicos, como la neuromodulación, el tratamiento psicosocial,[18] la rehabilitación cognitiva,[28,29] y el EF,[30] está ofreciendo estrategias más innovadoras con resultados esperanzadores. Sin embargo, es importante destacar que los tratamientos no farmacológicos no tratan de reemplazar el tratamiento farmacológico adecuado, pero puede ser una herramienta complementaria muy valiosa para mejorar la CdV y el bienestar emocional de las personas que padecen este desorden mental. En este sentido, un reciente metaanálisis ha demostrado que la AF, y particularmente el EF estructurado, puede mejorar significativamente los síntomas positivos, los síntomas negativos y el funcionamiento social de las personas con SZ.[31] Así, mediante la mejora de la capacidad cardiorrespiratoria (CCR) y el estado metabólico, el EF puede también reducir los problemas de salud física asociados a la SZ como son la obesidad y la DM, que contribuyen claramente a la reducción de la expectativa de vida que sufren estas personas.[32] En general, estudios sobre el efecto del EF en la progresión de la SZ han mostrado que siendo la persona físicamente activa se protege el cerebro elevando la expresión de los factores neurotróficos, incrementando la liberación de neurotransmisores y aumentando también la neurogénesis.[33] Además, la SZ, al igual que otras enfermedades neurológicas, se caracteriza por un estado crónico de neuroinflamación, sabiendo que uno de los beneficios del EF es también una reducción de ese estado inflamatorio.[33]

Por tanto, vistos los efectos del estilo de vida sobre la salud de la población, es un objetivo primordial poner el foco sobre ello y promover una vida activa como eje principal en la prevención y el tratamiento de enfermedades.

2. MARCO TEÓRICO / Theoretical framework

2.1. ¿Cómo están las personas con esquizofrenia?

Teniendo en cuenta todos los factores expuestos previamente, no es sorprendente que, según un metaanálisis reciente sobre la esperanza de vida en personas con SZ en comparación con la población general, esta se reduzca entre 10 y 20 años,[34] aunque hay estudios que concluyeron que la reducción era aún mayor, de 28,5 años de media.[35] La mayoría de las muertes son debidas a causas naturales relacionadas con ECV,[36] cáncer, DM y enfermedad pulmonar obstructiva crónica.[35] Los factores que contribuyen al exceso de mortalidad incluyen los sociales y económicos, hábito tabáquico y los factores de riesgo cardiometabólicos.[37] Así, el síndrome metabólico, con la inclusión de tres de los siguientes factores de riesgo cardiometabólico (*i.e.*, concentraciones bajas de HDL-C, elevado perímetro de cintura, niveles altos de triglicéridos en plasma, alto nivel de glucosa en ayunas y tensión arterial [TA] elevada), es muy frecuente en este tipo de población.

El consumo de tabaco es el factor de riesgo de muerte modificable más importante a nivel mundial.[38] Las personas con SZ fuman tres veces más que la media poblacional, con unas tasas de prevalencia de hasta el 62%,[24] y con una gran dificultad para abandonar el hábito a corto plazo y mantenerse abstinentes a largo plazo.[39] Además, estudios recientes han proporcionado fuertes indicios de que el tabaquismo es un factor causal en la aparición de la SZ.[40] Estos resultados están en consonancia con múltiples metaanálisis que demuestran que el tabaquismo se asocia a un mayor riesgo prospectivo de trastornos mentales, a una edad más temprana de aparición y a resultados adversos en quienes padecen enfermedades mentales.[41,42]

La alimentación es también una causa importante y modificable de ECV.[43] En las personas con SZ se caracteriza por una alimentación alta en grasas y azúcares, y en cambio, baja en frutas y verduras.[44] Una mala alimentación está relacionada con varios factores característicos en personas con SZ: 1) presencia de sintomatología especialmente negativa y cognitiva que dificulta las rutinas diarias para adquirir alimentos y posteriormente cocinarlos de manera saludable;[45] y 2) normalmente se encuentran en situaciones de desempleo y presentan un nivel socioeconómico más bajo.[46]

La AF es un predictor independiente de mortalidad y morbilidad.[47] Revisiones sistemáticas han demostrado que las personas con SZ se caracterizan por un alto nivel de comportamientos sedentarios especialmente en la falta de AF de intensidades moderadas a vigorosas.[22,48] Solo el 25% de las personas con SZ realiza la AF mínima aconsejada.[49] De este modo, los hospitales psiquiátricos podrían proporcionar un entorno favorable para iniciarse en el EF, y ofrecer una amplia variedad de programas de EF a las personas hospitalizadas.[50] Sin embargo, solo entre el 25% y el 50% de las personas hospitalizadas participan en dichos programas y una vez que reciben el alta médica, el porcentaje disminuye aún más.[50] Diferentes factores (*i.e.,* intrapersonales, interpersonales y ambientales) influyen en la no realización de la AF mínima necesaria, especialmente a través de programas de EF. Entre los factores intrapersonales se encuentran el tratamiento farmacológico,[51-53] los síntomas y características de la SZ,[53] la propia salud física de la persona y el dolor musculo- esquelético por la falta de habito a realizar AF.[51] En cuanto a los factores interpersonales se podría señalar el apoyo social, tanto del grupo de trabajadores del hospital,[54,55] el apoyo de familiares y círculo cercano,[56,57] como del apoyo de su grupo de compañeras y compañeros.[58] Finalmente, en los factores ambientales se incluye realizar AF en un contexto extra hospitalario,[54] factores socioeconómicos,[51,53] y problemas de transporte.[51]

Por lo tanto, una dieta no saludable y la inactividad física, contribuyen a una mayor prevalencia de obesidad, de hipertensión arterial (HTA) y de síndrome metabólico, siendo el riesgo de obesidad 2-3 veces mayor que el de la población general.[59] Por todo ello, en esta población, el conocimiento de los factores de riesgo cardiovascular (RCV), especialmente los factores de riesgo modificables, tales como el hábito del tabaquismo, dieta poco saludable, HTA, sobrepeso/obesidad e inactividad física es algo esencial y su tratamiento podría contribuir a una reducción en la incidencia de las ECV en personas con SZ.[60]

En la actualidad, la prevención de las ECV se relaciona con una cuantificación del RCV total, junto con un enfoque terapéutico basado en tratamientos farmacológicos y no farmacológicos. Esta necesidad nos dirige a técnicas de modificación de conducta y cambios de estilo de vida.

2.1.1. Riesgo cardiovascular

El concepto de RCV se define como la probabilidad que tiene cada persona de sufrir una ECV en un plazo determinado, normalmente de 10 años.

A la hora de analizar el RCV, normalmente se tienen en cuenta tres conceptos claves. Primero, la población a la que pertenecen esas personas, es decir, un país desarrollado o subdesarrollado no tendrán las mismas posibilidades de RCV. Segundo, la clasificación de la ECV (*i.e.,* mortal o no mortal). Finalmente, el tiempo en el que puede aparecer la ECV, normalmente se calcula en un plazo de 10 años, aunque también hay otro tipo de sistemas que calculan a 5 años, 30 años o durante el resto de vida.[61] El riesgo absoluto se aplica a nivel individual. Explicándolo mediante un ejemplo claro, si hubiese que calcular el RCV de una persona, donde obtiene un 10%, significaría que tiene una probabilidad del 10% de presentar una ECV en los próximos 10 años, es decir, que de cada 100 personas iguales (en cuanto a la edad, el sexo y los diversos factores de riesgo), 10 personas tendrán un evento en los próximos 10 años.[61]

2.1.1.1. Factores de riesgo cardiovascular

La SZ presenta una relación bidireccional, los síntomas de la enfermedad influyen en una peor salud de la persona, y viceversa, una peor salud influye en agravar la sintomatología de la enfermedad. Tanto es así, que la SZ ha sido identificada como un factor de riesgo intrínseco para desarrollar ECV e intolerancia a la glucosa.[62]

El RCV está determinado por una combinación de factores de riesgo, que pueden ser modificables o no modificables. Los factores de RCV no modificables incluyen la edad, el sexo y la historia familiar de ECV. El envejecimiento aumenta el riesgo de sufrir ECV, de hecho, las personas de edad avanzada son las principales afectadas por cardiopatías. En cuanto al sexo, es de resaltar que el porcentaje RCV es siempre más elevado en hombres que en mujeres aun teniendo los mismos valores en el resto de los parámetros que definen el RCV.[63] Así mismo, se incluye como parámetro la edad superior a 55 años en hombres y la superior a 65 años en las mujeres. Por lo que respecta a la historia familiar de ECV prematura, se considera como factor de RCV el antecedente de la misma en un familiar de primer grado en hombres antes de los 55 años y en mujeres antes de los 65 años.[64]

Por otro lado, los factores genéticos también pueden influir en el riesgo cardiometabólico, es decir, hay una asociación entre tener SZ y presentar factores de RCV modificables (*i.e.,* valores elevados de triglicéridos, lipoproteínas de baja densidad [LDL-C], tensión arterial sistólica [TAS], índice de masa corporal [IMC] y una disminución de HDL-C).[64] Así mismo, la inflamación juega un papel clave en la psicopatología de la enfermedad y se ha sugerido que el aumento de mediadores inflamatorios puede explicar que se inicien cambios en el metabolismo de la glucosa y lípidos, contribuyendo al desarrollo de factores de riesgo de ECV.[65] Los factores de riesgo modificables, como el nombre bien indica, pueden ser modificados a través del estilo de vida, donde un estilo de vida insano lo podría empeorar.[43] Los factores de RCV modificables son la adiposidad, tabaquismo, HTA, DM, y dislipidemia (DLP).[66]

En el estudio *Survey of High Impact Psychosis* con datos de más de 1800 personas con SZ, encontraron que: (1) tres cuartas partes de las personas tenían sobrepeso u obesidad con más del 80% con obesidad abdominal central,[67] definido como una acumulación anormal o excesiva de grasa que puede ser perjudicial para la salud.[68] El IMC (kg/m^2) es un valor usado para determinar si una persona tiene una masa corporal saludable en relación con su estatura. La OMS clasifica como sobrepeso los valores de IMC iguales o superiores a 25 kg/m^2 y como obesidad el IMC igual o mayor que 30 kg/m^2.[68] Los análisis sugieren una relación lineal entre el IMC y la mortalidad en personas no fumadoras y una relación en forma de J en las que han fumado alguna vez.[69] Sin embargo, aun siendo el IMC una herramienta sencilla, rápida y útil, hay que considerarla a título indicativo porque es posible que no se corresponda con el mismo nivel de adiposidad en diferentes personas.[68] Por ello, el perímetro de cintura también se utiliza como marcador de obesidad y RCV, siendo > 88 cm en mujeres y > 102 cm en hombres los valores recomendados.[70] Un meta análisis concluyó que tanto el IMC como el perímetro de cintura se asocian de forma similar, fuerte y continua con ECV y la DM tipo 2.[71] Así mismo, (2) dos tercios de las personas eran fumadoras actuales de tabaco.[67] El tabaquismo es la adicción al tabaco provocada principalmente, por uno de sus componentes activos, la nicotina, y es responsable del 50% de todas las muertes evitables en personas fumadoras, la mitad de las cuales se deben a ECV. Una persona fumadora de por vida tiene un 50% de probabilidades de morir a causa del tabaco, y puede llegar a perder una media de 10 años de vida.[72] El riesgo de ECV en las personas fumadoras de menos de 50 años es cinco veces mayor que en las no fumadoras.[73] El tabaquismo es el principal factor de riesgo de años de vida ajustados por discapacidad.[74] Además, la posibilidad de padecer un evento cardiaco es proporcional a la cantidad de cigarrillos fumados al día y al número de años en los que se mantiene el hábito.[75,76] Existen dos factores principales por los que el tabaco puede producir una isquemia coronaria. Por un lado, la nicotina, que desencadena la liberación de las catecolaminas (adrenalina y noradrenalina) que producen daño en la pared interna de las arterias (*i.e.,* endotelio), aumenta el tono coronario con espasmo, produce alteraciones de la coagulación, incrementa los niveles de colesterol de LDL-C y reduce los de HDL-C. Por el otro lado, el monóxido de carbono que disminuye el aporte de oxígeno al miocardio y aumenta el colesterol total (CT) y la agregación plaquetaria (su capacidad de unirse y formar coágulos).[77] Además, (3) más de la mitad de las personas en el estudio cumplían los criterios para padecer síndrome metabólico.[67] Un factor de RCV asociado al síndrome metabólico es la HTA.[43] Una elevación crónica de la TA es lo que se conoce como HTA.[78] Los estudios longitudinales y epidemiológicos genéticos han demostrado que tener HTA es un factor importante de padecer ECV, siendo responsable de 9,4 millones de muertes y del 7% de los años de vida ajustados por discapacidad.[79] La HTA es un factor de riesgo para el desarrollo de enfermedades coronarias, cerebrovasculares, renales crónicas y fibrilación auricular entre otras. El riesgo de muerte por enfermedad coronaria o ictus aumenta linealmente a partir de niveles de TA de 90/75 mmHg.[80,81] Se ha comprobado también que la reducción de 20/10 mmHg en la TA habitual de hombres y mujeres con edades comprendidas entre los 40 y 89 años, está asociada con una disminución a la mitad de las muertes debidas a eventos relacionados con accidentes cerebro vasculares o enfermedad isquémica de corazón.[78] La causa de la relación entre el RCV y la TA es que cuando la TA es elevada, las paredes de las arterias experimentan un estrés constante y aumentado. Con el tiempo, este estrés puede causar daño en las paredes arteriales, lo que puede llevar a la formación de placas (*i.e.,* aterosclerosis), acumulándose en las paredes arteriales, estrechando y endureciendo las arterias, esto reduce el flujo sanguíneo y aumenta el riesgo de obstrucciones arteriales. Por lo tanto, el corazón tiene que trabajar más para bombear la sangre a través de las arterias, y esto puede llevar a un aumento en el grosor del músculo cardíaco (*i.e.,* hipertrofia ventricular izquierda), lo que aumenta el riesgo de insuficiencia cardíaca y arritmias. En el peor de los casos, la HTA puede reblandecer las paredes de la aorta y provocar su dilatación (aneurisma) o rotura (lo que inevitablemente causa la muerte). En aquellas personas que ya han tenido una ECV, la HTA puede intensificar el daño.[15]

Otro factor clave en el síndrome metabólico es la DLP, donde la evidencia científica ha demostrado la relación lineal entre los niveles séricos de CT y el riesgo de ECV. La DLP es un trastorno caracterizado por niveles alterados de lípidos en la sangre. Los lípidos incluyen el CT y los triglicéridos, que son componentes esenciales para el funcionamiento del cuerpo, pero que pueden volverse problemáticos cuando sus niveles están desequilibrados. La DLP generalmente se refiere a niveles elevados de CT, LDL-C y/o triglicéridos, y niveles bajos de HDL-C.[82] Tanto la hiperlipidemia, uno de los principales factores de RCV para el desarrollo de la arteriosclerosis y de la ECV,[82] como la hipercolesterolemia (*i.e.,* valores de CT ≥ 250 mg/dL, y valores de LDL-C ≥ 160 mg/dL), la más frecuente e importante en la ECV arteriosclerótica,[83] son claves en el RCV de las personas.

En un meta análisis descubrieron que las personas con SZ tenían cuatro veces más probabilidades de padecer obesidad abdominal, 2,4 veces más probabilidades de padecer síndrome metabólico y dos veces más probabilidades de padecer DM en comparación con la población general.[84] La DM es un factor de riesgo independiente de ECV, es una enfermedad metabólica crónica que se caracteriza por niveles elevados de glucosa en sangre, que con el tiempo conduce a daños graves en el corazón, los vasos sanguíneos, los ojos, los riñones y los nervios.[85] Siguiendo las directrices de las sociedades científicas internacionales, se considera como DM la presencia de una glucemia en ayunas > 7,0 mmol/L (126 mg/dL) o una glucemia postprandial > 11,0 mmol/L (198 mg/dL). Tanto si la producción de insulina es insuficiente como si existe una resistencia a su acción, la glucosa se acumula en la sangre dañando progresivamente los vasos sanguíneos (arterias y venas) acelerando el proceso de aterosclerosis aumentando el riesgo de padecer una ECV (*i.e.,* angina, infarto agudo de miocardio y la muerte cardiaca súbita).[86]

La sintomatología de la enfermedad también juega un papel importante en el RCV. En la SZ, la presencia de síntomas negativos (*i.e.,* abulia y anhedonia), a diferencia de los síntomas positivos (*i.e.,* delirios o alucinaciones),[87] influyen de manera significativa en el resultado funcional y metabólico de la enfermedad, con un aumento del RCV,[88,89] y de la inactividad física.[88] La sintomatología negativa es considerada factor clave en la disminución del interés y la motivación para realizar una actividad cotidiana,[90,91] especialmente si hay que involucrar hábitos de vida saludables como la AF o una alimentación saludable.[92] Por lo tanto, en esa relación bidireccional nos encontramos que las personas con SZ que presentan mayor sintomatología negativa, tienen una peor alimentación y condición física, junto con el incremento del IMC, perímetro abdominal, riesgo de DM tipo 2 y de DLP (mayor CT y menor HDL-C).[93] Así mismo, otro de los síntomas característicos de la SZ es la desorganización que les complica mucho la rutina diaria, especialmente a la hora de participar en diferentes actividades, sobre todo aquellas que necesiten un mínimo de comprensión.[87,94] Estudios previos sugieren que el deterioro cognitivo conduce, de forma moderada, a una menor capacidad para elegir alimentos saludables y para comprender la necesidad de realizar EF.[93]

En este sentido, se ha identificado la condición física como un factor crítico que influye en la función cognitiva.[95] Varias revisiones cualitativas,[52,96] y cuantitativas,[88] han examinado los beneficios de un estilo de vida saludable, así como la AF en relación con los síntomas psiquiátricos, destacando la necesidad de seguir investigando en estudios prospectivos e intervenciones para mejorar las variables modificables. En un estudio realizado en personas con SZ, revelaron que un nivel bajo de condición física y, por lo tanto, de estilo de vida no saludable se asociaba con la gravedad de los síntomas negativos y un mayor IMC.[93] Por lo tanto, esto sugiere que las intervenciones dirigidas a aumentar la condición física y disminuir el IMC también pueden conducir a una reducción de la sintomatología negativa,[97,98] mejorando la CdV en esta población.[99]

2.1.1.2. Predicción de riesgo cardiovascular

Se recomienda el control y la evaluación del RCV en personas con SZ según diferentes guías clínicas.[21,100,101] Sin embargo, aunque parecen ser coste-efectivas,[102,103] en este momento no se están implementando en la atención clínica.[104] Los factores de RCV deben gestionarse en función del riesgo total de ECV, y evaluarse mediante diferentes escalas. Así, dos son las escalas más utilizadas a nivel global: *Framingham Heart Study* (FHS) y *Systematic Coronary Risk Estimation* (SCORE2). Por un lado, el FHS se trata de funciones matemáticas multivariables derivadas que asignan ponderaciones a los principales factores de riesgo de padecer una ECV, como el sexo, la edad (30-74 años), la TAS, el CT, HDL-C, LDL-C, el hábito tabáquico y DM. La escala fue inicialmente validada en 1998, y fue revisada dos veces a posteriori en 2002 y 2008.[63] En el caso de una persona sin ECV, sus factores de riesgo de ECV se introducen en la función para obtener una estimación de la probabilidad de desarrollar una ECV dentro de un determinado periodo de tiempo. Es decir, sabiendo que una puntuación del 10% significa que hay un 10% de probabilidad de tener una ECV en los próximos 10 años,[63] el riesgo absoluto de cada persona puede situarse dentro de unos rangos según la puntuación conseguida. Una puntuación menor del 6% se considera riesgo bajo, entre 6 y 20% riesgo medio, y una puntuación de 20% o mayor riesgo alto.[63]

Por otro lado, el sistema SCORE2, es una herramienta que nace del FHS pero calibrado para las características de la población europea y revisado después de mejorar la primera versión (*i.e.,* SCORE).[105]

SCORE2 es un algoritmo de predicción del riesgo, desarrollado por la Sociedad Europea de Cardiología, que calcula el riesgo de padecer ECV en 10 años. Las tablas de puntuación del riesgo calculan el riesgo en función a la población a la que pertenecen esas personas, a la edad (40-69 años), el sexo, el hábito tabáquico, la TAS y el no HDL-C.[106] Los valores de corte de cada categoría divergen según la edad, donde menores de 50 años, una puntuación menor del 2,5% se considera riesgo bajo-moderado, entre 2,5% y 7,5% se considera riesgo alto, y una puntuación de 7,5% o mayor ya es considerado riesgo muy alto. Entre 50 y 69 años, una puntuación menor del 5% se considera riesgo bajo-moderado, entre 5% y 10% se considera riesgo alto, y una puntuación de 10% o mayor ya se considera riesgo muy alto.[106]

Sin embargo, las personas con SZ suelen ser más jóvenes y tienen más probabilidades de ser fumadoras en comparación con las poblaciones utilizadas para derivar los sistemas tradicionales de puntuación del riesgo de ECV.[107] Por lo tanto, la última declaración de posición de la Asociación Europea de Psiquiatría recomienda la decisión de incluir una tabla de riesgo relativo para las personas con enfermedades mentales graves basada en el hábito tabáquico, la TAS y el CT.[100]

Finalmente, tratando de simplificar y ayudar a la persona, basado en el método FHS, la edad vascular (EV) es otro instrumento más sencillo que simplifica la comunicación del estado de riesgo de la persona y podría mejorar la adherencia como herramienta útil.[108] La EV es una herramienta para calcular la edad biológica de las arterias de una persona (*i.e.,* la edad del sistema vascular de una persona con diferentes factores de RCV) con los datos de los factores de RCV.[61,109] Simplemente demuestra los años que la persona puede ganar o perder según controle sus factores de riesgo.[63] Por lo tanto, si la edad cronológica y EV son similares la situación de riesgo de la persona es tolerable con independencia del valor del riesgo absoluto, y viceversa, si la diferencia es considerable, podría preocupar su situación.[61]

2.1.2. Perfil cardiometabólico y bioquímico

Todos los factores de riesgo mencionados anteriormente coexisten entre ellos.[110] Aun así, las personas con sobrepeso u obesidad pueden tener alteraciones metabólicas o no. Aproximadamente solo entre el 10% y 25% de ellas no presentan otros factores de riesgo como resistencia a la insulina, DLP u otros. Cuando esto sucede, se plantea el concepto de la obesidad metabólicamente sana (ObMS). Se podría indicar, por tanto, que la ObMS es la de una persona que se presenta con un IMC > 30 kg/m^2, pero que no tiene ningún desorden cardiometabólico definido. Hay establecidos diferentes criterios a la hora de definir la ObMS, concepto del cual deriva una forma de clasificar a las personas, teniendo en cuenta varios marcadores cardiometabólicos. Según los criterios modificados de *Wildman,*[111] de los siguientes seis marcadores cardiometabólicos si se cumplen dos o más, estaríamos ante una persona metabólicamente enferma. Los marcadores serían: 1) TA elevada ≥ 130/85 mmHg o uso de medicación antihipertensiva; 2) nivel de triglicéridos elevado en ayunas ≥ 150 mg/dL; 3) nivel de HDL-C reducido < 40 mg/dL en hombres o < 50 mg/dL en mujeres o uso de medicación hipolipemiante; 4) nivel de glucosa elevado en ayunas ≥ 100 mg/dL o uso de medicación antidiabética; 5) resistencia a la insulina ≥ 3,8 (*i.e.*, el percentil 90); y 6) inflamación sistémica con niveles de proteína C reactiva > 3 mg/L (*i.e.,* el percentil 90).[111] De este modo, la clasificación enmarca diferentes tipos en función de las variables analizadas: personas con normopeso metabólicamente sanas (IMC < 25 kg/m^2 y < 2 anormalidades cardiometabólicas), con normopeso metabólicamente enfermas (IMC < 25 kg/m^2 y ≥ 2 anormalidades cardiometabólicas), con sobrepeso metabólicamente sanas (SobMS, IMC 25,0 - 29,9 kg/m^2 y < 2 anormalidades cardiometabólicas), con sobrepeso metabólicamente enfermas (SobME, IMC 25,0 - 29,9 kg/m^2 y ≥ 2 anormalidades cardiometabólicas), con obesidad metabólicamente sanas (ObMS, IMC ≥ 30 kg/m^2 y < 2 anormalidades cardiometabólicas) o con obesidad metabólicamente enfermas (ObME, IMC ≥ 30 kg/m^2 y ≥ 2 anormalidades cardiometabólicas).[111]

En un meta análisis reciente donde compararon los niveles de AF y de CCR entre las personas ObMS y ObME, demostraron que las personas ObMS mostraban valores superiores de AF y CCR, y además presentaban valores inferiores de comportamientos sedentarios, sugiriendo que el perfil metabólico podría estar influenciado por un estilo de vida más saludable.[112] Por ello, se podría considerar la CCR como un criterio a tener en cuenta en la salud metabólica, y que podría ayudar a identificar a las personas con ObMS.[113]

El perfil cardiometabólico está altamente relacionado con el perfil bioquímico. En una población con SZ, en el perfil bioquímico, el marcador proteína C reactiva cobra un especial interés. No solo porque sea un predictor de ECV,[114] o tener relación con el síndrome metabolico,[115,116] sino porque es un marcador inflamatorio. La SZ, al igual que otras enfermedades neurológicas, se caracteriza por estado crónico de neuroinflamación, sabiendo que uno de los beneficios del EF es también una reducción de ese estado inflamatorio.[33]

2.1.3. Capacidad cardiorrespiratoria

Además de los parámetros tradicionales, la CCR (*i.e.,* la capacidad que tienen los sistemas respiratorio y circulatorio de aportar oxígeno a la musculatura esquelética durante una AF continuada),[117,118] se considera un signo vital y ha surgido como un factor de riesgo modificable para atenuar el riesgo de desarrollar enfermedades no transmisibles.[119,120] Así, es de conocimiento general la fuerte asociación entre un menor RCV y mayores niveles de CCR, también inversamente asociados con la mortalidad por ECV.[120]

En este sentido, la medición y valoración de la CCR representa una conclusión clínica importante en la evaluación del RCV. Así, se ha demostrado que en personas con SZ mejoras en la CCR se asocian con un menor riesgo de mortalidad independientemente de la edad, el tabaco y la composición corporal.[121] A su vez, se han observado relaciones directas entre la CCR y la función cognitiva, resultando un menor declive en la función cognitiva en aquellas personas con una mayor CCR, de forma específica en la memoria verbal y velocidad psicomotora.[122] Estudios recientes han demostrado que las personas con SZ tienen un 15% menos de CCR que la población en general,[123,124] donde la falta de AF puede explicar esa reducción,[22] principalmente por la combinación de los siguientes factores: sintomatología de la enfermedad, especialmente los síntomas negativos, depresión, efectos secundarios de la medicación (*i.e.,* sedación), baja autoeficacia en el EF, conocimiento limitado de los beneficios de la AF, dificultad de acceso a infraestructuras y pobreza.[125] Resulta, por ello, fundamental la valoración de la CCR como punto de partida para la evaluación y seguimiento del RCV, junto con un enfoque terapéutico basado en tratamientos farmacológicos y no farmacológicos. Esta necesidad nos dirige a técnicas de modificación de conducta y cambios de estilo de vida como intervenciones de EF.[43]

Las medidas de referencia, más conocidas en investigación como criterios de referencia, para valorar la CCR, así como para prescribir y diseñar programas de EF son el consumo de oxígeno ($\dot{V}O_2$) máximo o pico ($\dot{V}O_{2pico}$), tanto en valores absolutos ($L \cdot min^{-1}$) como relativos a la masa corporal ($mL \cdot kg^{-1} \cdot min^{-1}$), y los umbrales ventilatorios primero y segundo, resultando descriptores fisiológicos sobre el transporte y utilización de oxígeno en respuesta al EF.[119,126-129] A la hora de valorar la CCR, otra medida muy común es el termino MET, siendo una medida utilizada para cuantificar la intensidad de la AF o EF en relación con el gasto de energía en reposo (*i.e.,* gasto energético necesario para mantener las funciones básicas del cuerpo en estado de reposo, valorado en 1 MET lo que equivale a 3,5 $mL \cdot kg^{-1} \cdot min^{-1}$).[130] Se ha demostrado que el incremento de 1 MET en la CCR se asocia con una reducción del riesgo de mortalidad del 13% y una reducción del riesgo de ECV del 15%.[117,131]

Existen numerosas pruebas de valoración tanto directas como indirectas (estimadas) para determinar la CCR de una persona.[118]

Método directo

A la hora de valorar la CCR, los métodos directos son los métodos más precisos para determinar el $\dot{V}O_{2pico}$ a través de una prueba de esfuerzo cardiopulmonar (CPET, del inglés *cardiopulmonary exercise test*). La CPET evalúa la capacidad funcional del sistema cardiovascular y respiratorio de una persona mientras realiza EF (*i.e.,* información sobre la respuesta al EF). Para que la prueba de CPET sea óptima y aceptable, tiene que darse bajo condiciones controladas en laboratorio y con aparatos de ergometría, siempre supervisando la intensidad del EF mediante el análisis de gases ($\dot{V}O_2$ y producción de dióxido de carbono, $\dot{V}CO_2$).[117] Esta prueba proporciona información valiosa sobre el estado de salud cardiovascular, la función pulmonar y la capacidad física de una persona, es decir, el rendimiento cardiovascular y los criterios ventilatorios se evalúan durante un estímulo de EF de intensidad progresiva para proporcionar un análisis integrado de las respuestas fisiológicas requeridas por los sistemas cardiovascular y respiratorio para satisfacer las demandas metabólicas del músculo esquelético (*i.e.,* la demanda de oxígeno durante el EF).[132,133] La premisa fundamental de la CPET es que la evaluación del intercambio de gases ($\dot{V}O_2$ y $\dot{V}CO_2$) durante el EF proporciona una perspectiva sobre la fisiología general del cuerpo, es decir, refleja la capacidad de rendimiento del corazón, los pulmones, y la circulación sanguínea para mantener el oxígeno y eliminar dióxido de carbono que son críticos para la homeostasis celular.[132,133] Por lo tanto, la CPET mediante análisis de gases ha aumentado significativamente la fiabilidad, reproducibilidad y utilidad clínica puesto que proporciona una cuantificación de la CCR significativamente más precisa.[117]

Método indirecto

Los métodos indirectos son pruebas más económicas, requieren de menos aparatos, son más sencillas y, por lo tanto, tardan menos tiempo en ser preparadas y ejecutarlas. Además, el método directo no está siempre disponible y su coste es elevado, por lo que existen otro tipo de métodos para estimar la CCR o valores de $\dot{V}O_2$ submáximos sin medición directa, como pruebas de esfuerzo, diversas pruebas de campo que simulan el CPET, y ecuaciones de regresión para estimar el $\dot{V}O_{2pico}$. Los métodos alternativos al CPET son cada vez más utilizados y en poblaciones clínicas más específicas, pero la estimación indirecta de la CCR, conlleva un error de estimación, aproximadamente entre el 4,2 y 7,0 $mL·kg^{-1}·min^{-1}$, por lo que se recomienda que cuando se requiere una determinación precisa de la CCR para el diagnóstico, la investigación clínica, el diseño del EF o la valoración del RCV, la medición directa del $\dot{V}O_{2pico}$ continue siendo el criterio de referencia, es decir, a través de la CPET.[117]

En este sentido, cuando la CPET no es factible, la CCR puede estimarse utilizando diversas pruebas de campo mediante la realización de una prueba de EF con un esfuerzo máximo para alcanzar altos índices de esfuerzo percibido.[134] Los test de campo y demás métodos de estimación del $\dot{V}O_{2pico}$ permiten hacer seguimiento de la CCR a lo largo del tiempo, y no solo eso, a la hora de programar intervenciones con EF, facilitan el diseño de la intensidad de EF.[118] Ejemplo de ello es el test incremental de ida y vuelta caminando (*Incremental Shuttle Walk Test*),[135] o su variante (*Modified Shuttle Walk Test*, MSWT).[136] Así, una de las pruebas de campo más utilizadas es la prueba MSWT, que se considera adecuada para todos los niveles de capacidad funcional y permite obtener una respuesta máxima. Estudios previos han evaluado la asociación entre el MSWT y el $\dot{V}O_{2pico}$ en diferentes poblaciones (*i.e.,* adolescentes, personas sedentarias, cáncer de pulmón, enfermedad pulmonar obstructiva crónica, mujeres obesas, hipertensión arterial pulmonar e hipertensión primaria) concluyendo que este test de marcha de campo es objetivo, seguro, válido, eficaz, fiable y altamente predictivo para la valoración de la capacidad funcional en cada una de las poblaciones examinadas.[137-142] No obstante, al igual que el resto de pruebas, puede no ser válida en todas las poblaciones, por lo que debería realizarse un análisis de las propiedades de la prueba (*i.e.,* validez, fiabilidad, repetitividad y sensibilidad).[143] Originalmente, Singh *et al*.[135] propusieron una ecuación para evaluar la capacidad funcional en personas con enfermedad pulmonar obstructiva crónica utilizando un protocolo de 12 niveles *Incremental Shuttle Walk Test*, la versión previa del MSWT,[141] y más recientemente Jurio-Iriarte *et al.* desarrollaron otra para personas con HTA primaria y obesidad utilizando el MSWT.[144]

El MSWT no ha sido validado en personas con SZ. Por ello, si esta prueba pudiese ofrecer la información que se obtiene a través de CPET de forma válida, fiable y precisa, supondría un avance en la medición y valoración de la CCR, en la estimación del RCV y en la programación de EF de estas personas, ya que simplificaría y abarataría el proceso.

2.1.4. Calidad del sueño

La calidad del sueño es otro aspecto crucial para la salud y el bienestar general de una persona. El sueño se compone de varios ciclos, que incluyen etapas de sueño no REM que se caracteriza por ser un sueño de ondas lentas en el que no existen movimientos oculares rápidos, fases de sueño superficial 1 y 2, sueño profundo de ondas lentas y la fase del sueño caracterizada por los movimientos oculares rápidos o fase REM.[145] Durante el periodo de sueño debemos pasar por diferentes fases que contribuyen a que se produzcan una serie de cambios a nivel cardiovascular, respiratorio, hormonal, renal, digestivo y en general de todo el organismo, y son esenciales para una recuperación efectiva y un funcionamiento adecuado del cuerpo y la mente.[146] Por ello, la ECV está asociada bidireccionalmente con las alteraciones del sueño, ya que los trastornos del sueño pueden alterar de manera importante el sistema cardiovascular, lo que lleva a un mayor RCV.[146] Se ha demostrado que una corta duración del sueño se asocia con el desarrollo de ECV, DM y obesidad, después de ajustarse por factores de riesgo socioeconómicos, demográficos y comorbilidades, así como falta de concentración, la disminución del rendimiento cognitivo, irritabilidad, depresión y ansiedad.[147]

Aunque investigaciones anteriores indican que cada persona debería dormir dependiendo de las necesidades individuales, en general, se concluye que el patrón de sueño adecuado tiene que ser el intermedio, es decir, dormir diariamente una media de 7-8 horas, ya que se asocia con una reducción en el desarrollo de patologías u en consecuencias negativas en la salud.[148] En este sentido, numerosos estudios han demostrado que las personas que duermen de 7 a 8h tienen el menor riesgo de mortalidad.[149] Además, muchos estudios muestran la presencia de una asociación en forma de U, aquellas personas con duraciones de sueño más cortas y más largas tienen un riesgo significativamente mayor de mortalidad,[150] ECV y obesidad.[151]

Además de lo mencionado anteriormente, diferentes estudios han demostrado que una mala calidad del sueño desempeña un papel importante en la menor CdV que mantienen las personas con SZ.[152] Además, esta asociación parece darse tanto de forma independiente como sinérgica con un mayor riesgo de suicidio,[153] síntomas de depresión y angustia, así como con los propios efectos secundarios de la medicación.[154] Del mismo modo, estudios con muestras amplias encontraron una asociación independiente entre el insomnio y la CdV en personas con SZ,[155,156] y el deterioro del sueño se asoció con una menor satisfacción con la vida.[157]

Mantener una buena higiene del sueño implica adoptar prácticas y rutinas que promuevan un sueño de calidad. Estas pueden incluir mantener un horario regular de sueño, crear un entorno propicio para el descanso, evitar estimulantes como la cafeína antes de acostarse y limitar el uso de dispositivos electrónicos antes de dormir, así como mantener un estilo de vida saludable. Entre ellos el EF juega un papel fundamental, ya que hay una asociación directa ente calidad del sueño y EF, donde parece que las personas con SZ que presentan más alteraciones del sueño también muestran un patrón de EF pobre y una intensidad de EF más ligera en comparación con la población en general.[153] Del mismo modo, el EF regular se asocia con una mejor calidad del sueño evaluada a través del Índice de Calidad del Sueño de Pittsburg en personas con SZ, mostrando que, a mayor asistencia a sesiones grupales de intensidad moderada, mejor calidad del sueño.[158] Por ello, las organizaciones internacionales recomiendan programas de estilo de vida, incluido el EF, para las personas con discapacidad en general,[159] y con SZ en particular.[160] Por lo tanto, aunque el EF de intensidad ligera tiene beneficios para la salud, las personas con SZ deben cumplir las recomendaciones generales de la OMS para personas con SZ.[159]

Por ello, el sueño es sin duda un excelente indicador del estado de salud general, bienestar y CdV de la población. En cualquier caso, merece la pena tomarse en serio los déficits asociados a los modelos que se desvían de los patrones normales de sueño, para así prevenir las graves consecuencias que se le asocian.[148]

2.1.5. Calidad de vida

La CdV se define como una evaluación subjetiva de bienestar, satisfacción y nivel de comodidad que una persona experimenta en su vida cotidiana. Es un concepto amplio y subjetivo que abarca varios aspectos de la vida de una persona, incluyendo su salud física y mental, relaciones interpersonales, entorno social y económico, y satisfacción con diferentes áreas de la vida.[161]

Uno de los cuestionarios más utilizados para evaluar la salud ha sido el perfil de salud de Nottingham debido a su aceptabilidad y brevedad.[162] Sin embargo, también ha sido criticado por su incapacidad para detectar niveles bajos de discapacidad que son importantes no sólo desde el punto de vista clínico, sino también para las personas encuestadas.[163] El cuestionario de *Short-Form Health Survey de 36 ítems* (SF-36) no sólo es una herramienta potencialmente valiosa para la investigación médica, sino que también ha servido para evaluar la CdV en diferentes poblaciones con enfermedades, como fibromialgia, artrosis de rodilla y lumbalgia crónica,[164] cáncer,[165] psoriasis,[166] y enfermedad renal crónica.[167] En este sentido, ha ganado cada vez más aceptación en la investigación psiquiátrica junto con las evaluaciones tradicionales de los resultados clínicos, especialmente en la población con SZ.[168]

Las propiedades psicométricas de las puntuaciones del cuestionario SF-36 han sido validadas en la población con SZ,[168] con una versión traducida al castellano.[169] Los ítems del cuestionario informan de estados positivos y negativos del resumen del componente físico y del resumen del componente mental, identificando ocho dimensiones de la salud: funcionamiento físico, rol físico, dolor corporal, salud general, vitalidad, funcionamiento social, rol emocional y salud mental.[170]

En las personas con SZ, los factores psicosociales (*i.e.,* la disminución de la autoestima y el estigma social) y psicopatológicos (*i.e.,* los síntomas negativos y positivos), así como un estilo de vida poco saludable, influyen negativamente en la CdV relacionada con la salud.[171] Así, en general, las personas con SZ informan de una mayor discapacidad y puntuaciones más bajas en la CdV física y mental que la población en general.[172] En este sentido, tras un análisis de regresión logística, se ha sugerido que el funcionamiento físico y emocional, y el dolor corporal evaluado mediante el cuestionario SF-36 eran los mejores predictores de una peor CdV en la población con SZ en comparación con la población en general.[173]

2.2. ¿Cómo deberían estar?

En la actualidad, la prevención de la ECV se relaciona con una cuantificación del RCV total, incluyendo la valoración de la CCR como punto de partida para la evaluación y seguimiento del RCV. Investigaciones previas sugieren con fuerza que la orientación de un enfoque integral que incluya tratamientos farmacológicos, así como intervenciones no farmacológicas (*i.e.,* el EF), podría ser eficaz y beneficioso en la evolución de la enfermedad.[43]

2.2.1. Ejercicio físico como programa adyuvante

Las guías internacionales promueven intervenciones de EF como una herramienta no farmacológica adyuvante al tratamiento en personas con SZ, reduciendo la mortalidad y el RCV, mejorando la CdV de esta población, induciendo mejoras sustanciales en la salud física y mental.[7,160,174] Son muchos los estudios realizados acerca del efecto que tiene el EF en personas con SZ. Esta acumulación de efectos beneficiosos hace del EF una intervención interesante para esta población ya que tiene un potencial considerable para actuar como una polipíldora en múltiples dominios (físico, mental y, cognitivo).[175]

Diferentes estudios han demostrado mejoras en la funcionalidad y CdV a través de un programa de EF en personas con SZ.[176,177] El EF parece favorecer el bienestar general y la autoconfianza,[180] la socialización, la distracción, una mejora de la percepción de la competencia y de la autoeficacia.[178] El EF afecta de forma favorable a los factores de RCV. Además de la reducción de la TA, reporta consigo otros beneficios para la salud cardiovascular, como reducción de la masa corporal, de la adiposidad visceral y total, del perímetro de cintura, de la resistencia a la insulina, de concentraciones de LDL-C y aumento de concentraciones de HDL-C.[15] Aun así, un meta análisis reciente concluyó que no hubo cambios en los marcadores de salud metabólica, como la composición corporal y algunos parámetros bioquímicos tras una intervención de EF en personas con SZ.[31] El RCV se ve también disminuido por la mejora de la CCR, por pequeña que esta sea, el riesgo resulta menor cuanto mayor es la CCR, llegando a considerar que las personas en baja forma física tienen el doble de riesgo de muerte, independientemente del IMC.[179] Es bien sabido que la CCR se considera un factor predictivo de los resultados de salud y, de hecho, un reflejo de la salud corporal total, lo que justifica que los programas de EF dejen de centrarse en el "*fatness*" para centrarse en el "*fitness*".[121]

La evidencia ha revelado que el entrenamiento combinado de EF puede actuar como un programa adyuvante en personas con SZ mejorando tanto los síntomas psiquiátricos como los indicadores de condición física relacionados con la salud.[180] Las mejoras en la CCR pueden deberse a las adaptaciones al estrés, que previamente han demostrado provocar notables adaptaciones celulares, vasculares y metabólicas durante el entrenamiento combinado, especialmente el entrenamiento interválico de alta intensidad (*High-Intensity Interval Training*, HIIT),[181] y este paradigma ha surgido desde entonces como un modo de EF seguro y más eficiente en el tiempo.[182] Además, una intervención de EF, especialmente importante en el caso de trastornos neurológicos como la SZ, sirve para prevenir y tratar diversas patologías y justifica una cuidadosa disección de las señales, redes y mediadores de la diafonía interorgánica que se origina en el músculo esquelético,[183] y de forma multidimensional en la función cerebral.[184]

En este sentido, durante los últimos años, se han obtenido muchas pruebas sobre la comunicación entre el cerebro y el músculo esquelético a través del EF para lograr una mejor salud mental, abogando por el EF como un programa adyuvante relevante para las enfermedades cerebrales. La comunicación endocrina con moléculas derivadas del mioquinoma que pueden atravesar eficazmente la barrera hematoencefálica y desempeñar funciones neuroactivas sigue siendo objeto de investigación.[185] Sin embargo, el HIIT se ha considerado relevante para la salud cerebral debido a los efectos del trabajo de alta intensidad junto con sus respuestas y adaptaciones.[184] En esta línea, ya se han presentado los posibles efectos positivos del EF sobre la síntesis de dopamina y su impacto en la salud mental conociendo la regulación de otros neurotransmisores (*i.e.,* noradrenalina y serotonina),[186] y el posible efecto beneficioso sobre la disfunción del sistema dopaminérgico en personas con SZ.[187] Además, parece que el HIIT aumenta la secreción de melatonina y controla mejor el reloj circadiano interno de las personas y el bucle entre las irregularidades del sueño y la dopamina.[153,188]

2.2.2. Recomendaciones actuales de ejercicio físico

La AF está bien reconocida como un factor clave para la prevención y la gestión del desorden mental, incluidos, entre otros, trastornos mentales graves como la depresión, la ansiedad y el trastorno de estrés postraumático. Desde finales de la década de 1970, las personas expertas a nivel internacional en este campo han elaborado y perfeccionado directrices sobre la AF para la salud a lo largo de varias décadas.[189] En términos generales, el propósito de las directrices de AF es proporcionar recomendaciones para mejorar la salud y el bienestar general. Originalmente, las directrices de AF se propusieron para prevenir la mortalidad relacionada con la ECV y, posteriormente, se desarrollaron para abarcar otras afecciones crónicas prevalentes (*i.e.,* cáncer o DM).[190] Actualmente, las recomendaciones mundiales se basan en la reducción del riesgo de enfermedades crónicas, relacionadas específicamente con la salud cardiorrespiratoria, la salud metabólica, la salud musculo esquelética, el cáncer, la salud funcional y la depresión.[7]

Aunque varios programas de AF han demostrado su eficacia en personas con SZ, la prescripción óptima de AF para las personas con SZ aún no está totalmente establecida. En consecuencia, las recomendaciones de AF para las personas con SZ son generalizadas, indicando que deben evitar la inactividad y realizar EF aeróbico y de fuerza.[160] Investigaciones previas han comentado que la AF no es una intervención de talla única,[191,192] y que la atención no debe centrarse en la dosis-respuesta general más ideal (*i.e.,* la eficacia), sino más bien en cómo las personas con SZ pueden incluir la AF en su vida diaria (*i.e.,* la efectividad). En las últimas guías de recomendaciones generales de AF, la OMS ha incluido a las personas con SZ, donde no difieren de aquellas dirigidas a la población en general, es decir, realizar al menos 150 minutos de AF aeróbica a intensidad moderada o 75 minutos a intensidad vigorosa, o una combinación equivalente de actividades moderadas y vigorosas a lo largo de la semana y, al menos dos veces por semana, realizar actividades de fortalecimiento que ejerciten los principales grupos musculares.[7] Por otro lado, hay encuestas que muestran que existe un llamamiento por parte de las personas especialistas clínicas de todo el mundo para investigar con mayor detalle cuál podría ser la prescripción de AF más ideal, al tiempo que se considera que no existe una prescripción de AF perfecta.[193]

Con el fin de encontrar la dosis óptima de EF y poder diseñar de una forma sistemática, progresiva e individualizada, los principales componentes modificables son la frecuencia, la intensidad, el tipo y el tiempo (*i.e.,* el principio FITT). La frecuencia del EF (número de sesiones por semana) y el tiempo (duración o volumen de cada ejercicio o sesión) son dos características clave de un programa de EF, pero un factor igualmente importante es la intensidad (el grado del esfuerzo al que se realiza la actividad) y el tipo de EF (patrón de entrenamiento).[194]

Se han llevado a cabo diferentes estudios para analizar los efectos del EF en personas con SZ. Los estudios más comunes son los relacionados con el entrenamiento aeróbico que se ha mencionado anteriormente.[195-199] Sin embargo, menos estudios han analizado los efectos del entrenamiento de fuerza resistencia en esta población,[200-202] y hasta donde sabemos, sólo un estudio con un pequeño tamaño de muestra exclusivamente varones, bajas tasas de cumplimiento y altas tasas de abandono ha aplicado el entrenamiento de EF combinado.[201,203] Finalmente, hay otro tipo de estudios que también encontraron resultados positivos en yoga,[204-206] Tai Chi,[207] y actividades de aventura al aire libre (como piragüismo, kayak, escalada en roca, cursos de cuerdas),[208] aunque hace faltan más estudios para corroborar tales resultados.

Una revisión sistemática recomienda una frecuencia de al menos tres veces por semana durante un mínimo de 12 semanas en las personas con SZ,[209] mientras que otros estudios muestran una pérdida de masa corporal modesta pero significativa o una mejora de la CCR independientemente de la duración de la intervención (mayor o menor de 12 semanas).[210] La intensidad de la AF es un componente importante que puede manipularse. Las recomendaciones generales de la OMS aconsejan intercalar intensidades moderadas y vigorosas porque se pueden llegar a conseguir mayores beneficios para la salud.[7] En este sentido, existe un interés creciente por examinar el papel de la actividad de intensidad vigorosa o el HIIT.[211] Estudios anteriores además de descubrir efectos beneficiosos del entrenamiento aeróbico a intensidad moderada, han integrado el entrenamiento HIIT, encontrando efectos positivos sobre la salud física y mental en personas con SZ.[195-199]

El tiempo, duración o volumen también puede manipularse en el diseño del EF. Los estudios adicionales que exploran los efectos de la manipulación de los diferentes componentes de la prescripción de EF ayudarán a determinar su impacto en resultados específicos y es de esperar que perfeccionen las actuales recomendaciones generales de AF para las personas con SZ.[193]

Así, diferentes estudios sugieren que el HIIT de bajo volumen (LV-HIIT) es un protocolo eficaz y eficiente en términos de tiempo en poblaciones clínicas que responde a la pregunta "¿Puede menos ser más?".[212,213] Como tal, puede ser que el LV-HIIT sea más atractivo para personas que no disponen de tiempo suficiente para entrenar durante periodos prolongados, para aquellas que padecen afecciones médicas que les impiden realizar EF durante periodos de tiempo prolongados o para aquellas personas que les interese combinar EF aeróbico y fuerza resistencia en la misma sesión.[181,214] Por ello, teniendo en cuenta la necesidad urgente de aumentar los niveles de AF y CCR en esta población, el LV-HIIT podría ser una opción para adaptar el EF supervisado junto con las recomendaciones diarias de AF de menor intensidad.[215]

2.3. ¿Es suficiente con análisis cuantitativos?

La investigación cuantitativa se centra en la recopilación y el análisis de datos numéricos para identificar patrones y tendencias. Aun así, es posible que a través de los datos no se llegue a representar toda la realidad que se ha investigado. La investigación cualitativa, por otro lado, se enfoca en la comprensión profunda de las experiencias, percepciones y contextos de las personas involucradas en el estudio. Al combinar ambos enfoques, se puede obtener una imagen más completa y rica del fenómeno de estudio.

Para comprender plenamente el papel holístico de la AF para las personas con SZ, es importante captar e investigar las experiencias reales de esta población que participa en programas de EF. A través de métodos cualitativos, las experiencias, opiniones y percepciones de las personas que han participado en un programa de EF, y el papel que desempeña para ellas, pueden entenderse desde las perspectivas de aquellas para las que está diseñado.[216] Explorar las experiencias de las personas para con el EF y lo que contribuye a facilitar esas experiencias (positiva y negativamente) puede arrojar luz sobre el papel de esta opción de tratamiento para las personas con trastornos de salud mental.[217] Esta información se puede utilizar para desarrollar más directrices para aquellas personas profesionales en esta área y garantizar que estén informadas para facilitar que las personas participen, disfruten y se beneficien de participar en programas de EF.

A pesar de lo que se sabe sobre el EF para la salud mental y los llamamientos a su uso, sigue habiendo una escasez de estudios que investiguen las experiencias de las personas con condiciones específicas de salud mental,[218] como la SZ. Otros estudios cualitativos han investigado grupos heterogéneos de personas con enfermedades mentales.[219] Centrarse en una única población clínica pone de relieve el papel específico que desempeña la AF en el manejo y tratamiento de la enfermedad.

2.4. What is known, and what remains to be known on this topic?

People with schizophrenia (SZ) present an unhealthy lifestyle; therefore, cardiovascular disease is the most common cause of death. Hence, promoting a healthy lifestyle,[160,220] and interventions aiming to increase physical activity (PA), specifically increasing moderate-vigorous PA, should be a priority given the health benefits and the role of exercise as an anti-inflammatory adjuvant program.[119] Then, as part of an educational program to change lifestyle, it has been shown that an exercise intervention has a positive effect on improving cardiorespiratory fitness (CRF),[121] controlling metabolic disorders, and mental health parameters (*i.e*., positive, negative, general, and total symptoms).[221] High-intensity interval training (HIIT) exercise (*i.e*., alternating loads of high-intensity exercise with periods of light-to-moderate intensity) has found to have positive effects on physical and mental health in patients with SZ.[195-199] However, fewer studies have analyzed the effects of resistance training in this population.[207-209] To our knowledge, only one study with a small sample size of solely male participants, low compliance rates, and high drop-out rates has applied combined exercise training (*i.e*., the combination of resistance and aerobic training in the same exercise session).[201,203] All these studies have been unified in a recent systematic review and meta-analysis, where all exercise modalities (aerobic, resistance, or combined) are supported for their beneficial effects on people living with SZ.[180] It seems that combining resistance and aerobic exercise enhances functional capacity more than aerobic exercise alone due to different molecular and metabolic pathways, which could generate a “general adaptation profile” in untrained people.[222] Further, minimizing overall exercise volume in both types of exercise, including cycling as aerobic exercise as opposed to running, could contradict the “muscle interference” hypothesis.[223,224]

The biggest challenge for patients with SZ who wish to exercise is to make an optimum intervention for each case. Therefore, this study aimed to determine changes in body composition, CRF, and biochemical variables following 20-week combined exercise training in adults with SZ characterized at baseline as metabolically unhealthy overweight/obesity (MUO) with low CRF.

Capítulo 2 / Chapter 2

Objetivos e hipótesis/Objectives and hypotheses

3. OBJECTIVES AND HYPOTHESES / Objetivos e hipótesis

3.1. Objectives

- ***To determine key physical, physiological, and biochemical markers of health status, including sleep quality, and to estimate cardiovascular risk (CVR) and vascular age (VA) through different methods in adults with SZ compared to a healthy control (HC) population before starting a non-pharmacological therapeutic strategy.***
- ***To validate the equation presented in the original study by Singh et al. for evaluating the relationship between the Modified Shuttle Walk Test (MSWT) with peak oxygen consumption ($\dot{V}O_{2peak}$) in adults with SZ, to develop a new equation for the MSWT to $\dot{V}O_{2peak}$, and to validate the new equation.***
- ***To analyze the predictive value of CRF and body mass index (BMI) on clinical symptom factors in the SZ population.***
- ***To determine changes in body composition, CRF, and biochemical variables following 20-week combined exercise training in adults with SZ characterized at baseline as MUO with low CRF.***
- ***To address the voices of people with SZ and their personal experiences of a combined exercise program designed to improve their physical and mental health through participation.***

3.2. Hypothesis

- ***The studied population will present worse physical, physiological, clinical, and, therefore, CVR and VA patterns than the HC group, suggesting key behaviors such as improving CRF through exercise interventions.***
- ***The existing equation for estimating CRF in the population with respiratory failure will have a large estimation error in the study population, even though the relationship between MSWT and CRF is extensive. The new equation will allow a more accurate estimation.***
- ***People with higher CRF will have less symptomatology and vice versa. BMI will help CRF predict symptomatology.***
- ***Exercise treatment will result in superior blood pressure (BP), body composition, and CRF improvements in adults with SZ compared to the treatment-as-usual control (TAU) group.***
- ***Despite having many limitations to exercise, people with SZ had a great experience and would have liked to continue.***

Capítulo 3 / Chapter 3

Métodos/Methods

4. METHODS / Métodos

4.1. Study design

The CORTEX-SP study is a randomized, single-blind (medical specialists who evaluated the psychiatric variables) controlled experimental trial (Clinical Trials.gov identifier, NCT03509597). The study was approved by the Clinical Research Ethics Committee of the Autonomous Region of the Basque Country (PI2017044), and written informed consent was obtained from all participants before any data collection.

After baseline measurements, participants were randomized (www.randomization.com) to one of the two intervention groups: TAU group or supervised exercise (EX) group. The participants were followed for 20 consecutive weeks. All follow-up examinations were performed in the same laboratory (Laboratory of Sport Performance Analysis, Department of Physical Education and Sport, University of the Basque Country UPV/EHU) setting and by the same researchers as in the baseline measurements.

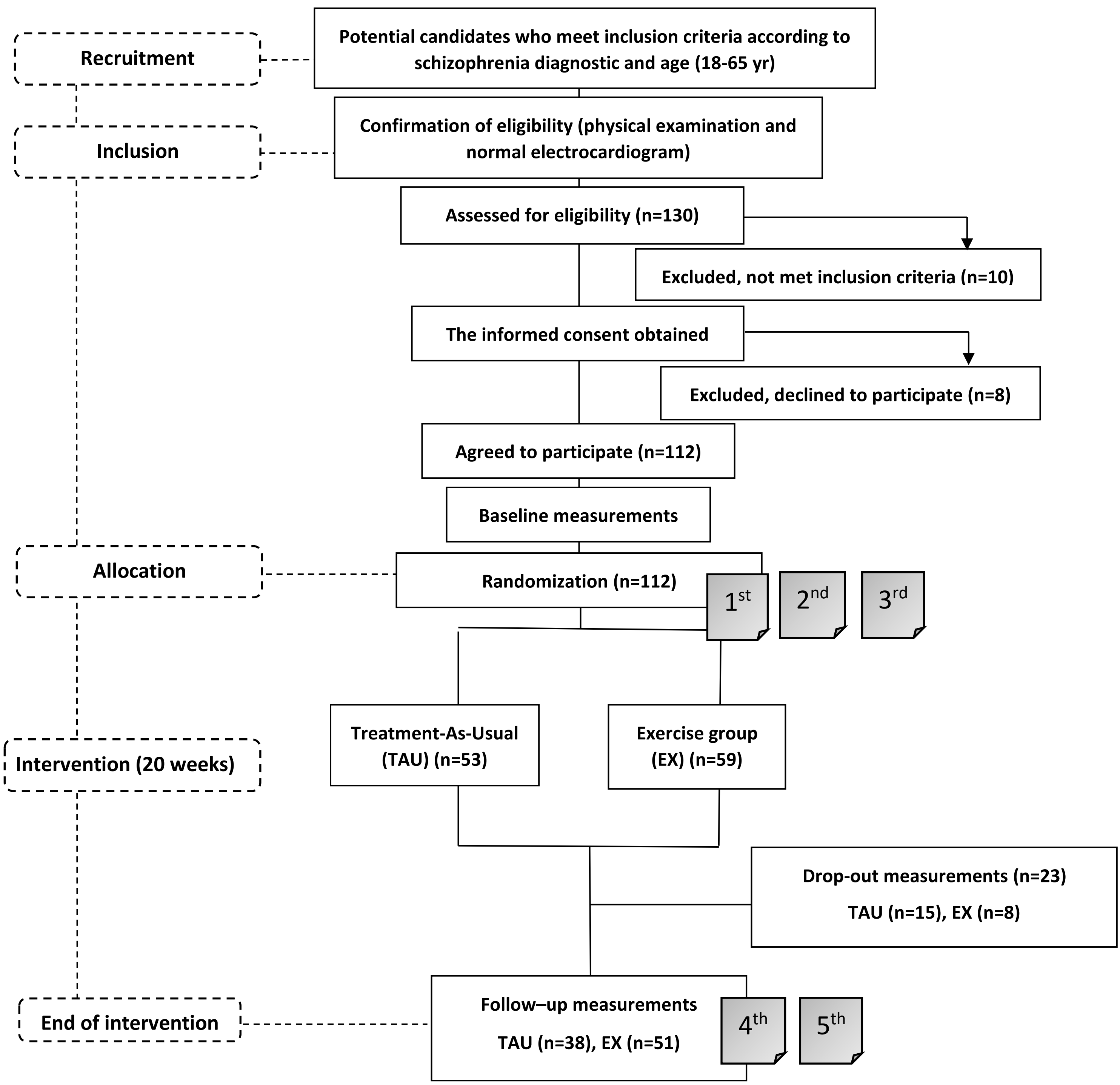

Figure 1. Flow diagram of the present doctoral thesis project and related to published articles.

4.2. Participants and selection criteria

One hundred and twelve (Figure 1) non-Hispanic white participants (41.3±10.4 years old, n=87 men [77.7%] and n=25 women [22.3%]) were enrolled in the study from May 2018 to July 2021 in Vitoria-Gasteiz (Basque Country, Spain). All participants were recruited from the Mental Health Network in Alava, Basque Country, which provides psychiatric care to the population living in the community. Before starting the study, a screening process was performed for all candidates, and all provided written informed consent before any data collection. Patients from the study met the diagnostic criteria for SZ according to DSM-5, with a disease evolution time greater than two years and stable. Briefly, the exclusion criteria included were clinically unstable patients; cognitive impairment secondary to another disease; main diagnosis of substance use disorder or presenting active substance use at the time of the study; patients who have required relevant modifications of antipsychotic drug treatment in the previous three months; secondary hypertension; left ventricular hypertrophy; the presence of one severe or, uncontrolled cardiovascular risk factor; musculoskeletal problems interfering with exercise; or any other medical condition or disease that is life-threatening or that can interfere with or be aggravated by exercise. The included participants were inpatients (46.3%) and outpatients (53.7%). The former were hospitalized at a psychiatric rehabilitation unit with close discharge to the community setting. The inclusion and exclusion criteria for the CORTEX-SP study are shown in Table 1.

In the qualitative methodology, considering the difficulty of communication and sociability of people with SZ, all EX-group participants were asked voluntarily at the beginning of the program who wanted to participate in a recorded interview. Ten of them agreed. Once the intervention was completed after five months, and with the confidence gained in the person who conducted the sessions, 25 more people agreed to be interviewed (a total of 35 participants in this study). Participants (mean age 41.6 ± 10.3 years, 26 men and nine women) were recruited and thus included from hospital inpatients (n=16) and outpatients (n=19).

In addition to the CORTEX-SP study participants, another group was created to compare with an HC population (n = 30, 13 men [43.3%] and 17 women [56.7%], 40.0 ± 9.0 years) who did not receive any intervention. Only baseline measurements were assessed for comparison to the CORTEX-SP study participants. Inclusion for HC criteria was to be 25-55 years of age, and the candidates were excluded if they had any chronic medical illness, were taking any daily prescription medications, had current medical symptoms, had abnormal findings on physical examination (including blood pressure, BP ≥ 140/90 mmHg, or body mass index, BMI ≥ 25 kg/m^2), or had abnormal results on screening test both at rest and in exercise electrocardiogram.

Table 1. Inclusion and exclusion criteria for CORTEX-SP study.

Inclusion criteria
- Age: 18-65 years old. - Diagnosis of schizophrenia (DSM-5 F20.9). - Time of evolution of the disease greater than two years. - Stable and moderate cognitive impairment in MATRICS scores (T score < 40 in at least one of the seven cognitive domains). - Written informed consent.
Exclusion criteria
- Clinically unstable patients (PANSS-Positive total score >19). - Cognitive impairment secondary to another disease (dementia, mental retardation). - Primary diagnosis of substance use disorder or presenting active intoxicant use at the time of the study. - Patients who have required relevant modifications of antipsychotic pharmacological treatment in the previous three months. - Patients with active major affective disorder. - Incompatibilities with the MRI study: claustrophobia, metallic implants in the body, patients undergoing deep brain stimulation treatment. - Secondary hypertension. - Left ventricular hypertrophy (estimated left ventricular mass up to 103 g/m^2 for men and up to 89 g/m^2 for women). - The presence of one severe or uncontrolled cardiovascular risk factor or diabetes mellitus for more than ten years since diagnosis or with associated organopathy. - Other significant medical conditions: Including but not limited to chronic or recurrent respiratory, gastrointestinal, neuromuscular, neurological, or psychiatric conditions; musculoskeletal problems interfering with exercise; autoimmune or collagen vascular diseases; immunodeficiency diseases or a positive HIV test; anemias, bleeding disorders, chronic thrombotic disorders, or hypercoagulable states; malignancies in the past five years, except for skin cancer therapeutically controlled; endocrine and metabolic disorders, including type 1 diabetes mellitus; any other medical condition or disease that is life-threatening or that can interfere with or be aggravated by exercise. - Pregnancy or breast-feeding. - Plans to be out of the city for more than two weeks.

4.3. Measurements

The measurements used in the protocol for the current study were taken before and after a 20-week intervention period. The post-intervention test was scheduled for the following week after finishing the intervention period. The HC sample only performed baseline measurements with no intervention procedures. The primary outcome variable was CRF measured through $\dot{V}O_{2peak}$. A priori power analysis through G*Power 3 software (ver. 3.1.9.7; Heinrich-Heine Universität Düsseldorf, Germany) was performed.[225,226] A sample size of 106 participants (53 in each group) was estimated to obtain an effect size of d = 0.64 to observe inter groups differences, with 90% power and a 5% of the significance level.

The secondary outcome variables included BP (through 24-hour ambulatory measurement), body composition (body mass index, waist and hip perimeters, and bioimpedance), cardiometabolic profile, sleep quality (accelerometry) and subjective experiences (interviews). Both baseline and follow-up measurements were divided into four sessions (Table 2).

Age, sex, and cigarette smoking status were assessed by self-report. All medications prescribed to participants were recorded and classified into their groups (Aripiprazole, Clozapine, Paliperidone, Olanzapine, Quetiapine, Haloperidol, Risperidone, Ziprasidone, Levomepromazine, Perphenazine, and Lurasidone), and transformed into chlorpromazine-equivalents by using the defined daily dose method.

Anthropometry and body composition

Stature (SECA 213, Hamburg, Germany) and total body mass (SECA 869, Hamburg, Germany) were measured, and BMI was calculated as the total body mass divided by height squared (kg/m^2). Waist and hip circumferences were taken, and waist-to-hip ratio was defined as waist circumference divided by hip circumference in centimeters. All measurements followed the International Society for the Advancement of Kinanthropometry guidelines. Moreover, the estimation of fat-free mass, total body water, and fat mass were made by bioelectrical impedance (Tanita, BF 350, Arlington Heights, IL, USA).

Blood pressure

Ambulatory BP monitoring was performed with oscillometric ambulatory BP monitoring 6100 and 7100 recorders (Welch Allyn, New York, USA). We followed the report's recommendations by the ESC/ESH guidelines to ensure the best methodology.[15] The device measured BP at 30-minute intervals during the daytime and at 60-minute intervals during night-time. Participants had previously self-disclosed their typical bedtime and wake-up time, and it was used to define the assessments per 30-minute intervals and the beginning per 60-minute intervals. Recorded data were downloaded with participants' attendance to correct the bedtime and wake-up time in case of change. The recording was accepted if at least 75% of the recordings were obtained. If the ambulatory BP failed to measure the BP, another ambulatory BP was performed.

Table 2. Overview of the assessment schedule at baseline and follow-up in the CORTEX-SP study.

Session	Measurement	Methodology
DAY 1	FIRST VISIT	
	Age, sex, cigarette smoking	Self-report
	Medication	Psychiatrist
	Clinical symptoms	Psychiatrist
	PHYSICAL MEASUREMENTS	
	Stature (cm)	Stadiometer
	Body mass (kg)	Scale
	Waist and hip circumferences (cm)	Non-elastic tape
	Fat-free mass, fat mass, total body water	Bioelectrical impedance
	Systolic and diastolic blood pressure	Oscillometric monitor device
	Rest electrocardiogram	12-lead electrocardiogram
	BLOOD PRESSURE ASSESSMENT	
	Mean systolic and diastolic blood pressure, mean arterial pressure & pulse pressure (24 h)	Ambulatory blood pressure monitor
DAY 2	QUALITATIVE ASSESSMENT	
	Subjective experiences	Interviews
	PHYSICAL FITNESS	
	Cardiorespiratory fitness	Cardiopulmonary exercise test (bike)
DAY 3	MEASUREMENTS	
	Cardiorespiratory fitness	Modified Shuttle Walk Test
	Sleep quality	Accelerometer
DAY 4	BIOCHEMICAL MEASURES	
	Glucose (mg/dL)	Enzymatic spectrophotometry
	Insulin	Immunoassay chemiluminescent
	Haemoglobin A1c (%)	High-performance liquid chromatography ion exchange
	Total cholesterol, HDL-C, and LDL-C (mg/dL)	Enzymatic spectrophotometry
	Tryglicerides (mg/dL)	Enzymatic spectrophotometry
	Alanine aminotransferase (U/L)	Enzymatic spectrophotometry
	Aspartate aminotrnsferase (U/L)	Enzymatic spectrophotometry
	C-reactive protein (g/dL)	Enzyme immunoassay

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Physical fitness

Physical fitness measurements included a symptom-limited cardiopulmonary exercise test (CPET) and the MSWT.[136] The two tests were conducted on different days.

The CPET was performed on an electronically braked Lode Excalibur Sport cycle ergometer (Groningen, The Netherlands). The test protocol started at 40W for SZ individuals and at 70W for the HC group (~70 rpm), with gradual increments of 10W applied every minute until volitional exhaustion occurred with continuous electrocardiogram monitoring. Each participant's bike setup (*i.e*., saddle height, reach, and handlebar height) was recorded and registered to replicate at follow-up. Expired gas was analyzed with a system (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) that was calibrated before each test for the determination of peak oxygen consumption ($\dot{V}O_{2peak}$), which was defined as the highest oxygen uptake value attained toward the end of the test. Achievement of $\dot{V}O_{2peak}$ was assumed with the presence of two or more of the following criteria: 1) volitional fatigue (> 18 on Borg scale), 2) peak respiratory exchange ratio ≥ 1.1, 3) achieving > 85% of age-predicted maximum heart rate (HR), and 4) failure of oxygen consumption ($\dot{V}O_2$) and/or HR to increase with further increases in work rate.[126] BP was assessed every two minutes (Lode Excalibur automated BP module), and a self-reported Borg scale (6 to 20 scale) was recorded at the end of each stage. After completing the test, participants remained on the bike for five minutes of passive recovery with electrocardiogram and BP monitoring. In addition, the cardiorespiratory optimal point was assessed objectively. Thus, it considers the achievement of the cardiorespiratory optimal point at the nadir of the ventilation ratio ($L \cdot min^{-1}$) and $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$) obtained at every minute during the maximum exercise test, the so-called ventilatory equivalent for oxygen uptake.[227] First ventilatory threshold (VT1) was identified as the point of transition in the carbon dioxide production vs. $\dot{V}O_2$ slope from less than 1 to greater than 1, or VT1 was also recognized as the nadir of the ventilation ratio of oxygen uptake vs*.* work rate relationship.[126] Based on VT1 and VT2, the three exercise intensity domains were determined: (R1) light to moderate exercise intensity with HR values below VT1; (R2) moderate to high or vigorous exercise intensity with HR values between VT1 and VT2; and (R3) high to severe intensity exercise intensity with HR values up to VT2 to peak intensity. When the identification of the VT2 was not possible, exercise intensity ranges were designed considering percentages of HR reserve (HRR). In this sense, moderate intensity was defined between 50-75% of HRR, and high intensity between 76-95% of HRR.

The MSWT required the participant to walk up and down a 10 m course, and it was performed as previously described by Singh *et al.*[135] Participants walked along a flat, indoor 10 m course marked by two cones placed 0.5 m in from each end of the course. A shuttle refers to one 10 m lap. Standardized pre-recorded instructions for the test were played from a digital recording immediately before beginning the test. The test was externally paced, with signal beeps at regular intervals to indicate when the participant should be turning around the cone to commence the next shuttle. A triple beep signaled the next level and an increase in walking speed. Participants began the test at a walking speed of 0.5 m/seconds (level 1), allowing the participant 20 seconds to complete each of the three shuttles in level 1. There was a speed increment of 0.17 m/seconds each minute for a maximum of 15 minutes. The test was stopped when the participant could no longer maintain the required pace or was more than 0.5 m from the cone before the signal beep after one opportunity to catch up or if the test was completed. Additional criteria for early termination of the test included patient distress, dizziness, angina, the onset of severe musculoskeletal pain, failure of the HR to increase with exercise or attainment of 85% of the maximum HR. The number of shuttles completed was recorded at each test's completion and converted to the distance walked. Prior to commencing the test, with the participant in a seated position, baseline HR and BP were recorded. The HR and Borg scale (6 to 20) were monitored throughout the test, and BP and HR were recorded five more minutes after the test.

Accelerometry

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 (24 hours), except during water-based activities. Each participant was given oral instructions on wearing the accelerometer and completing the diary log. On the eighth day after the accelerometers were provided, both accelerometers and diaries were collected. Accelerometer data were downloaded, cleaned, and analyzed using the manufacturer's software (Actilife 6.11.9) with a 60-s epoch length. The following sleep variables were derived from ActiGraph data: total sleep time (min of sleep between sleep onset and wake time), bedtime (total min in bed), wakefulness after sleep onset (total min awake once they fall asleep), and sleep efficiency, that is obtained from ([total sleep time/total bedtime] × 100), and values below 85% are generally considered indicative of clinically significant reduced sleep efficiency.[228] Sleep patterns were assessed using a previously validated software algorithm based on the Cole-Kripke scoring method that analyzes the raw ActiGraph data to calculate sleep time.[229]

Interviews

A qualitative approach with semi-structured face-to-face interviews was chosen for the study. These were adopted to meet the research objectives to explore participants' involvement in the exercise program and their attitudes and beliefs regarding its role in managing their condition, general health, and well-being. Further, using semi-structured interviews through an interview schedule enabled the researcher to guide the discussion while leaving space for the participant to offer additional meaning and their understanding/perception of the topic.[230] The interview schedule was developed in line with the research aims and informed by existing literature on the topic. The PRE interview schedule included questions about the participants' conception and motivation of the program, their perception of exercise and sport, expectations regarding participation, and their life habits. The POST interview schedule included questions related to the context of the program (space, instructors, duration, and timetable), social relations, perceived benefits, satisfaction level, and plans. All interviews lasted 30-45 minutes, and 35 min on average duration.

Clinical symptoms

Two scales by the psychiatrists participating in the research assessed clinical symptoms: the Positive and Negative Syndrome Scale (PANSS),[231] and the Brief Negative Symptom Scale (BNSS).[232] 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.[233] The BNSS is used to assess the severity of negative symptoms.[234] It consists of 13 items, rated on a seven-point scale from 0 (normal) to 6 (extremely severe). The items are 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,[235] 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-MATRICS Consensus Statement on Negative Symptoms.[232,236]

4.4. Intervention

After baseline testing, participants were randomized to one of the two intervention groups (EX and TAU). The participants in the EX-group took part in exercise sessions three days per week for five 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). The exercise intensity for each participant was individually scheduled based on CRF and ventilatory thresholds (VT1 and VT2), which were determined from the peak oxygen consumption (VO_{2peak}) obtained by an ergospirometry (Lode Excalibur SportCycle, Netherlands) and expired gas analysis (Ergocard Medisoft SS, Belgium Ref. USM001 V1.0). Based on the identification of the two VTs, the three intensity ranges of exercise were determined: (R1) light to moderate intensity with HR values below VT1; (R2) moderate to high intensity with HR values between VT1 and VT2; and (R3) high to severe intensity with HR values from VT2 to the maximum HR achieved in the cardiopulmonary exercise test. All the exercise sessions started and finished with BP monitoring. Training intensity was controlled by HR monitoring (Polar Electro, Kempele, Finland) and through the rate of perceived exertion using Borg's original scale (6-20 points). Each session included a 10-minute warm-up with joint mobility and a 10-minute cool-down period with passive stretching exercises.

Table 3. Intervention program for exercise group on the bike. Volume and intensity progression.

LV-HIIT				
	HIGH-INTENSITY INTERVAL		**MODERATE-INTENSITY INTERVAL**	
Weeks	Volume (min)	Intensity (%HRR)	Volume (min)	Intensity (%HRR)
1	2	80	18	60
2	2.5	80	17.5	60
3	3	80	17	60
4	3.5	80	16.5	60
5	4	80	16	60
6-10	4.5	85	15.5	65
11-20	4.5	90	15.5	70

HRR: Heart rate reserve; LV-HIIT: low-volume and high-intensity interval training; min: minutes.

Combined exercise training was performed in the main part of each session (40 min). Each training session consisted of both a low-volume-HIIT (LV-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 (BH Fitness equipment), and a resistance circuit-training program (20 min). The intensity on the bike was individually tailored to each participant's HR at moderate (R2) or vigorous (R3) intensities. The LV-HIIT protocol on the bike was carried out in a 5-10-minute warm-up period at a moderate intensity, and after that, the participant cycled for 30 s at R3 followed by 60 s at R2. Four repetitions (1 rep = 30 s at R3 followed by 60 s at R2) were initially performed and gradually increased to nine repetitions. Intensity was individually tailored to HR at moderate or vigorous intensities, adjusting the bike speed to achieve the planned target HR (Table 3). The exercise specialists kept detailed records of all the exercise sessions, reporting the HR and Borg scale values of every interval. The importance of targeting moderate and high intensity was emphasized.

The resistance-circuit training was performed with three circuits (Figure 2), one for each week's workout, with ten different exercises. They were organized by major motor patterns (*i.e.*, knee dominant, hip dominant, press, pull, core, and micro impacts), and the exercises were alternately ordered based on whether they were upper or lower body. Each exercise was worked for 1 min with 30 s recovery. Initially, a single round of exercises was performed and gradually increased to two rounds. Several strategies were implemented to maximize adherence, including music in all sessions, individualized attention at the intervention sessions, and telephone calls following missed sessions.

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

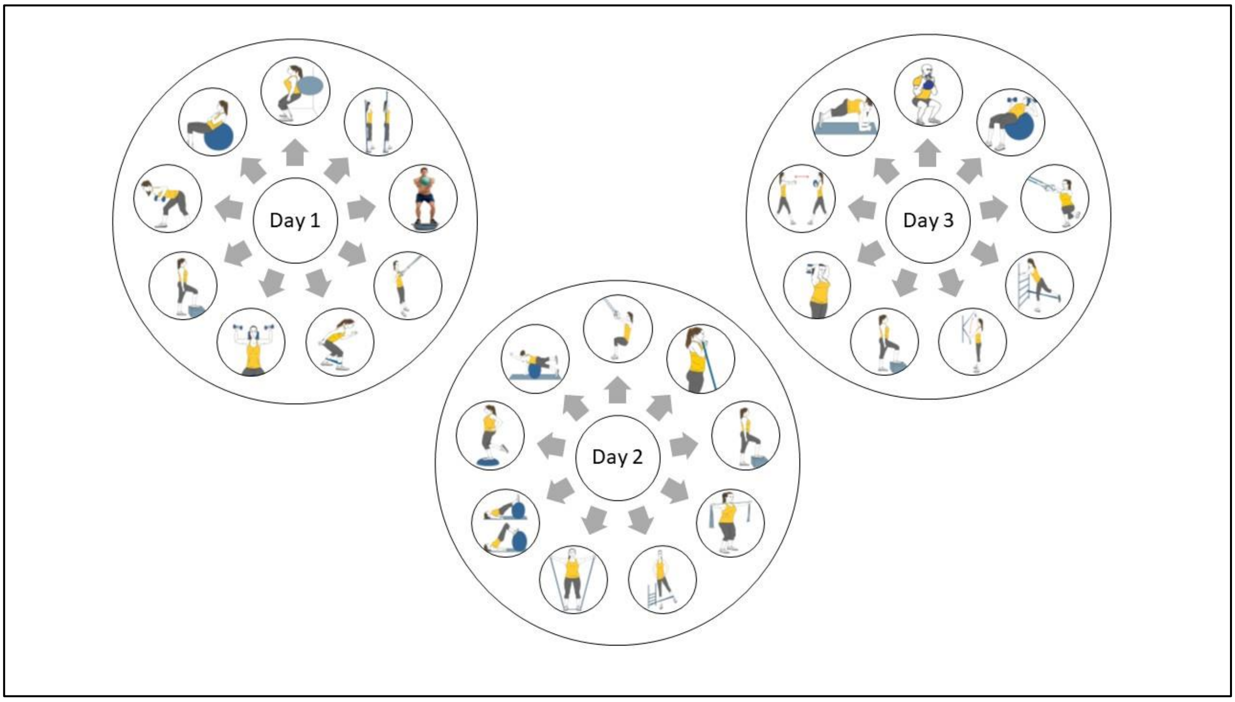

Figure 2. Resistance training circuit of the CORTEX-SP study.

Capítulo 4 / Chapter 4

Discusión/Discussion

5. DISCUSIÓN / Discussion

5.1. Artículo 1: *"Clinical, physical, physiological, and cardiovascular risk patterns of adults with schizophrenia: CORTEX-SP study."*

Referencia:

Tous-Espelosin M, Ruiz de Azua S, Iriarte-Yoller N, MartínezAguirre-Betolaza A, Sanchez P, Corres P, Arratibel-Imaz I, Sampedro A, Peña J, Maldonado-Martín S. Clinical, physical, physiological, and cardiovascular risk patterns of adults with schizophrenia: CORTEX-SP study: Characterization of adults with schizophrenia. *Psychiatry Res.* 2021;295:113580.

En este primer estudio el objetivo fue determinar algunos marcadores físicos, fisiológicos y bioquímicos clave del estado de salud, incluida la calidad del sueño, y estimar el RCV y la EV mediante diferentes métodos en personas adultas con SZ en comparación con HC. Tras el análisis estadístico, los principales hallazgos del presente estudio transversal fueron:

1) Las personas con SZ mostraron un perfil físico, fisiológico y bioquímico más pobre que las personas del grupo HC, con sobrepeso/obesidad, e incluyendo tanto valores más altos de LDL-C, índice aterogénico, proteína C reactiva y ácido úrico; como valores inferiores de CCR, capacidad ventilatoria y HDL-C.
2) Ambos grupos mostraron una eficiencia del sueño óptima similar (> 85% de eficiencia de sueño), pero las personas con SZ duermen más tiempo y también pasan más tiempo despiertas una vez que se duermen en comparación con las del grupo HC.
3) El RCV fue significativamente mayor en las personas con SZ que en las del grupo HC, independientemente del sistema de puntuación. Estos resultados ponen de relieve la importancia de la evaluación del RCV en las personas con SZ para la prevención de la ECV en la práctica clínica.

Las enfermedades cardiometabólicas y la SZ ensamblan antecedentes genéticos que conducen a una mayor predisposición al RCV,[237] y la inflamación crónica.[238] Por otro lado, en la SZ, hoy en día prevalece el uso de antipsicóticos de segunda generación sobre los de primera, lo que conlleva un cambio en los efectos adversos (es decir, de anomalías extrapiramidales a metabólicas).[26] Así, estudios previos han demostrado que al inicio de la enfermedad psicótica y tras unas pocas semanas de exposición a antipsicóticos, se identifican anomalías metabólicas relacionadas de por vida.[37] Asimismo, las personas estables con SZ que toman antipsicóticos de segunda generación conviven con numerosos efectos secundarios, entre ellos el aumento de masa corporal,[239] y la DLP.[27] En este sentido, cada vez hay más evidencia de que los antipsicóticos de segunda generación inducen a un aumento significativo del apetito relacionado con la alteración de la actividad hormonal del tejido adiposo (es decir, desregulación de las hormonas adiponectina, leptina, resistina y visfatina), lo que conduce a alteraciones del perfil lipídico.[237,240] En el presente estudio, el 94% de las personas con SZ estaban en tratamiento con fármacos antipsicóticos atípicos denominados de segunda generación y corroboran lo presentado en la literatura científica mencionada. Así, las personas del presente estudio mostraron un claro perfil de altos niveles de tabaquismo, sobrepeso (> 25 kg/m^2), obesidad (masa corporal grasa = 26,5%), alto riesgo metabólico basado en valores de perímetro de cintura (> 88 cm en mujeres y > 102 cm en hombres),[70] e índices de riesgo metabólico (DLP con LDL-C e índice aterogénico elevados, y concentraciones bajas de HDL-C; inflamación sistémica con nivel elevado de proteína C reactiva; e hiperuricemia) en comparación con la muestra de HC de edad similar. Como resultado, aunque la población con SZ de este estudio presentaba algunas características metabólicas favorables como perfil glucémico, triglicéridos y enzimas hepáticas, los otros factores de riesgo cardiometabólico llevaron a categorizar la muestra como SobME, según los criterios modificados de *Wildman*.[111] Añadido a estos resultados, en el presente estudio, los valores de FC en reposo fueron un 39,1% superiores en la población con SZ (81 ± 11 lpm) en comparación con la población HC (58 ± 7 lpm). Este resultado confirma la desregulación autónoma en la SZ con hipoactividad parasimpática acompañada de una relativa dominancia simpática.[241,242] Parece que los fármacos antipsicóticos ejercen un efecto significativo dependiente de la dosis sobre la actividad del sistema nervioso autónomo que conduce a un desequilibrio simpato-vagal y que se requiere una dosis óptima de antipsicóticos para evitar posibles efectos adversos de ECV.[242] Por lo tanto, un conjunto coordinado de acciones para eliminar o minimizar los factores del RCV y el impacto en la ECV debe ser el objetivo en esta población específica como en la población general.[108]

Sumado a esto, un metaanálisis previo ha confirmado que las personas con SZ realizan menos AF moderada a vigorosa (es decir, el determinante clave para producir adaptaciones biológicas para aumentar la CCR) en comparación con las personas sanas.[22] Por lo tanto, en el estudio actual el grupo con SZ presentaba valores bajos de CCR en comparación (-55%, $P < 0{,}001$, d de Cohen = 2,59) con el grupo HC ($\dot{V}O_{2pico}$ = 22,5 ± 9,0 *vs.* 50,0 ± 12,0 mL·kg^{-1}·min^{-1}; MET = 6,4 ± 2,7 *vs.* 14,2 ± 3,2),[133] en combinación con los altos valores del punto óptimo cardiorrespiratorio (es decir, ineficiencia ventilatoria > 30) podrían ser predictores de mortalidad por todas las causas.[243] Así, la trilogía de SobME, baja CCR y altos niveles del punto óptimo cardiorrespiratorio confirma un perfil RCV potente en la población de SZ estudiada. Diferentes factores podrían justificar las disparidades mencionadas: síntomas negativos, depresión, falta de acceso a infraestructuras o instalaciones, pobreza, baja autoeficacia en el EF, conocimiento limitado de los beneficios de la AF, procesos facilitadores limitados y conductas de riesgo generales.[125] Además, en la presente investigación, es importante mencionar los probables efectos de otros medicamentos concomitantes aparte de los antipsicóticos, como los estabilizadores del estado de ánimo (50% de la muestra) o los antidepresivos (27%) para aumentar el comportamiento sedentario y/o la falta de AF.

Por otro lado, la literatura suele presentar a la población con SZ como hipertensa primaria.[210] No obstante, los hallazgos del presente estudio muestran valores normales de TA en el grupo con SZ (115/70 mmHg), sin diferencias significativas con el grupo HC (113/68 mmHg). Se ha demostrado que un tratamiento antipsicótico más prolongado se asocia con una TAS más baja debido al bloqueo α-adrenérgico.[37] Estudios previos han demostrado que la Clozapina y la Olanzapina redujeron significativamente la TAS y se asociaron con hipotensión (se debería tener en cuenta que el 43% y el 21,1% de las personas que participaban tomaban Clozapina y Olanzapina, respectivamente).[244,245]

Se ha confirmado que dormir mal se asocia con una amplia gama de áreas de bienestar psicológico y físico deterioradas en la población con SZ.[238] Aunque investigaciones previas indican que cada persona debería dormir en función de sus necesidades individuales, en general se concluye que el patrón de sueño adecuado debería de ser el intermedio (*i.e.*, una media de 7-9 horas) para encontrar una asociación positiva entre la duración del sueño y la salud general.[246] En el presente estudio, cabe destacar que mientras el grupo con SZ mostró una duración media diaria del sueño de 554 minutos (*i.e.*, 9,2h), el grupo HC, por el contrario, presentó una duración significativamente inferior (*i.e.*, 415 min = 6,9h). No hay datos experimentales que sugieran un papel causal de la larga duración del sueño en relación con la salud mental, y tampoco hay pruebas claras de un mayor riesgo de ECV e HTA para una duración del sueño > 8 horas. En este sentido, la somnolencia/sedación es uno de los principales efectos secundarios de la toma de antipsicóticos de segunda generación,[239] y también uno de los efectos secundarios comunicados más prevalentes para la interrupción en el caso de Ziprasidona y Haloperidol.[247] Por otro lado, según las recomendaciones generales de la *National Sleep Foundation*, los principales indicadores de una buena calidad del sueño son la eficiencia del sueño y la vigilia tras el inicio del sueño.[248] En la presente investigación, ambos grupos mostraron una muy buena eficiencia del sueño >85% (es decir, la relación entre el tiempo total de sueño y la hora de acostarse);[228] sin embargo, cuando se analizó la vigilia tras el inicio del sueño se observaron diferencias significativas con valores más altos para el grupo con SZ en comparación con el grupo HC (50 ± 28 frente a 33 ± 13 min, Δ = 51%). En este sentido, sabiendo que una vigilia tras el inicio del sueño ≥ 41 minutos no indica una buena calidad del sueño,[248] esto podría cuestionarse en la población estudiada con SZ. La evidencia científica sugiere fuertemente que el sueño interrumpido y el ritmo circadiano disfuncional es una característica común del trastorno de SZ con alteraciones en la señalización de la dopamina.[249] Además, también hay pruebas de que los antipsicóticos afectan al sistema circadiano, lo que demuestra la importancia de un momento adecuado de administración del fármaco para evitar una mayor alteración del sueño y del ritmo circadiano.[249]

Teniendo en cuenta todo ello, parece esencial disponer de una evaluación rápida y precisa del RCV a través de diferentes cribados sistemáticos.[108] En el presente estudio, independientemente del modelo de estimación del RCV, el grupo con SZ mostró perfiles de RCV significativamente superiores en comparación con el grupo HC. Así, con respecto al riesgo coronario a 10 años mediante FHS, el grupo con SZ presentó un RCV moderado (8,4%), mientras que el grupo HC un riesgo bajo (2,7%). Estos resultados en la población SZ fueron similares a los encontrados en investigaciones previas.[103] Además, los datos del SCORE2 indicaron que el riesgo total de ECV, aunque significativamente diferente, es bajo para ambos grupos estudiados. Sin embargo, como se señaló en la introducción, SCORE2 está diseñado para personas > 50 años, y un riesgo absoluto bajo puede estar enmascarando un riesgo relativo mayor. Por lo tanto, cuando se utilizó la tabla de riesgo relativo basada en el hábito tabáquico, la TAS y el CT,[250] el grupo con SZ se clasificó de riesgo bajo a moderado (2%) y el grupo HC de riesgo bajo (1%). En consecuencia, la EV fue significativamente superior ($P < 0{,}001$) a la edad cronológica en el grupo con SZ (48 *vs.* 42 años) e inferior ($P < 0{,}001$) en el grupo HC (36 *vs.* 40 años). De este modo, la edad del sistema vascular en el grupo con SZ fue "mayor", pero "menor" en el grupo HC. Así, la presentación de la EV a la persona podría ser una herramienta útil en la comunicación de información sobre RCV, pudiendo entender lo que significa el riesgo particular en términos de vida.[61]

En conjunto, estos hallazgos ponen de manifiesto la necesidad de ofrecer un estilo de vida saludable (es decir, AF, dieta sana y control de sustancias tóxicas) para reducir el RCV y prevenir la ECV. Así pues, el siguiente paso podría ser desarrollar un enfoque más personalizado tanto en el tratamiento farmacológico como en el no farmacológico.

5.2. Artículo 2: “*Cross-validation of predictive equation for cardiorespiratory fitness by modified shuttle walk test in adults with schizophrenia: a secondary analysis of the CORTEX-SP study.*”

Referencia:

Tous-Espelosin M, Ruiz de Azua S, Iriarte-Yoller N, Sanchez PM, Elizagarate E, Sampedro A, Maldonado-Martín S. Cross-Validation of Predictive Equation for Cardiorespiratory Fitness by Modified Shuttle Walk Test in Adults with Schizophrenia: A Secondary Analysis of the CORTEX-SP Study. *Int J Environ Res Public Health*. 2021;18(21):11390.

Los objetivos de este segundo estudio fueron validar la ecuación presentada en el estudio original de Singh *et al*.[135] para evaluar la relación entre MSWT y $\dot{V}O_{2pico}$ en personas adultas con SZ, así como desarrollar y validar una nueva ecuación para que el MSWT prediga el $\dot{V}O_{2pico}$. Tras el análisis estadístico, los principales hallazgos del presente estudio transversal fueron:

1) Una nueva ecuación que incorpora el IMC, la FC en reposo y la distancia de la prueba MSWT funcionó mejor que la ecuación original de Singh *et al*.[135] para estimar el $\dot{V}O_{2pico}$ en la población estudiada.
2) El método de validación cruzada a posteriori confirmó la estabilidad del modelo.

Estudios anteriores también han presentado correlaciones entre las medidas del MSWT y la CPET que explican el 40,6% (en hombres sanos),[137] y el 57% (en personas con cirugía general) de la varianza del $\dot{V}O_{2pico}$,[251] y muestran viabilidad para la predicción del $\dot{V}O_{2pico}$. Sin embargo, de acuerdo con los presentes resultados, estas ecuaciones e incluso la ecuación de Singh *et al*.[135] pueden no ser un método apropiado para estimar la CCR a través del MSWT para la evaluación de la capacidad funcional en personas con SZ. Así, la ecuación de estimación de Singh *et al*.[135] mostró que los valores residuales estaban mal centrados y sólo explica el 57% de la varianza (R^2 ajustado = 0,57). La falta de precisión podría deberse a que Singh *et al*.[135] generaron la ecuación para personas con obstrucción crónica de las vías respiratorias cuya principal limitación para el EF es la disnea. A diferencia de las personas con problemas pulmonares, el rendimiento de las personas con SZ no suele estar limitado por la disnea, sino por el agotamiento, la baja CCR, los efectos secundarios relacionados con el tratamiento (fármacos antipsicóticos), la anhedonia y la falta de motivación.[252,253] Por tanto, entre las variables obtenidas en los modelos propuestos, el IMC y la FC en reposo, junto con la distancia recorrida en el MSWT, resultaron ser los predictores más relevantes. Estas variables explicaron el 60% de la variación del $\dot{V}O_{2pico}$ para la nueva ecuación, aumentando el R^2 y disminuyendo el SEE en comparación con la ecuación de Singh *et al*.[135] De acuerdo con esto, para la muestra estudiada, cuanto más elevados eran el IMC y la FC en reposo, y cuanto menor era la distancia recorrida en el MSWT, peor era la CCR. Esto puede explicarse por las asociaciones inversas de un IMC elevado, incluido un exceso de tejido adiposo visceral (*i.e.*, inflamación sistémica) y una FC en reposo elevada (*i.e.*, aumento de la actividad simpática) con una baja CCR.[254,255] Un ejemplo de uso de la ecuación recién generada podría ser el siguiente: si proporcionamos dos valores reales observados para dos personas con valores opuestos de CCR incluidos en esta muestra (Persona 1: $\dot{V}O_{2pico}$ = 40 $mL·kg^{-1}·min^{-1}$; IMC = 21,3 kg/m^2; distancia en MSWT = 1500 m; FC en reposo = 67 ppm. Persona 2: $\dot{V}O_{2pico}$ = 11 $mL·kg^{-1}·min^{-1}$; IMC = 46,6 kg/m^2; distancia en MSWT = 330 m; FC en reposo = 97 ppm), los valores estimados de $\dot{V}O_{2pico}$ serían 39,6 y 9,7 $mL·kg^{-1}·min^{-1}$, respectivamente, lo que se corresponde con un error de estimación muy bajo (0,4 y 1,3 $mL·kg^{-1}·min^{-1}$, respectivamente).

Uno de los objetivos científicos del presente estudio era predecir un resultado (*i.e.*, el $\dot{V}O_{2pico}$). Por lo tanto, debe decidirse la métrica con la que evaluar la calidad de la predicción.[256] En estudios anteriores no se ha validado la fórmula original,[135,140] o se ha obtenido un resultado de validación media sin un apoyo pleno de la validez de la ecuación.[144] En el presente estudio, tras el método de validación cruzada, se concluyó que el modelo era estable con un R^2 = 0,626, y presentaba una gran similitud con la ecuación recién generada (R^2 = 0,617). Así pues, los presentes resultados apoyan la validez de la ecuación para determinar de forma rutinaria la CCR de las personas con SZ utilizando el MSWT y la ecuación generada. Sin embargo, debemos ser cautelosos con esta afirmación, ya que la validez de $\dot{V}O_{2pico}$ estimado por la MSWT sigue siendo moderada (60% de la varianza). En este sentido, en el ámbito clínico, cuando la determinación precisa de la CCR es crítica, la CPET (con la evaluación objetiva de la $\dot{V}O_{2pico}$) seguirá siendo el patrón de oro.

5.3. Artículo 3: "*Does higher cardiorespiratory fitness impact the clinical symptoms in individuals with schizophrenia? A tertiary analysis of the CORTEX-SP study.*"

Referencia:

Tous-Espelosin M, Ruiz de Azua S, Pavon C, Elizagarate E, Sampedro A, Maldonado-Martín S. Does higher cardiorespiratory fitness impact the clinical symptoms in individuals with schizophrenia? A tertiary analysis of the CORTEX-SP study. *Journal of Physical Education & Sport*. 2023;23(7).

Este tercer estudio de la presente tesis doctoral tenía por objetivo el analizar el valor predictivo de la CCR y el IMC sobre los factores sintomáticos clínicos en la población con SZ. Los hallazgos principales del estudio fueron:

1) Las personas con menor CCR también mostraron una mayor presencia de síntomas negativos.
2) Tras el análisis de regresión, la CCR resultó ser el mejor predictor de los síntomas negativos, lo que indica que las personas con SZ con mayor CCR tenían menos probabilidades de experimentar síntomas negativos graves.
3) La variable IMC también contribuyó a predecir los síntomas negativos junto con la CCR.

Las personas que participaron en este estudio demostraron valores de sobrepeso evaluados según el IMC (> 25 kg/m^2),[257] niveles bajos de $\dot{V}O_{2pico}$ (< 25 mL·kg^{-1}·min^{-1}),[133] atribuidos a un estilo de vida predominantemente poco saludable,[22,23,37] y efectos adversos de los fármacos (*i.e.*, aumento de la masa corporal y síndrome metabólico).[258]

El tratamiento con fármacos antipsicóticos, aplicado como terapia de primera línea, normalmente conduce a una reducción de los síntomas positivos con un impacto mínimo en los síntomas negativos y cognitivos.[259] Por lo tanto, la pregunta abordada en este estudio fue si una mayor capacidad física afecta positivamente a los síntomas clínicos en la población con SZ. Investigaciones previas han indicado una fuerte asociación entre la reducción de la CCR en la población con SZ y los síntomas negativos y cognitivos.[88,260] Los hallazgos de este estudio se alinean con investigaciones previas,[98,123] porque las personas del estudio con mayor $\dot{V}O_{2pico}$ relativo (mL·kg^{-1}·min^{-1}) mostraron puntuaciones totales (P = 0,001) y puntuaciones de subescala general (P = 0,016) más bajas. Además, aquellas con mayor $\dot{V}O_{2pico}$ absoluto (L·min^{-1}) mostraron menores puntuaciones de síntomas negativos

(P > 0,001). Esto sugiere que las intervenciones de EF que aumentan la CCR, como el entrenamiento aeróbico a intervalos de alta intensidad,[197,200,261] pueden ser muy relevantes como programas adyuvantes para la población con SZ. Sin embargo, es crucial ser cauteloso en esta afirmación ya que las mejoras en los síntomas negativos a través del tratamiento farmacológico también pueden conducir a un aumento de la CCR porque las personas se vuelven más activas, comprometidas y motivadas para participar en programas de AF.

En este estudio, el $\dot{V}O_{2pico}$ ($L \cdot min^{-1}$) y el IMC explicaron significativamente el 11,1% ($P < 0{,}001$) y el 4% ($P = 0{,}019$) de la varianza en los síntomas negativos, respectivamente, dando lugar a una predicción total del 22,8%. Además, el $\dot{V}O_{2pico}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) explicó el 12,3% y el 17,8% de la varianza en los síntomas generales y totales, respectivamente. Aunque el intervalo de 11,1-17,8% puede parecer modesto en la predicción de los síntomas clínicos a través de la CCR, en particular con el parámetro patrón-oro (*i.e.,* $\dot{V}O_{2pico}$), no debe subestimarse la influencia de esta variable. Estudios previos en personas con SZ han demostrado una posible asociación bidireccional entre la CCR y las funciones cognitivas,[122] la sintomatología de la enfermedad,[262] y la gravedad de los síntomas negativos.[88,98] Aunque el diseño de este estudio no permite establecer vías causales entre la CCR y la cognición o la sintomatología, existen pruebas prometedoras sobre la diafonía endocrina entre el músculo esquelético y el cerebro a través del EF.[183,185,263] Investigaciones recientes han revelado vías biológicas y moleculares afectadas por el EF en personas con SZ, arrojando luz sobre los mecanismos subyacentes de la anhedonia, uno de los principales síntomas negativos de este trastorno.[264] El programa de AF en personas con SZ parecía regular el sistema ubiquitina-proteasoma, incluyendo proteínas implicadas en la regulación neuronal y neuroinflamatoria, así como proteínas del citoesqueleto de las células.[264]

Investigaciones previas en personas con SZ han demostrado una asociación entre un mayor IMC y una menor CCR.[98] En nuestro estudio actual, el IMC proporcionó una contribución adicional del 4% para predecir los síntomas negativos, junto con la CCR. Esto subraya la importancia de mejorar la salud física, como se observa en la disminución de la combinación de sobrepeso/obesidad con baja CCR, lo que pone de relieve la necesidad de cambios en el estilo de vida, como adoptar una dieta saludable y realizar AF regular, para controlar mejor los síntomas clínicos en esta población.

Dados los hallazgos mencionados, es crucial tener en cuenta la CCR tanto para evaluar el estado de condición física de las personas con SZ como para implementar intervenciones de EF dirigidas a aumentar la CCR, lo que puede conducir a una probable mejora de los síntomas de la enfermedad.

5.4. Artículo 4: "*As we were and as we should be, combined exercise training in adults with schizophrenia: CORTEX-SP study part I.*"

Referencia:

Tous-Espelosin M, Ruiz de Azua S, Iriarte-Yoller N, Sanchez P, Elizagarate E, Maldonado-Martín S. As we were and as we Should Be, Combined Exercise Training in Adults with Schizophrenia: CORTEX-SP Study Part I. *Med Sci Sports Exerc.* 2023. doi: 10.1249/MSS.0000000000003284.

Este cuarto estudio de la presente tesis doctoral tenía por objetivo el determinar los cambios en la composición corporal, CCR y las variables bioquímicas tras 20 semanas de entrenamiento combinado con EF en personas adultas con SZ caracterizadas al inicio como SobME con baja CCR. Los hallazgos principales del estudio (Figura 3) fueron:

1) El programa de EF combinado indujo cambios positivos y beneficiosos en la CCR sin cambios significativos en la composición corporal y las variables bioquímicas.
2) El grupo tratamiento habitual (TH), sin intervención de EF, no mostró ningún cambio significativo en las variables de estudio.
3) Se observaron diferencias significativas entre grupos en la CCR, umbrales ventilatorios y FC pico tras el periodo de intervención, favoreciendo al GEF.

Las personas con SZ suelen presentar un estilo de vida poco saludable (es decir, hábitos no saludables de alimentación, inactividad física y toxinas ambientales) unido al impacto negativo de factores socioeconómicos.[37] En ese sentido, las anomalías en la inflamación subyacentes a la enfermedad se ven agravadas por los factores de RCV relacionados con el estilo de vida, junto con la inflexibilidad metabólica, el aumento de la actividad proinflamatoria y la alteración de la regulación hormonal del apetito asociada al uso de antipsicóticos.[237,238] Las directrices sobre prevención de ECV en la práctica clínica recomiendan encarecidamente la necesidad de intensificar la atención y el apoyo para mejorar el cumplimiento de los cambios en el estilo de vida de las personas con trastornos mentales, incluida la reducción del tiempo de sedentarismo y el seguimiento de las recomendaciones generales de AF y EF.[43]

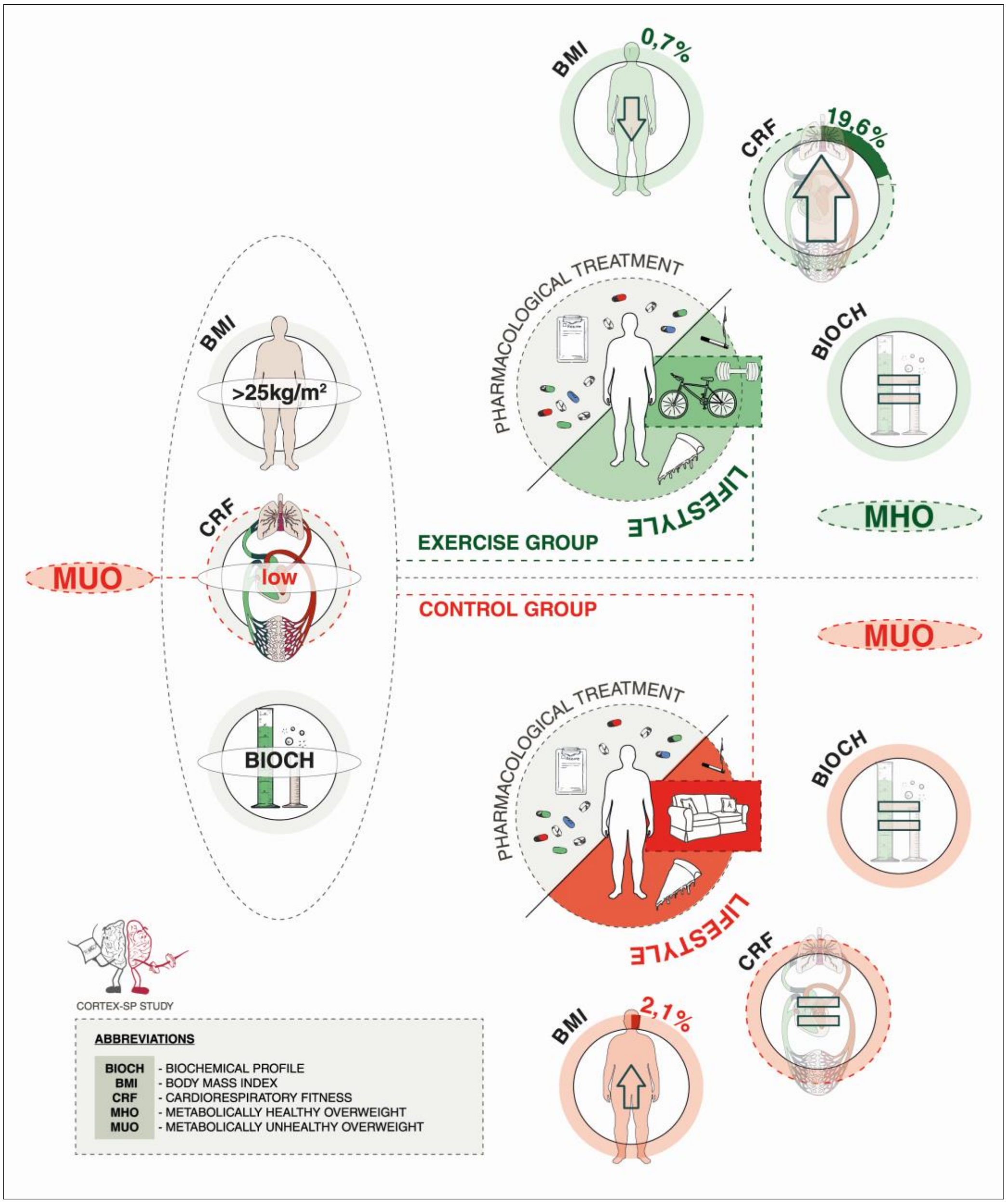

Figura 3. Infografía del artículo "*As we were and as we should be, combined exercise training in adults with schizophrenia: CORTEX-SP study part I.*"

Los resultados del presente estudio concuerdan con un metaanálisis previo que no demostró cambios en los marcadores de salud metabólica, como la composición corporal y algunos parámetros bioquímicos tras una intervención de EF en personas con SZ.[31] Estos resultados podrían explicarse en parte por: 1) centrarse totalmente en el EF como único componente de la intervención. Por lo tanto, se excluyeron programas más amplios de "vida sana", como una dieta saludable;[31] y 2) el tratamiento farmacológico como componente eficaz y necesario del tratamiento de la SZ. Así, la población con SZ ha mostrado anomalías metabólicas,[37] como un aumento de la masa corporal, obesidad abdominal y DM tipo 2.[26]

Tras 20 semanas de intervención combinada de EF (tres días/semana), las personas del presente estudio, categorizados como SobME con baja CCR al inicio,[252] no mostraron cambios significativos en la composición corporal ni en algunos de los parámetros metabólicos inflamatorios (es decir, IMC > 25 kg/m^2, LDL > 100 mg/dL, índice aterogénico > 3,5 mg/dL y proteína C reactiva > 3 mg/dL) asociados con síntomas de anhedonia en la SZ.[238] Sin embargo, la CCR, que se considera un factor clave en la salud cardiometabólica y que ayuda a disminuir el RCV,[195] aumentó significativamente en el GEF en comparación con el grupo TH (Δ = 19,6%, P < 0,001; valor F = 20,102), elevando el valor de referencia del VO_{2pico} del percentil 20 al 50%.[265] De acuerdo con esto y con respecto al impacto crítico de la CCR, las personas que participaban en el GEF del presente estudio podrían ser caracterizadas como SobMS, apoyando la noción de que una CCR más alta debería ser considerada como un rasgo más del fenotipo SobMS, y un factor de confusión en el análisis.[266,267]

Las pruebas han revelado que el entrenamiento combinado de EF puede actuar como programa adyuvante en personas con SZ mejorando tanto los síntomas psiquiátricos como los indicadores de forma física relacionados con la salud.[180] Las mejoras en la CCR pueden deberse a las adaptaciones al EF, que previamente han demostrado provocar notables adaptaciones celulares, vasculares y metabólicas durante el entrenamiento combinado, especialmente HIIT,[181] y este paradigma ha surgido desde entonces como un modo de EF seguro y más eficiente en el tiempo.[182] Además, una intervención con EF, especialmente importante en el caso de trastornos neurológicos como la SZ, sirve para prevenir y tratar diversas patologías y justifica una cuidadosa disección de las señales, redes y mediadores de la diafonía interorgánica que se origina en el músculo esquelético,[183] y de forma multidimensional en la función cerebral.[184] Además, teniendo en cuenta que en el presente estudio, el 60% de las personas que participaron en el GEF respondieron al programa de EF con un incremento superior a 1,02 MET y que por cada MET incrementado, el riesgo de mortalidad disminuía,[268] el papel del EF como enfoque adyuvante antiinflamatorio eficaz debería tenerse muy en cuenta en la población con SZ, y en otros trastornos mentales.

5.5. Artículo 5: *“'It Helped Me to Disconnect My Mind from the Problems': The Subjective Experiences of People with Schizophrenia Taking Part in a Concurrent Exercise Program.”*

Referencia:

Tous-Espelosin M, Crone D, Ruiz de Azua S, Iriarte-Yoller N, Sampedro A, Maldonado-Martín S. 'It Helped Me to Disconnect My Mind from the Problems': The Subjective Experiences of People with Schizophrenia Taking Part in a Concurrent Exercise Program. *Issues Ment Health Nurs.* 2023:1-9.

Este quinto y último estudio de la presente tesis doctoral tenía por objetivo el de dar a conocer las voces de las personas con SZ y sus experiencias subjetivas de un programa de EF combinado diseñado para mejorar su salud física y mental, a través de la participación. Los hallazgos principales del estudio fueron:

1) Del análisis surgieron seis temas. Los temas "expectativas sobre la participación" y "actitud hacia el EF, el programa y el estilo de vida en general" parecían influir en el grupo de participantes. El acto (y los factores asociados) de "participar" condujo a los subsiguientes "resultados percibidos" y "planes de futuro".
2) Los resultados de este estudio cualitativo revelaron que, al inicio del programa de EF, las personas que participaban sentían aprensión, pero la confianza en las personas que dirigían las sesiones, y la asistencia a las mismas a lo largo del tiempo, ayudaron a reducir esta aprensión con el paso del tiempo.

Esto apoya hallazgos previos sobre la importancia de las experiencias positivas del EF y la necesidad del apoyo social para facilitar la participación.[96] La literatura identifica que las personas con SZ son sensibles a las percepciones de los demás, como las personas profesionales sanitarias, especialmente cuando no existe una buena relación entre las personas.[58] Los hallazgos de este estudio identificaron que había un buen ambiente en las sesiones, entre las personas que dirigían la sesión y las personas que participaban. Este buen ambiente provocó una perspectiva positiva y una cultura motivadora para que pudieran continuar. Se han observado resultados similares en otros estudios en los que se generó confianza entre el grupo de personas que participaban (intragrupo) y entre la muestra que participaba y las personas que dirigían la sesión (intergrupo), lo que dio lugar a una alta adherencia al programa de EF.[269]

El estudio identificó varias barreras para participar y asistir, pero el apoyo social de las personas que dirigían la sesión, de otras personas del grupo y de la familia pareció ser importante para poder animar a su continuidad en el programa. Se han encontrado hallazgos similares en otros lugares, donde las barreras clínicas y un estilo de vida poco saludable, incluida la inactividad física,[22] el tabaquismo, el abuso de alcohol y/o cafeína y una dieta desequilibrada,[23] junto con los efectos adversos de los medicamentos,[258] y los factores socioeconómicos (por ejemplo, el acceso a la atención sanitaria),[37] se han identificado previamente como factores que afectan a la participación y la adherencia a lo largo del tiempo. En este estudio, se encontró que el apoyo social tanto de la atención sanitaria como directamente de la familia era importante para que algunas personas comenzaran y continuaran haciendo EF. Por lo tanto, el entorno social y familiar se identificaron como facilitadores de la participación en el EF. Estos hallazgos se hacen eco de los de otros estudios en los que el entorno social y el entorno familiar se identificaron como facilitadores de la modificación del estilo de vida.[54,56]

Este estudio encontró que las personas identificaron las mejoras generales que experimentaron, durante y después de las sesiones de EF, así como los cambios positivos en la salud física y mental y la CdV durante el programa. Otros estudios también han encontrado resultados similares.[54,253] Este estudio también ha identificado el disfrute de experiencias sociales positivas con otras personas que participaban en el programa y con las personas que dirigían la sesión. Otros, por ejemplo,[269,270] identificaron que las experiencias positivas de las personas durante la participación en el programa pueden ayudar a cambiar su percepción de algunas de las barreras antes de comenzar el programa (*i.e.*, la dificultad física del programa y el estado físico de las personas).

En el presente estudio, las personas que participaban expresaron en general su preferencia por el EF en grupo, aunque hay que señalar que hubo algunas excepciones. Sin embargo, a pesar de estas excepciones, es evidente la importancia de la dinámica de grupo para aumentar la motivación y facilitar la interacción social que resulta en hacer las actividades más agradables a través del apoyo social y del grupo.[56,270,271] Así, se apoya la importancia de un programa de EF en grupo para personas con SZ, cuando además se evidencian factores como la dinámica de grupo y un entorno de apoyo. Sin embargo, en la misma línea que un estudio previo,[56] algunas personas destacaron que, si los grupos no están equilibrados en cuanto a condición física y habilidades, podría producirse una disminución de la motivación. Además, en una actividad de grupo, siempre habrá diferentes opiniones sobre lo que la gente prefiere hacer, y en línea con otro estudio,[52] las personas que participaban en el presente estudio querrían poder elegir el tipo de EF realizado en el programa, principalmente porque se presentaban diferentes opiniones y creían que el programa debía ser más individualizado.

Uno de los hallazgos significativos de nuestro estudio fue el especial énfasis puesto por el grupo en que el programa de EF se llevara a cabo fuera del hospital. Esto apoya la literatura con respecto al papel clave que desempeña el entorno de EF para lograr el éxito de la intervención,[269] resultando en un factor facilitador para un resultado positivo, y proporcionando integración en la comunidad para aquellas personas que provienen de un entorno hospitalario.[54]

Uno de los hallazgos decepcionantes de este estudio fue la constatación de que, una vez finalizado el programa, las personas que participaban en el programa encontraban dificultades y frustración por no poder continuar haciendo EF. Al igual que estudios anteriores,[54,253] el grupo deseaba seguir practicando EF con regularidad para mantener los resultados y las experiencias positivas.[270] Sin embargo, en las experiencias de estas personas, los desafíos económicos de continuar,[54] y la falta de recursos en general,[253] fueron barreras para los programas de EF sostenibles a largo plazo. Las implicaciones para futuros programas consistirían en incorporar un elemento más sostenible al proyecto, tal vez mediante la vinculación con programas de EF realizados a nivel local, de modo que las personas pudieran incorporarse a programas de EF existentes y asequibles para permitir su continuación.

Capítulo 5 / Chapter 5

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6. REFERENCIAS / References

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Capítulo 6 / Chapter 6

Across the finish line

7. Across the finish line

7.1. CONCLUSIONS / Conclusiones

- ***Identifying specific clinical, physical, and physiological CVR profiles in SZ illness compared to healthy people strongly suggests that targeting a comprehensive approach, including non-pharmacological interventions, such as exercise and/or cognitive rehabilitation, could be effective and beneficial in the evolution of the disease.***

- ***The findings of this study support the validity of a new regression equation incorporating resting HR, BMI, and distance from MSWT to predict $\dot{V}O_{2peak}$ for assessment of CRF in people with SZ. However, when an accurate determination of functional capacity is required for diagnosis, clinical research, and exercise design, the direct measurement of $\dot{V}O_{2peak}$ will continue to be the "gold standard."***

- ***Individuals with lower CRF demonstrated a higher presence of negative symptoms. CRF emerged as the most potent predictor of negative symptoms, indicating that people with SZ and 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 SZ disorder. These findings can potentially enhance comprehensive treatment strategies for individuals with SZ.***

- ***A supervised combined exercise program in people with SZ helps to improve CRF levels leading. to an essential clinical change in the characterization from MUO (they were) to a metabolically healthy population with overweight or obesity (they should be). Hence, exercise should be considered a co-adjuvant program in treating the SZ population.***

- ***Exercise is an approach in treating and maintaining holistic health for people with SZ. Building a continuation plan for participation is also imperative to ensure sustainable and longer-term involvement in such programs. The program's location appears important to consider (i.e., out-of-hospital), as does the constitution of the group, the type of people, and the exercise program itself. For these participants, the program not only serves as an intervention for physical and mental improvement, but it also has the potential for holistic***

health benefits, such as well-being and essential opportunities for social interaction for this clinical group.

7.2. Limitaciones y propuestas de futuro

El presente estudio tiene varios puntos fuertes: 1) no existe ningún estudio con una muestra tan amplia de personas con SZ que realicen un programa combinado de EF durante cinco meses; 2) el presente estudio ha proporcionado pruebas claras de los beneficios del entrenamiento combinado de EF en personas con SZ; y 3) la muestra estudiada refleja fielmente las características clínicas y el tratamiento que reciben las personas con SZ que viven en la comunidad.

Sin embargo, deben tenerse en cuenta algunas limitaciones: 1) las personas que participaron fueron tratadas con una muestra heterogénea de antipsicóticos que refleja la práctica clínica habitual en la provincia de Araba/Álava. Cada familia de antipsicóticos tiene efectos diferentes sobre muchas de las variables medidas, pero estos efectos no se han estudiado en el análisis de los datos; 2) no se realizaron evaluaciones de fuerza que podrían haber aportado variables más interesantes para analizar y justificar los resultados; 3) la muestra es altamente representativa de la población con SZ de los centros de salud mental comunitaria de la misma comunidad (Araba/Álava), donde la salud mental y la atención social están muy bien consideradas, y puede no representar al resto de ciudades o comunidades de todo el mundo; y 4) el presente estudio no representa una división paritaria por sexo (es decir, 22,3% mujeres).

Para finalizar, como futuras línea de investigación se podría valorar el incorporar el entrenamiento de fuerza con cargas más altas, en comparación con el entrenamiento de resistencia. Para ello, sería interesante valorar la fuerza de todas las personas antes y después de la intervención de EF. Otro aspecto importante podría ser el de incorporar actividades al aire libre complementarias al programa. Por otro lado, el principal reto para este campo es establecer y evaluar programas integrados en la práctica clínica habitual que beneficien a largo plazo a las personas con SZ. En otras palabras, encontrar la forma de que los beneficios observados en ensayos clínicos de 12 o 18 meses de duración se mantengan durante 6, 12, 18 o más años para las personas con SZ. Finalmente, se podría valorar el efecto de la rehabilitación cognitiva junto con el EF y sus efectos en la salud de personas con SZ, para diseñar intervenciones adyuvantes más completas.

7.3. ¿Y ahora qué?

He de reconocer que la presente tesis doctoral la he realizado con una temática que me apasionaba, con una beca que me permitía poder vivir y rodeado de grandes profesionales que han hecho que todo fuera rodado. Por lo tanto, me siento un afortunado y me quedo con un muy buen sabor de boca en relación con el mundo de la investigación.

Puede sorprender que ahora que voy a conseguir ser doctor, me dé más respeto lo que está por venir. Aun así, siempre me he considerado positivo, intentando dejar fluir a la vida. Nada llega de manera inmediata, por eso hay que aprender a disfrutar del proceso.

Tengo las herramientas, los medios y las personas con las que quiero seguir construyendo, y a pesar de la incertidumbre que genera el mundo laboral universitario, tengo ganas de continuar, luchar y trabajar por mis sueños. Como diría Mario Alonso Puig, no es tanto el sueño, sino la persona en la que tienes que convertirte para conseguirlo.

Nunca sabes si el camino o decisiones que has tomado son las correctas, pero con mis errores y aciertos, mejores y peores momentos, volvería a escoger este camino y creo que lo mejor está por venir.

Capítulo 7 / Chapter 7

Publicaciones/Publications

8. PUBLICACIONES / Publications

8.1. Anexo 1: *"Clinical, physical, physiological, and cardiovascular risk patterns of adults with schizophrenia: CORTEX-SP study."*

Los indicadores de calidad de la revista del primer artículo publicado, según Journal Citation Reports (JCR) y Scientific Journal Rankings (SJR) en el año 2021 son los siguientes:

Revista		PSYCHIATRY RESEARCH
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País		NETHERLANDS
Categoría		PSYCHIATRY
JCR	JCR	1,46
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Clinical, physical, physiological, and cardiovascular risk patterns of adults with schizophrenia: CORTEX-SP study
Characterization of adults with schizophrenia

Mikel Tous-Espelosin[a,b], Sonia Ruiz de Azua[c], Nagore Iriarte-Yoller[d], Aitor MartínezAguirre-Betolaza[a,b], Pedro M. Sanchez[d], Pablo Corres[a], Iñaki Arratibel-Imaz[a], Agurne Sampedro[e], Javier Peña[e], Sara Maldonado-Martín[a,b,*]

[a] GIzartea, Kirola eta Ariketa Fisikoa Ikerkuntza Taldea (GIKAFIT). Society, Sports, and Physical Exercise Research Group. Department of Physical Education and Sport. Faculty of Education and Sport-Physical Activity and Sport Sciences Section. University of the Basque Country (UPV/EHU). Vitoria-Gasteiz. Araba/Álava. The Basque Country, Spain

[b] Bioaraba, GIKAFIT, Vitoria-Gasteiz, The Basque Country, Spain

[c] Department of Neuroscience, University of the Basque Country (UPV/EHU). Cibersam. The Basque Country, Spain

[d] Refractory Psychosis Unit, Hospital Psiquiátrico de Álava. Osakidetza. Vitoria-Gasteiz. Araba/Álava. The Basque Country, Spain

[e] Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Spain

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ABSTRACT

Schizophrenia (SP) is a severe mental illness with high rates of premature morbidity and mortality, associated with an unhealthy lifestyle and the side effects of drug treatment. The aims of the study were: 1) to determine some key physical, physiological and biochemical markers of health status, including sleep quality, in adults (42±10 yr) with SP (n=126), 2) to estimate cardiovascular risk (CVR), and 3) to compare all studied variables with a healthy control (HC) population (n=30). Assessment was based on body composition, blood pressure, cardiorespiratory condition, sleep quality with triaxial accelerometry for eight days and biochemical analysis. Participants with SP showed a cardiovascular risk profile including "overweight metabolically abnormal", low cardiorespiratory fitness, and impairment of ventilatory efficiency. Although individuals with SP slept more compared to HC, similar sleep efficiency was shown by both groups, but with significantly higher levels of wake after sleep onset by SP. The assessment of CVR revealed significantly higher values in SP (moderate risk) compared to HC (low risk) regardless of the estimation system. The identification of specific clinical, physical, and physiological CVR profiles in SP illness compared to healthy people strongly suggests targeting a comprehensive approach including non-pharmacological interventions.

Clinical Trials.gov identifier, NCT03509597. Date of registration: April 26th, 2018

Introduction

Schizophrenia (SP) is a chronic severe mental illness caused by a combination of genetic and ambient factors affecting 1% of people worldwide (Lieberman et al., 2006). Individuals with SP are diagnosed at an early age (~19-25 yr old), frequently follow a chronic course (Lieberman and First, 2018), and present a shorter life expectancy (*i.e.*, ~28.5 years less) than the general population (Olfson et al., 2015). The higher mortality rate in SP (Laursen et al., 2012) is not only caused by increased suicide but also associated with physical illness, cardiovascular disease being the most common one (Olfson et al., 2015).

An unhealthy lifestyle, including lack of physical activity (Stubbs et al., 2016), smoking, abuse of alcohol or caffeine, poor diet (Ratliff et al., 2012), along with adverse effects of medications (Mukundan et al., 2010), and social and economic factors (*e.g.*, access to health care) (Correll et al., 2014) have an important bearing on the presence of cardiovascular risk (CVR) factors, such as high blood pressure, elevated waist circumference, dyslipidemia, and glucose dysregulation (Ratliff et al., 2012).

Therefore, control and assessment of CVR in SP patients are

* Corresponding author: Sara Maldonado-Martín, Department of Physical Education and Sport. Faculty of Education and Sport. University of the Basque Country (UPV/EHU). Portal de Lasarte, 71. 01007 Vitoria-Gasteiz (Araba/Alava)-The Basque Country, Spain. Tel.: +34 945013534. Fax: +34 945013501.

E-mail address: sara.maldonado@ehu.eus (S. Maldonado-Martín).

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recommended according to different clinical guidelines (De Hert et al., 2009,Saiz Ruiz et al., 2008,American Diabetes Association et al., 2004). However, even though they appear to be cost-effective (Bruggeman et al., 2008,Gutierrez-Rojas et al., 2016), at this time they are not being implemented in the clinical care of patients (Mackin et al., 2007). Guidelines in people with SP include the need for comprehensive control of physical health monitorization, and recommend the control of physical activity levels, body mass gain through the waist-to-hip ratio and/or waist circumference, blood pressure, use of tobacco and alcohol or other substances, dietary intake, fasting blood glucose level, fasting blood lipids, and prolactin levels (National Collaborating Centre for Mental Health (UK), 2009,De Hert et al., 2009). The risk factors should be managed according to the total cardiovascular disease risk, and assessed by the score risk charts such as the Framingham Heart Study (FHS) and the Systematic Coronary Risk Estimation (SCORE) system, which calculate risk according to age, smoking habit, sex, systolic blood pressure and total cholesterol (TC), or the ratio of total to high-density lipoprotein cholesterol (HDL-C) (Piepoli et al., 2017,De Hert et al., 2009). However, individuals with SP are typically younger, and more likely to be smokers compared to the populations used to derive traditional cardiovascular disease risk scoring systems (Taxis et al., 2008). Therefore, the latest position statement from the European Psychiatric Association recommends the decision to include a relative risk chart for severe mental illness patients based on smoking habit, systolic blood pressure, and TC (De Hert et al., 2009). In addition, and also based on the FHS method, the vascular age (VA) is another useful tool for calculating the biological age of an individual's arteries (*i.e.,* the age of the vascular system of a person with different CVR factors) with the data on CVR factors (Cuende et al., 2010,Piepoli et al., 2017).

Besides traditional parameters, cardiorespiratory fitness (CRF; *i.e.*, the maximum amount of oxygen that can be taken in, transported to and utilized by the working tissue during exercise) (Hill and Hartley Lupton, 1923) is considered a vital sign and has emerged as a modifiable risk factor to attenuate the risk of developing non-communicable diseases (Despres, 2016,Kaminsky et al., 2019). Thus, the strong association between reduced CVR and higher levels of CRF, also inversely associated with cardiovascular disease mortality, is common knowledge (Kaminsky et al., 2019). In this sense, early studies with SP have shown 15% lower CRF values than healthy controls (Scheewe et al., 2012).

Another parameter that plays an essential role in our physical and mental health, wellness and overall vitality is good sleep quality, including sleep continuity variables (*i.e.*, sleep latency, number of awakenings, wake after sleep onset [WASO], and sleep efficiency) (Ohayon et al., 2017). A consensus recommendation for the minimum amount of sleep duration to support optimal health in adults was set at 7 hours, with uncertainty regarding the appropriateness of >9 hours. Disrupted sleep is common in SP and is associated with symptom severity (Ashton and Jagannath, 2020). Traditional sedative-hypnotics and second-generation sedating antipsychotics are the usual drugs prescribed for sleep stabilization (Ashton and Jagannath, 2020). However, when second-generation antipsychotics are taken by stable patients with SP, activating and sedating side effects, and body mass gain are presented, which could be associated with daily functionality (Tandon et al., 2020).

To the best of our knowledge, no reports are available that have carried out a clinical, physical, and physiological characterization of the SP population, including cardiovascular risk profiles through different methods. Therefore, the main purposes of this study were: 1) to determine some key physical, physiological and biochemical markers of health status, including sleep quality, in adults with SP, 2) to estimate CVR through different methods, and 3) to compare all studied variables with a healthy population.

Methods

Study participants

The CORTEX-SP study was conducted between May 2018 and July 2020 in Vitoria-Gasteiz (The Basque Country, Spain). The current baseline study comprised a total of 126 participants (CORTEX) aged between 18 and 65 years (mean 41.6±10.3 years), 105 men (83.3%), and 21 women (16.7%). All participants had a diagnosis of SP according to DSM-5 F20.9 (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*), with a disease evolution time greater than two years, stable and at least moderate cognitive impairment in the MATRICS variables (T score <40 in at least one of the seven cognitive domains). The exclusion criteria were: clinically unstable patients (total PANSS-Positive score >19); cognitive impairment secondary to another disease (dementia, mental retardation); main diagnosis of substance use disorder or presenting active substance use at the time of the study; patients who have required relevant modifications of antipsychotic drug treatment in the previous three months; patients doing another specific program of cognitive rehabilitation; patients with active major affective disorder; incompatibilities with the magnetic resonance imaging study (*i.e.,* claustrophobia, metal implants in the body, patients undergoing treatment by deep brain stimulation); secondary hypertension; left ventricular hypertrophy (estimated left ventricular mass up to 103 g/m^2 for men and up to 89 g/m^2 for women) (Lang et al., 2015); the presence of one severe or, uncontrolled CVR factor, or diabetes mellitus (more than 10 years since diagnosis), or with associated organopathy; other significant medical conditions including but not limited to chronic or recurrent respiratory, gastrointestinal, or neuromuscular conditions; musculoskeletal problems interfering with exercise; autoimmune or collagen vascular diseases; immunodeficiency diseases or a positive HIV test; anemias, bleeding disorders, chronic thrombotic disorders, or hypercoagulable states; malignancies in the past 5 years, with the exception of therapeutically controlled skin cancer; any other medical condition or disease that is life-threatening or that can interfere with or be aggravated by exercise, pregnancy or breast-feeding and plans to be out of the city for more than two weeks. The study was approved by the Research Ethics Committee of the Basque Country (PI2017044), and written informed consent was obtained from all participants before any data collection (Clinical Trials.gov identifier, NCT03509597).

On the other hand, a healthy control (HC) sample (n=30, 40.0±9.0 yr old, 40% men, and 60% women) was recruited from the community (approved by the Ethics Committee of the University of the Basque Country, UPV/EHU, M10/2018/229) and excluded if they had any chronic medical illness, were taking any daily prescription medications, had current medical symptoms, had abnormal findings on physical examination (including blood pressure≥140/90 mmHg, or overweight ≥25 kg/m^2), or had abnormal results on the screening test (rest and exercise electrocardiogram).

Measurements

Stature and body mass were measured, and body mass index was calculated as the total body mass divided by height squared (kg/m^2). Waist and hip circumferences were taken, and waist-to-hip ratio was defined as waist circumference divided by hip circumference both in centimeters. Moreover, the estimation of fat-free mass, total body water, and fat mass were made by bioelectrical impedance (Tanita, BF 350, Arlington Heights, IL, USA).

Blood pressure measurements were obtained using an ambulatory blood pressure monitoring recorder (ABPM) (6100 and 7100, Welch Allyn, New York, NY, USA) for a whole day (24h), through intervals of 30 minutes during the day and intervals of 60 minutes during the night. The variables considered from the ABPM measurements were mean values of systolic blood pressure, diastolic blood pressure, and heart rate.

Age, diabetes mellitus and cigarette smoking status were assessed by self-report. All medications prescribed to participants were recorded and classified in their groups: aripiprazole, clozapine, paliperidone, olanzapine, quetiapine, haloperidol, risperidone, ziprasidone, levomepromazine, perphenazine, and lurasidone.

Physical fitness measurements included a symptom-limited cardiopulmonary exercise peak test and the Modified Shuttle Walking Test (Bradley et al., 1999). The exercise test was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, Netherlands) starting at 40W with a gradual increment of 10W each minute in ramp protocol. Expired gas was analyzed with a system (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) that was calibrated before each test for the determination of peak oxygen consumption (VO_{2peak}), which was defined as the highest oxygen uptake value attained toward the end of the test. Achievement of VO_{2peak} was assumed with the presence of two or more of the following criteria: 1) volitional fatigue (>18 on Borg scale), 2) peak respiratory exchange ratio ≥1.1, 3) achieving >85% of age-predicted maximum heart rate, and 4) failure of oxygen consumption (VO_2) and/or heart rate to increase with further increases in work rate (Mezzani et al., 2012). In addition, the cardiorespiratory optimal point (COP) was assessed objectively. Thus, it considers the achievement of the COP at the nadir of the ventilation ratio (VE) ($L{\bullet}min^{-1}$) and VO_2 ($mL{\bullet}kg^{-1}{\bullet}min^{-1}$) obtained at every minute during the maximum exercise test, the so-called ventilatory equivalent for VO_2 (VE/VO_2) (Ramos et al., 2012). First ventilatory threshold (VT_1) was identified as the point of transition in the carbon dioxide production (VCO_2) *vs.* VO_2 slope from less than 1 to greater than 1, or VT_1 was also identified as the nadir of the VE of VO_2 *vs.* work rate relationship (Mezzani et al., 2012).

A blood sample (12.5 mL) was collected from each participant in the Alava Psychiatric Hospital after an overnight fast to determine the biochemical profile including hemoglobin, hematocrit, TC, HDL-C, LDL-C, TG, glucose, insulin, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), C-reactive protein, uric acid, creatinine, sodium, potassium, and albumin. HOMA-IR was used to evaluate insulin resistance [fasting serum insulin (μU/mL) × fasting plasma glucose (mg/dL)/405] (Matthews et al., 1985).

Sleep quality analysis was objectively and continuously assessed through a triaxial accelerometer (ActiGraph GT3X+, Pensacola, Florida, USA). Participants always wore the accelerometer on their non-dominant wrist with a velcro strap for eight consecutive days (24-hrs), except during water-based activities, and no other device was implemented during this period (*e.g.,* ABMP). On the eighth day, the accelerometer was returned to the investigators. The sleep measurements were calculated from raw ActiGraph data for each unit, they were downloaded, treated, and analyzed using the manufacturer's software (Actilife 6.11.9) with 60-s epoch length. The following sleep variables were derived from ActiGraph data: Total sleep time (TST) (min of sleep between sleep onset and wake time), WASO (total min awake once they fall asleep) and sleep efficiency, that is obtained from [(total sleep time/total bed time) × 100], and values below 85% are generally considered indicative of clinically significant reduced sleep efficiency (Schutte-Rodin et al., 2008). Sleep patterns were assessed using a previously validated software algorithm based on the Cole-Kripke scoring method (Cole et al., 1992) that analyzes the raw ActiGraph data to calculate sleep time.

The CVR profile was calculated with the FHS, SCORE, and a relative risk chart, which are quantitative methods used in primary care for assessment of the general CVR profile. In the FHS method, the sex-specific risk factors considered were: age, HDL-C, TC, systolic blood pressure, diabetes mellitus and smoking status. Each variable received a weighted score, and the sum of the score for each variable was then transformed into a percentage risk for a cardiovascular event in 10 years. Thus, a score of 10% means that there is a 10% chance of having a cardiovascular event within the next 10 years, under 6% is considered low risk, between 6 and 20% is considered medium risk, and a score of at least 20% is considered high risk (D'Agostino RB et al., 2008). On the other hand, and applying the FHS method, the VA indicates the biological age of the individual's vascular system, as the age a person would be with the same calculated CVR but whose risk factors were all within normal ranges. (D'Agostino RB et al., 2008). The SCORE charts were developed to estimate cardiovascular risk in European populations (adult men >40 years of age and women >50 years of age or post-menopausal) according to age, sex, smoking habit, systolic blood pressure and TC. The risk categorization was: calculated SCORE<1% low risk, ≥1% and <5% low- to moderate-risk, ≥5% and <10% high-risk, and ≥10% very high-risk (Graham et al., 2007,Piepoli et al., 2017). The relative risk chart, including in the European Guidelines on cardiovascular disease prevention, was based on smoking habit, systolic blood pressure and TC (De Hert et al., 2009,Piepoli et al., 2017).

Statistical analysis

To determine the normality a Shapiro-Wilk test was performed. Apart from body mass index, fat-free mass, total body water, fat body mass, systolic blood pressure, VO_{2peak}, peak metabolic equivalent of task (MET_{peak}), VCO_{2peak}, COP, workload, time, distance, peak diastolic blood pressure, peak respiratory exchange ratio, VT_1, Modified Shuttle Walk Test, glucose, HOMA, insulin, HDL-C, TC/HDL-C ratio, TG, AST, ALT, GGT, creatine, sodium, potassium, C-reactive protein, VA, sleep efficiency, WASO and TST, the rest of the variables were deemed normally distributed. Descriptive statistics were calculated for all variables. Data were expressed as mean±standard deviation (SD) when normality was met and as median±interquartile range when there was non-normal distribution. An independent samples t-test was used to determine whether there was a significant group difference for all parametric variables, and a Bonferroni post-hoc test was used to determine the level of significance when a significant main effect was found .In non-normal distribution variables, the Mann–Whitney U test was used to test differential between groups, and a Kruskal-Wallis Bonferroni post-hoc test was used to determine the level of significance when a significant main effect was found. Cohen's d was calculated to describe the standardized mean difference in between-group effect sizes. The effect sizes were interpreted as small (d=0.2), medium (d=0.5), and large (d=0.8) based on benchmarks suggested by Cohen (Cohen, 1998). The Chi-square test was used to test differences in categorical variables between groups and Cramer's V was calculated to describe the standardized mean difference between-group effect sizes. Cramer's V is between 0 and 1, when it is greater than 0.26 it is considered a significant correlation, 0.6 means relatively intense correlation and 1, a perfect relationship (McHugh, 2013). The Friedman test, a non-normal related test with data matrix segmentation, was used to calculate the differences between VA and chronological age. Statistical significance was set at $P<0.05$. The statistical analyses were performed with the SPSS version 25.0 software package.

Results

There were 162 participants enrolled for eligibility. However, 26 declined to participate and 36 did not meet the exclusion criteria. Therefore, 126 individuals diagnosed with SP performed a comprehensive assessment.

Characteristics of the studied populations are shown in Table 1. Related to body composition, CORTEX showed higher ($P<0.001$) values in body mass (Δ=26.6%), body mass index (Δ=21.6%), waist (Δ=29.2%), hip (Δ=8.2%), waist-to-hip ratio (Δ=17.9%), and fat body mass (Δ=23.3%), but lower ($P<0.001$) values in fat-free mass (Δ=-6.4%) and total body water (Δ=-6.4%) compared to HC. As a consequence, HC values are within normality, but not those in CORTEX, which are considered as CVR factors (body mass index>25 kg/m^2 as overweight, fat body mass=26.5% as obesity, and waist circumference=96.5 cm as high metabolic risk) (US Department of Health and

Table 1
Characteristics of the studied populations.

Variables	CORTEX n=126	HC n=30	$P_{CORTEX\ vs.\ HC}$	d Cohen/ Cramer's V
Age (yrs)	41.6±10.2	40.0±9.0	0.419	0.17
Body mass (kg)	83.7±16.2	66.1±10.5	<0.001***	1.29
BMI (kg/m^2)	27.6±7.4	22.7±2.6	<0.001***	0.88
Waist (cm)	96.5±14.3	74.7±8.1	<0.001***	1.88
Hip (cm)	104.2±9.5	96.3±5.5	<0.001***	1.02
WHR	0.92±0.09	0.78±0.07	<0.001***	1.74
FFM (%)	73.5±10.4	78.5±10.3	<0.001***	0.48
TBW (%)	53.8±7.7	57.5±7.5	<0.001***	0.49
FBM (%)	26.5±10.4	21.5±10.4	<0.001***	0.48
SBP (mmHg)	115±13	113±10	0.505	0.17
DBP (mmHg)	70±8	68±7	0.070	0.37
Mean HR (bpm)	81±11	58±6	<0.001***	2.43
Cigarette smoking (%)	62.7	16.1	<0.001***	0.37
Diabetes Mellitus (%)	8.7	-	-	-
Antipsychotic treatment (%)	100	-	-	-
First-generation	2.4	-	-	-
Second-generation	93.6	-	-	-
Mixed	4.0	-	-	-
First-generation				
Haloperidol (%)	3.1	-	-	-
Levomepromazine (%)	3.1	-	-	-
Perphenazine (%)	0.8	-	-	-
Second-generation				
Aripiprazole (%)	20.3	-	-	-
Clozapine (%)	43.0	-	-	-
Lurasidone (%)	1.6	-	-	-
Olanzapine (%)	21.1	-	-	-
Paliperidone (%)	31.3	-	-	-
Quetiapine (%)	5.5	-	-	-
Risperidone (%)	7.0	-	-	-
Ziprasidone (%)	2.3	-	-	-
Concomitant medication				
Anticholinergics (%)	7.3	-	-	-
Antidepressants (%)	27.3	-	-	-
Benzodiacepines (%)	49.1	-	-	-
Mood stabilizers (%)	13.6	-	-	-

HC, healthy control; BMI, body mass index; WHR, waist to hip ratio; FFM, fat-free mass; TBW, total body water; FBM, fat body mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate
Significant difference between CORTEX and HC was set at $P<0.05$
*$P<0.05$, ** $P<0.01$, *** $P<0.001$

Human Services, 2013).

Both groups showed optimal blood pressure values (*i.e.*, systolic blood pressure<120 mmHg, diastolic blood pressure<80 mmHg) (Volpe et al., 2019) with no differences ($P>0.05$) between groups. However, the mean heart rate was higher ($P<0.001$, Δ=39.1%) in CORTEX compared to HC, showing 23 more beats per minute. Approximately 63% of CORTEX participants reported currently smoking cigarettes, compared ($P<0.001$) with 16% in HC.

As for the medication-pharmacological therapy, HC did not take any regularly prescribed drug, while CORTEX all received controlled, regular, and mandatory antipsychotic medication therapy (Table 1).

When **exercise function** was assessed CORTEX showed lower values ($P<0.001$) of CRF (relative VO_{2peak}, Δ=-55.0%; MET_{peak}, Δ=-54.9%), test duration (Δ=-44.4%), distance performed (Δ=-64.4%), peak workload (Δ=-45.9%), peak heart rate (Δ=-15.2%), VT_1 (Δ=-57.1%), and distance in Modified Shuttle Walk Test (Δ=-47.0%) compared to HC (Table 2). According to Kaminsky et al. (Kaminsky et al., 2017), CORTEX participants were classified in the 20th percentile with a low physical condition (VO_{2peak} =22.5±9.0 mL•kg ^{1}•min ^{1}). Further, CORTEX showed higher values in the COP variable ($P<0.001$, Δ=20%), compared to HC, showing a lower ventilatory capacity (Ramos et al., 2012), and peak diastolic blood pressure ($P=0.034$, Δ=10.4%). No

Table 2
Participants' exercise function.

Variables	CORTEX n=122	HC n=30	$P_{CORTEX\ vs.\ HC}$	d Cohen
Workload $_{peak}$ (W)	126±54	233±76	<0.001***	1.62
Time (min)	10±6	18±7	<0.001***	1.22
Distance (km)	1.6±1.3	4.5±2.6	<0.001***	1.41
SBP_{peak} (mmHg)	183±29	185±26	0.784	0.06
DBP_{peak} (mmHg)	85±22	77±18	0.034*	0.40
HR_{peak} (bpm)	153±18	180±10	<0.001***	1.81
VO_{2peak} (L•min ^{1})	1.8±0.8	3.1±1.1	<0.001***	1.35
VO_{2peak} (mL•kg ^{1}•min ^{1})	22.5±9.0	50.0±12.0	<0.001***	2.59
VCO_{2peak} (L•min ^{1})	2.2±1.0	3.4±1.4	<0.001***	0.99
RER_{peak}	1.2±0.1	1.1±0.1	0.607	1
MET_{peak}	6.4±2.7	14.2±3.2	<0.001***	2.63
VT_1 (mL•kg ^{1}•min ^{1})	12.0±6.0	28.0±10.5	<0.001***	1.87
COP	30±6	25±4	<0.001***	1.21
MSWT (m)	795±390	1500±180	<0.001***	2.32

HC, healthy control; SBP_{peak}, peak systolic blood pressure; DBP_{peak}, peak diastolic blood pressure; HR_{peak}, peak heart rate; VO_{2peak}, peak oxygen uptake; VCO_{2peak}, peak carbon dioxide production; RER_{peak}, peak respiratory exchange ratio; MET_{peak}, peak metabolic equivalent of task; VT_1, first ventilatory threshold; COP, cardiorespiratory optimal point; MSWT, modified shuttle walking test distance.
Significant difference between CORTEX and HC was set at $P<0.05$
*$P<0.05$, **$P<0.01$, ***$P<0.001$

significant differences were shown when comparing the peak systolic blood pressure and peak respiratory exchange ratio values between groups (Table 2).

Regarding **biochemical profile** characteristics (Table 3) CORTEX participants showed upper optimal concentration of LDL-C (>100 mg/dL), atherogenic index (i.e., TC/HDL-C>3.5) (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002), C-reactive protein, a proinflammatory biomarker which is considered cardiometabolically unhealthy in values >3 mg/L (Hamer and Stamatakis, 2012), and borderline-serum uric acid concentration (6.0±1.3 mg/dL) (Johnson, 2015) and HDL-C (40.0±15.0 mg/dL). On the other hand, both groups (*i.e.*, CORTEX and HC) presented normal concentrations for TC (<200 mg/dL), TG (<200 mg/dL) (National Cholesterol Education Program (NCEP) Expert Panel on Detection,

Table 3
Biochemical profile characteristics of the study's participants.

Variables	CORTEX n=125	HC n=30	$P_{CORTEX\ vs.\ HC}$	d Cohen
Hemoglobin (mg/dL)	14.8±1.3	14.3±0.9	0.039*	0.45
Hematocrit (%)	44.2±3.7	43.8±3.2	0.593	0.12
Glucose (mg/dL)	91.0±14.0	85.0±13.0	<0.001***	0.44
HOMA-IR	1.8±1.7	0.9±0.4	<0.001***	0.73
Insulin (µU/mL)	7.8±6.8	4.1±1.9	<0.001***	0.74
TC (mg/dL)	187.1±42.4	183.6±35.1	0.686	0.09
HDL-C (mg/dL)	40.0±15.0	63.0±17.0	<0.001***	1.43
LDL-C (mg/dL)	114.6±39.0	104.8±30.3	0.223	0.28
TC/HDL-C ratio	4.7±1.9	2.9±0.9	<0.001***	1.21
TG (mg/dL)	115.0±85.0	65.0±25.0	<0.001***	0.80
AST (U/L)	18.0±6.0	21.0±4.0	<0.001***	0.59
ALT (U/L)	21.5±14.0	18.0±9.0	0.010*	0.30
GGT (U/L)	20.0±14.0	14.0±7.0	<0.001***	0.54
Uric acid (mg/dL)	6.0±1.3	4.7±1.1	<0.001***	1.08
CRP (mg/L)	3.1±4.6	0.5±0.6	<0.001***	0.79

HC, healthy control; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; CRP, C-reactive protein
Significant difference between CORTEX and HC was set at $P<0.05$
*$P<0.05$, **$P<0.01$, ***$P<0.001$.

Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002), fasting plasma glucose (<100 mg/dL) and insulin (<16.7 μU/mL) concentrations, HOMA-IR (<3.8) (Alberti et al., 2006), and the three hepatic enzymes (AST>30 U/L, ALT>30 U/L, GGT>50 U/L) (Nagano et al., 2010). After comparing both groups, CORTEX showed higher ($P<0.05$) values in hemoglobin (mean difference, MD=0.5; 95% confidence interval, CI=0.0, 1.0 mg/dL), glucose (MD=13.1; 95% CI=3.3, 22.8 mg/dL), HOMA-IR (MD=2.5; 95% CI=1.2, 3.7), insulin (MD=8.5; 95% CI=5.3, 11.7 μU/mL), TC/HDL-C ratio (MD=1.8; 95% CI=1.4, 2.1), TG (MD=77.4; 95% CI=57.2, 97.5 mg/dL), ALT (MD=6.7; 95% CI=3.4, 10.1 U/L), GGT (MD=9.3; 95% CI=0.6, 17.9 U/L), uric acid (MD=1.2; 95% CI=0.7, 1.8 mg/dL), and CRP (MD=5.1; 95% CI=3.1, 7.1 mg/L) compared to HC. Moreover, HDL-C (MD=-21.5; 95% CI=-26.1, 17.0 mg/dL) and AST (MD=-2.6; 95% CI=-5.3, 0.0 mg/dL) concentrations were lower in CORTEX than in HC group.

The analysis of **sleep quality** from actigraphy (Table 4) showed higher TST ($P<$ 0.001, Δ=33.3%) and WASO ($P=0.004$, Δ=50.7%) in CORTEX compared to HC. However, when sleep efficiency (*i.e.*, the relationship between sleeping time and bedtime) was analyzed no significant differences ($P=0.987$) between groups were found, with both exceeding 85%, which is considered optimal sleep efficiency.

The **CVR assessment** (Figure 1) showed differences ($P<0.001$) between groups with higher values in CORTEX compared to HC (FHS, MD=5.7, 95% CI=4.0, 7.5%; SCORE, MD=0.4, 95% CI=0.2, 0.7%; and relative risk chart, MD=1.0, 95% CI=0.7, 1.3%). Thus, in accordance with the ACC/AHA Guidelines on the assessment of CVR (D'Agostino RB et al., 2008) and European Guidelines on cardiovascular disease prevention (Piepoli et al., 2017), considering SCORE, both groups were classified as low risk; but taking into account FHS and relative chart, CORTEX was considered to have moderate risk, while HC low risk. When VA was analyzed (Figure 2): 1) CORTEX showed higher ($P<0.001$) values than HC (MD=15.4, 95% CI=−9.5, 21.3 years) and higher ($P<0.001$) values than their chronological age (MD=7.6, 95% CI=5.6, 9.5 years), and 2) VA in HC was lower ($P<0.001$) than their chronological age (MD=-6.5, 95% CI=-9.6, 3.4 years).

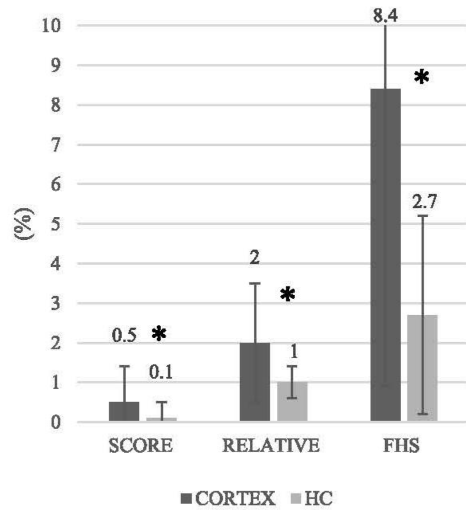

Fig. 1. Comparison of cardiovascular risk estimation in the studied groups. SCORE: Systematic Coronary Risk Estimation; RELATIVE: Relative Risk; FHS: Framingham Heart Study. *$P<0.001$: Significant difference between CORTEX and healthy control (HC).

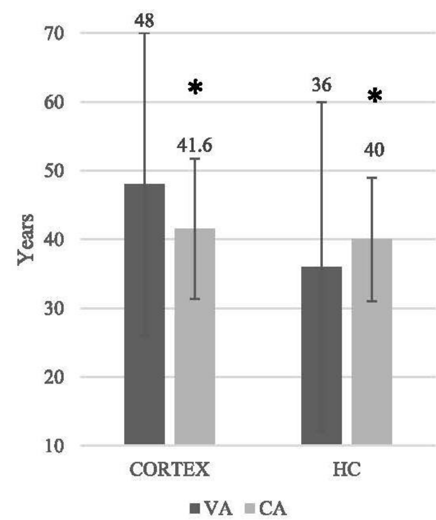

Fig. 2. Comparison of vascular age (VA) and chronological age (CA) in the studied groups. *$P<0.001$: Significant difference between CORTEX and HEALTHY.

Discussion

In the present study, an analysis of physical, physiological, and biochemical markers of the health status in people with SP (*i.e.*, CORTEX sample) was carried out and compared to a HC sample. The main findings of this study were: 1) CORTEX showed a worse physical, physiological and biochemical profile than HC with overweight/obesity; upper optimal LDL-C, atherogenic index, C-reactive protein and uric acid concentration; low CRF, ventilatory capacity and HDL-C concentrations, and high mean heart rate, 2) both groups showed similar optimal sleep efficiency, but CORTEX sleep more time and also spend more time awake once they fall sleep than HC, and 3) CVR was significantly higher in CORTEX than in HC regardless of the scoring system. These findings highlight the importance of CVR assessment of people with SP for the prevention of cardiovascular disease in clinical practice.

Cardiometabolic diseases and SP disorder share overlapping genetic backgrounds leading to higher CVR predisposition (Lis et al., 2020), and chronic inflammation (Fond et al., 2020). On the other hand, for SP disorder, there is, nowadays, a prevailing use of second-generation over first-generation antipsychotics leading a shift in the adverse effects (*i.e.*, from extrapyramidal to metabolic abnormalities) (Maayan et al., 2010). Thus, previous studies have shown that early in the psychotic illness and after a few weeks of antipsychotic exposure, lifetime-related metabolic abnormalities are identified (Correll et al., 2014). Likewise, stable patients with SP taking second-generation antipsychotics are living with many side effects including body mass gain (Tandon et al., 2020) and dyslipidemia (Huang, T. L. and Chen, 2005). In this sense, there is now some growing evidence that second-generation antipsychotics induce

Table 4
Sleep variables analysis of study population.

Variables	CORTEX n=113	HC n=30	$P_{CORTEX\ vs.\ HC}$	*d Cohen*
Sleep Efficiency (%)	91.5±5.4	92.4±3.5	0.987	0.20
TST (min)	553.9±145.2	415.3±70.6	<0.001***	1.21
WASO (min)	49.6±28.0	32.9±13.1	0.004**	0.76

HC, healthy control; TST, total sleep time; WASO, wake after sleep onset.
Significant difference between CORTEX and HC was set at $P<0.05$
*$P<0.05$, **$P<0.01$, ***$P<0.001$

significant appetite increase related to the impaired hormonal activity of adipose tissue (*i.e.*, dysregulation in adiponectin, leptin, resistin and visfatin hormones) leading to lipid profile disturbances (Huang, J. et al., 2020,Lis et al., 2020). In the present study, ~94% of SP participants were treated with atypical called second-generation antipsychotic drugs (Table 1) and corroborate what is presented in the aforementioned scientific literature. They showed a clear profile of increased cigarette smoking, overweight (>25 kg/m^2), obesity (fat body mass=26.5%), high metabolic risk based on waist circumference values (>88 cm in women and >102 cm in men) (ACSM, 2018) and several metabolic risk indices (dyslipidemia with high LDL-C and atherogenic index, and low HDL-C concentrations; systemic inflammation with high C-reactive protein level; and hyperuricemia) compared with similarly aged HC sample. As a result, although the SP population of this study presented some favorable metabolic features such as glycemic profile, TG, and hepatic enzymes, the other cardiometabolic risk factors led to categorizing the sample as "*overweight metabolically abnormal*" according to Wildman modified criteria (Martinez-Larrad et al., 2014). Adding to the abovementioned picture, in the present study, resting heart rate values are 39.1% higher in the CORTEX (81±11 bpm) than the HC (58±7 bpm) population (Table 1). This result confirms the autonomic dysregulation in SP with parasympathetic hypoactivity accompanied by relative sympathetic dominance (Montaquila et al., 2015,Iwamoto et al., 2012). It seems that antipsychotic drugs exert a significant dose-dependent effect on autonomic nervous system activity leading to a sympathovagal imbalance and that optimal antipsychotic dose is required to avoid possible cardiovascular disease adverse events (Iwamoto et al., 2012). Hence, a coordinated set of actions to eliminate or minimize the CVR factors and the impact on cardiovascular disease should be the aim in this specific as in the general population (Piepoli et al., 2017).

Adding to that, a previous meta-analysis has confirmed that people with SP engage in less moderate-to-vigorous physical activity (*i.e.*, the key determinant to produced biological adaptations to increase CRF) compared to healthy controls (Stubbs et al., 2016). Therefore, in the current study the low physical condition (Kaminsky et al., 2017) presented by CORTEX compared (-55%, $P<0.001$, *d* Cohen=2.59) to HC (VO_{2peak}: 22.5±9.0 *vs.* 50.0±12.0 mL•kg ^{1}•min ^{1}; MET_{peak}: 6.4±2.7 *vs.* 14.2±3.2), in combination with the high COP (*i.e.*, ventilatory inefficiency >30) might be predictors of all-cause mortality (Ramos and Araujo, 2017). Thus, the trilogy of "*overweight metabolically abnormal, low CRF and high COP*" confirms a powerful CVR profile in the studied SP population. Different factors could justify the aforementioned disparities: negative symptoms, depression, lack of access to infrastructures or facilities, poverty, low self-efficacy in exercise, limited knowledge of the benefits of physical activity, facilitating processes limited and general risk behaviors (Bassilios et al., 2015). Further, in the present investigation, it is important to mention the likely effects of other concomitant medications apart from antipsychotics, such as mood stabilizers (~50% of participants) or antidepressants (27%) to increase the sedentary behavior and/or lack of physical activity.

On the other hand, literature often presents the SP population as suffering from primary hypertension (Tumiel et al., 2019). Nonetheless, the findings of the present study show normal blood pressure values in CORTEX (115/70 mmHg), with no significant difference to HC (113/68 mmHg). It has been shown that longer antipsychotic treatment is associated with lower systolic blood pressure due to α-adrenergic blockade (Correll et al., 2014). Previous studies have shown that clozapine (Parks et al., 2018) and olanzapine (Choure et al., 2014) significantly reduced systolic blood pressure and were associated with hypotension (note that 43.0% and 21.1% of our participants were taking clozapine and olanzapine, respectively).

It has been confirmed that poor sleep is associated with a wide range of impaired psychological and physical areas of well-being in the SP population (Fond et al., 2020). Although previous research indicates that each person should sleep depending on individual needs, it is generally concluded that the appropriate sleep pattern has to be the intermediate one (*i.e.*, an average of 7-9 hours) to find a positive association between sleep duration and general health (Watson et al., 2015). In the present study, it was noteworthy that while CORTEX showed a daily average sleep duration of 554 minutes (*i.e.*, 9.2 h), HC, by contrast, presented significantly lower duration (*i.e.*, 415 min=6.9 h). There are no experimental data to suggest a causal role for long sleep duration in relation to mental health, and there is also no clear evidence for increased risk of cardiovascular disease and hypertension for sleep duration >8 hours (Watson et al., 2015). In this sense, sleepiness/sedation is one of the main side effects of taking second-generation antipsychotics (Tandon et al., 2020), and also one of the most prevalent reported secondary effects for discontinuation in the case of ziprasidone and haloperidol (Gómez-Revuelta et al., 2020). On the other hand, according to the general recommendations of the National Sleep Foundation, the main indicators for good sleep quality are sleep efficiency and WASO (Ohayon et al., 2017). In the current investigation, both groups showed very good sleep efficiency >85% (*i.e.*, the relationship between TST and bedtime) (Schutte-Rodin et al., 2008); however, when WASO was analyzed significant differences were observed with higher values for CORTEX compared to HC (50±28 *vs.* 33±13 min, Δ=51%). In this sense, knowing that a WASO≥41 minutes does not indicate good sleep quality (Ohayon et al., 2017), this could be questioned in the SP studied population. The scientific evidence strongly suggests that disrupted sleep and dysfunctional circadian rhythm is a common feature of SP disorder with alterations in dopamine signaling to be central to this role (Ashton and Jagannath, 2020). Further, there is also evidence that antipsychotics affect the circadian system, demonstrating the importance of appropriate timing of drug administration to prevent further sleep and circadian disturbance (Ashton and Jagannath, 2020).

Taken into account altogether, it seems essential to have a rapid and accurate CVR assessment through different systematic screening (Piepoli et al., 2017). In the present study, regardless of the CVR estimation model, CORTEX showed significantly higher CVR profiles compared to HC (Figures 1 & 2). Thus, with regard to 10-year coronary risk through FHS, CORTEX presented moderate CVR (8.4%), while HC low risk (2.7%). These results in the SP population were similar to those found in previous research (Gutierrez-Rojas et al., 2016). Further, the SCORE data indicated that the total CV event risk, although significantly different, is low for both the studied groups. However, as noted in the introduction, SCORE is designed for people >50 years, and a low absolute risk may be masking a higher relative risk. Therefore, when the relative risk chart based on smoking habit, systolic blood pressure and TC (De Hert et al., 2009) was used, CORTEX was classified from low-to-moderate risk (2%) and HC low risk (1%). Accordingly, VA was significantly higher ($P<0.001$) than chronological age in CORTEX (48 *vs.* 42 years) and lower ($P<0.001$) in HC group (36 *vs.* 40.0 years). In this way, the age of the vascular system in CORTEX was "older", but "younger" in HC (Figure 2). Thus, the presentation of VA to the patient could be a useful tool in communicating information about CVR, being able to understand what the particular risk means in terms of life (Cuende et al., 2010).

Taken together, these findings highlight the view and counseling to offer a healthy lifestyle (*i.e.*, physical activity, healthy diet and toxic substance control) in order to reduce CVR and prevent cardiovascular disease. Thus, the next step could be to develop a more personalized approach in both pharmacological and non-pharmacological treatment.

Although the present study has highlighted the significant differences in a population with SP compared to similarly aged HC people according to physical, physiological, and biochemical characteristics, several limitations should be acknowledged. First, while the sample size could be sufficient as an initial investigation, it would not be comparable with that of larger epidemiological studies. Secondly, the current study only presented 17% of women in the SP studied population, which does not represent an equal gender split of the sample, and it has been the main reason for not analyzing differences by sex. However, taking into account the difficulties involved in recruiting volunteers with mental disfunction, we could argue that the sample is adequate. Finally, the strict exclusion criteria limited the recruitment of some candidates during the screening period; therefore, this might limit the generalization of the results to an ordinary SP population in treatment.

In closing, the identification of specific clinical, physical and physiological CVR profiles in SP illness compared to healthy people strongly suggests that targeting a comprehensive approach including non-pharmacological interventions, such as physical exercise and/or cognitive rehabilitation, could be effective and beneficial in the evolution of the disease.

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CRediT author's contribution

Mikel Tous-Espelosin: Conceptualization, Formal analysis, Investigation, Data Curation, Writing-Original draft, Writing-Review & Editing, Visualization. **Sonia Ruiz de Azua:** Writing-Review & Editing, Supervision, Funding acquisition. **Nagore Iriarte-Yoller:** Investigation, Resources, Project administration. **Aitor MartinezAguirre-Betolaza:** Investigation, Data Curation, Writing-Review & Editing. **Pedro M. Sanchez:** Methodology, Investigation, Resources, Supervision, Project administration, Funding acquisition. **Pablo Corres:** Investigation, Data Curation, Writing-Review & Editing. **Iñaki Arratibel-Imaz:** Investigation, Data Curation, Supervision. **Agurne Sampedro:** Investigation, Data Curation, Writing-Review & Editing. **Javier Peña:** Investigation, Data Curation, Writing-Review & Editing. **Sara Maldonado-Martin:** Conceptualization, Methodology, Investigation, Resources, Writing-Original draft, Writing-Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

Conflicts of Interest

The authors declare no conflict of interest.

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Article

Cross-Validation of Predictive Equation for Cardiorespiratory Fitness by Modified Shuttle Walk Test in Adults with Schizophrenia: A Secondary Analysis of the CORTEX-SP Study

Mikel Tous-Espelosin [1,2], Sonia Ruiz de Azua [3], Nagore Iriarte-Yoller [4], Pedro M. Sanchez [4,5], Edorta Elizagarate [4], Agurne Sampedro [6] and Sara Maldonado-Martín [1,2,*]

1 GIzartea, Kirola eta Ariketa Fisikoa Ikerkuntza Taldea (GIKAFIT), Society, Sports and Physical Exercise Research Group, Department of Physical Education and Sport, Faculty of Education and Sport-Physical Activity and Sport Sciences Section, University of the Basque Country (UPV/EHU), 01007 Vitoria-Gasteiz, Araba/Álava, Basque Country, Spain; mikel.tous@ehu.eus
2 Physical Activity, Exercise and Health Group, Bioaraba Health Research Institute, 01009 Vitoria-Gasteiz, Araba/Álava, Basque Country, Spain
3 Cibersam, Department of Neuroscience, University of the Basque Country (UPV/EHU), 48940 Leioa, Bizkaia, Basque Country, Spain; sonia.ruizdeazua@ehu.eus
4 Refractory Psychosis Unit, Psychiatric Hospital of Alava, 01007 Vitoria-Gasteiz, Araba/Álava, Basque Country, Spain; nagore.iriarteyoller@osakidetza.eus (N.I.-Y.); pedromanuel.sanchezgomez@osakidetza.eus (P.M.S.); eduardojose.elizagaratezabala@osakidetza.eus (E.E.)
5 Faculty of Medicine, University of Deusto, 48007 Bilbao, Basque Country, Spain
6 Department of Psychology, Faculty of Health Sciences, University of Deusto, 48007 Bilbao, Basque Country, Spain; a.sampedro@deusto.es
* Correspondence: sara.maldonado@ehu.eus; Tel.: +34-945013534; Fax: +34-945013501

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Abstract: Cardiorespiratory fitness (CRF) can be direct or estimated from different field tests. The Modified Shuttle Walk Test (MSWT) is suitable for all levels of function, allowing a peak response to be elicited. Therefore, we aimed (1) to validate the equation presented in the original study by Singh et al. for evaluating the relationship between MSWT with peak oxygen uptake (VO_{2peak}) in adults with schizophrenia (SZ), (2) to develop a new equation for the MSWT to predict VO_{2peak}, and (3) to validate the new equation. Participants (N = 144, 41.3 ± 10.2 years old) with SZ performed a direct measurement of VO_{2peak} through a cardiopulmonary exercise test and the MSWT. A new equation incorporating resting heart rate, body mass index, and distance from MSWT ($R^2 = 0.617$; adjusted $R^2 = 0.60$; $p < 0.001$) performs better than the Singh et al. equation ($R^2 = 0.57$; adjusted $R^2 = 0.57$; $p < 0.001$) to estimate VO_{2peak} for the studied population. The *posteriori* cross-validation method confirmed the model's stability ($R^2 = 0.617$ vs. 0.626). The findings of the current study support the validity of the new regression equation incorporating resting heart rate, body mass index, and distance from MSWT to predict VO_{2peak} for assessment of CRF in people with SZ.

Keywords: assessment; equation for estimation; field test; peak oxygen uptake; validation

1. Introduction

Schizophrenia (SZ) is a chronic severe mental illness with an important bearing on the presence of cardiovascular risk (CVR) factors due to an unhealthy lifestyle, including lack of physical activity [1], smoking, substance abuse, and poor diet [2], along with adverse effects of medications [3] and social and economic factors [4].

Hence, according to different clinical guidelines, the control and assessment of CVR in SZ patients are recommended [5–7]. In this regard, a previous study has shown that people with SZ have a moderate CVR compared to a low CVR in healthy controls [8]. Therefore, any physical exercise program offered to SZ patients as a non-pharmacological co-adjuvant intervention should include a previous assessment.

Besides the traditional parameters, cardiorespiratory fitness (CRF, i.e., the capacity of the cardiovascular and pulmonary systems to meet the oxygen demands of skeletal muscle during physical work) is considered a vital sign and has emerged as a modifiable risk factor to attenuate the risk of developing non-communicable diseases [9,10]. Thus, a poor CRF level has been associated with a higher increased mortality risk, independently of other clinical risk factors [9].

The measurement of CRF can be direct, expressed as maximum or peak oxygen consumption (VO_{2max} or VO_{2peak}), or estimated from different ergometer or field tests [11]. The gold standard for directly measuring and assessing CRF is the cardiopulmonary exercise test (CPET), both in healthy and clinical populations [11]. However, even though in recent years the CPET has become a more feasible choice for CRF assessment, it is time-consuming, requires specialized and expensive laboratory facilities as well as expert personnel to supervise and is not widely available in many centers [12]. Therefore, the general population, and people with SZ in particular, rarely have the opportunity to perform this test, and as a result, CRF is the only major risk factor that is not regularly assessed in the clinical setting [13]. Thus, the recommendations suggest that when an exercise program is to be carried out, it should include the determination of CRF using at least predictive equations [11].

In this respect, when CPET is not feasible, CRF can be estimated using a variety of field tests by performing an exercise test with maximal effort to achieve high rates of perceived exertion and a percentage of an age-estimated maximum heart rate (HR) [14]. Accordingly, one of the most widely used field tests is the Modified Shuttle Walk Test (MSWT), which is considered suitable for all levels of function and allows a peak response to be elicited. Previous studies have assessed the association between the MSWT and VO_{2peak} in different populations (i.e., adolescents, sedentary, lung cancer, chronic obstructive pulmonary disease, obese women, pulmonary arterial hypertension, and primary hypertension), concluding that this field walk test is objective, safe, valid, effective, reliable, and highly predictive for the assessment of functional capacity in each of the populations examined [15–24]. Nevertheless, like the rest of the tests, it may not be valid in all populations, and therefore, an analysis of the properties of the test (i.e., validity, reliability, repeatability, and sensitivity) should be carried out [25]. Originally, Singh et al. [26] proposed an equation to assess functional capacity in patients with chronic obstructive pulmonary disease using a 12-level protocol Incremental Shuttle Walk Test, the previous version of MSWT [19] and, more recently Jurio-Iriarte et al. developed another one for people with primary hypertension and obesity using the MSWT [27]. However, to the best of our knowledge, no reports are available that have analysed the relationship between the MSWT and VO_{2peak} in a cohort of adults with SZ. Therefore, the aims of the present study were: (1) to validate the equation presented in the original study by Singh et al. for evaluating the relationship between MSWT with VO_{2peak} in adults with SZ, (2) to develop a new equation for the MSWT to predict VO_{2peak}, and (3) to validate the new equation.

2. Materials and Methods

2.1. Study Participants

The CORTEX-SP study was conducted between May 2018 and June 2021 in Vitoria-Gasteiz (Basque Country, Spain). This is a secondary baseline analysis of the study comprising a total of 144 participants (CORTEX) aged between 18 and 65 years (41.3 ± 10.2 years), 118 men (81.9%), and 26 women (18.1%). All participants had a diagnosis of SZ according to DSM-5 F20.9 (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*). All the selection criteria (exclusion and inclusion criteria) and procedures for the CORTEX-SP study have previously been described in the primary analysis [8]. The study was approved by the Research Ethics Committee of the Basque Country (PI2017044), and written informed consent was obtained from all participants before any data collection.

2.2. *Measurements*

Body mass index (BMI) was calculated as the total body mass divided by height squared in meters (kg/m^2). Waist and hip circumferences were taken, and the waist to hip ratio (WHR) was defined as waist circumference divided by hip circumference, both in centimeters. An ambulatory blood pressure (BP) monitoring recorder (ABPM) (6100 and 7100, Welch Allyn, New York, NY, USA) was used to measure BP for a whole day (24 h), through intervals of 30 min during the day and intervals of 60 min during the night. The variables considered from the ABPM measures were mean values of systolic BP, diastolic BP, and HR, all considered as resting values.

The CRF was assessed through a CPET and MSWT [28] on separate days. The CPET was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, the Netherlands) starting at 40 W with a gradual increment of 10 W each minute in ramp protocol. The expired gas was analyzed with a system (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) that was calibrated before each test in order to determine VO_{2peak}, which was defined as the highest oxygen uptake value attained toward the end of the test. Achievement of VO_{2peak} was assumed with the presence of two or more of the following criteria: (1) volitional fatigue (>18 on Borg scale), (2) peak respiratory exchange ratio (RER) $\geq$ 1.1, (3) achieving >85% of age-predicted maximum heart rate, and (4) failure of oxygen consumption (VO_2) and/or HR to increase with further increases in work rate [29]. The MSWT consisted of walking/running up and down a 10 m corridor at an incremental speed, as previously described by Bradley et al. [28]. The test was finished when the participant (1) reached the end of level 15, (2) was too breathless to maintain the required speed, (3) was more than 0.5 m away from the cone when the beep sounded, (4) achieving >85% of age-predicted maximum HR, or (5) if the patient experienced chest pain or angina, dizziness, mental confusion, or extreme muscle fatigue [28,30].

2.3. *Statistical Analysis*

Statistical analyses were performed using the R software package. Descriptive statistics were performed on the baseline participants' characteristics. The Ordinary Least Squares method was used to estimate the β parameters of the equation from the sample data available. Subsequently, multiple linear regression was used to generalize a model, and we determined which variables were the strongest predictors of VO_{2peak} through a variable selection algorithm. Forward stepwise linear regression was performed to test the effects of sex, age, body mass, BMI, WHR, systolic BP, diastolic BP, resting HR, peak HR at MSWT, and distance performed in the CPET, and to determine which variables are the strongest predictors of VO_{2peak}. In the residual analysis of the regression model, the type of method used for the assessment of outliers was Bonferroni test, for autocorrelation was Durbin—Watson test, and for homoscedasticity was Non-constant Variance Score test. Finally, for the validation of the model, we decided to use the k-fold cross-validation method (k = 5). Statistical significance was set at $p < 0.05$.

3. Results

Descriptive data from the sample are presented in Table 1, and descriptive results have already been presented [8].

The formula of Singh et al. [26] in the present cohort was calculated as:

$$VO_{2peak} = [6.271 + (0.021 - \text{MSWT distance in meters})]$$

The residuals showed poorly centered values by analyzing the median (−0.811) and the minimum (−8.476) and maximum (15.071) ranges. Likewise, the predicted VO_{2peak} was significant yet of moderate strength ($R^2 = 0.57$), explaining 57% of the variance (adjusted $R^2 = 0.57$; $p < 0.001$) and indicating a standard error of the estimate (SEE) of 4.75 $mL \cdot kg^{-1} \cdot min^{-1}$. In the residual analysis of the regression model, the tests applied for the assessment of outliers ($p = 0.122$) and autocorrelation ($p = 0.712$) returned insignificant

p-values. However, the p-value obtained by the homoscedasticity values ($p = 0.012$) (i.e., constant variance) was significant.

Table 1. Characteristics of the studied population. Values are means ± standard deviation or percentage (%).

Variables	$n = 144$
Age (yrs)	41.3 ± 10.2
Body mass (kg)	83.6 ± 16.4
BMI (kg/m^2)	28.7 ± 7.4
Waist (cm)	96.6 ± 14.1
Hip (cm)	104.3 ± 9.5
WHR	0.93 ± 0.09
Resting systolic BP (mmHg)	116 ± 13
Resting diastolic BP (mmHg)	71 ± 8
Resting HR (bpm)	81 ± 11
Cigarette smoking (%)	66
Diabetes Mellitus (%)	7.6
Antipsychotic treatment (%)	100
First-generation	2.4
Second-generation	93.6
Mixed	4.0
CPET variables	
Workload peak (W)	126 ± 37.7
Distance (km)	1.7 ± 0.9
HRpeak (bpm)	152.3 ± 19.7
VO_{2peak} (mL·kg^{-1}·min^{-1})	23.3 ± 7.2
RER_{peak}	1.2 ± 0.1
MSWT (m)	798.9 ± 265
HR_{peak} in MSWT (bpm)	153 ± 22.4

BMI, body mass index; WHR, waist to hip ratio; BP, blood pressure; HR, heart rate; CPET: cardiopulmonary exercise test; HR_{peak}, peak heart rate; VO_{2peak}, peak oxygen uptake; RER_{peak}, peak respiratory exchange ratio; MSWT, modified shuttle walking test.

To potentially improve the prediction of VO_{2peak}, the present investigation used forward stepwise regression to identify other variables that may refine the prediction of VO_{2peak}. In such a procedure, variables were added sequentially to the regression model as long as they significantly improved the predictive power of the model. Only the variables that contribute to the estimates using backward stepwise approach were used in the model. In the residual analysis of the regression model, the tests applied for the assessment of outliers ($p = 0.248$) and autocorrelation ($p = 0.868$) returned insignificant p-values. However, the p-value obtained by the homoscedasticity values ($p = 0.001$), (i.e., constant variance) was significant. A logarithmic transformation was performed to try to correct the heteroscedasticity. After the logarithmic transformation, homoscedasticity hypothesis was finally satisfied ($p = 0.828$). In this case, the VO_{2peak} was also significant, but still of moderate strength ($R^2 = 0.617$), explaining, therefore, 60% of the variance (adjusted $R^2 = 0.60$; $p < 0.001$) and indicating a SEE of 4.55 mL·kg^{-1}·min^{-1} (Figure 1).

The equation generated in this study to calculate VO_{2peak} (mL·kg^{-1}·min^{-1}) from the MSWT can be formulated as follows:

$$VO_{2peak} = 20.168 - [0.226 \cdot \text{BMI}] - [0.064 \cdot \text{Resting HR}] + [0.019 \cdot \text{Distance}_{MSWT}],$$

where BMI is expressed as kg/m^2, resting HR (beats per minute) is measured before starting the MSWT with at least 5 minutes of resting time, and distance is measured in meters travelled in the MSWT.

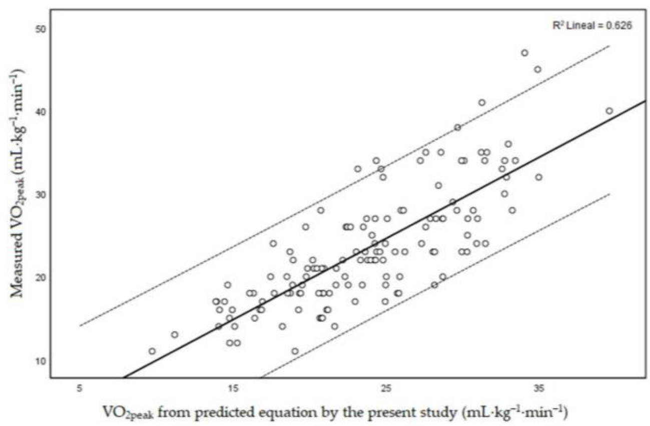

Figure 1. Relationship between measured VO_{2peak} and VO_{2peak} values from the predicted equation generated in the present study. The central line represents the linear regression line, and the flanking lines represent the 95% individual prediction intervals. CPET, cardiopulmonary exercise test; VO_{2peak}, peak oxygen uptake.

Figure 2 illustrates the proportional bias ($p < 0.001$) with limits of agreement from -8.9 to 8.2 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$. This indicates that using the new equation, the VO_{2peak} assessment of 95% of participants with SZ would range from 8.9 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ less to 8.2 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ more than their objective measure by CPET. Bland-Altman plot (Figure 2) shows that the biggest and smallest individual means of VO_{2peak} between the two tests correspond with the biggest limits of agreement on a proportional basis.

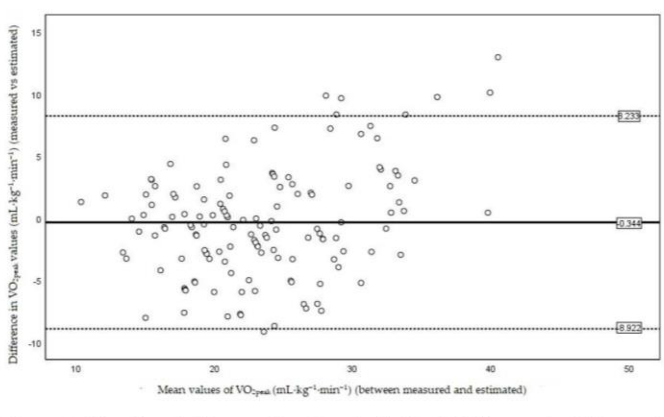

Figure 2. Bland and Altman plot. Intraindividual difference in VO_{2peak} ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) between two exercise tests (MSWT vs. CPET) plotted against intraindividual mean values of the exercise tests (MSWT and CPET). The central line represents the mean of the intraindividual differences, and the flanking lines represent the 95% limits of agreement.

For the agreement and validity of the new equation, the summary of sample sizes created the five subsets (Table 2) and indicated the sample size of each of them (109, 109, 110, 108, 108). The R^2 was 0.626 (Figure 1), compared with that of the original model, which was 0.617. Hence, it can be indicated that they are very similar and that the model is robust. Likewise, the average standard deviation of the subsets (SD = 0.092) was low, indicating a low variability between the models created. In summary, after the cross-validation method, it was concluded that the model was stable.

Table 2. The evaluation indices for the 5-fold cross-validation.

Subsets	RMSE	R^2	MAE
1	4.617	0.668	3.302
2	4.292	0.681	3.307
3	4.862	0.557	3.757
4	4.196	0.636	3.155
5	4.617	0.586	3.906

RMSE, Root mean square error; MAE, mean absolute error.

4. Discussion

In the present study, an analysis of the relationship between the MSWT and VO_{2peak} in a cohort of the SZ population was carried out. The main findings of this study were: (1) a new equation incorporating BMI, resting HR, and distance from MSWT performed better than the original Singh et al. equation [26] to estimate VO_{2peak} for the studied population, and (2) the *posteriori* cross-validation method confirmed the model's stability.

Previous studies have also presented correlations between measures of the shuttle walk test and CPET, explaining the 40.6% (healthy men) [16] and 57% (general surgical patients) [31] of the variance in VO_{2peak} and showing viability for the prediction of VO_{2peak}. However, according to the present results, these equations, and even the equation of Singh et al. [26], may not be an appropriate method to estimate CRF through the MSWT for the assessment of functional capacity in people with SZ. Thus, the estimation equation by Singh et al. [26] showed that the residual values were poorly centered and only explained 57% of the variance (adjusted $R^2 = 0.57$). The lack of precision could be because Singh et al. [26] generated the equation for patients with chronic airway obstruction, whose main limitation to exercise is dyspnea. In contrast to pulmonary patients, the performance of people with SZ is not usually limited by breathlessness but by exhaustion, low CRF, side effects relating to treatment (antipsychotic drugs), anhedonia, and lack of motivation [8,32]. Hence, among the variables obtained in the proposed models, BMI, and resting HR, together with the distance walked in the MSWT, proved to be the most relevant predictors. These variables explained the 60% of the variation in VO_{2peak} for the new equation, increasing the R^2 and decreasing the SEE compared to Singh et al. equation (Figure 1). According to that, for the sample studied, the higher the BMI and resting HR, and the lower the distance walked at MSWT, the poorer the CRF. This can be explained by the inverse associations of high BMI, including an excess visceral adipose tissue (i.e., systemic inflammation) and elevated resting HR (i.e., increased sympathetic activity) with low CRF [33,34]. As an example of using the newly generated equation could be the following: if we provide two actual values observed for two participants with opposite CRF values included in this sample (Participant 1: measured VO_{2peak} = 40 $mL \cdot kg^{-1} \cdot min^{-1}$; BMI = 21.3 kg/m^2; distance at MSWT = 1500 m; resting HR = 67 bpm. Participant 2: measured VO_{2peak} = 11 $mL \cdot kg^{-1} \cdot min^{-1}$; BMI = 46.6 kg/m^2; distance at MSWT = 330 m; resting HR = 97 bpm), the estimated VO_{2peak} values would be 39.6 and 9.7 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively, which corresponds with a very low error of estimate (0.4 and 1.3 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively).

One of the scientific goals of the present study was to predict an outcome (i.e., the VO_{2peak}). Therefore, the metric by which to assess the quality of the prediction should be decided [35]. Previous studies have not validated the original formula [18,26] or there was a medium-validation result [27] without full support of the equation validity. In the current study, after using the cross-validation method, it was concluded that the model was stable with an $R^2 = 0.626$ and had a high similarity with the newly generated equation ($R^2 = 0.617$). Thus, the present results support the validity of the equation for routinely determining the CRF of SZ patients using the MSWT and the generated equation. However, we must be cautious with this statement since the validity of the MSWT-estimated VO_{2peak} is still moderate (60% of the variance). In this sense, in the clinical setting, when an accurate determination of CRF is critical, the CPET (with objective VO_{2peak} assessment) will remain the "gold standard".

The current study has several strengths. Considering the difficulties involved in recruiting volunteers with a mental dysfunction, we could argue a relatively large sample (n = 144). Furthermore, the new equation could be a very useful and easy tool in the evaluation of this population, and the results obtained with this prediction are better compared to previous studies. There are, however, some limitations of this study that should be considered: (1) Symptoms affect each individual differently and have a direct bearing when assessing stress testing. (2) Cycle ergometer and MSWT tests are performed on different days and the motivation for exercise is highly variable from day-to-day in this population. (3) It has been observed that VO_{2peak} tends to be somewhat higher in those tests performed on a treadmill compared to those on a bike ergometer. Therefore, the SEE of the new equation (4.55 $mL \cdot kg^{-1} \cdot min^{-1}$) could be increased, since the direct measurement of VO_{2peak} has been done on the bike while the MSWT test is performed walking [36]. (4) The average age of the current cohort was 41.3 $\pm$ 10.2 years (range 18–65 years). This could limit the accuracy of the equation in younger or older individuals. (5) The ethnicity in the present study was predominantly white non-Hispanic (99%), suggesting that there may be potential ethnicity-related differences in the accuracy of the equation.

Finally, these results provide evidence for an easy, fast, and simple way to evaluate the CRF of people with SZ when objective measurements are not available. This would allow the necessary pre-design assessment of exercise in both clinical and non-clinical settings, and the promotion of exercise programs in this population.

5. Conclusions

In summary, the findings of this study support the validity of a new regression equation incorporating resting HR, BMI, and distance from MSWT to predict VO_{2peak} for assessment of CRF in people with SZ. However, when an accurate determination of functional capacity is required for diagnosis, clinical research, and exercise design, the direct measurement of VO_{2peak} will continue to be the "gold standard".

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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8.3. Anexo 3: “*Does higher cardiorespiratory fitness impact the clinical symptoms in individuals with schizophrenia? A tertiary analysis of the CORTEX-SP study.*”

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

MIKEL TOUS-ESPELOSIN[1,2], SONIA RUIZ DE AZUA[3], CRISTOBAL PAVON[4,5], EDORTA ELIZAGARATE[4,5], AGURNE SAMPEDRO[6], SARA MALDONADO-MARTÍN[1,2]
[1]GIzartea, Kirola eta Ariketa Fisikoa Ikerkuntza Taldea (GIKAFIT). Society, Sports, and Exercise Research Group. Department of Physical Education and Sport. Faculty of Education and Sport-Physical Activity and Sport Sciences Section. University of the Basque Country (UPV/EHU). Vitoria-Gasteiz. Araba/Álava. Basque Country, SPAIN
[2]Bioaraba Health Research Institute, Physical Activity, Exercise, and Health group. Vitoria-Gasteiz, Basque Country, SPAIN
[3]Department of Neuroscience, University of the Basque Country (UPV/EHU). Cibersam. Basque Country, SPAIN
[4]Bioaraba, New Therapies in Mental Health Group, Vitoria-Gasteiz, Spain, Spain; 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 Psychology and Education, University of Deusto, Bilbao, SPAIN

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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 ($mL \cdot kg^{-1} \cdot min^{-1}$) ($B = -0.252$; $P < 0.001$). The regression analysis showed that lower peak oxygen uptake ($L \cdot min^{-1}$) ($P < 0.001$) 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 ($mL \cdot kg^{-1} \cdot min^{-1}$) ($P = 0.016$) predicted general symptoms ($R^2 = 12.3\%$; $F = 5.135$; $P = 0.002$), and lower peak oxygen uptake ($mL \cdot kg^{-1} \cdot min^{-1}$) ($P = 0.001$) 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

Corresponding Author: MIKEL TOUS-ESPELOSIN, E-mail: mikel.tous@ehu.eus

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 $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$). 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-MATRICS 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 ± standard deviation or percentages (%)

Variables	n = 122
Age (yrs)	41.7 ± 10.3
Cigarette smoking/day	11.6 ± 12.1
Medication dosage (mg/day)	483.3 ± 287.2
Total PANSS	73.9 ± 18.5
General PANSS	36.4 ± 10.6
Positive PANSS	15.3 ± 6.0
Negative PANSS	22.2 ± 6.6
BNSS	31.8 ± 14.6
BMI (kg/m^2)	28.7 ± 5.3
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	23.6 ± 7.4
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	1.97 ± 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 $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) (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
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	−.134	−.106	−.108	−.181
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	−.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 $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$) ($P < 0.001$) 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 $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) ($P = 0.016$) predicted general symptoms ($R^2 = 12.3\%$; F = 5.135; $P = 0.002$), and lower $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) ($P = 0.001$) 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%	−.373	-4.086	<0.001	$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)
		4%	.202	2.384	0.019	BMI
Positive symptoms	19.3%	2%				x
General symptoms	12.3%	4.8%	−.232	-2.454	0.016	$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)
Total symptoms	17.8%	8.9%	−.315	-3.455	0.001	$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)

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 kg/m^2) (Khan et al., 2018), low levels of $\dot{V}O_{2peak}$ (<25 $mL \cdot kg^{-1} \cdot min^{-1}$) (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 $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) displayed lower total scores (P = 0.001) and general subscale scores (P = 0.016) in the PANSS. Additionally, those with higher absolute $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$) 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, $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$) 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, $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) 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 ($\dot{V}O_{2peak}$), 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.

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Declaration of Interest statement

The authors have no conflicts of interest to declare.

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8.4. Anexo 4: *"As we were and as we should be, combined exercise training in adults with schizophrenia: CORTEX-SP study part I."*

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Mikel Tous-Espelosin[1,2], Sonia Ruiz de Azua[3], Nagore Iriarte-Yoller[4,5], Pedro M. Sanchez[4,5], Edorta Elizagarate[4], and Sara Maldonado-Martín[1,2]

[1]GIzartea, Kirola eta Ariketa Fisikoa Ikerkuntza Taldea (GIKAFIT). Society, Sports, and Exercise Research Group, Department of Physical Education and Sport, Faculty of Education and Sport-Physical Activity and Sport Sciences Section, University of the Basque Country (UPV/EHU), Vitoria-Gasteiz, Araba/Álava, Basque Country, SPAIN; [2]Bioaraba Health Research Institute, Physical Activity, Exercise, and Health group, Vitoria-Gasteiz, Basque Country, Spain; [3]Department of Neuroscience, University of the Basque Country (UPV/EHU), Cibersam, Basque Country, SPAIN; [4]Bioaraba, New Therapies in Mental Health Group, Vitoria-Gasteiz, Spain, Spain; 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

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Mikel Tous-Espelosin[1,2], Sonia Ruiz de Azua[3], Nagore Iriarte-Yoller[4,5], Pedro M. Sanchez[4,5], Edorta Elizagarate[4], and Sara Maldonado-Martín[1,2]

[1]GIzartea, Kirola eta Ariketa Fisikoa Ikerkuntza Taldea (GIKAFIT). Society, Sports, and Exercise Research Group, Department of Physical Education and Sport, Faculty of Education and Sport-Physical Activity and Sport Sciences Section, University of the Basque Country (UPV/EHU), Vitoria-Gasteiz, Araba/Álava, Basque Country, SPAIN; [2]Bioaraba Health Research Institute, Physical Activity, Exercise, and Health group, Vitoria-Gasteiz, Basque Country, Spain; [3]Department of Neuroscience, University of the Basque Country (UPV/EHU), Cibersam, Basque Country, SPAIN; [4]Bioaraba, New Therapies in Mental Health Group, Vitoria-Gasteiz, Spain, Spain; 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

Address for Correspondence: Sara Maldonado-Martin. Department of Physical Education and Sport. Faculty of Education and Sport. University of the Basque Country (UPV/EHU). Portal de Lasarte, 71. 01007 Vitoria-Gasteiz (Araba/Alava)-Basque Country, Spain; Phone: +34 945013534; E-mail: sara.maldonado@ehu.eus

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ABSTRACT

Introduction: Given the health benefits and the role of exercise as an anti-inflammatory adjuvant program, this study aimed to determine the effectiveness of a combined exercise program on cardiorespiratory fitness (CRF), body composition, and biochemical levels in adults with schizophrenia (SZ) characterized at baseline as metabolically unhealthy overweight with low CRF. **Methods:** Participants diagnosed with SZ (n=112, 41.3±10.4 yr, 28.7% women) were randomly assigned into a Treatment-As-Usual (TAU) control group (n=53) or a supervised exercise group (n=59, 3 days/week). Each combined exercise session consisted of both a low-volume high-intensity interval training (less than 10 min of high-intensity time per session) and a resistance circuit-training program. All variables were assessed pre-and post-intervention (20 weeks). For the assessment of CRF, a peak cardiopulmonary exercise test on a cycle ergometer was used. **Results:** Following the intervention, participants from the exercise group (n=51) showed increases in CRF (P<0.001) through peak oxygen uptake ($L \cdot min^{-1}$; Δ=17.6%; $mL \cdot kg^{-1} \cdot min^{-1}$, Δ=19.6%) and the metabolic equivalent of task (Δ=19%), with no significant changes (P>0.05) in body composition and biochemical variables. However, the TAU group (n=38) did not show any significant change in the study variables (P>0.05). Between-group significant differences ($P \leq 0.05$) were observed in CRF, first ventilatory threshold, and heart rate peak after the intervention period favoring the exercise group. **Conclusions:** This study demonstrated that a supervised combined exercise program in people with SZ helps to maintain body composition values and improve CRF levels. This could lead to an important clinical change in the characterization from metabolically unhealthy overweight to a metabolically healthy overweight population. Hence, exercise should be considered a co-adjuvant program in the treatment of the SZ population.

Key Words: MENTAL DISORDER, CARDIORESPIRATORY FITNESS, PHYSICAL ACTIVITY, BODY COMPOSITION, METABOLICALLY HEALTHY

INTRODUCTION

Systematic reviews confirm that people with schizophrenia (SZ) engage in significantly less moderate and vigorous physical activity *vs.* age-matched healthy peers (1-3). These results may indicate the lack of motivation and absence of prioritizing physical activity in this population by the healthcare system (4). There is also evidence showing that sedentary behavior, independent of physical activity, is a distinct risk factor in people with SZ (5), thus increasing the pathophysiological underpinnings of inflammation in SZ (6). In this sense, baseline data from the CORTEX study have shown that people with SZ exhibit significantly higher cardiovascular risk, lower cardiorespiratory fitness (CRF), and unhealthy data related to physiological and inflammatory biochemical variables in comparison to healthy controls; leading to a metabolically unhealthy overweight/obesity profile (7).

It is very well known that CRF is considered a predictor of health outcomes and indeed a reflection of total body health, justifying a shift in exercise programs away from "fatness" towards "fitness" (8). Indeed, a low CRF seems to be a strong predictor of risk for adverse cardiovascular outcomes. Therefore, efforts to assess and improve CRF through exercise should become a standard of clinical values (9). Hence, the promotion of a healthy lifestyle (10, 11) and interventions aiming to increase physical activity and specifically increasing moderate-vigorous physical activity should be a priority given the health benefits and the role of exercise as an anti-inflammatory adjuvant program (12). Then, as part of an educational program to change lifestyle, it has been shown that an exercise intervention has a positive effect on improving CRF (8), controlling metabolic disorders, and mental health parameters (*i.e.,* positive, negative, general, and total symptoms) (13).

According to the new World Health Organization guidelines on physical activity and sedentary behavior, recommendations for people living with disability (including those with SZ), do not differ from those of the general elderly population (*i.e.,* a minimum of 150 min per week of moderate-high intensity or 75 min of high-severe intensity across the week, as well as at least three days a week of varied multicomponent physical activities that prioritize functional balance and moderate-to-higher resistance training) (14). In this sense, previous researchers have integrated High-Intensity Interval Training (HIIT) exercise (*i.e.*, alternation of loads of high-intensity exercise with periods of light-to-moderate intensity) finding positive effects on physical and mental health in patients with SZ (15-19). However, fewer studies have analyzed the effects of resistance training in this population (20-22), and to our knowledge, only one study with a small sample size of solely male participants, low compliance rates, and high drop-out rates has applied combined exercise training (*i.e.,* the combination of resistance and aerobic training in the same exercise session) (21, 23). All these studies have been unified in a recent systematic review and meta-analysis where all exercise modalities (aerobic, resistance, or combined) are supported for their beneficial effects on people living with SZ (24). It seems that combining resistance and aerobic exercise enhances functional capacity more than aerobic exercise alone, due to different molecular and metabolic pathways, which could generate a "general adaptation profile" in untrained people (25). Further, minimizing overall exercise volume in both types of exercise, including cycling as aerobic exercise as opposed to running, could contradict the "muscle interference" hypothesis (26, 27).

Given the current physical activity recommendations by the Word Health Organization for people with mental disorders, the previous benefits of combined exercise training in other populations, and the lack of research including a combined exercise training program in adults diagnosed with SP, this study aimed to determine changes in body composition, CRF, and biochemical variables following 20-week combined exercise training in adults with SP characterized at baseline as metabolically unhealthy overweight/obesity with low CRF.

METHODS

Study design

The CORTEX-SP study is a randomized, single-blind (medical specialists who evaluated the psychiatric variables) controlled experimental trial (Clinical Trials.gov identifier, NCT03509597). The study was approved by the Clinical Research Ethics Committee of the Autonomous Region of the Basque Country (PI2017044), and written informed consent was obtained from all participants before any data collection. After baseline measurements, participants were randomized (www.randomization.com) to one of the two intervention groups: Treatment-As-Usual control (TAU) group, or supervised exercise (EX) group.

Study participants

One hundred and twelve non-Hispanic white participants (41.3±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). Figure 1 presents a flow diagram of the study process. All participants were recruited from the Mental Health Network in Alava, Basque Country, which provides psychiatric care to the population living in the community. Patients from the study met the diagnostic criteria for SZ according to DSM-5 (28), with a disease evolution time greater than two years and stable The exclusion criteria have been previously published (7). Briefly, clinically unstable patients; cognitive impairment secondary to another disease; main diagnosis of substance use disorder or presenting active substance use at the time of the study; patients who have required relevant modifications of antipsychotic drug treatment in the previous three months; secondary hypertension; left ventricular hypertrophy; the presence of one severe or, uncontrolled cardiovascular risk factor; musculoskeletal problems interfering with exercise; or any other medical condition or disease that is life-threatening or that can interfere with or be aggravated by exercise. The included participants were both inpatients (46,3%) and outpatients (53,7%). The former ones were hospitalized at a psychiatric rehabilitation unit with imminent hospital discharge to the community setting.

Measurements

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

Age, sex, and cigarette smoking status were assessed by self-report. All medications prescribed to participants were recorded, and classified into their groups (aripiprazole, clozapine, paliperidone, olanzapine, quetiapine, haloperidol, risperidone, ziprasidone, levomepromazine, perphenazine, and lurasidone), and transformed into chlorpromazine-equivalents by using the defined daily dose method (29, 30). Data regarding medication have been previously published (7). All pre- and post-intervention assessments and exercise interventions were performed with the pharmacological treatment prescribed by the psychiatric specialists.

Clinical symptoms were measured using the Positive and Negative Symptoms Scale (PANSS) (31) and the Brief Negative Symptom Scale (BNSS) (32).

The measurements of body composition, blood pressure (BP), physical fitness, and biochemical parameters have been previously explained and published (7). Briefly, bioelectrical impedance was used to estimate fat-free mass, total body water, and fat mass (Tanita, BF 350, Arlington Heights, IL, USA). Blood pressure measurements were analyzed through an ambulatory BP recorder (6100 and 7100, Welch Allyn, New York, NY, USA) for a whole day (24h). Both a symptom-limited cardiopulmonary exercise peak test and the Modified Shuttle Walking Test were performed to measure physical fitness. The progressive and ramped protocol for objective determination of peak oxygen consumption (VO_{2peak}) and ventilatory thresholds (VT1 and VT2) started at 40W with gradual increments of 10W per minute on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, Netherlands). The biochemical profile was determined with a fasting blood sample (12.5 mL) collected at the hospital for each participant.

Intervention

The participants in the EX group took part in exercise sessions, three days per week, for a five-month duration 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). The exercise intensity for each participant was individually scheduled based on CRF and VT1 and VT2, which were determined from the VO_{2peak} obtained by an ergospirometry (Lode Excalibur SportCycle, Netherlands) and expired gas analysis (Ergocard Medisoft SS, Belgium Ref.

USM001 V1.0). Based on the identification of the two VTs, the three intensity ranges of exercise were determined: (R1) light to moderate intensity with heart rate (HR) values below VT1; (R2) moderate to high intensity with HR values between VT1 and VT2; and (R3) high to severe intensity with HR values from VT2 to the maximum HR achieved in the cardiopulmonary exercise test. More specific information regarding the exercise cardiopulmonary test and VT assessment have been previously published (7). All the exercise sessions started and finished with blood pressure monitoring. Training intensity was controlled by HR monitoring (Polar Electro, Kempele, Finland) and through the rate of perceived exertion using Borg's original scale (6-20 points). Each session included a 10 min warm-up with joint mobility and a 10 min cool-down period with passive stretching exercises.

In the main part of each session (40 min), combined exercise training was performed. Each training session consisted of both 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 HR at moderate (R2) or vigorous (R3) intensities. The HIIT protocol on the bike was carried out in a 5-10-min warm-up period at a moderate intensity and after that, the participant cycled for 30 s at R3 followed by 60 s at R2. Four repetitions (1 rep = 30 s at R3 followed by 60 s at R2) were initially performed and gradually increased to nine repetitions. The resistance-circuit training was performed with three circuits, one for each workout of the week, with 10 different exercises. They were organized by major motor patterns (*i.e.,* knee dominant, hip dominant, press, pull, core, and micro impacts) and the exercises were alternately ordered based on whether they were upper or lower body. Each exercise was worked for 1 min with 30 s recovery. Initially, a single round of exercises was performed and gradually increased to two rounds.

A minimum of 85% of exercise program compliance was required for the EX participants to be included in the final statistical analyses. For a deeper analysis of the improvement in CRF, the calculation of the typical error (TE) of measurement in the metabolic equivalent task (MET) variable was the established criteria to categorize the EX participants as "responders" to the exercise-training program. 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 MET results (post minus pre-intervention value) (33) with a result of TE = 1.02. Hence, in the present study, a "responder" was defined as a person who increased more than 1.02 METs after exercise intervention.

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

Statistical analysis

Descriptive statistics were calculated for all variables. Data are expressed as mean±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-Square 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 (Δ) score for each group (TAU, EX), adjusting for age and sex. Bonferroni correction is an adjustment made to *P* values when several dependent or independent statistical tests are being performed simultaneously on a single data set. Data were analyzed according to the intention-to-treat principle. Statistical significance was set at $P \leq 0.05$. All statistical analyses were performed with the SPSS version 25.0.

Cardiorespiratory fitness through VO_{2peak} was considered the primary outcome of this study, and it was thereby considered for the calculation of the sample size in the present study. A priori power analysis through G*Power 3 software (ver. 3.1.9.7; Heinrich-Heine Universität Düsseldorf, Germany) was performed (34, 35). A sample size of 106 participants (53 in each group) was estimated to obtain an effect size of $d = 0.64$ to observe inter groups differences, with 90% power and a 5% of the significance level.

RESULTS

No adverse events were reported during the exercise intervention, and mean exercise adherence reached higher than 85% of the 60 scheduled sessions. Medication was not changed in any of the participants during the intervention period unless psychiatric instability was present.

Baseline characteristics (Table 1).

Baseline data for all participants have been previously published (7). The results suggested that no significant between-group differences were observed for psychopathological (except PANSS positive subscale, with higher values for EX group, P=0.008), pharmacological treatment, anthropometric, body composition, hemodynamic (except systolic blood pressure and diastolic blood pressure, P=0.006 and P=0.007, respectively), CRF and biochemical data. According to a previous investigation, participants were classified in the low-medium range (*i.e.,* 15-50th percentile) on PANSS subscales. (*i.e.,* General PANSS 25th, Positive PANSS 15th, Negative PANSS 45th) (36). Further, published baseline results classified participants as metabolically unhealthy overweight/obesity according to Wildman modified criteria (37), with low CRF (7).

Anthropometric and body composition changes (Table 2).

After a 20-week intervention period, no significant differences (P>0.05) were observed in both groups. However, it should be noted that no significant increase in body mass (BM, Δ=1.9%, P=0.066), BM index (BMI, Δ=2.1%, P=0.067), and fat body mass (FBM, Δ=0.7%, P=0.862), and a no significant decrease for fat-free mass (FFM, Δ=-0.3%, P=0.862) was observed in the TAU group. On the contrary, a no significant decrease in BM (Δ=-0.7%, P=0.518), BMI (Δ=-0.7%, P=0.575) and FBM (Δ=-0.7%, P=0.697), and a no significant increase in FFM (Δ=0.4%, p=0.697) were found in the EX group. Following the Bonferroni correction, there were between-group significant differences, with the EX group showing significantly (P=0.05) lower values compared with the TAU group in BM (difference = -2.5 kg; 95% CI, -4.9-

0) and BMI (difference = -0.8 kg·m^{-2}; 95% CI, -1.7-0). No significant between-group differences were found in any other anthropometric and body composition variables.

Physiological changes (Table 2).

After the intervention period, CRF increased significantly (*P*<0.001) in the EX group expressed as $\dot{V}O_{2peak}$ (L·min^{-1}, Δ=17.6%; mL·kg^{-1}·min^{-1}, Δ=19.6%), MET (Δ=19%), and VT_1 (mL·kg^{-1}·min^{-1}, Δ=21.9%, *P*=0.001). In the same way, significant increases were also observed following the training period for the EX group in the exercise test duration (min, Δ=25.8%, *P*<0.001), peak power on the cycle ergometer (Watts, Δ=20.1%, *P*<0.001), and exercise distance (km, Δ= 56.2%, *P*<0.001). In contrast, no significant changes were seen in the TAU group for any of the physiological variables studied, except a significant decrease in HR_{peak} (bpm, Δ=-3.9%, *P*=0.008). Following the Bonferroni correction, there were significant between-group differences with the EX group showing significant (*P*<0.001) improvements (*i.e,* higher values) compared with the TAU group in CRF, expressed as relative $\dot{V}O_{2peak}$ (difference = 4.6 mL·kg^{-1}·min^{-1}; 95% CI, 2.6-6.7), absolute $\dot{V}O_{2peak}$ (difference = 0.3 L·min^{-1}; 95% CI, 0.2-0.5), and MET (difference = 1.2 L·min^{-1}; 95% CI, 0.6-1.8), and in the secondary variables such as peak power (difference = 21.8 W_{peak}; 95% CI, 10.4-33.1), exercise duration (difference = 2.6 min; 95% CI, 1.6-3.5), exercise distance (difference = 0.9 km; 95% CI, 0.4-1.3), HR_{peak} (*P*=0.017) (difference = 6.7 bpm; 95% CI, 1.2-12.2) and VT_1 (*P*=0.029) (difference = 2.6 mL·kg^{-1}·min^{-1}; 95% CI, 0.3-4.9).

In the current study, 60% (n=30) of the EX participants were considered "responders" with an increase greater than 1.02 MET after the exercise intervention program.

Biochemical changes (Table 3).

After a 20-week intervention, no significant differences (P>0.05) were observed in either group or significant between-group differences in any biochemical variables after Bonferroni assessment.

DISCUSSION

To our knowledge, this is the largest study to date investigating the effects of a highly demanding and supervised combined exercise training program (low-volume HIIT + resistance exercise training) in adults diagnosed with SZ compared to a TAU group on body composition, CRF, and biochemical variables. Primarily, this study showed that combined exercise program induced positive and beneficial changes in CRF with no significant changes in body composition and biochemical variables. However, the TAU group, with no exercise intervention, did not show any significant change in the study variables, and between-group significant differences were observed in CRF, VT, and HR_{peak} after the intervention period favoring the EX group (Figure 2).

People with SZ often present an unhealthy lifestyle (*i.e.,* poor diet, physical inactivity, and environmental toxins) coupled with the negative impact of socio-economic factors (38). In that sense, abnormalities in inflammation underlying the disease are aggravated by lifestyle-related cardiovascular risk factors, along with metabolic inflexibility, increased pro-inflammatory activity, and impaired hormonal regulation of appetite associated with the use of antipsychotics (6, 39). The guidelines on cardiovascular disease prevention in clinical practice strongly recommend the need for intensified attention and support to improve adherence to lifestyle changes in patients with mental disorders, including reduced sedentary time and following general physical activity and exercise recommendations (40).

The results of the present study are consistent with a previous meta-analysis demonstrating no changes in markers of metabolic health, such as body composition and some biochemical parameters following an exercise intervention in people with SZ (41). These results could in part be explained by: 1) focusing entirely on exercise as the sole component of the intervention. Therefore, broader 'healthy living' programs were excluded, such as a healthy diet (41); and 2) pharmacological treatment as an effective and necessary component of the management of SZ. Thus, the SZ population has shown metabolic abnormalities (38), such as an increase in BM, abdominal obesity, and diabetes mellitus type 2 (42).

After 20 weeks of combined exercise intervention (3 days/week), the participants of the present study, categorized as "metabolically unhealthy overweight/obesity with low CRF" at baseline (7), showed no significant changes in body composition and some of the inflammatory metabolic parameters (*i.e.,* BMI>25 kg/m^2, LDL>100 mg/dL, atherogenic index>3.5 mg/dL, and C-reactive protein >3 mg/dL) associated with symptoms of anhedonia in SP (6). However, CRF, which is considered a key factor in cardiometabolic health helping to decrease cardiovascular risk (15), was significantly increased in the EX group compared to the TAU group (Δ=19.6%, P<0.001; F-value: 20.102), raising the reference value from the 20^{th} to 50^{th} percentile VO_{2max} (43). According to that and regarding the critical impact of CRF, participants in the EX group from the present study could be prognosed and characterized (Figure 2) as metabolically healthy overweight/obese , supporting the notion that a higher CRF should be considered as one more trait of the metabolically healthy overweight/obese phenotype, and a confounder in the analysis (44, 45).

Evidence has revealed that combined exercise training may act as a coadjuvant program in people with SZ improving both psychiatric symptoms and health-related physical fitness indicators (24). The improvements in CRF may be due to stress adaptations that have previously been shown to elicit remarkable cellular, vascular, and metabolic adaptations during combined training, especially HIIT (46), and this paradigm has since emerged as a safe and more time-efficient mode of exercise (47). In addition, an exercise intervention, especially important in the case of neurological disorders such as SZ, serves to prevent and treat various pathologies and warrants careful dissection of the signals, networks, and mediators of interorgan crosstalk originating in skeletal muscle (48), and in a multidimensional way on brain function (49). Further, considering that in the present study, 60% of the EX participants responded to the exercise program with an increase greater than 1.02 MET and that for each MET increased, the risk of mortality decreased (50), the role of exercise as an efficient anti-inflammatory adjuvant approach should be taken seriously in consideration in SZ population, and other mental disorders.

The current study has several strengths: 1) there is no study with such a large sample of people with SZ performing a combined exercise program for five months; 2) the current study has provided clear evidence for the benefits of combined exercise training in people with SZ; and 3) the sample studied closely reflects the clinical characteristics and treatment received by people with SZ living in the community. However, some limitations should be considered: 1) the patients were treated with a heterogeneous sample of antipsychotics reflecting the usual clinical practice in the province of Alava. Each family of antipsychotics has different effects on many of the variables measured, but these effects have not been studied in the data analysis, 2) strength assessments that could have provided more interesting variables to analyze and justify the results were not carried out. and 3) the sample is highly representative of the SZ population from the community mental health centers in the same city (Vitoria-Gasteiz), where mental health and social care are highly regarded, and may not represent the rest of the cities or communities around the globe.

CONCLUSIONS

In summary, the present study demonstrated that a supervised combined exercise program in people with SZ helps to improve CRF levels. This could lead to an important clinical change in the characterization from metabolically unhealthy overweight/obesity (they were) to a metabolically healthy population with overweight or obesity (they should be). Hence, exercise should be considered a co-adjuvant program in the treatment of the SZ population.

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FIGURE LEGENDS

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

Figure 2. Effects of concurrent exercise training on body composition, cardiorespiratory fitness, and biochemical profile in people diagnosed with schizophrenia. Infographic composition

Figure 1

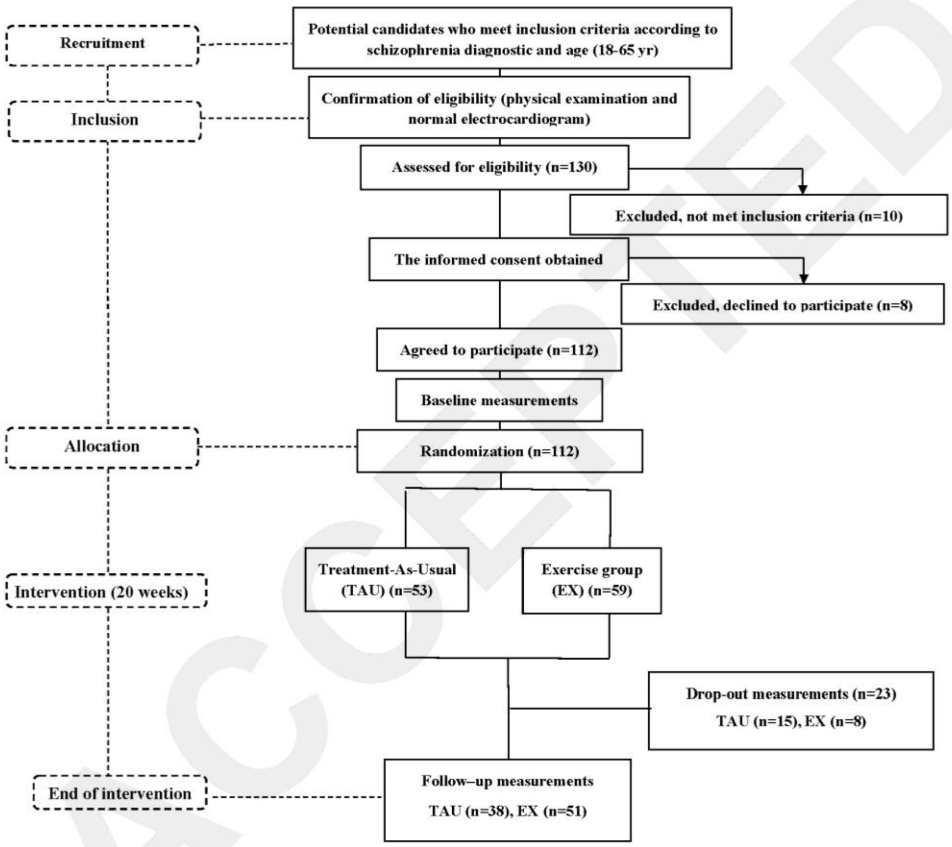
Recruitment
Potential candidates who meet inclusion criteria according to schizophrenia diagnostic and age (18-65 yr)
Inclusion
Confirmation of eligibility (physical examination and normal electrocardiogram)
Assessed for eligibility (n=130)
Excluded, not met inclusion criteria (n=10)
The informed consent obtained
Excluded, declined to participate (n=8)
Agreed to participate (n=112)
Baseline measurements
Allocation
Randomization (n=112)
Intervention (20 weeks)
Treatment-As-Usual (TAU) (n=53)
Exercise group (EX) (n=59)
Drop-out measurements (n=23)
TAU (n=15), EX (n=8)
End of intervention
Follow–up measurements
TAU (n=38), EX (n=51)

Table 1. Physical, physiological, and biochemical characteristics at baseline for each group of participants (N=112). Values are mean±SD, percent (%), or number.

	ALL (N=112)	TAU (N=53)	EX (N=59)	*P* *TAU vs. EX*	*Cohen's d*
Sex (men/women)	87/25	41/12	46/13	0.939	-
Age (yrs)	41.3±10.4	42.5±9.9	40.1±10.9	0.224	0.23
Cigarette smoking (%)	71.6	62.0	79.7	0.046	-
DM (%)	7.3	10.0	5.1	0.344	-
Medication dosage (mg/day)	457.1±276.8	458.3±254.4	454.9±317.2	0.444	0.01
Total PANSS	76.6±20.4	73.2±17.5	80.1±22.6	0.103	0.34
General PANSS	37.3±11.4	35.8±10.6	38.8±12.1	0.208	0.26
Positive PANSS	15.7±6.6	13.9±4.7	17.6±7.8	0.008	0.57
Negative PANSS	23.6±6.8	23.5±6.3	23.7±7.3	0.876	0.03
BNSS	33.7±15.8	34.2±14.4	33.2±17.3	0.766	0.06
Body mass (kg)	85.0±16.8	85.5±17.6	84.6±16.2	0.782	0.05
BMI (kg m^{-2})	29.3±5.4	29.5±5.4	29.2±5.4	0.831	0.05
Waist (cm)	99.1±14.8	99.8±16.1	98.4±13.8	0.622	0.09
Hip (cm)	104.9±9.1	104.9±8.9	105.0±9.4	0.985	0.01
Waist/hip ratio	0.94±0.09	0.95±0.11	0.94±0.09	0.513	0.10
FFM (%)	71.4±9.7	71.2±9.1	71.6±10.3	0.845	0.04
FBM (%)	28.6±9.7	28.8±9.1	28.4±10.3	0.845	0.04
Rest SBP (mmHg)	117.7±13.7	121.8±14.9	114.5±11.6	0.006	0.55
Rest DBP (mmHg)	71.3±8.7	73.8±8.8	69.3±8.1	0.007	0.53
Rest HR (beats·min^{-1})	82.0±11.3	82.3±11.6	81.8±11.2	0.855	0.04
$Workload_{peak}$ (W)	119.2±32.3	117.3±31.1	120.6±33.3	0.620	0.10
Time (min)	9.4±3.2	9.3±3.0	9.5±3.4	0.701	0.06
Distance (km)	1.6±0.7	1.51±0.61	1.60±0.80	0.559	0.13
HR_{peak} (bpm)	150.2±19.8	148.0±18.2	151.9±20.9	0.322	0.20
$\dot{V}O_{2peak}$ (L min^{-1})	1.83±0.52	1.83±0.49	1.82±0.54	0.911	0.02
$\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1})	22.0±6.4	22.0±6.1	22.0±6.7	0.968	0
RER_{peak}	1.18±0.11	1.19±0.12	1.17±0.10	0.309	0.18
MET_{peak}	6.2±1.8	6.2±1.7	6.3±1.9	0.758	0.05
VT_1 (mL kg^{-1} min^{-1})	12.6±3.6	12.8±3.8	12.4±3.5	0.598	0.11
VT_2 (mL kg^{-1} min^{-1})	18.8±5.7	18.7±5.0	19.0±6.2	0.823	0.05
COP	30.3±4.8	30.9±4.5	29.8±5.0	0.234	0.23
Hemoglobin (mg/dL)	14.8±1.3	14.8±1.4	14.8±1.3	0.896	0
Hematocrit (%)	44.5±3.8	44.5±4.1	44.4±3.6	0.877	0.03
Glucose (mg/dL)	95.4±26.9	95.4±20.2	95.2±32.0	0.970	0.01
HOMA-IR	3.4±6.3	5.1±9.9	2.5±2.1	0.144	0.36
Insulin (μU/mL)	13.1±15.8	18.0±23.6	10.1±7.5	0.068	0.45
TC (mg/dL)	187.4±39.2	190.2±40.4	183.6±37.2	0.367	0.17
HDL-C (mg/dL)	41.8±11.6	41.7±9.7	41.8±13.1	0.991	0.01
LDL-C (mg/dL)	116.4±34.9	118.2±36.5	114.2±33.6	0.571	0.11
TC/HDL-C ratio	4.7±1.4	4.7±1.4	4.7±1.4	0.823	0
TG (mg/dL)	137.9±84.7	142.0±98.2	132.6±72.1	0.574	0.11
AST (U/L)	20.0±7.2	19.8±5.7	20.2±8.3	0.751	0.06

ALT (U/L)	26.6±14.9	25.9±14.2	27.2±15.8	0.658	0.09
GGT (U/L)	29.8±29.6	31.6±33.4	28.4±26.8	0.584	0.11
Uric acid (mg/dL)	5.9±1.2	6.1±1.2	5.8±1.2	0.153	0.25
CRP (mg/L)	6.2±8.9	6.3±8.3	6.1±9.4	0.926	0.02

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BNSS, brief negative symptom scale; COP, cardiorespiratory optimal point; CRP, C-reactive protein; DBP diastolic blood pressure; DM, diabetes mellitus; EX, exercise group; FFM, fat-free mass; FBM, fat body mass; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; MET_{peak}, peak metabolic equivalent of task; RER_{peak}, peak respiratory exchange ratio; PANSS, positive and negative syndrome scale; SBP, systolic blood pressure; TAU, treatment-as-usual; TC, total cholesterol; TG, triglycerides; $\dot{V}O_{2peak}$, peak oxygen uptake; VT, ventilatory threshold. P≤0.05.

Table 2. Body composition, and cardiopulmonary exercise physiological data for all groups before and after the intervention period. Mean±SD

	TAU (N=38)	EX (N=51)	*P*	*F-value*	*%Variance*
Body mass (kg)					
T0	84.4±18.2	86.7±16.1			
T1	86.0±20.2	86.1±14.7	0.050	3.965	0.045
BMI (kg m^{-2})					
T0	29.0±5.7	29.8±5.4			
T1	29.6±6.6	29.6±5.1	0.050	3.727	0.042
Waist/hip ratio					
T0	0.94±0.11	0.94±0.09			
T1	0.95±0.11	0.94±0.09	0.820	0.052	0.001
FFM (%)					
T0	71.5±9.7	70.7±10.3			
T1	71.3±8.5	71.0±9.9	0.727	0.122	0.001
FBM (%)					
T0	28.5±9.7	29.2±10.3			
T1	28.7±8.5	29.0±9.9	0.727	0.122	0.001
Workload$_{peak}$ (W)					
T0	111.1±28.2	123.2±34.0			
T1	113.4±28.5	148.0±52.6***	<0.001	14.578	0.157
Time (min)					
T0	8.9±2.8	9.7±3.5			
T1	8.7±2.8	12.2±4.9***	<0.001	30.828	0.266
Distance (km)					
T0	1.4±0.5	1.6±0.8			
T1	1.4±0.6	2.5±1.7***	<0.001	13.707	0.139
HR$_{peak}$ (bpm)					
T0	147.6±18.7	152.0±21.5			
T1	141.9±20.4**	153.1±20.2	0.017	5.921	0.065
$\dot{V}O_{2peak}$ (L min^{-1})					
T0	1.76±0.44	1.87±0.57			
T1	1.74±0.46	2.20±0.72***	<0.001	15.155	0.151
$\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1})					
T0	21.6±6.2	21.9±7.1			
T1	21.0±6.5	26.2±9.6***	<0.001	20.102	0.191
RER$_{peak}$					
T0	1.21±0.12	1.17±0.11			
T1	1.18±0.10	1.16±0.11	0.326	0.975	0.011
MET$_{peak}$					
T0	6.0±1.8	6.3±2.0			
T1	5.9±1.7	7.5±2.7***	<0.001	15.836	0.157
VT_1 (mL kg^{-1} min^{-1})					
T0	12.5±4.0	12.3±3.7			
T1	12.5±4.2	15.0±6.6**	0.029	4.921	0.060
VT_2 (mL kg^{-1} min^{-1})					
T0	18.1±5.1	19.2±6.6			
T1	18.0±6.4	20.3±8.5	0.499	0.461	0.006
COP					
T0	31.2±4.7	29.5±5.1			
T1	30.8±4.3	30.0±4.4	0.371	0.809	0.009

BMI, body mass index; COP, cardiorespiratory optimal point; DBP, diastolic blood pressure; EX, exercise group; FBM, fat body mass; FFM, fat-free mass; HR, heart rate; MET_{peak}, peak metabolic equivalent of task; RER_{peak}, peak respiratory exchange ratio; TAU, treatment-as-usual; VT, ventilatory threshold; SBP, systolic blood pressure; $\dot{V}O_{2peak}$, peak oxygen uptake.
****P* <0.001; ***P* <0.01; **P* <0.05 between T0 and T1.

8.5. Anexo 5: *“'It Helped Me to Disconnect My Mind from the Problems': The Subjective Experiences of People with Schizophrenia Taking Part in a Concurrent Exercise Program.”*

Los indicadores de calidad de la revista del tercer artículo publicado, según Journal CitationReports (JCR) y Scientific Journal Rankings (SJR) en el año 2023 son los siguientes:

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'It Helped Me to Disconnect My Mind from the Problems': The Subjective Experiences of People with Schizophrenia Taking Part in a Concurrent Exercise Program

Mikel Tous-Espelosin, MS[a,b], Diane Crone, PhD[c], Sonia Ruiz de Azua, PhD[d], Nagore Iriarte-Yoller, MD[e,f,g], Agurne Sampedro, PhD[h] and Sara Maldonado-Martín, PhD[a,b]

[a]GIzartea, Kirola eta Ariketa Fisikoa Ikerkuntza Taldea (GIKAFIT), Society, Sports, and Physical Exercise Research Group, Department of Physical Education and Sport, Faculty of Education and Sport-Physical Activity and Sport Sciences Section, University of the Basque Country (UPV/EHU), Vitoria-Gasteiz, Spain; [b]Bioaraba Health Research Institute, Physical Activity, Exercise, and Health group, Vitoria-Gasteiz, Spain; [c]Centre for Health, Activity and Wellbeing Research, Cardiff Metropolitan University, Cardiff, UK; [d]Department of Neuroscience, University of the Basque Country (UPV/EHU), Leioa, Spain; [e]Bioaraba, New Therapies in Mental Health Group, Vitoria-Gasteiz, Spain, Spain; [f]Osakidetza Basque Health Service. Araba Mental Health Network, Psychiatric Hospital of Alava, Vitoria-Gasteiz, Spain; [g]Department of Medicine, Faculty of Health Sciences, University of Deusto, Bilbao, Spain; [h]Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Spain

ABSTRACT
The aim of this study was to investigate the subjective experiences of a concurrent exercise program designed to improve both physical and mental health, through participation, for people with schizophrenia. Participants diagnosed with schizophrenia (n = 35, 41.6 ± 10.3 years) received an intensive concurrent exercise program for a 5-month duration, three times a week, at out-of-hospital facilities. Qualitative data was collected *via* individual, semi-structured interviews, organized, and analyzed with thematic analysis. The findings highlight the participants' perspective in supporting an out-of-hospital exercise program as an acceptable and beneficial adjunct to usual treatment in people with schizophrenia for holistic health improvements.

Introduction

According to the World Health Organization schizophrenia, a chronic and complex neuropsychiatric disorder, affects ~24 million people worldwide, causing a significant impact on the quality of life of people with this condition and their families. Adding to that, stigma and discrimination are common in people with schizophrenia hindering effective care choices (World Health Organization, 2022).

In this sense, pharmacological treatment plays a fundamental role in the management of positive symptoms (symptoms that are present) of the schizophrenia disorder (i.e. delusions and hallucinations) (Bueno-Antequera & Munguía-Izquierdo, 2020). However, there is an absence of effective treatments for negative symptoms (e.g. a lack of motivation, social withdrawal, as well as cognitive dysfunction) that affects this disease (Miyamoto et al., 2012). In recent years, exercise programs have been promoted as an interesting and useful non-pharmacological resource as an adjuvant treatment of mental disorders such as schizophrenia (Bueno-Antequera & Munguía-Izquierdo, 2020; Vancampfort et al., 2016; Yung & Firth, 2017). In fact, they have been found to improve symptoms, globally cognition, and quality of life (Stubbs et al., 2018). Exercise programs, when successful, can also help to address known health inequalities within this population compared to the general population, including higher rates of physical inactivity and body mass index (Stubbs et al., 2016), poor diet, and smoking prevalence (Ratliff et al., 2012) all of which can result in higher levels of morbidity and premature mortality (Laursen et al., 2012). In this sense, there are very well-known benefits and powerful protective effects of regular and single bouts of aerobic and resistance exercise against the development of cardiovascular, metabolic, immune, and neurological diseases (Barad et al., 2022; Thijssen et al., 2022; Valenzuela et al., 2023). Adding to that, recent investigations have shown the exercise-induced modulation of neuroinflammation in preventing, reversing, or minimizing the age-associated impaired function of the brain (Barad et al., 2022). Furthermore, there have been international calls to incorporate the use of physical activity programs into the treatment plans of people with mental health problems. These programs would aim to ensure an overall culture change, improvements in infrastructure, and staff training increasing the prevalence of physical activity in the holistic treatment of people with mental health problems (Rosenbaum et al., 2018).

CONTACT Mikel Tous-Espelosin mikel.tous@ehu.eus Department of Physical Education and Sport, Faculty of Education and Sport, University of the Basque Country (UPV/EHU), Portal de Lasarte, 71, 01007 Vitoria-Gasteiz, (Araba/Alava)-Basque Country, Spain.

To fully understand the holistic role of physical activity for people with schizophrenia, it is important to capture and investigate the actual experiences of this population participating in exercise programs. Through qualitative methods, the experiences, opinions, and perceptions of participants in an exercise program, and the role it plays for them, can be understood from the perspectives of those that it is designed for (Riddoch et al., 1998). Exploring people's experiences with exercise and what contributes to facilitating those experiences (positively and negatively) can shed light on the role of this treatment option for people with mental health disorders (Carlbo et al., 2018). This information can be used to develop further guidelines for practitioners in this area and ensure they are user informed to enable people to participate, enjoy and benefit from taking part in exercise programs.

World Health Organization 2020 guidelines on physical activity and sedentary behavior recommendations for people with schizophrenia do not differ from the general population (Bull et al., 2020). These exercise prescription recommendations complement the calls for training of health professionals in the use of exercise for mental health, a cultural change regarding its use, and funding to support exercise programs in treatment plans (Pratt et al., 2016; Vancampfort et al., 2012).

Despite what is known about exercise for mental health and calls for its use, there remains a dearth of studies investigating the experiences of people with specific mental health conditions (Gerber et al., 2022), in this case, schizophrenia. Other qualitative studies have investigated heterogenous groups of patients (Mason & Holt, 2012), but the present study includes only people with schizophrenia. Focusing on a single clinical population highlights the specific role that physical activity plays in the management and treatment of the disease. Therefore, this study aimed to address this lack of focus on homogenous patient groups and provides the voices of people with schizophrenia and their subjective experiences of a concurrent exercise program designed to improve both their physical and mental health, through participation.

Methods

Ethical considerations

The study was approved by the local Research Ethics Committee (PI2017044), and written informed consent was obtained from all participants before any data collection.

Settings and participants

The CORTEX-SP study was conducted between May 2018 and July 2021 and for the present analysis, 35 participants were included, all of them diagnosed with schizophrenia from two locations (a psychiatric hospital and a mental health network). Participants were aged between 18 and 65 years (mean age 41.6 ± 10.3 years, 26 men and 9 women). Participants were recruited and thus included, from hospital inpatients ($n = 16$), and outpatients ($n = 19$); people living in foster care, and people living in their own homes. Included patients met the diagnostic criteria for schizophrenia according to DSM-5 (American Psychiatric Association, 2013), with a disease evolution time greater than 2 years, stable and at least moderate cognitive impairment in the MATRICS variables (T score <40 in at least one of the seven cognitive domains). All the selection criteria (exclusion and inclusion criteria) and procedures for the CORTEX-SP study have previously been described (Tous-Espelosin et al., 2021). The diagnosis and evaluation of the participants were carried out by specialists in psychiatry.

Intervention

The participants took part in exercise sessions, 3 days per week, for a 5-month duration under the supervision of exercise specialists, at out-of-hospital facilities. Each session included a warm-up (10 min) and a cool-down (10 min). In the main part of each session, concurrent exercise training (i.e. endurance and resistance training within the same session) was performed (Bishop et al., 2019). The endurance part of each training session consisted of both a high-intensity and low-volume aerobic exercise (20 min as total volume, with less than 10 min at high or vigorous-intensity) cycling on a stationary bike (BH Fitness equipment). The exercise intensity was individually tailored to each participant's heart rate (HR) at moderate or vigorous-intensities from a cardiopulmonary exercise test. Based on the identification of the two ventilatory thresholds (VT1 and VT2), the three intensity ranges of exercise were determined: (R1) light to moderate intensity with HR values below VT1; (R2) moderate to high intensity with HR values between VT1 and VT2; and (R3) high to severe intensity with HR values from VT2 to the maximum HR achieved in the cardiopulmonary exercise test. The exercise cardiopulmonary test and VT assessment have been previously published (Tous-Espelosin et al., 2021). The HIIT protocol on the bike was carried out in a 5-10-min warm-up period R2 and after that, the participant cycled for 30 s at R3 followed by 60 s at R2. Four repetitions (1 rep = 30 s at R3 followed by 60 s at R2) were initially performed and gradually increased to nine repetitions. The resistance-circuit training was performed with three circuits, one for each workout of the week, with 10 different exercises. They were organized by major motor patterns (i.e. knee dominant, hip dominant, press, pull, core, and micro impacts) and the exercises were alternately ordered based on whether they were upper or lower body. Each exercise was worked for 1 min with 30 s recovery. Initially, a single round of exercises was performed and gradually increased to two rounds. The total duration of each session was 60 min.

Design, data collection methods, and procedure

A qualitative approach with semi-structured face-to-face interviews was chosen for the study. These were adopted to meet the research objectives to allow for the exploration of understanding participants' participation in the exercise program, and their attitudes and opinions regarding its role in the management of their condition, general health, and wellbeing. Further, the use of semi-structured interviews through an interview schedule enabled the researcher to guide the discussion whilst also leaving space for the participant to offer additional meaning and their understanding/perception of the topic (Eatough & Smith, 2008). The interview schedule was developed in line with the research aims and informed by existing literature on the topic. The PRE interview schedule included questions relating to the participants' conception and motivation of the program, their perception of exercise and sport, expectations regarding participation, and questions relating to their life habits. The POST interview schedule included questions related to the context of the program (space, instructors, duration, and timetable), social relations, benefits perceived, level of satisfaction, and future plans. All interviews lasted between 30–45 min, and 35 min on average duration. Taking into account the difficulty of communication and sociability of people with schizophrenia, they were asked voluntarily at the beginning of the program who wanted to participate in a recorded interview. Ten of them agreed. Once the intervention was completed after 5 months, and with the confidence gained in the person who conducted the sessions, 25 more people agreed to be interviewed (a total of 35 who participated in this study).

Data analysis

All 35 audio recordings were conducted in Spanish (the native language of the participants and researcher) and manually transcribed verbatim. To manage the analysis process, transcripts were imported into NVivo9 (QSR International Pty Ltd, 2010) and the analysis process was managed using the qualitative software.

To analyze the data Thematic analysis (Braun & Clarke, 2006) was used. This included the six stages of the analysis process, familiarization with the data (1), generating initial codes (2), searching for themes (3), reviewing themes (4), defining and naming themes (5), and producing the report, including information on how this was undertaken in this study.

To assist with the transparency of the analysis process the first author was involved in conducting the interviews, transcribing, coding, and data analysis. Once this process had taken place a second researcher was involved in refining the themes and supported in stages 4, 5, and 6 through cross-checking the consistency of the themes, theme content, and their titles, and the relationships between them (Gale et al., 2013). Once themes were agreed upon and finalized, the two researchers reviewed the themes for relationships and connections to each other to help form the conceptual framework (Figure 1). The framework visually explains how the findings are connected and assist in understanding the meaning of taking part in the program, from the perspectives of the people who took part in it. The themes and the model are explained in the next section.

Results

Six themes emerged from the analysis. Each theme had sub-themes which are presented along with quotations from participants to enable the voices to be heard within the text. Quotations are presented in italics, with pseudonyms to preserve the participants' confidentiality. Quotations are included to provide the lived experience of participants and to assist in ensuring trustworthiness (Erlandson et al., 1993). The themes are presented in a conceptual framework, in Figure 1, with connections (where they exist), which explain the relationships of the themes, to each other.

The diagram (Figure 1) presents the relationships between themes, e.g. the themes 'expectations about taking part' and 'attitude to exercise, the program, and general lifestyle' appeared to influence participants to take part and are pre-intervention interviews. The act (and factors associated with) 'taking part' then led to subsequent 'perceived outcomes' and 'plans' should be considered post-intervention

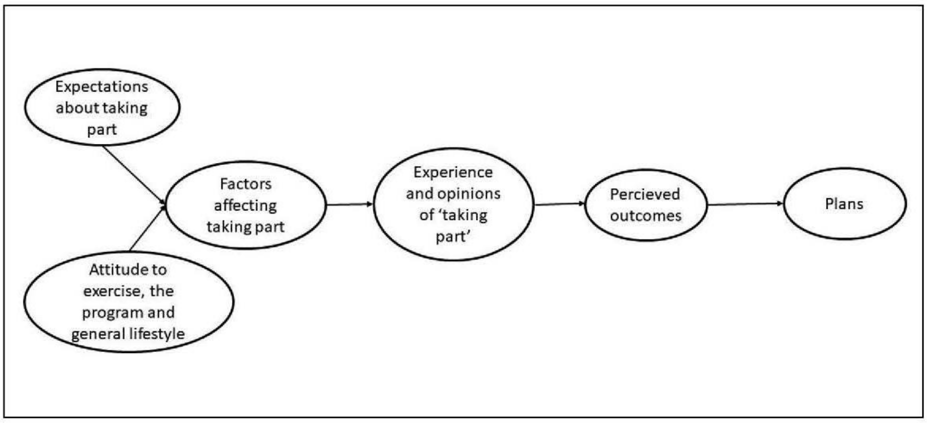

Figure 1. Conceptual framework explaining the subjective experiences of participants with schizophrenia on the exercise program.

interviews. The themes are presented as they appear in the framework.

Expectations about taking part

The "expectations" theme is related to the benefits participants expected to receive from taking part. Most participants agree that they expected physical improvements, mainly to reduce body mass ("weight" in colloquial language) and be more flexible; "I would like to lose weight and be able to bend or kneel without pain" (James). For others, they had expectations and hopes for having a clearer mind, being less sleepy, improving the ability to react, and being more accepting of themselves; "I would like to be more independent, be more responsible, increase my physical and emotional health, and accept more myself" (Amelia). Some were also hoping that participation would enable them to reduce prescribed medication, such as for hypertension, and high cholesterol. There were some differing expectations from the participants who had been referred directly from the hospital who believed, at the early stages, to expect nothing as it had been a required hospital activity for them; "At the beginning, my first reaction was one of rejection because it was a hospital activity" (Robert).

Attitude to exercise, the program, and general lifestyle

This theme has three sub-themes: relationship with exercise in the past, motivation to start, and fears about the program.

Relationships with exercise included participants' previous experiences of exercise both as children in school, and then more recently before starting the program. All participants had good childhood memories of sports, such as playing soccer, handball, and basketball, and they believed that these fond memories helped them to be able to participate in the program; "Yes, I have good memories, I think it helped me [with the program]" (Michael). Prior to starting the program, most participants were not taking part in exercise because they either did not like it, did not have the energy, or because of factors such as illness or medication preventing them from doing so; "Now with what I smoke and the medication I take, it leaves me flat, so I don't have the energy to exercise" (William). Others did do some activities for example they went for walks, and some took part in activities promoted by the psychiatric hospital; "One day a week, on Tuesday mornings, we go hiking from the hospital" (Olivia).

Motivation to start the program was associated with their reasons for taking part. Generally, people found it hard to start an activity but once they had started it, they found it less difficult; "I'm super lazy, but it's for everything, not just this. It costs me a lot to motivate myself and to start because I have to think a lot while sitting there on the couch. It's a daily struggle. Then I start and I'm fine" (Isla).

Attitude to exercise also included fears about the program and concerns about their ability to participate. Before starting the program, these were due to their already busy schedule (from the hospital); "Well, a little bit of fear, a little bit because I am quite busy with the workshop, so it is already very busy and then it was a burden for me…" (Richard). But mostly their concern was about how hard the program would be for them, especially as they were quite physically deconditioned; "Yes, but I was afraid of the high intensity, to see if they were going to make a mess of us" (William) and from expectations of the exercise leaders regarding their fitness levels; "Because they did not know exactly what physical condition I was in" (Joseph).

Factors affecting taking part

The theme 'factors affecting taking part' has four sub-themes including consequences of the disease, motivation to attend, social support, and role of music.

'Consequences of the disease' represents how the symptomatology of the illness affects the participants, which includes both positive and negative symptoms. Positive symptoms, e.g. a feeling of their head spinning, improved through taking part in the exercise as it reduced the likelihood of this, along with some negative symptoms such as feelings of sadness and energy levels; "Before doing the study I had some symptoms such as sadness, lack of energy and a lot of head spins, but thanks to the program they disappeared" (Charles). Other positive symptomatology, such as paranoia and delusions also reduced during the intervention; "Before the program I had paranoia, but they seem to have disappeared, I have not had any for a year now, I am better, yes" (Emily).

Negative symptoms, experienced every day, include sadness, anxiety, fears, and nervousness, and can result in differing states of mind during the day. These fluctuations of mood affect the ability to develop a habit of exercise which can problematic because without regular participation, people will not improve their conditioned state, and there is, therefore, an increased risk of experiencing exercise-related pain, e.g., "I have a bad time after the exercise, because of the lack of habit… I have a bad time, pains in my legs, body, back… Until after a while, I recover little by little and I feel better" (Thomas). Furthermore, the negative symptoms also result in cognitive deficits that can make it difficult to concentrate in an exercise session, and can result in clumsy behavior, for example; "Well, at first I noticed that I was a bit clumsy, in terms of coordination especially I was having a hard time concentrating on the exercises I was doing" (Alexander). In addition, for some, the negative symptoms result in them socially isolating themselves, which can affect their attendance; "In the end, the disease makes you sadder and more fatigued, and you end up shutting yourself up at home and interacting less with others" (Ethan).

Motivation to attend included different elements that increased their motivation, such as the good atmosphere in the sessions; "I was cycling every day in the unit and I told the psychiatrist that I didn't like it, here I like it because it's different, it's lively and there's a good vibe" (Noah). To experience improvements was also a source of motivation, e.g. weight loss; "Losing weight was very important but what motivated me the most was the vital tone I had after exercising, that I was much more active, then to help my mother at home with the housework and not let the disease eat me" (James).

Social support was provided by family and friends, and the staff. Participants stated that family and friends were supportive of their participation in the program. Indeed, many felt that family and friends were an indispensable part of maintaining adherence to the program which expressed itself through disappointment when participants ceased taking part; "When I dropped out my mother looked disgruntled, and she blamed me for it." (Liam). Participants stated that support was provided by prompts and reminders to attend from family and friends, by reinforcing a more physically active life through activities of daily living, taking part with them, and helping them plan strategies to maintain their exercise habits: "My roommate usually goes jogging, and the other day I went with him " (Robert). Not all participants, however, needed this external support, for example, Harry reported being intrinsically motivated to attend; "I don't care if my family encourages me, I'll do my own thing" (Harry).

Staff also provided social support, for example, the psychiatrist who was directly responsible for referral into the program provided encouragement and support through the act of recommending the program; "I trust my psychiatrist. And as I know that she is overseeing this intervention, it kind of encourages me…" (Olivia). The exercise session staff also supported them to take part by facilitating an enjoyable experience and helping them to work hard during the sessions; "They [session staff] encouraged us to work harder, to do more, but we also laughed and teased each other from time to time" (William). When they compared the qualified personnel (exercise specialists) to the hospital personnel, they preferred to be supported in the exercise sessions by the qualified exercise professional; "Because he [the exercise leader] has studied for this and nurses are not the same as [exercise] professionals. He knows when, how much and why exercise" (George).

The role of music played during the sessions was also a very positive factor in their experiences of taking part. Music was influential for motivation, positive emotions, such as feeling at ease, and in facilitating connecting with people which helped participants improve their performance; "Music is very helpful for people with mental disorders, it makes us think less and motivates us at the same time" (Isla). Participants appreciated doing the sessions with music as it improved the experience for them; "With music better, livelier, more at ease" (Thomas).

Experiences and opinions of 'taking part'

This theme includes the sub-themes of 'the FITT principle', 'place and timing of the sessions, 'staff', and 'other participants.

'The FITT principle' sub-theme includes experiences and opinions of the FITT (frequency, intensity, time, and type) principle used to program and guide the exercise sessions. Frequency includes how many days a week the exercise program should be carried out. Most of them were happy with 3 days, but only if the days were alternated and not consecutive days. Hence, in the present program, doing 2 days consecutively was sometimes physically difficult for them, especially at the beginning, but as time progressed it seemed more manageable; "Wednesday and Thursday were back-to-back, and on Thursday I got a little tired" (John).

Intensity is how physically hard the sessions were and participants agreed that at the beginning it was physically difficult because they were not used to exercise; "At the beginning, I was scared because I knew I wasn't ready as I've already lost a lot of physical fitness and I smoked a lot" (William). However, as the program progressed, they improved; "We were encouraged to do more, more… and the exercises were good, I liked it" (William).

Time relates to the duration of the program. In the beginning, participants felt that 5 months was a long duration; "I think five months is too long" (Charlie). At the end of the program, they changed their opinion and conversely, found it too short; "The duration of the program is short. Before it seemed long and now no, because you are comfortable, and I would continue if I have the opportunity" (Oliver). Further, participants were comfortable with the length of the sessions; "They lasted an hour, and once we finished the warm-up, the sessions were over very quickly, mainly because they were very dynamic" (George).

Type includes the exercises in the sessions. The participants preferred cycling to resistance exercises because it was deemed more dynamic and enjoyable; "What I liked the most was the bike because it was quite enjoyable, they made you make changes of pace and it seemed like a game. So you didn't get bored, it went by fast" (Richard). However, for some, it was too hard, for example, core stability exercises such as the Bosu Ball (an exercise ball cut in half) and the plank exercise were the most difficult and affected their opinion of the exercise; "I didn't like balancing on a semi-circle very much, I wasn't very good at it and I was a bit angry about it" (Richard).

The place of the sessions includes the program location, which was a community-based setting. The fact that the program was in the community (and not in a hospital), was preferred by most, as it was an opportunity to get out of the hospital, feel the fresh air and see different people, be in different surroundings; "I prefer to go outside the hospital because I have spent enough time there, change of scenery and clear your mind because the psychiatric hospital is a bit sad." (William). Also, for several participants the hospital was associated with negative memories and was the reason they preferred to change environment: "Once I left the psychiatric hospital behind, I don't want to remember it again, I'll start remembering things from the past… pff… things that happened six years ago, it would have been horrible." (Ethan).

The time of the session includes which hour they preferred for the sessions. As part of their daily schedule (when permitted), some had 2 hours off in the evening when they were allowed to leave the hospital and take a walk, have a refreshment at the local café in the community, and so on.

Therefore, those hours were precious to them, and they preferred to exercise before that time; "I had problems with the psychiatrist because he sent me to the exercise program in my free time" (Reece). However, some of them felt that during autumn-winter they did not like going to the program in the evening, when it was dark outside, as this created a feeling of sadness or even fear; "It is not the same, no, better early in the afternoon because in the evening you are already tired and that is when paranoia and hallucinations are more common" (Amelia).

Other participants were also part of the experiences of taking part. Attending a group program, as well as the commitment between group members, contributed to creating more motivation to attend; "If you go with a group it forces you more because if it is on my own, one day I might do something, another day I might not feel like going, but the other way, since you have already signed up, you have to go not to look bad" (Robert). However, other participants preferred to exercise on their own, either because they have always done so or because they like being on their own; "I prefer to do it alone, I don't need others, I prefer to be with myself" (Harry). There were also opinions regarding the type of participants in the program. For example, a preference of participating with other similar people with mental health disorders was preferred because it was explained that there could be a feeling of rejection, prejudice, or insecurity from people who do not have a mental health disorder; "The gestures, the looks, the comments" (Charles). So, some participants preferred to exercise with people similar to them; "That way we are all equal, we do as much as we can and there are no comparisons" (Thomas) and better understood; "I feel more comfortable when people were like me, one day they greet me, another day they don't, and I do the same. Everyone is quiet, and nothing happens. We already knew that nothing happened, and it was normal" (Isla). Other opinions on exercising with others were that it would be better to participate with all kinds of people to normalize the disorder and not always be marginalized; "Better to be with other people so that it's not a ghetto so that sick people are not pushed into a corner" (Liam).

Perceived outcomes

The theme of perceived outcomes includes the improvements felt by the participants from taking part, such as the quality of life, physical health, and mental and social health changes. All participants expressed that they had had a general improvement in their quality of life from taking part; "When I started, I was a real disaster, lying in my room watching movies and smoking joints, I have changed, and my quality of life has improved a lot" (Joe).

In terms of physical health improvements, as the exercise program progressed, participants became more agile, had more coordination and flexibility, and also weight loss; "Before I would bend down to pick up some keys on the floor and poof… I've lost 15 kilograms or so. I'm doing well, … I walk lighter before sometimes I was walking, and I had to stop" (Michael). George also commented that the physical fitness improvement he had experienced, helps him to concentrate more; "I have noticed a lot the physical fitness and strength, and when I am doing something, I concentrate much more" (George).

As for mental and social health improvements, the program provided many benefits, including:

- helping them to socialize more with people; "I wasn't used to socializing much, but now I relate more with people, inside and outside the program. I can open up to others, something that before I was locked up in a world that I couldn't get out of. This is more like a family and, whether you like it or not, that creates a bond, a bond that I didn't want before" (Kyle);
- to have time away from their thoughts; "It helped me to disconnect my mind from the problems and everything a little bit. You think not, but in the end, exercise improves mental capacity, it's like that because you are distracted" (William);
- reducing the symptoms of the disease; "When I was exercising, I forgot everything, all the ideas went out of my head and so on, but then they came back again, and I felt worse. But here I felt very well" (Damian);
- quality of life; "Well, I was in a better mood, I had more confidence, more will, and more responsibility" (Amelia).

However, despite these improvements, once the program had finished many did not continue with the exercise regime and participants reported that some of the improvements had since been lost; "Now I have lost them because before, thanks to the exercise I was tired, I rested better, and I didn't have to take sleeping pills. Now if I don't, I can't sleep, I feel very sleepless" (William). Furthermore, anxiety levels had also increased due to the cessation of exercise; "Well, before I was more active, I was less sleepy during the day, I was much more vital, happy. I argued less, I had less anxiety, now I have a lot of anxiety" (James).

In summary, the participants agree that exercise is a necessary tool to improve and maintain all aspects of life; "Of course, exercise always helps you. Exercise is good for everything, it's good, I like to exercise" (Isabella).

Plans

This theme has two sub-themes: 'plans to continue' and 'cost barriers'. Plans to continue were evident but once the program ended, the participants tried to continue with the exercise habits that they had acquired during the program at home, but these efforts were not sustained; "After the program, I have been exercising at home, cycling and some resistance exercises. But it didn't last long, 1-2 months. But it was different, you can't do many exercises, you have to make do with the material at home and you don't have the exercise leader" (James). Others tried to sign up for community-based exercise programs, but this was not a suitable option for them either; "In the program, the other people were thin, were used to doing sports and I felt out of place. On top of that, if I didn't go, there was no one to call me to encourage me like in this program" (Isla). Despite these efforts, some were continuing with activity, choosing to go for a walk as an alternative option to exercise; "Now I'm walking one day out of two, walking for an hour" (Jake). One participant did not want to continue as they saw the program as a treatment that they didn't feel they needed anymore; "I don't want to continue as I am now, because I am already fine" (Emily).

The cost of the sessions impacted the plans of the participants due to the cost-prohibitive nature of continuing with the exercise in community venues. Furthermore, participants commented that due to reductions in income support for people with mental health disorders, they were forced to focus on working rather than finding the time or indeed funds for exercise; "Yes, but things have been bad for me. My income has been reduced considerably and I don't know what's going to happen. First it is the day to day and to maintain the job" (Oliver).

Discussion

The results of this qualitative study found that at the beginning of the exercise program, participants felt apprehension, but confidence in the people leading the sessions, and attending over time, helped to reduce this apprehension over time. This supports previous findings on the importance of positive exercise experiences and the need for social support in facilitating participation (Johnstone et al., 2009). The literature identifies that people with schizophrenia are sensitive to the perceptions of others, such as healthcare professionals, especially when there is no good therapeutic relationship between professionals and patients (Soundy et al., 2014). The findings of this study identified that there was a good atmosphere in the sessions, among the people leading the session and the participants. This good atmosphere provoked a positive perspective and a motivating culture for participants to continue. Similar results have been observed in other studies where trust was built among participants (intra-group) and between participants and leaders (inter-groups) resulting in high adherence to the exercise program (Gomes et al., 2014).

The study identified several barriers to taking part and attending, but social support from the leader, others in the group, and family appeared to be important in encouraging them to continue with the program. The social and family environments were therefore identified as facilitators for participation in the exercise. These findings echo those of other studies where the social environment and family environment were identified as facilitators of lifestyle modification (Gandhi et al., 2019; Karlsson & Danielsson, 2022). Thus, clinical barriers and an unhealthy lifestyle, including physical inactivity (Stubbs et al., 2016), smoking, abuse of alcohol and/or caffeine, and poor diet (Ratliff et al., 2012), along with adverse effects of medications (Mukundan et al., 2010), and socio-economic factors (e.g. access to health care) (Correll et al., 2014) have all previously been identified as affecting participation and adherence over time.

This study found that participants identified the general improvements they experienced, during and after the exercise sessions, as well as the positive changes in physical and mental health and quality of life during the program. Other studies have also found similar results (Karlsson & Danielsson, 2022; Rastad et al., 2014). This study has also identified the participants' enjoyment of positive social experiences with others in the group and with the leader. Others, for example, (Fogarty & Happell, 2005; Gomes et al., 2014), identified that participants' positive experiences during program participation can help change their perception of some of the barriers before starting the program (i.e. the physical difficulty of the program and the participants' physical fitness).

In the study, participants generally expressed a preference for group exercise, although it must be noted that there were some exceptions. However, despite these exceptions, the importance of group dynamics to increase motivation and facilitate social interaction resulting in making activities more enjoyable through peer and social support is evident (Chapman et al., 2016; Fogarty & Happell, 2005; Gandhi et al., 2019). Thus, the importance of a group-based exercise program for people with schizophrenia is supported, when factors such as group dynamics and a supportive environment are also evident. However, in the same vein as this study (Gandhi et al., 2019), some participants highlighted that if the groups are not balanced in terms of physical condition and skills, a decrease in motivation could occur. Furthermore, in a group activity, there will always be differing opinions of what people prefer to do, and in line with another study (McDevitt et al., 2006), participants wanted to have a choice in the type of exercise performed in the program, mainly because different opinions were presented and they believed that the program needed to be more individualized. In this line, it was explained to the participants that the program was individualized concerning the intensity, but that since it was a research project, all of them had to perform the same type of exercises, to try to endorse the benefits of the program in the disease, and thus be able to organize community programs.

One of the significant findings in our study was the special emphasis placed by participants on the exercise program being carried out outside the hospital. This supports the literature regarding the key role that the exercise environment plays in achieving the success of the intervention (Gomes et al., 2014), resulting in a facilitating factor for a positive outcome (Karlsson & Danielsson, 2022), and providing integration in the community for those from a hospital setting.

One of the disappointing findings from this study was the finding that when the program had finished participants found difficulty and frustration with not being able to continue exercising. Similar to the findings of others (Karlsson & Danielsson, 2022; Rastad et al., 2014) participants were keen to continue their involvement in regular exercise to maintain positive outcomes and experiences (Fogarty & Happell, 2005). However, in the experiences of these participants, the economic challenges of carrying on, also detailed by (Karlsson & Danielsson, 2022) and the lack of resources generally (Rastad et al., 2014) were barriers to longer-term sustainable exercise programs. Implications for future programs would be to build in a more sustainable element to the project, perhaps by linking with locally delivered exercise programs so that participants could be fed into existing, and affordable, exercise provisions to enable continuation.

Limitations and strengths of the study

The qualitative nature of this study provides some rich experiences from people with schizophrenia taking part in an exercise program. However, it is important to acknowledge the findings from this study cannot be generalized. However, the findings do suggest that considering exercise as a component of a lifestyle-enhancing program, for people with schizophrenia is important, valued, and could be effective and beneficial in the management of their condition and indeed for their quality of life.

The current study has several further strengths. Considering the difficulties involved in recruiting participants with schizophrenia in a concurrent training exercise intervention, with an exercise session duration of between 30 and 45 min each, and for 5 months, we could argue that the analyzed sample ($n = 35$ people) constitutes a rich data set. Secondly, participants were familiar with, liked, and trusted the researcher (interviewer), and during the study a positive relationship developed through long (5 months) and close contact (3 d/week). On reflection, we believe that this developed a trusting relationship which, in turn, encouraged more honest and detailed discussions in the interviews. However, having a pre-established relationship with the interviewers may also be a limitation in that the participants could respond with socially desirable answers (i.e. say what they think the interviewer wanted them to say).

Conclusions

Findings from the study support the case (Rosenbaum et al., 2018) for the strategic use of exercise in the treatment and maintenance of holistic health for people with schizophrenia. However, as this study also demonstrates, building a continuation plan for participation is also imperative to ensure sustainable and longer-term participation in such programs. The location of the program appears important to consider (i.e. out-of-hospital), as does the constitution of the group, the type of people, and the exercise program itself. For these participants, the program does not only function as an intervention for physical and mental improvement, but it also has the potential for holistic health benefits, such as well-being and important opportunities for social interaction for this clinical group.

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15. Tous-Espelosin M, Etxaniz-Oses J, Cañas Garcia M, Ortiz de Zarate A, Pavon-Navajas C. Programa de ejercicio físico en pacientes con trastorno depresivo resistente a tratamiento (TRACE- RMD): resultados preliminares psicopatológicos. Congreso Nacional de Enfermería de Salud Mental. 2022. Pamplona, España.
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25. Tous-Espelosin M, Crone D, Iriarte N, Maldonado-Martin S. ‘It helped me to disconnect from the problems’: a qualitative study exploring the subjective experiences of people with schizophrenia in a concurrent exercise program. European Network for the Promotion of Health-Enhancing Physical Activity.2023, Leuven, Belgium.

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27. Tous-Espelosin M, Iriarte N, Pavón C, Maldonado-Martin S. Hábito tabáquico y capacidad cardiorrespiratoria en personas con esquizofrenia: estudio CORTEX-SP. VIII Simposio EXERNET: ejercicio físico para la salud a lo largo de la vida. 2023, Almería, España.

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