Relevant associations of Metabolic Syndrome in first episodes of psychosis at 10-year follow-up: the importance of therapeutic exercise

Master`sThesis

MASTER“INICIACIÓN A LA INVESTIGACIÓN EN SALUD MENTAL”FROM THE UNIVERSITY OF CANTABRIA

Curso 2017-2018

Author: Jose Antonio Cortés Fernández

Physiotherapy Graduate from the University of Cantabria

Director: Dr. Rosa Ayesa Arriola

Certificate of approval

The master´s thesis entitled "Relevant associations of Metabolic Syndrome in first episodes psychosis at 10-year follow-up: the importance of therapeutic exercise" conducted and submitted by Jose Antonio Cortés Fernández in partial fulfilment of the requirements for the degree of the Master "Iniciación a la Investigación en Salud Mental" of the Univesrity of Cantabria, has been examined and is recommended for acceptance and approval for Oral Examination.

Dr. Rosa Ayesa Arriola

Santander, 6 July 2018.

Declaration

I hereby declare that the project entitled "*Relevant associations of Metabolic Syndrome in first episodes psychosis at 10-year follow-up: the importance of therapeutic exercise*" submitted by me for the partial fulfilment for the Master "Iniciación a la Investigación en Salud Mental" under University of Cantabria, is my original work and has not been submitted earlier to any other University or Institution for the fulfilment of requirement for any course of study.

Firma

Acknowledgement

Writing a master`s thesis is not a one-man show. It is the product of many hands and has given me the opportunity to co-operate with competent colleagues during the process.

There are a number of people without whose support this thesis probably would not have been written. Their contributions are sincerely appreciated and gratefully acknowledged.

I would like to express my deep appreciation and indebtedness particulary to the following:

All PAFIP research team who helped with data collection, and specially to Dr. Rosa Ayesa, my primary supervisor, who has been enormously supportive and encouraging, has provided invaluable advice and constructive feedback, and has always found time to be there when needed. Thank you for interesting consults regarding research, mental health and statictic.

I would also like to thank all patients and family members who participated in the study.

To all relatives, friends and others who in one way or another shared their support, either morally and physically. Finally, very special thanks go to my couple Carmen Flor. I could not have done this without you.

Thank you.

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Abstract

Background: Multiple studies have identified various metabolic abnormalities in patients with first-episode psychosis (FEP). There is a fivefold increase in metabolic syndrome (MetS) within the first few years of treatment, which heightens the risk of cardiovascular diseases and contributes towards the premature mortality. The aim of the present study is to explore whether or not there are differences between presence and absence of MetS in patients with a first psychotic episode at 10-year follow-up. A secondary aim is to analyze the importance of therapeutic exercise in these patients.

Method: A total of 168 patients were recruited from a large epidemiological cohort of patients who have been treated in a longitudinal intervention program of FEP called PAFIP. In the present study information about clinical, cognitive, metabolic and physical characteristic was assessed in patients with MetS (n=52) and without Mets (n=116).

Results: High associations were found. The incidence of MetS after 10 years was greatest positively and significantly associated with metabolic (weight, systolic blood pressure, triglycerides and gamma-glutamyl transferase levels (GGT), physical (practice physical activity), clinical (age of psychosis onset, DAS, GAF, negative symptoms dimension and diagnosis), cognitive and sociodemografic characteristics.

Conclusions: There are differences between presence and absence of MetS in patients with a first psychotic episode at 10-year follow-up. Significant assotiations were found in metabolic, physical, cognitive, and clinical variables. Preventive and therapeutic programs for physical comorbidity should be established.

Key words: First episode psychosis; metabolic syndrome; exercise; physical activity; therapeutic exercise.

1. Introduction

Schizophrenia is a chronic mental health condition that most often presents in early adulthood and can lead to disabling outcomes. The most recent version of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5), defines schizophrenia as: the presence of two or more of the five core symptoms (delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms), with at least one of the symptoms being delusions, hallucinations, or disorganized speech, and the presence of symptoms for at least 6 months (1).Schizophrenia is a condition characterised by episodes of psychosis, hallmarked by an alteration of perception, thoughts, mood or behaviour (2). Schizophrenia is a lifelong, chronic and severely debilitating mental illness that often strikes in young adulthood (3). Although studying the first stages of psychosis is very important (4)analyzing the evolution of these patients at long-term follow-up allows us to better understand the associated comorbidity.

Schizophrenia is often referred to as one of the most severe mental disorders, primarily because of the very high mortality rates of those with the disorder. Persons with schizophrenia have an exceptionally short life expectancy. High mortality is found in all age groups, resulting in a life expectancy of approximately 20 years below that of the general population(5). Part of this excess of mortality comes from a constellation of metabolic risk factors called the metabolic syndrome (MetS), already described to be increased in treated patients, and correlated with clinical psychopathology (6). According to a recent long-term observational study on a sample of N = 335 schizophrenia patients, Healy and colleagues found that after 10 years, 8 of 33 deaths resulted from cardiovascular disorders (7).

MetS was defined by the Adult Treatment Panel III (ATP-III) report as at least three of the following: waist circumference > 102 cm (> 88 cm for females); high-density lipoprotein cholesterol < 40 mg/dL (< 50 mg/dL for females); triglycerides ≥ 150 mg/dL; blood pressure ≥

130/≥ 85 mm Hg; and fasting blood glucose ≥ 110 mg/dL. MetS is a strong predictor of coronary heart disease and diabetes mellitus(8). Those medical comorbidities seem to underlie the increased mortality in those patients detected even at the onset of a mental disorder(9).

The Table 1 shows an overview of 5 examined studies. These studies have identified various metabolic abnormalities in patients with first-episode psychosis (FEP). Part of this increased risk might also be related to the metabolic side effects of antipsychotics, which have been associated with substantial weight gain, which is a major risk factor for Type 2 Diabetes Mellitus (T2DM) and Cardiovascular Diseases(10). Olanzapine has the maximum prevalence of MetS,with 20-25% in FEP,followed by risperidone with 9-24% and haloperidol with 0-3%(11). Antipsychotic medications are a cornerstone of medical care to reduce the positive symptoms of schizophrenia and to improve psychosocial functioning (12). Unfortunately, antipsychotic medication and particularly second-generation antipsychotics (SGAs) have been shown to cause significant weight gain and metabolic abnormalities.

Several studies have reported higher prevalence rates of MetS in schizophrenia patients treated with antipsychotics, with figures ranging from 32 to 68%(13).Those disparate results depend on the sample and the methods used. The prevalence of MetS in FEP was 18%; 24,6% in recent-onset patients (<10years); 39,6% in subchronic patients (10 to 20 years) and 44,3% in chronic patients (<20 years)(14).Whereas in untreated patients, MetS rates of between 3.3% and 26% have been found (13).

This clinical situation promoted the implementation of physical health monitoring in patients with FEP, as suggested by international societies and systematic evaluations(15) and the need to establish program to increase physical activity participation among young people with FEP.

FEP is a critical period for attenuating weight gain and metabolic dysfunction, which begins within weeks of starting antipsychotic medication. There is a fivefold increase in

metabolic syndrome within the first few years of treatment, which heightens the risk of cardiovascular diseases and contributes towards the premature mortality(16). On this point it is important to stress the difference between physical activity, physical exercise and therapeutic exercise.

The human body can be found in two states: stationary or in physical activity. Working, walking, playing an instrument, dancing or cleaning are physical activities. When the physical activity is already planned, structured, repeated and directed with the purpose of maintaining or improving an individual´s fitness, it is then called physical excercise. The objective of physical exercise is aimed to increase strength, elasticity or speed.

On the other hand, Taylor et al., 2007 (17) defined therapeutic exercise as the prescription of a physical exercise program that involves the client undertaking voluntary muscle contraction and/or body movement with the aim of relieving symptoms, improving function or improving, retaining or slowing deterioration of health.

In order to understand these concepts, it is necessary to establish the type of physical intervention in a patient with FEP.

Psychotic disorders are associated with impairments in emotional, cognitive, social and physical functioning and potentially lead to long-term disability (6).

2. Objectives

The aim of the present study is to explore whether or not there are differences between presence and absence of MetS in patients with a first psychotic episode at 10-year follow-up. A secondary aim is to analyze the physical health needs in people after a first psychotic episode.

We hypothesized that patients with MetS would be associated with more severe cognitive impairment, social and physical status, which would justify the implementation of physical health programs.

Table 1. Syndrome metabolic and FEP

Studies	N	Design	Outcomes	Conclusion
Rizo et al. (2017)	182	Cases and controls	The MetS prevalence in naıve patients with a first episode of non-affective psychosis is not higher than the regular population either by direct comparison like our study or described by epidemiological studies in the applied general population	New strategies must be implemented in patients at the onset of the disease.
Kesebir et al. (2017)	150	Predictive study	Previous depressive episode, seasonality, negative family history and childhood trauma are determined as the predictors of MetS	This may contribute to protective and individual-spesific treatment options.
Medeiros-Ferreira et al (2016)	60	Cross-sectional study	Patients with MetS rated a higher number of needs (physical health, psychotic symtoms,Money…) compared to the group without this condition.	An analysis of both physical and mental needs could provide improving quality of life
Sahoo Saddichha et al. (2007)	99	Prospective study	The prevalence of MetS in our sample of patients with schizophrenia is at least five times as high when compared to the matched healthy control group	Early monitoring of patients can possibly play an important role in prevention of the MetS.
De Hert et al. (2006)	415	Prospective study	The prevalence of the metabolic syndrome was 18% in FEP, 24,6% in recent-onset patients (<10yr), 39,6% in subchronic patients (10 to 20 yr) and 44,3 in chronic patients (<20 yr)	The data underscore the need for screening for metabolic abnormalities in patients with FEP.

3. Material and methods

This was an observational longitudinal study. A longitudinal study is one that is non-interventional with an unrestricted population, where the basis is the clinical practice and the focus is on the need for changes in practice.

3.1. Design

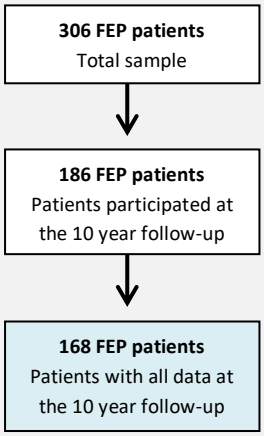
Data for the present research were obtained from a large epidemiological cohort of patients who have been treated in a longitudinal intervention program of FEP called PAFIP (Programa de Atención a Fases Iniciales de Psicosis) conducted at the University Hospital Marqués de Valdecilla in Cantabria, Spain. Prior to international standards for research ethics, the program´s written explanation given to patients , the informed consent form and the program procedure itself were reviewed and approved by the regional institutional review boards.

If any patient refused to give the consent or they requested withdrawal from the program, they were able to be immediately withdrawn from the program. A more detailed description of the programme has been previously reported(18).

3.2. Sample

The original sample included 306 individuals recruited from the PAFIP, from 2001 to 2008, with a FEP. The number of patients enrolled at 10 year follow-up was 186, out of which complete data was available for 168 (52 with MetS and 116 without MetS) which have been reported here.

Figure 1. Patient´sflowchart



All subjects met the inclusion criteria for PAFIF: (a) being on the range of age between 15-60; (b) living in the catchment area; (c) having experienced the first episode of psychosis; (d) not having been on treatment with antidepressant or having been treated but in a period of less than 6 weeks; (e) meeting DSM-IV criteria for brief psychotic disorder, schizophrenia, schizophreniform disorder, not otherwise specified psychosis or schizoaffective disorder. The exclusion criteria for the present study were as follows: have a history of (a) neurological disease; (b) head injury; (c) mental retardation (using DSM-IV criteria); (d) drug dependence (using DSM-IV criteria). Even, those patients who at six months evaluation (from the baseline visit) were diagnosed with the following diagnoses (using DSM-IV criteria), were excluded from the programm: schizoaffective disorder, mental retardation or substance dependence (with the exception of nicotine dependence). Patients who accepted to participate and met these criteria, and whose families provided written informed consent to be included in the program, are the ones on which this study is based.

3.3. Relevant variables to the analysis

3.3.1. Metabolic syndrome

Metabolic syndrome was diagnosed with the definitions of the modified ATP III for Korea (three or more of the following five criteria): abdominal obesity, defined as a waist circumference ≥90 cm in men and ≥85 cm in women serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides; serum HDL cholesterol<40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL cholesterol; blood pressure ≥130/85 mm Hg or drug treatment for elevated blood pressure; and FPG ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

Figure 2 Diagnostic criteria for metabolic syndrome according to the modified "National Cholesterol Education Program Adult Panel (NEC ATP IIIA)

NEC ATP IIIA (AHA, 2004) 3 or more of the following criteria
1. Fasting glucoce ≥100mg/dl (including diabetes mellitus) 2. Abdominal obesity: • Men >102 cm • Women >88 cm 3. Low HDL • Men <40 mg/dl • Women <50 mg/dl 4. Blood pressure ≥130/85 mmHg 5. Triglycerides ≥150 mg/dl

3.3.2. Sociodemographic and environmental variables

Patients were screened for the following sociodemographic characteristics: gender, age, ethnicity ("Caucasian" vs. "others") and years of education. The environmental factors were socioeconomic status ("low qualification worker" vs. "other"), living area ("urban" vs. "rural", defined urban as at least 10,000 inhabitants) and substance use (amount of alcohol, cigarettes and cannabis consumed).

3.3.3. Clinical variables

Clinical assessment was carried out by the same trained psychiatrist B.C.F., and clinical psychologists. A structured interview from DSM-IV (SCID) was conducted at the 6th month since the baseline visit, to confirm the diagnoses. Current positive and negative symptoms were assessed using means from the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). The SAPS and SANS scales were administered to generate dimensions of positive symptoms (hallucinations and delusions), disorganized symptoms (formal thought disorder, bizarre behavior and inappropriate affect) and negative symptoms (scores for alogia, affective flattening, apathy and anhedonia).

The duration of untreated psychosis (DUP) was defined as the time from the onset of the first psychotic symptom (corresponding to a score of 4 or higher on one of the SAPS items) to the initiation of treatment with appropriate antipsychotic. The duration of untreated illness (DUI), however, was considered as the time from the onset of the first unspecific symptoms related to psychosis to initiation of appropiate antipsychotic treatment. The age of onset of psychosis was defined as the age when the first psychotic symptoms (hallucinations, delusions, bizarre behavior, formal thought disorder, or inappropriate affect) which remained present most of the time, appeared.

Secundary effects were assessed with the Side Effect Rating Scale (UKU) with subscores of psychic, neurological and autonomic side effects.

Level of functioning was assessed with the Global Assessment of Functioning (GAF). It is used clinically to rate how a person's symptoms affect his or her day-to-day life on a scale of 0 to 100. GAF is known worldwide and it is Axis V of the internationally accepted Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR).

To determine the presence of functional disability, we used the Spanish version of Disability Assessment Schedule (DAS). The DAS assesses several areas of psychosocial functioning including general behavior and social performance, it specifically considers: Cognition: understanding and communicating; Mobility: moving and getting around; Self-care: hygiene, dressing, eating and staying alone; Getting along: interacting with other people; Life activities: domestic responsibilities, leisure, work and school and Participation: joining in community activities. The global disability item has a score ranging from 0 (no disability) to 5 (gross disability); scores of 1 indicate a minimal disability, scores of 2 and above indicate obvious disability. Scores above 1 were established as the cutoff point to consider presence of Functional Disability. With these criteria, we created a variable of Functional Recovery that implied minimal disability at one and three years follow up.

To collect first-degree family history of psychotic illness, diabetes, hypertension, dyslipemia and overweight, an interview (patient and closer family) was conducted. Informants were asked to provide information about each person in the family tree who had had mental health disorders (disorders with psychotic symptoms such as schizophrenia or bipolar disorders), medication, psychotherapy, hospitalization or suicide (suicidal ideation and behavior, intent of attempt and lethality of attempt).

3.3.4. Physical health factors

All patients were evaluated using a clinical questionnaire called “Physical health 10A” that included the Spanish reduced version of Minnesota Leisured-time Physical Activity Questionnaire (VREM), and information on comorbidity, anthropometric measurements (weight, height, BMI, waist circumference and blood pressure) and lifestyle (diet, physical exercise, substance use).

VREM measured the Metabolic Equivalent of Task (MET), or simply metabolic equivalent. MET is a physiological measure expressing the energy cost of physical activities.

Patients were screened for the following physical health characteristic: dieting during last year (yes vs. no), eating habits during last year (more or equal eating than usual vs. less eating than usual) and physical activity habits during last year (more or equal phsysical activity than usual vs. less physical activity than usal).

3.3.5. Neurocognitive variables

A comprehensive neuropsychological battery was administered to patients by trained psychologists to assess the following eight domains: (1) learning (verbal learning) and memory (delayed memory); (2) Information processing speed; (3) working memory; (4) executive function; (5) motor dexterity; (6) theory of mind; (7) attention; and (8) premorbid IQ.

- *Learning and memory*

The Rey Auditory Verbal Learning Test (RAVLT) and the Rey Complex Figure Testwere administered to assess verbal learning and memory (delayed memory). The RAVLT consists in giving to the participants a list of 15 unrelated words repeated over five different trials. The subjects have to memorize and repeat the words. Then another differentlist of 15 unrelarted words is given, and participants have to repeat the first list, and then again after 30 minutes. In this study RAVLT trial 5 and 7 scores were used to evaluate the verbal memory and delayed memory (after 30 minutes). The Rey Complex Figure Test consists in presenting to the subjects an abstract linear shape and patients are instructed to make a copy, as accurate as possible. Three minutes after completion of the copy, participants will be asked to perform a reproduction of the figure. 20 minutes after the first copy, they will be requested to replay the figure.

- *Information processing speed*

WAIS-III Digit Symbol-Coding subtest (19) and Trail Making Test Part A, was given to participants as a mesure of information processing speed. Digit Symbol-Coding subtest consists in presenting to the participants a table with numbers from 1 to 9. Below each numbers there is a symbol that represents the number. Participants have to place under each number the corresponding symbol as shown in the table and as quickly as possible (time period of 120 sec) (Salthouse 1992; Brébion et al. 1998). The Trail Making Test (TMT) is a task that originally was included in the Army Individual Battery Test and it´s divided into two parts: TMT-Part A and TMT-Part B. TMT-Part A consists of 25 circles distributed over a sheet of paper and participants are asked to draw lines to connect the numbers in decreasing order as fast as possible.

- *Working memory*

WAISS-III Digits subtest was administered to assess the working memory. The test consists in two separate parts of aplication: digits forward and digits backwards. The task consists in presenting to the participants digits sequences and then these are asked to repeat the sequences forward and backwards. In this study digits-backwards scores were used to mesure working memory.

- *Executive function*

The tower of London, the Trail Making Test Part B and the Stroop Test were administered to evaluate the executive function. The Tower of London (ToL), consists in presenting to the participants two tables (examiner and examinee tables) with three diferent coloured balls (red, green, blue) arranged on three pegs. Participants are asked to preplan mentally a sequence of movements, and then to execute the moves one by one in order to make the arrangement of balls identical to the opossing table (examiner table). This task has a maximum limit of 20 movements and a time period of 2 minutes for the completion of each design. The Trail

Making Test (TMT), is a task that originally was included in the Army Individual Battery Test and it´s divided into two parts: TMT-Part A and TMT-Part B. In TMT Part B, the circles include both, numbers and letters. The participants have to draw lines to connect the circles (as in Part A) in ascending order but with the added task of alterning between the number and letters (number- letter). Finally, the Stroop test consists of three pages: a Word Page with color words printed in black ink; a Color Page with 'X's printed in diferent colours (red, blue or green); and a Color-Word Page with words printed in colours (red, blue or green). In the first page, participants have to read down each sheet as quickly as possible. In the second page, the respondents are asked to name the ink colour as quickly as possible too. In the last page, they have to name the colour of the ink, not the word written. The test yields three scores based on the number of items completed on each of the three pages. In the present study Colour Word test scores were used to evaluate the executive function.

- *Motor dexterity*

The Gooved Pegboard Test (Lafayette Instrument Company) was utilized to evaluate the motor dexterity. This test consist of a table with twenty five holes with randomly positioned slots and pegs with a key along one side. The pegs must be rotated to insert them in the holes.The participants are asked to insert the pegs in each hole as quickly as possible. At first the participants have to put the pegs into the boards as fast as possible using only the dominant hand. If their dominant hand is the right hand, they have to fill the top row completely, from left side to right side and vice versa. Then, they will repeat the task using the other hand.

- *Attention*

The computerized version of the Continuous Performance Test (CPT) was provided to participants as a measure of attention. The task is presented to the participants in a computer

screen in which letters appear. The respondents are required to respond by pressing a key on the computer, every time a stimulus previously indicated appears.

- *Theory of mind*

Reading the mind (Eye Task) is a task from the Theory of Mind (20). This test of presenting to the patients a computer screen, which shows 36 black and white photographs of the region of eyes. For each set of eyes, the participants have to choose between four adjetives, choosing the word which best describes what the person in the picture is feeling or thinking.

- *Premorbid IQ*

WAIS-III Vocabulary subtest was applied in order to measure de Premorbid IQ of the subjects. In this test a list of words of increasing difficulty are presented orally and the subjects have to define each word.

3.3.6. Metabolic assessments

- *Laboratory and Anthropometric measurements*

Patients received a full clinical examination and metabolic screening. The metabolic screening consisted of a full-fasting laboratory test. During the clinical examination, blood pressure and anthropometric measurements were obtained by use of standard protocols and techniques. Three blood pressure measurements were obtained with the participant in the seated position after 5 min of rest. Waist circumference was measured at 1 cm above the navel at minimal respiration.

Weight (kg), height (cm), waist circumference (cm) and blood pressure (mmHg) were assessed at baseline and at 10 years. Fasting venous blood samples were collected between 8:00 and 10:00 am after 10 − 12 hours of fasting. Triglycerides, glycemia, high-density lipoproteins cholesterol (HDL-c), low-density lipoproteins colesterol (LDL-c) and Gamma-

Glutamyl Transferase (GGT) were measured. All determinations were performed in our hospital.

3.4. Statistical analyses

Initially participants were separated into 2 independent groups: patients with MetS and patients without MetS. Statistical analyses addressed the following prediction: patients with MetS would be associated with more impaired cognitive, social and physical performance.

The differences between groups in dichotomous and qualitative variables were analyzed using the chi-square test (e.g., gender) and quantitative variables using Student's t-test.Two-tailed tests were used on all findings and a p-value lower than–0.01 was considered very statistically significant (***), between 0.01 and 0.05 was considered statistically significant(**), and from 0.05 to 0.1 was considered trend towards significance(*).

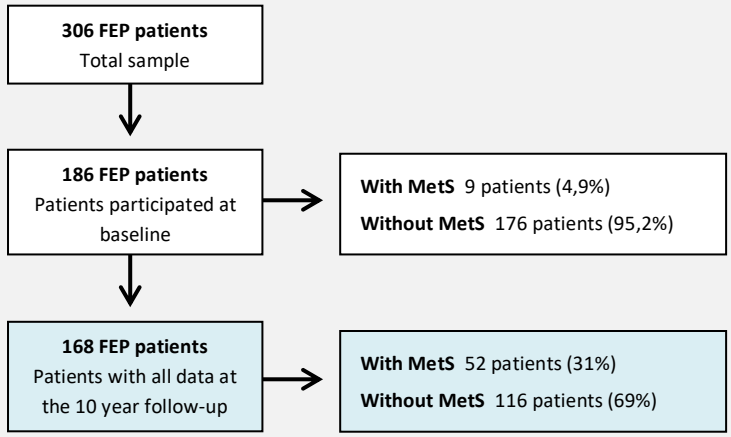
Analyses were run using the Statistic Package for Social Science program (SPSS) version 19.0. The characteristics of the subjects will be described, showing the frequencies and percentages of dichotomous and qualitative variables, and presenting mean±standard deviation (S.D.) of continuous variables, in the whole sample and divided by two groups: cases group (patients with MetS) and control group (patients without MetS). Both groups were compared according to socio-demographic, enviromental, clinical, cognitive, metabolic and physical health characteristic and prevalence metabolic syndrome.

4. Results

4.1. Sample description

The sample comprised 186 individuals. Only 9 (4,9%) out of all participants met the criteria for metabolic syndrome in baseline. After 10 years, 168 participants completed all the data. From this final sample, 52 individuals (31%) met the criteria for metabolic syndrome.

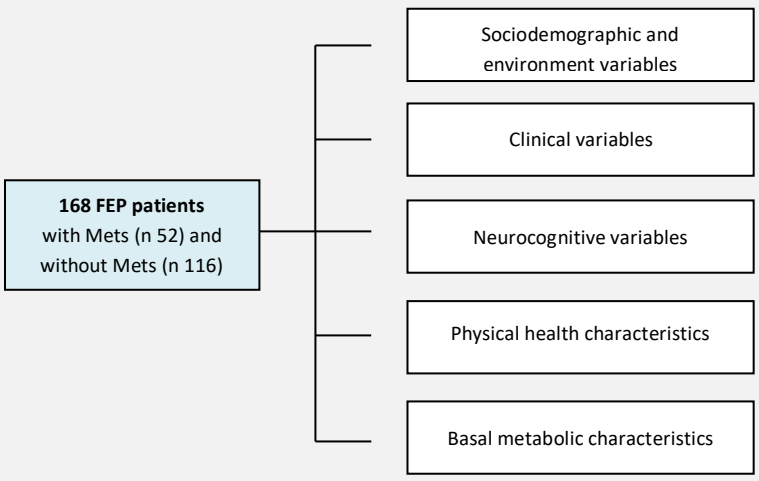
Figure 3. Flow chart.



4.2. Relevant associations between patients with MetS and patients without MetS

The sample of PAFIP 10 has beed divided in two groups: patients with MetS and patients without Mets.The aim of this study is to find associations between these groups.

Figure 4. Flow chart.



4.2.1 Associations in sociodemographic and environmental variables

The sociodemographic and environmental characteristics according to the absence/presence of MetS in participants with FEP are shown in Table 2.

The mean age of the patients was 39.2 years (std 8.6). Among the 168 participants, 91 (54.2%) were males and 77 were females, 165 (98.2%) were causcasian and their mean age at admission was 21.21±8.66 years.

There were significant statistical differences between metabolic syndrome and age at admission (p = 0.016) and years of education (p = 0.018). The older patients that were admitted were, the greater MetS. About education, patients with fewer years of education were more vunerable to MetS. Male gender showed a high tencence (p=0.051). No significant differences were found between patients with MetS and without by race, area, socioeconomic status and substance use (all ps>0.1).

Table 2. Sociodemographic and environmentalcharacteristic divided into patients with MetS and patients without MetS.

	Total (*n* = 168)	**Patients with MetS(*n* = 52)**	**Patients without MetS(*n* = 116)**	**Statistical**	***Pvalue***
Age at admission (years), mean (S.D.)**	29,21 (8.66)	31.69 (9.46)	28.11 (8.46)	*t* = 2.44	0.016**
Education (years), mean (S.D.)**	10,76 (3.44)	9.80 (2.92)	11.18 (3.66)	*t* = -2.383	0.018**
Male gender, n (%)*	91 (54.2)	34 (65.4)	57 (49.1)	X^2 = 3.817	0.051*
Causcasian, n (%)	165 (98.2)	52 (100)	113 (97.4)	X^2 = 1.369	0.242
Low socioeconomic status, n (%)	89 (53.6)	29 (55.8)	60 (52.6)	X^2 = 1.41	0.740
Urban area, n (%)	116 (69)	37 (71.2)	79 (68.1)	X^2 = 0.156	0.722
Smoking, n (%) (yes)	89 (53)	30 (57.70)	59 (50.9)	X^2 = 0.672	0.412
Alcohol, n (%) (yes)	37 (22)	12 (23.1)	25 (21.6)	X^2 = 0.049	0.826
Cannabis, n (%) (yes)	15 (8.9)	3 (5.8)	12 (10.3)	X^2 = 0.924	0.336

Abbreviations: Metabolic Syndrome (MetS).

4.2.2. Associations in physical health characteristics

We found that MetS was associated with physical activity habits during last year (p=0.006) but there were not significant statistical differences in MET and eating habits. The variable of physical activity was dicitomized in "more or equal phsysical activity than usual during last year and less physical activity than usual during last year". Practicing more or equal physical activity than usual during last year was associated with less presence of MetS.

Table 3. Physical health characteristic divided into patients with MetS and patients without MetS.

	Total (*n* = 168)	**Patients with MetS(*n* = 52)**	**Patients without MetS(*n* = 116)**	**Statistical**	***P*value**
MET years (ml O2/kg x min), mean (S.D.)	10,76 (3.44)	83859 (73981)	109374 (7367)	*t* = -0.790	0.430
Physical activity (same or more), n (%)**	134 (82.70)	36 (70.6)	98 (88.3)	X^2 = 7.658	0.006**
Diet, n (%) (yes)	18 (11.10)	6 (11.8)	12 (10.80)	X^2 = 0.032	0.858
Diet habit (to eat less), n (%)	24 (14.80)	8(15.7)	16 (14.40)	X^2 = 0.045	0.832

Abbreviations: Metabolic Syndrome (MetS) and Metabolic Equivalent of Task (MET)

4.2.3. Associations in clinical variables

As shown in Table 4, negative symptoms dimension and neurological effect of the medication (UKU) was significantly lower than the patients without MetS (p=0.036; p=0.015). The greatest difference was observed in Global DAS score, which was very low in patients without MetS (p=0.005). Significant improvements were also observed in GAF Scale. Patients without MetS show a higher score in the assessment of functioning (p = 0.036).

Late age of psychosis onset (p = 0.024), schizophrenia diagnosis (p = 0.015), family history of diabetes (p = 0.037) and family history of hypertension (p = 0.020) were positively associated with the metabolic group.

Table 4. Clinical characteristic divided into patients with MetS and patients without MetS.

	Total (*n* = 168)	Patients with MetS (*n* = 52)	Patients without MetS(*n* = 116)	Statistical	*Pvalue*
Age of psychosis onset, mean (S.D.)**	28,02 (8.23)	30.26 (8.68)	27.10 (8.11)	*t* = 2.279	0.024**
DUI (months), mean (S.D.)	26.43 (37.42)	32.84 (46.72)	23.47 (32.89)	*t* = 1.465	0.145
DUP (months), mean (S.D.)	13,34 (30.81)	17.16 (41.85)	10.57 (2.17)	*t* = 1.301	0.195
Total SAPS, mean (S.D.)	1.55 (3.03)	1.40 (2.44)	1.62 (3.27)	*t* = -0.315	0.667
Total SANS, mean (S.D.)	4.66 (5.22)	5.66 (5.12)	4.21 (5.23)	*t* = 1.656	0.100
Global DAS, mean (S.D.)**	0.98 (1.13)	1.35 (1.22)	0.80 (1.05)	*t* = 2.827	0.005**
GAF, mean (S.D.)**	83.37 (16.59)	79.29 (18.73)	85.33 (15.17)	*t* = -2.121	0.036**
Positive dimension, mean (S.D.)	1.03 (2.01)	1.03 (1.74)	1.02 (2.14)	*t* = 0.036	0.971
Disorganisation dimension, mean (S.D.)	0.51 (1.37)	0.36 (0.97)	0.58 (1.52)	*t* = -1.132	0.260
Negative dimension, mean (S.D.)**	4.19 (4.67)	5.33 (4.74)	3.68 (4.56)	*t* = 2.117	0.036**
UKU psychic effects, mean (S.D.)	1.33 (2.23)	1.53 (2.27)	1.23 (2.22)	*t*= 0.788	0.432
UKU neurological effects, mean (S.D.)**	0.26 (0.69)	0.45 (0.94)	0.16 (0.52)	*t* = 2.462	0.015**
UKU autonomic effects, mean (S.D.)	0.49 (1.36)	0.45 (0.96)	0.50 (1.52)	*t* = -0.230	0.818
Schizophrenia diagnosis, n (%)**	121 (73.3)	43 (86)	78 (67.8)	X^2 = 5.886	0.015**
Family history of psychosis, n (%)	40 (24)	13 (25)	27 (23.5)	X^2 = 0.046	0.831
Family history of diabetes, n (%)**	19 (63.3)	6 (100)	13 (54.2)	X^2 = 4.342	0.037*
Family history of hypertension, n (%)**	15 (46.9)	6 (85.7)	9 (36)	X^2 = 5.428	0.020**
Family history of dyslipedemia, n (%)	12 (40)	1 (16.7)	11 (45.8)	X^2 = 1.701	0.192
Family history of overweight, n (%)	14 (45.2)	4 (66.7)	10 (40)	X^2 = 1.389	0.239

Abbreviations: Metabolic Syndrome (MetS), Duration of untreated psychosis (DUP), Scale for the Assessment of Positive Symptoms (SAPS), Assessment of Negative Symptoms (SANS), Disability Assessment Schedule (DAS), Global Assessment of Functioning (GAF) and Side Effect Rating Scale (UKU).

4.2.4. Associations in cognitive variables

To avoid unnecesary multiple testing, all cognitive data are presented as domains consisting of several individual subtests. Table 5.1 shows metabolic syndrome dichotomized into “patients with MetS” and “patients without Mets “. In MetS patients sample, significantly negative performances have been found on the following domains: Premorbid IQ (WAIS-III vocabulary score, p=0.030), Verbal memory (RAVLT Trial 5, p=0.001), executive function (Stroop color word, p=0.011), Delayed memory (RAVLT Tial 7, p=0.000; Rey figure delayed, p=0.032), Motor dexterity (Gooved pegboard, p=0.012), Theory of mind (Eje task total correct, p=0.002) and Attention (CPT total correct score, p=0.031). It was also observed that patients who experienced MetS had not significantly poorer functioning on Information processing speed and Working Memory (both p > 0.1) domains.

The metabolic group was associated with worse verbal memory (RAVLT trial 5), less vocabulary (WAIS-III vocabulary store), worse delayed memory (RAVLT Trial 7 and Rey figure delayed), slower motor dexterity (Gooved pegboard dom.), worse attention (CPT total correct) and more difficulties to describe what the person is feeling or thinking (Eye task total correct).

Table 5.1 Cognitive characteristic divided into patients with MetS and patients without MetS.

	Total (*n* = 168)	**Patients with MetS (*n* = 52)**	**Patients without MetS (*n* = 116)**	**Statistical**	***Pvalue***
Premorbid IQ					
WAIS-III vocabulary score, mean (S.D.)**	40.52 (8.37)	38.30 (8.23)	41.55 (8.28)	*t* = -0.727	0.030**
Verbal learning/memory					
RAVLT trial 5, mean (S.D.)***	8.36 (3.24)	9.50 (2.32)	11.07 (2.53)	*t* = -3.532	0.001***
Information processing speed					
WAIS-III digit symbol, mean (S.D.)	9.46 (2.83)	9.24 (2.75)	9.56 (2.87)	*t* = -0.625	0.533
TMT-A (sec), mean (S.D.)	47.43 (20.96)	46.54 (24.45)	47.84 (19.25)	*t* = -0.345	0.731
Executive function					
TMT-B (sec), mean (S.D.)	95.53 (44.28)	102.90 (52.38)	92.34 (40.15)	*t* = 1.295	0.198
Stroop color-word, mean (S.D.)**	36.58 (9.49)	33.67 (10.02)	37.94 (8.96)	*t* = -2.562	0.011**
Working memory					
WAIS-III digits backward, mean (S.D.)	5.48 (1.87)	5.14 (1.78)	5.64 (1.89)	*t* = -1.515	0.130
Delayed memory					
RAVLT Trial 7, mean (S.D.)***	8.36 (3.24)	6.93 (3.07)	9.02 (3.11)	*t* = -3.769	0.000***
Rey figure delayed, mean (S.D.)**	2.05 (1.27)	16.06 (5.52)	12.27 (5.70)	*t* = -2.172	0.032**
Motor dexterity					
Gooved pegboard dom. (sec), mean (S.D.)**	74.08 (27.05)	82.30 (32.14)	70.26 (23.54)	*t* = 2.542	0.012**
Attention					
CPT total correct score, mean (S.D.)**	70.96 (12.15)	66.44 (17.79)	72.99 (11.73)	*t* = -2.571	0.031**
Theory of mind					
Eye task total correct, mean (S.D.)**	32 (21.30)	19.48 (5.41)	22.14 (4.41)	*t* = -3.139	0.002**

Abbreviations: Metabolic Syndrome (MetS)

Also basal cognitive characteristics was analized. There were not differences into patients with MetS and patients without MetS, except in the verbal learning/memory (p=0.029). These results could explain the cognitive impairment in patient with FEP during disease progression.

Table 5.2 Basal cognitive characteristic divided into patients with MetS and patients without MetS.

	Total (*n* = 168)	**Patients with MetS (*n* = 52)**	**Patients without MetS (*n* = 116)**	**Statistical**	***Pvalue***
Premorbid IQ					
WAIS-III vocabulary score, mean (S.D.)	38.65 (10.04)	37.63 (11.06)	39.06 (9.86)	*t* = -0.713	0.479
Verbal learning/memory					
RAVL trial 5, mean (S.D.)**	10.48 (2.61)	9.70 (2.53)	10.74 (2.59)	*t* = -2.214	0.029**
Information processing speed					
WAIS-III digit symbol, mean (S.D.)	6.55 (3.00)	6.44 (2.64)	6.44 (3.09)	*t* = 0.000	1.000
TMT-A (sec), mean (S.D.)	44.33 (19.23)	43.14 (18.34)	45.16 (20.03)	*t* = -0.566	0.572
Executive function					
TMT-B (sec), mean (S.D.)	101.88 (49.8)	108.31 (59.70)	96.56 (41.00)	*t* = 1.163	0.250
Stroop color-word, mean (S.D.)	33.88 (10.18)	34.85 (9.78)	33.71 (10.68)	*t* = 0.402	0.689
Working memory					
WAIS-III digits backward, mean (S.D.)	5.46 (1.95)	5.29 (1.75)	5.59 (2.02)	*t* = -0.852	0.396
Delayed memory					
RAVL Trial 7, mean (S.D.)	7.53 (3.16)	6.72 (3.15)	7.82 (3.15)	*t* = -1.912	0.058
Rey figure delayed, mean (S.D.)	18.20 (7.11)	17.04 (6.71)	18.81 (6.92)	*t* = -1.397	0.165
Motor dexterity					
Gooved pegboard dom. (sec), mean (S.D.)	73.47 (28.03)	78.63 (45.58)	71.97 (17.17)	*t* = 1.235	0.219
Theory of mind					
Eye task total correct, mean (S.D.)	20.06 (4.53)	19.60 (4.14)	20.33 (4.62)	*t* = -0.596	0.553
Attention					
CPT total correct score, mean (S.D.)	68.39 (15.19)	68.05 (15.58)	68.47 (15.59)	*t* = -0.137	0.891

Abbreviations: Metabolic Syndrome (MetS)

4.2.5. Basal metabolic characteristics

As it can be seen in Table 6, the incidence of MetS after 10 years was greatest positively and significantly associated with high weight (p = 0.000), increase TAS levels (p = 0.044), rise triglycerides levels (p = 0.003) and high GGT levels (p = 0.002) at baseline. Additionally, waist circumference showed a tendence (p = 0.081). No statistical differences were found between patients with MetS and without MetS regarding any cholesterol and glycemia levels.

Table 6. Basal metabolic characteristic divided into patients with MetS and patients without MetS.

	Total (*n* = 168)	**Patients with MetS (*n* = 52)**	**Patients without MetS (*n* = 116)**	**Statistical**	***Pvalue***
Weight (kg), mean (S.D.)***	67,44 (13.46)	73.96 (12.90)	64.54 (13.04)	*t* = 4.307	0.000***
Waist circumference (cm), mean (S.D.)*	83.86 (11.88)	87.83 (10.15)	82.08 (12.21)	*t* = 1.758	0.084*
TAS (mmHG), mean (S.D.)**	117.76 (15.31)	122.73 (15.76)	116.33 (14.86)	*t* = 2.040	0.044**
TAD (mmHG), mean (S.D.)	67.04 (9.92)	66.67 (8.63)	67.72 (10.58)	*t* = -0.506	0.614
Triglycerides (mg dL), mean (S.D.)**	84.36 (40.51)	100.33 (48.73)	75.34 (35.20)	*t* = 3.110	0.003**
HDL - C (mg dL), mean (S.D.)	49.89 (13.17)	47.41 (14.15)	51.58 (12.67)	*t* = -1.767	0.079
LDL - C (mg dL), mean (S.D.)	109.26 (33.38)	113.20 (29.23)	108.22 (31.51)	*t* = 0.903	0.368
GGT (UI/L), mean (S.D.)**	18.77 (18.26)	22.81 (15.79)	11.88 (6.73)	*t* = 3.337	0.002**
Glycemia (mg dL), mean (S.D.)	88.37 (22.08)	92.33 (38.62)	87.37 (9.89)	*t* = 0.904	0.370

Abbreviations: Metabolic Syndrome (MetS), Systolic Blood Pressure (TAS); Diastolic Blood Pressure (TAD); HDL-C,high-densitylipoproteincholesterol; LDL-C,low-densitylipoproteincholesterol; gamma-glutamyl transferase (GGT).

5. Discussion

MetS is an important topic for research and clinical practice in the field of FEP(21). Our findings are consistent with studies in long-term schizophrenia, showing that in patients with FEP the risk of MetS increases. Furthermore, the MetS in these patients is associated with sociodemographic variables(22), neurocognitives disturbances (23) and clinical characteristics (10, 24).The most urgent research agenda concerns primary candidates for modifiable factors contributing to increased risk of mortality, i.e., side effects of treatment and lifestyle factors, as well as sufficient prevention and treatment of physical comorbidity(5).

5.1. Physiotherapy in mental health

Physiotherapy in Mental Health is defined as the specialty of physiotherapy responsible for recognizing and treating physical problems in people with mental disorders. This is achieved through specific techniques, aimed to prevent such problems and promote the physical health of these patients.

The implementatios of physiotherapy in mental health care and psychiatry has a long and strong tradition of more than 50 years in education and clinical practice, and in several countries it receives government support. Unfortunately, this is not the case in all countries. The use of physiotherapy in mental health care and psychiatry is not common and is often overlooked.

Physiotherapy in mental health aims to optimize wellbeing and empower the individual by promoting functional movement, movement awareness, physical activity and exercises, bringing together physical and mental aspects. Physiotherapists in mental health contribute to the multidisciplanary team and interprefessional care. Physiotherapy in mental health is based on the available scientific and best clinical evidence(25).

To preserve or acquire a profesional patform in the long term and to present a distinct profile of physiotherapy in mental health to policymakers, mental health physiotherapists must prove that what they do is well founded and provides significant additional value to the person who request aid. Therefore research in this field is important.

Physiotherapists have an integral role in the multidisciplinary care of people with schizophrenia. It is important that all physiotherapits are trained in recognizing and adequately addressing symptoms of FEP, physical comorbidities and side-effects of antipsychotic medication(26).

5.2. Physical cormobidity in FEP

Patients with FEP present somatic disorders that curiously appear with greater frequency than in people without FEP. These disorders do not appear as a cause or as a consequence of FEP, but simply as comorbidity. These physical disorders coexist in the pathology of patients with FEP. Examples of this process are the presence of MetS (as this thesis supports), diabetes (27), low back pain, arthritis, proprioceptive dysfunctions...

People with FEP should receive optimal medical care and healthcare provision to adress these physical comorbidities (28). Between 66% (unmedicated patients) and 80% (long-term ill and medicated patients) of all patients with schizophrenia spectrum disorders have at least one kind of motor disturbance. In a study by Docx et al. (2012), 35% of 124 patients had catatonia, 43% had problems with coordination, 51% had difficulties with complex motor sequences, 18% had motor speed dificulties and 24% han parkinsonism. Among all the patients, 91% had more tan one motor disturbance, 57% had more tha two kinds of disturbance, 25% more tan three kinds and 7% hada ll kinds of motor disturbances (29).

A metaanalysis established thah around a third of patients experience clinical pain, and physiotherapists hace a key role in addressing this important and often undetected

phenomenom (30). Recently, a large study involving over 93.000 people with schizophrenia found thah 35% and 21% are affected by arthitic pain and chronic low-back pain, respectively (31). A recent systematic review establised thah half of patients with schizophrenia have a reduced bone mass and are thus susceptible to fractures (32).

The primary cause of this premature mortality is the increased prevalence of physical comorbities (33). Of particular concern are metabolic and cardiovascular diseases (CVD), and patients with schizophrenia are also four times more likely to be overweight, have a twofold increased risk for diabetes and show a two to three time higher prevalence of dyslipidemia compared with the general population. Our results also show the increase of MetS since baseline to 10 years follow-up.

5.3. Evidence for therapeutic exercise in patients with FEP

International guidelines state that physical activity should be one of the cornerstones in the multidisciplinary treatment. It has been reported that physical exercise might improve glycemic control, lowers blood pressure, improves lipid profile and decreases abdominal fat mass. Unfortunately, only 25% of patients with schizophrenia meet the minimum health recommendations of 150 min of at least moderate intensity physical activity per week and long-term adherence to supervised physical activity programmes is generally poor (34). Further, Whalther S. et al., 2015 (35)showed that reduced motor activity is a marker of deterioration in the course of schizophrenia spectrum disorders. Lee et al., 2015 (36) divided their sample in physically inactive patients and physically active patients. They showed that inactive patients had more positive and negative symptoms and SANS total. Early intervention for psychosis should target to improve patients' physical activity level which may help subsequent functioning.

A recent review (37), support that exercise represents a promising new treatment option that may supplement current psychosocial and pharmacological interventions for psychosis. A

large body of work suggests that exercise can improve cardio-metabolic and health behavior and facilitate neurogenesis in areas of the brain that are notably impacted by psychosis. Recent efforts to incorporate exercise as either stand-alone or adjunctive treatment for individuals with schizophrenia. These exercises range from yoga and light stretching to moderately intense walking, bike riding, or team sports. These interventions suggest that moderately intense exercise may be beneficial for improving both positive and negative symptomatology, cognition, and functioning. Indeed, exercise may be beneficial for decreasing risk factors for a wide range of health problems often observed in patients with FEP, including weight gain and metabolic syndrome as well as tobacco and substance use. Given the positive results from interventions in schizophrenia patients, there is an impetus for incorporating exercise in the early stages of the disorder.

In order to understand the concept, specific interventions related to therapeutic exercise include:

- Aerobic training
- Muscle strength training
- Flexibility exercise
- Balance and coordination training
- Relaxation techniques

The first-episode of psychosis (FEP) may be the optimal time for implementing exercise for several reasons. First, this is a 'critical period' for attenuating the metabolic side-effects of antipsychotic treatment as prevention of cardiometabolic abnormalities may be more feasible than reversing them. Second, persons with FEP are younger and more active than those with long-term schizophrenia and thus potentially more readily engaged in moderate-to-vigorous exercise. Third, providing effective treatment for negative and cognitive symptoms from the early stages of psychosis reduces the likelihood of enduring disability(16). Interventions aiming to increase exercise, regardless of intensity are indicated for people with FEP, while specifically

increasing moderate-vigorous physical activity should be a priority given the established health benefits.

5.3.1. High intensity physical exercise as a physiotherapeutic method in the treatment of FEP

- *Aerobic and strenght training in the treatment of FEP*

The evidence of therapeutic exercise in FEP is presented in Table 7. It has been demonstrated that aerobic and strenght training reduces positive and negative symptoms, and improves cardio-metabolic functioning. Firth et al., 2016 (16)gives gym training sessions twice per week to the participants. This was the first study to examine the effects of exercise on psychiatric symptoms in early psychosis. Sessions aimed to achieve 45–60min of moderate-to-vigorous activity using aerobic and resistance exercises. The specific activities for any given session were selected on the basis of participant preference, in order to maximize adherence and engagement with exercise. Options for aerobic exercise to improve cardiovascular health included treadmills, cycle ergometers and rowing machines. Resistance training included exercises for all the major muscle groups of the arms, legs and torso to increase muscle tone and strength. For resistance exercises, participants completed three sets of 8–12 repetitions per exercise. Additionally or alternatively to the gym training sessions, participants were able to undertake other sporting activities to meet their weekly exercise targets (swimming, cyling…). They were supervised by a research assistant who had several years of exercise experience. The greatest differences were observed in negative symptoms, which reduced by 33% in the intervention group (P=0.013). Significant improvements were also observed in psychosocial functioning and verbal short-term memory. Increases in cardiovascular fitness and processing speed were positively associated with the amounts of exercise achieved by participants.

McEwen and colleagues (38) demonstrated that low compared with high physical activity levels were associated with signifi- cantly smaller volumes of total, prefrontal cortical, and hippocampal gray matter as well as of cortical thickness in the dorsolateral and orbitofrontal prefrontal cortex in 14 patients with FEP.

Nuechterlein et al., 2016 (39)shown the improve cognitive deficits in FEP. In this pilot study, 7 patients with a recent onset of schizophrenia were assigned to CognitiveTraining & Exercise (CT&E) and 9 to CT alone for a 10-week period. Both groups participated in these training sessions 2d/wk, 2h/d. The CT&E group also participated in an aerobic conditioning program for 30 minutes at our clinic 2d/wk and at home 2d/wk. Functional outcome, particularly independent living skills, also tended to improve more in the CT&E than in the CT group. Muscular endurance, cardiovascular fitness, and diastolic blood pressure also showed relative improvement in the CT&E compared to the CT group.

- *Aerobic interval training (AIT) program*

Abdel-Baki et al., 2013 (40) implemented a 14-week aerobic interval training (AIT) program within a first-episode psychosis (FEP) service and its efficacy in improving metabolic outcomes and cardiorespiratory fitness. Twenty-five male subjects participated in 30-minute sessions of AIT twice a week. There was a significant decrease in waist circumference (WC), resting heart rate and a 38% increase in VO2max. The decrease in WC was more pronounced for subjects who completed at least 64% of the planned sessions. As conclusión, they support that an AIT program could be implemented in FEP patients and improve WC and cardiorespiratory fitness over a relatively short period.

5.3.2. Low intensity physical exercise in the treatment of FEP

- *Yoga as a physiotherapeutic methoh in the treatment of FEP*

Lin et al., (2015) (41) recruit 140 female patients and 124 received the allocated intervention in a randomized controlled study of 12 weeks of yoga or aerobic exercise compared

with a waitlist group. Both programs lasted 60 min for each session, and were held three times a week. The primary outcomes were cognitive functions including memory and attention. Secondary outcome measures were the severity of psychotic and depressive symptoms, and hippocampal volume. Both yoga and aerobic exercise groups demonstrated significant improvements in working memory with moderate to large effect sizes compared with the waitlist control group. The yoga group showed additional benefits in verbal acquisition and attention. Both types of exercise improved overall and depressive symptoms after 12 weeks. Small increases in hippocampal volume were observed in the aerobic exercise group compared with waitlist. They support the application of yoga and aerobic exercise as adjunctive treatments for early psychosis merits serious consideration.

- *Basic Body Awareness Therapy in the treatment of FEP*

Basic Body Awareness Therapy (BBAT) was originally developed as a physiotherapeutic intervention for people with schizophrenia, and the premature research findings indicated improvements in movement function, body image and anxiety. Recent qualitative resear reported improvements in body balance and postural control, increased seld-esteem, and an improved ability to think in people with schizophrenia folowing physiotherapy base don basic body awareness exercise. However, rigorous research in needed before BBAT can be considered effective in multidisciplinary treatment for people with schizophrenia(42).

5.4. Limitations and future research

As with all long-term follow-up studies, it is possible that selection or information bias might occur as a result of loss to follow-up/missing data. Objective assessment tools are often costly and time-consuming, rendering them difficult to use routinely in mental health-care settings. Our methods for measuring physical activity (more or equal physical activity than previous first episode psycotic or less physical activity), offer self-reported estimates of physical activity and they dont remove many of the issues of recall and response bias. This may cause increased measurement errors.

Future research should include longitudinal studies investigating basal predictors of MetS. More studies are also needed to demonstrate that therapeutic exercise is an effective preventive measure for the development of MetS in FEP.

Table 7. The evidence of therapeutic exercise in FEP

Studies	N	Therapeutic exercise	Metodology	Outcomes
Firth et al. (2016)	38	Gym training: aerobic and resistance exercises.	Sessions 45-60 min twice per week at their gym. Moderate-to-vigorous activity	Positive and Negative Syndrome Scale total scores reduced after 10 weeks of exercise in comparation with the control group (p = 0.010). Significant improvements were also observed in psychosocial functioning , verbal short-term memory, cardiovascular fitness and processing speed.
Nuechterlein et al., 2016	16	Aerobic exercise(E) and cognitive training (CT)	30 minutes at our clinic 2d/wk and at home 2d/wk for a 10-week period	Functional outcome, particularly independent living skills, also tended to improve more in the CT&E than in the CT group. Muscular endurance, cardiovascular fitness, and diastolic blood pressure also showed relative improvement in the CT&E compared to the CT group.
Lin et al. (2015)	140	Aerobic exercise or yoga	Both programs lasted 60 min for each session, and were held three times a week for 12 weeks	Both yoga and aerobic exercise groups demonstrated significant improvements in working memory ($P<0.01$) with moderate to large effect sizes compared with the waitlist control group. The yogagroup showed additional benefits in verbal acquisition ($P<0.01$) and attention ($P=0.01$). Both types of exercise improved overall and depressive symptoms (all $P\leqslant 0.01$) after 12 weeks.
Abdel-Baki et al. (2013)	25	Aerobic interval training (AIT) program	30-minute sessions of AIT twice a week for 14 weeks	There was a significant decrease in waist circumference (WC), resting heart rate and a 38% increase in VO2max.

6. Conclusion

In conclusion, the present study supports previous data suggesting the higher prevalence rates of MetS in patients with FEP. Obtained results suggest that the presence of MetS in patients with a first psychotic episode at 10-year follow-up has a different effect on metabolic, clinic, physical and cognitive functions. Therefore, the results of this study pose many questions and many therapeutic alternatives to improve the quality and expectancy of life of patients with FEP. The results highligth the importance of implementing a therapeutic exercise programme as a significant variable in the treatment and prevention of this disorder. Future work should investigate novel methods for connecting mental health service with therapeutic exercise resources, and for embedding specialists within these services, in order to maximize accessibility and broaden possibilities for delivering such interventions in clinical practice.

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Appendices

- *Cuestionario PAFIF. Salud física: visita a los 10 años*

CUESTIONARIO ANTROPOMÉTRICO

1.1	Talla (en centímetros)	.
1.2	Peso (en kilos)	.
1.3	Perímetro de la cintura abdominal (en centímetros)	.
1.4	Tensión arterial sistólica	☐☐☐
1.5	Tensión arterial diastólica	☐☐☐
1.6	Fecha de extracción sanguínea	/ / (d d m m a a)

CUESTIONARIO DIETA

2.1	Hábito dietético en el último año	1 Come más de lo habitual 2 Come igual que siempre 3 Come menos de lo habitual	☐
2.2	¿Ha seguido algún tipo de dieta en el último año?	1 Sí 2 No	☐
2.3	Actividad física en el último año	1 Más actividad de la habitual 2 Igual que siempre 3 Menos actividad de la habitual	☐
2.4	¿Ha precisado ser remitido a la consulta de endocrino ó dietista para el control del peso en el último año?	1 Sí 2 No	☐

CUESTIONARIO DE SALUD FÍSICA

I. MÉDICO DE CABECERA (A.P.)

4.1 Desde su derivación a Salud Mental, ¿ha seguido habitualmente controles con:

1. Médico de familia
2. Enfermera/o
3. Ambos
4. Sin controles

☐

4.2 Tipo de controles:

		Frecuencias:		
1.	Analítico	c/mes	1-6 meses	año
2.	Tensión arterial	c/mes	1-6 meses	año
3.	Peso	c/mes	1-6 meses	año
4.	Otros	c/mes	1-6 meses	año

4.3 ¿En este momento tiene tratamiento para algún problema físico?

1. Sí
2. No

☐

- Diagnóstico: _____
- Tratamiento: _____

- Diagnóstico: _____
- Tratamiento: _____

II. ATENCION ESPECIALIZADA

5.1 ¿Ha precisado Atención Especializada? 1. Sí 2. No ☐

5.2 En caso afirmativo, indicar a continuación:

1. Especialidad: _____
   - Diagnóstico: _____
   - ¿Tiene tratamiento y seguimiento? SI NO]
   - Fecha de inicio: _____
   - ¿Alta? SI NO]

2. Especialidad: _____
   - Diagnóstico: _____
   - ¿Tiene tratamiento y seguimiento? SI NO]
   - Fecha de inicio: _____
   - ¿Alta? SI NO]

3. Especialidad: _____
   - Diagnóstico: _____
   - ¿Tiene tratamiento y seguimiento? SI NO
   - Fecha de inicio: _____
   - ¿Alta? SI NO

4. Especialidad: _____
   - Diagnóstico: _____
   - ¿Tiene tratamiento y seguimiento? SI NO
   - Fecha de inicio: _____
   - ¿Alta? SI NO

5.3 ¿Ha tenido intervenciones quirúrgicas o traumatismos? 1. Sí 2. No

5.4 En caso afirmativo, indicar a continuación:

- Tipo: _____
- Fecha: _____

- Tipo: _____
- Fecha: _____

- Tipo: _____
- Fecha: _____

VREM – Versión Reducida en Español del cuestionario de actividad física en el tiempo libre de Minnesota

Sexo:_____Edad: _____

¿Qué actividad física ha realizado durante su tiempo libre en el **ÚLTIMO MES O MES HABITUAL**?

1.- **Caminar**. Días/mes _____Minutos/día_____Meses/año _____

2.- **Trabajar en el huerto**. Días/mes_____Minutos/día_____Meses/año _____

3.- **Hacer deporte o bailar**. ¿Qué tipo de deporte o baile?

Tipo de deporte/baile:_____Días/mes _____Minutos/día _____Meses/año

Tipo de deporte/baile:_____Días/mes _____Minutos/día _____Meses/año

Tipo de deporte/baile:_____Días/mes_Minutos/día_Meses/año _____

4.- **Subir escaleras**. Días/mes_____Pisos/día_____

En **LA ÚLTIMA SEMANA O SEMANA HABITUAL**

5.- ¿Cuánto tiempo dedica a **ir a comprar a PIE**? Minutos/semana _____