The European Journal of Psychiatry 38 (2024) 100262

THE EUROPEAN JOURNAL OF PSYCHIATRY

www.elsevier.es/ejpsy

ORIGINAL ARTICLE

Psychopathological and cardiometabolic efficacy of a nutritional education intervention based on symbiotics in schizophrenia spectrum disorders. Two-arm Randomised Clinical Trial

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Received 9 February 2024; accepted 17 April 2024
Available online 16 July 2024

KEYWORDS
Diet therapy;
Mental health;
Nursing;
Schizophrenia spectrum and other psychotic disorders;
Randomized controlled trial

Abstract
Background and objectives: Advances in knowledge have contributed to the global understanding of nutritional patterns' influence on mental health. The aim was to determine the impact of a high-symbiotic diet on cardio-metabolic and psychopathological outcomes in schizophrenia.
Methods: A randomised clinical trial (two-arm, double-blind, balanced-block, six-month intervention) was conducted on 50 individuals diagnosed with schizophrenia spectrum disorder. The control group received conventional dietary advice individually. The intervention group received intensive dietary advice based on the increasing consumption of food with high symbiotic content (fermented foods, whole grains, green leafy vegetables and fruits high in dietary fibre, among others). Researchers collected data on cardiovascular and psychopathological status at baseline, three and six months. In addition, anthropometric parameters were analysed monthly.
Results: Forty-four subjects were analysed. Compared to the control group, the intervention group demonstrated improvements in the PANSS-GP subscale and the PSP scale scores over 3—6 months ($p < 0.05$). Anthropometric values were decreased in all the variables ($p < 0.05$). Systolic blood pressure decreased between 3 and 6 months ($p = 0.049$).
Conclusions: Nutrition education for increasing the consumption of foods with high symbiotic content has positively impacted the cardio-metabolic and psychopathological profile in patients with schizophrenia spectrum disorders. In addition, advanced practice mental health nurses

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https://doi.org/10.1016/j.ejpsy.2024.100262

have been shown to play a prominent role in developing nutrition education and promoting healthy lifestyles in these patients.

Introduction

Schizophrenia is a chronic mental illness characterised by significant clinical heterogeneity, with periods of psychotic exacerbation and stabilization[1]. The semiology of this chronic disease is established in positive and negative symptoms, with variable dysfunction and clinical presentation levels, and having an essential impact on the patient's quality of life.[1,3] Similarly, schizophrenia-spectrum disorder involves significant neurocognitive impairment as an integral part of the semiological sphere, including difficulties in attention, executive function or memory (among others), which impacts and often debilitates social and occupational functioning.[2,3]

Currently, the prevalence of schizophrenia spectrum disorders is 3.3 % in Western countries, with lower figures in rural or developing regions.[4] However, in Spain, this prevalence ranges between 0.7 and 1.5 % of the general population.[5]

The traditional therapeutic approach has perceived the role of nutrition as a minor intervention in psychiatry, especially in psychotic disorders such as schizophrenia.[6,7] However, the advances in the last decade, mainly associated with the development of the holobionte theory and the evolution of metagenomics[8,9] and the increasing dietary patterns of low nutritional quality in different western societies,[9] have contributed to the understanding of the role of nutritional patterns on the functioning of the central nervous system and possible mechanisms or etiological pathways of psychiatric disorders.[7,10]

Evidence shows a high rate of disability, morbidity and mortality in people suffering from psychiatric disorders compared with the general population. This difference is especially significant in those patients with a severe and long-term mental disorder (LTMD).[7,12-15] The morbidity and mortality rate in the psychiatric population is up to 20 % higher and, quantitatively, represents an average of 15 years of life lost.[7,12,13,15] Besides, patients suffering from LTMD have reduced their life expectancy by 20 % compared to the general population.[12,15] Therefore, it is estimated that the relative risk of this disease is 2.4 higher for mortality from any cause,[11,12,16] and it is linked to cardiovascular, infectious, respiratory, and endocrine diseases,[12-15] with suicide being the leading cause of non-natural death.[16]

Furthermore, this population's leading causes of death are closely linked to the development of Metabolic Syndrome (MS). This syndrome consists of several cardio-metabolic risk factors and a predisposition to insulin resistance and hyperglycaemia, weight gain, hypertension, atherogenic dyslipidaemia (hypertriglyceridaemia, reduced HDL-cholesterol and increased LDL-cholesterol) and prothrombotic state.[12-15,17-20] Finally, MS is considered a determining factor in the patient's physical health, tripling the incidence of cardio-metabolic diseases, and represents one of the major public health problems of the 21st century.[15,20]

The main aetiopathogenic determinants of MS in schizophrenic disorders are linked to the inherent characteristics of the disease itself, therapeutic modality (notably the use of atypical antipsychotics), and resistance to optimal care in terms of physical health and lifestyles.[6,12,13] In addition, this resistance is fostered by the difficulty of adequate health accessibility and the poor preventive and health promotion culture in the psychiatric population, among others.[6,7,12,13,15]

The prevalence of MS in schizophrenic disorders is over 30 %,[21] associated with high cardiovascular morbidity and mortality[13]. Despite this, interventions aimed at modifying lifestyles are insufficient; they do not play an essential role in therapy and are not part of routine clinical practice in the psychiatric population.[6,7,11,17] This fact could be explained by the lack of understanding of the multiple mechanisms and etiological factors involved in the neurogenesis of schizophrenia[1], and leads to a multidisciplinary approach, but essentially psychopharmacological and psychotherapeutic.[3,6,15] Therefore, it is vital to address modifiable factors within lifestyles, including dietary patterns (determined by the quality and quantity of food eaten and how it is prepared and consumed), which have[17]. These interventions have been proven efficient in improving both psychopathological dysfunction and physical health and can be considered an addition to the conventional therapeutic approach.[6,11,15]

In this sense, some dietary interventions have been carried out to modulate intestinal microbiota in psychotic disorders through the use of "psychobiotics".[22–24] This term refers to the set of symbiotic substances that include probiotics and/or prebiotics and whose administration causes health benefits in psychiatric patients[22,25]. Probiotics include microorganisms of the intestinal biota, which, provided in adequate quantities, offer a benefit for the host (highlighting the genera Lactobacillus and Bifidobacterium, among others).[11,22,24,26] On the other hand, prebiotics are non-digestible dietary fibre (mainly fructooligosaccharides and oligosaccharides, inulin or pectins),[9] which are substances that promote optimal growth and development of probiotics in the gastrointestinal tract, reducing pathogenic microbiota.[11,27]

According to Balanzá (2017)[11] and Patra (2016),[23] adequate dietary planning in psychiatric patients with psychopathological dysfunction and at risk of iatrogenic metabolic syndrome could be considered a therapy of choice. Furthermore, this approach could improve unhealthy lifestyles, allowing higher patient empowerment during treatment. Similarly, adequate nutritional management could be an adjunct to antipsychotic pharmacotherapy.[23] Likewise, it could provide an optimal approach for preventing the

development of metabolic and cardiovascular diseases,[6] reducing the number of homeostatic drugs or even replacing them in cases of intolerance.[7,8,22]

In short, the future of the development of Mental Health is determined by the need for a multimodal approach, where nutritional factors represent a potentially important complement in achieving optimal health outcomes, level of functioning and thus the quality of life for psychiatric patients. This relevance is related to the fact that they allow the improvement of altered clinical patterns (cardiovascular and metabolic, among others) and the cessation of unhealthy lifestyles.[6,15] Likewise, dietary modulation has the added value of improving the morbidity and mortality associated with schizophrenia,[17,21] with optimal levels in terms of cost-effectiveness, better than those shown by the approaches currently used.[28]

The study's objective was to determine the impact of a high-symbiotic diet on cardio-metabolic and psychopathological outcomes in patients diagnosed with a schizophrenia spectrum disorder.

Materials and methods

Study design

A controlled, double-blind, two-arm, parallel design, balanced-block, randomised, 6-month intervention clinical trial was developed in psychiatric patients diagnosed with schizophrenia spectrum disorders. The study design is shown in Fig. 1.

Participants

The sample was selected from the Zamora Psychiatry Service, in patients with outpatient follow-up, from June 2020 to February 2021. Inclusion criteria were: (1) patients diagnosed on the spectrum of schizophrenia (without distinction by type), according to criteria DSM-5 and/or ICD-11; (2) age between 18 and 65 years; (3) absence of gastrointestinal comorbidity that contraindicates the use of prebiotics and/or probiotics (intolerance, explosive diarrhoea, acute abdominal pain, etc.); (4) to show clinical stability for six months before the beginning of the study (absence of psychiatric hospitalisation, maintenance of the level of functionality, and lack of social and occupational absenteeism); (5) to manifest agreement to participate in the study and to sign of informed consent.

However, participants were excluded if: (1) they did not meet the inclusion criteria; (2) suffered from a somatic or neurocognitive situation that prevents participation and collaboration in the fulfilment of the protocol; (3) difficulty following the proposed interventions due to low involvement and independence in daily meal planning and preparation (catering, institutional or collective feeding, etc.); (4) refused to participate in the study.

Sample size

To determine the minimum sample size necessary to detect a statistically significant effect, a sample size of 22 individuals has been estimated (11 for the control group -CG- and 11 for the intervention group -IG-), with a power of 80 % and a

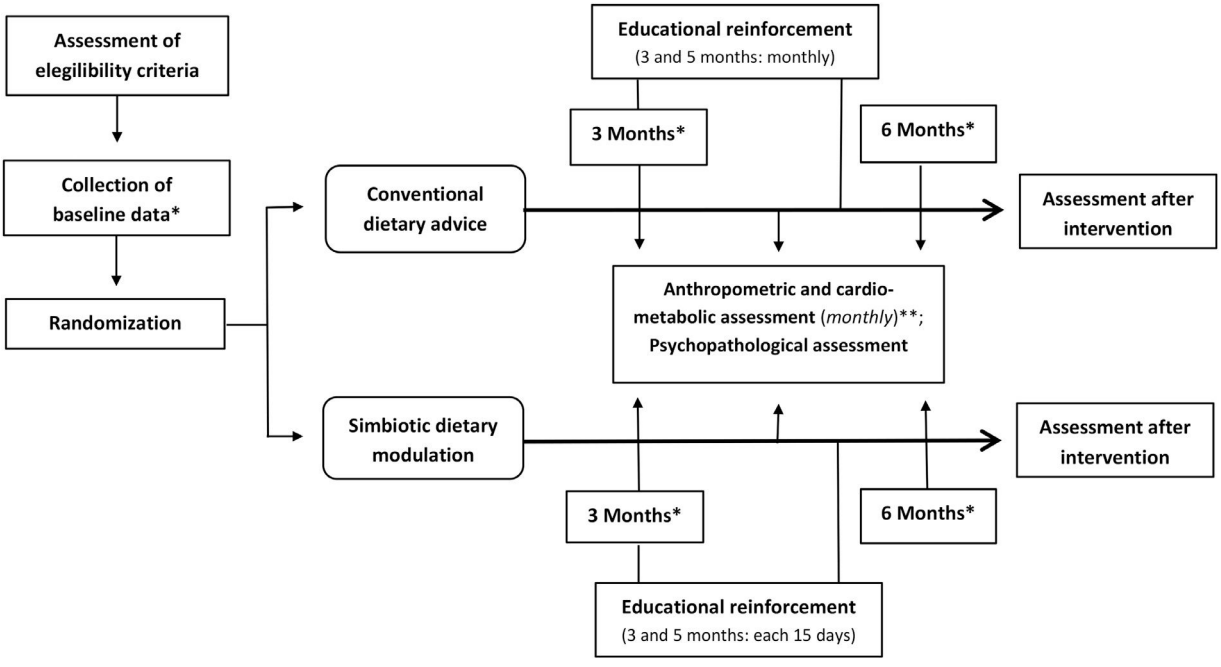

Fig. 1 Study Design. *Data collected at baseline, 3 and 6 months of intervention: (1) Psychopathological data (Positive and Negative Syndromes Scale -PANSS- and the Personal and Social Functioning Scale -PSP-). ** Data collected at baseline and monthly during intervention: (1) Anthropometric data (weight, height, Body Mass Index -BMI-, waist circumference and waist-to-height ratio -WHtR-); (2) Cardio-metabolic data (systolic blood pressure, diastolic blood pressure and heart rate).

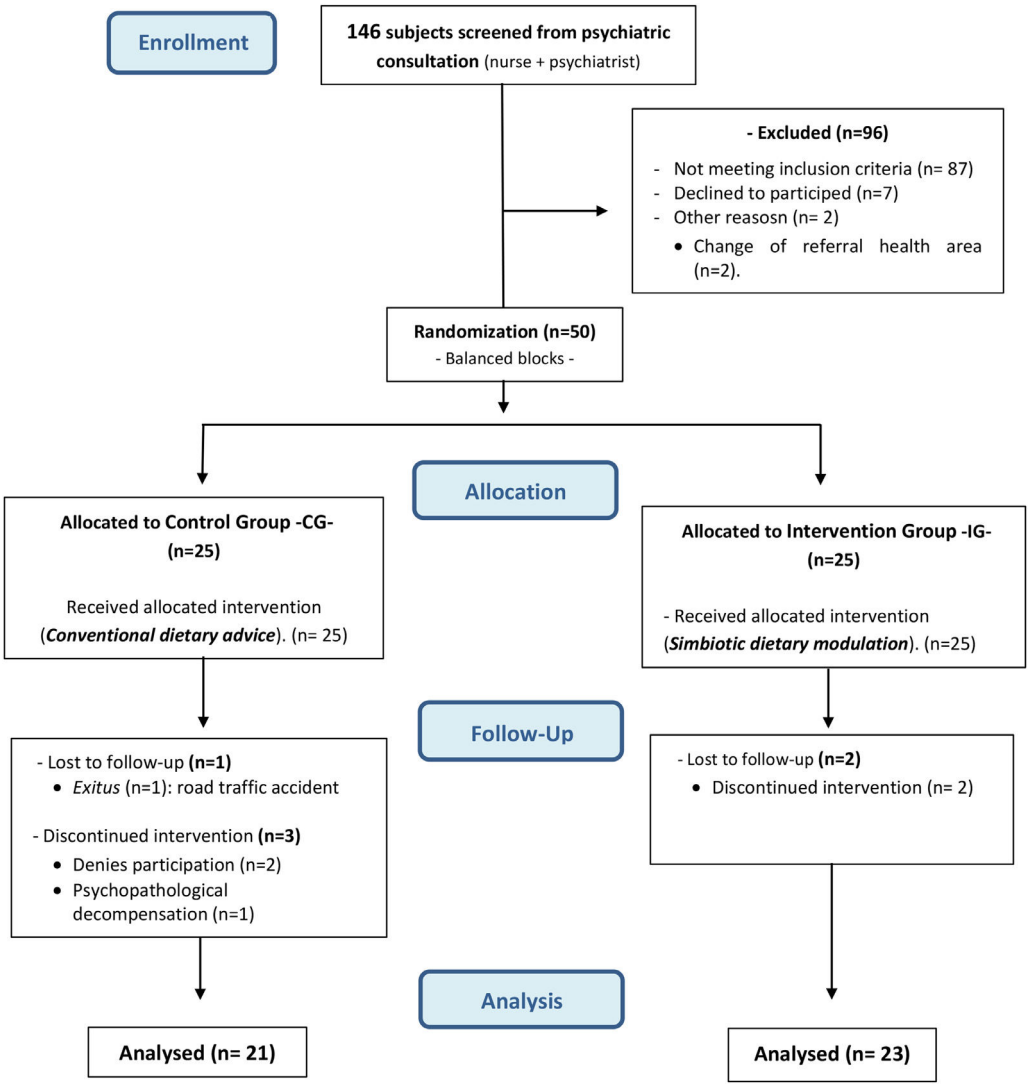

Fig. 2 CONSORT flow diagram.

confidence of 95 %, expecting a risk/prevalence difference of 63 % post-intervention.[29] The final size of 50 individuals was established (25 for the CG and 25 for the IG) to minimise the effect of possible losses. By balanced block randomisation, selected participants were assigned to IG or CG (Fig. 2). Randomisation was conducted according to the results found in cardio-metabolic analysis (balancing the prevalence of MS in both groups).

Data collection

The control group -CG- consisted of those participants who received regular (basic) dietary advice[30] on an individual basis. On the other hand, the intervention group -IG- was established individually through intensive dietary advice[31] based on the increasing consumption of food with high symbiotic content (fermented foods, whole grains, green leafy vegetables and fruits high in dietary fibre, among others). Nurses specialised in psychiatric care developed this intervention, allowing for the reinforcement of those dietary recommendations that required a more extensive intervention. Traditionally, the main objective of intensive dietary advice (IG) is to strengthen the set of recommendations that constitute the Basic Dietary Advice (offered to the CG). Traditionally, it is given exclusively to people for whom the basic intervention has been ineffective or insufficient.[31] In both groups, specialised nurses used educational resources of visual support during the consultations (healthy food pyramid, Harvard plate, table and illustrations of main prebiotic and probiotic foods, etc.).[32] The study began with a group session to present the research project to the health centre staff and Psychiatry Service. Subsequently, the 6-month individual nutrition education program was implemented (with two months of educational reinforcement, monthly for the CG and fortnightly for the IG). Similarly, data on cardio-metabolic and anthropometric status (BMI, waist to height ratio -WHtR-, blood pressure, heart rate and waist circumference) were collected monthly, by advanced practice nurses with prior training, following standardised recommendations,[33] thus ensuring the reliability of the data obtained. Likewise, the hetero-administered use of the Positive and Negative Syndromes Scale -PANSS-[34] and the Personal and Social Functioning Scale -PSP-[35] for the assessment of the psychopathological status (baseline, 3 and 6 months, respectively), was set by a psychiatrist.

Data analysis

The quantitative variables have been presented with mean and standard deviation, whereas the qualitative ones with frequencies and percentages. The Kolmogorov-Smirnov test was used for the study of normality in quantitative variables. Student's *t*-test for paired data, Pearson's correlation coefficient and repeated-measures ANOVA, were used to study the relationship between quantitative variables. Chi-square with its corrections (Fisher or Yates) and the Mc Nemar test were computed to study the association between qualitative variables. The repeated-measures ANOVA was calculated to compare values of quantitative variables at baseline, 3 and 6 months of intervention. The two-by-two comparisons (0—3 months, 0—6 months and 3—6 months) were performed using the Bonferroni method. If the homoscedasticity criterion were not met, non-parametric versions of the previous tests were carried out. The 2 log-likelihood, goodness of fit statistic, Cox and Snell R2, Nagelkerke R2 and Hosmer-Lemeshow tests were used to assess the overall model fit. For all statistical analyses, a probability of alpha error of less than 5 % ($p < 0.05$) and a 95 % confidence interval was accepted. SPSS (version 25.0) and EPIDAT (version 4.2) software were used for statistical analysis.

Results

During the recruitment period, the eligible population was 50 subjects. However, six participants were excluded throughout the intervention phase (4 participants refused to participate, 1 suffered a psychopathological decompensation that prevented the intervention from taking place, and 1 participant died during the study). Finally, 21 subjects in the CG and 23 for the IG were included in the analysis. The flow chart of the participants is shown in Fig. 2.

A total of 32 (72.7 %) men and 12 (27.3 %) women participated, with a mean age of 49.2 ± 11.2 years. The principal psychiatric diagnosis was schizophrenia [7 (84.1 %)], with a mean duration of illness of 21.6 ± 12.4 years. The average consumption of intoxicants was 29 (65.9 %) for tobacco, followed by cannabis [10 (22.7 %)] and alcohol [6 (13.6 %)]. The number of subjects with an associated cardio-metabolic diagnosis was 20 (45.5 %), and the sample shows an average of 17 (38.6 %) for hyperlipidaemia, 10 (22.7 %) for hypertension, and 7 (15.9 %) for Diabetes Mellitus. Similarly, regarding the baseline analysis of tolerability and modulation of the dietary-nutritional pattern, 27 (61.4 %) knew how to cook and were responsible for it, while 38.6 % were not responsible for their dietary pattern. Finally, the baseline analysis of dependent variables showed no significant differences between allocation groups. Table 1 and Table 2 show the baseline characteristics of the independent and dependent variables, respectively, showing homogeneity between the two groups.

Table 3 shows the changes in variables at baseline, 3 and 6 months of intervention in CG and IG, respectively. The intra-group analysis of the psychopathological and anthropometric profile, using ANOVA -mixed design-, shown a significant interaction ($p < 0.05$) between the results of these variables (0-3-6 months) and the group assigned. In order to identify the degree of variation in both groups, a post-hoc analysis was used, showing several reductions in the values were in both groups, being more pronounced in the IG (0—3—6 months). However, the inter-group difference did not show significant results.

The percentage analysis and comparison of means in both groups (Tables 4 and 5) were analysed to elucidate relevant changes between the different stages of intervention. The results evidenced statistically significant inter-group differences between 3 and 6 months for the psychopathological profile (PANSS-T), highlighting the PANSS-GP and PSP variables, with no significant changes in the daily dose of antipsychotics. Likewise, the anthropometric profile between baseline-6 months and between 3 and 6 months of intervention maintained a significant difference in all variables in the IG. Finally, no statistical differences were found for the cardiovascular profile, except for systolic blood pressure (SBP) between the 3—6 months of intervention.

Discussion

This study showed that when a nutritional programme focused on dietary modulation of high symbiotic content is offered to patients diagnosed with schizophrenia spectrum disorder, the anthropometric profile (in all its variables) and, therefore, risk of MS improve significantly in the IG. Similar results were obtained by Sugawara et al. (2018)[29] and Caemmerer et al. (2012).[28] In addition, the intervention led to a statistical reduction in the prevalence of cardiovascular risk factors and MS and, thus, indirectly, to a decrease in morbidity and mortality associated with the development of this syndrome.[12,13,15] Several studies have evidenced metabolic abnormalities associated with antipsychotic treatment in patients with schizophrenia.[14,15,19,20] In this sense, the meta-analysis developed by Teasdale et al. (2017)[36] showed that non-pharmacological interventions (dietary modulation and nutritional education) are the therapies of choice for iatrogenic dysmetabolic states, beyond conventional treatment[37], and improving the tolerance and acceptance rates.[29]

It is essential to highlight the complexity of the aetiopathogenesis of schizophrenia, where multiple factors (genetic, environmental, psychosocial, etc.) can modify the response to the therapeutic approach and functionality of the patients.[1-3] Thus, according to Firth et al. (2020),[6] the acquisition of healthier lifestyles is determined by interventions focused on improving dietary patterns and promoting physical exercise.

The use of prebiotics and probiotics allows for improving dysbiosis associated with IM, leading to a reduction in oxidative stress and low-grade systemic inflammation[7,10,27] and improving the prevalent imbalance of energy homeostasis in dysmetabolic states[7]. The new evidence shows that these interventions, based on the use of psychobiotics, allow an excellent therapeutic approach to obesity[7], as well as in psychophysiological terms (affective disorders, anxiety or cognition).[24,26,38]

On the other hand, in this study, the psychopathological assessment after six months of intervention in the IG showed significant results not present in preliminary studies. Thus, this clinical trial is the first to demonstrate a positive effect on the level of personal and social functioning (PSP scale)

Table 1 Sample characteristics *(independent variables)*: Baseline.

Variables		TOTAL (*n* = 44)	Control Group (*n* = 21)	Intervention Group (*n* = 23)	p
Socio-demographic variables					
Sex					
	Men	32 (72.7 %)	14 (31.8 %)	18 (40.9 %)	0.388
	Women	12 (27.3 %)	7 (15.9 %)	5 (11.4 %)	
Age (years)		49.2 (11.2)	48.8 (13.8)	49.5 (10.1)	0.897
Legal representative					
	No	36 (81.8 %)	14 (31.8 %)	22 (50 %)	0.019
	Yes	8 (18.2 %)	7 (15.9 %)	1 (2.3 %)	
Household composition					
	Individual	12 (27.3 %)	5 (11.4 %)	7 (15.9 %)	0.893
	Horizontal	3 (6.8 %)	1 (2.3 %)	2 (4.5 %)	
	Complete	3 (6.8 %)	1 (2.3 %)	2 (4.5 %)	
	Own family home	7 (15.9 %)	4 (9.1 %)	3 (6.8 %)	
	Other: Supervised flat	19 (43.2 %)	10 (22.7 %)	9 (20.5 %)	
Economic level					
	High	6 (13.6 %)	3 (6.8 %)	3 (6.8 %)	0.651
	Medium	26 (59.1 %)	11 (25 %)	15 (34.1 %)	
	Low	12 (27.3 %)	7 (15.9 %)	5 (11.4 %)	
Level of education					
	Uneducated	4 (9.1 %)	2 (4.5 %)	2 (4.5 %)	
	Primary	19 (43.2 %)	11 (25 %)	8 (18.2 %)	0.590
	Secondary	17 (38.6 %)	7 (15.9 %)	10 (22.7 %)	
	University	4 (9.1 %)	1 (2.3 %)	3 (6.8 %)	
Area of residence					
	Urban	38 (86.4 %)	18 (40.9 %)	20 (45.5 %)	1.00
	Rural	6 (13.6 %)	3 (6.8 %)	3 (6.8 %)	
Clinical Variables					
Psychiatric diagnosis					
	Schizophrenia	37 (84.1 %)	19 (43.2 %)	18 (40.9 %)	0.419
	Schizoaffective Disorder	5 (11.4 %)	1 (2.3 %)	4 (9.1 %)	
	Delusional Disorder	2 (4.5 %)	1 (2.3 %)	1 (2.3 %)	
Duration of illness *(years)*		21.6 (12.4)	22.5 (12.6)	20.9 (12.5)	0.715
Age at first hospitalisation *(years)*		31.4 (11)	31.4 (11.4)	31.4 (10.7)	0.572
Consumption of toxics					
	No	15 (34.1 %)	5 (11.4 %)	10 (22.7 %)	0.169
	Yes	29 (65.9 %)	16 (36.4 %)	13 (29.5 %)	
Type of toxics					
	Alcohol	6 (13.6 %)	3 (6.8 %)	3 (6.8 %)	0.775
	Tobacco	29 (65.9 %)	15 (34 %)	14 (31.8 %)	
	Cocaine	3 (6.8 %)	1 (2.3 %)	2 (4.5 %)	
	Opioids	2 (4.6 %)	1 (2.3 %)	1 (2.3 %)	
	Amphetamines	3 (6.8 %)	2 (4.5 %)	1 (2.3 %)	
	Cannabis	10 (22.7 %)	5 (11.6 %)	5 (11.3 %)	
Cardio-metabolic diagnosis					
	No	24 (54.5 %)	11 (25 %)	13 (29.5 %)	0.783
	Yes	20 (45.5 %)	10 (22.7 %)	10 (22.7 %)	
Type Cardio-metabolic diagnosis					
	AHT	10 (22.7 %)	6 (13.6 %)	4 (9.1 %)	0.407
	DM	7 (15.9 %)	5 (11.3 %)	2 (4.5 %)	
	Hyperlipemia	17 (38.6 %)	8 (18.1 %)	9 (20.4 %)	

Table 1 (*Continued*)

Variables		TOTAL (*n* = 44)	Control Group (*n* = 21)	Intervention Group (*n* = 23)	p
Therapeutic Variables					
Reason for Change: Antipsychotic Treatment					
	Unchanged	31 (70.5 %)	16 (51.6 %)	15 (48.4 %)	0.660
	Lack of efficiency	5 (11.4 %)	1 (2.3 %)	4 (9.1 %)	
	Tolerability/safety issues	2 (4.5 %)	1 (2.3 %)	1 (2.3 %)	
	Patient's own choice	3 (6.8 %)	1 (2.3 %)	2 (4.5 %)	
	Other: Clinical improvement	3 (6.8 %)	2 (4.5 %)	1 (2.3 %)	
Anthropometric Variables					
Height *(cm)*		168.5 (9.2)	166.4 (10.7)	170.3 (7.4)	0.245
Tolerability and Modulation of Dietary and Nutritional Patterns					
Culinary knowledge and food responsibility					
	Can cook and he/she is in charge of it	27 (61.4 %)	9 (20.5 %)	18 (40.9 %)	0.004
	Can cook but he/she is not in charge of it	6 (13.6 %)	2 (4.5 %)	4 (9.1 %)	
	Cannot cook and he/she is not in charge of it	11 (25 %)	10 (22.7 %)	1 (2.3 %)	
AHT: Arterial hypertension; DM: diabetes mellitus.					

Table 2 Sample characteristics *(dependent variables):* Baseline.

Variables	TOTAL (*n* = 44)	Control Group (*n* = 21)	Intervention Group (*n* = 23)	p
Psychopathological Profile				
PANSS-T	64.5 (16.8)	68.0 (17.7)	61.3 (15.6)	0.190
PANSS-P	10.9 (4.8)	12.1 (6)	9.9 (3)	0.304
PANSS-N	22.2 (7.2)	23.2 (7.3)	21.3 (7.1)	0.341
PANSS Composite Index	11.2 (7.3)	11.1(8.3)	11.4 (6.4)	0.972
PANSS-GP	31.3 (7.7)	32.6 (7.7)	30.1 (7.7)	0.248
PSP	61.3 (14.5)	57.3 (15.5)	64.9 (12.9)	0.067
Anthropometric Profile				
Weight *(kg)*	81.4 (17.6)	76.6 (18)	85.7 (16.3)	0.086
Waist circumference *(cm)*	101.9 (17)	97.6 (21)	105.7 (11.5)	0.312
BMI *(kg/m2)*	28.5 (5)	27.5 (5.2)	29.5 (4.8)	0.307
WHtR	0.6 (0.1)	0.6 (0.1)	0.6 (0.0)	0.518
Cardiovascular Profile				
SBP *(mmHg)*	127.2 (15)	125.6(16.3)	128.7 (13.9)	0.391
DBP *(mmHg)*	84.2 (10.7)	82.6 (9.7)	85.6 (11.5)	0.548
HR (bpm)	84.8 (14.5)	88.5 (16.4)	81.4 (12)	0.110
Therapeutic Variables				
N° of associated antipsychotic	1.3 (0.5)	1.3 (0.5)	1.3 (0.4)	0.597
DDD antipsychotics *(mg)*	271.4 (242.5)	286.7 (222.3)	257.4 (242.5)	0.458

PANSS: positive and negative syndrome scale; PANSS-T: PANSS total scale; PANSS-P: PANSS positive scale; PANSS-N: negative scale PANSS; PANSS-GP: general psychopathology PANSS; PSP: personal and social performance scale; BMI: body mass index; WHtR: waist-to-height ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Antipsychotic DDD: defined daily dose antipsychotics.

Table 3 Modifications in allocation groups: control group and experimental group.

	Control Group (n = 21)				Intervention Group (n = 23)				p**
Variables	Basal	3 months	6 months	p*	Basal	3 months	6 months	p*	
Psychopathological Profile									
PANSS-T	68 (17.7)	53.1 (15.9)	53.8 (19.8)	< 0.001	61.3 (15.6)	52.2 (15.7)	47.8 (13.15)	< 0.001	0.272
PANSS-P	12.1 (6)	10 (5.2)	10 (5.9)	0.076	9.9 (3)	10.4 (4.1)	9.4 (3.6)	0.228	0.077
PANSS-N	23.2 (7.3)	16 (5.4)	16 (6.4)	< 0.001	21.3 (7.1)	15.2 (6.2)	13.6 (5)	< 0.001	0.518
PANSS Composite Index	11.1(8.3)	5.9 (5.4)	6 (4.9)	0.002	11.4 (6.4)	5.2 (4.9)	4.8 (4)	< 0.001	0.612
PANSS-GP	32.6 (7.7)	27 (7.1)	27.7 (8.9)	0.001	30.1 (7.7)	26.6 (7.4)	24.8 (6.3)	0.007	0.354
PSP	57.3 (15.5)	64.2 (13.4)	65.7 (14.3)	0.015	64.9 (12.9)	68 (16.3)	72.8 (13.2)	0.036	0.473
Anthropometric Profile									
Weight *(kg)*	76.6 (18)	76.2 (19.3)	75.8 (17.7)	0.539	85.7 (16.3)	83.6 (15.1)	81.3 (14.6)	< 0.001	0.007
Waist circumference *(cm)*	97.6 (21)	101 (14.3)	101.2 (13.5)	0.342	105.7 (11.5)	104.3 (11.8)	102.1 (11.7)	< 0.001	0.068
BMI *(kg/m2)*	27.5 (5.2)	27.3 (5.6)	27.2 (5.3)	0.472	29.5 (4.8)	28.7 (4.3)	27.9 (4.3)	< 0.001	0.006
WHtR	0.6 (0.12)	0.6 (0.1)	0.6 (0.08)	0.348	0.6 (0.06)	0.6 (0.06)	0.6 (0.06)	< 0.001	0.077
Cardiovascular Profile									
SBP *(mmHg)*	125.6(16.3)	120.2 (27.9)	129.8 (11.2)	0.141	128.7 (13.9)	129.1 (15)	126.8 (10.6)	0.741	0.102
DBP *(mmHg)*	82.6 (9.7)	80.5 (8.8)	82.2 (7.9)	0.452	85.6 (11.5)	79.2 (8.2)	80.8 (7.5)	0.006	0.126
HR (bpm)	88.5 (16.4)	86.2 (15.9)	87.4 (14.2)	0.799	81.4 (12)	77.9 (13.7)	80.8 (9.4)	0.295	0.899
Therapeutic Variables									
N° of associated antipsychotic	1.3 (0.5)	1.3 (0.4)	1.3 (0.4)	0.460	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)	0.786	0.863
DDD antipsychotics *(mg)*	286.7 (222.3)	265.2 (221.3)	260.5 (221.5)	0.259	269 (263.9)	229.1 (234.8)	247.4 (225.9)	0.129	0.571

p*: Intragroup statistical significance; p**: Inter-group statistical significance; PANSS: positive and negative syndrome scale; PANSS-T: PANSS total scale; PANSS-P: PANSS positive scale; PANSS-N: negative scale PANSS; PANSS-GP: general psychopathology PANSS; PSP: personal and social performance scale; BMI: body mass index; WHtR: waist-to-height ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Antipsychotic DDD: defined daily dose antipsychotics.

Table 4 Gradient analysis: assignment groups.

	Control Group (n = 21)			Intervention Group (n = 23)			p*	p**	p***
Variables	Basal - 3 months	Basal - 6 months	3 months - 6 months	Basal - 3 months	Basal - 6 months	3 months - 6 months			
Psychopathological Profile									
PANSS-T	14.9 (13.1)	14.1 (16)	−0.7 (9.3)	9.04 (16.3)	13.5 (14.2)	4.4 (7.6)	0.199	0.892	0.047
PANSS-P	2.1 (4.2)	2.1 (5.7)	0.0 (2.5)	- 0.5 (3.2)	0.5 (2.9)	1 (2.3)	0.025	0.249	0.158
PANSS-N	7.2 (5.9)	7.2 (5.7)	- 0.0 (3.4)	6.1 (6.7)	7.7 (5.8)	1.5 (3.7)	0.567	0.773	0.142
PANSS Composite Index	- 5.1 (7)	- 5.1 (7)	0.0 (2.2)	- 5.9 (6.7)	- 6.6 (5.6)	- 0.7 (4)	0.712	0.434	0.457
PANSS-GP	5.5 (6.6)	4.8 (7.7)	- 0.7 (4.5)	3.4 (8.2)	5.3 (7.1)	1.8 (3.3)	0.351	0.843	0.036
PSP	- 6.9 (13.2)	- 8.4 (14.1)	- 1.5 (4.9)	- 3.1 (16)	- 8 (14.3)	- 4.8 (6.9)	0.402	0.921	0.052
Anthropometric Profile									
Weight *(kg)*	0.4 (2)	0.8 (4)	0.4 (4.3)	2.1 (3.8)	4.4 (4.3)	2.3 (2.3)	0.068	0.007	0.076
Waist circumference *(cm)*	- 3.3 (15.6)	- 3.5 (15.9)	- 0.2 (3.6)	1.4 (3.2)	3.6 (4)	2.2 (3.2)	0.159	0.042	0.024
BMI *(kg/m2)*	0.2 (0.7)	0.3 (1.3)	0.1 (1.4)	0.7 (1.3)	1.5 (1.4)	0.7 (0.8)	0.089	0.006	0.054
WHtR	- 0.021 (0.1)	- 0.02 (0.1)	- 0.011 (0.02)	0.008 (0.02)	0.021 (0.02)	0.013 (0.02)	0.167	0.048	0.024
Cardiovascular Profile									
SBP *(mmHg)*	5.4 (25.1)	- 4.3 (12.2)	- 9.6 (23.5)	- 0.4 (13.6)	1.8 (16.5)	2.3 (15)	0.339	0.171	0.049
DBP *(mmHg)*	2 (7.9)	0.3 (7.8)	- 1.7 (8)	6.4 (8.1)	4.8 (10.6)	- 1.5 (6.3)	0.078	0.117	0.945
HR (bpm)	2.3 (16.4)	1.1 (16.7)	- 1.1 (13.4)	3.5 (14)	0.5 (9.4)	- 3 (10.6)	0.789	0.882	0.613
Therapeutic Variables									
N° of associated antipsychotic	0.1 (0.4)	0.1 (0.4)	0.0 (0.3)	0.0 (0.3)	0.0 (0.3)	0.0 (0.3)	0.671	0.671	1.000
DDD antipsychotics *(mg)*	21.4 (90.1)	26.1 (96.7)	4.7 (21.5)	39.9 (104.7)	21.6 (95.8)	- 18.3 (65.9)	0.570	0.879	0.136

Repeated measures ANOVA (Factorial Analysis - Mixed Design). Two-by-two comparisons were performed using the Bonferroni method. p*: Inter-group statistical significance Baseline-3 months; p**: Inter-group statistical significance Baseline-6 months; p***: Inter-group statistical significance 3 months −6 months. PANSS: positive and negative syndrome scale; PANSS-T: PANSS total scale; PANSS-P: PANSS positive scale; PANSS-N: negative scale PANSS; PANSS-GP: general psychopathology PANSS; PSP: personal and social performance scale; BMI: body mass index; WHtR: waist-to-height ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Antipsychotic DDD: defined daily dose antipsychotics.

Table 5 Percentage variance analysis: allocation groups.

Variables	Control Group (n = 21)			Intervention Group (n = 23)			p*	p**	p***
	Basal - 3 months	Basal - 6 months	3 months - 6 months	Basal - 3 months	Basal - 6 months	3 months - 6 months			
Psychopathological Profile									
PANSS-T	−58.3 (45.6)	−57.4 (58.1)	4.1 (53.2)	−27.7 (67.9)	−52.54 (55.7)	−19.4 (40.2)	0.091	0.779	0.104
PANSS-P	- 14.4 (22)	- 13.8 (28.3)	1.1 (22.3)	6.6 (29.3)	- 3.7 (26.2)	- 7.2 (20.8)	0.011	0.225	0.209
PANSS-N	- 28.1 (20.3)	- 29.5 (19.8)	0.5 (21.3)	- 25.3 (26.9)	- 33.2 (21)	- 6.6 (20.5)	0.700	0.552	0.263
PANSS Composite Index	- 34 (45.5)	- 39 (39.4)	- 5.9 (34.5)	- 38.2 (37.9)	- 53 (23.2)	15.8 (168.4)	0.530	0.199	0.623
PANSS-GP	- 15.8 (16.1)	- 14 (19.1)	2.5 (15.5)	- 9.1 (23.1)	- 15.6 (16.8)	- 5.5 (10.7)	0.279	0.772	0.05
PSP	19.7 (44)	22.4 (47.7)	2.2 (9)	7.6 (32.1)	15.6 (28.7)	10 (16.5)	0.302	0.570	0.051
Anthropometric Profile									
Weight *(kg)*	- 0.9 (2.5)	- 0.9 (4.4)	- 0.01 (4.3)	- 2.2 (3.8)	- 4.9 (4)	- 2.7 (2.7)	0.194	0.004	0.017
Waist circumference *(cm)*	12.7 (58.7)	13 (58.8)	0.3 (3.4)	- 1.3 (3)	- 3.4 (3.5)	- 2.1 (2.9)	0.258	0.186	0.014
BMI *(kg/m2)*	- 1 (2.5)	- 1 (4.5)	- 0.01 (4.3)	- 2.3 (3.8)	- 4.9 (4)	- 2.7 (2.7)	0.194	0.004	0.017
WHtR	12.7 (58.7)	13 (58.8)	0.3 (3.4)	- 1.3 (3)	- 3.4 (3.5)	- 2.1 (2.9)	0.258	0.186	0.014
Cardiovascular Profile									
SBP *(mmHg)*	- 4.2 (22.9)	4.2 (9)	58.6 (248.9)	0.7 (10.4)	- 0.4 (13.5)	- 0.8 (11.9)	0.346	0.190	0.258
DBP *(mmHg)*	- 1.9 (9.9)	0.2 (8.9)	2.8 (9.6)	- 6.8 (9.1)	- 4.6 (11.8)	1.3 (4.5)	0.099	0.134	0.493
HR (bpm)	- 0.7 (19.1)	0.9 (19.5)	3 (16.6)	- 3.5 (15.9)	0.3 (11.1)	5.7 (15.6)	0.605	0.905	0.577
Therapeutic Variables									
N° of associated antipsychotic	- 2.4 (29.4)	- 2.4 (29.4)	2.4 (24.8)	0.0 (26.1)	0.0 (26.1)	2.1 (23.7)	0.778	0.778	0.978
DDD antipsychotics *(mg)*	- 5.2 (21.9)	- 6.4 (23.6)	- 1.5 (7.1)	1.7 (60.8)	54.7 (276.7)	148.4 (618.2)	0.622	0.320	0.273

Repeated measures ANOVA (Factorial Analysis - Mixed Design). Two-by-two comparisons were performed using the Bonferroni method. p*: Inter-group statistical significance Baseline-3 months; p**: Inter-group statistical significance Baseline-6 months; p***: Inter-group statistical significance 3 months −6 months. PANSS: positive and negative syndrome scale; PANSS-T: PANSS total scale; PANSS-P: PANSS positive scale; PANSS-N: negative scale PANSS; PANSS-GP: general psychopathology PANSS; PSP: personal and social performance scale; BMI: body mass index; WHtR: waist-to-height ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Antipsychotic DDD: defined daily dose antipsychotics.

and the improvement of general psychopathology (PANSS-T), highlighting the significance achieved in the PANSS-GP subscale between 3 and 6 months of intervention. However, Teasdale et al. (2017)[36] reflected that this result is the outcome of an intensive and individualised dietary-nutritional intervention, where a traditional intervention and the resulting cognitive dysfunction in CG may limit the understanding and achievement of optimal outcomes.[39] Nevertheless, these results reinforce the feasibility of dietary-nutritional impact on psychopathological areas in psychiatric patients, in line with the SMILES study,[40,41] a 12-week randomised controlled intervention trial.

Clinical trials with nutritional supplements or dietary approaches in the absence of psychopharmacological treatment are limited[43] and show marked heterogeneity and lack of methodological rigour.[42,43] However, although the results obtained in the literature are not consistent, the findings of Samochowiec et al. (2021)[44] and Zeng et al. (2021)[45] support our results, where the multimodal symbiotic approach, with nutraceutical action, looks to be effective as a complementary strategy in the treatment of schizophrenic disorders.

Finally, according to Balanzá (2017),[11] it is stated that the effectiveness of dietary-nutritional interventions in the psychiatric population is determined by multidisciplinary action, highlighting the role of advanced practice nurses in mental health where nutritional advice can play a relevant role.

Limitations

The main limitations of this research are related to the sample size and the possible loss or lack of cooperation of participants in the intervention phase. However, this small sample size could explain why we found few significant differences concerning the PSP scale[35] and the SBP variable. Also, regarding the associated cardiometabolic diagnosis, a minority were on pharmacological treatment before the study.

It should be noted that more than 60 % of the participating subjects maintained the psychopharmacological therapy until the end of the study, with no variation in the prescribed dosage. This fact may impact the variability of the intestinal microbiome, which, together with the absence of quantification of this biota through stool cultures, may lead to a potential limitation in the determination of the results.

On the other hand, the variable use and interpretation of psychopathological assessment instruments (PANSS and PSP scales,[34,35] respectively) by the psychiatrist and the clinical heterogeneity of schizophrenia may lead to the variability of results and limitation in the reliability of the data obtained.

Furthermore, the available evidence on the topic of study makes it difficult to contrast the results obtained in different healthcare settings. Finally, it is essential to highlight that this study was conducted during the SARS-CoV-2 pandemic, making the intervention more difficult and could explain the improvements evidenced after three months of intervention. In addition, it is necessary to keep in mind that these patients are particularly vulnerable to changes.

Conclusions

A dietary-nutritional intervention with high symbiotic content in patients diagnosed with schizophrenia has effectively improved clinical outcomes in psychopathological and cardio-metabolic terms. These dietary recommendations improve the nutritional status of patients who adhere to them. Consequently, it seems they can operate as psychopharmacological adjuvants because they increase tolerance to possible side effects and decrease the risk of MS associated with the antipsychotic treatment. Furthermore, this approach offers a promising solution to dysfunctionality, which is highly prevalent in LTMD, improving patients' quality of life. Similarly, advanced practice nursing in mental health brings added value in providing care focused on prevention and health promotion in psychiatry through dietary-nutritional education. These functions can positively improve the general health status of patients with schizophrenia and control the side effects of the pharmacological treatment that is usually prescribed to them. However, further studies with larger sample sizes are needed.

Ethics approval and consent to participate

The study will be carried out respecting the fundamental principles established in the Declaration of Helsinki (1964), the Council of Europe Convention on Human Rights and Biomedicine (1997), the UNESCO Universal Declaration on the Human Genome and Human Rights (1997). Research will also follow the requirements established by Spanish legislation (Organic Law 3/2018 of 5 December and Law 41/2002 of 14 November). This study protocol has been registered in the platform clinicaltrials.gov (No. reg. NCT04366401; First Submitted: 28/04/2020; First Registration: 25/06/2020). The study received ethical approval from Zamora Health Area Drug Research Ethics Committee at the Regional Government of Castile and León, Spain (No. reg. 468). All the information analysed by the principal investigator of this study is subject to the maintenance of professional secrecy.

In any case, each participant must agree to participate in the study and sign the informed consent form (the patient can refused to participate in the study at any time) and will be assigned a code as a registry, where all the relative data will be mechanized in an anonymous way, delimiting the access to the database only to the personnel linked to the development of the study, previous authorization of the investigator in charge of it.

Consent for publication

Not applicable.

Authors' contributions

ASJ, GMR, and MRS contributed to conception and design to the study; ASJ, GMR, JAGM, RML and MRS contributed to acquisition, analysis, and interpretation of results; ASJ and GMR drafted the manuscript; ASJ, GMR and MRS critically revised the manuscript. All authors read and approved the final manuscript and theyŕe agree to be accountable for all aspects of work ensuring integrity and accuracy.

Ethical considerations

This research has the permission of the Zamora Health Area Drug Research Ethics Committee at the Regional Government of Castile and León, Spain (No. reg.468). Clinical Trials ID: NCT04366401. First Submitted: April 28, 2020.

Disclosure statement

The authors warrant that the article is original and not submitted.

Data availability

The collected data that support the findings of this study are available on reasonable request from the corresponding author.

Declaration of competing interest

The authors declare that they have no competing interests.

Funding

This publication is partially funded by the XXVII Nursing Research Grant of the Illustrious Official College of Nursing of Córdoba, Spain.

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