UNIVERSIDAD D CÓRDOBA

TESIS DOCTORAL

- Programa de doctorado: *Biociencias y Ciencias Agroalimentarias* -

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Eficacia de la modulación dietética con alto contenido prebiótico y probiótico sobre el estado nutricional y metabólico en trastornos del espectro esquizofrénico.

Efficacy of dietary modulation with high prebiotic and probiotic content on nutritional and metabolic status in schizophrenia spectrum disorders.

[Memoria presentada para optar al título de Doctor por la Universidad de Córdoba]

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Depósito:

Córdoba, marzo de 2023.

TITULO: *Eficacia de la modulación dietética con alto contenido prebiótico y probiótico sobre el estado nutricional y metabólico en trastornos del espectro esquizofrénico*

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TÍTULO DE LA TESIS:

Eficacia de la modulación dietética con alto contenido prebiótico y probiótico sobre el estado nutricional y metabólico en trastornos del espectro esquizofrénico.

DOCTORANDO/A: Alfonso Sevillano Jiménez

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

El doctorando ha llevado a cabo su tesis doctoral bajo nuestra supervisión directa, realizando un ensayo clínico para evaluar la eficacia de una intervención nutricional en pacientes con trastornos del espectro esquizofrénico, cuya finalidad era reducir la presencia de componentes del síndrome metabólico. Cabe destacar que esta intervención se llevó a cabo durante las primeras oleadas de la COVID-19, incluyendo el periodo de confinamiento, lo que dificultó aún más el valioso trabajo de Alfonso.

En cuanto al texto, destacar que en la Introducción, el doctorando muestra un profundo conocimiento y experiencia en el tema de investigación. Los objetivos planteados están correctamente formulados y han sido alcanzados en la investigación desarrollada. La metodología es adecuada, empleando un diseño experimental aleatorizado de dos brazos paralelos y apoyado en un amplio, sólido y avanzado análisis estadístico. Los resultados son descritos con exhaustividad, claridad y meticulosidad. De la misma manera, la discusión ha sido bien hilvanada y suficientemente respaldada por las referencias bibliográficas más importantes. Las conclusiones son acordes con los objetivos formulados. Por último, las referencias bibliográficas son amplias y actualizadas.

Al presentarse como tesis por compendio de artículos, parte del texto de la misma se encuentra descrito siguiendo los manuscritos que Alfonso ha publicado en revistas de alto de impacto:

- Sevillano-Jiménez A, Molina-Recio G, García-Mellado JA, García-Rodríguez M, Molina-Luque R, Romero-Saldaña M. Efficacy of nutrition education for the increase of symbiotic intake on nutritional and metabolic status in schizophrenic spectrum disorders: A two-arm protocol. Front Nutr. 2022 Aug 10;9:912783. doi: 10.3389/fnut.2022.912783.
- Sevillano-Jiménez A, Romero-Saldaña M, García-Mellado JA, Carrascal-Laso L, García-Rodríguez M, Molina-Luque R, Molina-Recio G. Impact of high prebiotic and probiotic dietary education in the SARS-CoV-2 era: improved cardio-metabolic profile in schizophrenia spectrum disorders. BMC Psychiatry. 2022 Dec 12;22(1):781. doi: 10.1186/s12888-022-04426-9. PMID: 36510155; PMCID: PMC9743108.
- Sevillano-Jiménez A, Romero-Saldaña M, García-Rodríguez M, Molina-Luque R, Molina-Recio G. Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing-Two-Arm Randomised Clinical Trial. Nutrients. 2022 Dec 19;14(24):5388. doi: 10.3390/nu14245388.

Además, es preciso destacar que otro cuarto artículo se encuentra en revisión y que estos estudios han obtenido varias becas y premios de diversas sociedades científicas de Enfermería. Como consecuencia, su trabajo ha mostrado un alto grado de traslación al haberse presentado sus resultados, de forma parcial, en un elevado número de Congresos nacionales e internacionales y en forma de comunicaciones y ponencias invitadas.

Por último, y dejando de lado los aspectos estrictamente académicos, es preciso destacar la gran capacidad de aprendizaje del doctorando, tanto en lo referido a conocimientos relacionados con la bioestadística y los diseños epidemiológicos, como a su notable mejora en la redacción de artículos científicos. Estamos convencidos de que, tras la defensa de su tesis doctoral, D. Alfonso Sevillano Jiménez continuará desempeñando una brillante carrera investigadora y, en el caso de que lo desee y que su actividad asistencial se lo permita, también podrá jugar un papel destacado como docente universitario, especializado en algo tan relevante para la sociedad actual

como es la Salud Mental. Para nosotros, sería un privilegio poder compartir con él la responsabilidad de formar a los futuros profesionales de Enfermería desde el Departamento de Enfermería, Farmacología y Fisioterapia de esta Universidad.

Por todo ello, se autoriza la presentación de la tesis doctoral.

Córdoba, a 14 de marzo de 2023

Firma del/de los director/es

Fdo.:Prof. Dr. Manuel Romero Saldaña Fdo.: Prof. Dr. Guillermo Molina Recio

"Nada tiene tanto poder para ampliar la mente como la capacidad de investigar de forma sistemática y real, todo lo que es susceptible de observación en la vida"

Marco Aurelio (121 d.C-180d.C)

Tesis Doctoral como Compendio de Publicaciones

1. Sevillano-Jiménez A, Molina-Recio G, García-Mellado JA, García-Rodríguez M, Molina-Luque R, Romero-Saldaña M. Efficacy of nutrition education for the increase of symbiotic intake on nutritional and metabolic status in schizophrenic spectrum disorders: A two-arm protocol. Front Nutr. 2022;9:912783. DOI: 10.3389/fnut.2022.912783

2. Sevillano-Jiménez A, Romero-Saldaña M, García-Rodríguez M, Molina-Luque R, Molina-Recio G. Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing-Two-Arm Randomised Clinical Trial. Nutrients. 2022;14(24):5388. DOI: 10.3390/nu14245388.

3. Sevillano-Jiménez A, Romero-Saldaña M, García-Mellado JA, Carrascal-Laso L, García-Rodríguez M, Molina-Luque R, Molina-Recio G. Impact of high prebiotic and probiotic dietary education in the SARS-CoV-2 era: improved cardio-metabolic profile in schizophrenia spectrum disorders. BMC Psychiatry. 2022;22(1):781. DOI: 10.1186/s12888-022-04426-9.

4. Psychopathological and cardiometabolic efficacy of a nutritional education intervention based on symbiotics in schizophrenia spectrum disorders. Two-arm Randomised Clinical Trial. *(*Manuscrito enviado para su publicación en *International Journal of Psychiatry in Clinical Practice**: Bajo revisión actual**)*

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Resumen

Introducción: El enfoque terapéutico tradicional ha percibido el papel de la nutrición y modificación de estilos de vida como una intervención menor en salud mental. El avance en términos de psiquiatría nutricional y desarrollo de nuevas premisas etiológicas respecto a los trastornos mentales, destacando la teoría del eje microbiota-intestino-cerebro, evidencia la influencia de los psicobióticos (prebióticos y probióticos de acción nutracéutica) en la mejora de variables clínicas alteradas de trastornos neuropsiquiátricos, en términos de salud física y disfunción psicopatológica.

Objetivos: Determinar la eficacia de la modulación dietética de alto contenido prebiótico y probiótico en pacientes diagnosticados del espectro esquizofrénico, atendiendo al impacto nutricional, cardio-metabólico y psicopatológico.

Material y Métodos: Se desarrolló un ensayo clínico de dos brazos, aleatorizado mediante bloques balanceados, doble ciego, de seis meses de intervención, en un grupo de 50 individuos diagnosticados de trastornos del espectro esquizofrénico (sin distinción por tipo). El grupo control (n=25) estuvo constituido por aquellos participantes que recibieron consejo dietético estandarizado de forma individual. En el grupo de intervención (n=25), ésta se estableció individualmente mediante consejo nutricional intensivo para el incremento del consumo de alimentos con alto contenido prebiótico y probiótico (lácteos y alimentos fermentados, verduras de hoja verde, fruta rica en fibra, cereales integrales, etc.). En ambos grupos, se empleó material educativo de apoyo visual durante las sesiones impartidas La intervención dietética fue diseñada y supervisada por personal titulado y con competencias reconocidas (enfermeras y dietistas-nutricionistas). Del mismo modo, se establecieron grupos focales previos que permitieron redifinir y orientar la adecuación del estudio. Durante el desarrollo del ensayo clínico, se obtuvieron datos sobre el estado psicopatológico (escalas PANSS y PSP) y del perfil analítico (hemograma y bioquímica), de forma basal, a los tres y seis meses de intervención, respectivamente. Del mismo modo, se determinó la estimación de la microbiota intestinal mediante coprocultivo, así como evaluación del patrón dietético y nutricional (Cuestionario de Frecuencia de Consumo de Alimentos) al inicio y a los seis meses de intervención. Para la valoración del grado de adherencia entre grupos de asignación, se cumplimentó un registro semanal de los principales platos y alimentos simbióticos consumidos. Finalmente, se analizaron parámetros antropométricos de forma mensual.

Resultados: 44 participantes completaron el seguimiento y fueron analizados. El análisis nutricional mostró una reducción estadísticamente significativa de las ingestas de macro y micronutrientes con una mayor aproximación a las ingestas dietéticas recomendadas. Así mismo, se evidenció una reducción intragrupo ($p < 0,05$) del perfil proteico, azúcares y alimentos ultraprocesados. Respecto al grado de adherencia entre grupos de asignación, se evidenció un aumento en el consumo de alimentos con alto contenido simbiótico en el grupo de intervención. Por otro lado, con relación al impacto cardio-metabólico, se obtuvieron diferencias estadísticas ($p < 0,001$) en todas las variables del perfil antropométrico en el grupo experimental. Tras 6 meses de estudio, se observó una reducción del 27,4% en la prevalencia de factores de riesgo del síndrome metabólico en todos sus componentes, lo que condujo a una mejora clínicamente significativa del riesgo cardiovascular en el grupo de intervención. Por último, distante del impacto psicopatológico observado en el grupo control, los resultados mostraron una mejora estadísticamente significativa ($p < 0,05$) en las puntuaciones de la subescala PANSS-PG y de la escala PSP, a lo largo de 3-6 meses de intervención.

Conclusiones: El grado de evidencia alcanzado permite establecer el consejo nutricional centrado en el incremento de la ingesta de alimentos con alto contenido simbiótico como una terapia coadyuvante eficaz en el abordaje de trastornos esquizofrénicos en términos dietético-nutricionales, cardio-metabólicos y psicopatológicos. Así mismo, el uso de prebióticos y probióticos ha demostrado ofrecer una solución relevante y prometedora en diferentes contextos de aplicación. Enfermería de práctica avanzada adquiere un papel destacado en la coordinación multidisciplinar y en la consecución de óptimos resultados en salud, mediante la prevención y promoción de estilos de vida saludables en salud mental, a través de la educación nutricional.

Palabras Clave: Dietoterapia; Prebiótico; Probiótico; Síndrome metabólico; Salud mental; Espectro esquizofrénico y otros trastornos psicóticos.

Abstract

Introduction: The traditional therapeutic approach has perceived the role of nutrition and lifestyle modification as a minor intervention in mental health. Progress in terms of nutritional psychiatry and the development of new aetiological premises regarding mental disorders, highlighting the theory of the microbiota-gut-brain axis, shows the influence of psychobiotics (prebiotics and probiotics with nutraceutical action) in the improvement of altered clinical variables of neuropsychiatric disorders, in terms of physical health and psychopathological dysfunction.

Objectives: To determine the efficacy of dietary modulation of high prebiotic and probiotic content in patients diagnosed with schizophrenia spectrum disorder, taking into account the nutritional, cardio-metabolic and psychopathological impact

Material and Methods: A two-arm, randomised, balanced-block, double-blind, six-month intervention trial was conducted in a group of 50 individuals diagnosed with schizophrenia spectrum disorders (without distinction by type). The control group (n=25) consisted of those participants who received individual standardised dietary advice. In the intervention group (n=25), the intervention was established individually by intensive nutritional advice with high prebiotic and probiotic content (dairy and fermented foods, green leafy vegetables, fibre-rich fruit, whole grains, etc.). The dietary intervention was designed and supervised by qualified staff with recognised competencies (nurses and dietician-nutritionists). From the same, serial focus groups were established to redefine and guide the appropriateness of the study. During the clinical trial, data were obtained on the psychopathological state (PANSS and PSP scales) and analytical profile (haemogram and biochemistry), at baseline, three and six months after the intervention, respectively. Similarly, the estimation of the intestinal microbiota was determined by stool culture, as well as assessment of the dietary and nutritional pattern (Food Consumption Frequency Questionnaire) at baseline and at six months of intervention. In order to assess the degree of adherence between allocation groups, a weekly record of the main dishes and symbiotic foods consumed was completed. Finally, anthropometric parameters were analysed on a monthly basis.

Results: 44 participants completed follow-up and were analysed. Nutritional analysis showed a statistically significant reduction in macro- and micronutrient intakes with a closer approximation to recommended dietary intakes. There was also an intra-group reduction ($p < 0.05$) in protein profile, sugars and ultra-processed foods. Regarding the degree of adherence between allocation groups, there was an increase in the consumption of foods with a high

symbiotic content in the intervention group. On the other hand, in relation to the cardio-metabolic impact, statistical differences were obtained ($p < 0.001$) in all variables of the anthropometric profile in the experimental group. After 6 months of study, a 27.4% reduction in the prevalence of metabolic syndrome risk factors in all its components was observed, leading to a clinically significant improvement in cardiovascular risk in the intervention group. Finally, distant from the psychopathological impact observed in the control group, the results showed a statistically significant ($p < 0.05$) improvement in PANSS-PG subscale and PSP scale scores over 3-6 months of intervention.

Conclusions: The degree of evidence achieved allows establishing nutritional management with high symbiotic content as an effective adjuvant therapy in the management of schizophrenic disorders in terms of dietary-nutritional, cardio-metabolic and psychopathological disorders. Likewise, the use of prebiotics and probiotics has been shown to offer a relevant and promising solution in different application contexts. Advanced practice nursing takes a leading role in multidisciplinary coordination and achievement of optimal health outcomes, through prevention and promotion of healthy lifestyles in mental health, through nutritional education.

Keywords: Diet Therapy; Prebiotic; Probiotic; Metabolic Syndrome; Mental Health; Schizophrenia Spectrum and Other Psychotic Disorders.

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Abreviaturas y acrónimos

% IDR	% Ingesta Diaria Recomendada
ARN	Ácido Ribonucleico
AVAD	Años de Vida Ajustados por Discapacidad
AVP	Años de Vida Perdidos por Mortalidad Prematura
AVD	Años de Vida por Discapacidad
CFCA	Cuestionario de Frecuencia de Consumo de Alimentos
CIE-11	Clasificación Internacional de Enfermedades, 11ª Edición
DPNT	Duración de la Psicosis No Tratada
DSM-V	*Diagnostic and Statistical Manual of Mental Disorders, 5ª Edition* (Manual diagnóstico y estadístico de los trastornos mentales, 5ª Edición)
GABA	Ácido Gamma-Aminobutírico
HDL	*High Density Lipoprotein* (Lipoproteína de Alta Densidad)
IL-6	Interleucinas tipo 6
IL-1ß	Interleucinas tipo 1ß
LDL	*Low Density Lipoprotein* (Lipoproteína de Baja Densidad)
MI	Microbiota Intestinal
PANSS	*Positive and Negative Syndrome Scale* (Escala de Síndrome Positivo y Negativo)
pCr	Proteína C-Reactiva
PSP	*Personal and Social Performance* (Escala de Funcionamiento Personal y Social)
SM	Síndrome Metabólico
SNC	Sistema Nervioso Central
TMG	Trastorno Mental Grave
TGF-ß	Factor de Crecimiento Transformante ß
TNF-ὰ	Factor de Necrosis Tumoral ὰ
UFC/g	Unidades Formadoras de Colonias/gramo

1. Introducción

1.1. Marco Teórico

El trastorno mental grave (TMG) es definido como el conjunto de categorías diagnósticas regidas por el cumplimiento de patrones distintivos claramente diferenciados, destacando: la previsión de una evolución prolongada en el tiempo, la existencia de una alta repercusión clínica en términos de autocuidados y funcionalidad socio-laboral, así como una marcada complejidad terapéutica que precisa la intervención de múltiples dispositivos asistenciales y socio-familiares[1,2]. El conjunto de entidades psicopatológicas que engloba el TMG se encuentra supeditado a criterios de clasificación diagnósticos, basados principalmente en el DSM-V y CIE-11, destacando los trastornos del espectro esquizofrénico, entre otros[1].

En seste sentido, la esquizofrenia desataca por encima de la amalgama de desórdenes mentales que engloba el TMG, estableciéndose como aquella enfermedad mental crónica caracterizada por la heterogeneidad significativa de su clínica, siendo determinada por periodos de exacerbación psicótica (precedidos por síntomas subclínicos que conformarían la fase prodrómica) y periodos de estabilización[3,4]. La compleja semiología de esta enfermedad es representada a través de síntomas positivos (alucinaciones, delirios o conductas desorganizadas, entre otros) y negativos (aplanamiento afectivo, anhedonia, abulia, retraimiento social, etc.)[3], siendo variable el nivel de disfunción y presentación clínica inter-sujeto[2,5]. La dificultad existente en poder discernir el debut psicótico (siendo relevante en casos de evolución insidiosa), así como las características clínicas individuales y la duración de psicosis no tratada (DPNT), condicionan el pronóstico y modalidad terapéutica instaurada[6].

La evidencia muestra la asociación de numerosas entidades nosológicas con relación al espectro esquizofrénico, destacando: trastorno psicótico breve, trastorno de ideas delirantes, trastorno esquizoafectivo, trastorno esquizofreniforme y trastorno de personalidad esquizotípico[3,4]. Éstas conllevan un importante deterioro neurocognitivo asociado, prevaleciendo junto a éste, el detrimento de la funcionalidad social y laboral, incidiendo de forma significativa en la calidad de vida del paciente[5].

En la actualidad, a nivel mundial, los trastornos del espectro esquizofrénico presentan una prevalencia relativamente baja, oscilando en torno al 3,3% en países occidentales, y observándose cifras inferiores en las regiones rurales o en vías de desarrollo[7]. Sin embargo, en España, esta prevalencia oscila entre el 0,7 y el 1,5% de la población general[8], existiendo equidad en la proporción de hombres y mujeres diagnosticadas de esquizofrenia[9]. No obstante, a pesar de la baja prevalencia descrita, los trastornos neuropsiquiátricos suponen una de las principales causas de años de vida ajustados por discapacidad (AVAD), hasta un 15% en la población española[9],

englobando éste los años de vida perdidos por mortalidad prematura (AVP) y los años de vida por discapacidad (AVD)[4,9]. Como consecuencia, los trastornos mentales representan una constante fuente de costes directos e indirectos para el sistema sanitario, siendo objeto de atención en el desarrollo e implementación de políticas socio-sanitarias[1,2,10]. Este alto grado de AVAD conlleva el agravamiento de la percepción de salud y calidad de vida del propio paciente, así como el aumento de la carga asociada al cuidador familiar[11].

Son múltiples las teorías establecidas que tratan de esclarecer el origen de la esquizofrenia, donde la complejidad de su etiopatogenia resulta un factor determinante para el establecimiento de un adecuado, específico y eficaz abordaje terapéutico[3,12]. No obstante, a pesar de las numerosas premisas etiológicas definidas, los mecanismos glutamatérgicos (glutamato/GABA) y dopaminérgicos han adquirido una mayor magnitud en la neurogénesis de la esquizofrenia[13,14]. Del mismo modo, la evidencia actual ha puesto de relieve la importancia del nervio vago, cuya desregulación implicaría el origen y agravamiento de los trastornos mentales[15-17], convergiendo numerosos mecanismos patogénicos asociados, entre los que destacan la inflamación sistémica de bajo grado y el estrés oxidativo[12,18]. En este sentido, se entiende por inflamación sistémica de bajo grado a aquel estado latente caracterizado por la presencia de citocinas pro-inflamatorias (proteína C-reactiva -pCr-, factor de necrosis tumoral ά [FNT-ά] o interleucinas tipo 6 ó 1ß [IL-6, IL-1ß], entre otros), y al aumento de células inmunes circundantes (macrófagos, linfocitos T, etc.)[19], desembocando en un estado inflamatorio en el que no se induce lesión o pérdida de funciones primarias del tejido infiltrado (principal rasgo distintivo)[20]. Por otro lado, el estrés oxidativo es definido como el desequilibrio existente entre agentes oxidantes y la carencia de productos antioxidantes que permitan paliar el estado oxidativo resultante[21]. La combinación de los mecanismos anteriormente descritos, y dada la singular sensibilidad del tejido nervioso a éstos, conlleva la degeneración y pérdida de la funcionalidad neuronal, agravando trastornos mentales subyacentes o siendo causa incipiente de éstos[22].

La relevancia descrita que adquiere el nervio vago se encuentra íntimamente ligada al papel de la microbiota intestinal (MI), siendo la principal vía de comunicación entre ésta y el sistema nervioso central (SNC)[17]. No obstante, esta conexión no es exclusiva, existiendo otras rutas de comunicación secundarias, como son las hormonas intestinales, citoquinas, exosomas y micro ARNs[18,23,24]. La MI es responsable de múltiples funciones vitales, entre las que destacan: el desarrollo y maduración del SNC, la nutrición, la respuesta inmune o inflamación sistémica, entre otros[12,17,18,24]. La concentración de la flora intestinal (considerando concentraciones normales alrededor de 10^{13}UFC/g)[25] se encuentra determinada por los propios patrones dietéticos del individuo (principal), así como por factores genéticos, antibioterapia iatrogénica (en especial,

antibióticos de amplio espectro), tipo de lactancia (materna o de fórmula), edad, ejercicio y estrés continuo, entre otros[23,25-28]. Así, la existencia de posibles modificaciones en la concentración de dicha biota puede desencadenar alteraciones homeostáticas o agravar estados patogénicos en el organismo, hecho comúnmente denominado *disbiosis*[23,27,29].

Con ello, surge el concepto del "*Eje Microbiota-Intestino-Cerebro*", término utilizado para hacer mención a la comunicación bidireccional establecida entre el SNC, tracto gastrointestinal y la MI[24,25,28]. Su conexión se encuentra condicionada por los propios metabolitos microbianos de productos dietéticos, entre los que destacan: fibra alimentaria, triptófano o arginina, así como por mecanismos endocrinos (péptidos hormonales) y neuronales[26,30]. Respecto a estos últimos, la íntima relación que se establece entre la MI y el SNC radica en la producción de multitud de neurotransmisores indispensables para el adecuado funcionamiento neuronal: serotonina, ácido glutámico (precursor del GABA), dopamina o noradrenalina, etc., responsables del equilibrio neural excitatorio-inhibidor, estado de ánimo, aprendizaje o funciones cognitivas[18,28,31]. Del mismo modo, la MI ejerce importantes funciones tróficas, metabólicas y de protección, que suponen un factor determinante en el normo-funcionamiento neuropsiquiátrico del organismo[28,31].

Así, según la teoría de inflamación sistémica de bajo grado, cuando se produce un estado de disbiosis en la MI simbionte, éste genera una cascada de agentes proinflamatorios, donde destaca el lipopolisacárido[17-20], endotoxina bacteriana capaz de modificar tanto la integridad como la propia permeabilidad de los enterocitos en la luz intestinal[29]. Esta alteración desencadena la liberación de citoquinas proinflamatorias (FNT-ά, pCr o IL-6, IL-1ß)[12,18,19] capaces de alterar la integridad del tejido intestinal, originando sinergias entre inflamación, incremento del estrés oxidativo y desequilibrio de la homeostasis energética[19-22]. Finalmente, esta cascada de reacciones provoca un incremento de la neurodegeneración y excitotoxicidad, mediada por el nervio vago[12,19,22-24]. Con ello, se ha evidenciado que la activación de un estado de bajo grado de inflamación se relaciona con un peor pronóstico de la esquizofrenia respecto a síntomas positivos y negativos, rendimiento cognitivo y pérdida del volumen cerebral[12,30]. Del mismo modo, se han descrito alteraciones en *marcadores de estado*, citoquinas proinflamatorias específicas (IL-6 o factor de crecimiento transformante ß [TGF-ß])[12], ante recaídas psicóticas o fases prodrómicas, así como la disminución de su concentración sérica tras la instauración de tratamiento antipsicótico, evidenciando la consiguiente mejoría psicopatológica[30].

1.2. Justificación

La producción científica evidencia una elevada tasa de discapacidad, morbilidad y mortalidad en aquellas personas que padecen algún tipo de trastorno psiquiátrico en comparación

con la población clínica general[32,33]. Esta diferencia es particularmente significativa en aquellos pacientes con TMG, especialmente en esquizofrenia[32-35]. Se calcula que la tasa de morbimortalidad en la población psiquiátrica es hasta un 20% superior y, cuantitativamente, representa una media de 15 años de vida perdidos[32,33,35], mermando notablemente la esperanza de vida de este colectivo (hasta un 20%)[32,35]. Del mismo modo, se estima que el riesgo relativo de mortalidad por causas naturales en TMG es hasta 2,4 veces mayor respecto a la población general[33,36], íntimamente relacionada con enfermedades cardiovasculares, infecciosas, respiratorias y endocrinas[33-34], y siendo el suicidio la primera causa de muerte no natural[36]. Sin embargo, no sólo los factores físicos condicionan la morbimortalidad descrita, siendo preciso remarcar la importancia de los aspectos culturales, cognitivo-emocionales o espirituales, considerados como factores protectores o de riesgo determinantes en salud mental[37].

Referente a las múltiples causas de defunción enunciadas, la instauración del síndrome metabólico (SM) alcanza una prevalencia superior al 30% en los trastornos esquizofrénicos[38] y representa hasta el 60% de las muertes prematuras en la población psiquiátrica[23,33]. La relevancia del SM se encuentra determinada por los numerosos factores de riesgo cardio-metabólicos que engloba, existiendo un consenso armonizado sobre los criterios que lo conforman, siendo éstos: predisposición a la resistencia de insulina e hiperglucemia, aumento de peso, hipertensión arterial, dislipidemia aterogénica (hipertrigliceridemia, reducción del colesterol HDL y aumento del colesterol LDL) y estado protrombótico[39]. El SM es considerado un factor determinante en la salud física del paciente, triplicando la incidencia de enfermedades cardio-metabólicas (hipertensión arterial, diabetes mellitus, cardiopatía isquémica, etc.), y representa uno de los principales problemas de salud pública del siglo XXI[35,40].

Así, los principales determinantes etiopatogénicos del SM en los trastornos del espectro esquizofrénico se encuentran condicionados por las características inherentes de la propia enfermedad, factores genéticos y la resistencia a una óptima atención en términos de salud física y estilos de vida (principal)[32,33,41]. Además, las dificultades de accesibilidad sanitaria y la escasa cultura preventiva y de promoción de la salud en la población psiquiátrica favorecen la resistencia descrita[32,33,41]. Sin embargo, existe un determinante crucial en el incremento del riesgo cardiovascular que, en la mayoría de las ocasiones, pasa desapercibido dentro de la atención estándar en salud mental: la modalidad terapéutica instaurada, basada en el uso de antipsicóticos de segunda generación (o atípicos), así como la existencia de una alta tasa de politerapia psicofarmacológica en TMG[32-34]. En este sentido, existen evidencia que la terapia antipsicótica (primordialmente clozapina y olanzapina), conlleva un aumento exponencial de SM iatrogénico, así como alteraciones cardio-fisiológicas y endocrinas (alargamiento del segmento QTc e hiperprolactinemia), que limitan la consecución de óptimos resultados en salud[33,34].

A pesar de la magnitud y gravedad del problema, la atención centrada en la modificación de los estilos de vida en salud mental no alcanza la relevancia terapéutica suficiente[15,42]. Este hecho podría explicarse por el claro desconocimiento de los múltiples mecanismos y factores etiológicos implicados en la neurogénesis de la esquizofrenia[3], desembocando, irremediablemente, en un abordaje multidisciplinar, pero esencialmente psicofarmacológico y psicoterapéutico[5,35,41]. En este sentido, debido a la alta tasa de morbimortalidad en trastornos del espectro esquizofrénico, resulta crucial el abordaje de los factores modificables, considerándose coadyuvante del abordaje terapéutico convencional, y habiendo demostrado eficacia en la mejora de la salud física y en el proceso de recuperación mental[41,42].

No obstante, las intervenciones dirigidas a modificar los patrones nutricionales y las conductas alimentarias desempeñan un papel minoritario en la práctica psiquiátrica tradicional[42-44]. La evidencia establece altos niveles de malnutrición y la adquisición de hábitos dietéticos poco saludables en TMG, alejados de los estándares dietéticos de referencia e ingestas diarias recomendadas (%IDR)[43,44]. En este sentido, el patrón dietético en pacientes esquizofrénicos es caracterizado por el consumo de alimentos ultraprocesados, de alta densidad energética e índice glucémico[41,45], entendiendo éstos como aquellas formulaciones alimentarias que incluyen grasas, azúcares y sal, así como múltiples aditivos que aumentan la palatabilidad del alimento[45]. Del mismo modo, existe un deficiente consumo de fibra, frutas y verduras, así como una mayor predisposición hacia la ingesta alcohólica[42,46,47]. Por último, se han demostrado bajos niveles de actividad física o, lo que es lo mismo, un alto grado de sedentarismo en la población psiquiátrica[44,48].

De este modo, la persistencia de patrones dietéticos de baja calidad nutricional en la población diana conduce a una alteración en la concentración de la MI, obteniendo como resultado una mayor propensión a la disbiosis[50]. Como se indicó anteriormente, este hecho conlleva un aumento en la producción de metabolitos pro-inflamatorios, dando lugar a un estado de inflamación sistémica de bajo grado y estrés oxidativo[17-20,22]. Como resultado, se obtiene un mayor riesgo de disfunción cardio-metabólica y psicopatológica, condicionante del nivel de plasticidad neuronal y reserva cognitiva [15,50]. Ésta última es definida como el grado de tolerancia y resistencia cerebral ante el deterioro originado por el trastorno mental subyacente, sin clínica asociada[51].

Sin duda, el desarrollo de la teoría holobionte, definida como el conjunto de organismos superiores y su microbioma, así como la evolución de la metagenómica (ciencia encargada del estudio del genoma de los microorganismos), han conllevado importantes avances en términos de *Psiquiatría Nutricional,* disciplina centrada en explorar los efectos del patrón dietético y nutrientes sobre la salud mental[18,52]. Su progreso ha puesto de relieve la importancia de los estilos

de vida modificables y la cognición emocional asociadas al patrón dietético-nutricional, impulsando la atención holística en salud mental[49,50,52]. Este hecho, junto a la identificación de nuevos patrones alimentarios de baja calidad nutricional en las diferentes sociedades occidentales, explora nuevas rutas de investigación que permitan aumentar la comprensión global sobre los mecanismos etiológicos de los trastornos neuropsiquiátricos, así como el óptimo abordaje de éstos en términos nutricionales[15].

Como resultado de los numerosos avances descritos en la última década, en la actualidad, existe un creciente esfuerzo por evidenciar el potencial que adquieren las intervenciones dietéticas en la modulación de la MI en trastornos psicóticos, a través de la utilización de *psicobióticos,* a modo de nutracéuticos[15,26,30]. Este término hace referencia al conjunto de sustancias simbióticas (prebióticos y probióticos), incluidas en productos nutricionales y complementos alimenticios[53], cuya administración conlleva beneficios para la salud en pacientes psiquiátricos[15,26]. Los probióticos (hallados en lácteos fermentados) incluyen microorganismos de la biota intestinal que, administrados en cantidades adecuadas, conllevan un beneficio para el huésped[53,54]. La evidencia actual destaca los géneros *Lactobacillus* y *Bifidobacterium*, con reportes de eficacia en cuanto a la mejora de funciones cognitivas, así como efectos ansiolíticos o antidepresivos, entre otros[12,18,25,27]. En cambio, los prebióticos favorecen el óptimo crecimiento y desarrollo del componente probiótico en el tracto gastrointestinal, a modo de sustrato, reduciendo la microbiota patógena[24,27,53]. Se encuentran conformados por fibras alimentarias no digeribles, destacando los fructooligosacáridos, oligosacáridos, inulina y pectinas, localizadas en: granos integrales, frutas, verduras de hoja verde, cebolla, etc.[18,23,28]. La ingesta de alimentos prebióticos o probióticos debe realizarse en el contexto de una alimentación equilibrada y balanceada[53].

En la actualidad, la influencia que ejercen los prebióticos y/o probióticos sobre el eje microbiota-intestino-cerebro es considerada un objeto relevante de estudio en el campo de la Psiquiatría Nutricional[52]. Así, una adecuada planificación dietética de alto contenido simbiótico en trastornos esquizofrénicos con disfunción psicopatológica y en riesgo de SM iatrogénico, podría articularse como terapia de elección en estos sujetos, mejorando los patrones clínicos alterados y las dificultades en el rendimiento vital[26,45]. Además, este abordaje permitiría mejorar estilos de vida no saludables, fomentando un mayor nivel de empoderamiento del paciente durante el proceso de recuperación y de seguimiento del plan terapéutico instaurado[42,44]. Del mismo modo, un adecuado manejo nutricional permitiría emplearse como coadyuvante de la farmacoterapia antipsicótica, proporcionando un óptimo abordaje en la prevención de enfermedades cardio-metabólicas y reduciendo el número de fármacos homeostáticos o incluso sustituyéndolos en casos de intolerancia[23,30,50].

A pesar de la relevancia descrita respecto al óptimo abordaje de los factores modificables en salud mental, la efectividad del equipo multidisciplinar representa una condición primordial en la adecuada atención del TMG[55]. En este sentido, enfermería se postula como piedra angular en la provisión de cuidados centrados en la modificación de estilos de vida, siendo relevante en enfermedades crónicas y de alta complejidad[56]. Así, dentro de las múltiples intervenciones enfermeras, el asesoramiento nutricional es reconocido como una herramienta esencial en la prevención y manejo de numerosas patologías cardio-metabólicas y procesos oncológicos, entre otros[57-59]. Sin embargo, a pesar del desafío que representa el abandono de las medidas adoptadas durante el consejo dietético ofrecido, la atención holística y de alta frecuentación brindada por la disciplina enfermera conlleva altas tasas de cumplimiento y satisfacción en el usuario[56]. Por último, resulta evidente la necesidad de fomentar el rol de la enfermería de práctica avanzada en nutrición mediante la capacitación e implementación en los diferentes ámbitos asistenciales, de especial interés en salud mental[58], así como la cooperación interdisciplinar con dietistas y nutricionistas[57,59].

En suma, el futuro del desarrollo de la Salud Mental se encuentra determinado por la necesidad de un abordaje multimodal, donde los factores modificables representan un potencial complemento en la consecución de resultados óptimos en salud[41,44,45,57]. Así mismo, el empleo de psicobióticos presenta el valor añadido de mejorar la morbimortalidad asociada a la esquizofrenia, con niveles idóneos en términos de costo-eficacia respecto a modelos de atención convencionales[57], de especial interés en el progreso de políticas socio-sanitarias[1,2].

2. Hipótesis y objetivos de estudio

2.1. Hipótesis de estudio

La integración de alimentos prebióticos y/o probióticos en el patrón alimentario convencional de trastornos del espectro esquizofrénico (en cualquiera de sus variantes), conllevaría una mejora del estado nutricional y, por consiguiente, un aumento del nivel de salud física de la población objeto de estudio. Así mismo, la modulación dietética de alto contenido simbiótico permitiría mejorar el estado psicopatológico en aquellas áreas clínicas alteradas por el trastorno mental subyacente.

2.2. Objetivos de estudio

2.2.1. Objetivo principal

Determinar la eficacia a nivel nutricional y cardio-metabólica de una intervención dietética prebiótica y probiótica en pacientes que presentan trastornos del espectro de la esquizofrenia.

2.2.2. Objetivos específicos

1) Conocer la evidencia científica existente respecto al constructo de factores (explícitos e implícitos) influyentes en el eje microbiota-intestino-cerebro.

2) Determinar el patrón dietético y estado nutricional basal en trastornos del espectro esquizofrénico.

3) Identificar los patrones dietéticos post-intervención en población objeto de estudio, esclareciendo el valor nutricional de los principales platos consumidos, así como su vinculación con el estado de salud física de los individuos.

4) Evaluar el impacto cardio-metabólico de una planificación dietética estandarizada con alto contenido prebiótico y probiótico, adaptada a las características inherentes de la población psiquiátrica.

5) Evaluar el impacto psicopatológico de la incorporación de prebióticos y probióticos en el patrón dietético-nutricional habitual en pacientes con diagnóstico de trastorno del espectro de la esquizofrenia.

6) Desarrollar y validar un programa que permita la detección de áreas de mejora, estableciendo estrategias de valoración y un plan de actuación pertinentes en Salud Mental, que permitan una adecuada atención dietética mediante el uso de psicobióticos.

3. Resultados

3.1. Capítulo I

Eficacia de la educación nutricional para el aumento de la ingesta de simbióticos sobre el estado nutricional y metabólico en los trastornos del espectro esquizofrénico: Un protocolo de dos brazos

Sevillano-Jiménez A, Molina-Recio G, García-Mellado JA, García-Rodríguez M, Molina-Luque R, Romero-Saldaña M. Efficacy of nutrition education for the increase of symbiotic intake on nutritional and metabolic status in schizophrenic spectrum disorders: A two-arm protocol. Front Nutr. 2022;9:912783. DOI: 10.3389/fnut.2022.912783

frontiers | Frontiers in Nutrition

TYPE Study Protocol
PUBLISHED 10 August 2022
DOI 10.3389/fnut.2022.912783

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 21 April 2022
ACCEPTED 07 July 2022
PUBLISHED 10 August 2022

CITATION
Sevillano-Jiménez A, Molina-Recio G, García-Mellado JA, García-Rodríguez M, Molina-Luque R and Romero-Saldaña M (2022) Efficacy of nutrition education for the increase of symbiotic intake on nutritional and metabolic status in schizophrenic spectrum disorders: A two-arm protocol.
Front. Nutr. 9:912783.
doi: 10.3389/fnut.2022.912783

Efficacy of nutrition education for the increase of symbiotic intake on nutritional and metabolic status in schizophrenic spectrum disorders: A two-arm protocol

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Background/Objectives: The microbiota plays a vital role in the two-way communication between the gastrointestinal tract and numerous neuropsychiatric disorders, such as schizophrenia. Besides, the microbiota modulation through the use of psychobiotics (prebiotics and probiotics with nutraceutical action) is related to the improvement of the physical and psychopathological health. The objective to this study was to test the efficacy of prebiotic/probiotic dietary modulation in patients diagnosed with schizophrenia, attending to the nutritional and cardio-metabolic impact.

Methods: Two-arms, double-blind, randomized in balanced blocks clinical trial of 6 months of intervention, will be developed in a group of 50 individuals. The control group will receive conventional dietary advice individually from specialized mental health nurses. In the intervention group, an individual dietetic-nutritional education program with high prebiotic and probiotic content (dairy and fermented foods, green leafy vegetables, high-fiber fruit, whole grains, etc.) will be developed by these nurses. Data will be collected on the psychopathological state, and blood test (at the beginning, at 3 and 6 months). The estimation of intestinal microbiota and the usual nutritional pattern will also be assessed at the beginning and 6 months, using a stool test. To evaluate the degree of adherence, the intervention group will fill a specific weekly record of the main dishes/food consumed. Anthropometric parameters will also be analyzed monthly.

Discussion: The study is anticipated to establish feasibility an adequate dietary modulation with a high simbiotic content, leads to a significant improvement in the nutritional status and cardio-metabolic. Furthermore, it is presumed to reach a degree of evidence that allows establishing nutritional management

as an effective therapeutic intervention in the psychopathological treatment of patients with schizophrenia spectrum disorders.

Clinical Trial Registration: [www.ClinicalTrials.gov], identifier [NCT04366401].

KEYWORDS

prebiotic, probiotic, schizophrenia spectrum and other psychotic disorders, diet therapy, mental health

Background

Schizophrenia is a chronic mental illness characterized by significant clinical heterogeneity and a long evolution over time, determined by periods of psychotic exacerbation and phases of stabilization (1–3). The semiology of this nosological entity is established in positive and negative symptoms, with variable levels of dysfunction and clinical presentation, and having an essential impact on the patient's quality of life (2, 4). Similarly, surrounding the schizophrenic spectrum, the existence of the associated neurocognitive impairment stands out, prevailing the disorders of social and occupational functioning, as well as a significant degree of disorganization (2, 3, 5, 6).

Many theories have tried to elucidate the origin of schizophrenia, where the complexity of its etiopathogenesis is a determining factor in establishing an appropriate, specific, and effective therapeutic approach (1, 7). In this sense, despite the numerous etiological premises, the glutamatergic (glutamate/GABA) and dopaminergic hypotheses have acquired greater strength in the development of schizophrenia (8, 9). In addition, however, recent studies have highlighted the theory of vagus nerve dysregulation as a possible etiological factor in the origin and aggravation of mental disorders (1, 5, 10), with numerous associated pathogenic mechanisms, particularly low-grade systemic inflammation and oxidative stress (7, 10, 11).

Undoubtedly, the traditional therapeutic approach has perceived the role of nutrition as a minor intervention in psychiatry, especially in psychotic disorders such as schizophrenia (12). However, the advances established in the last decade, mainly associated with the development of the holobionte theory and the evolution of metagenomics (11, 13), as well as the presence of new dietary patterns of low nutritional quality in different western societies (1, 3), have contributed significantly to the global understanding of the role of nutritional patterns on the functioning of the Central Nervous System (CNS), as well as on the possible mechanisms or etiological pathways of psychiatric disorders (1, 11, 12, 14).

In this regard, it is necessary to highlight the role of the intestinal microbiota (IM) and the intimate relationship it exerts on the numerous functions of the body, such as the development and maturation of the CNS, nutrition, immune response or systemic inflammation (7, 11, 12, 15). This effect is carried out through various established communication pathways: vagal nerve (primary), intestinal hormones, cytokines, exosomes, and microRNAs (10, 14–16). Thus, the existence of possible modifications in the concentration of this biota (considering average concentrations around 1,013 CFU/g) (17, 18), may trigger homeostatic alterations or aggravate pathogenic conditions, a fact commonly called dysbiosis (11–13, 17, 19). This concentration of microbiota is fundamentally determined by dietary patterns, genetic factors, iatrogenic antibiotherapy [highlighting the broad-spectrum ones, reducing the potential for small intestinal bacterial overgrowth (SIBO)], type of breastfeeding (maternal or formula), age, exercise, and continuous stress, among others (10, 18–20).

As a consequence of these discoveries, the concept of the "*Microbiota-Intestine-Brain Axis*" emerges. This term refers to the two-way communication pathway established between the CNS, the gastrointestinal tract, and the IM (1, 13–15, 18), mediated by the microbial metabolites of dietary products such as dietary fiber, tryptophan or arginine, as well as by endocrine and neuronal mechanisms (19, 21). The close relationship established between IM and the CNS lies in the production of a multitude of neurotransmitters essential for normal neuronal functioning, such as serotonin, GABA, dopamine or noradrenaline, among others (11–13, 19, 22). Similarly, IM exerts essential trophic, metabolic, and protective functions, which are a determining factor in the normal neuropsychiatric function (17, 22).

Thus, according to the theory of low-grade systemic inflammation, when a state of dysbiosis occurs in the symbiote IM, it generates a cascade of pro-inflammatory agents, such as lipopolysaccharide (10, 11, 23), a bacterial endotoxin, capable of modifying both the integrity and the permeability of enterocytes (12). This alteration triggers the release of pro-inflammatory cytokines [tumor necrosis factor $\acute{\alpha}$ (TNF-$\acute{\alpha}$) or interleukins type 6 or 1β (IL-6, IL-1β) (7, 11), both capable of altering intestinal tissue integrity], originating synergies between inflammation, increased oxidative stress and imbalance of energetic homeostasis. This cascade of reactions

causes an increase in neurodegeneration and excitotoxicity, mediated by the vagus nerve (7, 12, 15). Thus, it has been shown that the activation of a state of low inflammation is related to a worse prognosis of schizophrenia concerning positive and negative symptoms, cognitive performance, and loss of brain volume (7, 21, 24). Similarly, alterations in specific pro-inflammatory cytokines or state markers have been described, especially in psychotic relapses or prodromal phases (IL-6, TGF-β, among others) (7, 10), as well as a decrease in their concentration after the introduction of antipsychotic treatment, with consequent clinical improvement (21).

Justification

Existing scientific production shows a high rate of disability and morbimortality in people suffering from some psychiatric disorder concerning the rest of the general clinical population, especially in those patients with a severe and long-term mental disorder (LTMD) (1, 12, 14, 24–28), highlighting dysfunctions of the psychotic and affective spectrum: schizophrenia and bipolar disorder, (respectively) (24, 27). This morbidity and mortality rate in the psychiatric population is up to 20% higher and, quantitatively, represents an average of 25 years of life lost (24–27, 29). Besides, patients with LTMD have a life expectancy of less than 20% (57 years in men and 65 years in women) (14, 25). It is estimated that the relative risk of this disease is 2.41 higher for mortality from any causes (24), these being mainly comprised of cardiovascular, infectious, respiratory, and endocrine diseases (60% of premature deaths in this clinical population) (14, 25, 30). Also, the leading established causes of mortality are closely linked to the development of the Metabolic Syndrome (MS) (1, 3, 25–28, 31–33), also called insulin resistance syndrome (24, 33). The MS is considered a determining factor in the physical health of the patient, tripling the incidence of cardio-metabolic diseases (27–29).

The main etiopathogenic determinants of this fact are the factors inherent to the disease itself, as well as genetic factors (3, 24–26, 34) and resistance to adequate care in terms of physical health (27, 33, 35). However, the main modifiable risk factor in the LTMD population lies in the acquisition of unhealthy lifestyles, characterized by high-energy dietary patterns, with high consumption of ultra-processed foods and low fruit and vegetable intake (36). In addition, the psychiatric population has low levels of physical activity, with increased rates of smoking and associated substance abuse (3, 27, 37, 38).

Despite the magnitude and severity of the problem, interventions aimed to modify lifestyles do not play an essential role in therapy and are not part of the usual clinical practice with the psychiatric population (1, 27, 31, 33). This fact could be explained by the lack of understanding of the multiple mechanisms and etiological factors involved in the neurogenesis of schizophrenia (2), and leads to a multidisciplinary approach, but essentially psychopharmacological and psychotherapeutic (33, 39). It is, therefore, vital to address modifiable factors such as dietary patterns, which have evidenced to be an efficient therapeutic intervention to improve both the psychopathological dysfunction and the physical health of the subjects and can be considered as an addition to the conventional therapeutic approach (1, 3, 7, 17, 40).

In this sense, some dietary interventions carried out to modulate intestinal microbiota in psychotic disorders through the use of so-called "psychobiotics" (1, 17–22). This term refers to the set of substances that include probiotics and/or prebiotics and whose administration causes health benefits in psychiatric patients (20–22). 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) (1, 7, 8, 12, 16–21). On the other hand, prebiotics are non-digestible dietary fiber (mainly fructooligosaccharides and oligosaccharides, inulin or pectins) (1, 17), which are substances that promote optimal growth and development of probiotics in the gastrointestinal tract, reducing pathogenic microbiota (7, 12, 15, 19), through the production of short-chain fatty acids (17, 21).

It is worth noting the growing effort to highlight the role played by prebiotics and or probiotics in the microbiota-intestine-brain axis, which is currently a relevant object of study (1, 22, 41).

In this regard, according to Patra (19) and Teasdale et al. (37), adequate dietary planning in psychiatric patients with psychopathological dysfunction and at risk of iatrogenic metabolic syndrome, could be considered as a therapy of choice in these subjects, improving altered clinical patterns and difficulties in the patient's vital and functional performance. Similarly, adequate nutritional management could be used as an adjunct to antipsychotic pharmacotherapy and the cardio-metabolic approach, reducing the number of homeostatic drugs or even replacing them in cases of intolerance in the target population (14, 39).

In short, the future of the development of Mental Health is determined by the need for a multimodal approach, where nutritional factors represent the cornerstone in achieving optimal results in health, level of functionality, and, therefore, quality of life of patients (35, 42).

Likewise, dietary advice on modulation with high prebiotic and probiotic content has the added value of improving the morbidity and mortality associated with schizophrenia, with optimal levels in terms of cost-effectiveness, better than those shown by the approaches currently used.

Methods/design

Study aims

Main objective

Determination of the nutritional and cardio-metabolic efficacy of a prebiotic and probiotic dietary intervention in patients with schizophrenia spectrum disorders.

Specific objectives

- To determine the baseline nutritional status of the target population.
- To identify the usual dietary patterns in this population, clarifying the nutritional value of the main dishes consumed, as well as their link with the physical health status of individuals.
- To know the existing scientific evidence regarding the construction of determinants (explicit and implicit) that influence the microbiota-intestine-brain axis.
- To evaluate the psychopathological impact of the incorporation of prebiotics and probiotics in the habitual dietetic-nutritional pattern in patients diagnosed with the spectrum of schizophrenia.
- To evaluate the cardio-metabolic impact of a standardized dietary planning with high prebiotic and probiotic content, adapted to the inherent characteristics of the psychiatric population.
- To develop and validate a program that allows for the detection of areas of improvement, establishing assessment strategies, and an appropriate action plan in Mental Health, which allows for adequate dietary care through the use of psychobiotics.

Study design

A two-arms, double-blind, randomized in balanced blocks clinical trial of 6 months of intervention, will be carried out in psychiatric patients diagnosed with schizophrenic spectrum disorders (without distinction by type). The control group (CG) will be made up of those participants who will receive conventional dietary advice (43) on an individual basis. In the intervention group (IG), this advice will be established individually through intensive nutritional guidance (44) offering a food pattern with a high prebiotic and probiotic content. In both intervention groups, educational material of visual support will be used during the sessions. The dietary intervention will be designed and supervised by qualified personnel with recognized competencies for this intervention (nurses and dietitians), carried out by specialized mental health nurses, and will be agreed upon through serial interviews and focus groups. In this sense, these focus groups will be applied to improve the established dietetic-nutritional intervention, guaranteeing its correct adaptation, according to the study population.

The study will begin with a group session for the presentation of the research project in the health center and/or psychiatric service consultation. During the development of the study, data will be collected on the psychopathological state [Positive and Negative Syndrome Scale (PANSS) (45) and Personal and Social Functioning Scale (PSP) (46) scales; **Supplementary Tables 1, 2**], and blood test (hemogram, lipid profile, etc.). Measures will be taken at the beginning (basal), at 3 and 6 months. The estimation of intestinal microbiota and the usual nutritional pattern will also be assessed at the beginning and 6 months, using a stool test and a validated Food Frequency Questionnaire (FFQ) (47), respectively. The use of the FFQ will allow us to know both the average intake of grams of fiber, fat, etc. and the frequency of consumption by food groups (with particular attention to fermented foods). However, the main reason for using this tool is that it will allow us to assess changes in dietary patterns over the medium term (39). To evaluate the degree of adherence, participants in the IG will fill a specific weekly record of the main dishes/food consumed with a high prebiotic and/or probiotic content will be measured by the weekly completion (during the 6 months of intervention) of a record that includes the main foods consumed with a high symbiotic value (fermented foods, whole grains, green leafy vegetables, fruit, etc.) (**Supplementary Figure 1**). This record will be completed by the patients themselves or, in cases of incapacity or lack of autonomy in preparing the dishes consumed by family members or the primary caregiver. At least, anthropometric parameters will also be analyzed monthly (BMI, blood pressure, heart rate, abdominal perimeter) (**Supplementary Table 3**).

Selection of participants

For the assessment of the method's effectiveness, a sample size of 22 individuals has been estimated (11 for the IG and 11 for the CG, with a power of 80% and a confidence of 95%, expecting a risk/prevalence difference of 63% post-intervention (48). The final size of 50 individuals has been established (25 for the IG and 25 for the GC) to minimize the effect of possible losses and the low study completion rates, especially in participants with significant negative symptoms. Participants who express a clear wish to participate voluntarily in the study will be assigned, through randomization in balanced blocks, to the IG or CG (**Figure 1**). Randomization will be conducted according to the results found in stool culture analysis (balancing the prevalence of dysbiosis in both groups).

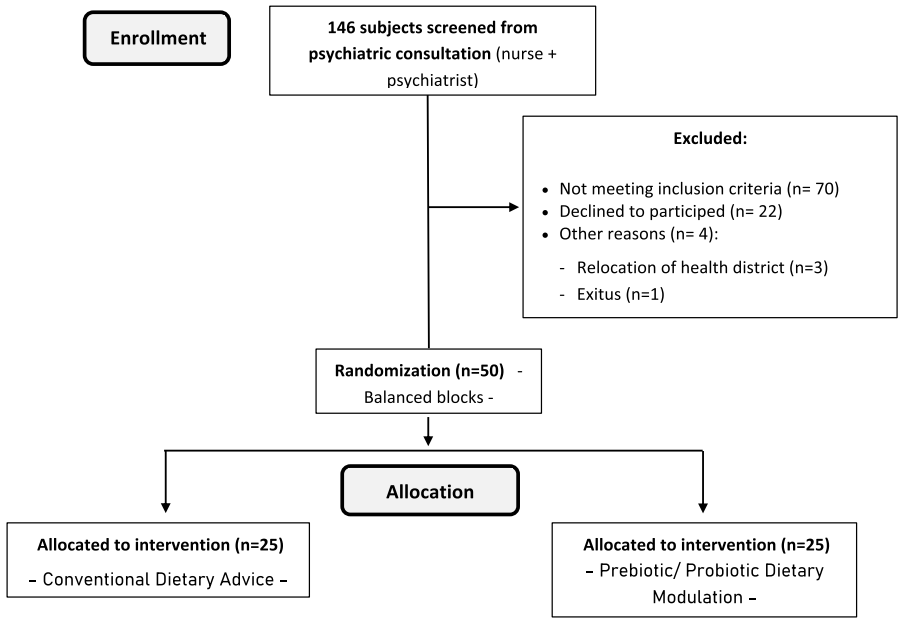

FIGURE 1
Flow chart of the participants (CONSORT diagram).

Concerning the established inclusion/exclusion criteria, these will be:

Inclusion criteria

- Patients diagnosed on the spectrum of schizophrenia (without distinction by type), according to criteria DSM-5 and/or ICD-11.
- Age between 18 and 65 years.
- Absence of gastrointestinal comorbidity that contraindicates the use of prebiotics and/or probiotics (intolerance, explosive diarrhea, acute abdominal pain, etc.).
- To show clinical stability for 6 months before the start of the study (absence of psychiatric hospitalization, maintenance of the level of functionality, and lack of social and occupational absenteeism).
- To manifest agreement to participate in the study and to sign of informed consent (**Supplementary Appendices I–III**).

Exclusion criteria

- To suffer from somatic or neurocognitive situation that prevents participation and collaboration in the fulfillment of the protocol.
- To follow standardized dietary planning not modulated by the population under study (catering, institutional or collective feeding, etc.).
- Concomitant administration of antibiotherapy during the intervention phase.
- Refusal to participate in the study.

Study variables

Result variables

Clinical efficacy of prebiotic/probiotic dietary modulation

- Scale for Positive and Negative Schizophrenia Syndrome (45) (categorized PANSS): discrete.
- Personal and Social Functioning Scale (46) (categorized PSP) outcome: discrete.

Tolerability and modulation of the nutritional dietary pattern

- Food Frequency Questionnaire (FFQ) (47) result: continuous
- Culinary knowledge and responsibility for feeding: nominal.

Anthropometric variables and physical health

Weight (kg, continuous), height (cm, continuous), BMI (kg/m^2, continuous) abdominal circumference (cm, continuous), systolic blood pressure (mmHg, continuous),

TABLE 1 Blood test variables: Abbreviations.

	Abbreviation	Meaning
Hematological profile	M.C.V	Mean corpuscular volume
	H.C.M	Mean corpuscular hemoglobin
	M.C.H.C	Mean corpuscular hemoglobin concentration
	R.D.W	Red cell distribution width
	M.P.V	Mean platelet volume
Biochemical profile	ALT	Alanine transaminase
	GPT	Glutamic pyruvic transaminase enzyme
	G-GT	Gamma-glutamyl transferase
	ALP	Alkaline phosphatase
	Na^+	Sodium
	K^+	Potassium
	Cl^-	Chlorine
	Ca^{2+}	Calcium
	HbA1c	Glycosylated hemoglobin
	IFCC	International federation of clinical chemistry and laboratory medicine
	Fe^{2+}	Iron
	FRT	Ferritin
	LDH	Lactate dehydrogenase
	C-HDL	High-density lipoprotein
	C-LDL	Low-density lipoprotein
	TSH	Thyroid stimulating hormone
	PRL	Prolactin
	LUES	Syphilis
	HCV	Hepatitis C virus
	HAV	Hepatitis A virus
	HIV	Human immunodeficiency virus

diastolic blood pressure (mmHg, continuous), heart rate (ppm, discrete).

Blood test variables

- *Hematological profile*: Red blood cells (x10e^6/mm^3, continuous), hemoglobin (g/dL, continuous), hematocrit (%, continuous), M.C.V. (fL, discrete), H.C.M. (pg, discrete), C.H.C.M. (g/dL, discrete), R.D.W (%, continuous), leukocytes (×10e^3/mm^3, discrete), neutrophils (×10e^3/m, continuous), lymphocytes (×10e^3/m, continuous), monocytes (×10e^3/m, continuous), eosinophils (×10e^3/m, continuous), basophils (×10e^3/m, continuous), platelets (×0e^3/mm^3, discrete), M.P.V. (fL, discrete). See **Table 1** for abbreviations corresponding to the blood test variables.
- *Biochemical profile.* ALT/GPT (IU/L, discrete), G-GT (IU/L, discrete), FAL (IU/L, discrete), Na^+/K^+ (mEq/L, discrete/continuous, respectively), Cl^- (mEq/L, continuous), Ca^{2+} (mEq/L, continuous), urate (mg/dL, continuous), glucose (mg/dL, discrete), HbA1c (%, continuous), HbA1c IFCC (mmol/mol, continuous), fructosamine (mcmol/L, discrete), creatinine (mg/dL, continuous), Fe^{2+} (mcg/dL, discrete), FRT (mcg/dL, discrete), folate (mcg/dL, continuous), vit.B12 (ng/mL, discrete), vit.D total (D2 + D3) 25-OH (ng/mL, discrete) cholesterol (mg/dL, discrete), triglycerides (mg/dL, discrete), LDH (IU/L, discrete), C-HDL (mg/dL, discrete), C-LDL (mg/dL, discrete), total cholesterol/C-HDL (mg/dL, discrete), glomerular filtrate estimation (mL/m/173, discrete), TSH (mU/L, continuous), PRL (ng/dL, continuous), LUES (IU/L, nominal/discrete), a-HAV-M (IU/L, nominal/discrete), a-HCV (IU/L, nominal/discrete), HBsAg (UI/L, nominal/discrete), a-HBC-IgG (UI/L, nominal/discrete), a-HBs (UI/L, continuous), a-HIV (mcL, nominal/discrete).

Stool variables

Stool culture

General bacteriology. Usual mixed flora: Lactobacillus (CFU/g, continuous), Bifidobacterium (CFU/g, continuous)//Disbiosis: *Salmonella* spp. (nominal, Presence/absence), *Shigella* spp. (nominal, presence/absence), *Yersinia* spp. (nominal, presence/absence), Hafnia alvei (nominal, presence/absence), *Aermonas* spp. (nominal, presence/absence), *Campylobacter* spp. (nominal, presence/absence).

Independent variables

Sociodemographic variables

Age (continuous), gender (nominal), legal representative (nominal), household composition (nominal), economic level (ordinal), level of studies (ordinal), area of residence (nominal).

Therapeutic variables

Previous antipsychotic (nominal), the dose of antipsychotic (mg, continuous), the reason for a change in antipsychotic treatment (nominal).

Clinical variables

Type of psychotic disorder (nominal), duration of illness (continuous), age of first hospitalization (continuous), number of previous hospitalizations (discrete), number of previous relapses (discrete), number of previous suicidal behaviors (discrete), number of subsequent hospitalizations (discrete), number of subsequent relapses (discrete), number of subsequent suicidal behaviors (discrete), number of subsequent unscheduled consultations (discrete), substance abuse (nominal), type of substance (nominal), associated cardio-metabolic diagnosis (nominal).

Anthropometric measurements will be collected following the recommendations of the Manual of Standardized

Anthropometry (49). Weight, height, and BMI shall be measured with an SECA® 703s stadiometer and scale, with an accuracy of 0.1 kg and 0.1 cm, respectively. The abdominal perimeter shall be determined at the midpoint between the last rib and the iliac crest at the end of a normal expiration. The WelchAllyn® ProBP 2,400 digital sphingomanometer shall be used for the study of blood pressure and heart rate.

Statistical analysis

Quantitative variables will be presented with mean and standard deviation, and qualitative variables will be shown in frequencies and percentages.

The Kolmogorov-Smirnov test will be used to compare the goodness of fit to a normal distribution of data from quantitative variables. For the contrast of bivariate hypotheses, the Student *t*-test will be performed for two means, while for qualitative variables, the Chi-Square and Fisher's exact test will be used, when necessary. Likewise, for the analysis of three or more means, the ANOVA of repeated means will be used. On the other hand, the correlation between quantitative variables will be verified through the Pearson's coefficient r. When the normality or homoscedasticity criteria are not met, non-parametric versions of the above tests will be performed.

Logistic regressions will be carried out to determine which variables can determine the improvement of the nutritional pattern and physical health through the FFQ (47), as well as blood and stool analytical values. Similarly, this analysis will be established concerning the psychopathological status through the PSP (46) and PANSS (45) scales, both of which have a discrete quantitative and nominal result values, according to established cut-off points and clinical interpretation. Raw and adjusted odds ratios will be calculated. Log-likelihood, the goodness of fit statistic, Cox and Snell R2, Nagelkerke R2, and Hosmer-Lemeshow tests should be used to assess the overall model fit. The exponentiation will be used to calculate the beta coefficients.

These multivariate tests will allow us to identify and adjust for the possible confounding effect of the independent variables on the outcome variables.

For all statistical analyses, an alpha error probability of less than 5% ($p < 0.05$) will be accepted, and the confidence interval will be calculated at 95%. The software SPSS (version 25.0) and EPIDAT (version 4.2) shall be used for the statistical analysis.

Work plan

An intervention schedule has been established, with a total duration of 6 months, which is divided into three blocks:

Block 1

This first block focuses on the selection of the target population according to inclusion criteria. Firstly, a group session to present the program and the methodology of the study will be carried out. During the first 15 days of the study, a focus group with professionals to reach a consensus on the intervention will be held. Subsequently, the appropriate modifications will be made to improve and adapt to the dietary and nutritional intervention.

Consequently, the recruitment and initial psychopathological and nutritional assessment of the participants will be carried out, using the PANSS (45) and PSP (46) scales. For the nutritional evaluation, the analytical and anthropometric basal determination of the participating patients will be carried out, as well as the evaluation of the habitual dietary pattern through a validated FFQ (47) and weekly record of the main dishes and foods consumed. Similarly, an estimate of the intestinal bacterial flora is required employing stool culture.

Block 2

The second block includes the implementation of the 6-month individual nutrition education program (associated with 2 months of educational reinforcement, according to block 3). It will consist of eight sessions, the first four being biweekly, followed by 4 monthly, to which four sessions of educational reinforcement will be added to the 3 and 5 months of study. The minimum duration of each session has been established for 30 min. However, this length could be different, considering the characteristics of the participants. The control group will be made up of those participants who will receive standardized dietary advice (35). In this sense, the education content in the intervention group will be based on general principles of conventional dietary advice in an intensified manner (36), centered on the acquisition of specific knowledge about: (I) Underlying mental pathology, lifestyles and associated comorbidities; (II) Immediate principles: Carbohydrates, lipids, proteins, fiber, vitamins, and minerals; energy needs; consumption requirements; (III) Water requirements; (IV) Foodstuff; (V) Description and justification of prescribed prebiotic and probiotic diet; (VI) Culinary techniques: conservation of properties of the prebiotic and probiotic diet; (VII) Optimal distribution and interchange of foods with high prebiotic and probiotic content; (VIII) Feeding in particular situations.

In both the IG and the CG, visual support resources will be used during the development of the established sessions.

Block 3

Finally, to evaluate the effectiveness of the intervention, the modification in the nutritional, the cardio-metabolic, and the psychopathological area will be assessed. For doing this, researchers will carry out anthropometric determination, clinical evaluation, the performance of stool culture, and the study of the dietary pattern, as we commented above.

Likewise, in this block, an educational reinforcement (both in IG and CG) of what was treated in Block 2 will be offered, 3 and 5 months after the beginning of the block, every 15 days for the IG and monthly for the CG.

Once the intervention is concluded, the analysis of the collected data will be performed, culminating in the development of the scientific production and the writing of the research report.

Discussion

Firstly, it is expected to obtain the necessary information for the determination of the optimal dietary pattern for those participants in the study, thus allowing the development of a nutritional intervention with high prebiotic and probiotic content, appropriate for the population under study.

Likewise, the aim is to ensure that all participants improve their health status through the adaptation of the feeding pattern, developing adherence to healthier lifestyles adapted to the conditions of each patient.

Finally, it is expected to demonstrate that an adequate dietary modulation with a high prebiotic and probiotic content, leads to a significant improvement in the nutritional status and, therefore, the cardio-metabolic, of the participants, mediated by the microbiota-intestine-brain axis. Furthermore, it is presumed to reach a degree of evidence that allows establishing nutritional management as an effective therapeutic intervention in the psychopathological treatment of patients with schizophrenia spectrum disorders, in any of its variants.

Limitations

Potential limitations lie in the sample size of subjects included during the recruitment phase, the possible loss or non-cooperation of participants, and the loss or non-cooperation of participants in the intervention phase (especially those subjects with a predominance of negative schizophrenia symptomatology). This fact can lead to a possible lack of representativeness of the target population. Thus, to reverse this situation, the recruitment of the target population will be increased (more than doubled).

Likewise, the lack of capacity to prescribe symbiotic formulas and placebo management by mental health nurses, according to the legislative context in which the study will be carried out, prevents us from knowing the accurate range that an intervention with a high symbiotic content could have on these patients. Nevertheless, it is essential to emphasize that the main objective of the intervention is to assess the efficacy of a strategy based on health education. This tool is very cost-effective and is available for nursing professionals. Furthermore, from our perspective, this intervention can significantly impact the lifestyle habits of these patients in a sphere that has been forgotten as part of the traditional treatments.

Finally, the available evidence on the object of study makes it difficult to contrast the results obtained in different contexts of application.

Ethics statement

The study will be carried out respecting the fundamental principles established in the Declaration of Helsinki (1964)50, the Council of Europe Convention on Human Rights and Biomedicine (1997)51, the UNESCO Universal Declaration on the Human Genome and Human Rights (1997)52. The 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 on the platform clinicaltrials.gov (NCT04366401). This research also has the permission of the Zamora Health Area Drug Research Ethics Committee at the Regional Government of Castile and León, Spain (No. reg. 468). All the information analyzed by the principal investigator of this study is subject to the maintenance of professional secrecy. In any case, each participant will be assigned a code as a registry, where all the comparative data will be mechanised in an anonymous way, delimiting the access to the database only to the personnel linked to the development of the study, previous authorisation of the investigator in charge of it.

Author contributions

AS-J, GM-R, MG-R, and MR-S contributed to the conception and design of the study. AS-J, GM-R, JAG-M, RM-L, and MR-S contributed to the acquisition, analysis, and interpretation of results. AS-J and GM-R drafted the manuscript. AS-J, GM-R, and MR-S critically revised the manuscript. All authors contributed and approved the submitted version and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

Acknowledgments

This publication is partially funded by the National Association of Nutrition and Dietetic Nurses (ADENYD) Nursing Research Award.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.912783/full#supplementary-material

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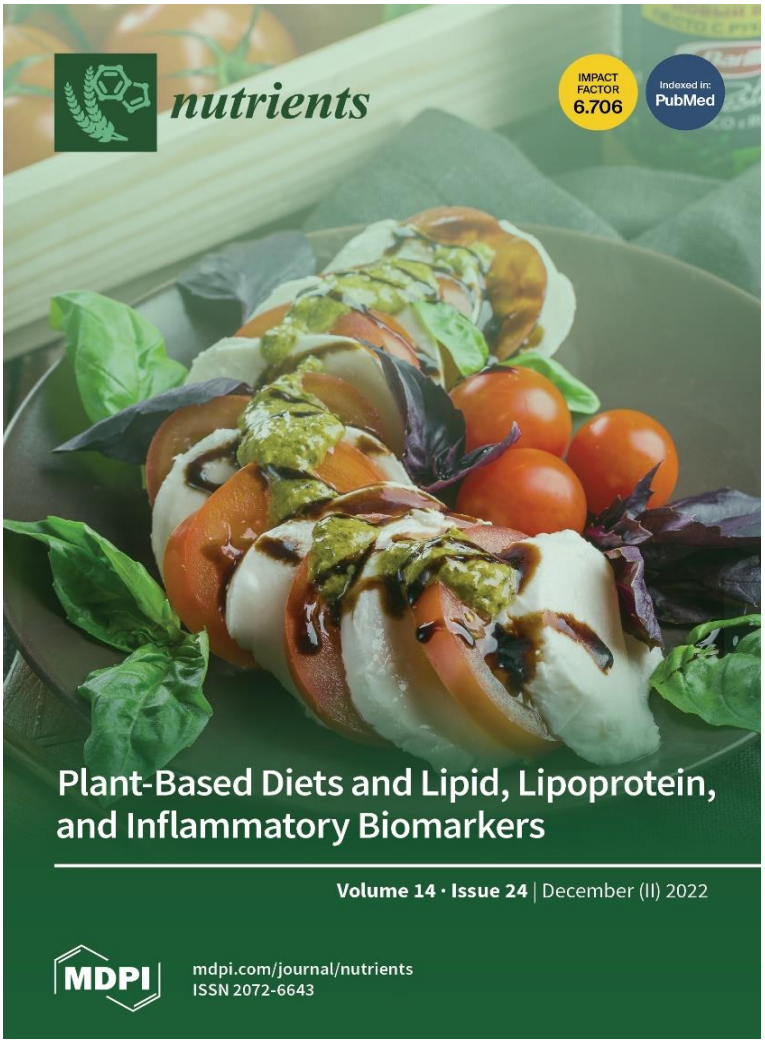
3.2. Capítulo II



[***Special Issue*:** Clinical Nutrition for Prevention and Treatment of Chronic Diseases]

Impacto nutricional y cambios en el patrón alimentario en trastornos del espectro esquizofrénico tras un programa de educación sanitaria sobre modulación dietética simbiótica ofrecido por enfermería psiquiátrica especializada: ensayo clínico aleatorizado de dos brazos.

Sevillano-Jiménez A, Romero-Saldaña M, García-Rodríguez M, Molina-Luque R, Molina-Recio G. Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing-Two-Arm Randomised Clinical Trial. Nutrients. 2022;14(24):5388. DOI: 10.3390/nu14245388

nutrients

MDPI

Article

Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing–Two-Arm Randomised Clinical Trial

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Citation: Sevillano-Jiménez, A.; Romero-Saldaña, M.; García-Rodríguez, M.; Molina-Luque, R.; Molina-Recio, G. Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing–Two-Arm Randomised Clinical Trial. *Nutrients* **2022**, *14*, 5388. https://doi.org/10.3390/nu14245388

Academic Editor: Rosa Casas

Received: 18 November 2022
Accepted: 16 December 2022
Published: 19 December 2022

Abstract: Background: The traditional therapeutic approach has perceived the role of nutrition as a minor intervention in psychiatry. The microbiota–gut–brain axis theory evidences the influence of dietary and nutritional patterns on mental health. Aims: To evidence the impact of dietary advice on increasing symbiotic intake on nutritional status and dietary habits in individuals with schizophrenia spectrum disorders. Methods: Randomised clinical trial (two-arm, double-blind, balanced-block, six-month intervention) in 50 individuals diagnosed with schizophrenia spectrum disorders. The control group received conventional dietary advice on an individual basis. A personal nutritional education programme was established in the intervention group (IG) to increase prebiotic and probiotic intake through dietary advice (dairy and fermented foods, green leafy vegetables, high-fibre fruit, whole grains, etc.). Data on nutritional status and dietary habits were collected (baseline and six months). The degree of dietary adherence to the recommended patterns was recorded weekly. Anthropometric parameters were also analysed monthly. Results: Finally, 44 subjects completed the follow-up. All participants exceeded the dietary reference intakes. The overall and intra-group analysis showed a statistically significant ($p < 0.05$) reduction in macro and micronutrient intakes with a closer approximation to the recommended dietary intakes, except for polyunsaturated fatty acids, oligosaccharides, polysaccharides and dietary fibre. After six months of intervention, statistical differences ($p < 0.001$) were found in all variables of the anthropometric profile in the IG, as well as an increase in the consumption of foods with a high symbiotic content (at baseline and six months). Likewise, a reduction in eggs, meat, fish, sugars and ultra-processed foods was evident, leading to significant intra-group differences ($p < 0.05$). Conclusions: Implementing conventional nutritional education strategies and specific nutritional advice with a symbiotic effect improves the dietary-nutritional profile in patients with schizophrenia spectrum disorders. Furthermore, it highlights the nutritional impact on mental health, stating itself as adjuvant therapy for physical health and lifestyle improvement.

Keywords: eating behaviour; diet; food; nutrition; nursing; schizophrenia spectrum; psychotic disorders; mental health

1. Introduction

Historical evolution has evidenced the role of nutritional psychiatry as a minor intervention in the traditional therapeutic conception of Mental Health [1,2]. However, the advances in the last decade, mainly associated with the development of holobiont theory and metagenomics [2,3], as well as the detection of new dietary patterns of poor nutritional quality in different Western societies [1,3,4], have highlighted the influence exerted by the dietary and nutritional pattern on the functioning of the Central Nervous System (CNS) [5]. Furthermore, the possible mechanisms or aetiological pathways of psychiatric disorders have been established [2,3,5], especially in severe and long-term mental disorders (LTMD), such as schizophrenia [5]. Consequently, the "Microbiota–Gut–Brain Axis" concept has emerged. This term refers to the bidirectional communication pathway between the CNS, the gastrointestinal tract, and the microbiota (IM) [4,6]. Its determinant role in the organism's normal functioning has been defined: development and maturation of the CNS, nutrition and metabolism, immune response or systemic inflammation [7–11]. Thus, according to low-grade systemic inflammation theory, when the state of dysbiosis appears, a cascade of pro-inflammatory agents can modify both the integrity and the permeability of enterocytes [3,9,10]. This response triggers the release of pro-inflammatory cytokines (tumour necrosis factor-alpha or interleukins type 6 or 1ß) [2,8,10], leading to synergies between inflammation, increased oxidative stress and energy imbalance [8]. These reactions result in homeostatic disturbances and neuropsychiatric dysfunction [9,11,12].

Dysregulation of the microbiota–gut–brain axis is determined by the acquisition of unhealthy lifestyles [1,5] based on poor nutritional quality dietary patterns and inadequate physical activity performance, which are especially common in LTMD [4,13–15]. Likewise, the current adoption of social distancing and home quarantine strategies established by the different governments within the global SARS-CoV-2 pandemic [16,17] promotes the acquisition of unhealthy habits in the vulnerable population, worsening previous pathogenic states [14].

Background

Concerning mental problems, the evidence shows a high rate of disability and morbidity and mortality (up to 20% higher) [16–19], being especially significant in LTMD [3,5,15,18,19]. Furthermore, these figures are closely linked to the development of Metabolic Syndrome (MetS) [2,4,15–19], considered a determining factor in the patient's physical health and tripling the incidence of cardio-metabolic diseases [17–20]. Finally, the main etiopathogenic determinants of MetS and the level of neuro-functional disability in the psychiatric population are linked to the characteristics of the disease, the exclusive psychopharmacological approach, and resistance to optimal care in terms of physical health and lifestyles [17–19,21].

Despite the magnitude and severity of the problem, interventions aimed at modifying nutritional patterns and eating behaviours play a minority role in the routine clinical practice of psychiatric healthcare professionals [4,15,16,21,22]. The evidence establishes high levels of malnutrition and the acquisition of unhealthy dietary habits in LTMD (far from the dietary reference standard) [4,15,22], based on the consumption of ultra-processed foods with high energy and glycaemic index and low consumption of fibre, fruit and vegetables [14,17,22–24]. Thus, the persistence of dietary patterns of low nutritional quality in the target population leads to a higher propensity for dysbiosis and, consequently, to a state of low-grade systemic inflammation. This state determines a higher risk of cardio-metabolic and psychopathological dysfunction that conditions the level of neuronal plasticity and cognitive performance [1,5,12].

In response to the evidence described above, there is currently a growing effort to develop and implement dietary interventions focused on modulating the gut microbiota in psychotic disorders through the use of "*psychobiotics*" [5,11–13] in the form of nutraceuticals. This term refers to a set of symbiotic substances (prebiotics and probiotics) whose administration leads to health benefits in psychiatric patients [5,10,11,25]. Probiotics include

micro-organisms from the intestinal biota, which benefit the host when administered in adequate amounts (notably the genera Lactobacillus and Bifidobacterium, among others) [8,10,25,26]. On the other hand, prebiotics is non-digestible dietary fibre (fructo- and oligosaccharides, inulin or pectins) [2,5], which promote optimal growth and the development of probiotics in the gastrointestinal tract, reducing pathogenic microbiota [8,9,26].

In short, the future of the new models of care in Mental Health is determined by the approach to nutritional factors and the detection of unhealthy dietary habits [1,6,10,23,24]. This fact is conditioned by the appropriate use of nutritional counselling in the multifactorial approach to the psychiatric patient, representing the cornerstone in achieving optimal and cost-effective health outcomes for the health system [27,28].

For all the above, this study aimed to evaluate the impact of nutritional counselling to follow a high-symbiotic diet in patients diagnosed with a schizophrenia spectrum disorder and in the context of confinement and social restriction due to the SARS-CoV-2 pandemic.

2. Materials and Methods

2.1. Study Design

A 6-month, double-blind, two-arm, parallel-arm, balanced-block, randomised clinical trial was conducted on patients diagnosed with schizophrenia spectrum disorders (without distinction by type). The study design is shown in Figure 1.

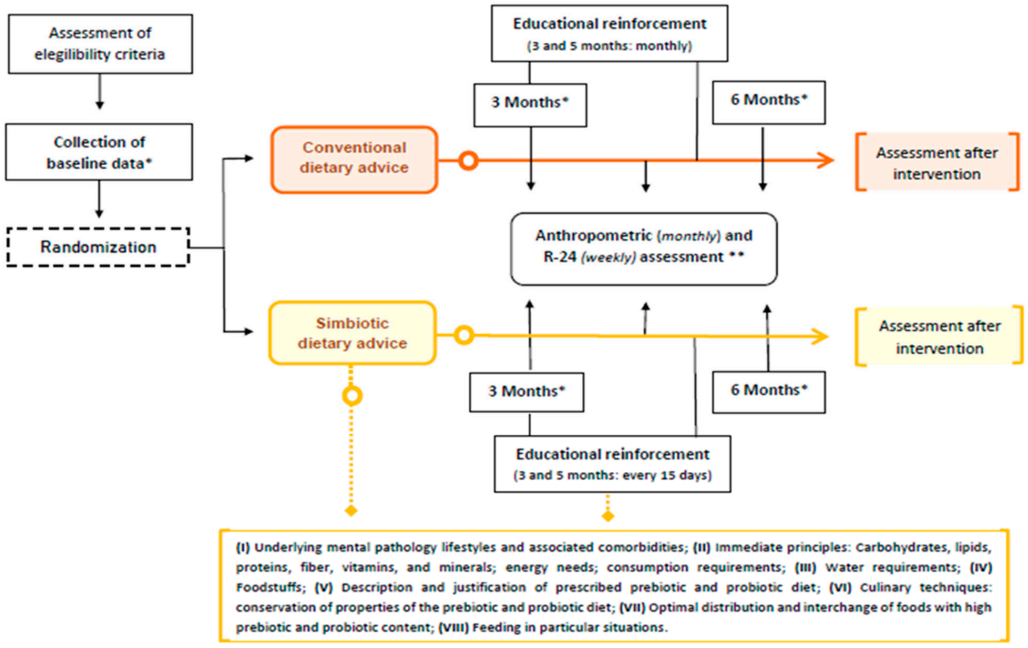

Figure 1. Study Design. * Data collected at baseline and six months of intervention: (1) Nutritional profile. ** Data collected at baseline and monthly during the intervention: (1) Anthropometric data (weight, height, Body Mass Index—BMI, waist circumference and waist-to-height ratio—WHtR-); (2) R-24 (weekly determination of foods with high symbiotic content in adherence to established dietary plan).

2.2. Population Eligibility Criteria

The sample was selected from the referral Psychiatry Service 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 18–65 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. Reasons for exclusion of participants were: (1) suffering from a somatic or neurocognitive condition that prevented participation and collaboration in compliance with the protocol; (2) standardised dietary planning not modulated by the study population (catering, institutional or collective feeding, etc.); (3) refusal to participate in the study.

2.3. Sample Size

The researchers estimated a 22 individuals sample size to assess the efficacy of the intervention (11 for the control group (CG) and 11 for the intervention group (IG), with a power of 80% and safety of 95%, expecting a risk/prevalence difference of 63% post-intervention [29]. Finally, the sample was increased by more than 50% to minimise the effect of possible losses, obtaining a final size of 50 individuals (25 for the CG and 25 for the IG). Randomisation was performed according to the anthropometric analysis results, allowing the prevalence of MetS in both groups to be balanced.

2.4. Intervention

The CG consisted of those participants who received conventional dietary advice [30] on an individual basis. Similarly, the IG intervention was developed individually through intensive nutritional intervention [31] (designed and supervised by registered dietitians) from specialised nurses on psychiatric care and based on counselling for the increasing consumption of food with high prebiotic and probiotic content. In both allocation groups, visually supportive educational resources were used during the consultations [32]. The study was initiated with focus groups that improved the set dietary-nutritional intervention, ensuring its correct adaptation according to the study population. The research project was also presented to the referred psychiatry service staff. Subsequently, a 6-month dietary-nutritional education programme was implemented, associated with two months of educational reinforcement every 15 days for the IG and monthly for the CG. During the intervention phase, the anthropometric status (weight, body mass index—BMI, waist-to-height ratio—WHtR-, and waist circumference) was determined monthly, as well as the dietary-nutritional pattern using a validated Food Frequency Questionnaire (FFQ) for the Spanish population [33], focusing on those food groups and main dishes with the most significant symbiotic impact, at baseline and six months after the intervention. Finally, to assess the degree of adherence to the established dietary plan, a weekly record was kept of the main dishes and foods consumed with a prebiotic and probiotic effect (fermented foods, whole grains, green leafy vegetables, fruit, etc.).

2.5. Data Analysis

The data were described using means and standard deviation for quantitative variables and frequencies and percentages for qualitative variables. The Kolmogorov-Smirnov test was used to assess normality in quantitative variables. The Student's t-test for paired data, Mann-Whitney U test and repeated-means ANOVA were used to analyse the relationship between quantitative variables. Similarly, the association between qualitative variables was determined by Chi-square (Fisher or Yates corrections) and McNemar's test. Non-parametric versions of the tests described above were performed if homoscedasticity criteria were not met. A probability of alpha error of less than 5% ($p < 0.05$) and a confidence interval of 95% were accepted during the analysis. Finally, SPSS (version 25.0) and EPIDAT (version 4.2) software were used for computing these tests. Similarly, the Nutriplato 2.0 (version 4.6) software tool [34] was used in the FFQ analysis.

3. Results

During recruitment, the eligible population was 50 subjects. Six participants were excluded during the intervention phase, resulting in 21 subjects in the CG and 23 in the IG. The flow chart of the participants is shown in Figure 2.

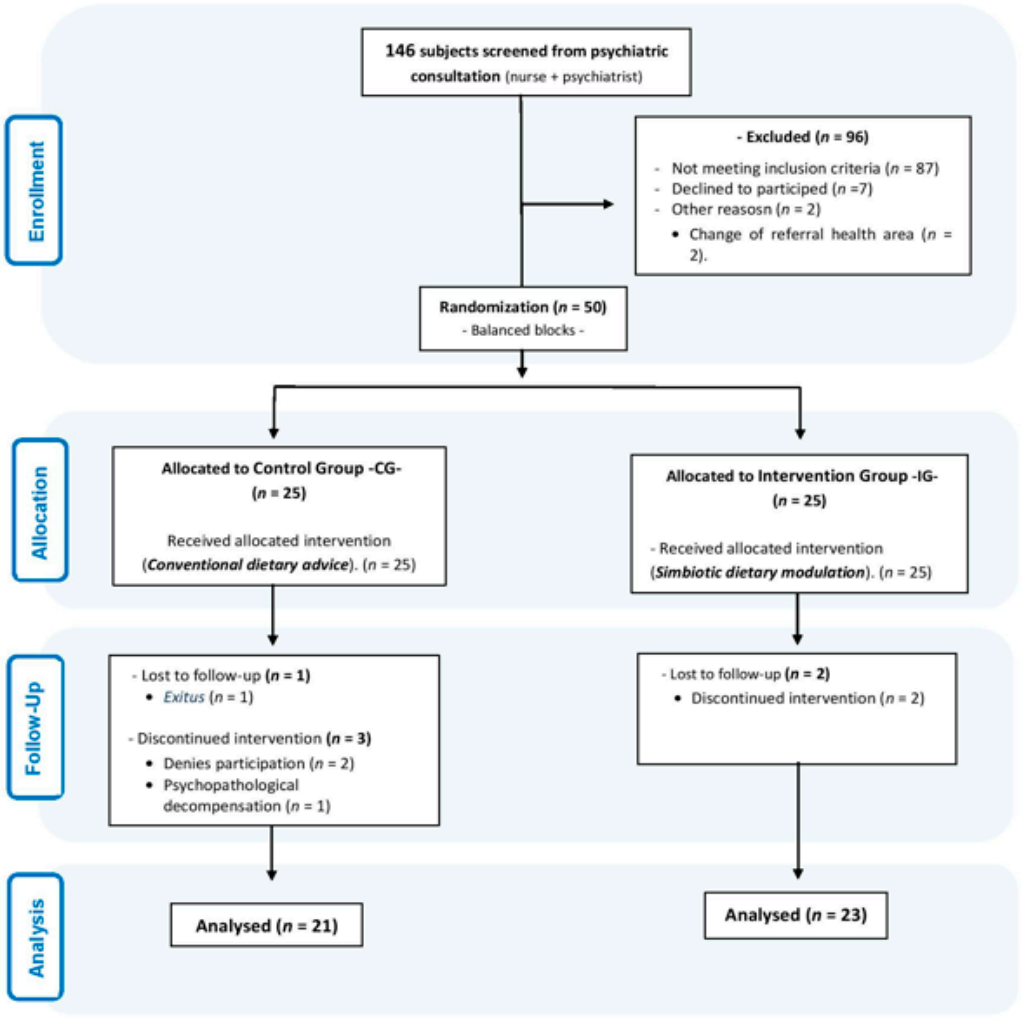

Figure 2. CONSORT flow diagram.

Thirty-two men (72.7%) and 12 women (27.3%) participated, with 49.2 ± 11.9 years on average. The primary psychiatric diagnosis was schizophrenia [37 (84.1%)], with a mean duration of illness of 21.6 ± 12.4 years. Drug use was reported by 29 smokers (65.9%), ten subjects who used cannabis (22.7%) and 6 participants who reported drinking alcohol (13.6%) regularly. Regarding the number of subjects with associated cardio-metabolic risk factors, 17 subjects showed dyslipidaemia (38.6%), ten high blood pressure (22.7%), and seven suffered from diabetes mellitus (15.9%). Moreover, 27 participants (61.4%) knew how to cook and were responsible for it.

Finally, the baseline analysis of the dependent variables showed significant differences in sugars and ultra-processed products and the mean calculation (weekly, monthly and quarterly) of the main foods and dishes consumed with high symbiotic value. Tables 1 and 2 show the baseline characteristics of the independent and dependent variables, respectively, showing homogeneity between the two allocation groups.

Table 3 shows the changes in outcome variables at baseline and six months of intervention in CG and IG, respectively. The overall analysis showed that almost all participants significantly exceeded the Recommended Daily Allowances (% RDA), except for the vitamin D variable, were lower than recommended throughout the intervention phase. Likewise, the overall analysis showed a significant improvement ($p < 0.05$) in all macronutrient and micronutrient profile variables, except for polyunsaturated fatty acids, oligosaccharides, polysaccharides, dietary fibre, copper, manganese, biotin, ascorbic acid and vitamin D.

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
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%)	
Family home	7 (15.9%)	4 (9.1%)	3 (6.8%)	
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%)	
Education level				
Uneducated	4 (9.1%)	2 (4.5%)	2 (4.5%)	0.590
Primary	19 (43.2%)	11 (25%)	8 (18.2%)	
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 condition				
No	24 (54.5%)	11 (25%)	13 (29.5%)	0.783
Yes	20 (45.5%)	10 (22.7%)	10 (22.7%)	
Type Cardio-metabolic condition				
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%)	
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%)	
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
	Macronutrients (RDA)			
Energy (%)	177.4 (48.4)	182 (47.3)	173.2 (50.1)	0.329
Proteins (g)	432 (152.5)	443.2 (159.6)	421.9 (148.6)	0.597
Lipids (g)	207.8 (63.1)	212.4 (68.2)	203.5 (59.4)	0.716
Saturated fatty acids (g)	392.3 (222.2)	414.9 (260.6)	371.7 (183.9)	0.698
Monounsaturated fatty acids (g)	147.7 (60.9)	140.9 (63.6)	154 (59)	0.613
Polyunsaturated fatty acids (g)	138.9 (103.7)	145.1 (131.3)	133.2 (72.8)	0.716
Cholesterol (mg)	247.2 (135.8)	224.6 (70.3)	267.9 (175)	0.787
Carbohydrates (g)	159.6 (53.4)	161.8 (48.2)	157.5 (58.7)	0.518
Oligosaccharides (g)	303.4 (205.7)	342.7 (203.8)	267.5 (205.2)	0.088
Polysaccharides (g)	123.2 (74.6)	139.8 (87.2)	108 (58.8)	0.378
Fibre (g)	215.1 (124.8)	196 (130.5)	232.5 (119.5)	0.245
	Micronutrients (RDA)			
Ca (mg)	181.1 (68.8)	194.1 (64.7)	169.2 (71.2)	0.124
Mg (mg)	292.8 (95.4)	285.3 (88.8)	299.7 (102.6)	0.823
P (mg)	352.9 (107.7)	372.7 (123.5)	334.8 (89.9)	0.209
Na (mg)	310.8 (93.6)	320.9 (112.4)	301.5 (73.7)	0.630
K (mg)	236 (83.8)	232.4 (90.2)	239.2 (79.5)	0.664
Fe (mg)	216 (70.5)	211.1 (64.1)	220.5 (77.1)	0.953
Cu (mg)	173.7 (91.2)	170 (118.9)	177 (58.1)	0.184
Zn (mg)	260.4 (101.3)	251.2 (83.4)	268.7 (116.6)	0.916
Mn (mg)	714.7 (595.6)	575.9 (360.2)	841.3 (735)	0.264
I (ug)	252.7 (102.1)	278.4 (120.9)	229.2 (76.7)	0.177
Se (mg)	501.4 (229)	471 (203)	529.2 (251.7)	0.518
Thiamine (mg)	261.4 (81.4)	261 (74.1)	261.7 (89.2)	0.769
Riboflavin (mg)	289.2 (92.7)	299.5 (92.1)	279.8 (94.4)	0.226
Niacin (mg)	388.5 (116.3)	392.7 (113)	384.7 (121.6)	0.503
Pantothenic acid (mg)	97.3 (44.6)	103.6 (46.9)	91.6 (42.7)	0.329
Vit B6 (mg)	314.1 (105.7)	305.5 (94.4)	321.9 (116.7)	0.842
Biotin (ug)	117.7 (76.2)	135.7 (87.3)	101.2 (61.7)	0.162
Folic Acid (ug)	205.4 (81.4)	199.1 (86.1)	211.2 (78.4)	0.565
Vit B12 (ug)	636.2 (273.9)	657.5 (321.6)	616.6 (227.5)	0.842
Ascorbic Acid (mg)	451.6 (244.3)	431.2 (248.7)	470.2 (244.2)	0.647
Vit A (ug)	239.5 (93.4)	250.7 (86.9)	229.3 (99.8)	0.549
Vit D (ug)	64.9 (65.9)	69.5 (80.5)	60.6 (50.6)	0.897
Vit E (mg)	228.5 (143.7)	191.8 (100.7)	262.1 (169.4)	0.065
	Food Group: Weekly Consumption			
Dairy Products (n°. consumed/week)	21.2 (13)	22.7 (14.9)	19.9 (11.1)	0.487
Eggs, Meats and Fish (n°. consumed/week)	23.3 (9.3)	21.8 (10.9)	24.6 (7.5)	0.188
Vegetables (n°. consumed/week)	25.3 (12.9)	23.7 (14.2)	26.8 (11.8)	0.188
Fruits (n°. consumed/week)	22.4 (17.7)	19 (18.4)	25.4 (16.8)	0.086
Legumes and Cereals (n°. consumed/week)	6.6 (4.9)	5.9 (3.9)	7.2 (5.7)	0.687
Sugars and ultra-processed products (n°. consumed/week)	53.9 (22.4)	45.5 (14.9)	61.6 (25.4)	0.03
	Weekly food record			
R24-weekly (n°. of symbiotic foods consumed/week)	24.4 (7.8)	20.6 (7.8)	27.8 (6.2)	0.001
R24-monthly (n°. of symbiotic foods consumed/week)	97.7 (31.4)	82.6 (31.3)	111.4 (25)	0.001
R24-trimestral (n°. of symbiotic foods consumed/week)	293.1 (94.3)	247.9 (94.1)	334.3 (75)	0.001
	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/m^2)	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
Height (cm)	168.5 (9.2)	166.4 (10.7)	170.3 (7.4)	0.245
	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

RDA: Recommended Dietary Allowance; Ca: calcium; Mg: magnesium: P: phosphorus; Na: sodium; K: potassium; Fe: iron; Cu: copper; Zn: zinc; Mn: manganese; I: iodine; Se: selenium; Vit.B6: vitamin B6; Vit.B12: vitamin B12; Vit.A: vitamin A; Vit.D: vitamin D; Vit.E: vitamin E; Food Group-Weekly Consumption: Calculation of average consumption of main foods (weekly) by food group; Weekly food record: weekly determination of foods with high symbiotic content in adherence to established dietary plan; R24-weekly: average (weekly) calculation of the main foods and dishes consumed according to the established dietary plan; R24-monthly: average (monthly) calculation of the main foods and dishes consumed according to the established dietary plan; R24-quarterly: average (quarterly) calculation of the main foods and dishes consumed according to the established dietary plan BMI: body mass index; WHtR: waist-to-height ratio; Antipsychotic DDD: defined daily dose antipsychotics.

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

	Total (n = 44)			Control Group (n = 21)			Intervention Group (n = 23)			p *	p **
Variables	**Basal**	**6 Months**	p	**Basal**	**6 Months**	p	**Basal**	**6 Months**	p		
				Macronutrients (RDA)							
Energy (%)	177.4 (48.4)	128.2 (31.7)	<0.001	182 (47.3)	130.9 (37.8)	0.001	173.2 (50.1)	125.8 (25.4)	<0.001	0.329	0.647
Proteins (g)	432 (152.5)	328.4 (116.7)	<0.001	443.2 (159.6)	311.1 (134.1)	0.003	421.9 (148.6)	344.2 (98.6)	0.011	0.597	0.209
Lipids (g)	207.8 (63.1)	143.2 (39.2)	<0.001	212.4 (68.2)	149.6 (47)	0.002	203.5 (59.4)	137.3 (30.2)	<0.001	0.716	0.245
Saturated fatty acids (g)	392.3 (222.2)	251.6 (93.8)	<0.001	414.9 (260.6)	252.4 (99.4)	0.002	371.7 (183.9)	250.9 (90.7)	0.008	0.698	0.897
Monounsaturated fatty acids (g)	147.7 (60.9)	108.7 (40.2)	<0.001	140.9 (63.6)	103.1 (35.9)	0.006	154 (59)	113.9 (43.9)	0.018	0.613	0.418
Polyunsaturated fatty acids (g)	138.9 (103.7)	120.6 (115.8)	0.264	145.1 (131.3)	144.6 (160)	0.985	133.2 (72.8)	98.7 (43.3)	0.095	0.716	0.733
Cholesterol (mg)	247.2 (135.8)	173.1 (80.7)	0.001	224.6 (70.3)	160.1 (76.7)	0.002	267.9 (175)	185 (84.2)	0.027	0.787	0.285
Carbohydrates (g)	159.6 (53.4)	118.7 (35.2)	<0.001	161.8 (48.2)	120.3 (38.5)	0.003	157.5 (58.7)	117.3 (32.6)	0.004	0.518	0.897
Oligosaccharides (g)	303.4 (205.7)	204.8 (98.6)	0.005	342.7 (203.8)	214 (113.4)	0.015	267.5 (205.2)	196.5 (84.6)	0.134	0.088	0.805
Polysaccharides (g)	123.2 (74.6)	96.6 (40.7)	0.019	139.8 (87.2)	89.1 (44.4)	0.003	108 (58.8)	103.5 (36.6)	0.762	0.378	0.177
Fibre (g)	215.1 (124.8)	185.8 (111)	0.229	196 (130.5)	175.8 (116.8)	0.560	232.5 (119.5)	194.8 (107.3)	0.288	0.245	0.431
				Micronutrients (RDA)							
Ca (mg)	181 (68.8)	142 (56)	0.004	194.1 (64.7)	142.8 (64.6)	0.02	169.2 (71.2)	141.3 (48.2)	0.099	0.124	0.751
Mg (mg)	292.8 (95.4)	238.2 (102.7)	0.002	285.3 (88.8)	220.2 (116.8)	0.013	299.7 (102.6)	254.7 (87.3)	0.07	0.823	0.118
P (mg)	352.9 (107.7)	270.9 (77.8)	<0.001	372.7 (123.5)	265.6 (88.2)	0.003	334.8 (89.9)	275.7 (68.6)	0.009	0.209	0.318
Na (mg)	310.8 (93.6)	201 (60.7)	<0.001	320.9 (112.4)	200.5 (67.6)	0.001	301.5 (73.7)	201.5 (55.2)	<0.001	0.630	0.860
K (mg)	236 (83.8)	195.5 (84.4)	0.007	232.4 (90.2)	178.4 (87.7)	0.03	239.2 (79.5)	211 (80.1)	0.120	0.664	0.136
Fe (mg)	216 (70.5)	169.5 (57.6)	<0.001	211.1 (64.1)	166.9 (66.3)	0.008	220.5 (77.1)	171.8 (49.8)	0.003	0.953	0.953
Cu (mg)	173.7 (91.2)	154.8 (73.8)	0.170	170 (118.9)	133.9 (74.5)	0.132	177 (58.1)	173.8 (69.3)	0.829	0.184	0.08
Zn (mg)	260.4 (101.3)	202.3 (76.4)	0.003	251.2 (83.4)	206.3 (96.5)	0.118	268.7 (116.6)	198.6 (53.9)	0.013	0.916	0.565
Mn (mg)	714.7 (595.6)	632.8 (437.2)	0.413	575.9 (360.2)	495.5 (376.9)	0.290	841.3 (735)	758.3 (458.3)	0.648	0.264	0.028
I (ug)	252.7 (102.1)	194.9 (91.9)	0.009	278.4 (120.9)	204.2 (114.7)	0.061	229.2 (76.7)	186.4 (66.3)	0.063	0.177	0.953
Se (mg)	501.4 (229)	392.4 (147.6)	0.004	471 (203)	360.4 (136.2)	0.034	529.2 (251.7)	421.6 (154.4)	0.055	0.518	0.162
Thiamine (mg)	261.4 (81.4)	209.6 (65.2)	<0.001	261 (74.1)	203.5 (76.8)	0.006	261.7 (89.2)	215.2 (53.7)	0.024	0.769	0.503
Riboflavin (mg)	289.2 (92.7)	237.2 (72)	0.005	299.5 (92.1)	230.3 (79.9)	0.019	279.8 (94.4)	243.5 (65)	0.135	0.226	0.534
Niacin (mg)	388.5 (116.3)	318 (98.4)	0.001	392.7 (113)	295.9 (114.4)	0.002	384.7 (121.6)	338.1 (78.3)	0.104	0.503	0.107
Pantothenic acid (mg)	97.3 (44.6)	82.3 (32.2)	0.051	103.6 (46.9)	73 (29.4)	0.019	91.6 (42.7)	90.8 (32.8)	0.929	0.329	0.08
Vit B6 (mg)	314.1 (102.7)	262.9 (97.8)	0.007	305.5 (94.4)	244.2 (104.5)	0.025	321.9 (116.7)	279.9 (90.2)	0.128	0.842	0.155
Biotin (ug)	117.7 (76.2)	104.6 (73.6)	0.363	135.7 (87.3)	93.5 (62.3)	0.07	101.2 (61.7)	114.7 (82.7)	0.429	0.162	0.296
Folic Acid (ug)	205.4 (81.4)	174.8 (69.9)	0.02	199.1 (86.1)	158.3 (64.7)	0.057	211.2 (78.4)	189.9 (72.4)	0.195	0.565	0.142
Vit. B12 (ug)	636.2 (273.9)	475.6 (198.3)	0.002	657.5 (321.6)	449.5 (183.2)	0.021	616.6 (227.5)	499.4 (212.3)	0.04	0.842	0.549
Ascorbic Acid (mg)	451.6 (244.3)	429 (206.7)	0.529	431.2 (248.7)	383.2 (226.1)	0.292	470.2 (244.2)	470.8 (287.3)	0.992	0.647	0.254
Vit. A (ug)	239.5 (93.4)	219 (80.1)	0.212	250.7 (86.9)	208.6 (75.7)	0.079	229.3 (99.8)	228.6 (84.4)	0.974	0.549	0.366
Vit. D (ug)	64.9 (65.9)	52.4 (56.1)	0.13	69.5 (80.5)	56.4 (78.4)	0.201	60.6 (50.6)	48.8 (23.1)	0.361	0.897	0.445
Vit. E (mg)	228.5 (143.7)	156.4 (52.8)	0.002	191.8 (100.7)	146.9 (64.3)	0.059	262.1 (169.4)	165.1 (39.1)	0.014	0.065	0.062

Table 3. *Cont.*

Variables	Total (n = 44)			Control Group (n = 21)			Intervention Group (n = 23)			p *	p **
	Basal	6 Months	p	Basal	6 Months	p	Basal	6 Months	p		
Food Group: Weekly Consumption											
Dairy Products (n°. consumed/week)	21.3 (13)	22.4 (11.9)	0.625	22.7 (14.9)	24.4 (13.8)	0.670	19.9 (11.1)	20.5 (9.8)	0.822	0.487	0.316
Eggs, Meats and Fish (n°. consumed/week)	23.3 (9.3)	20 (7.6)	0.097	21.8 (10.9)	22.1 (8.7)	0.927	24.6 (7.5)	18.1 (5.9)	0.009	0.188	0.09
Vegetables (n°. consumed/week)	25.3 (12.9)	23.8 (11.1)	0.517	23.7 (14.2)	23 (12.9)	0.848	26.8 (11.8)	24.6 (9.4)	0.407	0.188	0.284
Fruits (n°. consumed/week)	22.4 (17.7)	18.2 (14.4)	0.074	19 (18.4)	15.3 (14)	0.276	25.4 (16.8)	20.8 (14.6)	0.165	0.086	0.148
Legumes and Cereals (n°. consumed/week)	6.6 (4.9)	7.2 (4.2)	0.380	5.9 (3.9)	6.4 (2.5)	0.562	7.2 (5.7)	7.9 (5.2)	0.522	0.687	0.661
Sugars and ultra-processed products (n°. consumed/week)	53.9 (22.4)	57.4 (28.4)	0.505	45.5 (14.9)	67.2 (34.1)	0.006	61.6 (25.4)	48.4 (18.5)	0.03	0.03	0.037
Weekly food record											
R24-weekly (n°. of symbiotic foods consumed/week)	24.4 (7.8)	-	-	20.6 (7.8)	-	-	27.8 (6.2)	-	-	0.001	-
R24-monthly (n°. of symbiotic foods consumed/week)	97.7 (31.4)	-	-	82.6 (31.3)	-	-	111.4 (25)	-	-	0.001	-
R24- quarterly (n°. of symbiotic foods consumed/week)	293.1 (94.3)	-	-	247.9 (94.1)	-	-	334.3 (75)	-	-	0.001	-
Anthropometric Profile											
Weight (kg)	81.4 (17.6)	78.7 (16.2)	<0.001	76.6 (18)	75.8 (17.7)	0.382	85.7 (16.3)	81.3 (14.6)	<0.001	0.086	0.275
Waist circumference (cm)	101.9 (17)	101.6 (12.5)	0.898	97.6 (21)	101.2 (13.5)	0.322	105.7 (11.5)	102.1 (11.7)	<0.001	0.397	0.981
BMI (kg/m^2)	28.5 (5)	27.6 (4.7)	<0.001	27.5 (5.2)	27.2 (5.3)	0.323	29.5 (4.8)	27.9 (4.3)	<0.001	0.307	0.869
WHtR	0.6 (0.09)	0.6 (0.07)	0.932	0.6 (0.12)	0.6 (0.08)	0.345	0.6 (0.06)	0.6 (0.06)	<0.001	0.597	0.378
Therapeutic Variables											
N° of associated antipsychotic	1.3 (0.5)	1.2 (0.4)	0.262	1.38 (0.49)	1.28 (0.46)	0.329	1.3 (0.47)	1.26 (0.44)	0.575	0.597	0.855
DDD antipsychotics (mg)	271.4 (242.5)	241.2 (226.7)	0.108	286.7 (222.3)	260.5 (221.5)	0.230	257.4 (263.7)	247.4 (225.9)	0.301	0.458	0.789

p: intragroup statistical significance; p *: baseline intergroup statistical significance; p **: 6 months intergroup statistical significance; RDA: Recommended Dietary Allowance Ca: calcium; Mg: magnesium: P: phosphorus; Na: sodium; K: potassium; Fe: iron; Cu: copper; Zn: zinc; Mn: manganese; I: iodine; Se: selenium; Vit.B6: vitamin B6; Vit.B12: vitamin B12; Vit.A: vitamin A; Vit.D: vitamin D; Vit.E: vitamin E; Food Group-Weekly Consumption: Calculation of average consumption of main foods (weekly) by food group; Weekly food record: weekly determination of foods with high symbiotic content in adherence to established dietary plan; R24-weekly: average (weekly) calculation of the main foods and dishes consumed according to the established dietary plan; R24-monthly: average (monthly) calculation of the main foods and dishes consumed according to the established dietary plan R24-quarterly: average (quarterly) calculation of the main foods and dishes consumed according to the established dietary plan BMI: body mass index; WHtR: waist-to-height ratio; Antipsychotic DDD: defined daily dose antipsychotics.

Similarly, the overall analysis of weekly, monthly and quarterly records of consumption of foods with high symbiotic content showed statistically significant differences, with a subsequent decrease and increase in consumption coinciding with the implementation of social distancing and confinement measures in the SARS-CoV-2 era.

Regarding the intra-group analysis of macronutrients between the CG and IG, we observed concordance with those results obtained from the global analysis, obtaining statistically significant differences in all variables, except for polyunsaturated fatty acids oligosaccharides, polysaccharides and dietary fibre. However, the intra-group analysis of micronutrients showed statistically significant differences in the IG for phosphorus, sodium, iron, zinc, thiamin, vitamin B12 and vitamin E.

Similarly, in terms of weekly consumption by food group in the IG, there was a reduction in protein consumption of eggs, meat and fish, and sugars and ultra-processed foods, compared to the increase obtained in the CG. This fact is related to the non-statistical significance at the global level. In addition, there was an increase in the consumption of dairy products, legumes and cereals between the two allocation groups and a decrease in the intake of fruit, vegetables and greens. However, these variations were not significant. Finally, anthropometric variables improved significantly ($p < 0.001$) in the IG, while waist circumference increased in the CG. These modifications did not lead to significant differences in the number of antipsychotics and dosage prescribed.

Regarding the global inter-group analysis at baseline and at six months of intervention, except for the improvement observed in the consumption of sugars and ultra-processed food ($p < 0.05$) in IG, no statistically significant results were shown for the rest of the dependent variables.

4. Discussion

This study focuses on the nutritional impact of a high symbiotic dietary modulation throughout health education intervention by specialised psychiatric nurses in patients suffering from schizophrenia spectrum disorder, reducing macro and micronutrient intake towards a closer approximation to the % RDA between allocation groups. However, the findings confirm the results described by Gill R et al. (2021). They found that implementing an intensified educational approach does not yield significant benefits compared to a conventional dietary-nutritional intervention in schizophrenic disorders [24].

On the other hand, from our perspective, we consider that the statistically significant intra-group differences are a reason for not reaching inter-group statistical results, a condition supported by the significance reached for the overall analysis of the group. However, the results obtained reflect a clinically significant trend toward healthier nutritional patterns in the IG, compared to the increased consumption of ultra-processed, higher energy and higher glycaemic index foods in the CG [4,15,16,35,36], a highly prevalent condition in the target population ($p < 0.05$) [20,32]. The scientific evidence supports and clarifies the results obtained, with an increase in dietary habits of low nutritional quality in psychotic disorders (up to 60%) [21,32,36]. These patterns exceed % RDA [35,36] and are characterised by a higher intake of refined carbohydrates, saturated fats, sodium and phosphorus, as well as a lower intake of vitamin D, calcium, potassium, iron, polyunsaturated fatty acids, fruit and vegetables and, therefore, lower intake of dietary fibre (among others) [1,4,15,16,22,35–42]. In this regard, according to Gill R et al. (2021), Stefańska E et al. (2019) and Kowalski K et al. (2022), low adherence to Mediterranean dietary patterns leads to a higher propensity for nutritional deficiencies [24,36,41] and, consequently, a higher risk of exacerbation of underlying cardio-metabolic and neuropsychiatric disorders [39–41].

Undoubtedly, the improvement of the anthropometric profile (in all variables) and, therefore, the significant decrease in the risk of MetS in the GI ($p < 0.05$) after intensive dietary advice with high prebiotic and probiotic content is noteworthy. Similar findings were obtained by Sugawara et al. (2018) and Caemmerer et al. (2012) [29,42]. Again, the results presented in the present study support the meta-analysis developed by

Teasdale et al. (2017), showing that non-pharmacological interventions focused on improving the dietary-nutritional pattern are established as coadjuvant therapies for metabolic abnormalities [43], relevant to improving the lifestyles of the target population [1,4,15,23,35]. Concerning the level of compliance and results obtained in both allocation groups, it is essential to highlight the contextual framework of the global SARS-CoV-2 pandemic in which this clinical trial was conducted. Solé et al. (2021) indicated that most preliminary studies during the current pandemic have focused on psychological distress in the general population [14], with limited evidence regarding the dietary pattern followed in patients with schizophrenia spectrum disorders. Likewise, the particular vulnerability of the target population in this context of confinement and the global pandemic [14,16,17] stands out. This population has limited the acquisition of coping strategies, which has encouraged the development of unhealthy lifestyles [14–17,23,39], where hypercaloric dietary patterns and the restriction of physical activity stand out [23,24,40,41]. For these reasons, the effectiveness of the intervention may have been reduced. Thus, according to Stefánska et al. (2019), Stefánska et al. (2017), and Cheikl et al. (2021), poor sun exposure during states of confinement and the characteristics of schizophrenic disorder in terms of social restriction has made it challenging to achieve optimal vitamin D results in line with % RDA [35,36,40].

As established by Costa et al. (2019) and Giannouli (2017), the high prevalence of morbidity and mortality in LTMD is not only determined by the nutritional outcome and dysmetabolic status but also by the aetiological condition that derives from it [23,44]. In this sense, cultural, cognitive-emotional or spiritual factors stand out as aspects to be considered when elucidating which ones behave as protective or risk agents in the prediction of morbidity and mortality in the psychiatric population [44,45], especially in contexts of social restriction [14,17,40].

Thus, risk behaviours associated with the consumption of intoxicants, such as alcohol, tobacco or cannabis (among others), are a proven condition related to the factors above (cultural, cognitive, etc.) [44], with an impact on unhealthy lifestyles [23,28,39,40] and the development of disruptive behaviours [44,45]. However, despite the particular vulnerability of the psychiatric population to states of confinement [14,17,18], the latter has been postulated as a protective factor against the development of harmful habits with marked social content, such as substance consumption, among which alcohol consumption stands out. This fact has made it possible to minimise the potential impact of alcohol intake on the results obtained regarding the nutritional and cardio-metabolic profile.

However, despite the significant difficulties of intervention in the schizophrenic population [1,17,32], this study highlights the feasibility of high-symbiotic dietary intervention on cardio-metabolic health and marked improvement of the nutritional profile, different from the current evidence available in confinement settings [16,18,24,38]. Longitudinal studies are needed to demonstrate the impact of hygienic-dietary measures on the macro and micronutrient profile in the psychiatric population [17,41].

The available evidence shows that clinical trials with dietary approaches in the absence of psychopharmacological treatment are limited [38], show marked heterogeneity and lack methodological rigour [5,10]. However, as Stefánska et al. (2019) and Dabke et al. (2019) point out, the association of the individual nutritional programme with a symbiotic approach may have a high synergistic impact on the improvement of dysmetabolic states [35,46], a highly prevalent condition in the population studied [17,18,20].

Finally, according to Balanzá (2017), the role of advanced practice nurses stands out as the cornerstone of the multidisciplinary approach and the main person responsible for the dietary advice offered [5]. Likewise, psychiatric nurses are the leading active players in the emotional and cognitive regulation associated with the dietary patterns established as part of the care provided to the psychiatric population [28,32].

Limitations

The main limitations of this study are related to the sample size and the participants' loss or lack of cooperation during the intervention phase. However, this limited and het-

erogeneous sample size could explain the scarce significant differences between macro and micronutrient profile variables and weekly consumption by food group. Thus, significant intra-group differences meant that no inter-group statistical results were achieved. Finally, since the authors followed the usual procedures for sample size estimation, it is possible that the risk/prevalence difference between IG and CG was overestimated (63%).

The results obtained may be linked to the difficulty of using FFQ in assessing the dietary-nutritional pattern. This fact is based on the low degree of dietary knowledge and food responsibility, psychopathological state and, therefore, possible associated neurocognitive impairment in the population under study, which may result in overestimated data relating to the RDAs [1,35].

Likewise, the non-inclusion of biochemical parameters in this manuscript may be a potential limitation, preventing the comparison of nutritional and cardio-metabolic results (blood glucose, lipid profile, etc.). The reason for not including these data was that the main objective was to assess the intervention's efficacy in modifying this population's dietary patterns with such particular characteristics. However, readers interested in this type of information can consult a recent paper in which these results have been included [47].

It would be relevant to know the psychopathological impact of increased consumption of prebiotics and probiotics on psychiatric disorders, of particular interest in LTMD. To this end, using Visual Evoked Potentials (VEP) is an effective diagnostic technique in analysing the neurophysiology of subjective disorders and interruption of functional recovery in psychopathological worsening, common in schizophrenia [48]. Unfortunately, this test could not be applied during the development of the trial, so subsequent studies that included it could provide more information on this vital topic.

It is essential to note that this study was conducted during the SARS-CoV-2 pandemic, making it difficult to achieve the proposed intervention, especially in acquiring and strengthening healthy lifestyles. Furthermore, it is necessary to consider the inherent characteristics of the subjects under study, a population that is particularly vulnerable to change, especially in a context of confinement and a global pandemic [14,17].

Finally, the scarcity of existing research on nutritional patterns and dietary habits in subjects diagnosed with schizophrenia makes it difficult to contrast the results obtained in different healthcare settings.

5. Conclusions

The development of a dietary-nutritional education programme in patients diagnosed with schizophrenia spectrum disorders and based on dietary advice by psychiatric nurses has not shown significant differences from conventional health education models, both being proposed as effective interventions in improving the nutritional pattern and dietary habits of the population under study. However, implementing a dietary-nutritional intervention with a high symbiotic content improves cardio-metabolic outcomes effectively in a global pandemic such as SARS-CoV-2. Furthermore, despite the inherent lifestyle dysfunctionalities of the target population, prebiotics and probiotics have been shown to offer a relevant and promising solution in different settings. Finally, further studies with larger sample sizes and outside the context of pandemics and confinement are needed to assess better the efficacy of these interventions.

Author Contributions: Investigation, A.S.-J., M.R.-S. and G.M.-R.; methodology, M.R.-S., M.G.-R., R.M.-L. and G.M.-R.; writing—review & editing, A.S.-J., M.R.-S. and G.M.-R. All authors have read and agreed to the published version of the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement: The study was conducted respecting the fundamental principles established in the Declaration of Helsinki (1964), the Council of Europe Convention on Human Rights and Biomedicine (1997), and the UNESCO Universal Declaration on the Human Genome and Human Rights (1997). Research also followed the requirements established by Spanish legislation

(Organic Law 3/2018 of 5 December and Law 41/2002 of 14 November). The referral Research Ethics Committee approved the study in November 2019 (reg. 468) and retrospectively registered on the Clinical Trials platform: clinicaltrials.gov (ID: NCT04366401; First Submission: 28 April 2020; First Registration: 9 September 2020; URL: https://register.clinicaltrials.gov/prs/app/action/LoginUser?ts=1&cx=-jg9qo4 [accessed on 9 September 2022]). All the information analysed by the principal investigator of this study was subject to the maintenance of professional secrecy. In any case, each participant was assigned a code as a register, where all the relative data were typed anonymously, limiting access to the database only to personnel linked to the development of the study, with the prior authorisation of the researcher responsible for the study.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

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

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

Conflicts of Interest: The authors declare that they have no competing interest.

Trial Registration: The referral Research Ethics Committee approved the study protocol in November 2019 (reg. 468) and retrospectively registered at clinicaltrials.gov (NCT0436366401. First Submitted: 28 April 2020).

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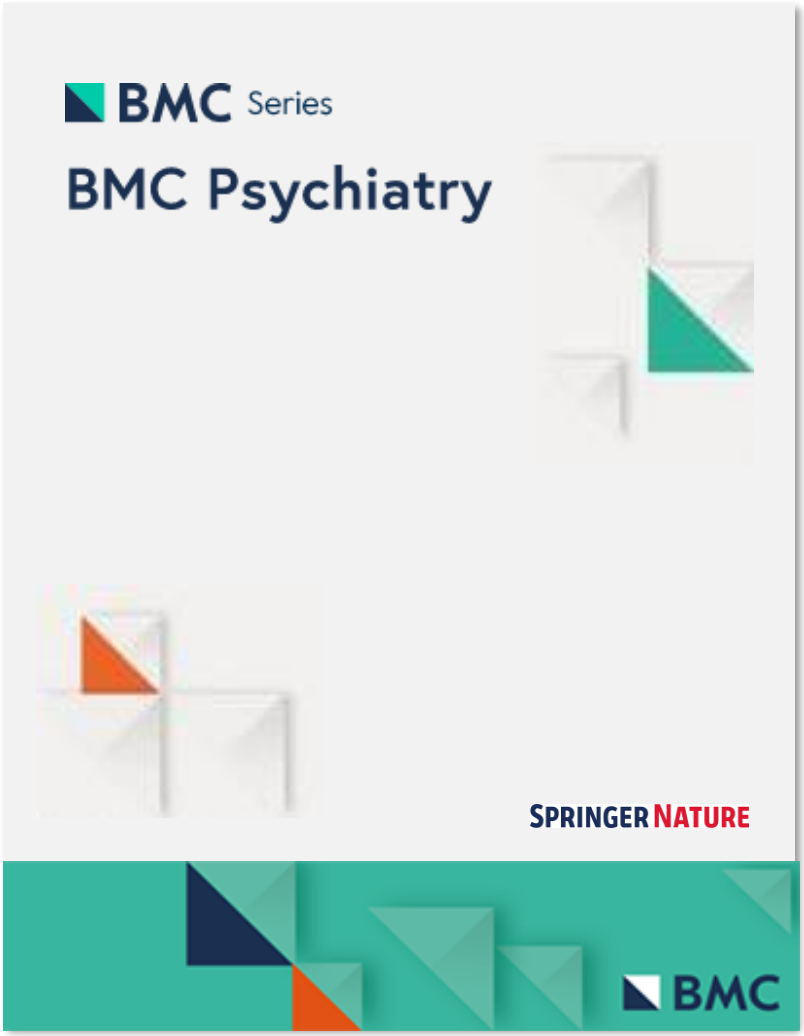
3.3. Capítulo III



Impacto de una educación dietética alta en prebióticos y probióticos en la era SARS-CoV-2: mejora del perfil cardio-metabólico en trastornos del espectro esquizofrénico

Sevillano-Jiménez A, Romero-Saldaña M, García-Mellado JA, Carrascal-Laso L, García-Rodríguez M, Molina-Luque R, Molina-Recio G. Impact of high prebiotic and probiotic dietary education in the SARS-CoV-2 era: improved cardio-metabolic profile in schizophrenia spectrum disorders. BMC Psychiatry. 2022;22(1):781. DOI: 10.1186/s12888-022-04426-9.

BMC Psychiatry

RESEARCH

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Impact of high prebiotic and probiotic dietary education in the SARS-CoV-2 era: improved cardio-metabolic profile in schizophrenia spectrum disorders

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Abstract

Background: The development of new aetiological premises, such as the microbiota-gut-brain axis theory, evidences the influence of dietary and nutritional patterns on mental health, affecting the patient's quality of life in terms of physical and cardiovascular health. The aim was to determine the impact of a nutritional programme focused on increasing the intake of prebiotic and probiotic food on cardio-metabolic status in individuals with schizophrenia spectrum disorders in the contextual setting of the SARS-CoV-2 era.

Methods: A randomised clinical trial (two-arm, double-blind, balanced-block, six-month intervention) was conducted in a group of 50 individuals diagnosed with schizophrenia spectrum disorder during the SARS-CoV-2 confinement period. The control group received conventional dietary counselling on an individual basis. In the intervention group, an individual nutritional education programme with a high content of prebiotics and probiotics (dairy and fermented foods, green leafy vegetables, high-fibre fruit, whole grains, etc.) was established. Data on cardiovascular status were collected at baseline, three and six months. In addition, anthropometric parameters were analysed monthly.

Results: Forty-four subjects completed follow-up and were analysed. Statistical differences ($p < 0.05$) were found in all anthropometric variables at baseline and six months of intervention. A 27.4% reduction in the prevalence of metabolic syndrome risk factors in all its components was evidenced, leading to a clinically significant improvement (decrease in cardiovascular risk) in the intervention group at six months.

Conclusions: The development of a nutritional programme focused on increasing the dietary content of prebiotics and probiotics effectively improves the cardio-metabolic profile in schizophrenia spectrum disorders. Therefore, nursing assumes an essential role in the effectiveness of dietary interventions through nutritional education and the promotion of healthy lifestyles. Likewise, nursing acquires a relevant role in interdisciplinary coordination in confinement contexts.

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Trial registration: The study protocol complied with the Declaration of Helsinki for medical studies; the study received ethical approval from referral Research Ethics Committee in November 2019 (reg. no. 468) and retrospectively registered in clinicaltrials.gov (NCT04366401. First Submitted: 28th April 2020; First Registration: 25th June 2020).

Keywords: Metabolic Syndrome, Cardiometabolic Risk Factors, Schizophrenia Spectrum and Other Psychotic Disorders, Nursing, SARS-CoV-2

Introduction

Undoubtedly, the traditional therapeutic approach in psychiatry has perceived the role of nutrition as a minor intervention, especially in severe and long-term mental disorders (LTMD) such as schizophrenia [1]. However, advances in the last decade in terms of Nutritional Psychiatry (focused on the impact of eating patterns on how people feel emotionally) and the presence of new unhealthy dietary practices have contributed to understanding the role of nutritional habits on the central nervous system (CNS) functioning and possible mechanisms or aetiological pathways of psychiatric disorders [1–3].

Similarly, with the development of holobiont theory and the evolution of metagenomics, the concept of the "Microbiota-Gut-Brain Axis " [2, 3] emerged and is currently the subject of study in mental health as part of Nutritional Psychiatry. This term refers to the bidirectional communication pathway between the CNS, gastrointestinal tract, and microbiota (MI) [2, 4], which determines the organism's normal functioning: development and maturation of the CNS, metabolism, immune response, and systemic inflammation [3–7]. Thus, the existence of possible modifications in the concentration of this biota (determined by dietary patterns) can trigger homeostatic alterations or aggravate pathogenic states; a fact commonly referred to as dysbiosis [1, 3, 6, 7]. Thus, according to the theory of low-grade systemic inflammation, a cascade of pro-inflammatory agents capable of modifying both the integrity and permeability of enterocytes [1, 5, 6, 8] is generated when a state of dysbiosis occurs. These agents trigger the release of pro-inflammatory cytokines (tumour necrosis factor ά or interleukins type 6 or 1ß) [4–6], which leads to synergies between inflammation, increased oxidative stress and imbalance in energy homeostasis [8].

The current context of an international health emergency and the measures implemented by governments to deal with the SARS-CoV-29 pandemic (border closures, social distancing and home quarantine) have favoured the deterioration of lifestyles [9–12]. This fact has increased the risk of homeostatic dysregulation in the particularly vulnerable population (LTMD) [9, 11]. In addition, the modification of dietary patterns may have altered the functioning of the microbiota-gut-brain axis.

Background

Evidence shows a high rate of disability, morbidity and mortality (up to 20% higher) [14, 15] in people suffering from psychiatric disorders, especially in patients with LTMD [1, 2, 13–16]. Moreover, these alterations are closely linked to the development of Metabolic Syndrome (MS) [2, 14, 16, 17], which is considered a determining factor in the patient's physical health and can triple the incidence of cardio-metabolic diseases (diabetes mellitus, ischaemic heart disease, etc.) [8, 18].

The main etiopathogenic determinants of MS in these patients are linked to the characteristics of the disease itself and resistance to optimal physical health and lifestyle care [13–16]. In addition, it is essential to note that the psychopharmacological treatment usually prescribed for these patients directly impacts the cardio-metabolic health of the psychiatric patient [13, 15, 16].

Despite the magnitude and severity of the problem, interventions aimed at modifying lifestyles do not play a prominent role in the routine clinical practice of the psychiatric population [2, 14, 17]. Therefore, it is vital to intervene on these factors (including dietary patterns) to improve cardio-metabolic dysfunction. This type of action should be considered as a complement to the conventional therapeutic approach [2–4, 19].

In this regard, some dietary interventions effectively modulate the gut microbiota through symbiotic products. These are a range of nutritional products and food supplements that include probiotics and prebiotics that have a health benefit for the host [20]. In this regard, the use of "psychobiotics" [7, 21–24], a term that refers to the set of probiotic and/or prebiotic substances whose administration has health benefits for psychiatric patients, is noteworthy [22, 24]. Probiotics include micro-organisms from the intestinal biota that, when administered in adequate amounts, benefit the host (notably the genera Lactobacillus and Bifidobacterium, among others) [4, 5, 22–24]. On the other hand, prebiotics is non-digestible dietary fibre (fructooligosaccharides and oligosaccharides, inulin or pectins) [1] and promote optimal growth and development of probiotics in the gastrointestinal tract, reducing pathogenic microbiota [3, 4, 24].

In short, the future of new models of care in Mental Health should include the focus and promotion of the approach and management of nutritional factors [25],

highlighting the educational tool developed by nurses, which may represent the cornerstone in achieving optimal health outcomes.

Therefore, this study aimed to assess the impact of a high-symbiotic diet on metabolic and cardiovascular health outcomes in patients diagnosed with a schizophrenia spectrum disorder in confinement and social restriction due to the SARS-CoV-2 pandemic.

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.

Population

The sample was selected from the referral Psychiatry Service 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 18–65 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) suffered from a somatic or neurocognitive situation that prevents participation and collaboration in the fulfilment of the protocol; (2) followed standardised dietary planning not modulated by the population under study (catering, institutional or collective feeding, etc.); (3) refused to participate in the study.

Sample size

A sample size of 22 individuals was estimated (11 for the control group -CG- and 11 for the intervention group -IG-). A power of 80%, a confidence of 95%, and a risk/prevalence difference of Metabolic Syndrome of 63% post-intervention were also expected [26]. The researchers established the final size of 50 individuals (25 in each group) to minimise the effect of possible losses.

Intervention

Advanced practice nurses developed nutritional intervention and education. The CG consisted of those participants who received regular dietary advice (energy needs; immediate principles and consumption requirements

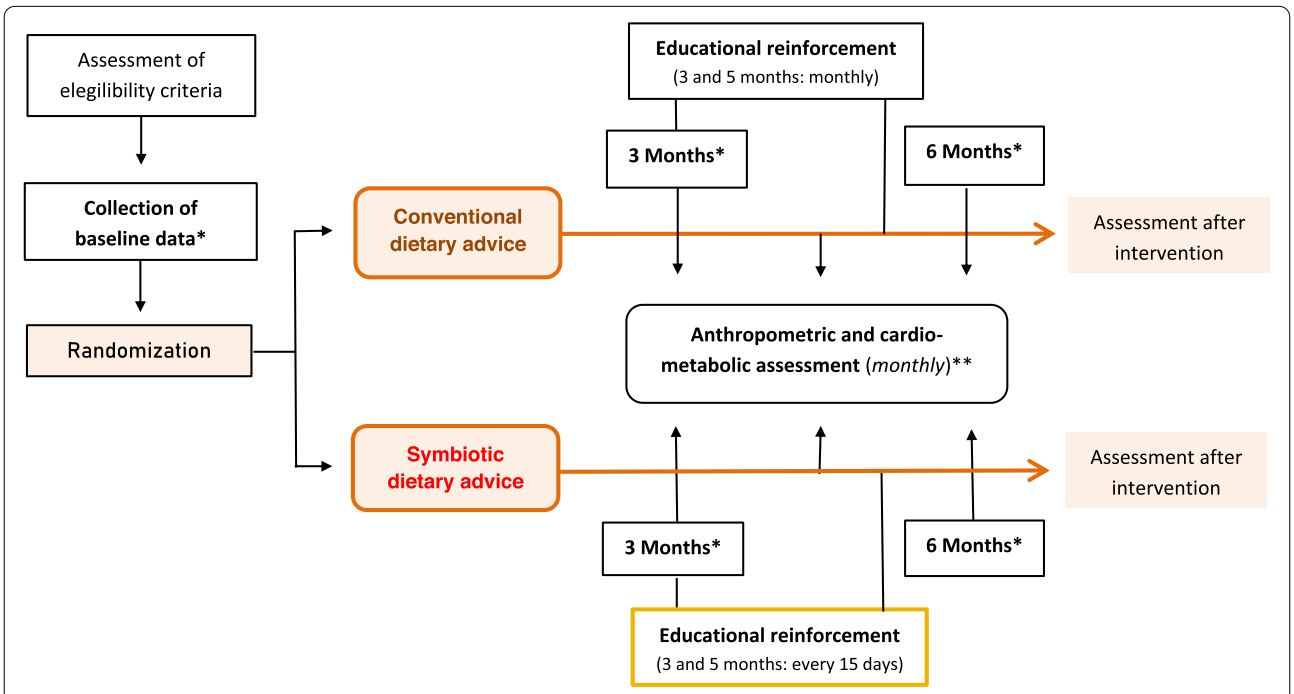

Fig. 1 Study Design. *Data collected at baseline, 3 and 6 months of intervention: (1) Biochemical profile. ** Data collected at baseline and monthly during intervention: (1) Anthropometric data (weight, height, Body Mass Index -BMI-, waist circumference and waist-to-height ratio -WHtR-); (2) Cardio-metabolic data (systolic blood pressure, diastolic blood pressure and heart rate)

-carbohydrates, lipids, proteins, fibre, vitamins, and minerals-; water requirements; regular physical activity) [27] on an individual basis. On the other hand, the intervention group was established individually through intensive nutritional advice [28] with high symbiotic content (Fig. 2). In both intervention groups, specialised nurses used educational resources of visual support during the consultations (Figure S1). Dietary education consisted of increasing the consumption of fermented foods, whole grains, green leafy vegetables and fruits high in dietary fibre, among others. A 6-month individual nutrition education program was implemented (with two months of educational reinforcement, every 15 days for the IG and monthly for the CG). Cardio-metabolic data on a biochemical profile were collected by nursing staff through blood sampling at baseline, 3 and 6 months. Anthropometric variables (BMI, waist-to-height ratio (WHtR), blood pressure, heart rate and waist circumference) were collected monthly by trained nurses, following international protocols [29] (Table S1). The risk of cardiovascular events at ten years was assessed using the REGICOR [30] and SCORE [31] risk functions after six months of intervention. These functions are based on systolic and diastolic blood pressure, age, sex, HDL cholesterol, and smoking, among others.

Finally, to assess adherence, IG participants completed a weekly record of the main dishes/foods consumed with a high prebiotic and probiotic content (fermented foods, whole grains, green leafy vegetables, fruits, etc.), which can be found in the Table S2.

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-means ANOVA, were used to study the relationship between quantitative variables. Chi-square with its corrections (Fisher or Yates) and the McNemar test were computed to study the association between qualitative variables. If the homoscedasticity criterion were not met, non-parametric versions of the previous tests were carried out. 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. Six participants were excluded during the intervention phase. Finally, the study was completed by 21 subjects in the CG and 23 in the IG. The flow chart of the participants is shown in Fig. 3.

32 (72.7%) men and 12 women participated, with a mean age of 49.2 ± 11.9 years. The leading psychiatric diagnosis was schizophrenia ($n=37$; 84.1%), with a mean duration of illness of 21.6 ± 12.4 years. The mean consumption of intoxicants was 29 smokers (65.9%) for tobacco, followed by 10 subjects who consumed cannabis (22.7%) and 6 participants who reported drinking alcohol (13.6%). Regarding the number of subjects with an associated cardio-metabolic risk factor diagnosis, 14 subjects (31.8%) had dyslipidaemia, 10 (22.7%) hypertension (22.7%), and 7 (15.9%) suffered from diabetes mellitus. Likewise, the prevalence of MS was 43.2% (19 subjects), not including all those with associated cardio-metabolic pathology already diagnosed [20 (45.5%)]. That is, we found a high percentage of subjects with cardiovascular and metabolic alterations prior to the intervention phase.

Finally, the baseline analysis of the dependent variables showed significant differences between the groups analysed for HDL-C, weight, waist circumference and BMI. Tables 1 and 2 contain the baseline characteristics of the independent and dependent variables, respectively, showing homogeneity between both allocation groups.

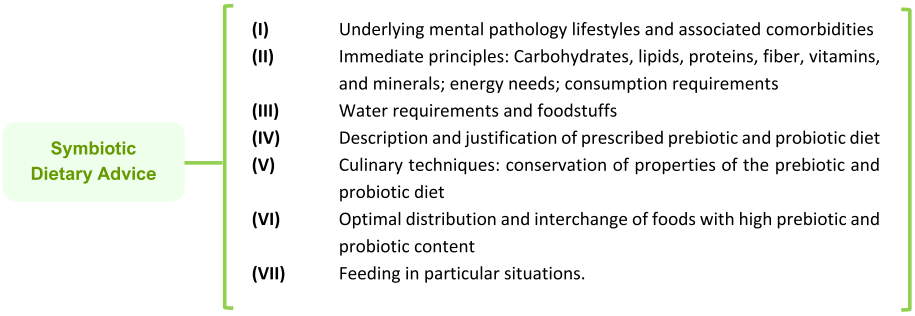

Fig. 2 Symbiotic dietary counselling: structure of consultations for the Intervention Group

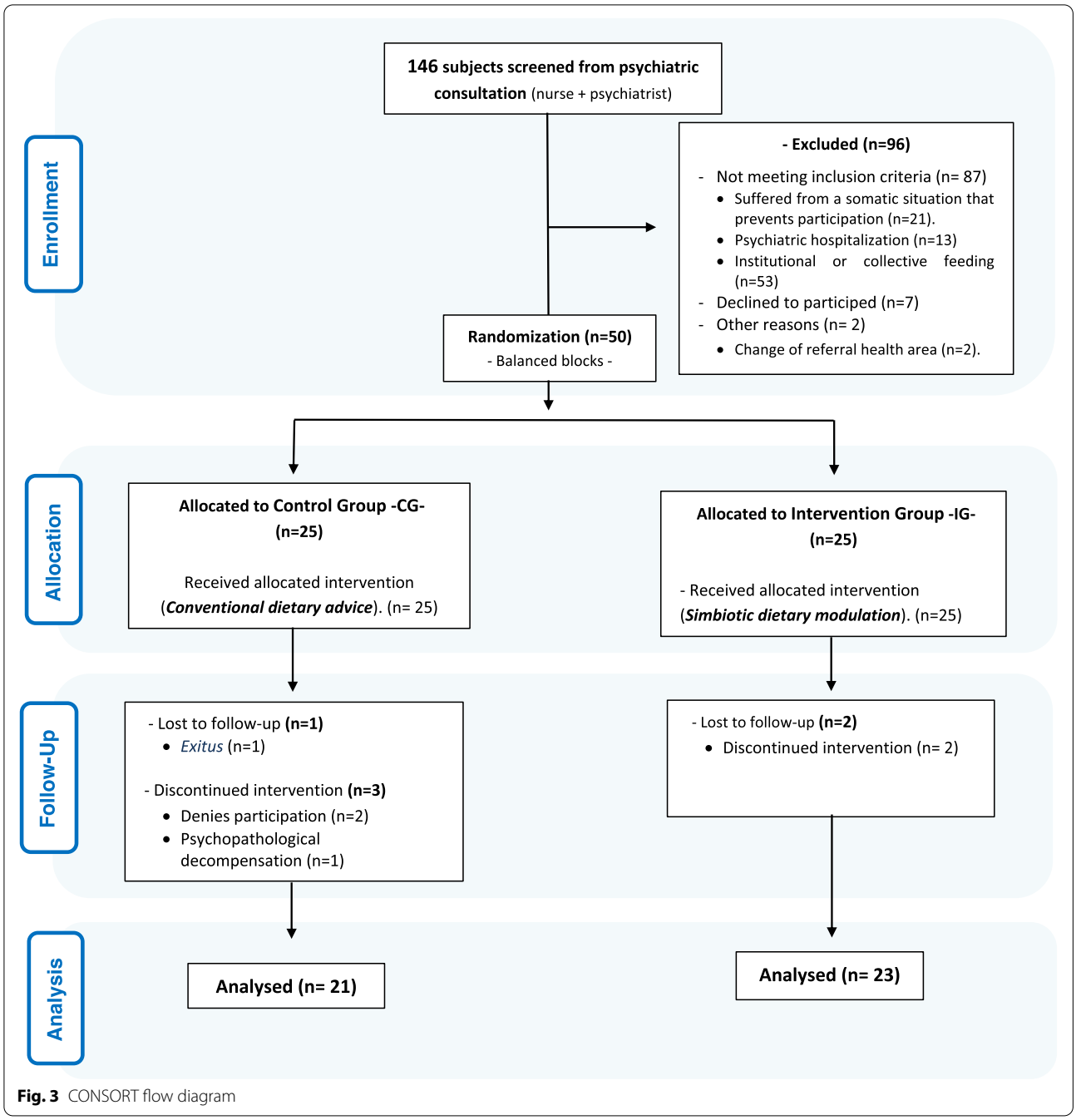

Fig. 3 CONSORT flow diagram

Table 3 shows changes in outcome variables at baseline and six months of intervention in CG and IG, respectively. Intragroup analysis showed a significant improvement ($p < 0.05$) in all anthropometric variables in the IG. However, no statistically significant differences were observed in the biochemical and cardiovascular profile and the number of antipsychotics and prescribed dose. Regarding the overall inter-group analysis, no statistically significant results were shown.

Given the results, to elucidate clinically relevant and significant changes between the different allocation groups, we decided to perform a post-hoc analysis of the percentual balance of the risk factors (components). We evidenced a percentage difference of 27.4% -$p > 0.05$- (increasing 14.3% in CG and reducing 13.1% in IG) in metabolic syndrome development at 6 month of intervention. In this regard, looking at the different components of the metabolic syndrome in both groups, a

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

Variables	TOTAL (*n* = 44)	Men (*n* = 32)	Women (*n* = 12)	*P*
Socio-demographic variables				
- Age (years)	49.2 (11.9)	50.7 (10.1)	45 (15.5)	0.897
- Legal representative				
• No	36 (81.8%)	28 (63.8%)	8 (18.2%)	0.185
• Yes	8 (18.2%)	4 (9.1%)	4 (9.1%)	
- Household composition				
• Individual	12 (27.3%)	10 (22.8%)	2 (4.5%)	0.285
• Horizontal	3 (6.8%)	1 (2.3%)	2 (4.5%)	
• Complete	3 (6.8%)	3 (6.8%)	0 (0%)	
• Own family home	7 (15.9%)	4 (9.1%)	3 (6.8%)	
• Other: Supervised flat	19 (43.2%)	14 (31.8%)	5 (11.4%)	
- Economic level				
• High	6 (13.6%)	5 (11.4%)	1 (2.3%)	0.754
• Medium	26 (59.1%)	19 (43.2%)	7 (15.9%)	
• Low	12 (27.3%)	8 (18.2%)	4 (9.1%)	
- Level of education				
• Uneducated	4 (9.1%)	3 (6.8%)	1 (2.3%)	0.009
• Primary	19 (43.2%)	9 (20.5%)	10 (22.7%)	
• Secondary	17 (38.6%)	16 (36.4%)	1 (2.3%)	
• University	4 (9.1%)	4 (9.1%)	0 (0%)	
- Area of residence				
• Urban	38 (86.4%)	29 (65.9%)	9 (20.5%)	0.321
• Rural	6 (13.6%)	3 (6.8%)	3 (6.8%)	
Clinical Variables				
-Psychiatric diagnosis				
• Schizophrenia	37 (84.1%)	26 (59.1%)	11 (25%)	0.608
• Schizoaffective Disorder	5 (11.4%)	4 (9.1%)	1 (2.3%)	
• Delusional Disorder	2 (4.5%)	2 (4.5%)	0 (0%)	
- Duration of illness (years)	21.6 (12.4)	22.4 (11)	16.6 (15.9)	0.715
- Age at first hospitalisation (years)	31.4 (11)	30.7 (10.8)	33.2 (11.5)	0.572
- Consumption of toxics				
• No	15 (34.1%)	9 (20.5%)	6 (13.6%)	0.284
• Yes	29 (65.9%)	23 (52.3%)	6 (13.6%)	
- Type of toxics				
• Alcohol	6 (13.6%)	5 (11.3%)	1 (2.3%)	1.00
• Tobacco	29 (65.9%)	23 (52.3%)	6 (13.6%)	
• Cocaine	3 (6.8%)	2 (4.5%)	1 (2.3%)	
• Opioids	2 (4.5%)	1 (2.3%)	1 (2.3%)	
• Amphetamines	3 (6.8%)	2 (4.5%)	1 (2.3%)	
• Cannabis	10 (22.7%)	7 (15.9%)	3 (6.8%)	
- Cardio-metabolic diagnosis				
• No	24 (54.5%)	15 (34.1%)	9 (20.5%)	0.095
• Yes	20 (45.5%)	17 (38.6%)	3 (6.8%)	
- Type Cardio-metabolic diagnosis				
• AHT	10 (22.7%)	8 (18.2%)	2 (4.5%)	0.059
• DM	7 (15.9%)	5 (11.4%)	2 (4.5%)	
• Hyperlipemia	14 (31.8%)	13 (29.6%)	1 (2.2%)	

Table 1 (continued)

Variables	TOTAL (*n* = 44)	Men (*n* = 32)	Women (*n* = 12)	*P*
Therapeutic Variables				
- Reason for Change: Antipsychotic Treatment				
• Unchanged	31 (70.5%)	20 (45.5%)	11 (25%)	0.302
• Lack of efficiency	5 (11.4%)	5 (11.4%)	0 (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%)	

AHT Arterial hypertension, *DM* diabetes mellitus

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

Variables	TOTAL (*n* = 44)	Men (*n* = 32)	Women (*n* = 12)	*P*
Biochemical profile				
- Glucose *(mg/dL)*	94.1 (13.7)	94.6 (14)	92.7 (13.2)	0.668
- HbA1c *(%)*	5.4 (0.3)	5.5 (0.3)	5.3 (0.3)	0.118
- Cholesterol *(mg/dL)*	186.7 (43.4)	182.3 (47.1)	198.5 (30.2)	0.224
- Triglycerides *(mg/dL)*	131.6 (71)	145.6 (75.7)	94.1 (38.3)	0.026
- LDH *(IU/L)*	185.9 (26.9)	185 (22.7)	94.1 (38.3)	0.948
- C-HDL *(mg/dL)*	49.9 (14.1)	45 (10.8)	63.1 (13.9)	< 0.001
- C-LDL *(mg/dL)*	112.1 (34.7)	110.5 (36.9)	116.3 (28.9)	0.594
- Total cholesterol/C-HDL *(mg/dL)*	3.9 (1.2)	4.1 (1.2)	3.2 (0.8)	0.037
Anthropometric Profile				
- Weight *(kg)*	81.4 (17.6)	87.6 (15)	64.6 (12.3)	< 0.001
- Waist circumference *(cm)*	101.9 (17)	104.4 (18.6)	95.2 (9.7)	0.01
- BMI *(kg/m2)*	28.5 (5)	29.6 (5)	64.6 (12.3)	0.011
- WHtR	0.6 (0.1)	0.6 (0.1)	0.6 (0.06)	0.866
- Height (cm)	168.5 (9.2)	172.1 (6.2)	158.7 (9)	0.245
Cardiovascular Profile				
- SBP *(mmHg)*	127.2 (15)	128.2 (14.9)	124.5 (15.5)	0.290
- DBP *(mmHg)*	84.2 (10.7)	85.4 (10.6)	80.7 (10.5)	0.204
- HR *(bpm)*	84.8 (14.5)	83.8 (16.5)	87.5 (7.1)	0.186
- Metabolic Syndrome				
No	25 (56.8%)	16 (36.4%)	9 (20.5%)	0.136
Yes	19 (43.2%)	15 (36.4%)	3 (6.8%)	
Therapeutic Variables				
- Nº of associated antipsychotic	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	0.969
- DDD antipsychotics *(mg)*	271.4 (242.5)	284.5 (241.1)	236.4 (253.3)	0.541

HbA1c glycosylated haemoglobin, *IFCC* International Federation of Clinical Chemistry and Laboratory Medicine, *LDH* lactate dehydrogenase, *C-HDL* high-density lipoprotein, *C-LDL* low-density lipoprotein, *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

significant percentage reduction was observed in the IG for waist circumference, abdominal circumference, triglycerides and HDL-C. Nevertheless, this percentage increased in the CG, giving an overall percentual balance of 13% ($p = 0.69$), 13.5% ($p = 0.601$) and 9.5% ($p = 0.599$), respectively. In addition, we found a significant diastolic blood pressure reduction in the IG (-21.8%, $p = 0.392$), and the systolic blood pressure remained without changes ($p = 0.365$). In the CG, there was a percentage increase. The glycaemic profile worsened (both groups' blood glucose levels were higher). However, this increase was lower in the IG -$p < 0.05$- (17.4% vs 38.4%). Figure S2

Table 3 Modifications in Metabolic Syndrome factors: control group and experimental group

	Control Group ($n=21$)			Intervention Group ($n=23$)				
Variables	**Basal**	**6 months**	***p***	**Basal**	**6 months**	***p***	***P****	***P*****
Biochemical profile								
- Glucose *(mg/dL)*	94.5 (16.8)	102.6 (18.9)	0.03	93.7 (10.4)	97.5 (13.5)	0.023	0.814	0.259
- HbA1c *(%)*	5.4 (0.4)	5.5 (0.3)	0.038	5.4 (0.3)	5.4 (0.6)	0.948	0.887	0.768
- Cholesterol *(mg/dL)*	173.2 (45.4)	171 (43.9)	0.664	199.1 (38.4)	179.4 (64.3)	0.072	0.115	0.155
- Triglycerides *(mg/dL)*	121.1 (67.4)	137.5 (75.8)	0.352	141.1 (74.3)	134.2 (69.4)	0.584	0.235	0.981
- LDH *(IU/L)*	182.5 (22.5)	172.4 (29.9)	0.141	189 (30.6)	172.4 (29.9)	0.049	0.533	0.647
- C-HDL *(mg/dL)*	50.2 (15.4)	48.4 (15.1)	0.067	49.7 (13.1)	52.4 (24.9)	0.611	0.962	0.760
- C-LDL *(mg/dL)*	100.4 (33.8)	96.9 (33.7)	0.446	123 (32.4)	119.3 (41.6)	0.7	0.048	0.067
- Total cholesterol/C-HDL *(mg/dL)*	3.6 (0.9)	3.6 (0.8)	0.522	4.2 (1.3)	4.2 (1.3)	0.905	0.058	0.180
Anthropometric Profile								
- Weight *(kg)*	76.6 (18)	75.8 (17.7)	0.382	85.7 (16.3)	81.3 (14.6)	< 0.001	0.086	0.275
- Waist circumference *(cm)*	100.9 (13.3)	101.2 (13.5)	0.818	105.7 (11.5)	102 (11.7)	< 0.001	0.397	0.981
- BMI *(kg/m2)*	27.5 (5.2)	27.2 (5.3)	0.323	29.5 (4.8)	27.9 (4.3)	< 0.001	0.307	0.869
- WHtR	0.59 (0.12)	0.61 (0.07)	0.345	0.61 (0.07)	0.59 (0.06)	< 0.001	0.597	0.378
Cardiovascular Profile								
- SBP *(mmHg)*	125.5 (16.3)	129.8 (11.2)	0.124	128.7(13.9)	126.8 (10.6)	0.593	0.391	0.359
- DBP *(mmHg)*	85.5 (9.7)	82.3 (7.9)	0.846	85.6 (11.5)	80.8 (7.5)	0.039	0.548	0.814
- HR (bpm)	88.5 (16.4)	87.4 (14.2)	0.757	81.4 (12)	80.8 (9.4)	0.792	0.110	0.226

p: intragroup statistical significance; *p**: baseline intergroup statistical significance; *p***: 6 months intergroup statistical significance; *HbA1c* Glycosylated haemoglobin, *LDH* Lactate dehydrogenase, *C-HDL* High-density lipoprotein, *C-LDL* Low-density lipoprotein, *BMI* Body mass index, *WHtR* Waist-to-height ratio, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *HR* Heart rate, *CG Evol*. Control group evolution, *IG Evol* Intervention group evolution, *% Balance* Percentage variation, *REGICOR* Calculation of 10-year coronary heart disease risk, *SCORE* Systematic coronary risk assessment for Spain, Antipsychotic *DDD* Defined daily dose antipsychotics

shows the components of MS evolution at baseline and six months of intervention in CG and IG. Likewise, Fig. 4 shows the percentual balance between the components of MS and lipid profile at six months of intervention in both groups. These results reached non-statistically significant trends, probably due to the limited sample size.

Finally, cardiovascular risk was analysed at baseline and after the intervention using the REGICOR and SCORE risk functions. According to the REGICOR equation, for the development of cardiovascular disease at ten years, we found a greater percentage reduction in the mean risk of 1.02% in the IG compared to the CG. Similarly, according to SCORE, a 0.12% lower percentual balance was obtained in IG (0.22%) compared to CG (0.34%) in terms of stratified risk.

Discussion

The present study demonstrated that, after implementing a nutritional programme focused on high prebiotic and probiotic dietary modulation in patients diagnosed with schizophrenia spectrum disorder, the anthropometric profile (all variables) and, therefore, the risk of MS improved significantly in the IG. Similar results were obtained by Caemmerer et al. (2012) and Sugawara et al. (2018) [25, 26]. Likewise, the intervention reduced the risk of morbidity and mortality associated with cardiovascular events. Despite the limited resulting percentage, as noted by Dabke et al. (2019), the association of the nutritional programme with the conventional therapeutic approach led to a high synergistic impact on the improvement of dysmetabolic states [8], which are very important frequent in this population [13, 15, 16]. In this sense, the clinically significant results obtained support the meta-analysis developed by Teasdale et al. (2017), showing non-pharmacological interventions (dietary modulation and nutritional education) are established as coadjuvant therapies for metabolic anomalies [32], improving tolerance and pharmacological acceptance rates [24].

Regarding the level of compliance and results obtained in both allocation groups, it is essential to highlight the contextual framework of the global SARS-CoV-2 pandemic in which this clinical trial has been developed. In this regard, as indicated by Solé et al. (2021), most preliminary studies during the current pandemic have focused on psychological distress in the general population [9]. However, this study has been the first to address cardio-metabolic improvement through a nutritional intervention focused on prebiotics and probiotics dietary modulation in schizophrenia spectrum disorders. Nevertheless, numerous associated difficulties have probably prevented us from obtaining more statistically significant

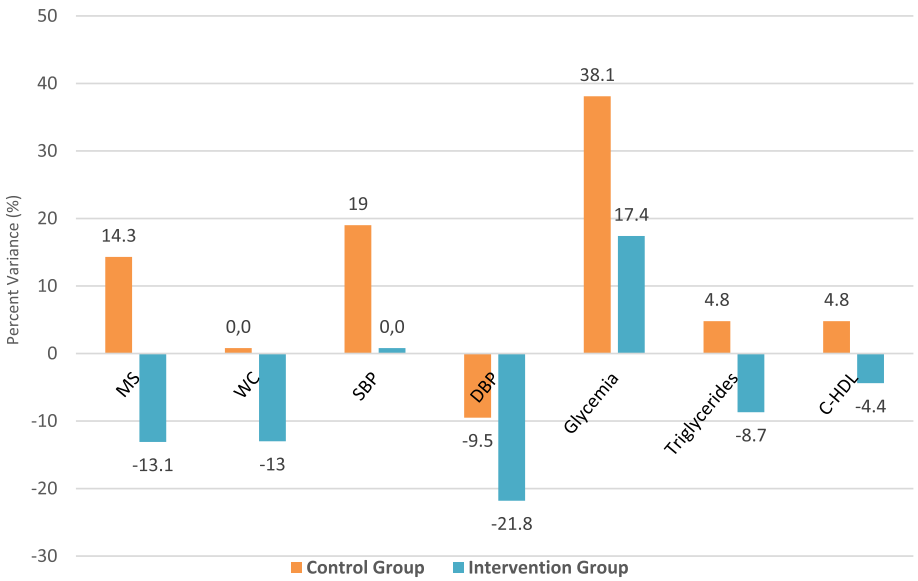

Fig. 4 Evolution in allocation groups at 6 months: Metabolic Syndrome and Lipid Profile. MS: metabolic Syndrome ($p=0.57$); WC: waist circumference ($p=0.69$); SBP: systolic blood pressure ($p=0.365$); DBP: diastolic blood pressure ($p=0.392$); Glycemia ($p=0.349$); Triglycerides ($p=0.601$); C-HDL: high-density lipoprotein ($p=0.235$)

results. In this sense, the particular vulnerability of the target population in a context of confinement and global pandemic [9, 11, 12] stands out. This situation affects tangentially and negatively physical health [23, 32]. Thus, evidence shows a high complexity approach to schizophrenia [2], to which a context of confinement and social restriction has been added. Furthermore, there is proof of the effect of this situation on these patients, who see limited adherence to coping strategies, encouraging an increase in unhealthy lifestyles [9] related to inadequate dietary and physical exercise patterns [11, 32]. This fact may have modified the response to the symbiotic approach under investigation [8, 23].

Scientific evidence supports and clarifies the results obtained in the present study, with an increase in cardiovascular risk factors and associated morbidity and mortality during the SARS-CoV-2 era, especially in susceptible subjects and those with pre-existing MS [12, 32, 33]. This situation seems to be linked to a modification of lifestyles and defined by hypercaloric dietary patterns and restrictions in physical activity (up to 60% lower) [10, 12, 32]. These conditions can increase body weight and worsen the glycaemic and lipid profile, even in the short term [12, 23, 34]. In this sense, Solé et al. (2021) and Rishi et al. (2020) support the need to develop new strategies for home-based care and monitoring in states of confinement, promoting appropriate lifestyles and optimal health outcomes [9, 23]. Furthermore, these strategies should be strongly supported by technological development [11].

On the other hand, clinical trials with nutritional supplements or dietary approaches in the absence of psychopharmacological treatment are limited [8] and show marked heterogeneity and lack of methodological rigour [2, 5]. However, although the results obtained in the literature are not consistent, the findings of Patra (2016) support our findings, where the multimodal symbiotic approach, with nutraceutical action, was found to be effective as a complementary strategy in the treatment of dysmetabolic states in schizophrenic disorders [7].

Finally, and in agreement with Balanzá (2017), it is necessary to highlight the role of advanced practice nursing, a cornerstone in the multidisciplinary approach and the main responsible for the effectiveness of dietetic-nutritional interventions and improvement of lifestyles in the psychiatric population [17]. Thus, contrary to what was stated by Teasdale et al. (2017) [32], the proposed interventions' effectiveness is influenced by dieticians' participation and other health professionals with nutrition skills. In this group, nurses highlight because they can provide added value in the holistic care of the psychiatric patient [14] for several reasons: (i) assuming a prominent role in the coordination of caring for this population, (ii) their capability to offer care in different settings (highlighting home care) and (iii) optimal multimodal management of socio-health resources in states of social restriction and confinement [9, 17, 23].

Limitations

The main limitations of the present study are related to the sample size and the possible loss or lack of cooperation of participants in the intervention phase. However, this limited sample size could explain the few significant differences in biochemical and cardiovascular profiles. Furthermore, regarding the associated cardio-metabolic diagnosis, it should be noted that a minority of the participants were on pharmacological treatment prior to the study.

It is worth highlighting the exclusion of those subjects with a potential risk of cardiovascular health problems during the debut or exacerbation of the underlying psychopathological process. This decision was taken because the research focused on chronic patient management. Consequently, the results cannot be extrapolated to a population in the initial stages of exacerbation of the disease.

In addition, this work does not show the changes in the dietary pattern of the subjects during the intervention, which may limit the significance and clinical relevance of the results obtained. Their analysis in further research would help clarify which nutritional factors are closely linked to improving the cardio-metabolic profile in the target population.

On the other hand, the available evidence on the subject of the study makes it difficult to contrast the results obtained in different health care settings.

Finally, it is essential to note that this study was conducted during the SARS-CoV-2 pandemic, making it difficult to achieve the proposed intervention. Furthermore, it is necessary to consider the inherent characteristics of the subjects under study, a population particularly vulnerable to change, especially in a context of confinement and a global pandemic.

Conclusions

The development of a dietary-nutritional intervention with high symbiotic content in patients diagnosed with schizophrenia spectrum disorders has been postulated as an effective and clinically significant therapy in reducing cardiovascular risk factors and improving metabolic outcomes in the context of the global SARS-CoV-2 pandemic. These dietary recommendations may work as an adjuvant in the metabolic syndrome of patients with schizophrenia spectrum disorders, leading to increased pharmacological tolerance and improved physical health. Thus, a decrease of 14.3 percentage points in the prevalence of MS in the IG has been observed, compared to an increase of 13.1 points in the CG, which represents a differential balance of 27.4% between groups. Furthermore, despite the target population's inherent lifestyle dysfunctionalities, prebiotics and probiotics have been shown to offer a relevant and promising solution in different application contexts, improving patients' quality of life and mitigating the risk of associated cardio-metabolic disorders. Nursing plays a prominent role in achieving optimal health outcomes, being a cornerstone in the multimodal approach and modulating lifestyles, through dietary-nutritional education. Finally, further studies with larger sample sizes are needed to corroborate these promising results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-022-04426-9.

Additional file 1: Table S1. Anthropometric Assessment and Physical HealthRecord. **Table S2.** WeeklySymbiotic Diet Register. **Figure S1.** Nutritional Information. **Figure S2.** Evolution of components of Metabolic Syndrome atbaseline and six months of intervention: Control group and intervention group.

Acknowledgements

This publication is partially funded by the XXVII Nursing Research Grant of the Illustrious Official College of Nursing of Córdoba, Spain.
Disclosure statement
The authors warrant that the article is original and not submitted.

Authors' contributions

ASJ, GMR, MGR and MRS contributed to conception and design to the study; ASJ, GMR, JAGM, LCL, 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 they're agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

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

Declarations

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.

Competing interests
The authors declare that they have no competing interests.

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Received: 8 March 2022 Accepted: 25 November 2022
Published online: 12 December 2022

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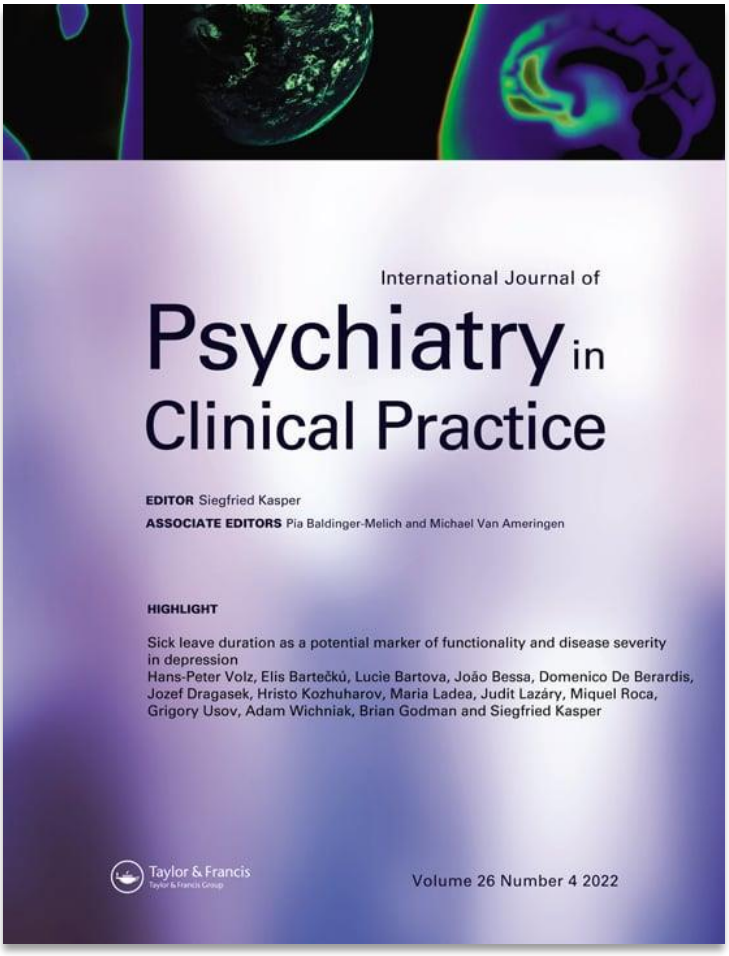
Publisher's Note

3.4. Capítulo IV

*(*Manuscrito enviado para su publicación*: Bajo revisión actual)*



Eficacia psicopatológica y cardiometabólica de una intervención de educación nutricional basada en simbióticos en trastornos del espectro esquizofrénico. Ensayo clínico aleatorizado de dos brazos.

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

ABSTRACT

Background: 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 3-6 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 have been shown to play a prominent role in developing nutrition education and promoting healthy lifestyles in these patients.

Trial registration: The study protocol complied with the Declaration of Helsinki for medical studies; the study received ethical approval from referral Research Ethics Committee in November 2019 (reg. no. 468) and retrospectively registered in clinicaltrials.gov (NCT04366401. First Submitted: 28th April 2020; First Registration: 25th June 2020).

Keywords: Diet Therapy; Mental Health; Nursing; Schizophrenia Spectrum and Other Psychotic Disorders; Randomized Controlled Trial.

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 a significant neurocognitive impairment, impacting and often debilitating social and occupational functioning[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].

Background

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 Figure 1.

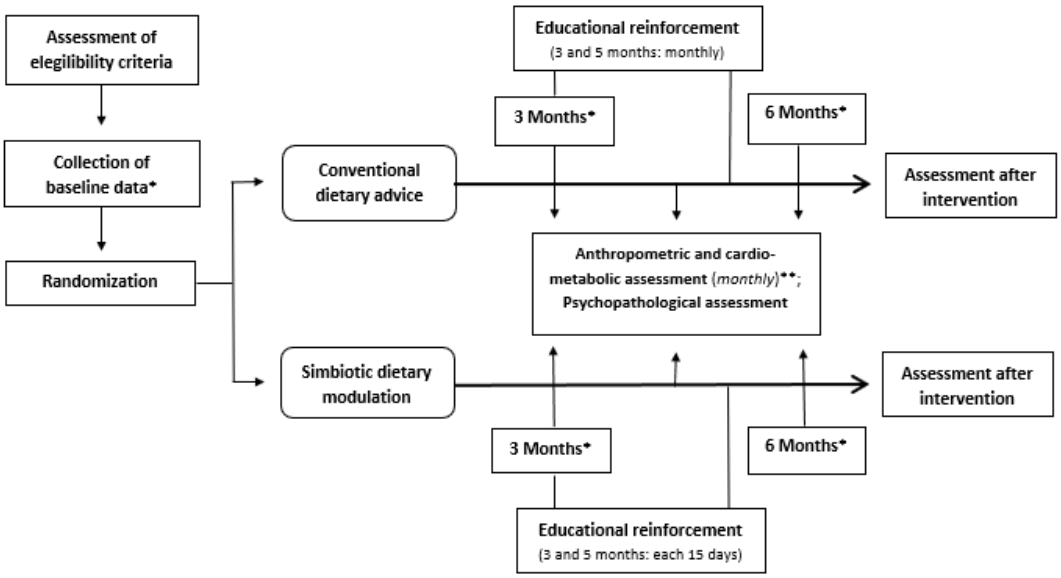


Figure 1. Study Design. *Data collected at baseline, 3 and 6 months of intervention: (1) Psychopathological data (Positive and Negative Syndromes Scale -PANSS- and the Personal and Social Functioning Scale -PSP-). ** Data collected at baseline and monthly during intervention: (1) Anthropometric data (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).

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 18-65 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 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 (Figure 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-means 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. 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 Figure 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.

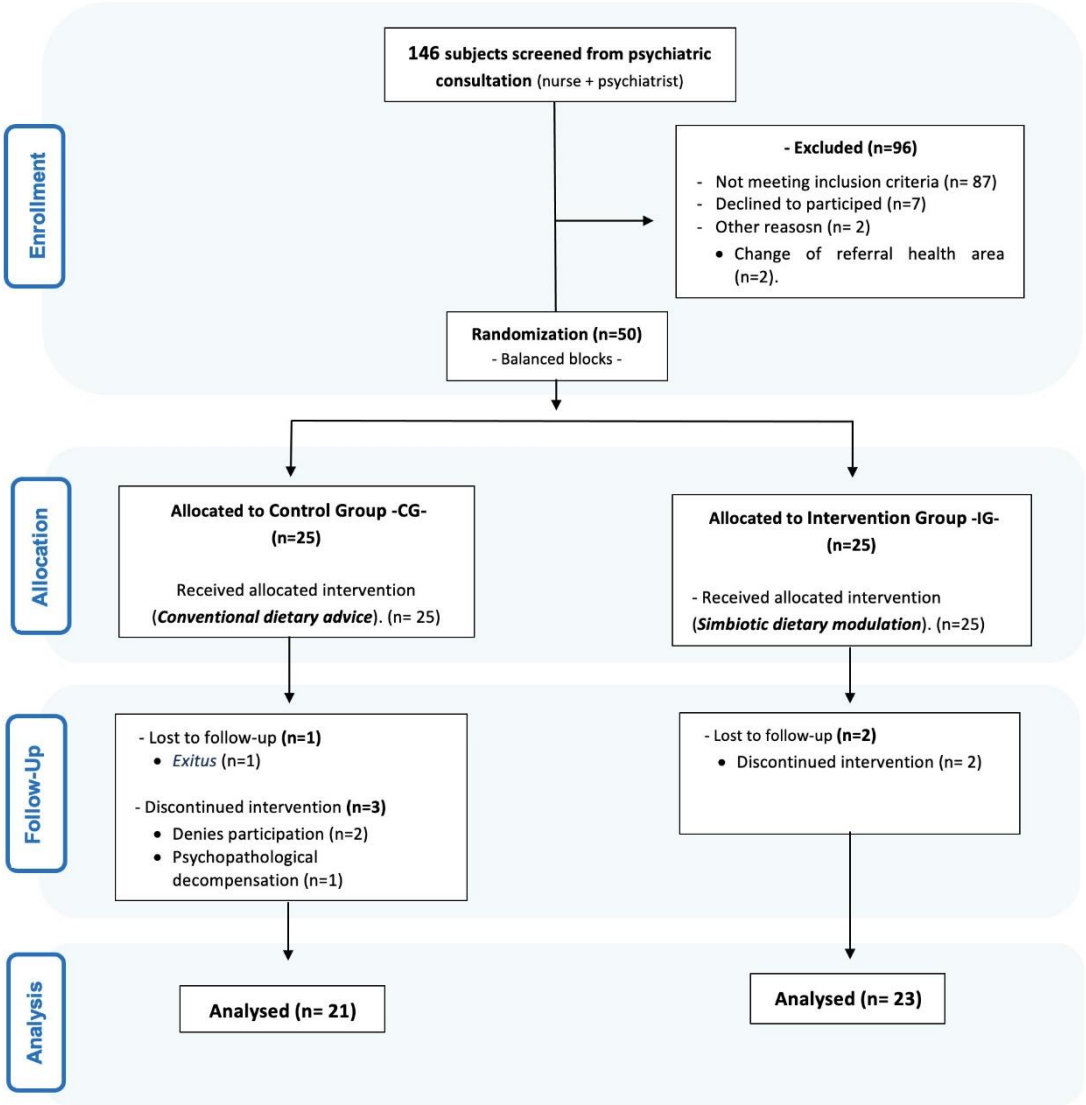


Figure 2. CONSORT flow diagram.

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, 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 3-6 months of intervention maintained a significant difference in all variables in the IG. Finally, not statistically 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.

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%)	
	Tobacco	29 (65.9%)	15 (34%)	14 (31.8%)	

	Cocaine	3 (6.8%)	1 (2.3%)	2 (4.5%)	0.775
	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%)	
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-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				
- Nº 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-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

Variables	Control Group (n=21)				Intervention Group (n=23)				p**
	Basal	3 months	6 months	p*	Basal	3 months	6 months	p*	
Psychopathological Profile									
- 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									
- Nº 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-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

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-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									
- Nº 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

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-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-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									
- Nº 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

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-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.

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) and the improvement in general psychopathology (PANSS-GP) between 3-6 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.

DECLARATIONS

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.

Data Availability Statement

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

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

ASJ, GMR, and MRS contributed to conception and design to the study; ASJ, GMR, MGR, 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.

Acknowledgements

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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4. Conclusiones

Derivadas de objetivo principal:

1) Determinar la eficacia a nivel nutricional y cardio-metabólica de una intervención dietética prebiótica y probiótica en pacientes que presentan trastornos del espectro de la esquizofrenia.

   - **Segunda publicación** (Capítulo II): *"Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing-Two-Arm Randomised Clinical Trial".*

     - **Conclusión 1:** Se evidencia una mejora del perfil nutricional, con una mayor aproximación hacia las ingestas dietéticas recomendadas, así como adquisición de patrones dietéticos saludables.

     - **Conclusión 2:** La enfermería de práctica avanzada asume un papel destacado en la consecución de resultados óptimos en salud, a través de la educación dietético-nutricional en salud mental.

   - **Tercera publicación** (Capítulo III): *"Impact of high prebiotic and probiotic dietary education in the SARS-CoV-2 era: improved cardio-metabolic profile in schizophrenia spectrum disorders".*

     - **Conclusión 1:** La inclusión de un enfoque simbiótico en contextos de confinamiento se ha postulado como una solución eficaz y clínicamente significativa en la mejora del riesgo de SM, en todos sus componentes (factores de riesgo).

Derivadas de los objetivos específicos:

1) Conocer la evidencia científica existente respecto al constructo de factores (explícitos e implícitos) influyentes en el eje microbiota-intestino-cerebro.

   - **Primera publicación** (Capítulo I): *"Efficacy of nutrition education for the increase of symbiotic intake on nutritional and metabolic status in schizophrenic spectrum disorders: A two-arm protocol".*

- **Conclusión 1:** El microbioma intestinal juega un papel fundamental en el eje microbiota-intestino-cerebro, a través de la comunicación bidireccional entre el tracto gastrointestinal y numerosos trastornos neuropsiquiátricos.

- **Conclusión 2:** El patrón dietético supone el principal determinante de la MI. De este modo, la regulación alimentaria mediante productos prebióticos y probióticos condiciona la concentración y perfil cualitativo de la microbiota.

- **Conclusión 3:** El uso de psicobióticos conlleva una mejora de la disbiosis asociada a la MI, condicionante de un estado de inflamación sistémica de bajo grado y estrés oxidativo. Así, el estado de eubiosis alcanzado por la acción de los productos simbióticos desencadena un reajuste en el desequilibrio psicopatológico y de la homeostasis energética, prevalente en los estados dismetabólicos.

2) Determinar el patrón dietético y estado nutricional basal en trastornos del espectro esquizofrénico.

❖ **Segunda publicación** (Capítulo II): *"Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing-Two-Arm Randomised Clinical Trial".*

- **Conclusión 1**: El patrón dietético analizado concuerda con la evidencia actual, existiendo un alto consumo de alimentos ultraprocesados, carbohidratos refinados, grasas saturadas y sodio, entre otros. Así mismo, se observa una deficiente ingesta de vitamina D, frutas y verduras.

- **Conclusión 2:** Prevalece un estado de baja calidad nutricional en la población objeto de estudio. En este sentido, se evidencia un patrón alimentario hipercalórico, de alto índice glucémico, así como un carente e irregular consumo de fibra dietética, distantes de las %IDR.

- **Conclusión 3:** La ausencia de una alimentación equilibrada y balanceada en trastornos esquizofrénicos conlleva una mayor propensión de deficiencias nutricionales. Este hecho aumenta el riesgo disfunción cardio-metabólica.

3) Identificar los patrones dietéticos post-intervención en población objeto de estudio, esclareciendo el valor nutricional de los principales platos consumidos, así como su vinculación con el estado de salud física de los individuos.

   - **Segunda publicación** (Capítulo II): *"Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing-Two-Arm Randomised Clinical Trial".*

     - **Conclusión 1:** Se evidencia una reducción en el consumo del perfil proteico (huevos, carnes y pescados), azúcares y alimentos ultraprocesados, así como una tendencia hacia la restricción de ingesta de frutas y verduras. No obstante, se observa un incremento del consumo de productos lácteos, legumbres y cereales.

     - **Conclusión 2:** Se alcanza una mejora en todas las variables del perfil de macronutrientes y micronutrientes, con una mayor aproximación hacia las %IDR. Sin embargo, prevalece un déficit de fibra dietética y vitamina D, alejado de los estándares nutricionales.

     - **Conclusión 3:** El desarrollo del consejo dietético de alto contenido simbiótico determina la adquisición de estilos de vida saludables en trastornos esquizofrénicos, a pesar de la dificultad asociada en contextos de confinamiento. Así, la inclusión de productos simbióticos en el patrón alimentario se establece como terapia coadyuvante en la mejora de la salud cardio-metabólica.

4) Evaluar el impacto cardio-metabólico de una planificación dietética estandarizada con alto contenido prebiótico y probiótico, adaptada a las características inherentes de la población psiquiátrica.

   - **Segunda publicación** (Capítulo II): *"Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing-Two-Arm Randomised Clinical Trial".*

     - **Conclusión 1:** La mejora del estado nutricional confiere un valor añadido en términos antropométricos, mejorando variables clínicas alteradas y, por ende, menor riesgo de SM.

- ❖ **Tercera publicación** (Capítulo III): *"Impact of high prebiotic and probiotic dietary education in the SARS-CoV-2 era: improved cardio-metabolic profile in schizophrenia spectrum disorders".*

  - **Conclusión 1:** Se evidencia una mejora clínicamente significativa del riesgo cardiovascular y adecuación de resultados metabólicos en trastornos esquizofrénicos (hasta un 27,4%, en contextos de confinamiento).

  - **Conclusión 2:** Las recomendaciones dietéticas propuestas se articulan como coadyuvantes en la atención del SM en salud mental. Su aplicación permite una mayor tolerancia y aceptación de la farmacoterapia homeostática.

  - **Conclusión 3:** La modulación simbiótica brinda una mejora en la calidad de vida, aumentando el nivel de empoderamiento y desarrollo de prácticas saludables.

- ❖ **Cuarta publicación** (Capítulo IV): *"Psychopathological and cardiometabolic efficacy of a nutritional education intervention based on symbiotics in schizophrenia spectrum disorders. Two-arm Randomised Clinical Trial".*

  - **Conclusión 1:** La intervención propuesta evidencia una disminución del SM iatrogénico, asociado al uso de antipsicóticos. Este hecho añade plausibilidad en la capacidad de predicción y control de efectos secundarios psicofarmacológicos.

5) Evaluar el impacto psicopatológico de la incorporación de prebióticos y probióticos en el patrón dietético-nutricional habitual en pacientes con diagnóstico de trastorno del espectro de la esquizofrenia.

- ❖ **Cuarta publicación** (Capítulo IV): *"Psychopathological and cardiometabolic efficacy of a nutritional education intervention based on symbiotics in schizophrenia spectrum disorders. Two-arm Randomised Clinical Trial".*

  - **Conclusión 1:** El abordaje psicobiótico multimodal ha demostrado una mejora significativa de la psicopatología general y de los síntomas asociados al mismo, así como una adecuación en las dificultades asociadas al desempeño social y funcional del paciente.

- **Conclusión 2:** Se ofrece una solución prometedora frente a la prevalente disfuncionalidad en TMG, mejorando la calidad de vida y, por consiguiente, adecuación del contexto sociofamiliar.

- **Conclusión 3:** Se precisa el desarrollo de estudios longitudinales que evidencien la viabilidad del uso de psicobióticos en régimen monoterapéutico en trastornos del espectro esquizofrénico.

6) Desarrollar y validar un programa que permita la detección de áreas de mejora, estableciendo estrategias de valoración y un plan de actuación pertinentes en Salud Mental, que permitan una adecuada atención dietética mediante el uso de psicobióticos.

❖ **Primera publicación** (Capítulo I): *"Efficacy of nutrition education for the increase of symbiotic intake on nutritional and metabolic status in schizophrenic spectrum disorders: A two-arm protocol".*

- **Conclusión 1:** Se precisa la valoración periódica del estado dietético-nutricional y de salud física en trastornos esquizofrénicos, mediante la determinación del perfil antropométrico y análisis bioquímico. La valoración de disbiosis se analizará a través de coprocultivos.

- **Conclusión 2:** Ante la evaluación del nivel de gravedad y progreso de recuperación mental, se requiere la evaluación psicopatológica y de funcionalidad social e interpersonal mediante escalas y cuestionarios validados, a través de personal sanitario con competencias reconocidas.

- **Conclusión 3:** Resulta crucial la adecuación del consejo dietético-nutricional a las características inherentes de la población objeto de estudio, así como la utilización de elementos visuales en cada sesión.

❖ **Segunda publicación** (Capítulo II): *"Nutritional Impact and Eating Pattern Changes in Schizophrenic Spectrum Disorders after Health Education Program on Symbiotic Dietary Modulation Offered by Specialised Psychiatric Nursing-Two-Arm Randomised Clinical Trial".*

- **Conclusión 1:** El desarrollo de un programa de educación dietético-nutricional intensivo no ha mostrado diferencias significativas con los modelos convencionales de educación para la salud. Ambas intervenciones resultan

efectivas en la mejora del patrón nutricional y adquisición de hábitos alimentarios saludables en la población objeto de estudio.

- **Conclusión 2:** El rol de la enfermería de práctica avanzada se articula como piedra angular en el abordaje multidisciplinar en salud mental. Del mismo modo, se postula como principal modulador de estilos de vida y responsable del asesoramiento dietético-nutricional.

❖ **Tercera publicación** (Capítulo III): *"Impact of high prebiotic and probiotic dietary education in the SARS-CoV-2 era: improved cardio-metabolic profile in schizophrenia spectrum disorders".*

- **Conclusión 1**: Resulta crucial el fomento de la cultura de prevención y promoción de estilos de vida saludables en salud mental.

- **Conclusión 2:** La inclusión de intervenciones no farmacológicas de enfoque simbiótico y fomento del ejercicio físico en contextos de confinamiento, arrojan resultados costo-efectivos prometedores en la práctica psiquiátrica convencional.

- **Conclusión 3**: La sinergia existente entre la intervención multimodal de enfermería y profesionales de salud con habilidades en nutrición, determinan la eficacia y correcta implementación de las estrategias dietéticas en salud mental.

❖ **Cuarta publicación** (Capítulo IV): *"Psychopathological and cardiometabolic efficacy of a nutritional education intervention based on symbiotics in schizophrenia spectrum disorders. Two-arm Randomised Clinical Trial".*

- **Conclusión 1:** Se ha demostrado la viabilidad del uso de psicobióticos desde una perspectiva dimensional (gravedad psicopatológica), disminuyendo el riesgo de recaídas y mejora del proceso de recuperación mental.

5. Indicios de calidad

PRIMERA PUBLICACIÓN	
Título	Efficacy of nutrition education for the increase of symbiotic intake on nutritional and metabolic status in schizophrenic spectrum disorders: A two-arm protocol
Autores (p.o. de firma)	Alfonso Sevillano-Jiménez, Guillermo Molina-Recio, Juan A. García-Mellado, María García-Rodríguez, Rafael Molina-Luque, Manuel Romero-Saldaña.
Revista (año, vol., pág.)	Frontiers in Nutrition. 2022; 9: 912783
Base de datos de indexación (año)	Journal of Citation Reports (JCR). 2021.
Categoría	Nutrition & Dietetics
Factor de impacto	6.509
Lugar que ocupa/Nº de revistas del Área temática	16/90 (Q1)

SEGUNDA PUBLICACIÓN	
Título	Nutritional impact and eating pattern changes in schizophrenic spectrum disorders after health education program on symbiotic dietary modulation offered by specialised psychiatric nursing-Two-arm randomised clinical trial
Autores (p.o. de firma)	Alfonso Sevillano-Jiménez, Manuel Romero-Saldaña, María García-Rodríguez, Rafael Molina-Luque, Guillermo Molina-Recio
Revista (año, vol., pág.)	Nutrients. 2022;14(24):5388
Base de datos de indexación (año)	Journal of Citation Reports (JCR). 2021.
Categoría	Nutrition & Dietetics
Factor de impacto	6.706
Lugar que ocupa/Nº de revistas del área temática	15/90 (Q1)

TERCERA PUBLICACIÓN	
Título	Impact of high prebiotic and probiotic dietary education in the SARS-CoV-2 era: Improved cardio-metabolic profile in schizophrenia spectrum disorders
Autores (p.o. de firma)	Alfonso Sevillano-Jiménez, Manuel Romero-Saldaña., Juan A. García-Mellado, Lorena Carrascal-Laso, María García-Rodríguez, Rafael Molina-Luque, Guillermo Molina-Recio
Revista (año, vol., pág.)	BMC Psychiatry. 2022;22(1):781.
Base de datos de indexación (año)	Journal of Citation Reports (JCR). 2021.
Categoría	Psychiatry
Factor de impacto	4.144
Lugar que ocupa/Nº de revistas del Área temática	75/155 (Q2)

6. Producción científica

A continuación, más allá de las publicaciones de alto impacto presentadas en el documento, se detallan las numerosas aportaciones científicas derivadas directamente del desarrollo de la tesis doctoral, destacando (por orden cronológico):

- Capítulos de libro:

    a) *Síndrome metabólico y antipsicóticos de segunda generación.* A. Sevillano Jiménez, B. García Sánchez, D. García Sangrador, S. Paz Porto y V. Berdión Marcos. Comunicación publicada como capítulo de libro y presentada en el XXXVIII Congreso Nacional de Enfermería de Salud Mental - Edición Virtual: *"Valor de los cuidados enfermeros en Salud Mental en la pandemia del COVID-19".* (ISBN: 978-84-122417-3-0). Mayo de 2021.

    b) *Modulación dietética de alto contenido simbiótico: impacto sobre el estado psicopatológico, nutricional y cardio-metabólico en trastornos del espectro esquizofrénico.* A. Sevillano Jiménez. Comunicación publicada como capítulo de libro en el III Congreso Internacional de Investigación FUDEN: *"Eje temático 3. Generando conocimiento enfermero en el cuidado de la persona, la familia y las comunidades*" (ISBN 978-84-18671-78-4 y Depósito Legal M-22876-2022). Junio de 2022

- Comunicaciones científicas a congresos:

    a) *Psicobióticos: implicaciones dietéticas ante el abordaje del síndrome metabólico en salud mental.* A. Sevillano Jiménez, N. Canas Junquera, V. Berdión Marcos, A.B. Romero Ruíz y C. Hernán Moreno. Comunicación en formato póster presentado en el XXXVII Congreso Nacional de Enfermería de Salud Mental y 3ª Conferencia Internacional - Edición Virtual-, octubre de 2020.

    b) *Eficacia de la modulación dietética con alto contenido prebiótico y probiótico sobre el estado nutricional y metabólico en trastornos del espectro esquizofrénico.* A. Sevillano Jiménez, G. Molina Recio y M. Romero Saldaña. Comunicación en formato póster presentado en el I Congreso Anual de Estudiantes de Doctorado de la Universidad Miguel Hernández de Elche, febrero de 2021.

c) *Síndrome metabólico y antipsicóticos de segunda generación.* A. Sevillano Jiménez, B. García Sánchez, D. García Sangrador, S. Paz Porto y V. Berdión Marcos. Comunicación oral presentada en el XXXVIII Congreso Nacional de Enfermería de Salud Mental - Edición Virtual-, mayo de 2021.

d) *Rol de enfermería en el abordaje del síndrome metabólico iatrogénico.* A. Sevillano Jiménez, B. García Sánchez, D. García Sangrador, S. Paz Porto y V. Berdión Marcos. Comunicación en formato póster presentado en el XXXVIII Congreso Nacional de Enfermería de Salud Mental - Edición Virtual-, mayo de 2021.

e) *Abordaje dietético-nutricional de alto contenido simbiótico y síndrome metabólico por antipsicóticos de segunda generación: rol de enfermería*. A. Sevillano Jiménez, M. Romero Saldaña, G. Molina Recio y A.B. Romero Ruíz. Comunicación oral presentada en el 21 Congreso-Foro ADENYD -Edición Virtual-, junio de 2021.

f) *Impacto nutracéutico en salud mental: psicobióticos y eje microbiota-intestino-cerebro.* A. Sevillano Jiménez, G. Molina Recio, M. Romero Saldaña y A.B. Romero Ruíz. Comunicación en formato póster presentado en el 21 Congreso-Foro ADENYD -Edición Virtual-, junio de 2021.

g) *Salud Física En El Paciente Psiquiátrico: Cuidados Enfermeros En El Síndrome Metabólico Iatrogénico.* A. Sevillano Jiménez y A.B. Romero Ruíz. Comunicación en formato póster presentado en el XII Congreso Internacional Virtual Ciudad de Granada -Edición Virtual-, octubre de 2021.

h) *Modulación dietética de alto contenido prebiótico y probiótico: impacto psicopatológico y cardio-metabólico en trastornos del espectro esquizofrénico.* A. Sevillano Jiménez, L. Carrascal Laso, A.B. Romero Ruíz, M. Montilla García y L. Padilla Obrero. Comunicación en formato póster presentado en el XXXIX Congreso Nacional de Enfermería de Salud Mental, abril de 2022.

i) *Impacto simbiótico en la era SARS- CoV-2: mejora del perfil cardiovascular en trastornos del espectro esquizofrénico*. A. Sevillano Jiménez, D. García Sangrador, M.D. Toledano García, M.A. Carreño Ruíz y L. Padilla Obrero.

Comunicación en formato póster presentado en el XXXIX Congreso Nacional de Enfermería de Salud Mental, abril de 2022.

j) *Modulación dietética de alto contenido simbiótico: impacto sobre el estado psicopatológico, nutricional y cardio-metabólico en trastornos del espectro esquizofrénico.* A. Sevillano Jiménez. Comunicación en formato póster presentada en el III Congreso Internacional de Investigación FUDEN, junio de 2022.

k) *Impacto de la modulación dietética con alto contenido simbiótico en los cuidados de enfermería sobre el estado cardio-metabólico en trastornos del espectro esquizofrénico.* A. Sevillano Jiménez. Ponencia del Premio ADENYD 2021 en el 22 Congreso-Foro ADENYD, junio 2022.

- Premios en investigación científica:

a) XXI Premio de Investigación AdENyD, otorgado por la Asociación de Enfermeras de Nutrición y Dietética (AdENyD), 2021. España. Título: "*Impacto de la modulación dietética con alto contenido simbiótico en los cuidados de enfermería sobre el estado cardio- metabólico en trastornos del espectro esquizofrénico"*

b) XXVII Premio-Beca de Investigación en Enfermería otorgado por el Ilustre Colegio Oficial de Enfermería de Córdoba, 2022. España. Título: "*Modulación nutracéutica de alto contenido simbiótico: impacto sobre el estado nutricional y cardiometabólico en trastornos del espectro esquizofrénico"*.

7. Bibliografía

1. Grupo de Trabajo de la Guía de Práctica Clínica de Intervenciones Psicosociales en el Trastorno Mental Grave. Guía de Práctica Clínica de Intervenciones Psicosociales en el Trastorno Mental Grave. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad y Política Social. Instituto Aragonés de Ciencias de la Salud-I+CS; Guías de Práctica Clínica en el SNS: I+CS Nº 2007/05; 2009.
2. Grupo de trabajo de la Guía de Práctica Clínica sobre la Esquizofrenia y el Trastorno Psicótico Incipiente., Fòrum de Salut Mental, coordinación. Guía de Práctica Clínica sobre la esquizofrenia y el Trastorno Psicótico Incipiente. Madrid: Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad y Consumo. Guía de Práctica Clínica: AATRM. No 2006/05-2. Agència d'Avaluació de Tecnologia i Recerca Mèdiques; 2009.
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8. Anexos

- ANEXO I: Hoja de información al paciente / Representante legal -

HOJA DE INFORMACIÓN AL PACIENTE / REPRESENTANTE LEGAL

Título del estudio: EFICACIA DE LA MODULACIÓN DIETÉTICA CON ALTO CONTENIDO PREBIÓTICO Y PROBIÓTICO SOBRE EL ESTADO NUTRICIONAL Y METABÓLICO EN TRASTORNOS DEL ESPECTRO ESQUIZOFRÉNICO.

Estimado/a Sr/Sra.,

El estudio en el que se le invita a participar consiste en proporcionar información fiable y precisa sobre los hábitos y patrón de consumo alimentario en pacientes diagnosticados de Esquizofrenia. Esto permitirá establecer pautas de alimentación y nutrición adecuadas ricas en contenido prebiótico, con el último fin de poder evaluar el impacto de esta dieta en la remisión y tolerabilidad clínica, así como el control cardio-metabólico en los participantes.

En caso de que decida aceptar participar en este estudio, será necesario que otorgue su consentimiento expresamente, firmando el documento adjunto, del cual le será entregada una copia y sobre el que podrá requerir, en cualquier momento, información ante cualquier duda suscitada o cuando estime conveniente, al investigador principal o al médico referente. Se ruega leer atentamente el documento adjunto proporcionado a continuación.

OBJETIVOS DEL ESTUDIO

El objetivo del presente estudio es establecer pautas de alimentación, ricas en contenido prebiótico, para la mejora del estado nutricional y cardio-metabólico, así como en la remisión y tolerabilidad clínica del mismo, en sujetos afectados de Esquizofrenia, en cualquiera de sus variantes.

DESCRIPCIÓN DEL ESTUDIO

- Para poder alcanzar los objetivos establecidos se ha diseñado un estudio en el que podrán participar todas aquellas personas diagnosticadas de Esquizofrenia, en cualquiera de sus variantes.

- Los datos requeridos para el estudio serán recogidos en las consultas programadas establecidas con su médico referente o investigador principal, no incluyéndose ningún parámetro identificativo de la persona participante.

- Se precisa del consentimiento por escrito mediante firma del documento adjunto como requisito indispensable en la participación del presente estudio ***(Anexo I y II).***

- Su participación en dicho proyecto de investigación requiere de la realización de pruebas clínicas adicionales de tipo diagnóstico o funcional (analíticas de sangre, determinación antropométrica y salud física seriadas), así como la cumplimentación de determinadas escalas y cuestionarios de valoración relacionadas fundamentalmente con su alimentación y, en menor medida, con su salud y estilos de vida. Toda esta información es necesaria para el adecuado control de la patología principal subyacente y la salud física, así como para la evaluación del patrón dietético individualizado de la persona participante.

- En caso de aceptar, deberá acudir a un número de visitas preestablecidas, pudiendo ser complementarias con aquéllas realizadas habitualmente en la atención sanitaria recibida.

RIESGOS DEL ESTUDIO

- Dado que este estudio la recogida de datos analíticos, antropométricos y variables de la salud física (tensión arterial y frecuencia cardíaca), así como evaluación del patrón dietético y nutricional, no se prevé que su participación pueda implicar más riesgos que los propios de las enfermedades que padece actualmente.

- Como medidas invasivas, cabe destacar los posibles efectos secundarios derivados de la extracción sanguínea que se precisa. Dichos efectos se establecen con escasa frecuencia pero, en caso de aparecer, éstos podrían incluir: mareos, dolor o formación de hematomas, entre otros.

BENEFICIOS DEL ESTUDIO

- Los resultados obtenidos en la consecución del estudio permitirán disponer de una información útil a los profesionales sanitarios sobre posibles condicionantes etiológicos de la Esquizofrenia, así como establecer estrategias terapéuticas basadas en el patrón nutricional y en el eje microbiota-intestino-cerebro. Dicha información podrá ser de utilidad en el beneficio de futuros pacientes.

AVANCES EN EL CONOCIMIENTO

- Los resultados obtenidos a partir del desarrollo del estudio serán convenientemente difundidos en comunicaciones y publicaciones de ámbito científico, por lo que cualquier avance o nuevo descubrimiento que se realice durante el curso del mismo le será facilitado. Su identidad no será desvelada en ningún momento.

PARTICIPACIÓN VOLUNTARIA

- Su participación es voluntaria. No tiene ninguna obligación de participar si no lo desea.

- Usted puede negarse a participar en el estudio o puede abandonarlo en cualquier momento, sin perjuicio ni pérdida de los derechos que le correspondan. En caso de retirarse del presente estudio, sólo deberá comunicárselo a su médico referente y/o investigador principal. Si decide no participar o abandonar el estudio, ello no repercutirá negativamente en sus cuidados sanitarios ni a su participación en futuros estudios de investigación.

- En el caso de que abandone el estudio no se añadirá ningún dato nuevo a la base de datos del mismo, aunque podrán utilizarse los datos que ya se hubieran obtenido hasta el momento.

CONFIDENCIALIDAD

- Los datos personales y de salud que consten en su historia clínica y que se recojan con motivo de este estudio, son los necesarios para cubrir los objetivos del mismo.

- En el informe de resultados, sus datos se usarán de manera anónima en forma de datos agregados, siendo éstos exclusivamente utilizados para los objetivos del estudio. Estos datos no podrán ser identificados al no contener ninguna información de carácter personal que pueda revelar su identidad.

- Los datos susceptibles de ser recogidos durante el estudio serán procesados y analizados con la principal finalidad de ser evaluados científicamente. Si usted decide participar en este estudio, estará consintiendo expresamente en el tratamiento de sus datos personales y de salud. Debe saber que usted podrá ejercitar en cualquier momento sus derechos de acceso, rectificación, cancelación y oposición, dirigiéndose al investigador principal o médico responsable que le atiende.

- Se garantiza que los datos personales serán tratados con absoluta confidencialidad. El estudio se desarrollará respetando los principios fundamentales establecidos en la Declaración de Helsinki (1964), Convenio del Consejo de Europa relativo a los derechos humanos y la biomedicina (1997), Declaración Universal de la UNESCO sobre el genoma humano y los derechos humanos (1997), así como la correcta cumplimentación de los requisitos establecidos por la legislación española, de acuerdo con la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos de Carácter Personal y Garantía de los Derechos Digitales y la Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica. Toda la información analizada por el investigador principal del presente estudio se encuentra sujeto al mantenimiento del secreto profesional.

INSTRUCCIONES PREVIAS

- Su respuesta es individual. Por ello, se ruega la abstención de participación de ningún familiar o allegado en cada una de las preguntas sin previa consulta ni debate con los mismos.

- Resulta muy importante leer y seguir detalladamente las instrucciones previas de cada cuestionario o registro facilitado. La mayoría de las preguntas tienen varias opciones de respuesta, debiendo señalar aquélla que considere describir mejor su situación actual, escogiendo una sola opción entre las posibles respuestas disponibles. Del mismo modo, existe la necesidad de descripción escrita y anotación mediante valor numérico.

- Es muy importante que se responda a todas las preguntas, ya que muchas de ellas se tratan de manera conjunta, perdiendo información y validez para el análisis de los resultados.

PERSONA DE CONTACTO

- El investigador principal deberá contestar a todas las preguntas suscitadas tras la lectura del presente documento. Si usted requiere información ante nuevos interrogantes durante el transcurso del estudio, necesidad de atención clínica derivada de la intervención, o sobre sus derechos como participante en este proyecto de investigación, puede dirigirse cuando sea necesario al investigador responsable o médico referente.

Si usted tiene alguna duda ahora o en algún momento durante el desarrollo del estudio, por favor contacte con:

Sr. [XXX XXX XXX]

- ***Dirección**:* Servicio de Psiquiatría. Hospital Provincial "Rodríguez Chamorro" de Zamora (Complejo Asistencial de Zamora).
- ***Teléfono (corporativo):*** [XX XX XX]
- ***E-mail*:** [XX XX XX]

En caso de que esté de acuerdo en participar en el presente estudio, por favor, rellene y firme el consentimiento adjunto, del que le será entregada una copia de este.

- ANEXO II: Consentimiento informado del paciente -

CONSENTIMIENTO INFORMADO DEL PACIENTE

Título del estudio: EFICACIA DE LA MODULACIÓN DIETÉTICA CON ALTO CONTENIDO PREBIÓTICOY PROBIÓTICO SOBRE EL ESTADO NUTRICIONAL Y METABÓLICO EN TRASTORNOS DEL ESPECTRO ESQUIZOFRÉNICO.

Yo, (*nombre y apellidos del sujeto participante*), D./Dª _____,

con DNI _____, una vez he sido debidamente informado por el investigador de todos los aspectos relacionados con el proyecto,

DECLARO QUE:

- He leído la hoja de información de la que se me ha hecho entrega.
- He podido hacer preguntas sobre el proyecto de investigación propuesto.
- He recibido suficiente información y resuelto dudas suscitadas sobre el estudio.
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio:
    - Cuando desee.
    - Sin tener que aportar justificación razonada.
    - Sin que esto repercuta en mi atención sanitaria.

- Entiendo que, con mi participación en el estudio, consiento en el tratamiento, comunicación y transferencia de mis datos personales y de salud en los términos establecidos en la Hoja de Información, de la cual se me ha hecho entrega.
- Presto libremente mi conformidad para la participación en el presente estudio.

En caso de presentar el sujeto participante impedimento para la escritura y rúbrica, el consentimiento se otorga oralmente en presencia del testigo D./Dª_____,

, con DNI/NIE_____, que firma a continuación.

Firma del Sujeto / Testigo.	**Firma del Investigador y Nº de Colegiado.**
	Nº Colegiado:
Fecha:	**Fecha:**

- ANEXO III: Consentimiento informado del representante legal del paciente -

CONSENTIMIENTO INFORMADO DEL REPRESENTANTE LEGAL DEL PACIENTE

Título del estudio: EFICACIA DE LA MODULACIÓN DIETÉTICA CON ALTO CONTENIDO PREBIÓTICO Y PROBIÓTICO SOBRE EL ESTADO NUTRICIONAL Y METABÓLICO EN TRASTORNOS DEL ESPECTRO ESQUIZOFRÉNICO.

Yo, (*nombre y apellidos del representante legal*) D./Dª _____, con DNI _____, en calidad de REPRESENTANTE LEGAL del residente (*nombre y apellidos del residente)* D./Dª _____, con DNI_____, una vez he sido debidamente informado por el investigador responsable de todos los aspectos relacionados con el proyecto,

DECLARO QUE:

- He leído esta hoja de información de la que se me ha hecho entrega.
- He podido hacer preguntas sobre el proyecto de investigación propuesto.
- He recibido suficiente información y resuelto dudas suscitadas sobre el estudio.
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio:
    - Cuando desee.
    - Sin tener que aportar justificación razonada.
    - Sin que esto repercuta en mi atención sanitaria.

- Entiendo que con mi participación en el estudio consiento en el tratamiento, comunicación y transferencia de mis datos personales y de salud en los términos establecidos en la Hoja de Información, de la cual se me ha hecho entrega.
- Presto libremente mi conformidad para su participación en el presente estudio.

En caso de presentar el sujeto participante impedimento para la escritura y rúbrica, el consentimiento se otorga oralmente en presencia del testigo D./Dª_____, con DNI/NIE_____, que firma a continuación.

Firma del Representante Legal / Testigo.	**Firma del Investigador y Nº de Colegiado.**
	Nº Colegiado:
Fecha:	**Fecha:**

- ANEXO IV: Aprobación del Comité de Ética -

Comité de Ética de Investigación con Medicamentos del Área de Salud de Zamora
(C.E.I.M. Área de Salud de Zamora)

Dr. Manuel A. Franco Martín, Secretario Técnico del Comité de Ética de Investigación con Medicamentos del Área de Salud de Zamora.

CERTIFICA:

Que este Comité ha evaluado el Proyecto de Investigación Nº REGISTRO 468 de D. ALFONSO SEVILLANO JIMÉNEZ como Investigador Principal, titulado:

EFICACIA DE LA MODULACIÓN DIETÉTICA CON ALTO CONTENIDO PREBIÓTICO Y PROBIÓTICO SOBRE EL ESTADO NUTRICIONAL Y METABÓLICO EN TRASTORNOS DEL ESPECTRO ESQUIZOFRÉNICO

Y considera que:

Se cumplen los requisitos necesarios de idoneidad del proyecto en relación con los objetivos del estudio.

Por tanto, este Comité acepta que dicho proyecto sea realizado por D. ALFONSO SEVILLANO JIMÉNEZ en el Servicio de Psiquiatría y Salud Mental de Zamora.

Zamora, 27 de noviembre de 2019.

El Secretario

C.E.I.m ÁREA DE SALUD DE ZAMORA

Fdo.: Manuel A. Franco Martín

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Hospital Provincial. Complejo Asistencial de Zamora
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- ANEXO V: Registro de variables -

- REGISTRO DE VARIABLES -

EFICACIA DE LA MODULACIÓN DIETÉTICA CON ALTO CONTENIDO PREBIÓTICO Y PROBIÓTICO SOBRE EL ESTADO NUTRICIONAL Y METABÓLICO EN TRASTORNOS DEL ESPECTRO ESQUIZOFRÉNICO.

I.- VARIABLES SOCIODEMOGRÁFICAS.

P.1. **Edad (años):** _____.

P.2. **Sexo:** 0. Varón ☐ 1. Mujer ☐

P.3. **Representante legal:** 0. NO ☐ 1. SI ☐

P.4. **Composición del hogar:**

0. Unipersonal ☐
1. Monoparental (con un solo padre) ☐
2. Horizontal (con amigos/hermanos) ☐
3. Completo (padre- madre -hermanos) ☐
4. Hogar familiar propio ☐
5. Otras ☐

Especificar (5):

_____

_____

P.5. **Nivel económico:**

0. Alto (>20 euros/día) ☐
1. Medio (5-20 euros/día) ☐
2. Bajo (0-5 euros/día) ☐
3. Nulo ☐

P.6. **Nivel de estudios:**

0. Primaria ☐
1. Secundaria ☐
2. Superior ☐
3. Nulo ☐

P.7. **Área de residencia:**

0. Urbana ☐
1. Rural ☐

II.- VARIABLES TERAPÉUTICAS.

P.8. **Antipsicótico previo y dosis (mg):**

_____

_____

_____

_____

P.9. **Motivo de cambio del tratamiento antipsicótico:**

0. Sin cambios ☐
1. Falta de eficacia ☐
2. Problemas de tolerabilidad/seguridad ☐
3. Elección del propio paciente ☐
4. Otras ☐

Especificar (4):

III.- VARIABLES ANTROPOMÉTRICAS Y SALUD FÍSICA.

(Ver documento adjunto en Anexo I: *Registro de Evaluación Antropométrica y Salud Física).*

III.- VARIABLES ANALÍTICAS.

P.10. **Perfil hematológico[1]:**

P.10.1. **BASAL**							
- HEMOGRAMA -							
Hematíes	Hemoglobina	Hematocrito	V.C.M.	H.C.M.	C.H.C.M.	R.D.W.	Leucocitos
- FÓRMULA LEUCOCITARIA -						- FÓRMULA PLAQUETARIA -	
Neutrófilos	Linfocitos	Monocitos	Eosinófilos	Basófilos		Plaquetas	V.P.M

P.10.2. **3 MESES**							
- HEMOGRAMA -							
Hematíes	Hemoglobina	Hematocrito	V.C.M.	H.C.M.	C.H.C.M.	R.D.W.	Leucocitos
- FÓRMULA LEUCOCITARIA -						- FÓRMULA PLAQUETARIA -	
Neutrófilos	Linfocitos	Monocitos	Eosinófilos	Basófilos		Plaquetas	V.P.M

P.10.3. **6 MESES**							
- HEMOGRAMA -							
Hematíes	Hemoglobina	Hematocrito	V.C.M.	H.C.M.	C.H.C.M.	R.D.W.	Leucocitos

- FÓRMULA LEUCOCITARIA -					- FÓRMULA PLAQUETARIA -	
Neutrófilos	Linfocitos	Monocitos	Eosinófilos	Basófilos	Plaquetas	V.P.M

1. ***Valores de Referencia:***

HEMOGRAMA:

- Hematíes [4.50 - 5.90] x10e^6/mm^3
- Hemoglobina [13.0 – 17.0] g/dL
- Hematocrito [40.0 – 54.0] %
- V.C.M. [80.0 – 100.0] fL
- H.C.M. [27.0 – 32.0] pg
- C.H.C.M. [32.0 – 36.0] g/dL
- R.D.W. [11.5 – 14.5] %
- Leucocitos [4.00 – 11.0] x10e^3/mm^3

FÓRMULA LEUCOCITARIA:

- Neutrófilos [45.0 – 70.0] % ó [2.0 – 7.5] x10e^3/m
- Linfocitos [20.0 – 45.0] % ó [1.0 – 4.8] x10e^3/m
- Monocitos [3.0 – 12.0] % ó [0.3 – 0.9] x10e^3/m
- Eosinófilos [0.0 – 5.0] % ó [0.0 – 0.5] x10e^3/m
- Basófilos [0.0 – 2.0] % ó [0.0 – 0.5] x10e^3/m

FÓRMULA PLAQUETARIA:

- Plaquetas [140 - 150] x10e^3/mm^3
- V.P.M. [7.0 – 14.0] fL

P.11. **Perfil bioquímico[2]:**

P.11.1. **BASAL**									
- ESTUDIO GENERAL –									
ALT (GPT)	G-GT	FAL	Na^+/K^+	CL-	Ca^{2+}	HbA1c / IFCC	Fructosamina	Glucosa	Creatinina
Urato	Fe	FRT		Folato		Vit.B12	Vit. D3 (25-OH)	Estimación Filtrado Glomerular	
- PERFIL LIPÍDICO -								- PERFIL HORMONAL -	
Colesterol	Triglicéridos	LDH	C-HDL	C-LDL		Colesterol total/C-HDL		TSH	PRL
- INMUNOSEROLOGÍA -									
LUES	a-HAV-M	a-HCV		HBsAG	a-HBC-IgG	a-HBs	a-HIV		

P.11.2. **3 MESES**									
- ESTUDIO GENERAL –									
ALT (GPT)	G-GT	FAL	Na^+/K^+	CL-	Ca^{2+}	HbA1c / IFCC	Fructosamina	Glucosa	Creatinina
Urato	Fe	FRT		Folato		Vit.B12	Vit. D3 (25-OH)	Estimación Filtrado Glomerular	
- PERFIL LIPÍDICO -								- PERFIL HORMONAL -	
Colesterol	Triglicéridos	LDH	C-HDL	C-LDL		Colesterol total/C-HDL		TSH	PRL
- INMUNOSEROLOGÍA -									

LUES	a-HAV-M	a-HCV	HBsAG	a-HBC-IgG	a-HBs	a-HIV

P.11.3. **6 MESES**									
- ESTUDIO GENERAL –									
ALT (GPT)	G-GT	FAL	Na^+/K^+	CL-	Ca^{2+}	HbA1c / IFCC	Fructosamina	Glucosa	Creatinina
Urato	Fe	FRT		Folato		Vit.B12	Vit. D3 (25-OH)	Estimación Filtrado Glomerular	
- PERFIL LIPÍDICO -								- PERFIL HORMONAL -	
Colesterol	Triglicéridos	LDH	C-HDL	C-LDL	Colesterol total/C-HDL			TSH	PRL
- INMUNOSEROLOGÍA -									
LUES	a-HAV-M	a-HCV		HBsAG	a-HBC-IgG	a-HBs	a-HIV		

2. ***Valores de Referencia:***

ESTUDIO GENERAL:

- ALT (GPT) [5 - 41] UI/L
- G-GT [3 - 60] UI/L
- FAL [40 - 130] UI/L
- Na+ [136 – 145] mEq/L
- K+ [3.5 – 5.1] mEq/L
- Fructosamina [<286] mcmol/L
- FRT [30-400] mcg/L
- Vit.B12 [200 - 900] pg/mL
- Estimación Filtrado Glomerular: Valores de referencia:
  - Estadio 1= > 90ml/min/1,73m^2: Normal o alto.
  - Estadio 2 = 60-89 ml/min/1,73 m^2: Levemente disminuido.
  - Estadio 3 = 30-59 ml/min/1,73 m^2: Descenso moderado.
  - Estadio 4 = 16-29 ml/min/1,73 m^2: Descenso grave.
  - Estadio 5 = < 15 ml/min/1,73 m^2: Fallo renal.
- Glucosa [74 – 106] mg/dL
- Creatinina [0.70 – 1.20] mg/dL
- Urato [3.4 – 7.0] mg/dL
- Ca^{2+} [8.4 – 10.2] mEq/L
- HbA1c [4.3 - 6.1] %
- Fe [33 - 193] mcg/dL
- Folato [3.5 - 27] mcg/L
- Vit.D3 (25-OH) [30 - 70] ng/mL

PERFIL LIPÍDICO:

- Colesterol [110 – 200] mg/dL
- Triglicéridos [40 – 160] mg/dL
- LDH [100 - 250] UI/L
- Colesterol Total/C-HDL [1.0 - 4.5] mg/dL
- C-LDL [0 - 130] mg/dL
- C-HDL: Valores asociados con el riesgo cardiovascular:
  - < 40 mg/dL, riesgo aumentado.
  - [41 - 59] mg/dL, riesgo promedio.
  - > 60 mg/dL, riesgo disminuido

PERFIL HORMONAL:

- TSH [0.30 – 4.50] mU/L
- PRL (> 15 ng/dL varones; > 20 ng/dL mujeres)

INMUNOSEROLOGÍA:

- LUES [<1/160] UI/L
- a-HAV-M [N] UI/L
- a-HCV [N] UI/L
- a-HIV [T-$CD4^+$ 640-1175 / T-$CD8^+$ 335-875] mcL
- HBsAg [N] UI/L
- a-HBC-IgG [N] UI/L
- a-HBs [0 -10.0] UI/L

P.12. **Coprocultivo[3]:**

P.12.1. **BASAL**
- BACTERIOLOGÍA GENERAL –

Flora Mixta Habitual		Disbacteriosis (especificar):			
Salmonella spp.	Shigella spp.	Yersinia spp.	Hafnia Alvei	Aeromonas spp.	Campylobacter spp.

P.12.3. **6 MESES**					
- BACTERIOLOGÍA GENERAL –					
Flora Mixta Habitual		Disbacteriosis (especificar):			
Salmonella spp.	Shigella spp.	Yersinia spp.	Hafnia Alvei	Aeromonas spp.	Campylobacter spp.

3. ***Valores de Referencia:***

BACTERIOLOGÍA GENERAL:

- Salmonella spp. [N] UFC/g
- Shigella spp. [N] UFC/g
- Yersinia spp. [N] UFC/g
- Hafnia Alvei [N] UFC/g
- Aeromonas spp. [N] UFC/g
- Campylobacter spp. [N] UFC/g

PARÁSITOS:

- Técnica de concentración (Richie): Positivo/Negativo (especificar agente parasitario)

IV.- VARIABLES CLÍNICAS.

P.13. **Diagnóstico psiquiátrico:**

1.- Esquizofrenia ☐
2.- Trastorno Esquizoafectivo ☐
3.- Trastorno Delirante ☐
4.- Trastorno Esquizotípico ☐
5.- Trastorno Esquizofreniforme ☐
6.- Trastorno Psicótico Breve ☐
7.- Otros ☐

Especificar (7):

P.14. **Duración de la enfermedad (años)**: _____.

P.15. **Edad de la primera hospitalización (años):** _____.

P.16. **Número de hospitalizaciones anteriores (últimos 6 meses):** _____.

P.17. **Número de recaídas anteriores (últimos 6 meses):** _____.

P.18. **Número de conductas suicidas anteriores (últimos 6 meses):** _____.

P.19. **Número de hospitalizaciones posteriores:**

BASAL (2020)	MES nº1 (2020)	MES nº2 (2020)	MES nº3 (2020)	MES nº4 (2020)	MES nº5 (2020)	MES nº6 (2020)

P.20. **Número de recaídas posteriores:**

BASAL (2020)	MES nº1 (2020)	MES nº2 (2020)	MES nº3 (2020)	MES nº4 (2020)	MES nº5 (2020)	MES nº6 (2020)

P.21. **Número de conductas suicidas posteriores:**

BASAL (2020)	MES nº1 (2020)	MES nº2 (2020)	MES nº3 (2020)	MES nº4 (2020)	MES nº5 (2020)	MES nº6 (2020)

P.22. **Número de consultas no programadas posteriores:**

BASAL (2020)	MES nº1 (2020)	MES nº2 (2020	MES nº3 (2020)	MES nº4 (2020)	MES nº5 (2020)	MES nº6 (2020)

P.23. **Consumo de tóxicos:** 0. NO ☐ 1. SI ☐

P.24. **Tipo de tóxicos:**

0. Alcohol	☐	1. Tabaco	☐
2. Cocaína	☐	3. Opiáceos	☐
4. Anfetaminas	☐	5. Benzodiacepinas	☐
6. Cannabis	☐	7.Otros	☐

Especificar (7):

P.25. **Administración concomitante de antibioterapia:** 0. NO ☐ 1.SI ☐

Especificar momento de la administración, tipo de antibiótico empleado y posología (1):

BASAL	3 MESES	6 MESES

P.26. **Diagnóstico cardio-metabólico asociado:**

V.- TOLERABILIDAD Y MODULACIÓN DEL PATRÓN DIETÉTICO Y NUTRICIONAL.

P.27. **Conocimientos culinarios y responsabilidad de alimentación:**

0. Sabe cocinar y es responsable de ello ☐
1. Sabe cocinar y no es responsable de ello ☐
2. No sabe cocinar y es responsable de ello ☐
3. No sabe cocinar y no es responsable de ello ☐

Especificar (1 y 3):

* (Ver documentos adjuntos: *Cuestionario de Frecuencia de Consumo de Alimentos).*

VI.- EFICACIA CLÍNICA DE LA MODULACIÓN DIETÉTICA PSICOBIÓTICA.

P.28**. Escala PANSS-P:**

BASAL	3 MESES	6 MESES

P.29. **Escala PANSS-N:**

BASAL	3 MESES	6 MESES

P.30**. Índice Compuesto (TOTAL PANSS-P) – (TOTAL PASS-N):**

BASAL	3 MESES	6 MESES

P.31. **Escala PANSS-PG:**

BASAL	3 MESES	6 MESES

P.32. **Funcionalidad (*Escala de Rendimiento Personal y Social -PSP*):**

BASAL	3 MESES	6 MESES

- OBSERVACIONES:

- ANEXO VI: Evaluación antropométrica y de salud física -

[BASAL]		- MES nº 1 -		- MES nº2 -		- MES nº3 -	
EVALUACIÓN ANTROPOMÉTRICA							
- PESO *(kg):*	**- PERÍMETRO ABDOMINAL** *(cm):*	**- PESO** *(kg):*	**- PERÍMETRO ABDOMINAL** *(cm):*	**- PESO** *(kg):*	**- PERÍMETRO ABDOMINAL** *(cm):*	**- PESO** *(kg):*	**- PERÍMETRO ABDOMINAL** *(cm):*
- TALLA *(cm):*	**- IMC** *(peso/ altura^2):*	**- TALLA** *(cm):*	**- IMC** *(peso/ altura^2):*	**- TALLA** *(cm):*	**- IMC** *(peso/ altura^2):*	**- TALLA** *(cm):*	**- IMC** *(peso/ altura^2):*
CONTROL CARDIOVASCULAR							
- TENSIÓN ARTERIAL *(mmHg):*	**- FRECUENCIA CARDÍACA** *(ppm):*	**- TENSIÓN ARTERIAL** *(mmHg):*	**- FRECUENCIA CARDÍACA** *(ppm):*	**- TENSIÓN ARTERIAL** *(mmHg):*	**- FRECUENCIA CARDÍACA** *(ppm):*	**- TENSIÓN ARTERIAL** *(mmHg):*	**- FRECUENCIA CARDÍACA** *(ppm):*

- **OBSERVACIONES:**

- MES nº4 -		- MES nº5 -		- MES nº6 -	
EVALUACIÓN ANTROPOMÉTRICA					
- PESO *(kg):*	**- PERÍMETRO ABDOMINAL** *(cm):*	**- PESO** *(kg):*	**- PERÍMETRO ABDOMINAL** *(cm):*	**- PESO** *(kg):*	**- PERÍMETRO ABDOMINAL** *(cm):*
- TALLA *(cm):*	**- IMC** *(peso/ altura²):*	**- TALLA** *(cm):*	**- IMC** *(peso/ altura²):*	**- TALLA** *(cm):*	**- IMC** *(peso/ altura²):*
CONTROL CARDIOVASCULAR					
- TENSIÓN ARTERIAL *(mmHg):*	**- FRECUENCIA CARDÍACA** *(ppm):*	**- TENSIÓN ARTERIAL** *(mmHg):*	**- FRECUENCIA CARDÍACA** *(ppm):*	**- TENSIÓN ARTERIAL** *(mmHg):*	**- FRECUENCIA CARDÍACA** *(ppm):*

- **OBSERVACIONES:**

- ANEXO VII: Positive and Negative Syndrome Scale -PANSS -

Escala Positiva (PANSS-P)							
Delirios	1	2	3	4	5	6	7
Desorganización Conductual	1	2	3	4	5	6	7
Alucinaciones	1	2	3	4	5	6	7
Excitación	1	2	3	4	5	6	7
Grandiosidad	1	2	3	4	5	6	7
Suspicacia/perjuicio	1	2	3	4	5	6	7
Hostilidad	1	2	3	4	5	6	7
Total PANSS-P							

Escala Negativa (PANSS-N)							
Embotamiento Afectivo	1	2	3	4	5	6	7
Retraimiento Emocional	1	2	3	4	5	6	7
Contacto pobre	1	2	3	4	5	6	7
Retraimiento social	1	2	3	4	5	6	7
Pensamiento abstracto	1	2	3	4	5	6	7
Fluidez de la conversación	1	2	3	4	5	6	7
Pensamiento estereotipado	1	2	3	4	5	6	7
Total PANSS-N							

Índice Compuesto (Total PANSS-P)-(Total PANSS-N)	

Psicopatología General (PANSS-PG)							
Preocupación somática	1	2	3	4	5	6	7
Ansiedad	1	2	3	4	5	6	7
Sentimientos de culpa	1	2	3	4	5	6	7
Tensión motora	1	2	3	4	5	6	7
Manierismos/posturas	1	2	3	4	5	6	7
Depresión	1	2	3	4	5	6	7
Enlentecimiento motor	1	2	3	4	5	6	7
Falta de colaboración	1	2	3	4	5	6	7
Pensamientos inusuales	1	2	3	4	5	6	7
Desorientación	1	2	3	4	5	6	7
Atención deficiente	1	2	3	4	5	6	7
Ausencia de insight	1	2	3	4	5	6	7
Trastornos de la volición	1	2	3	4	5	6	7
Control deficiente de los impulsos	1	2	3	4	5	6	7
Ensimismamiento	1	2	3	4	5	6	7
Evitación social activa	1	2	3	4	5	6	7
Total PANSS-PG							

- SÍNDROME POSITIVO		PUNTOS		PERCENTIL
- SÍNDROME NEGATIVO		PUNTOS		PERCENTIL
- INDICE COMPUESTO		PUNTOS		PERCENTIL
- PSICOPATOLOGÍA GENERAL		PUNTOS		PERCENTIL

- SISTEMA RESTRICTIVO
- SISTEMA INCLUSIVO

- NORMAS DE ADMINISTRACIÓN Y PUNTUACIÓN –

✓ Administración:

- Ha de ser administrada por un/a clínico/a, utilizando la técnica de entrevista semiestructurada.
- El tiempo aproximado de administración es de 30-40 minutos.

✓ Puntuación:

- Proporciona cuatro puntuaciones dimensionales:

  1. Síndrome positivo.
  2. Síndrome negativo.
  3. Escala compuesta.
  4. Psicopatología general.

- La puntuación en las escalas positiva (PANSS-P), negativa (PANNS-N), y psicopatología general (PANSS-PG) se obtiene sumando las puntuaciones de cada ítem. Las puntuaciones oscilarán por tanto entre 7 y 49 para las escalas positiva y negativa, y entre 16 y 112 para la psicopatología general.

- La puntuación en la escala compuesta (PANNS-C) se obtiene restando la puntuación en la escala negativa a la puntuación en la escala positiva. Esta escala puede tener valencia positiva o negativa, oscilando sus valores entre –42 y + 42.

- No existen puntos de corte para las puntuaciones directas obtenidas, sino que éstas se transforman mediante una tabla de conversión en percentiles.

- En la siguiente tabla se representan las puntuaciones directas que corresponden a los percentiles 5, 25, 50, 75 y 95.

PERCENTIL	PUNTUACIÓN PANSS-P	PUNTUACIÓN PANSS-N	PUNTUACIÓN PANSS-C	PUNTUACIÓN PANSS-PG
5	12	9	-24	28
25	21	19	-10	38
50	26	25	1	45
75	31	35	10	52
95	38	43	19	61

- Además de la puntuación dimensional comentada en los puntos anteriores, la PANSS proporciona también una información categorial, indicando si el trastorno esquizofrénico es positivo, negativo o mixto. Para ello, existen dos sistemas más o menos restrictivos.

  I. El más restrictivo: para establecer el tipo de trastorno esquizofrénico utiliza las puntuaciones obtenidas en los ítems de la escala positiva y negativa. Considera que el trastorno esquizofrénico es:

     1. *Positivo:* cuando en la escala positiva más de 2 ítems obtienen una puntuación superior a 3 y en la escala negativa menos de 3 ítems obtienen una puntuación superior a 3.
     2. *Negativo:* cuando en la escala negativa más de 2 ítems obtienen una puntuación superior a 3 y en la escala positiva menos de 3 ítems obtienen una puntuación superior a 3.

3. *Mixto:* cuando en ambas escalas hay más de 2 ítems que obtienen puntuaciones superiores a 3.

II. El menos restrictivo o inclusivo: para establecer el tipo utiliza la puntuación obtenida en la escala compuesta, y más en concreto su valencia, de forma que considera que el trastorno esquizofrénico es:

4. Positivo cuando la valencia en la escala compuesta es + .
5. Negativo cuando la valencia en la escala compuesta es –.

Referencia	*Andalusian Health Service, Andalusian Regional Ministry of Health. Assessment Instrument No. 8: Early Detection and Intervention in Psychosis. Positive and Negative Schizophrenia Syndrome Scale (PANSS). Andalusian Health Service. (2010). Available online at: https://www.sspa.juntadeandalucia.es/servicioandaluzdesalud/publicaciones/ deteccion-e-intervencion-temprana-en-laspsicosis-documentos-e-instrumentosde- evaluacion (accessed November 5, 2019).*

- ANEXO VIII: Personal and Social Performance - PSP -

1.- Califique el grado de disfunción del paciente durante el último mes en las siguientes 4 áreas principales *(marque una –X- en la situación habitual).* Para determinar el nivel de disfunctionalidad ha de utilizar los criterios operativos que se facilitan a continuación. Observe que hay unos criterios comunes para las áreas *a-c* y otros criterios específicos para el área *d.*

	Ausente	*Leve*	*Evidente*	*Marcado*	*Grave*	*Muy Grave*
a. Autocuidado	☐	☐	☐	☐	☐	☐
b. Relaciones personales y sociales	☐	☐	☐	☐	☐	☐
c. Actividades soc. funcionales: trabajo/estudio	☐	☐	☐	☐	☐	☐
d. Conductas perturbantes y agresivas	☐	☐	☐	☐	☐	☐

*Niveles de gravedad en áreas *a-c*

(I) ***Ausente***.
(II) ***Leve:*** Solamente conocido por alguien muy cercano a la persona.
(III) ***Evidente:*** Dificultades claramente identificables por otros, pero que no interfieren substancialmente en las habilidades personales para ejercer su rol en cada área, teniendo en cuenta el contexto socio-cultural, edad, sexo y nivel educativo de la persona.
(IV) ***Marcado:*** dificultades que interfieren fuertemente en el desempeño de roles en cada área; sin embargo, la persona es todavía capaz de hacer algunas cosas sin ayuda profesional o social, aunque inadecuadamente y/o ocasionalmente; si es ayudada, es capaz de alcanzar su nivel previo de funcionamiento.
(V) ***Grave:*** Dificultades que hacen que la persona sea incapaz de realizar ninguna función de cada área si no es ayudada profesionalmente, o presenta un patrón destructivo, aunque sin riesgos de supervivencia.
(VI) ***Muy Grave***: deterioros y dificultades tan graves que ponen en riesgo de supervivencia a la persona.

** Niveles de gravedad en área d

(I) ***Ausente.***
(II) ***Leve:*** Leve grosería, insociabilidad o quejas.
(III) ***Evidente:*** Hablar demasiado fuerte o de una manera demasiado familiar, o comer de un modo socialmente inaceptable.
(IV) ***Marcada:*** Insultar a otros en público, o romper objetos, actuando frecuentemente de una manera socialmente inapropiada pero no peligrosa (por ejemplo, desnudarse u orinar en público).
(V) ***Grave:*** Amenazas de agresiones verbales o físicas frecuentes, sin intención o posibilidad de lesiones graves.
(VI) ***Muy Grave***: Frecuentes actos de agresión, dirigidas o que puedan causar lesiones graves.

2.- Seleccione un intervalo de 10 puntos. La selección de dicho intervalo se basa en grados de disfunción que se ha determinado para las 4 áreas principales: a) autocuidado; b) relaciones personales y sociales; c) actividades socialmente funcionales: trabajo/estudio; d) Conductas perturbantes y agresivas.

100-91	Excelente funcionamiento en todas las áreas. Es reconocido/a por sus buenas cualidades, hace frente adecuadamente a los problemas de la vida, está involucrada en una amplia gama de actividades e intereses.
90-81	Buen funcionamiento en todas las áreas, sólo presenta problemas y dificultades comunes.
80-71	Leves dificultades en una o más áreas **a-c.**
70-61	Evidentes, pero no marcadas dificultades en una o más áreas **a-c**, o dificultades leves en - ***d -***.
60-51	Dificultades marcadas en una de las áreas **a-c**, o dificultades evidentes en - ***d -***.
50-41	Dificultades marcadas en 2 o más áreas **a-c,** o dificultades graves en una de las áreas **a-c**, con o sin dificultades evidentes en - ***d -***.
40-31	Dificultades graves en un área y marcadas por lo menos en otra área **a-c**, o dificultades marcadas en - ***d -***.

30-21	Dificultades graves en 2 de las áreas **a-c**, o dificultades graves en -***d***- con o sin deterioro en áreas **a-c**.
20-11	Dificultades graves en todas las áreas ***a-d,*** o muy graves en - ***d*** - con o sin deterioro en las áreas **a-c**. Si la persona reacciona a las indicaciones externas se sugiere una puntuación entre 16-20; si no lo hace se sugiere una puntuación entre 11-15.
10-1	Falta de autonomía en el funcionamiento básico con comportamientos extremos pero sin riesgo para la supervivencia (6-10) o con riesgo para la supervivencia (1-5), por ejemplo: riesgo de muerte debido a la malnutrición, deshidratación, infecciones, o incapacidad de reconocer situaciones de peligro evidente.

3.- Ajuste dentro del intervalo de 10 puntos.

- El nivel de disfunción en otras áreas deberá tenerse en cuenta para ajustar la puntuación dentro del intervalo decimal (p. ej., de 31 a 40), como:

  - Cuidados de salud física y psicológica
  - Alojamiento, área de residencia, cuidado de vivienda
  - Contribución a las actividades del hogar, participación en la vida familiar o en la vida del centro de día/ residencial
  - Relaciones íntimas y sexuales
  - Cuidado de los niños
  - Red social, amigos y colaboradores
  - Ajuste de las normas sociales
  - Intereses generales
  - Uso del transporte, teléfono
  - Estrategias de afrontamiento en situaciones de crisis

4.- Registre, entre 0-100, la **puntuación final:** ☐

- OBSERVACIONES:

Referencia	*García MP, Alejandra P, Bousoño M, Bascarán MT, Guzmán C, Bobes J. Validation of the Spanish personal and social performance scale (PSP) in outpatients with stable and unstable schizophrenia. Rev Psiquiatr Salud Ment (Barc). (2011) 4:9–18. DOI: 10.1016/j.rpsm.2010. 11.003*

- ANEXO IX: Cuestionario de Frecuencia de Consumo de Alimentos - CFCA –

Instrucciones previas:

1. Marque la casilla correspondiente según el listado de alimentos que aparece a continuación (una única opción para cada alimento), según especificaciones:

   BIEN: ■ MAL: ☒ ▭

2. Para cada alimento, marque el recuadro que indica la frecuencia de consumo por término medio durante el año pasado. Se trata de tener en cuenta también la variación verano/invierno. Por ejemplo, si toma helados 4 veces/semana sólo durante los meses de verano, el uso promedio al año es 1/semana.

		CONSUMO MEDIO DURANTE EL AÑO PASADO								
		NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
			1-3	1	2-4	5-6	1	2-3	4-6	6+
I. L.ACTEOS	1. Leche entera (1 taza, 200 cc)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	2. Leche semidesnatada (1 taza, 200 cc)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	3. Leche descremada (1 taza, 200 cc)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	4. Leche condensada (1 cucharada)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	5. Nata o crema de leche (1/2 taza)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	6. Batidos de leche (1 taza, 200 cc)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	7. Yogurt entero (1, 125 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	8. Yogurt descremado (1, 125 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	9. Petit suisse (1, 55 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	10. Requesón o cuajada (1/2 taza)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	11. Queso en porciones o cremoso (1, porción de 25 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	12. Otros quesos: curados, semicurados (Manchego, Bola, Emmental..) (50 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	13. Queso blanco o fresco (Burgos, cabra..) (50 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	14. Natillas, flan, pudding (1, 130 cc)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	15. Helados (1 cucurucho)	▭	▭	▭	▭	▭	▭	▭	▭	▭

- Un plato o ración de 100-150 gr, excepto cuando se indique otra cosa -

		CONSUMO MEDIO DURANTE EL AÑO PASADO								
		NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
			1-3	1	2-4	5-6	1	2-3	4-6	6+
II. LHUEVOS, CARNES, PESCADOS	16. Huevos de gallina (uno)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	17. Pollo o pavo CON piel (1 ración o pieza)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	18. Pollo o pavo SIN piel (1 ración o pieza)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	19. Carne de ternera o vaca (1 ración)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	20. Carne de cerdo (1ración)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	21. Carne de cordero (1ración)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	22. Conejo o liebre (1ración)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	23. Hígado (ternera, cerdo, pollo) (1ración)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	24. Otras vísceras (sesos, corazón , mollejas) (1ración)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	25. Jamón serrano o paletilla (1 loncha, 30 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	26. Jamón York, jamón cocido (1 loncha, 30 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	27. Carnes procesadas: salchichón, chorizo, salami, morcilla, butifarra, salchichas, sobrasada, 50 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	28. Paté, foie-gras (25 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	29. Hamburguesa (una, 50 gr.), albóndigas (3 unidades)	▭	▭	▭	▭	▭	▭	▭	▭	▭
	30. Tocino, bacon, panceta (50 gr.)	▭	▭	▭	▭	▭	▭	▭	▭	▭

31. Pescado blanco: mero, lenguado, besugo, merluza, pescadilla.. (1 plato, pieza o ración)	☐	☐	☐	☐	☐	☐	☐	☐	☐
32. Pescado azul: atún, sardinas, bonito, caballa, salmón.. (1 plato, pieza o ración 130 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
33. Pescados salados: bacalao, salazones (1 ración, 60 gr. En seco)	☐	☐	☐	☐	☐	☐	☐	☐	☐
34. Ostras, almejas, mejillones y similares (6 unidades)	☐	☐	☐	☐	☐	☐	☐	☐	☐
35. Calamares, pulpo, chipirones, jibia (sepia) (1 ración, 200 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
36. Crustáceos: gambas, langostinos, cigalas etc. (4-5 piezas, 200 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
37. Pescados y mariscos enlatados al natural (sardinas, anchoas, bonito, atún) (1 lata pequeña o media lata normal, 50 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
38. Pescados y mariscos en aceite (sardinas, anchoas, bonito, atún) (1 lata pequeña o media lata normal, 50 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐

- Un plato o ración de 200 gr, excepto cuando se indique otra cosa -

III. VERDURAS Y HORATILIZAAS

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
39. Acelgas, espinacas	☐	☐	☐	☐	☐	☐	☐	☐	☐
40. Col , coliflor, brócoles	☐	☐	☐	☐	☐	☐	☐	☐	☐
41. Lechuga, endivias, escarola (100 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
42. Tomate crudo (1, 150 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
43. Zanahoria, calabaza (100 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
44. Judías verdes	☐	☐	☐	☐	☐	☐	☐	☐	☐
45. Berenjenas, calabacines, pepinos	☐	☐	☐	☐	☐	☐	☐	☐	☐
46. Pimientos (150 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
47. Espárragos	☐	☐	☐	☐	☐	☐	☐	☐	☐
48. Gazpacho andaluz (1vaso, 200 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
49. Otras verduras (alcachofa, puerro, cardo, apio)	☐	☐	☐	☐	☐	☐	☐	☐	☐
50. Cebolla (media unidad, 50 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
51. Ajo (1 diente)	☐	☐	☐	☐	☐	☐	☐	☐	☐
52. Perejil, tomillo, laurel, orégano.. (1 pizca)	☐	☐	☐	☐	☐	☐	☐	☐	☐
53. Patatas fritas comerciales (1 bolsa, 50 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
54. Patatas fritas caseras (1 ración, 150 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
55. Patatas asadas o cocidas	☐	☐	☐	☐	☐	☐	☐	☐	☐
56. Setas, níscalos, champiñones	☐	☐	☐	☐	☐	☐	☐	☐	☐

- Una pieza o ración -

IV. FRUTAS

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
57. Naranja (una), pomelo (una), o mandarinas (dos)	☐	☐	☐	☐	☐	☐	☐	☐	☐
58. Plátano (uno)	☐	☐	☐	☐	☐	☐	☐	☐	☐
59. Manzana o pera (una)	☐	☐	☐	☐	☐	☐	☐	☐	☐
60. Fresas, fresones (6 unidades, 1 plato postre)	☐	☐	☐	☐	☐	☐	☐	☐	☐
61. Cerezas, picotas, ciruelas (1 plato postre)	☐	☐	☐	☐	☐	☐	☐	☐	☐
62. Melocotón, albaricoque, nectarina (una)	☐	☐	☐	☐	☐	☐	☐	☐	☐
63. Sandía (1 tajada, 200-250 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
64. Melón (1 tajada, 200-250 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐

65. Kiwi (1 unidad, 100 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
66. Uvas (1 racimo, 1 plato postre)	☐	☐	☐	☐	☐	☐	☐	☐	☐
67. Aceitunas (10 unidades)	☐	☐	☐	☐	☐	☐	☐	☐	☐
68. Frutas en almíbar o en su jugo (2 unidades)	☐	☐	☐	☐	☐	☐	☐	☐	☐
69. Dátiles, higos secos, uvas-pasas, ciruelas-pasas (150 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
70. Almendras, cacahuetes, avellanas, pistachos, piñones (30 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
71. Nueces (30 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
72. ¿Cuántos días a la semana toma fruta como postre?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐		

V. LEGUMBRES Y CEREALES

- Un plato o ración (150 gr.) -

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
73. Lentejas (1 plato, 150 gr. cocidas)	☐	☐	☐	☐	☐	☐	☐	☐	☐
74. Alubias (pintas, blancas o negras) (1 plato, 150 gr. cocidas)	☐	☐	☐	☐	☐	☐	☐	☐	☐
75. Garbanzos (1 plato, 150 gr. cocidos)	☐	☐	☐	☐	☐	☐	☐	☐	☐
76. Guisantes, habas (1 plato, 150 gr. cocidas)	☐	☐	☐	☐	☐	☐	☐	☐	☐
77. Pan blanco, pan de molde (3 rodajas, 75 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
78. Pan negro o integral (3 rodajas, 75 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
79. Cereales desayuno (30 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
80. Cereales integrales: muesli, copos avena, all-bran (30 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
81. Arroz blanco (60 gr. en crudo)	☐	☐	☐	☐	☐	☐	☐	☐	☐
82. Pasta: fideos, macarrones, espaguetis, otras (60 gr. en crudo)	☐	☐	☐	☐	☐	☐	☐	☐	☐
83. Pizza (1 ración, 200 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐

VI. ACEITES Y GRASAS

- Una cucharada o porción individual. Para freír, untar, mojar en el pan, para aliñar, o para ensaladas, utiliza en total: -

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
84. Aceite de oliva (una cucharada sopera)	☐	☐	☐	☐	☐	☐	☐	☐	☐
85. Aceite de oliva extra virgen (una cucharada sopera)	☐	☐	☐	☐	☐	☐	☐	☐	☐
86. Aceite de oliva de orujo (una cucharada sopera)	☐	☐	☐	☐	☐	☐	☐	☐	☐
87. Aceite de maíz (una cucharada sopera)	☐	☐	☐	☐	☐	☐	☐	☐	☐
88. Aceite de girasol (una cucharada sopera)	☐	☐	☐	☐	☐	☐	☐	☐	☐
89. Aceite de soja (una cucharada sopera	☐	☐	☐	☐	☐	☐	☐	☐	☐
90. Mezcla de los anteriores (una cucharada sopera)	☐	☐	☐	☐	☐	☐	☐	☐	☐
91. Margarina (porción individual, 12 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
92. Mantequilla (porción individual, 12 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
93. Manteca de cerdo (10 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐

94. Marca de aceite de oliva que usa habitualmente:

CONSUMO MEDIO DURANTE EL AÑO PASADO								
NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
	1-3	1	2-4	5-6	1	2-3	4-6	6+

VII. BOLLERÍA Y PASTELERÍA

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
95. Galletas tipo María (4-6 unidades, 50 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
96. Galletas integrales o de fibra (4-6 unidades, 50 gr.	☐	☐	☐	☐	☐	☐	☐	☐	☐
97. Galletas con chocolate (4 unidades, 50 gr.	☐	☐	☐	☐	☐	☐	☐	☐	☐
98. Repostería y bizcochos hechos en casa (50 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
99. Croissant, ensaimada, pastas de té u otra bollería industrial comercial ... (uno, 50 gr	☐	☐	☐	☐	☐	☐	☐	☐	☐
100. Donuts (uno)	☐	☐	☐	☐	☐	☐	☐	☐	☐
101. Magdalenas (1-2 unidades)	☐	☐	☐	☐	☐	☐	☐	☐	☐
102. Pasteles (uno, 50 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
103. Churros, porras y similares (1 ración, 100 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
104. Chocolates y bombones (30 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
105. Cacao en polvo-cacaos solubles (1 cucharada de postre)	☐	☐	☐	☐	☐	☐	☐	☐	☐
106. Turrón (1/8 de barra, 40 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
107. Mantecados, mazapán (90 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐

VIII. MISCELÁNEA

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
108. Croquetas, buñuelos, empanadillas, precocinados (una)	☐	☐	☐	☐	☐	☐	☐	☐	☐
109. Sopas y cremas de sobre (1 plato)	☐	☐	☐	☐	☐	☐	☐	☐	☐
110. Mostaza (una cucharadita de postre)	☐	☐	☐	☐	☐	☐	☐	☐	☐
111. Mayonesa comercial (1 cucharada sopera = 20 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
112. Salsa de tomate frito, ketchup (1 cucharadita)	☐	☐	☐	☐	☐	☐	☐	☐	☐
113. Picante: tabasco, pimienta, pimentón (una pizca)	☐	☐	☐	☐	☐	☐	☐	☐	☐
114. Sal (una pizca)	☐	☐	☐	☐	☐	☐	☐	☐	☐
115. Mermeladas (1 cucharadita)	☐	☐	☐	☐	☐	☐	☐	☐	☐
116. Azúcar (1 cucharadita)	☐	☐	☐	☐	☐	☐	☐	☐	☐
117. Miel (1 cucharadita)	☐	☐	☐	☐	☐	☐	☐	☐	☐
118. Snacks distintos de patatas fritas: gusanitos, palomitas, maíz, etc. (1 bolsa, 50 gr.)	☐	☐	☐	☐	☐	☐	☐	☐	☐

119. Otros alimentos de frecuente consumo:

IX. BEBIDAS

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1-3	1	2-4	5-6	1	2-3	4-6	6+
120. Bebidas carbonatadas con azúcar: bebidas con cola, limonadas, tónicas, etc. (1 botellín, 200 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
121. Bebidas carbonatadas bajas en calorías, bebidas light (1 botellín, 200 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
122. Zumo de naranja natural (1 vaso, 200 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
123. Zumos naturales de otras frutas (1 vaso, 200 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
124. Zumos de frutas en botella o enlatados (200 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
125. Café descafeinado (1 taza, 50 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
126. Café (1 taza, 50 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
127. Té (1 taza, 50 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
128. Mosto (100 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
129. Vaso de vino rosado (100 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
130. Vaso de vino moscatel (50 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
131. Vaso de vino tinto joven, del año (100 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐
132. Vaso de vino tinto anejo (100 cc)	☐	☐	☐	☐	☐	☐	☐	☐	☐

133. Vaso de vino blanco (1 00 cc)
134. Vaso de cava (100 cc)
135. Cerveza (1 jarra, 330 cc)
136. Licores, anís o anisetes.. (1 copa, 50 cc)
137. Destilados: whisky, vodka, ginebra, coñac (1 copa, 50 cc)

138. ¿A qué edad empezó a beber alcohol (vino, cerveza o licores), incluyendo el que toma con las comidas con regularidad (más de siete "bebidas" a la semana?

139. ¿Cuántos años ha bebido alcohol con regularidad (más de siete "bebidas" a la semana)?

- Si durante el año pasado tomó vitaminas y/o minerales (incluyendo calcio) o productos dietéticos especiales (salvados, aceite de onagra, flavonoides..), por favor, indique la marca y la frecuencia con las que los tomó -

140. (….):
141. (….):
142. (….):

CONSUMO MEDIO DURANTE EL AÑO PASADO								
NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
	1-3	1	2-4	5-6	1	2-3	4-6	6+

- OBSERVACIONES:

Referencia *Martín JM, Boyle P, Gorgojo L, Maisonneuve P, Fernández JC, Salvini S, et al. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol. (1993) 22:512–9. DOI: 10.1093/ije/22.3.512*

- ANEXO X: Información nutricional y registro semanal de dieta simbiótica -

ESTA SEMANA HE COMIDO

Marca con una x las opciones que hayas incluido en tu menú diario.

SEMANA: _____

	L	M	X	J	V	S	D	TOTAL DE DÍAS
1 plato de ensalada con hortalizas de diferentes colores.								
1 plato de verduras cocinadas (al vapor, cocidas, salteadas, al horno, etc.).								
Al menos una pieza de fruta.								
Más de una pieza de fruta.								
Cereales como la avena o el centeno, ya sea como pan integral, en repostería casera o mezclados con leche o yogurt.								
Al menos un yogurt natural.								
Más de un yogurt natural.								

Otro tipo de lácteo fermentado como requesón, queso fresco, leches fermentadas o kéfir.								
Un plato de legumbres (lentejas, alubias, garbanzos, habas o guisantes).								
Un guiso preparado con sofrito de cebolla y tomate (puede ser el de las legumbres).								
Un puñado de frutos secos crudos.								

LOS ALIMENTOS ESTRELLA

Estos alimentos, son los que contienen una mayor cantidad de fibra fermentablepor las bacterias de nuestro colon. Trata de incluir al menos 1 cada día.

HORTALIZAS:

- Cebolla
- Espárragos
- Alcachofas
- Puerros
- Tomate
- Pepino
- Zanahoria

LEGUMBRES:

- Alubias
- Guisantes

CEREALES:

- Avena
- Centeno

FRUTAS

Plátano; Manzana (mejor con piel); Naranja; Mandarina; Arándanos; Uvas

RECOMENDACIONES PARA UNA ALIMENTACIÓN SALUDABLE

Debes comer al menos, 2 raciones de verduras y hortalizas al día. Una de ellas debe ser en forma de verduras crudas, por ejemplo, en ensalada. Recuerda incluir hortalizas de colores diferentes.

Come cada día de 2 a 3 piezas de fruta fresca.

Trata de comer siempre los cereales integrales. Aunque nos aportan la misma cantidad de energía, contienen una mayor cantidad de fibra y nutrientes muy necesarios para el mantenimiento de la salud.

Incluye legumbres de 2 a 3 veces por semana. Éstas pueden comerse en guisos, en salteados con verduras, o en ensaladas.

También puedes comerlas como guarnición de carnes, pescados y huevos.

Recuerda incluir diariamente entre 2 y 3 raciones de lácteos, ytrata, que al menos una de ellassea de lácteos fermentados como el yogurt, los quesos frescos o el kéfir.

Debes consumir entre 3 y 4 raciones de pescado a la semana, alternando entre blancos (merluza, bacalao, rape,lenguado, etc.) y azules (boquerón, sardina, salmón, emperador, atún).

Utiliza agua como bebida siempre en tus comidas.

Intenta cocinar y aliñar tus ensaladas siempre con aceite de oliva virgen extra.

RECOMENDACIONES PARA UNA ALIMENTACIÓN SALUDABLE

EVITA:

Alimentos altamente procesados, como platos precocinados, salsas,aperitivos y bollería.

Los zumos, aunque sean naturales.

Aportan demasiado azúcar.

El azúcar, la bollería y los postres dulces, sobre todo si son industriales. Silos comes, que sea solo en ocasiones especiales y, preparados en casa para asegurarte de que se han utilizado ingredientes de calidad.

Refrescos azucarados

RECOMENDACIONES PARA UNA ALIMENTACIÓN SALUDABLE

(Ejemplo de menú semanal saludable)

	LUNES	MARTES	MIÉRCOLES	JUEVES	VIERNES	SÁBADO	DOMINGO
DESAYUNO	Café + Yogurt con avena y arándanos	Té + Tostada integral de centeno con aceite, tomate y jamón	Café de avena con leche, plátano, almendras y cacao puro	Té + Pan integral con aguacate y rodajas de tomate	Café + Tostadas integrales de centeno con mantequilla y mermelada sin azúcar	Té + Yogurt con avena y uvas	Café + Tarta casera de zanahoria con harina integral
MEDIA - MAÑANA	Plátano	Manzana	Rollitos de jamón cocido con rúcula y requesón	Requesón con fresas	Rollitos de pavo con guacamole y tomate	Manzana asada con canela	Un puñado de almendras
ALMUERZO	Ensalada con atún y aguacate + Judías estofadas con verduras + Naranja	Salteado de puerros y espárragos con gambas + Muslo de pollo al horno con patata asada + Pera	Hummus de garbanzos con palitos de zanahoria + Salmón a la plancha con espinacas + 2 Mandarinas	Tortilla de patatas con pimientos salteados + Manzana	Guisantes salteados con cebolla + Alitas de pollo + Plátano	Ensalada con queso curado + Patatas guisadas con pollo + Infusión	Cogollos con anchoas + Paella + Naranja
MERIENDA	1 puñado de nueces	1 puñado de anacardos	Infusión	Un puñado de almendras tostadas	Yogurt natural con anacardos	Banana	Café con leche
CENA	Crema de calabacín con queso parmesano rallado + Merluza a la plancha + Yogur natural	Ensalada de tomates cherry, queso fresco y aceitunas negras + Tortilla francesa	Champiñones salteados con ajo + Pavo a la plancha + Yogurt natural	Ensalada de espinacas y queso de cabra + Yogurt natural	Ensalada con huevo duro y caballa + Naranja	Alcachofas salteadas con ajo y pimentón + Tortilla francesa + Yogurt natural	Espinacas salteadas con piñones + Solomillo de cerdo a la plancha + Yogurt natural