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Dietary and metabolic approaches for mental health conditions

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Dietary and metabolic approaches for mental health conditions

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ORIGINAL RESEARCH
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The Ketogenic Diet for Refractory Mental Illness: A Retrospective Analysis of 31 Inpatients

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Background and Hypothesis: The robust evidence base supporting the therapeutic benefit of ketogenic diets in epilepsy and other neurological conditions suggests this same metabolic approach may also benefit psychiatric conditions.

Study Design: In this retrospective analysis of clinical care, 31 adults with severe, persistent mental illness (major depressive disorder, bipolar disorder, and schizoaffective disorder) whose symptoms were poorly controlled despite intensive psychiatric management were admitted to a psychiatric hospital and placed on a ketogenic diet restricted to a maximum of 20 grams of carbohydrate per day as an adjunct to conventional inpatient care. The duration of the intervention ranged from 6 to 248 days.

Study Results: Three patients were unable to adhere to the diet for >14 days and were excluded from the final analysis. Among included participants, means and standard deviations (SDs) improved for the Hamilton Depression Rating Scale scores from 25.4 (6.3) to 7.7 (4.2), $P < 0.001$ and the Montgomery-Åsberg Depression Rating Scale from 29.6 (7.8) to 10.1 (6.5), $P < 0.001$. Among the 10 patients with schizoaffective illness, mean (SD) of the Positive and Negative Syndrome Scale (PANSS) scores improved from 91.4 (15.3) to 49.3 (6.9), $P < 0.001$. Significant improvements were also observed in metabolic health measures including weight, blood pressure, blood glucose, and triglycerides.

Conclusions: The administration of a ketogenic diet in this semi-controlled setting to patients with treatment-refractory mental illness was feasible, well-tolerated, and associated with significant and substantial improvements in depression and psychosis symptoms and multiple markers of metabolic health.

Keywords: ketosis, schizophrenia, bipolar disorder, depression, mental disorders, diet therapy, inpatients

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INTRODUCTION

Globally, an estimated 85 million people suffer from serious, persistent bipolar mood and psychotic illnesses (1), and at least 280 million (2) are thought to be afflicted with depressive illness. Yet even among those with access to modern professional care, meaningful improvement eludes many, and remission is rare. Nearly half of those receiving treatment for bipolar disorder continue to experience recurrent mood episodes (3). Across Europe, approximately 19% of those

with depression are considered "treatment-resistant" (4). Worldwide, a mere 23% of those with schizophrenia respond well to antipsychotic medications (5), with symptom relief often coming at the expense of quality and length of life. Metabolic derangements such as hyperglycemia, hypertriglyceridemia, and weight gain are commonplace in those with bipolar disorder (6) as well as in those with schizophrenia (7), significantly increasing risk for obesity, type 2 diabetes, cardiovascular disease, and other chronic health conditions. Indeed, nearly two-thirds of patients initially hospitalized with acute psychosis develop obesity within 20 years of follow-up (8). Metabolic and other undesirable side effects drive approximately 74% of people to discontinue antipsychotic medicines within 18 months, contributing to high hospitalization and relapse rates (9).

These profound limitations of psychopharmacological treatments make the search for new approaches to mental illness of paramount importance. A compelling intervention attracting more attention in recent years is the ketogenic diet (KD), which restricts carbohydrate and induces lipolysis, generating circulating ketone bodies that serve as an adjunctive source of fuel for the brain, reducing its dependence on glucose (10).

Although the study of KDs for the treatment of psychiatric illnesses is in its infancy, the implementation of KDs in neurological illnesses dates back a century, when they first proved useful in the management of epilepsy (11). The now robust evidence base supporting the application of the KD to epilepsy and a growing number of other challenging neurological conditions (12) suggests this same metabolic approach may also benefit psychiatric conditions (13). For example, it is well established that epilepsy and bipolar illness share many neurochemical underpinnings, and this overlap is clinically supported by the fact that many of the same molecules prescribed to control seizures are also prescribed to stabilize mood (14). Indeed, the line separating brain illnesses considered neurological in nature from those considered psychiatric in nature may be more rhetorical than biological (15), as both categories of disease originate within the same organ and display many biochemical similarities, including dysregulation of neurotransmitter systems, destabilization of neural networks, neuroinflammation, excessive oxidative stress, impaired neuroplasticity, mitochondrial dysfunction, and disturbed cerebral glucose metabolism (16–18).

However, as rigorous clinical trial evidence is not yet available in this field, it remains unclear to what extent serious mental illnesses may benefit from a metabolic approach. Therefore, to the isolated case reports of individuals with major depressive illness (19), bipolar illness (20, 21), and psychotic illness (22) who have benefited from a KD, we add this case series of 31 patients with treatment-refractory mental illness treated with a KD in a semi-controlled hospital setting.

CONTEXT

Dr. Danan, the first author, has been a practicing psychiatrist in Toulouse, France for 35 years. The population he serves is comprised primarily of people of French and North African descent with serious, persistent mental illness, many of whom who also suffer from metabolic illnesses such as obesity, hypertension, and type 2 diabetes. Despite intensive outpatient psychopharmacologic and psychotherapeutic management, most of these individuals require frequent hospitalization and are unable to work due to psychiatric disability. After witnessing marked improvement in medication-refractory seizures and autism behaviors in a family member within several weeks of having adopted a KD, Dr. Danan became interested in the potential of the KD to improve the psychiatric and metabolic status of his most treatment-resistant patients, regardless of diagnosis. He created a metabolic psychiatry treatment program within the Clinique du Castelviel, a 129-bed general psychiatric hospital in Castelmarou, France where patients with chronic mental illness who had exhausted standard psychiatric therapies could attempt a KD in a supportive, medically supervised environment.

MATERIALS AND METHODS

This is a retrospective analysis of hospitalized adults with serious and persistent mental illness who were provided a KD in lieu of the standard hospital menu. Between May 2019 and April 2020, 31 adults whose chronic psychiatric symptoms were poorly controlled despite intensive psychopharmacological management were admitted to the Clinique du Castelviel and placed on a KD under the supervision of their treating psychiatrist, Dr. Danan. This treatment program was approved by Clinique du Castelviel administration and ethics review.

Participants

Participants were uncompensated volunteers selected by Dr. Danan from his outpatient psychiatric practice. Informed consent was obtained in every case. Eligibility criteria were failure to respond adequately to conventional psychiatric care and willingness to try a KD. Exclusion criteria were anorexia nervosa, BMI below 18.5 kg/m^2, pregnancy, breastfeeding, and contraindicated medical conditions (23). Primary psychiatric diagnoses were bipolar disorder type two ($n = 13$), schizoaffective disorder ($n = 12$), and major depressive disorder ($n = 7$). All participants had at least one indicator of poor metabolic health, such as overweight, obesity, hypertension, and/or elevated fasting blood glucose. Most participants had been in Dr. Danan's care for many years (mean [SD] 10 [7] years, range 5 months to 30 years), and all had been psychiatrically hospitalized in the past under his supervision one or more times either at this same facility or a similar affiliated facility with minimal clinical improvement. None of the participants had ever attempted to follow a low-carbohydrate diet before.

Of 31 patients, 22 were voluntarily admitted for the express purpose of initiating the KD in a monitored setting. The remaining 9 were initially admitted for conventional care but later agreed to the KD because non-dietary interventions proved ineffective. All 31 were taking psychotropic medication at the time of KD initiation.

In addition to the KD protocol, which was the cornerstone of their treatment plan, participants also received the usual care

available to all patients admitted to this unit. Hospital staff was comprised of 8 psychiatrists, 3 psychologists, 2 general medical practitioners, 2 social workers, an occupational therapist, an exercise instructor, and a dietitian. Illnesses typically treated at this facility included mood disorders, schizophrenia, substance use disorders, and eating disorders. Participants resided on the inpatient unit 6 days per week but were free to leave the hospital on weekends for up to 36 consecutive hours.

Statistical Analysis

Means and standard deviations were calculated for continuous variables; frequency distributions were calculated for nominal and ordinal variables. We used paired *t*-tests when the pre-post differences had a normal distribution and Wilcoxon signed-rank tests when the differences were skewed, using SPSS 28.0.1.1.

Interventions

The KD protocol employed was adapted from that used by Dr. Westman in clinical trials at Duke University (24); see **Supplementary Figure 1**: Ketogenic Diet Protocol for details and a sample meal plan. Briefly, carbohydrate intake was restricted to a maximum of 20 total grams per day (approximately 5% of daily calories), exclusively from vegetables, nuts, lemon juice, and small amounts of dark chocolate. Protein comprised 15–20% of daily calories and was sourced from meat, seafood, poultry, dairy products, eggs, and nuts. Fat comprised 75–80% of the diet; added fats permitted were olive oil, coconut oil, butter, mayonnaise, and sour cream.

Participants were provided with 3 protocol-compliant meals per day (prepared by the hospital dietitian to ensure sufficient protein and calories), 1 protocol-compliant snack box per day (formulated by Dr. Danan, purchased by participants, and dispensed daily by Dr. Danan), and a list of approved foods to adhere to at all times. Participants also received once-daily supplementation of fish oil (250 mg: 18% EPA, 12% DHA), magnesium oxide (300 mg), copper (1 mg), vitamin B1 (1.1 mg), vitamin B5 (6 mg), vitamin B6 (3.4 mg), vitamin B12 (2.5 mg), and vitamin C (330 mg).

Dr. Danan met individually with each participant 6 days per week to monitor clinical progress and provide dietary education and support. Dietary adherence was estimated using information gathered from these frequent physician interviews, participants' daily food journals, and nursing observations. Adherence was characterized as excellent in those who successfully limited carbohydrate intake to a maximum of 20 grams per day at least 6 days per week, good in those who met this goal at least 5 days per week, and fair in those who met this goal at least 4 days per week. Urine acetoacetate was measured at least once per participant during the intervention period. Metabolic monitoring including blood tests, blood pressure, and body weight was conducted on day 0 of the KD and again on the final day of the KD, just prior to hospital discharge.

Admission date, hospitalization length, KD duration, and non-dietary aspects of care varied depending on clinical circumstances. Medications were adjusted based on clinical judgment.

Main Outcome Measures

Main outcome measures determined prior to the intervention were change in depression symptoms as measured by the Hamilton Depression Rating Scale (HAM-D) (25) and the Montgomery-Åsberg Depression Rating Scale (MADRS) (26), and change in psychosis symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) (27, 28).

Secondary outcomes of interest included medical and psychiatric safety, effect on metabolic biomarkers, change in medication requirements, and change in illness severity, assessed using the Clinical Global Impressions Scale (CGI-S) (29, 30).

RESULTS

Patient Characteristics

Three of 31 patients (10%) were unable to follow a KD for >14 days and were excluded from the final analysis due to lack of outcome data; this case series is therefore comprised of 28 hospitalized adults [mean (SD) age, 50 (11.3) years, range 27–73 years; 71% female]. Mean (SD) hospitalization length was 85.4 (76.8) days (range 16–270 days) and mean (SD) duration of KD was 59.1 (49.6) days (range 15–248 days).

Dietary Adherence

Regarding the 3 excluded patients mentioned above: 1 discontinued the KD citing aversion to dietary fat, 1 cited lack of family and financial support, and 1 cited financial hardship, aversion to dietary fat, and dislike for the restrictiveness of the plan.

Among the included 28 patients who followed the diet for more than 2 weeks, urine ketone measurements were obtained once during the intervention and were positive in 18 of 28 patients (64%). Dietary adherence was characterized as excellent in 11 patients (39%), good in 12 patients (43%), and fair in 5 patients (18%).

Changes in the mental health measures described below are presented in **Table 1**. Noticeable improvements in mood and psychotic symptoms were observed in all 28 patients (100%) during the intervention, typically within 3 weeks or less of initiating the KD.

Schizophrenia Symptoms

Following the KD intervention, all 10 (100%) patients with a primary diagnosis of schizoaffective disorder exhibited improvement in PANSS scores, with the mean (SD) PANSS score falling from 91.4 (15.3) to 49.3 (6.9), $P < 0.001$, Cohen's $d = 3.5$. A reduction of 16.5 or more points in the PANSS score is considered the minimal clinically important difference (31) and was achieved in 10/10 (100%) patients.

Depression Symptoms

The HAM-D was administered to 23 of 28 patients, including all 18 with a primary diagnosis of a non-psychotic illness. Following the KD intervention, all 23 (100%) patients exhibited improvement in HAM-D scores,

TABLE 1 | Changes in mental health measures.

Clinical scale	*n*[a]	Pre-KD, mean (SD)	Post-KD, mean (SD)	Change	Percent change	Cohen's d	*P*-value
Overall							
HAM-D	23	25.4 (6.3)	7.7 (4.2)	−17.7 (5.7)	−69.2 (14.2)	3.1	<0.001
MADRS	21	29.6 (7.8)	10.1 (6.5)	−19.5 (5.4)	−67.4 (15.0)	3.6	<0.001
PANSS	10	91.4 (15.3)	49.3 (6.9)	−42.1 (12.1)	−45.4 (7.1)	3.5	<0.001
CGI-S	27	4.9 (1.2)	2.0 (1.1)	−2.9 (0.8)	−60.4 (14.8)	3.8	<0.001
Primary diagnosis: Bipolar disorder							
HAM-D	12	24.9 (7.3)	9.2 (5.1)	−15.8 (6.5)	−62.6 (16.1)	2.4	<0.001
MADRS	12	29.9 (8.5)	11.8 (7.6)	−18.2 (6.2)	−62.1 (16.7)	2.9	<0.001
PANSS	12	n/a	n/a	n/a	n/a	n/a	n/a
CGI-S	12	4.8 (1.2)	2.0 (1.3)	−2.8 (0.9)	−60.7 (18.4)	3.0	0.002
Primary diagnosis: Major depression							
HAM-D	6	24.0 (3.8)	5.5 (2.6)	−18.5 (2.3)	−77.8 (7.9)	7.9	0.026
MADRS	6	27.3 (5.3)	7.2 (3.2)	−20.2 (2.2)	−75.0 (7.9)	9.0	<0.001
PANSS	6	n/a	n/a	n/a	n/a	n/a	n/a
CGI-S	6	4.3 (0.5)	1.3 (0.5)	−0.3 (0.5)	−70.0 (7.7)	n/a[b]	0.014
Primary diagnosis: Schizoaffective disorder							
HAM-D	5	28.2 (6.1)	7.0 (1.6)	−21.2 (5.7)	−74.7 (5.8)	3.7	0.001
MADRS	3	32.7 (10.4)	9.3 (5.7)	−23.3 (6.1)	−73.3 (12.3)	3.8	0.022
PANSS	10	91.4 (15.3)	49.3 (6.9)	−42.1 (12.1)	−45.4 (7.1)	3.5	<0.001
CGI-S	9	5.4 (1.3)	2.6 (0.9)	−2.9 (0.8)	−53.7 (9.6)	3.7	0.007

HAM-D is a 17-item clinician-administered diagnostic questionnaire rated on a scale of 0 to 52, with ≤7 indicating no depression and ≥24 indicating severe depression. The MADRS is rated on a scale of 0 to 60, with ≤6 indicating no depression and ≥35 indicating severe depression. PANSS is rated on a scale of 30 to 210, with 30 considered the least severe and ≥116 considered severely ill. CGI-S is rated on a scale of 1 to 7, with 1 indicating normal and 7 indicating extreme illness.

[a]*As this is a retrospective analysis, HAM-D, MADRS, and CGI-S scores were not available for all 28 participants.*

[b]*Not calculated by SPSS.*

with the mean (SD) HAM-D score falling from 25.4 (6.3) to 7.7 (4.2), $P < 0.001$, Cohen's $d = 3.1$. The MADRS was administered to 21 of 28 patients, including all 18 with a primary diagnosis of a non-psychotic illness. Following the KD intervention, all 21 (100%) exhibited improvement in MADRS scores, with the mean (SD) MADRS score falling from 29.6 (7.8) to 10.1 (6.5), $P < 0.001$, Cohen's $d = 3.6$.

A reduction of 4 or more points in the HAM-D is considered the minimal clinically important difference and was achieved by all 22 patients in whom HAM-D scores were assessed, regardless of diagnosis. A reduction of 7 or more points, which is considered substantially clinically important, was achieved by 21/22 patients (95%) (32).

A reduction of at least 6 points in the MADRS is considered the minimal clinically important difference and was achieved by all 21 patients (100%) in whom MADRS scores were assessed, regardless of diagnosis.

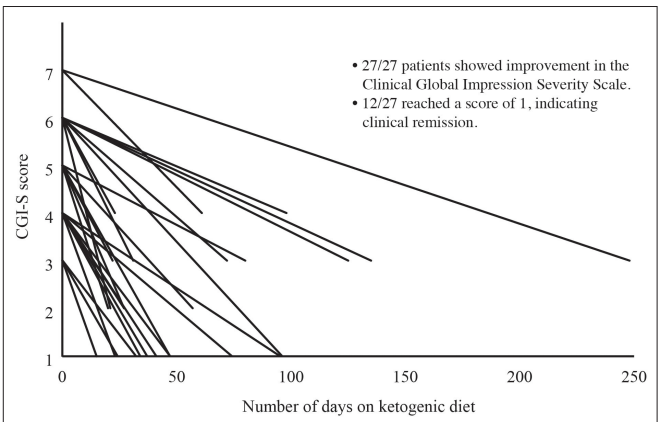

FIGURE 1 | Change in Clinical Global Impressions Severity Scale (CGI-S) Over Time. Severity of illness was assessed in 27 of 28 patients using the CGI-S. The CGI-S is rated on a scale of 1 to 7, with 1 indicating normal and 7 indicating extreme illness. Following the KD intervention, CGI-S had improved in all 27 patients, with 12 of 27 (44%) achieving a CGI-S of 1 (clinical remission).

CGI-S

Severity of illness was assessed in 27 of 28 patients using the CGI-S. Following the KD intervention, mean (SD) CGI-S improved from 4.9 (1.2) to 2.0 (1.1), Cohen's $d = 3.8$. As this change violated the assumption of normality, we conducted a Wilcoxon Signed-Ranks Test that indicated that the change was statistically significantly different, Z $= -4.65$, $P < 0.001$ (see **Figure 1**), with 12 of 28 patients (43%) achieving clinical remission. A reduction of 1 point on the CGI-S is considered the minimal clinically important difference (33). All patients achieved a reduction of at least 2 points on the CGI-S, regardless of diagnosis (Cohen's d = 3.8).

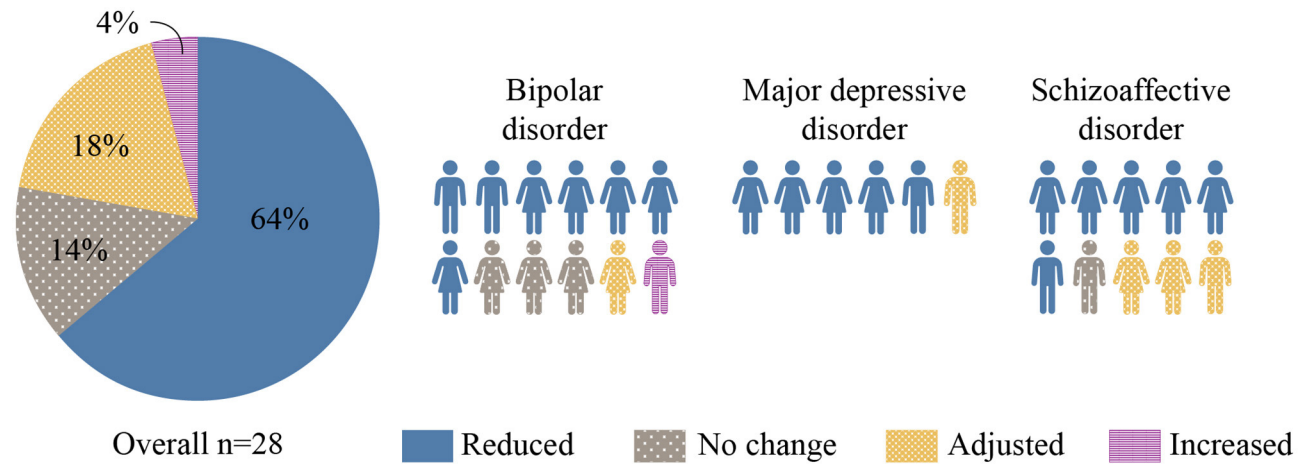

FIGURE 2 | Changes in Psychotropic Medication. Changes in the number and/or dosage of psychotropic medications associated with KD intervention are represented in this figure. The majority (64%) of participants were discharged on less medication.

Medication Changes

Prior to the intervention, the mean (SD) number of psychotropics taken per patient was 5.3 (2.0) with 25 of 28 (89%) patients taking at least one antipsychotic medication. By the end of the intervention, the number and/or dosage of psychotropic medications had been reduced in 18 of 28 (64%) patients (see **Figure 2**). Among the 7 patients who were also taking non-psychotropic medications, the number and/or dosage of those medications was reduced in 5 of 7 patients (71%). Somatic medications reduced and/or discontinued were insulin, metformin, atorvastatin, gliclazide, and ticagrelor.

Metabolic Health Measures

Metabolic health measures are detailed in **Table 2**. Prior to the intervention, mean (SD) body weight was 198.5 (42.1) lbs (range 145.7–310.9 lbs) and mean (SD) BMI was 31.9 (6.7) kg/m^2 (range 23.0–51.2 kg/m^2). Initial BMI lay in the normal range (18.5–24.9 kg/m^2) for 3/28 (10.7%) patients, in the overweight range (25.0–29.9 kg/m^2) for 7/28 (25.0%) patients, and in the obese range ($\geq$30.0 kg/m^2) for 18/28 (64.3%) patients. At the conclusion of the intervention, all but one patient (27 of 28; 96.4%) had lost weight. Of note, 24 of the 25 (96%) patients who were taking antipsychotic medications lost weight, and 12 of those 25 (48%) achieved clinically significant weight loss [defined as $\geq$5% reduction in body weight (34)]. Overall, weight change [mean (SD), −10.8 (−7.1) lbs]; and BMI change [mean (SD), −1.7 (1.2) kg/m^2] were both significant ($P < 0.001$), as were reductions in fasting blood glucose, hemoglobin A1c, systolic and diastolic blood pressure, and gamma-glutamyl transferase (GGT). There were also significant overall reductions in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, and triglycerides (TGs). Among the 14 of 28 (50%) patients who initially met criteria for hypertriglyceridemia (TG > 150 mg/dl), marked reductions of 100 mg/dl or more were seen in 7 (50%), with 5 patients (36%) no longer meeting criteria for hypertriglyceridemia following the intervention. C-reactive protein levels were also measured but due to several instances of infection, values were deemed unreliable.

Ketogenic Diet Tolerability

Most patients initially experienced one or more symptoms commonly reported during early keto-adaptation (35), such as headache, insomnia, irritability, excitation, dizziness, and carbohydrate cravings. These were mild, required no special medical or psychiatric management, and resolved within 2 weeks or less. Beyond this initial transition period, the KD was psychiatrically well tolerated by all patients, and 27 of 31 (87%) experienced no problematic somatic side effects. Two (excluded) patients cited fat intolerance, and 2 (included) patients experienced diarrhea and/or vomiting which resolved within 4 weeks. A fifth patient developed gastroenteritis during week 5 of the intervention and discontinued the diet, but later resumed the KD without ill effects, suggesting gastroenteritis was unlikely to have been KD related.

Post-Hospitalization Dietary Adherence

In the months following hospital discharge, 13 of the 28 included patients (46%) reported good adherence to the KD at home, 5 (18%) reported partial adherence, 6 (21%) discontinued the diet, 1 discontinued then later resumed, and 3 were lost to follow-up. Those who elected to continue the KD after discharge did so to maintain or improve upon the psychiatric and metabolic benefits experienced during hospitalization. Reasons for discontinuation included cost, difficulty preparing meals, restrictiveness, and low motivation.

DISCUSSION

This iteration of a KD was safe, feasible to administer in an inpatient setting, well tolerated by most patients, and associated with substantial and statistically significant improvements in symptoms of depression and psychosis not observed during

TABLE 2 | Metabolic health measures.

Clinical value	*n*[a]	Pre-KD, mean (SD)	Post-KD, mean (SD)	Change	Percent change	*P*-value
Overall						
Weight, lbs	28	198.5 (42.1)	187.7 (38.5)	−10.8 (7.1)	−5.3 (3.1)	<0.001
BMI, kg/m^2	28	31.9 (6.7)	30.1 (6.1)	−1.7 (1.2)	−5.3 (3.1)	<0.001
SBP, mmHg	26	134.5 (15.0)	123.4 (11.3)	−11.1 (12.6)	−7.6 (9.6)	<0.001
DBP, mmHg	26	85.7 (11.8)	78.7 (9.0)	−7.0 (8.5)	−7.4 (9.6)	<0.001
FBG, mg/dL	27	104.7 (26.7)	93.4 (14.2)	−11.2 (19.3)	−8.1 (14.9)	0.002
HbA1c, %	24	5.9 (0.7)	5.6 (0.5)	−0.2 (0.5)	−3.5 (6.5)	0.003
Trig, mg/dL	28	204.0 (194.7)	137.5 (69.5)	−66.5 (149.5)	−14.8 (35.4)	0.003
HDL-C, mg/dL	27	50.1 (11.6)	54.0 (17.0)	3.9 (12.9)	8.4 (26.6)	0.125
LDL-C, mg/dL	28	141.4 (40.6)	131.5 (29.7)	−9.9 (37.2)	−0.5 (36.8)	0.171
Total Chol, mg/dL	28	226.7 (44.6)	210.4 (31.0)	−16.3 (37.0)	−4.4 (21.1)	0.027
ALT, u/L	25	43.5 (74.2)	32.8 (28.6)	−10.7 (56.2)	−1.4 (55.7)	0.036
AST, u/L	26	27.7 (24.1)	22.5 (11.5)	−5.1 (17.2)	−9.0 (40.1)	0.009
GGT, u/L	26	64.4 (117.6)	36.4 (38.6)	−28.0 (81.2)	−21.0 (30.9)	0.002
TSH, μU/mL	24	2.1 (2.7)	1.8 (1.2)	−0.2 (2.3)	28.2 (95.1)	0.831
UA, mg/dL	24	56.3 (23.5)	53.6 (18.3)	−2.6 (15.0)	−0.3 (22.0)	0.749
Primary diagnosis: Bipolar disorder						
Weight, lbs	12	191.7 (32.9)	182.3 (31.3)	−9.4 (5.9)	4.9 (2.9)	<0.001
BMI, kg/m^2	12	31.0 (5.0)	29.5 (4.7)	−1.5 (1.0)	−4.9 (2.9)	<0.001
SBP, mmHg	12	131.2 (12.6)	120.9 (14.0)	−10.3 (11.6)	−7.6 (9.1)	0.011
DBP, mmHg	12	83.1 (13.0)	75.1 (9.9)	−8.0 (10.1)	−8.7 (11.1)	0.019
FBG, mg/dL	12	101.0 (19.7)	90.8 (15.5)	−10.3 (9.5)	−9.4 (8.9)	0.003
HbA1c, %	11	6.1 (0.7)	5.8 (0.5)	−0.3 (0.6)	−4.6 (8.1)	0.111
Trig, mg/dL	12	284.1 (267.2)	167.2 (86.4)	−116.9 (215.0)	−25.7 (32.3)	0.012
HDL-C, mg/dL	11	50.0 (12.9)	52.5 (19.7)	2.5 (12.6)	4.0 (27.4)	0.929
LDL-C, mg/dL	12	144.2 (40.6)	121.4 (35.2)	−22.8 (30.0)	−14.6 (19.1)	0.024
Total Chol, mg/dL	12	241.5 (42.9)	207.6 (36.6)	−33.9 (31.1)	−13.3 (11.9)	0.003
ALT, u/L	9	62.6 (110.6)	36.0 (31.7)	−26.6 (79.9)	−11.1 (29.3)	0.153
AST, u/L	11	34.2 (35.4)	23.0 (13.0)	−11.2 (22.8)	−21.0 (15.3)	0.003
GGT, u/L	12	100.5 (168.7)	46.8 (54.4)	−53.7 (115.6)	−34.3 (17.5)	0.002
TSH, μU/mL	10	1.7 (0.9)	2.0 (1.3)	0.4 (1.3)	45.4 (111.7)	0.414
UA, mg/dL	11	65.7 (23.7)	60.7 (15.8)	−5.0 (19.5)	−1.7 (26.3)	0.414
Primary diagnosis: Major depression						
Weight, lbs	6	213.7 (56.1)	203.1 (50.0)	−10.6 (7.1)	−4.6 (2.1)	0.015
BMI, kg/m^2	6	34.9 (8.0)	33.2 (7.1)	−1.7 (1.1)	−4.6 (2.1)	0.014
SBP, mmHg	5	144.0 (18.2)	129.4 (11.2)	−14.6 (10.4)	−9.6 (7.1)	0.035
DBP, mmHg	5	95.4 (12.4)	86.2 (8.6)	−9.2 (5.1)	−9.3 (4.4)	0.015
FBG, mg/dL	5	84.6 (14.7)	91.8 (10.8)	7.2 (11.6)	9.9 (14.9)	0.238
HbA1c, %	5	5.9 (0.6)	5.8 (0.5)	−0.1 (0.4)	−2.1 (7.0)	0.481
Trig, mg/dL	6	137.3 (98.3)	126.5 (53.8)	−10.8 (46.0)	6.0 (27.0)	0.917
HDL-C, mg/dL	6	48.2 (14.4)	52.7 (12.5)	4.5 (3.1)	11.1 (9.1)	0.016
LDL-C, mg/dL	6	141.3 (28.4)	155.3 (22.1)	14.0 (45.4)	15.6 (39.6)	0.484
Total Chol, mg/dL	6	217.7 (20.6)	219.2 (20.6)	1.5 (20.5)	1.0 (8.8)	0.500
ALT, u/L	5	32.8 (20.9)	43.6 (42.6)	10.8 (38.4)	31.2 (113.5)	0.686
AST, u/L	5	26.4 (12.3)	30.6 (13.4)	4.2 (16.8)	32.0 (70.8)	0.605
GGT, u/L	5	32.0 (19.1)	30.6 (13.3)	−1.4 (18.8)	7.1 (37.9)	0.876
TSH, μU/mL	5	1.4 (0.6)	1.9 (0.4)	0.5 (1.0)	70.6 (115.9)	0.317
UA, mg/dL	4	46.5 (11.5)	44.0 (17.0)	−2.5 (14.5)	−4.8 (30.9)	0.754
Primary diagnosis: Schizoaffective disorder						
Weight, lbs	10	197.6 (45.2)	185.0 (40.8)	−12.6 (8.5)	−6.2 (3.9)	0.001
BMI, kg/m^2	10	31.1 (7.8)	29.1 (7.0)	−2.0 (1.4)	−6.2 (3.8)	0.001

(Continued)

TABLE 2 | Continued

Clinical value	*n*[a]	Pre-KD, mean (SD)	Post-KD, mean (SD)	Change	Percent change	*P*-value
SBP, mmHg	9	133.8 (15.7)	123.4 (5.8)	−10.3 (15.7)	−6.5 (12.0)	0.084
DBP, mmHg	9	83.7 (6.9)	79.2 (5.2)	−4.4 (7.9)	−4.78 (9.9)	0.171
FBG, mg/dL	10	119.1 (31.8)	97.5 (14.5)	−12.6 (24.6)	−15.5 (14.1)	0.007
HbA1c, %	8	5.5 (0.5)	5.3 (0.5)	−0.2 (0.2)	−2.7 (3.5)	0.064
Trig, mg/dL	10	147.9 (78.5)	108.5 (39.8)	−39.4 (55.5)	−14.2 (40.4)	0.052
HDL-C, mg/dL	10	51.4 (9.1)	56.6 (17.4)	5.2 (17.0)	11.6 (33.4)	0.360
LDL-C, mg/dL	10	138.0 (49.6)	129.2 (18.2)	−8.8 (36.2)	6.7 (47.4)	0.462
Total Chol, mg/dL	10	214.4 (54.6)	208.6 (30.9)	−5.8 (44.0)	3.1 (30.5)	0.687
ALT, u/L	9	26.0 (8.9)	22.9 (9.7)	−3.1 (7.6)	−7.8 (30.8)	0.257
AST, u/L	10	21.1 (7.5)	18.0 (6.5)	−3.2 (4.4)	−16.2 (28.3)	0.047
GGT, u/L	9	34.2 (16.4)	25.8 (14.1)	−8.4 (13.5)	−18.8 (32.9)	0.098
TSH, μU/mL	9	2.8 (4.3)	1.5 (1.4)	−1.3 (3.4)	−14.4 (41.2)	0.123
UA, mg/dL	9	49.0 (24.7)	49.2 (20.2)	0.2 (8.7)	3.5 (11.8)	0.528

ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; GGT, gamma glutaryl transferase; HbA1c, hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; Total Chol, total cholesterol; Trig, serum triglycerides; TSH, thyroid stimulating hormone; UA, uric acid.

[a]*As this is a retrospective analysis, some values were not available for all 28 participants.*

previous hospitalizations. Effect sizes were large (Cohen's d > 0.8) (36) across all mental health outcome measures in all subgroups, and were very large among those with a primary diagnosis of major depression. Given that the interventions implemented during this hospitalization differed only in the addition of the KD to usual care, we believe it is likely that the KD contributed considerably to these unprecedented mental health improvements, particularly in the 79% of patients whose psychotropic medications were either reduced or unchanged. The notable improvements in multiple markers of metabolic health including body weight, blood pressure, blood glucose, and triglycerides observed in this series would be difficult to ascribe to any aspect of the hospitalization other than the KD, which is known to facilitate these healthy changes (37).

Historical and Scientific Context

A recent non-randomized study of 262 outpatients with type 2 diabetes treated with a KD detected significant improvement in mood. This cohort included 36 patients with mild clinical depression, more than half of whom no longer met criteria for depression at week 10 (38).

To the best of our knowledge, this case series represents the first exploration of the use of the KD in hospitalized patients with bipolar illness or severe depressive illness, and only the second exploration of the use of the KD in hospitalized patients with psychotic illness—the first having been published in 1965 (39). In that pilot study, a KD was administered to 10 women with treatment-refractory schizophrenia, resulting in statistically significant improvements in mean symptom scores after 2 weeks. Since that time, a number of isolated case reports describing people with mental illness who have benefited substantially from KDs have been documented; the first of these was published by one of us in 2009 (40) and offers an example of long-lasting resolution of psychotic symptoms and the ability to completely discontinue antipsychotic medication.

Biological Plausibility

The biological plausibility that KDs may be of therapeutic benefit in major depression, bipolar illness, and schizophrenia is strongly supported by the scientific literature (18, 41–44).

Major Depression

Inflammation is implicated in all three conditions but has been most extensively studied in depression. Inflammation plays a role in the development and course of many cases of clinical depression and is associated with poor response to antidepressant medications (45, 46). The KD has been shown to reduce inflammation via complex influences on both central and peripheral immunoregulatory pathways (47–50). The KD also influences multiple neurotransmitter systems involved in depression, including the dopaminergic, serotonergic, glutamatergic, and GABAergic systems (51).

Bipolar Disorder

Among those with bipolar illness, there is a higher prevalence of impaired glucose metabolism even in drug-naïve individuals (52). Calkin (53) found that those with insulin resistance or type 2 diabetes are more likely to experience rapid mood cycling, less likely to respond to lithium, and more likely to suffer a more progressive disease course. Proposed mechanisms by which glucose and insulin dysregulation may dysregulate mood include damaging oxidative stress which, in turn, could impair mitochondrial function (16). Napolitano et al. (54) recently discovered that the KD can increase brain levels of glutathione, a ubiquitous intracellular antioxidant key to buffering oxidative stress. Campbell and Campbell (55) hypothesize that the KD might help ameliorate symptoms of bipolar illness by shifting the brain's primary fuel source from glucose to ketone bodies, thereby bypassing existing mitochondrial defects and reducing further mitochondrial injury. Calkin et al. (56) have proposed that insulin resistance, via inflammatory damage to endothelial

cells, can compromise the integrity of the blood-brain barrier (BBB) in people with bipolar illness. Interestingly, disruption of the tight junctions critical to BBB structure and function has been observed not only in bipolar illness but also in major depression and schizophrenia (57).

Schizophrenia

Hyperinsulinemia, insulin resistance, and impaired glucose metabolism are more common in treatment-naïve individuals experiencing first-episode psychosis than in the general population (58). While this association alone is insufficient to support a causal relationship between metabolic dysregulation and psychotic symptoms, several cases of acute hyperglycemia associated with transient psychotic symptoms in patients with type 1 and type 2 diabetes have been reported (59). Pathophysiological features of schizophrenia shown in pre-clinical studies by Sarnyai et al. (44) to improve in response to a KD include N-methyl-D-aspartate (NMDA) receptor hypofunction, sensory gating deficits, and glutamate excitotoxicity.

KDs also help rebalance neurotransmitter systems, (16) stabilize neural networks (60), improve neuroplasticity (61), and bridge the energy gap resulting from the cerebral glucose hypometabolism associated with major depression, bipolar illness, and schizophrenia (17).

Strengths and Limitations

Unique strengths of this series include the diversity of psychiatric diagnoses and the relatively large number of patients exposed to the same intervention in the same semi-controlled clinical setting. It was with these elements in mind that we chose not to report these patient outcomes as individual case studies. The provision of education, monitoring, and support by a psychiatrist who had trusting therapeutic alliances with his patients prior to the intervention seemed to contribute to patients' openness to the intervention and likely improved dietary adherence and honesty about transgressions, although this special treatment context makes it unclear whether these same outcomes would be possible under different circumstances.

Neither the treating psychiatrist responsible for assessing outcomes nor the patients themselves were blinded to the intervention, therefore there is a risk that impressions of clinical progress may have been biased. While patients may have benefited simply from having been hospitalized, a strength of this cohort is that all patients had previously been hospitalized under Dr. Danan's care at least once (and in many cases, multiple times) at either this same facility or a sister facility where all non-dietary aspects of care were very similar, yet Dr. Danan reports never having observed this degree of clinical improvement in these patients before. These patients therefore might be considered to have served as their own historical comparison group, although mental health outcomes were not formally measured during previous hospitalizations.

As with any intervention in which ad libitum dietary patterns are replaced with a structured dietary pattern of interest, multiple dietary variables were manipulated, therefore even if it were possible to assign clinical benefits to the KD, it would still be difficult to determine which aspect(s) of the KD may be responsible for those benefits. For example, this iteration of the KD was not only low in carbohydrate—it was also grain-free, very low in processed foods, and supplemented with micronutrients. As KD meals and snacks were portion-controlled, patients may also have consumed fewer calories than usual.

It should also be noted that this setting did not allow for complete control over the dietary intervention, as participants were permitted to leave the unit on weekends, and while on the unit, could interact with nonparticipant patients who were served standard fare. As this was not a metabolic research ward, urine ketone monitoring (which can be helpful in assessing dietary adherence) was burdensome for busy staff, and therefore was conducted only once per patient. However, weight loss is another piece of evidence that patients were adherent to the dietary program, as most overweight or obese individuals will lose weight on a KD (24), and clinically meaningful weight loss in people with serious mental illness is otherwise unexpected, even when lifestyle interventions aimed at weight loss are implemented (62). All but one patient lost weight including 96% of those who were taking antipsychotics, and nearly half achieved clinically significant weight loss [defined as $\geq$5% reduction in body weight (34)]. This welcome outcome alone makes a compelling case for the implementation of the KD in people who are taking antipsychotic medications, whether or not psychiatric symptoms improve in response to the KD, as counteracting antipsychotic-induced weight gain is extremely difficult (63).

Whether weight loss alone could lead to a reduction in symptoms of depression, bipolar disorder (64), and/or psychosis remains a largely unanswered question. In people with type 2 diabetes treated with a KD, improvement in depression symptoms was not correlated with weight loss (38). While studies find that people with clinical depression who have undergone bariatric surgery report fewer depression symptoms 6 months or more following the procedure, weight change appears to be an unreliable predictor of improvements in mood (65). We are unaware of any studies evaluating the impact of weight loss alone on symptoms of bipolar or psychotic illnesses.

Practical Considerations

Ketogenic diet protocols exist on a spectrum ranging from the "classic" KD originally used to treat medication-refractory pediatric epilepsy (90% fat, 6% protein, 4% carbohydrate) to modified KDs which allow for higher percentages of protein, to modified Atkins diets (66), in which protein may be eaten to satiety (67). The protocol Dr. Danan chose to adapt for use with his patients falls into this last category, although protein intake was limited in this setting to 15–20% of daily calories at least 6 days per week. One advantage of this more liberal approach is that precision control of macronutrient ratios is not required, easing the logistics of both administration and adherence.

In addition to rare metabolic disorders typically diagnosed in childhood, there are several health conditions considered by many to be absolute contraindications to initiating KDs in adults; these include acute pancreatitis, nephrolithiasis, renal failure, liver failure, congestive heart failure, anorexia nervosa, and concurrent use of SGLT2 inhibitors.

A well-formulated KD can quickly and effectively lower levels of blood glucose, insulin, and blood pressure—all considered clinically desirable goals in many patients, particularly those with metabolic syndrome. However, these generally beneficial physiological adaptations to the KD necessitate careful medication management. Medications that lower blood glucose (such as insulin, sulfonylureas, and meglitinides) and medications that lower blood pressure (such as diuretics and ACE inhibitors) warrant diligent monitoring as some may need to be reduced or even discontinued as early as day 1 of KD initiation to minimize the risk of hypoglycemic, hypotensive, and hypovolemic events (68, 69).

We are unaware of published research on the potential interactions between ketogenic diets and psychotropic medications with the notable exception of anticonvulsants. Studies of patients with epilepsy treated with a KD find that anticonvulsant levels can change in response to the diet. Although these changes are typically small and clinically inconsequential, valproate levels can fall significantly (70). Since these agents have not yet been formally studied in people with psychiatric conditions, it would be prudent to monitor blood levels of all anticonvulsants as well as of any other psychiatric medications for which changes in blood level may be of clinical importance, such as lithium. With these cautions noted, for most adult patients, the potential benefits of simple, well-formulated KDs would seem to outweigh the potential risks (71).

As clinical response to the KD in this patient cohort typically occurred within 3 weeks or less, it should be noted that the highly variable and, in some cases, lengthy duration of hospitalization in this cohort was not related to the KD but largely to socioeconomic factors. In France, inpatient psychiatric care is cost-free for patients, bed availability is high, and hospitalization criteria are liberal, therefore stays lasting many months are commonplace. Given that this iteration of the KD was generally well tolerated and psychiatrically safe even in the complex cases that comprise this series, hospitalization may not be necessary so long as proper medical supervision is provided, particularly around medication management.

Key to the successful transition to a KD in any population is dietary education and support, and likely particularly important in this population was the provision of prepared meals and snacks, as depression, psychosis, and other serious psychiatric symptoms may otherwise have made the logistics of adopting and adhering to the KD (or any new diet) formidable. It is conceivable that a thoughtfully designed intensive outpatient program could provide the necessary structure and support for patients with serious mental illness to transition to a KD, and it is encouraging to see that nearly half of patients in this group managed to continue following a KD after discharge.

Future Research Considerations

Our observations warrant further research into the potential of the KD to improve the lives of people with mental illness. Many unanswered questions remain in this nascent field that carefully designed, adequately powered, randomized controlled trials—whether conducted in inpatient, outpatient, or virtual settings—could begin to address. As serum beta-hydroxybutyrate measurements are currently the most reliable method of assessing metabolic response to the KD, daily monitoring of this metric would help clinicians and patients understand whether the degree and consistency of ketosis are important to clinical outcomes.

CONCLUSION

In this retrospective analysis of clinical care, which to our knowledge represents the largest number of people with serious mental illness treated with a KD in a hospital setting thus far, we found that the KD was feasible, safe, well-tolerated, and associated with considerable improvements in mental health symptoms as well as in multiple markers of metabolic health. While more rigorous research is needed to confirm the association between the KD and improved mental health outcomes, these findings indicate that medically supervised carbohydrate restriction is a simple, safe, universally accessible intervention well worth considering as an adjunctive strategy in the treatment of serious mood and psychotic illnesses.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This treatment program was approved by the Clinique du Castelviel (Castelmarou, France) Administration and Ethics Review. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AD conceived of and implemented the intervention and generated clinical data and observations. GE conducted the literature review and wrote the manuscript. EW and LS performed statistical analyses. All authors contributed to the article and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.951376/full#supplementary-material

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The remaining 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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Twelve-month outcomes in overweight/obese users with mental disorders following a multi-element treatment including diet, physical activity, and positive thinking: The real-world "An Apple a Day" controlled trial

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The present study aimed to evaluate the 12-month effectiveness of a real-world weight loss transdiagnostic intervention in overweight/obese participants affected by mental disorders under psychopharmacological treatment. We conducted a real-world, controlled, pragmatic outpatient trial. We allocated 58 overweight/obese adults under psychopharmacological treatment from a mental health outpatient unit and 48 overweight/obese adults from a cardiovascular prevention outpatient unit, and assigned them to an intervention or treatment usual as condition (TAU) enriched by life-style advice. Participants in both intervention groups took part in a diet programme (the modified OMNIHeart dietary protocol) and monitoring of regular aerobic activity. A brief group programme ("An Apple a Day" Metacognitive Training, Apple-MCT) was added in the intervention group of participants affected by mental disorders. The primary outcome was weight loss. Secondary outcomes included anthropometric, clinical, and metabolic variables. Psychopathology and health-related quality of life were also evaluated in the psychiatric sample. At 12 months, both intervention groups showed a more marked mean decrease in weight (6.7 kg, SD: 3.57) than the TAU group (0.32 kg, SD: 1.96), and a statistically significant improvement in metabolic variables compared with the control groups. Furthermore, the participants affected by mental disorders included in the intervention group reported improved health-related quality

of life. Our findings suggest the need to implement integrated interventions based on a dietary protocol, physical activity, and modification of cognitive style in overweight/obese users with mental disorders.

KEYWORDS

diet protocol, physical activity, metacognitive group intervention, cardiovascular risk, mental disorders, obesity, metabolic syndrome, psychopharmacological treatment

Introduction

Individuals with severe mental disorders (SMDs) die, on average, 15–20 years earlier than the general population. This pre-mature mortality is mainly due to metabolic and cardiovascular diseases that occur more frequently, are not prevented, and are inadequately identified in this population (1, 2).

Cardiovascular risk factors in individuals with several SMDs—such as schizophrenia spectrum disorder, bipolar disorder, and major depression—include not only common factors, such as "unhealthy" dietary patterns, smoking habits, low levels of physical activity, obesity, hypertension, diabetes, and dyslipidaemia, but also drug-related factors, therapeutic inertia, and poor adherence to prescribed medication (3–7).

The assumption of consuming psychotropic drugs such as antipsychotics, antidepressants, and mood stabilizers seems to be associated with metabolic and clinical disorders, including weight gain, diabetes, dyslipidaemia, and hypertension (4, 8–10). There is a well-documented relationship between clinical/metabolic complications and second-generation antipsychotics, including olanzapine and clozapine, since they are used in the early stages of mental illness (11–19).

The problem of weight gain induced by psychotropic drugs is underestimated in terms of its consequences (8). It can compromise long-term treatment adherence (20) and increase relapse risk (21). Because of the associated metabolic complications, weight gain can negatively impact one's overall quality of life (22, 23) as well as social stigmas associated with mental disorders (24), life expectancy (25), self-esteem, and poorer psychosocial adaptation (26).

Patients in the early phases of schizophrenia and bipolar disorder are at extremely high risk for developing cardiovascular comorbidity; moreover, their metabolic profile worsens quickly (27, 28). Individuals with schizoaffective disorder are more likely to suffer from metabolic syndrome comorbidity than individuals with schizophrenia or other non-affective psychoses (29).

Not only do those affected by psychotic disorders display metabolic problems, but persons affected by depression (compared to non-depressed people) have a significantly greater risk for developing obesity, especially adolescent women (30), in light of the comorbidity of depression with metabolic ailments (31). The link between depression and cardiovascular disease is complex. Major depressive disorder and self-reported depressive symptoms are associated with elevated visceral adipose tissue and subcutaneous adipose tissue (32).

A very recent review (33) investigating the relationship among adipose tissue compartments, inflammation, and cardiovascular risk in depressive disorder emphasized the significant association of depressive symptoms with severe body composition changes starting in early adulthood. Stapel et al. (33) suggested that this group of patients could be predisposed to common physical disorders, such as diabetes mellitus type 2 and cardiovascular diseases. Increased activity of the HPA axis, physical inactivity, poor nourishment, poor adherence to treatment recommendations, and low-grade inflammation might directly or indirectly worsen this vicious cycle, resulting in higher morbidity and mortality rates due to cardiometabolic disorders (33). The same anxiety disorders were observed in frequent co-occurrence with various medical illnesses, with percentages of up to 30% in participants with cardiovascular diseases, 47.0% in those with diabetes mellitus, and vice versa. High rates of medical conditions were reported in samples of participants with anxiety disorders, and greater severity of both anxiety disorders and medical diseases are observed when they coexist (34).

Compared to the general population, individuals suffering from severe psychiatric disorders, especially schizophrenia, tend to engage in a low level of physical activity (35–37), are more inclined to smoke, and exhibit a greater preference for a high-calorie diet (38). This unhealthy lifestyle and non-adherence to treatment over time could be ascribed to a low level of self-regulatory behaviors (39), cognitive flexibility (40, 41), and low levels of self-esteem (42). In recent years, both national and international groups have developed cost-effective screening and monitoring guidelines (17, 43–46), although they are not being implemented in the clinical care of users (47, 48). Based on a review of the evidence that users with serious mental illness (SMI) are at increased risk of CVD and diabetes, the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC), published a statement regarding the guidelines of ESC and EASD Fourth Joint Task Force of the European Society of Cardiology and Other Societies on

Cardiovascular Disease Prevention in Clinical Practice (49). The initiative was aimed at improving the care of users suffering from SMI, initiating cooperation and shared care between different health care professionals to raise the awareness of psychiatrists and primary care physicians who care for patients with SMI for screening and treatment of cardiovascular risk factors and diabetes (50). More recently, a meta-analysis of physical activity interventions and their impact on health outcomes for people with SMI, including schizophrenia-spectrum disorders, major depressive disorder (MDD) and bipolar disorder (51), showed that PA can improve cardiorespiratory fitness, quality of life and depressive symptoms, with effects on depressive symptoms comparable to those of antidepressants and psychotherapy. For schizophrenia-spectrum disorders, much evidence indicates that aerobic physical activity can reduce psychiatric symptoms and improve cognition in various subdomains and cardiorespiratory fitness. In contrast, evidence for the impact on anthropometric measures was inconsistent. Lastly, there was a lack of studies investigating physical activity in bipolar disorder, precluding any definitive recommendations.

Among effective diet programs in clinical populations not affected by psychiatric disorders, some studies used a redistribution of dietary macroelements, from cholesterol and saturated fats to carbohydrates, at a low glycaemic index, based on results obtained from the Optimal Macronutrient Intake Trial, to prevent heart disease (OMNIHeart) (52). Moreover, diet and physical activity modification protocols are widely applied in populations affected by hypertension (53, 54).

At present, most studies on weight management during psychopharmacological treatment include behavioral advice, diet programmes, physical exercise (55), and tailored educational programmes (56). Many studies have used pharmacological or cognitive-behavioral approaches (57) rooted in programmes to change lifestyles to reduce weight gain in individuals with mental illness (58–63).

Our primary aim was to evaluate the effectiveness of a dietary protocol and regular aerobic activity on weight, laboratory, and clinical parameters in participants with and without mental disorders compared to an intervention based on correct lifestyle advice. Additionally, we aimed to evaluate the "add-on" results of a brief metacognitive group programme to enhance the intervention's effectiveness in the sample of overweight/obese users with mental disorders undergoing psychopharmacological treatment.

We hypothesized that (1) the dietary protocol and monitoring of regular aerobic activity would have beneficial effects in participants with and without mental disorders on weight, laboratory, and clinical parameters and would produce outcomes that are superior to advice to improve one's self-regulation of food intake and to engage in more physical activity; (2) integrating a brief, structured group metacognitive intervention could further improve the adhesion of participants affected by mental disorders to maintain metabolic and clinical improvements over time, thereby contributing to better mental health.

Materials and methods

Design

The design was a real-world, controlled, pragmatic trial comparing four parallel groups of consecutively allocated participants: those affected by mental disorders undergoing an intervention including a diet protocol, monitoring of regular aerobic activity, and the "An Apple a Day" group Metacognitive Training (Apple-MCT) (G1); participants affected by mental disorders, receiving TAU and advice on a better life-style and bimonthly clinical consultations (G2); participants affected by hypertensive disease undergoing an intervention including a diet protocol and monitoring of regular aerobic activity (G3); and participants affected by hypertensive disease receiving TAU and advice on a better life-style and bimonthly clinical consultations (G4) (Figure 1).

For the psychiatric sample, their assignment was adapted to users' preferences and logistic factors (home distance from the unit, work rotations, difficulty in reaching the unit *via* public transit, etc.). We considered the problems they expressed, mainly when they were offered inclusion in the group intervention and were estimated to attend group sessions.

The inclusion in the protocol did not involve additional fees for the participants.

We carried out the study in compliance with the ethical principles of the Declaration of Helsinki; it was approved by the Ethical Committee of the University of L'Aquila (approval date: 14 October 2014).

Participants and procedures

All participants were recruited over a 12-month period between January and December 2015 from the TRIP service (Psychosocial Rehabilitation Treatment, Early Interventions in Mental Health Unit) and from the Hypertension and Cardiovascular Prevention Outpatient Unit, both at the University of L'Aquila (Italy).

The participants (aged at least 18) were included according to the presence of at least two of the following:

1) body mass index (BMI) (kg/m^2) >26;
2) waist circumference (men >102 cm, women >88 cm);
3) hypertriglyceridaemia (≥150 mg/dl);
4) high-density lipoprotein cholesterol (HDLc) (men: <40 mg/dl, women: <50 mg/dl);
5) systolic/diastolic blood pressure levels (≥130/85 mmHg) or diagnosed hypertension;

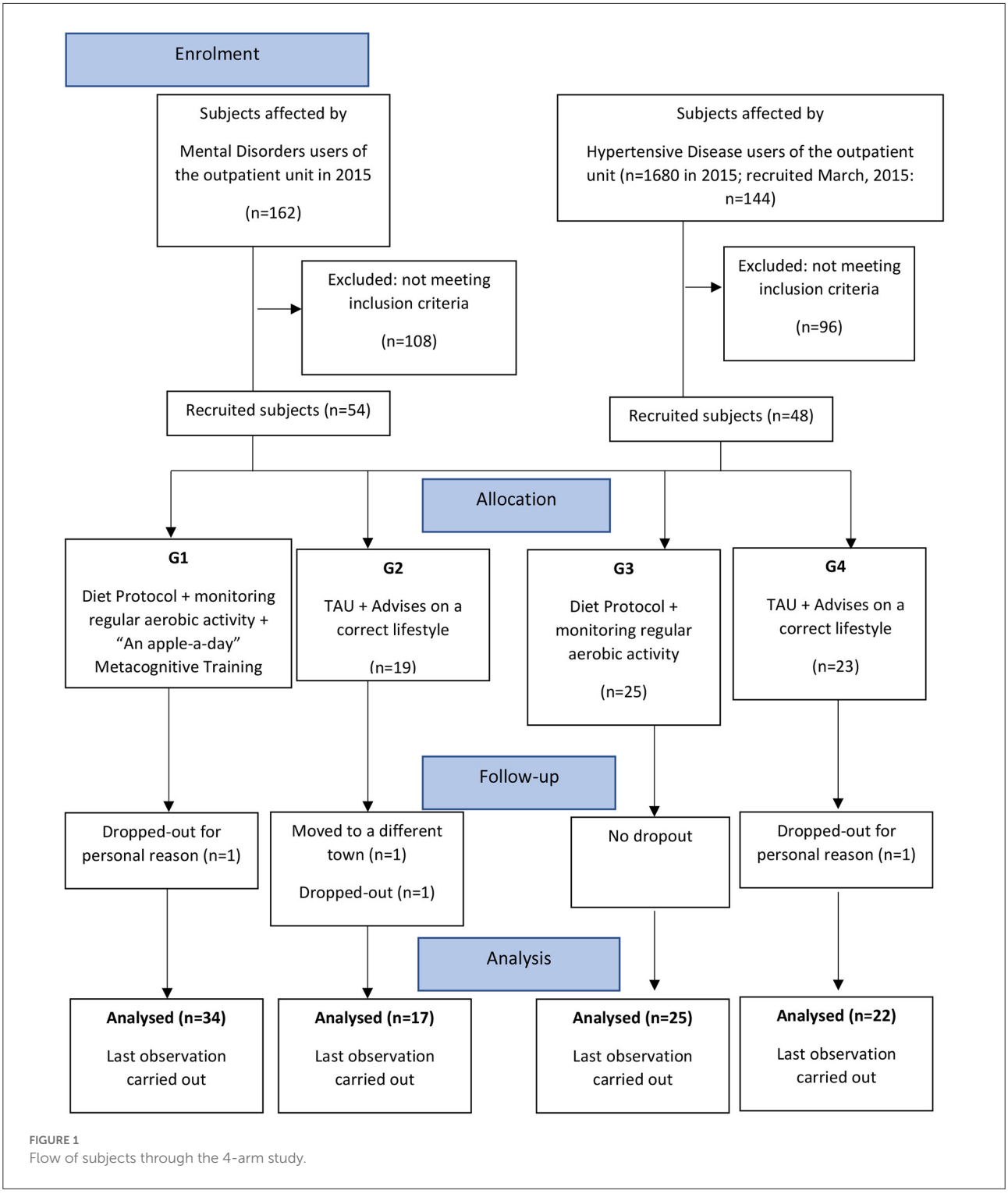

FIGURE 1
Flow of subjects through the 4-arm study.

6) fasting hyperglycaemia (≥100 mg/dl).

The presence of 3 or more of the abovementioned latter elements characterizes metabolic syndrome (MS) (64). MS represents a clustering of factors (hypertension, dyslipidaemia, abdominal obesity, impaired glucose tolerance) predicting an increased risk of cardiovascular disease and stroke (65).

The exclusion criteria for both groups were as follows:

1) severe neurological disorder or intellectual disability or developmental abnormalities or previous head injury;
2) diabetes mellitus, cancer or chronic ailments, prior cardiovascular disease, serum total cholesterol (TC) concentrations >310 mg/dl, triglyceride (TRG) concentrations >350 mg/dl, renal and/or liver insufficiency and any concomitant disease.

All participants included in the psychiatric sample (G1 and G2) received pharmacological treatment: selective serotonin reuptake inhibitor (SSRI) and noradrenergic and specific serotonergic antidepressants (NaSSAs); second-generation antipsychotics; anxiolytics; mood stabilizers; and first-generation antipsychotics (Table 1).

Waist circumference, height, weight, and blood pressure were measured by trained clinical staff during clinic visits, while fasting plasma lipid levels (triglycerides and low density lipoproteins) and fasting blood glucose levels were measured using regular hospital laboratories. Regarding the metabolic measures, serum low-density lipoprotein cholesterol (LDLc) levels were calculated according to the Friedewald formula (LDLc=TC-(HDL + TRG/5). All analyses were validated by the ISO 9001: 2000 EA: 38 CISQ n. 9122. ASL-IQNET n. IT-65188 quality system. Waist circumference was measured to the nearest 0.1 cm using a standard, inelastic tape maintained on a horizontal plane, with the participant standing with his/her weight distributed evenly on both feet. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (without shoes). Weight was measured to the nearest 0.1 kg using standard electronic scales (light clothing without shoes). Blood pressure (BP) was monitored through an OMRON healthcare M2 device while the participant was comfortably seated. Two measurements for SBP/DBP were recorded, and an average was computed.

In this study, BP (i.e., systolic and diastolic BP, SBP/DBP levels) was reported only for participants included in G1 and G2 every 3 months. Those in G3 and G4 consumed anti-hypertensive drugs and were stabilized based on this clinical parameter.

All participants were evaluated at baseline and at the end of treatment (12 months) through a complete electrochemical check.

Dietary monitoring was conducted "face-to-face" by the clinical nutritionist (AnnalisaA.) through meetings every 15 days to check adherence to the dietary protocol and physical activity. The participants included in G1 and G3 were asked to record their weekly physical activity on a form ("My physical activity diary") about their weekly activity, recorded in hours.

Our study design would investigate psychopathological and psychosocial dimensions only in the group of psychiatric subjects. The cardiovascular prevention outpatient unit clinicians considered that the psychopathological assessment would have taken longer, which is not consistent with the time-sparing organizational goals of the operating outpatient unit. Moreover, they wanted to avoid "psychiatrizing" their users.

Measures for participants included in the psychiatric groups

Participants affected by mental disorders (G1 and G2) were also evaluated through assessments of psychopathology, health-related quality of life, and personal resources.

The severity of psychopathology was assessed using the Brief Psychiatric Rating Scale-24, BPRS (66) in its Italian version (67). Each symptom on the 24-item scale was rated from 1 to 7 (1 = absence of symptoms; 7 = very severe symptoms). The key score was composed of the total item score.

Health-related quality of life was assessed by the SF-36 Health Survey (68). It is a short-form health survey with only 36 questions. The SF-36 contains eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0–100 scale, assuming that each question carries equal weight. The lower the score, the more severe the disability. The higher the score, the less severe the disability; i.e., a score of zero is equivalent to a maximum disability, and a score of 100 is equal to no disability. The eight sections are (1) vitality, (2) physical functioning, (3) bodily pain, (4) general health, (5) physical role functioning, (6) emotional role functioning, (7) social role functioning, and (8) mental health. In the present study, we only considered the "general health" domain.

Self-esteem was assessed by the Self-esteem Rating Scale (SERS) (69). The SERS consists of 40 items rated on a 7-point Likert scale, 20 scored positively and 20 scored negatively, with total scores ranging from −120 to +120. The SERS taps into multiple aspects of self-evaluation, such as overall self-worth, social competence, problem-solving ability, intellectual ability, self-competence, and worth compared to others. Positive scores are indicative of higher self-esteem. The instrument shows a high level of internal consistency ($\alpha = 0.97$) and good content and factorial validity.

Interventions

Diet protocol

The diet protocol consisted of the modified OMNI-heart programme diet, an individualized, moderately hypocaloric diet based on personal and daily caloric needs; it includes the following:

1) a reduction of 500 kcal/day;
2) daily carbohydrate energy intake of 45%, 50% from whole wheat, and 50% from fruits and vegetables, characterized

TABLE 1 The demographic and clinical characteristics of the 98 users participating in the study were divided into four groups.

	Participants affected by mental disorders ($n = 51$)		Participants affected by hypertensive disease ($n = 47$)	
	G1 ($n = 34$)	G2 ($n = 1$ 7)	G3 ($n = 25$)	G4 ($n = 22$)
Gender, *n* (%)				
Male	11 (32.4)	3 (17.6)	10 (40)	10 (45.5)
Female	23 (67.6)	14 (82.4)	15 (60)	12 (54.5)
Age, mean (SD)	41.3 (13.4)	43.5 (15.8)	49.1 (12.0)	49.3 (13.8)
Education, years, mean (SD)	13.2 (3.4)	13.4 (3.8)	14.7 (3.1)	13.4 (2.6)
Marital status *n* (%)				
Unmarried/single	23 (67.6)	9 (52.9)	9 (36)	8 (36.5)
Married	10 (29.4)	6 (35.2)	14 (56)	12 (54.5)
Divorced	–	1 (5.9)	2 (8)	1 (4.5)
Widower	1 (3)	1 (5.9)	–	1 (4.5)
Work status, *n* (%)				
Employed	24 (70.6)	13 (76.4)	19 (76)	18 (81.8)
Unemployed	7 (20.6)	2 (11.8)	5 (20)	3 (13.7)
Student	3 (8.8)	2 (11.8)	2 (4.3)	1 (4.5)
BMI overweight range (25–<30)%	20 (58.8)	5 (29.4)	12 (48)	9 (40.9)
BMI obesity range (≥30)%	14 (41.2)	12 (70.6)	13 (52)	13 (59.1)
Diagnosis (DSM-5) (%)				
Anxiety disorders	16 (47.1)	11 (64.7)		
Depressive disorder	10 (29.4)	4 (23.5)		
Psychotic non-affective disorder	6 (17.6)	2 (11.8)		
Bipolar disorder	2 (5.9)	–		
Length of illness, years, mean (SD)	4.9 (5.1)	3.1 (2.5)		
Medication (%)				
SSRI-NaSSAs antidepressants	23 (67.6)	14 (82.3)		
Second generation antipsychotics	5 (14.7)	2 (11.8)		
Anxiolytics	3 (8.8)	1 (5.9)		
Mood stabilizers	2 (5.9)	–		
First-generation antipsychotics	1 (3)			
Polidrug therapy (%)	6 (17.6)			

by a low glycaemic index with a predominance of fructose and sucrose compared to glucose;

3) daily protein energy intake of 25%: 60% from a vegetable source (soy, seitan, beans) and 40% from an animal source (white meat, fish, cheese, milk, and eggs);
4) daily fat energy intake of 30%: 10% Kcal saturated (70), 6% Kcal polyunsaturated fatty acids (omega 3–6), 14% Kcal monounsaturated (extra virgin olive oil);
5) vegetable fiber ≥20 g/die;
6) sodium intake <100 mmol/day, corresponding to a daily intake of 2.4 g;
7) potassium intake >150 mmol/day, corresponding to a daily intake of at least 5 servings of raw fruits and vegetables.

In the present study, the clinical nutritionist (A.A.) applied slight modifications to the basic OMNIHeart dietary protocol, with a carbohydrate decrease and a moderate increase in monounsaturated fatty acids (45% carbohydrates, 25% proteins, and 30% fats in the modified OMNIHeart dietary group and 50% carbohydrates, 25% proteins, and 25% fats in the basic OMNIHeart dietary group). The rationale of this OMNIHeart diet modification was justified by the high rate consumption of carbohydrates in the form of pasta, bread, and sweets (honey and jellies) in the population of L'Aquila in the Abruzzo region. At the same time, there was a relatively low consumption of fats in the form of extra virgin olive oil, which is useful for preventing cardiovascular risk factors. In addition, the increase in monounsaturated fatty acids makes food more palatable to ensure high adherence to the diet programme.

Physical activity protocol

Current physical activity levels were assessed by asking the participants about their weekly activity levels as measured using the Metabolic Equivalent of Task (MET) (71). The intensity of physical activity recommended was three METs, equal to a moderate degree (walking) for 3 h per week at 700 METs in accordance with the indications of the World Health Organization (WHO). The MET is a physiological measure expressing the energy cost of physical activities. It is defined as the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific physical activity to a reference metabolic rate, set by convention to 3.5 ml O2/kg/min or 1 kcal/kg/hour.

APPLE-MCT

Apple-MCT was a brief, positive, group health-based intervention, followed only by G1, including two modules from the metacognitive training portion (72), (73) using "drill and practice" tasks. The interventions were conducted by a clinical psychologist (L. G.) and a psychiatric rehabilitation technician (A. S.). According to the study protocol, each group was comprised of three to five participants. The Apple-MCT was introduced by a psychoeducational module, including crucial topics for mental and physical health such as sleep–wake cycle regulation, regular physical activity, the timing of meals and meal preparation, good management of comfort eating, and the identification of strengths, new hobbies, and interests, reflecting on what brings happiness. The Apple-MCT included four bimonthly sessions lasting 45–60 min and focused on two specific modules/kinds of content, each alternatively presented in two versions, including different exercises and tasks.

(1) Module 3 "Changing beliefs" with the target domain "bias against disconfirmatory evidence" aimed at reducing cognitive inflexibility and the tendency toward overconfidence. In Module 3 (versions A and B), it is explained to the user that it is important to withstand the normal tendency to stick to first impressions, as this response bias can lead to faulty decisions. It is therefore desirable to maintain an open mind. Some negative and dysfunctional beliefs represent severe obstacles to starting and adhering to a diet programme (i.e., "*I am a fickle person and I easily lose motivation*," "*I do not have the time to stick to a diet and exercise*," "*I'm destined to stay fat*").

(2) Module 8 Self-esteem and mood with the target domains "negative cognitive schemata" and "low self-esteem" (versions A and B) aimed at modifying dysfunctional thinking styles, which may contribute to the formation and maintenance of depression and low self-esteem; these are especially correlated with weight control and physical appearance, and lead to difficulty in changing one's eating habits, with an excessive focus on body image or body shape (i.e., "*I am fat and will never be successful in life*," "*No one will ever love me because of my body and my problems*," and "*It is all my fault because I neglected my health condition*").

The psychiatric and hypertension treatment as usual group

In the TAU groups, G2 and G4, the participants continued to receive the usual treatment, including regular outpatient assessments, pharmacological treatment, and managing the side effects of medication. Additionally, they were given non-structured information about weight gain and encouraged to limit their food intake and increase the degree to which they exercised.

Statistical analysis

Descriptive analyses were used to characterize our sample concerning sociodemographic and clinical details. Continuous variables are reported as means (standard deviations), and categorical variables are reported as frequencies (percentages). Baseline comparisons [chi-square, *t*-tests, and one-way analysis of variance (ANOVA)] were performed to assess differences between the psychiatric and medical samples and the four groups. Bonferroni *post-hoc* correction was calculated.

We developed general linear models for repeated measures analyses with a between-subjects factor (G1, G2, G3, G4) and a within-subjects factor (pre-treatment–T0 vs. post-treatment–T1) for physical and metabolic variables. For the variables not fitting the normal distribution, to test the intergroup differences for anthropometric and metabolic variables in the study arms, we used the Kruskal–Wallis test and then made paired comparisons with the *post-hoc* Bonferroni's correction test.

In the psychiatric sample, we employed a general linear model for repeated measures with a between-subjects factor (G1, G2) and a within-subjects factor (pre-treatment–T0 vs. post-treatment–T1) for psychopathological and health-related quality of life variables. Statistical analyses were performed using SPSS 27.0 (SPSS Inc., Chicago, IL, USA). All tests were two-tailed, and $P < 0.05$ was considered significant.

Results

We recruited a total of 102 people: 54 stabilized participants affected by anxiety disorders, mood, and psychotic disorders according to DSM-5 criteria (74), and 48 participants affected by hypertensive disease.

All participants signed informed written consent forms.

Table 1 describes the final analyzed sample's main demographic and clinical characteristics of 98 subjects.

In the entire sample, the mean age was 45.2 (SD: 13.9) (range: 18–75). The majority of the participants were women (65.3%). There were no statistically significant differences between the two groups (psychiatric and medical participants) concerning sociodemographic variables such as sex, education level, and employment status (Table 1). The medical participants in G3 and G4 were older than those in the psychiatric groups, G1 and G2 [49.23 (SD 12.8) vs. 42.10 (SD 14.10); *t*-test −2.613; $p = 0.010$], the latter showing a higher statistically significant proportion of singletons (62.7 vs. 36.2%; chi-square: 8–156; $p = 0.043$).

No statistically significant differences were found in the proportion of overweight/obese participants included in the four groups (chi-square: 4.357; d.f. 3; $p = 0.225$).

The majority of the participants included in the psychiatric sample were affected by anxiety and depressive disorders (80.4%). According to diagnosis and psychopathological severity, all participants affected by mental disorders were taking psychopharmacological treatments with differences in type and dosage. Regarding G1 and G2, there were no statistically significant differences for the diagnoses and psychopharmacological treatments (Table 1). The participants affected by hypertensive disease were administered hypertensive pharmacological therapies.

Anthropometric and metabolic variables

At baseline (T0), no statistically significant differences were found among the four groups concerning weight, BMI, and waist circumference.

After 12 months (T1), significant differences over time—but not among the four groups—were found in all measured physical and metabolic variables (Table 2). The significant effects of the interaction time × group ($p < 0.001$) for all the considered variables indicate the intervention's benefit over time, without highlighting differences in the four arms of the study.

Changes in anthropometric and metabolic variables at the 12-month follow-up (T1) compared to the time of entry into the study (T0) were analyzed.

At 12 months, both intervention groups showed a more marked mean decrease in weight at −6.7 kg (SD: 3.57) than the TAU groups at −0.32 kg (SD: 1.96) (Table 3).

A Kruskal–Wallis test and post hoc analysis provided strong evidence of differences between the mean ranks of the two groups (G1 and G3) compared to G2 and G4 at T1 concerning weight [H(3) = 59.811; $p = 0.00$], BMI [H(3) = 50.868; $p = 0.00$], and waist circumference [H(3) = 49.235; $p = 0.00$] reduction (Figures 2A–C). No differences in weight reduction, BMI, or waist circumference were noted between G1 and G3 or between G2 and G4. These results suggest that G1 and G3 exhibited a larger statistically significant improvement than G2 and G4 regarding anthropometric parameters, body weight, waist circumference, and BMI.

Figure 3 displays the percentages of participants meeting certain weight-loss thresholds at 12 months in the four groups, showing a significantly different proportion of subjects losing more weight (chi-square: 67.041; d.f. 6; $p = 0.000$). Briefly, the intervention groups G1 and G3 revealed a statistically significant difference in the proportion of participants who lost 5% (59.3%) or 10% (25.4%) of their baseline weight compared to participants included in G2 and G4 who lost 5% (7.7%) or 10% of their baseline weight (0%). Both control groups indicated that 92.3% of the participants recorded a <5% weight loss compared to the intervention groups (15.3%) (chi-square = 56.415; d.f. 2; $p = 0.000$).

A Kruskal–Wallis test and *post-hoc* analysis provided strong evidence of differences between the mean ranks of two groups (G1 and G3) compared to G2 and G4 at T1 concerning reduction of total cholesterol (mg/dl) [H(3) = 46.584; $p = 0.00$], LDLc (mg/dl) [H(3) = 55.415; $p = 0.00$], TRG (mg/dl) [H(3) = 46.954; $p = 0.00$], glucose (mg/dl) [H(3) = 50.198; $p = 0.00$] and an increase in HDLc (mg/dl) [H(3) = 54.172; $p = 0.00$; Figures 4A–E. No difference in such metabolic variables was observed between G1 and G3 or between G2 and G4. These results imply that G1 and G3 experienced a larger statistically significant improvement than G2 and G4 in terms of the metabolic variables.

Clinical measures

Blood pressure in the psychiatric sample

At baseline, T0, no significant differences were found among the psychiatric groups concerning SBP [G1 133.24 (SD 7.6) vs. G2 131.1 (9.1); *t*-test for paired samples: $t = 0.848$; $p = 0.400$] and DBP [G1 88.4 (SD 3.9) vs. G2 89.1 (4.4); *t*-test for paired samples: $t = -0.551$; $p = 0.584$].

After 12 months (T1), significant differences over time—but not between groups—were found for SBP (Figure 5A). At the end of the intervention, for DBP, a change over time with a significant *group for time interaction* ($F = 13.999$; $p = 0.001$; $\eta^2 = 0.221$) was found between the two groups ($F = 8.611$; $p = 0.005$; $\eta^2 = 0.149$), indicating a greater reduction in G1 compared to G2 (Figure 5B).

Life-Style

The main life-style behavior information (physical activity and smoking) upon entry is outlined in Table 4.

Regarding physical exercise, all participants practiced low physical activity (average of 2 h weekly < 3 MET). The majority of the participants (80.6%) did not engage in any physical activity, except the participants included in

TABLE 2 Anthropometric and metabolic variables upon entry into the study (T0) and at the 12-month follow-up (T1).

Characteristics	Participants affected by mental disorders ($n = 51$)				Participants affected by hypertensive disease ($n = 47$)				F (group × time interaction)	N_2p (estimated effect size)
	G1 ($n = 34$)		G2 ($n = 17$)		G3 ($n = 25$)		G4 ($n = 22$)			
	T0	T1	T0	T1	T0	T1	T0	T1		
Anthropometric variables, mean (SD)										
Weight, kg	81.3 (15.89)	74.2 (14.7)	85.7 (12.7)	85.0 (13.2)	85.30 (14.9)	79 (14.8)	84.9 (12.4)	84.9 (12.0)	Time: 122.281** Group: 1.651 Interaction: 35.016**	0.528
BMI, kg/m^2	30.7 (5.3)	28.0 (5)	32.4 (3.6)	31.8 (3.8)	31 (3.6)	28.7 (3.4)	30.9 (2.4)	30.9 (2.4)	Time: 81.606** Group: 2.045 Interaction: 20.923**	0.400
Waist circumference, cm	100.3 (10.7)	94.5 (9.3)	102 (7.3)	101.0 (8)	103 (6.1)	96.5 (6.3)	103.3 (8.6)	102.6 (9.6)	Time: 137.224** Group: 2.107 Interaction: 27.412**	0.467
Lipids, mean (SD)										
Total cholesterol, mg/dl	229.09 (35.0)	207.7 (27.2)	226.4 (29.3)	223.2 (33.6)	228.44 (23.4)	212 (21.2)	224.95 (23.6)	224.23 (24)	Time: 67.615** Group: 0.348 Interaction: 17.042**	0.352
LDLc, mg/dl	140.4 (26.4)	120.97 (17.9)	137.5 (32.6)	137.2 (32.4)	144.96 (22.2)	130.5 (17.4)	147.05 (25.5)	146.6 (25.08)	Time: 38.304** Group: 2.078 Interaction:13.129**	0.295
HDLc, mg/dl	43.12 (12.1)	47.03 (11.2)	44.8 (11.0)	44.7 (10.6)	44.7 (9.5)	47.8 (10.3)	40.1 (7.9)	39.3 (8.05)	Time: 32.666** Group: 1.827 Interaction: 20.083**	0.391
TRG, mg/dl	176.7 (71.5)	135.8 (46.5)	160.0 (68.1)	154.2 (68.1)	177.8 (65.4)	142.9 (35.0)	169.9 (35.3)	168.8 (34.8)	Time: 28.143** Group: 0.313 Interaction: 7.117**	0.185
Fasting glucose, mean (SD)										
GLU, mg/dl	97.6 (10)	87.09 (6.9)	93.3 (9)	92.8 (8.6)	97.2 (8.08)	89.5 (5.9)	96.3 (8.7)	96.0 (8.5)	Time: 69.701** Group: 1.114 Interaction: 23.637**	0.419

**$p = 0.01$.

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TABLE 3 Mean differences (SD) in anthropometric and metabolic variable changes at the 12-month follow-up (T1) compared to entry into the study (T0).

Variables	Change G1 (T1–T0)	Change G2 (T1–T0)	Change G3 (T0–T1)	Change G4 (T0–T1)
Physical, mean (SD)				
Weight, kg	−7.06 (4.21)	−0.76 (2.27)	−6.24 (2.47)	0.022 (1.67)
BMI, kg/m^2	−2.65 (1.97)	−0.53 (1.43)	−2.27 (1.04)	0.059 (0.57)
Waist circumference, cm	−5.88 (3.19)	−1.00 (3.18)	−6.48 (2.46)	−0.63 (2.46)
Lipids, mean (SD)				
Total cholesterol, mg/dl	−21.32 (16.70)	−3.17 (12.51)	−16.44 (8.82)	−0.72 (3.89)
LDLc, mg/dl	−19.44 (21.06)	−0.35 (2.66)	−14.40 (8.85)	−0.40 (3.63)
HDLc, mg/dl	+3.91 (3.75)	−0.05 (2.46)	+3.12 (1.48)	−0.81 (0.79)
TRG, mg/dl	−40.82 (50.39)	−5.76 (14.45)	−34.88 (42.51)	−1.09 (5.15)
Fasting glucose, mean (SD)				
GLU, mg/dl	−10.58 (7.28)	−0.47 (2.62)	−7.64 (5.62)	−0.27 (2.86)

G1, who showed significantly higher activity (chi-square: 18.955; df 6; $p = 0.004$). The four groups did not exhibit statistically significant differences in the proportion of smokers compared to non-smokers (chi-square: 0.556; df 3; $p = 0.906$).

Regarding eating habits, no statistically significant differences were found among the four groups at the time of entry into the study. All participants reported irregular eating habits (low consumption of fruits, vegetables, and olive oil; high consumption of sugar, alcohol, and saturated fats).

At the end of the intervention, concerning physical activity, a significant change over time (group for time interaction $F = 26.901$; $p = 0.000$; $\eta^2 = 0.467$) was observed in the four groups (Figure 6).

At the end of the study, significant differences were found between G1 and G2 (95% CI: 0.52, 1.50; $p = 0.000$), G1 and G4 (95% CI: 0.43, 1.44; $p = 0.000$), G2 and G3 (95% CI: −1.5, −0.37; $p = 0.000$), and G3 and G4 (95% CI: 0.27, 1.35; $p = 0.001$), showing a statistically significant increase in physical activity for both G1 and G3 compared to G2 and G4 (Figure 6).

No statistically significant differences were observed in smoking habits at T1 compared to T0.

Concerning eating habits, diet improvements can be mainly inferred from weight changes at T1.

Psychopathology

At baseline, no statistically significant differences were found between the G1 and G2 groups for BPRS total scores. There was a psychopathological improvement at the end of treatment with a significant *group for time interaction* and a decrease in the BPRS total score for both groups (Table 5).

Health-related quality of life

At baseline, no significant differences were found between the G1 and G2 groups concerning health-related quality of life, evaluated through the SF-36. At the end of the intervention, health-related quality of life scores changed for the two groups with a significant *group for time interaction*. Participants in G1 experienced better improvements in their health-related quality of life SF-36 scores than participants included in G2 (Figure 7).

Self-esteem

At baseline, low values of self-esteem, evaluated by the SERS, were reported by all participants included in G1 and G2, without significant differences between the two groups. At the end of the intervention, participants in both groups revealed increased SERS scores regarding self-esteem levels without a significant change over time and between the two groups (Table 5).

Discussion

To the best of our knowledge, the present study is the first Italian real-world pragmatic controlled study to assess the effectiveness of a multi-component intervention based on a modified OMNI-heart programme diet and physical activity, including a group metacognitive programme, in a sample of overweight/obese users of a psychiatric outpatient service.

The study showed the same effectiveness for overweight/obese participants affected by hypertension

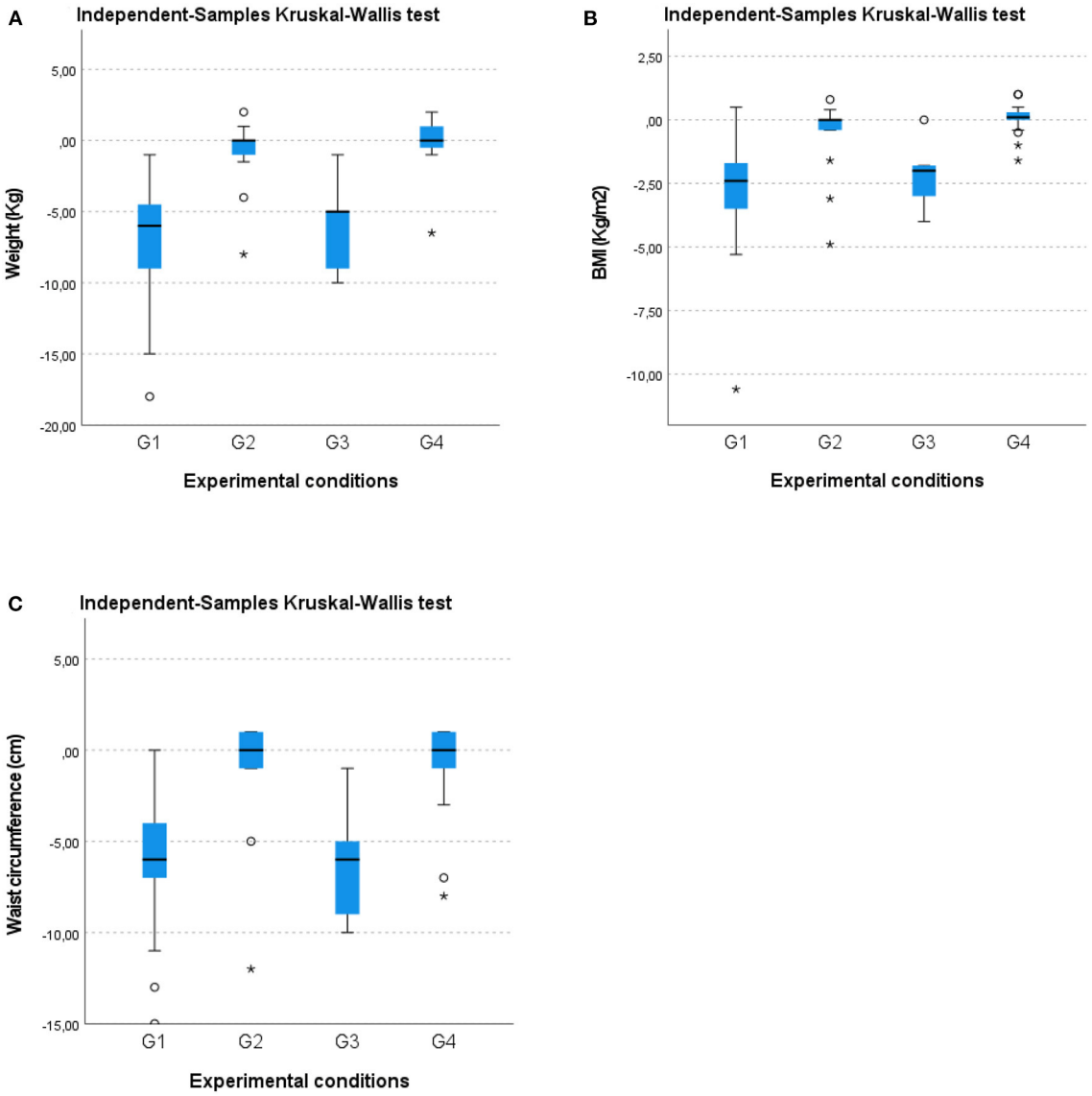

FIGURE 2
Box-whisker plots showing **(A)** weight (kg), **(B)** BMI (kg/m^2), and **(C)** waist circumference (cm) changes in the four groups at the 12-month follow-up (T1). O, Outliers; *, Extremes.

and overweight/obese participants affected by mental illness undergoing psychopharmacological treatment, with an added transdiagnostic brief metacognitive group programme, compared to an intervention limited to recommendations on how to live a better life-style. Moreover, at the 12-month follow-up, participants in this intervention group exhibited increased health-related quality of life compared to participants receiving only recommendations on a healthy life-style.

Our findings align with previous results about reducing body weight, modifying metabolic parameters, and life-style in both populations of psychiatric and hypertensive individuals using a multi-component intervention (53–55). Our overall cardiovascular risk reduction is comparable to prior multi-component studies in the psychiatric (61, 75) and general populations (76). The effects of the macro-element redistribution were investigated, which concerned almost all the other cardiovascular risk factors including TC, LDLc, HDLc, TRG, and fasting GLU; these are probably more reliable and robust, albeit with substantially quantitative differences. In particular, the impressive reduction of serum TRG levels in both intervention groups could be due to an array of independent factors such as the reduction of carbohydrate energy, concomitant increases in protein, and perhaps to a greater extent in unsaturated fats (77, 78). The observed

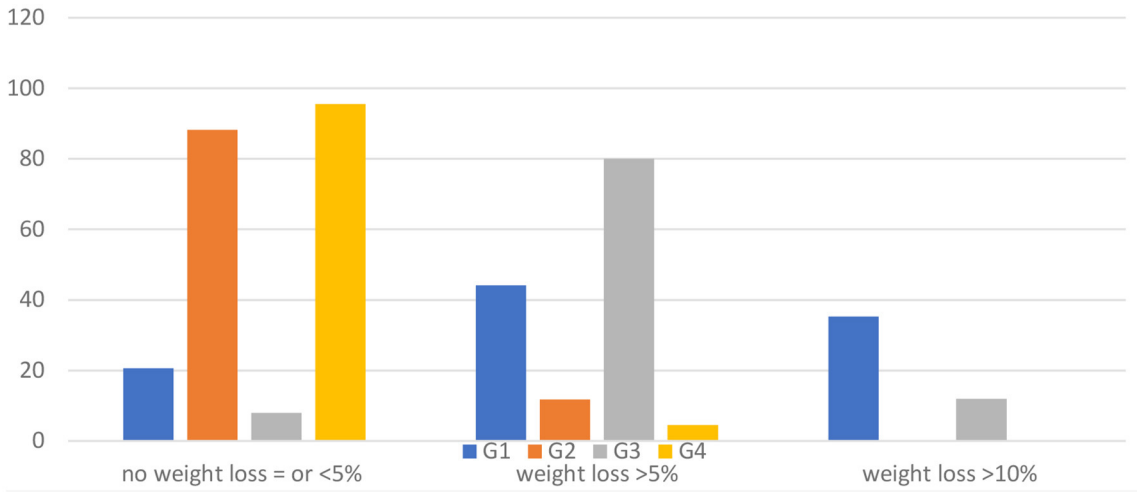

FIGURE 3
Percentage of weight change at the 12-month follow-up (T1) in the four groups compared to entry in the study (T0).

reduction in fasting glycaemia levels may also be due to the combination of low carbohydrates, high protein, and high-unsaturated fats in association with the moderately hypocaloric diet plus physical exercise.

Our results are encouraging and identify a new "target" of life-style interventions, not only for persons affected by severe mental illness, but also for a transdiagnostic group receiving mental health care, as proposed in a recent protocol for young people (79). Reduced weight loss in the range of 2% (80) to 4.2% (81) was reported in adults with severe mental illness, while we observed a mean weight loss of −8.6% for our psychiatric intervention group. Compared to studies including only psychotic populations, our findings seem to show a more marked net weight loss in the intervention group, presumably justified by a larger share of participants affected by anxiety and depressive disorders.

The length, the multi-component nature of our study, and the strict monitoring at 12 months could justify our results as better compared to the findings of a shorter 3 month intervention based only on an educational programme that demonstrated effectiveness only in increasing physical activity, but not for clinical and laboratory parameters (82). The critical aspect of the duration of life-style interventions of 12 months or more for treating overweight and obese people with serious mental illness was already stressed (83, 84), and their systematic reviews and meta-analyses reported that these interventions achieve more consistent outcomes.

Length does not seem to be the only critical variable in the effectiveness of life-style interventions. Our "face-to-face" intervention seems more promising than a multimodal web-based intervention administered by nurses to manage life-style changes in participants affected by severe mental illness (85). Using a web tool in the multi-modal, patient-centered life-style intervention did not seem to improve waist circumference and metabolic health after 12 months in a Dutch sample (85).

In a multi-component intervention, the "active ingredients" are difficult to identify. The added intervention for the psychiatric intervention group, including a group metacognitive programme, could have contributed to the intervention's effectiveness in the psychiatric group. We can hypothesize that the "An Apple a Day" metacognitive group intervention could have contributed to the outcomes, improving cognitive flexibility, a crucial variable specifically influencing self-regulatory behavior associated with healthier eating (86). Self-regulatory skills applied to controlled eating may be a far more critical factor than knowledge of appropriate nutrition principles in the behavioral treatment of obesity (87, 88). Additionally, the increased physical activity per week of the intervention group, favored by frequent checks leading to high user compliance (89), could have contributed to the outcomes. The health benefits of physical activity include the impact of exercise on cognitive functioning in general (90) and psychiatric populations (91).

At the 12-month follow-up, all participants affected by mental disorders improved their psychopathological conditions and self-esteem since they adhered to their pharmacological treatment and were compliant with the monthly consultations. Our intervention in the psychiatric group did not show specific symptomatologic benefits. Regarding psychopathology, our results are partially similar to those of a previous study on individuals with severe mental illness (81). The

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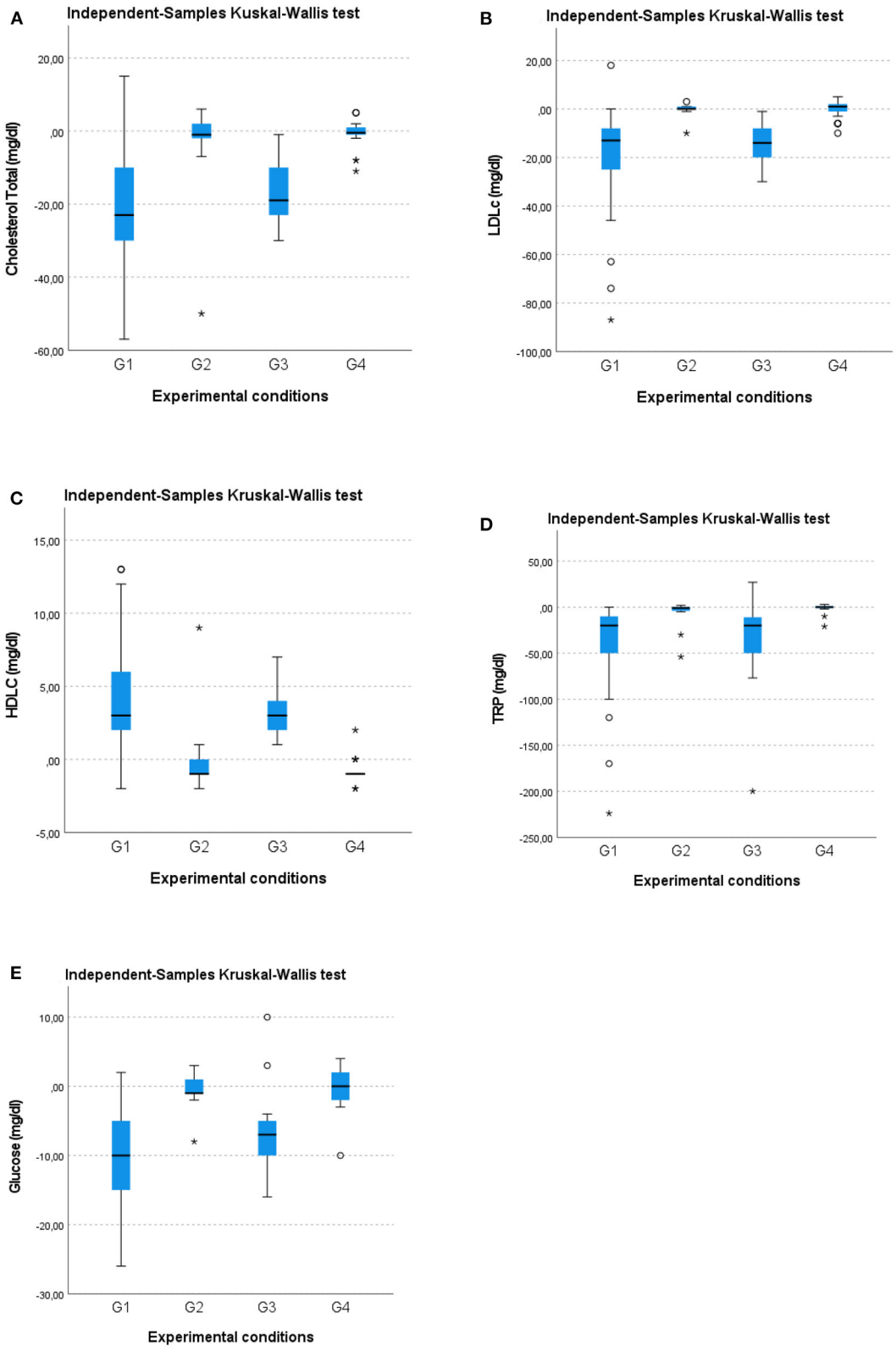

FIGURE 4
Box-whisker plots showing **(A)** total cholesterol (mg/dl), **(B)** low-density lipoprotein cholesterol, LDLc (mg/dl), **(C)** high-density lipoprotein cholesterol, HDLc (mg/dl), **(D)** triglycerides, TRG (mg/dl), and **(E)** glucose (mg/dl) changes in the four groups at the 12-month follow-up (T1). O, Outliers; *, Extremes.

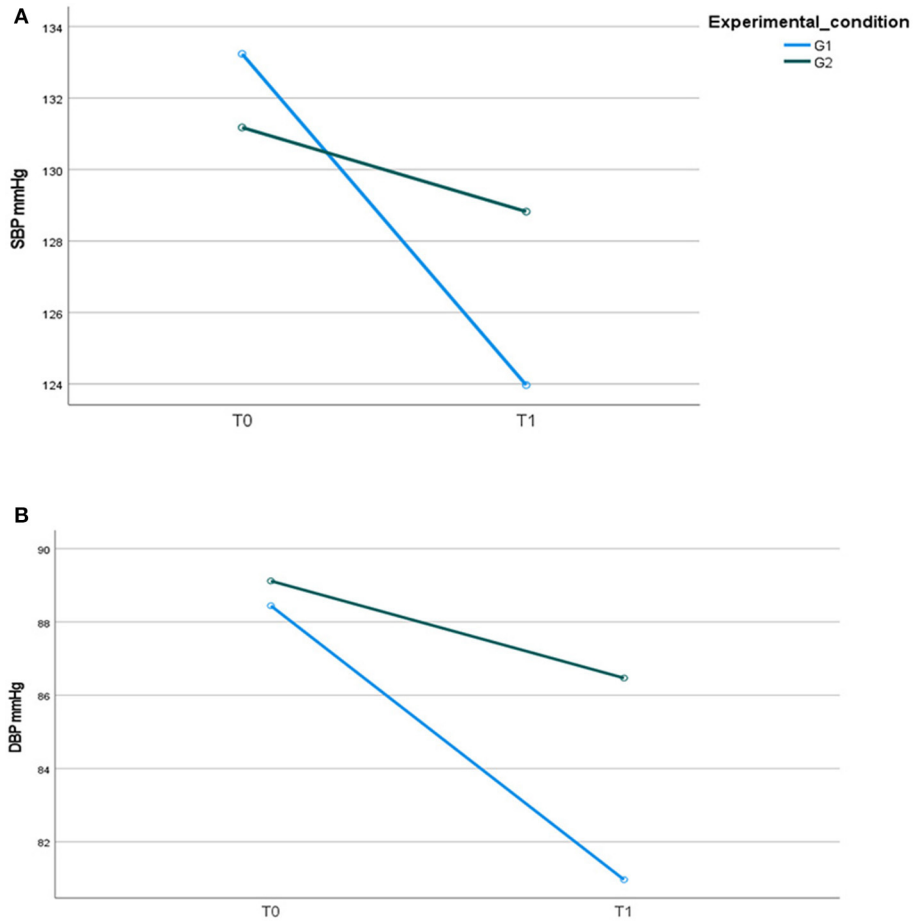

FIGURE 5
(A) Systolic blood pressure, SBP mmHg; **(B)** diastolic blood pressure, DBP mmHg, in the two psychiatric samples at T0 and T1.

TABLE 4 Physical activity and smoking habits of the participants included in the sample at the time of entry into the study.

	Participants affected by mental disorders ($n = 51$)		Participants affected by hypertensive disease ($n = 47$)	
Variables	**G1 ($n = 34$)**	**G2 ($n = 17$)**	**G3 ($n = 25$)**	**G4 ($n = 22$)**
Physical activity (hours/week) T0 (%)				
No physical activity	22 (64.7)	16 (94)	23 (92)	18 (81.8)
1 h	1 (2.9)	1 (6)	–	3 (13.6)
2 h	11 (32.4)	–	2 (8)	1 (4.6)
Smoking habits T0 (%)				
No smoking habits	18 (53)	8 (47)	11 (44)	10 (45.5)
1/2 cigarettes daily	2 (6)	2 (11.8)	–	3 (13.6)
5 cigarettes daily	6 (17.6)	1 (6)	3 (12)	2 (9.1)
10 cigarettes daily	3 (8.8)	3 (17.6)	8 (32)	3 (13.6)
20 cigarettes daily	5 (14.6)	3 (17.6)	3 (12)	4 (18.2)

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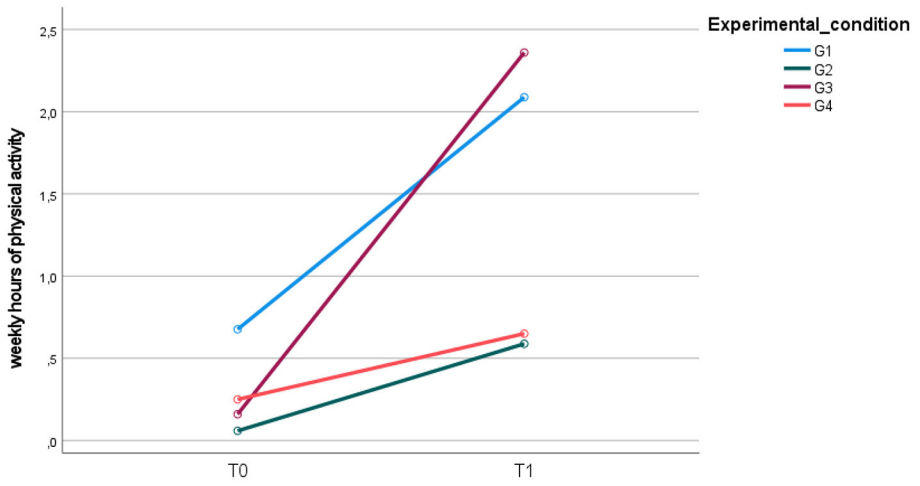

FIGURE 6
Mean weekly hours of physical activity upon entry into the study (T0) and at the 12-month follow-up (T1).

TABLE 5 Psychopathological, health-related quality of life, and personal resources in G1 and G2 at T0 and T1.

	Participants affected by mental disorders					
	G1 ($n = 34$)		G2 ($n = 17$)		*F*-value	η^2p
	T0	T1	T0	T1		
Psychopathology, mean (SD)						
Brief psychiatric rating scale-24, BPRS, total score	59.9 (5.8)	51.5 (4.7)	57.5 (4.8)	51.8 (5.5)	Time 138.568** Group 0.508 Interaction 5.359*	0.099
Health-Related quality of Life, mean (SD)						
Health-related quality of life, SF-36 self-perception general health	46.2 (10.2)	59.8 (8.6)	44.7 (9.9)	48.2 (11.5)	Time 134.427** Group 5.237* Interaction 46.419**	0.486
Personal resources variable, mean (SD)						
Self-Esteem rating scale, SERS	25.0 (30.6)	41.3 (26.4)	17.3 (26.4)	35.2 (21.6)	Time 66.966** Group 0.134 Interaction 0.781	0.003

*$p \leq 0.05$.
**$p \leq 0.01$.

study revealed significant improvement in total activity, weight, abdominal girth, systolic blood pressure, and HDL cholesterol following the Multidisciplinary Life-style enhancing Treatment for Inpatients (MULTI) compared to treatment as usual (TAU). Despite such improvement, the participants included in MULTI did not display psychopathological progress after 18 months (81). In addition, similar results were reported by Kahl et al. (92) in a randomized pilot study: they showed the favorable additional effect of a 6-week structured, supervised exercise program on visceral, in particular epicardial and subcutaneous, adipose tissue in users with MDD undergoing cognitive behavioral therapy, with significant improvement of factors constituting the metabolic syndrome.

A reduction in symptom severity was reported in physical activity interventions (35, 51, 93), which is not in line with our findings. A systematic review and meta-analysis of the future risk of mental illness indicated that the incidence of mental disorders and suicidality was inversely related to fitness (94).

Our psychiatric intervention sample showed significantly improved health-related quality of life compared to the controls,

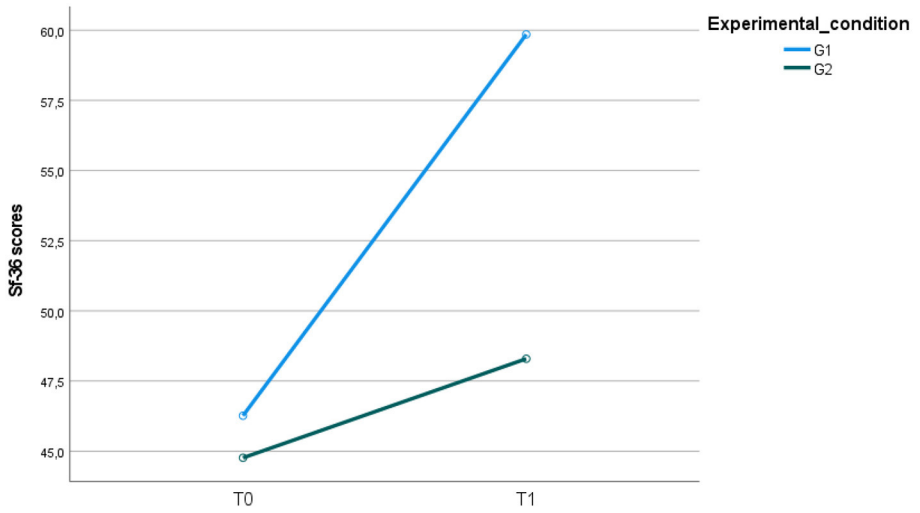

FIGURE 7
Health-related quality of life (SF-36) scores in the two psychiatric samples (G1, G2) at T0 and T1.

confirming recent findings (75, 88, 95). Improvements in body image and health-related quality of life seem closely linked to changes in weight (89).

However, our findings did not confirm increased psychological wellbeing in terms of self-esteem in our intervention group as an outcome frequently reported in life-style interventions (75, 96). Surprisingly, the participants in our psychiatric group did not display improved self-esteem, which was found to be inversely correlated with weight gain and good psychosocial adaptation (26).

The weight control issue is overwhelmingly salient in society and of great relevance and concern, also following the COVID-19 pandemic (97, 98). A general population study demonstrated that 22% of American adults gained weight during the COVID-19 pandemic. Lack of sleep, decreased physical activity, snacking after dinner, and eating in response to stress seemed to be behaviors tied to weight gain during self-quarantine (97). During the Italian COVID-19 lockdown, the perception of weight gain was observed in 48.6% of the general Italian population (99). More than 40% reported that they have gained weight to a slight extent, while 8.3% of the studied population said they have gained weight to a high extent. Prevention and management of obesity require consumption of a healthy and energy-balanced diet and adequate physical activity levels (100, 101).

As a pandemic-related physical health change, weight gain was also registered in psychiatric samples, with a greater impact than on the general population (102).

Strengths and limitations

To the best of our knowledge, no intervention studies have been conducted in psychiatric populations using an integrated intervention based on diet and physical activity programmes and metacognitive modules. The only experience reported was related to cardiac rehabilitation participants included in group metacognitive therapy (six sessions). The intervention successfully improved depression and anxiety compared with usual care, leading to more significant reductions in unhelpful metacognition and repetitive negative thinking (103).

Second, the strength of our study was based on the multi-component and transdiagnostic structure of our intervention, which was well-accepted by our participants. Beyond the diagnosis, from a comprehensive early intervention perspective, the protocol aimed to reduce weight and cardiovascular risk factors such as hyperglycaemia, dyslipidaemia, hypertension, and poor physical activity, all the more reason given the overweight/obese individuals already present and a source of concern for the users. All participants showed good adherence to treatment and reported being very glad to be offered an "extra service" to improve their physical health without any cost.

Our study has several main methodological limitations.

First, our study was a real-world pragmatic trial taking into account psychiatric users' needs and logistic factors. During the informed consent process, the clinicians informed the participants affected by mental disorders that they would have to take part in weekly group sessions. Working or living

far away from the site of our service seemed very difficult for some participants. Therefore, they were allocated to the "control" group.

Second, we used an exclusive univariate analytical approach without calculating the power and sample size due to the study's exploratory nature.

Third, the psychiatric sample, including psychopathologically stable participants, had different diagnoses and received different psychopharmacological treatments. Most of them (∼80%) were affected by depression and anxiety disorders and treated with SSRIs. The remaining 20%, affected by psychotic disorders, were treated with atypical antipsychotics. Although with varying degrees of severity, the impact of antidepressants and antipsychotics on weight seems sufficiently homogeneous, with an increase in body weight while taking these drugs (8, 104).

The weekly self-report of dietary and physical activity constituted a further limitation for participants in the intervention groups; every 15 days, during the clinical check-up, the clinical nutritionist (A. A.) weighed the participants based on the interventions. However, adherence to the physical activity protocol relied upon the users' statements only.

Conclusions

The study showed significant benefits of our intervention, including a modified OMNIHeart dietary protocol, in terms of percentage of weight reduction, improvement of metabolic parameters, as recently stressed by Volpe et al. (105), and increased physical activity for both our users and psychiatric and medical subjects. For the psychiatric intervention group, which experienced better health-related quality of life, these differences were found irrespective of medication in an overweight/obese population already presenting with a consistent cardiovascular risk. Life-style interventions can help to manage the physical and mental health symptoms of people affected by psychiatric disorders (106). Alongside medication, a range of psychosocial interventions and behavioral weight management needs to be included to achieve a full and sustained recovery for persons impacted by mental illnesses.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of the University of L'Aquila (approval date: 14 October 2014). The patients/participants provided their written informed consent to participate in this study.

Author contributions

LG, RR, and MC contributed to the design. VB, SM, and AS contributed to data acquisition. LG, RR, MC, CF, and SN participated in the analysis and interpretation. AAg carried out nutritional consultations for all patients involved in the study. CF and AAl contributed to the collection of clinical and metabolic data of hypertensive patients from the division of internal medicine and nephrology. All authors contributed to the manuscript, revised the work, agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, read, and approved the manuscript.

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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.

Publisher's note

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Possible antidepressant mechanisms of omega-3 polyunsaturated fatty acids acting on the central nervous system

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Omega-3 polyunsaturated fatty acids (PUFAs) can play important roles in maintaining mental health and resistance to stress, and omega-3 PUFAs supplementation can display beneficial effects on both the prevention and treatment of depressive disorders. Although the underlying mechanisms are still unclear, accumulated evidence indicates that omega-3 PUFAs can exhibit pleiotropic effects on the neural structure and function. Thus, they play fundamental roles in brain activities involved in the mood regulation. Since depressive symptoms have been assumed to be of central origin, this review aims to summarize the recently published studies to identify the potential neurobiological mechanisms underlying the anti-depressant effects of omega-3 PUFAs. These include that of (1) anti-neuroinflammatory; (2) hypothalamus-pituitary-adrenal (HPA) axis; (3) anti-oxidative stress; (4) anti-neurodegeneration; (5) neuroplasticity and synaptic plasticity; and (6) modulation of neurotransmitter systems. Despite many lines of evidence have hinted that these mechanisms may co-exist and work in concert to produce anti-depressive effects, the potentially multiple sites of action of omega-3 PUFAs need to be fully established. We also discussed the limitations of current studies and suggest future directions for preclinical and translational research in this field.

KEYWORDS

omega-3 PUFAs, depression, neurotransmitter systems, neuroplasticity, synaptic plasticity, neuroinflammation, neurodegeneration, HPA axis

Introduction

Depression is a mental disorder characterized by the sadness, loss of interest in activities, and decreased energy. It is often accompanied by the cognitive impairment and different physical symptoms. In severe cases, it may lead to suicidal tendencies (1). Depression is a high-incidence mental illness that has affected more than 264 million

people of all ages worldwide by 2021 (2). Subclinical depression has a higher incidence in the general population. The rate of subclinical depression can reach up to 17% in the primary care and community setting (3, 4). Moreover, the rate for the high school students is 22.9%, while that for the college students have reached 36.56%. Most currently available antidepressants can target monoamine neurotransmitter function. However, current pharmacological treatments of depression suffer from major problems, such as a low rate of response, slow onset of therapeutic effects, loss of efficacy over time, and serious side effects. Therefore, development of novel strategies both for the prevention and treatment of depression has become increasingly important in today's medical field.

Omega-3 polyunsaturated fatty acids (PUFAs) are currently an attractive candidate for the prevention and treatment of depressive symptoms (5, 6). Being an essential nutrient, humans cannot synthesize omega-3 PUFAs *de novo*, therefore, these fatty acids must be obtained through diet or supplementation. Fatty acids are the most abundant organic compounds in the brain, making up 60% of the dry weight, among which 20% of these fatty acids are PUFAs. The two most abundant PUFAs in the brain are omega-3 docosahexaenoic acid (DHA, C22:6 ω-3) and omega-6 PUFAs arachidonic acid (AA, C20:4 ω-6) (7). Brain function is heavily dependent on adequate omega-3 PUFAs levels. Omega-3 PUFAs, mainly DHA and eicosapentaenoic acid (EPA) which have strong anti-inflammatory and inflammation-resolving effects, also antagonizing the pro-inflammatory effects of omega-6 PUFAs which are the precursors of pro-inflammatory mediators. The balance between omega-6 PUFAs and omega-3 PUFAs is essential for homeostasis and the proper functioning of the central nervous system (CNS) to promote mental health and prevent neurological diseases (7, 8). Since omega-3 PUFAs and omega-6 PUFAs compete for incorporation into cell membranes, a balanced intake of these different type of PUFAs is essential (8). In modern society, human diets are unbalanced between omega-3 PUFAs and omega-6 PUFAs that may restrict the supply of omega-3 PUFAs to the tissues leading to a mild or severe omega-3 PUFAs deficiency in both developed and developing countries worldwide (9–12).

As an integral component of cell membranes, omega-3 PUFAs can increase membrane fluidity and permeability. Omega-3 PUFAs are largely esterified to the phospholipid in the cell membrane. Once omega-3 PUFAs are released from the membrane following neurotransmitter receptor-mediated activation of specific phospholipase A2 (PLA2) enzymes, they can act as secondary messengers and regulate signal transduction, either directly or indirectly by their bioactive derivatives (13, 14). Omega-3 PUFAs and their derivatives regulate various processes within the CNS, such as neuroinflammation, neurotransmission, synaptic plasticity, neurogenesis, neurodegeneration, and thereby mood and behavior. Omega-3 PUFAs deficiency are associated with many neurological disorders, including Alzheimer's disease, major depression and anxiety disorder (7, 14). There is a substantial body of evidence that provides general support for the beneficial effects of omega-3 PUFAs supplementation on brain structure and function in healthy human subjects (15).

There is a considerable amount of literature regarding the mechanism of action of omega-3 PUFAs to improve physical health and brain functioning [see, e.g., (8, 14, 16–18)], and many of them have been further considered as possible mechanisms for omega-3 PUFAs to improve depressive symptoms. Omega-3 PUFAs supplementation in depressed subjects has many structural and functional benefits for the brain, including promoting neurogenesis and neural repairment, preventing neuroinflammation and neurodegeneration, improving mood, cognition and memory etc., thus, exerting a wide range of ameliorating effects on depression (19–21). They are nutritious and safe, and when used in combination with other antidepressants, they can accelerate and increase efficacy significantly (5).

However, the antidepressant mechanisms of omega-3 PUFAs acting on the CNS are still not fully understood. Nowadays, there is limited data on human brain with respect to the antidepressant effect of omega-3 PUFAs. This paper, for the first time, makes a systematic review about the research progress in this field over the last decade, starting with the cellular and molecular basis of omega-3 PUFAs. This will provide information reference for the future research and clinical practice.

The cellular and molecular basis of omega-3 PUFAs

As shown in Figure 1, omega-3 PUFAs have a wide range of effects at the molecular and cellular levels, which may produce profound influences on mental health. We now summarize the main effects as follows:

Increasing cell membrane fluidity and lipid bilayer elasticity, thereby influencing the structure of lipid microdomains, the interaction and function of proteins (including receptors, channel proteins, enzymes) in the membrane

Through optimizing the membrane fluidity, omega-3 PUFAs can improve the binding of neurotransmitter and their receptors and ion channel function in the membrane (22, 23). It has been reported that DHA can facilitate gamma-aminobutyric acid (GABA) systems binding and increase the rate of its receptor desensitization by modulating the elasticity of the lipid bilayer (24–26).

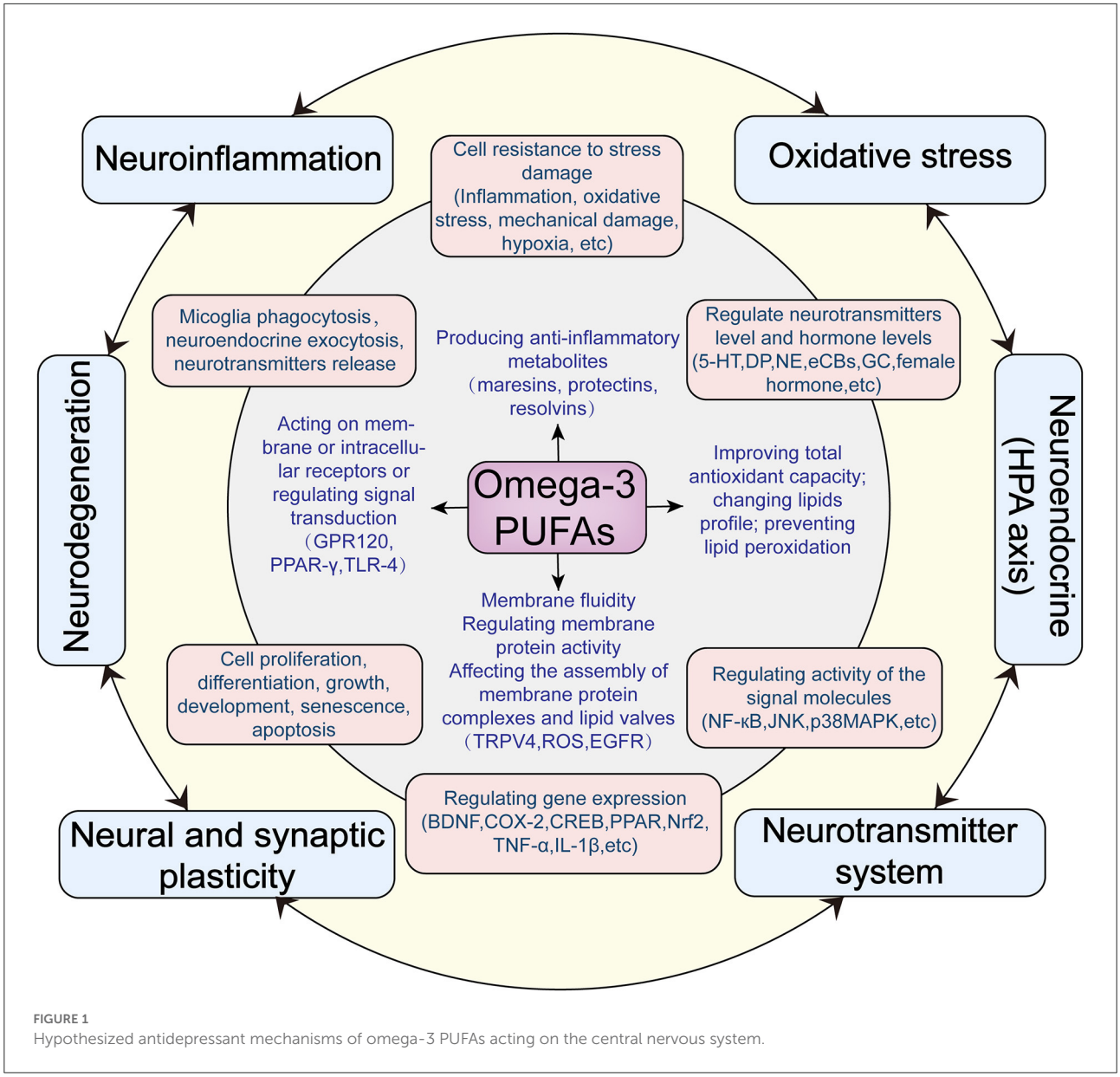

FIGURE 1
Hypothesized antidepressant mechanisms of omega-3 PUFAs acting on the central nervous system.

Stimulating cell membrane expansion and promoting membrane fusion

It has been found that by activating the plasma membrane protein syntaxin 3, omega-3 PUFAs can stimulate cell membrane expansion at the nerve growth cones, thereby promoting neurite outgrowth (27). As an enriched component in brain membrane phospholipids, DHA plays important roles in neurite outgrowth and neurotransmitter releases, the latter is a process involving membrane fusion and soluble N-ethylmaleimide-sensitive fusion factor attachment protein receptors (SNARE) complex binding or disassembly (23, 28).

Regulatory role on signal transduction

Omega-3 PUFAs can act as agonist ligands for G protein-coupled receptor 40 (GPR40) and G protein-coupled receptor 120 (GPR120), peroxisome proliferator-activated receptors (PPARs) and retinoid X receptor α (RXRA). In addition, omega-3 PUFAs can also downregulate nuclear factor kappa-B (NF-κB) through their inhibitory effects on toll-like receptor 4 (TLR4) or binding to peroxisome proliferator-activated receptor-γ (PPARγ) (29–31). Omega-3 PUFAs may exert neurological benefits through activating corresponding receptors such as GPR120, GPR40 as well as PPARs (23). Using RXRA conditional

knockout mice, unesterfied DHA has been found to promote spinogenesis, synapse formation and transmission *in vivo* in a RXRA-dependent manner (32).

Regulating gene expression and epigenetic modifications

As previously reported, numerous brain genes expression was found to be regulated by omega-3 PUFAs supplementation (33). In addition, omega-3 PUFAs supplementation can modulate DNA methylation and histone modifications (34, 35). For example, high-mobility group box 1 (HMGB1), a nuclear regulator of gene expression, acts as an endogenous danger signal to activate inflammatory responses (36). Omega-3 PUFAs can prevent traumatic brain injury-induced inflammatory response through deacetylation of the HMGB1/NF-κB pathway.

Antagonizing inflammation and modulating immune response

Omega-3 PUFAs and their derivatives are multifunctional regulators of inflammation (37). Omega-3 PUFAs can competitively inhibit AA metabolic enzymes by competing with AA *in vivo*, thereby inhibiting AA mediated production of inflammatory substances. Omega-3 PUFAs plays important roles as the precursor of specialized pro-resolving mediators (SPMs), such as maresins, protectins, resolvins, and lipoxins, all of which are involved in the process of inflammation resolution (38). Omega-3 PUFAs can regulate nuclear transcription factors in the nucleus to inhibit the expression of inflammatory factors. By binding to the specific receptor such as GPR120, omega-3 PUFAs can downregulate the proinflammatory signal pathways, such as NF-κB and c-Jun N-terminal kinases (JNK)-related pathways (39, 40). Omega-3 PUFAs can also inhibit TLR4 and tumor necrosis factor receptor (TNFR), thereby inhibiting the expression of pro-inflammatory factors (32). As to cellular immune response, omega-3 PUFAs can also increase the expression of the macrophage or microglia M2 phenotype, thereby promoting the resolution of inflammation (41, 42).

Affecting mitochondrial function and reactive oxygen species homeostasis

Through changing mitochondrial membrane phospholipid composition and membrane viscosity, omega-3 PUFAs have various effects on mitochondrial function (i.e., membrane potential, respiration, individual complex activities, and ROS production). Supplementation with omega-3 PUFAs increases EPA or DHA while decreases omega-6 PUFAs in mitochondrial membrane, and can increase cardiolipin, a critical phospholipid for optimal mitochondrial function. Some literature reports that omega-3 PUFAs increases the antioxidant potential through increasing the activity of glutathione-related antioxidant enzyme and superoxide dismutase activity (43). As to the effect of omega-3 PUFAs supplementation on ROS production within the mitochondria, studies have shown inconsistent results possibly due to different experimental conditions (43–45).

Affecting cell proliferation, cell viability, cell repair or apoptosis

Many studies have reported that dietary omega-3 PUFAs improves neural viability, promotes the proliferation of neurocytes, benefits brain cell survival and repair, and inhibits apoptosis through neurotrophic, anti-apoptotic, and anti-inflammatory signaling (46–48). In addition, DHA can increase neurogenesis through influencing cell-fate decision of adult neural stem cells and survival of the newly born cells (49).

Effects of omega-3 PUFAs on depression

A number of epidemiological studies have shown that appropriate omega-3 PUFAs intake or higher serum omega-3 PUFAs are associated with lower risk of depression (50–52). Similarly, the depressed people exhibited lower levels of omega-3 PUFAs in blood samples than the health controls (53, 54). Furthermore, many human studies have also pointed out that the intake ratio of omega-3 PUFAs: omega-6 PUFAs is inversely associated with the risk of depressive symptoms (55, 56). Selective dietary deprivation of omega-3 PUFAs over several generations or post-weaning has consistently been shown to increase the expression of depression/anxiety-like behavior without affecting general locomotor activity in rodents. Some researchers have further suggested that omega-3 PUFAs index (which refers to the sum of EPA and DHA in red blood cells) may be used as potential treatment response marker for youthful depressed patients receiving omega-3 PUFAs (57). The expert consensus panel has reached up to consensus on using omega-3 PUFAs in the prevention and treatment of MDD subgroups such as pregnant women, children, and older adults (5).

Low levels of omega-3 PUFAs, particularly EPA, are found to be associated with depressive/anxious mood, low cognitive function, sleep disturbance, aggression and impulsive behaviors (58–61). Omega-3 PUFAs supplementation can improve many aspects of depressed patients including emotion regulation skills, cognitive function, sleep, and so on (58, 62–64). In addition, it has been reported that lower omega-3 PUFAs intake or serum omega-3 PUFAs levels are associated with greater risk of suicide attempt and MDD (65).

Several cross-sectional studies fail to find significant associations between omega-3 PUFAs and depressive symptoms (66, 67). This may mean that not all subtypes of depression are responsive to omega-3 PUFAs treatment. MDD is well recognized as a multifactorial disease which can be caused by biological, psychological or social factors. A simple lack of omega-3 PUFAs does not necessarily trigger depression, or sufficient omega-3 PUFAs can certainly avoid depression. The effects of omega-3 PUFAs on depression can be confounded by the etiology, physical constitution of patients, characteristic of fish oil (including purity, ratio of EPA to DHA), dose and duration of fish oil intake and so on.

Possible anti-depressant mechanisms of action of omega-3 PUFAs

Anti-neuroinflammatory effects of omega-3 PUFAs

Multiple lines of evidence have shown that there is a strong correlation between inflammation and depression. This evidence includes: (1) Depression is often accompanied by increased neuroinflammation (68). In the CNS, increased pro-inflammatory cytokines, which may come from the periphery or be produced from cells within the CNS, and activation of microglia as the resident immune cells of the brain are observed in MDD by imaging and post-mortem studies (69–73). (2) The central administration of exogenous inflammatory irritants can induce depressive symptoms (74, 75). (3) Chronic psychological or physiological stress results in neuroinflammation, which plays an important role in the occurrence of depression (76–79). (4) Neuroinflammation has close relationships with deficiency of monoamine neurotransmitter, dysfunction of brain neurotransmitters, hyperactivation of HPA axis, oxidative stress, neurodegeneration, cognitive dissonance and so on (80).

Omega-3 PUFAs and their derivates are effective in reducing neuroinflammation and has the therapeutic potential in treating neuroinflammation-related brain or mental diseases, such as Alzheimer's disease and substance abuse (81–83). In addition, it has been found that during development, deficiency of omega-3 PUFAs in diet dysregulates offspring's microglial homeostasis and increases microglial-driven inflammatory response, resulting in excessive synaptic pruning and subsequent behavioral abnormalities in mice (84).

It has been suggested that inflammation can be used as a predictive biomarker for response to omega-3 PUFAs in MDD (85). Both chronic inflammation and omega-3 PUFAs deficiency have often been found to be associated with MDD (86, 87). A number of studies have pointed out that omega-3 PUFAs (particular EPA) can probably exert some of their clinical effects *via* anti-inflammatory mechanisms of action, and patients with high inflammation levels have better improvement in depressive symptoms in response to omega-3 PUFAs supplementation (17, 88). Indirect evidences have pointed out that anti-neuroinflammatory mechanisms may be implicated in the antidepressant effects of omega-3 PUFAs (89). *In vitro* cell culture studies have shown that omega-3 PUFAs prevents the inflammatory response of microglia, which may be implicated in its antidepressant effects (90, 91). Moreover, supplementation of omega-3 PUFAs significantly reduced doxycycline (DOX)-induced neuroinflammation and effectively protected DOX-induced depressive behaviors (92).

Role of omega-3 PUFAs in the modulation of functions of HPA axis

Hyperactivity of HPA axis, with resulting high cortisol levels is commonly found in depressed patients. Disfunction of glucocorticoid receptors (GRs) which impair the HPA axis negative feedback is one of the main causes of HPA axis hyperactivity. The brain GR, especially expressed in the hypothalamic paraventricular nucleus, hippocampus and prefrontal cortex, are generally assumed to subserve the bulk of glucocorticoid feedback regulation of the HPA axis (93).

Preclinical and clinical data has reported that low plasma omega-3 PUFAs levels have correlation with higher corticotrophin-releasing factor (CRF) (94) and higher plasma cortisol (95–97), while supplementation with omega-3 PUFAs can reduce CRF expression and corticosterone secretion (98, 99). Healthy men treated with 3 weeks of fish oil intake show a decreased cortisol response to acute mental stress (100). As to high chronically stressed men subjects, omega-3 PUFAs phosphatidylserine supplementation is also found to improve the function of HPA axis (101). In a rat model of depression, corticosterone hypersecretion induced by chronic restraint stress is dampened by omega-3 PUFAs supplementation (102). On the aspects of the CNS, evidence shows that nutritional omega-3 deficiency dampens the GR signaling pathway in the PFC of mice, which is associated with dendritic arborization in PFC as well as emotional deficits (103). It has also been shown that omega-3 PUFA supplement ameliorates the decreased expression of GR in the hippocampus of parous rats induced by the omega-3 deficient diet, which may promote the hyperactivity of the HPA axis and postpartum depression (104).

The possible mechanism of omega-3 PUFAs in regulating HPA activity may be related to the fact that omega-3 PUFAs can significantly down-regulate the expression of inflammatory factor while increasing the negative feedback sensitivity of HPA axis. Indeed, inflammatory cytokines and their related signaling pathways have been well-known to inhibit GR function, further leading to attenuated negative-feedback inhibition of the HPA axis (105, 106). The anti-inflammatory properties of

omega-3 PUFAs can thereby help to reduce the irritation of inflammatory stress on the secretion of CRF and thus inhibit HPA hyperactivity (107, 108). In rat cortical cultures, DHA treatment inhibits corticosterone-induced downregulation of GR expression on βIII- tubulin-positive neurons, which may contribute to the beneficial effect of DHA on ameliorating stress-induced neuronal damage (109). Up-regulation of GR expression by omega-3 PUFAs may also be related to down-regulation the expression of miRNA218 which is a post-transcriptional regulator of GR gene expression. Studies in female rats have reported that omega-3 PUFAs supplementation improve the maternal-pup separation-induced postpartum depression and post-menopausal depression, possibly involving the effects on HPA axis activities associated with reduced miRNA-218 expression and increased GR expression in the hippocampus (107, 110).

Anti-central oxidative stress effects of omega-3 PUFAs

Depression is often accompanied by excessive oxidative stress in the brain, which may lead to neurotoxicity and neuronal degenerative processes including decrease in neuroplasticity, neurogenesis, and an increase in apoptosis (111, 112). Many reasons including abundant O2.-/H2O2 by-products of mitochondrial respiration resulting from the brains extraordinary ATP demand, action potential dependent Ca2+ signaling-induced oxidative stress, glutamate (Glu)-induced excitotoxicity, extremely high content of unsaturated fatty acids and modest endogenous antioxidant defenses, make the brain especially vulnerable to oxidative stress (113–115). A number of the preclinical and clinical studies have reported increased oxidative biomarkers but lowered levels of antioxidants in the neurobiology of depression (116–118).

Evidence suggests that omega-3 PUFAs supplementation could attenuate oxidative stress in the brain (119–122), which might provide beneficial effects in depression prevention and treatment (51, 123). Postnatal omega-3 PUFAs supplementation can significantly enhance glutathione levels and reduce lipid peroxidation in the dentate gyrus and the cerebellum of prenatal ethanol exposure animals (124). A systematic review and meta-analysis of clinical trials have indicated that omega-3 PUFAs supplementation can enhance antioxidant defense through increasing serum total antioxidant capacity, glutathione peroxidase (GPx) activity, while reducing malondialdehyde levels (125). Oral administration of omega-3 prevents protein carbonylation and lipid peroxidation, and decreases the activity of myeloperoxidase, while improves the activities of superoxide dismutase and catalase in the brain of rats subjected to stress events (126). Using proton magnetic resonance spectroscopy, researchers found that the supplementation of 12-wk omega-3 decreases *in vivo* thalamus glutathione concentration in patients "at risk" for major depression (127). Several mechanisms can be suggested for the effect of omega-3 PUFAs on oxidative stress, including: (1) Increasing superoxide dismutase activity, elevating resistance to ROS damages and decreasing lipid peroxidation; (2) Inhibiting cyclooxygenase-2 (COX-2) enzyme activity. COX-2 metabolizes AA to inflammatory and oxidant prostaglandins which may promote lipid peroxidation; (3) Increasing the expression of nuclear factor-erythroid 2-related factor 2 (Nrf2) which is a transcriptional regulator that can effectively mediate antioxidant response by stimulating expression of the various antioxidant and anti-inflammatory genes (125, 128). In rat primary astrocytes, omega-3 PUFAs treatment can reduce ROS generation and enhance the antioxidant defense through Nrf2 activation under basal and oxidative stress conditions, suggesting that enrichment of astrocytes with omega-3 PUFAs may help to protect neurons in harmful conditions (129). Transcriptomic analyses of human hippocampal progenitor cell show that both EPA and DHA treatment regulates immune response pathways and Nrf2-mediated antioxidant pathways, which may be the molecular mechanisms underlying the preventive effect of omega-3 PUFAs on cortisol-induced decrease in neurogenesis and increase in apoptosis (130).

It has been found that only among participants with increased oxidative stress biomarkers, the omega-3 PUFAs index is negatively correlated with depressive symptoms, suggesting that oxidative stress status may be taken as a potential predictor of response to omega-3 PUFAs treatment of depression (131). Moreover, evidence indicates that omega-3 PUFAs may be more effective in improving the depressive symptoms of coronary heart disease patients with higher levels of oxidative stress marker (132). Omega-3 PUFAs can also prevent the brain's oxidative damage by decreasing the levels of protein carbonylation, lipid peroxidation, and the concentrations of nitrite/nitrate, and reducing myeloperoxidase activity, while increasing superoxide dismutase and catalase activities, which may contribute to the inhibitory effects of omega-3 PUFAs on the depressive-like behavior of the rats subjected to early or late life stress (126).

Anti-neurodegenerative effects of omega-3 PUFAs

Neurodegenerative disorders have been closely related to depression (133). The physiological factors underlying various neurodegenerative changes include: increased inflammation level, enhanced oxidative stress damage, decreased secretion of the brain-derived neurotrophic factor (BDNF) and excessive glucocorticoid level associated with the chronic stress. The evidence of the correlation between neurodegeneration and

depression can be mainly derived from the following aspects: (1) Hippocampal and the pre-frontal cortex (PFC) volume has been observed to be consistently reduced in the depressed patients (134–136); (2) Decreased levels of BDNF, dendritic atrophy, decreased neurogenesis, and increased neuronal death in patients with depression (137, 138); (3) Depression and other neurodegenerative diseases can exhibit a high co-morbidity (139). Previous epidemiological studies have shown that the co-morbidity rate of depression and Alzheimer's disease was about 40% (140), and the co-morbidity rate of Parkinson's disease was about 30% (141).

Omega-3 PUFAs play important roles in preventing neurodegeneration by inhibiting neuroinflammation, promoting synaptic plasticity and neurogenesis, facilitating nervous system repair, and protecting against the reduction of gray matter volume and the decline of white matter integrity (19, 142, 143). Studies have found that omega-3 PUFAs can promote the proliferation and migration of nerve cells, and inhibit apoptosis (48, 144). According to a ten-year follow-up study, higher levels of plasma EPA and DHA are associated with a slower decline in medial temporal lobe volume and a lower risk of dementia in older adults (145). Higher blood EPA level is found to have correlations with lower gray matter atrophy in the right amygdala, while higher atrophy of the right amygdala is correlated with more severe depressive symptoms (146).

Omega-3 PUFAs can prevent neurodegeneration through modulating a variety of pathways, including anti-apoptotic (147, 148), anti-oxidative (149–151), and anti-inflammatory pathways (152). Omega-3 PUFAs supplementation have been also found to increase the synthesis of neutrophic factor BDNF (153–155). BDNF plays important role in protecting against neurodegeneration and promoting neuronal plasticity, thereby having potential in depression treatment (156, 157). In addition, changes in the activities of telomerase and mammalian target of rapamycin (mTOR) may also be involved in the anti-neurodegeneration actions of omega-3 PUFAs (158, 159). Clinical trials have also confirmed that omega-3 PUFAs can effectively improve neurodegenerative diseases (such as Alzheimer's and Parkinson's diseases) with an associated improvement of the co-morbid depressive symptoms (160).

Pro-neuroplastic and pro-synaptic plasticity effects of omega-3 PUFAs

Depression is deeply connected with irregular neural plasticity processes which are often found in the prefrontal cortex, hippocampus, amygdala and other limbic systems (161). Impaired neural plasticity can be primarily reflected in decreased neurogenesis, reduced dendritic spine density, decreased synapse number and strength, reduced synaptic remodeling, dendritic atrophy, as well as reward circuit dysregulation (162–166). At present, it has been found that the vast majority of antidepressant treatments, including physical therapy (such as electroconvulsive therapy, transcranial direct current stimulation, and transcranial alternating current stimulation) and drug therapy (such as fluoxetine, ketamine, and TJZL184), can primarily exert their antidepressant effects by regulating neural plasticity (167–170).

Omega-3 PUFAs have been shown to promote neuroplasticity in multiple ways. DHA supplementation could effectively promote neurogenesis by increasing the proliferation of neural stem/progenitor cells (NSPCs) as well as the number of NSPCs differentiating into the neurons and promoting the survival of newly born neurons (49). Moreover, increasing the brain levels of omega-3 PUFAs can increase the synthesis of new dendritic spines and synapses (171). The underlying mechanisms for the pro-neurogenesis effect of omega-3 PUFAs may be related to activation of proliferation-related pathways involving signaling molecular including GPR40, p38 MAPK, cAMP-response element binding protein (CREB), and BDNF (172–174). By using transgenic fat-1 mice rich in endogenous omega-3 PUFAs, researchers have found that substantial increase in brain DHA can significantly promote hippocampal neurogenesis and increase the genesis of dendritic spines of CA1 pyramidal neurons (172).

Omega-3 PUFAs supplementation could also regulate synaptic formation, synaptic transmission and affect synaptic plasticity (32, 171, 175). Omega-3 PUFAs may play an important role in regulating the expression of several important neural and glial proteins such as E-cadherin, early growth response 1, postsynaptic density protein 95, and signaling factors that have been implicated in synaptic plasticity [such as N-methyl-D-aspartic acid (NMDA) receptor and Fyn] (176). It has been reported that omega-3 PUFAs deficiency can reduce long-term potentiation (LTP), the concentrations of glutamate receptor subunits, and synaptic vesicle proteins at the hippocampal glutamatergic synapses (177).

In addition, DHA and EPA can be converted into endocannabinoids (eCBs) docosahexaenoyl ethanolamide (DHEA) and eicosapentaenoyl ethanolamide (EPEA) which exerts physiological effects through activating eCB receptors. DHEA and EPEA have been reported to exhibit various immunomodulatory and anti-inflammatory activities and effects on food intake and mood (20, 178). The eCBs can induce short-term changes and long-term synaptic plasticity in the whole nervous system, because eCBs synthesized in the postsynaptic neurons can function reversely to regulate the presynaptic input (179). Maternal omega-3 PUFAs deficiency can induce the impairment of eCBs gating of LTP in hippocampus of weaned pups (180). It has been also found that life-long omega-3 PUFAs deficiency can lead to the specific inhibition of eCBs-mediated long-term synaptic depression in the prelimbic prefrontal cortex and the accumbens of adult mice. This effect is accompanied by decreased CB1

receptor function which is associated with impaired emotional behavior (181).

Neurotransmitter system modulatory effects of omega-3 PUFAs

The neurotransmitter and neurotransmitter receptor hypothesis of depression propose that various disorders in multiple neurotransmitter systems are involved in etiopathology of depression. Emerging literature has also shown that depression might be associated with the various molecular abnormalities and functional deficiency in brain transmitter systems including that in 5-hydroxytryptamine (5-HT), dopamine (DA), norepinephrine (NE), Glu and GABA (157). Accumulating evidences indicate that the neurotransmitter transmission predominantly depends on adequate level of omega-3 PUFAs or optimal omega-6 PUFAs: omega-3 PUFA ratio in the brain (23). Being rich in membranes of the synaptic terminals, DHA has been considered to be important for the function of neurochemical transmission. Low availability of omega-3 PUFAs can influence the synthesis, synaptic release, uptake of multiple neurotransmitters including 5-HT, DA, NE, Glu and GABA.

Accumulating evidences indicate that the normal functional activities of neurotransmitter systems depend on adequate levels of omega-3 PUFAs in the brain (23, 182). Omega-3 PUFAs have wide effects on the synthesis, synaptic release, uptake of multiple neurotransmitters including 5-HT, DA, NE, Glu and GABA (23, 183, 184). It has been pointed out that improving the transmission of 5-HT and DA; reducing 5-HT2 receptor and increasing D2 receptor in the frontal cortex may be the possible mechanisms underlying the beneficial effects of omega-3 PUFAs on depression (23). It is reported that fish-oil supplementation produces an antidepressant-like effect in LPS-induced depression model and this effect is related to decreased expression of indoleamine-2,3-Dioxygenase and elevated 5-HT levels in the hippocampus (185). Omega-3 PUFAs can also influence the expression levels of multiple neurotransmitter receptors. It has been shown that DHA supplementation can prevent the increase of binding density of 5-TH receptors (5-HT1A and 5-HT2A), CB1 and GABA-A receptors induced by the high saturated fat diet, which have been related to the cognitive function of the brain (186).

In addition, previous studies have demonstrated that omega-3 PUFAs deficiency can aggravate the age-associated decrease in glutamatergic synaptic efficacy in the hippocampal CA1 (187). It can further affect the glutamatergic synapse development and anxiety-like behavior in male adult rats (188). It has also been found to decrease the subunits of NMDA receptors NR2A, NR2B in rodents (188–190). Similarly, omega-3 PUFAs deficiency also leads to decreased concentrations of Glu receptor subunits (GluA1, GluA2 and NR2B) and other synaptic vesicle proteins in the hippocampal synaptosomes of mice (177).

Preclinical and clinical findings have suggested that eCBs/CB1R signaling can contribute to depression risk and omega-3 PUFAs can exert the anti-depressant effects through altering the PUFA-derived eCBs levels in the whole brain (181, 191–193). It has been reported that omega-3 PUFAs supplementation can increase plasma DHEA and EPEA levels and increased EPEA levels are positively related to the clinical remission rate of MDD patients (180).

The correlations of the six mechanisms of omega-3 PUFAs action

These six aspects of omega-3 PUFAs action may not play independent parts, but just like different aspects of the same thing they probably work in an interconnected system. The simplified model for the assumed interconnection of the six mechanisms are shown in Figure 1. Neuroinflammation and oxidative stress often flame each other and have been considered as the major causes of neurodegeneration followed by MDD (194). Chronic stress-induced hyperactivation of the HPA-axis and neuroinflammation can create a vicious cycle, lead to dysfunction of neurotransmitters system, impair neuroplasticity and promote neurodegeneration (195–199). It has been indicated that HPA axis hyperactivation causes inflammation response in MDD. Immunological communication between the CNS and the body periphery triggers neuroinflammation, which further induces the failure of glucocorticoid negative feedback within the brain. In addition, inflammatory factors activate the kynurenine pathway resulting in the reduction of serotonin biosynthesis and the increased production of neurotoxic metabolites, and eventually neurodegeneration (198). There are lots of papers which have reviewed the correlations between neuroinflammation and neural or synaptic plasticity, neuroinflammation and neurotransmitter systems, neurotransmitter systems and synaptic plasticity, which can be referred to the following references (200–203). We also summarized the experimental designs and results of animal studies reported in the references in this paper. As shown in Table 1.

According to research results, omega-3 PUFAs deficiency often leads to dysfunction of multiple neurobiological systems, such as neuroinflammation, inactivated GR signaling pathway and HPA axis hyperactivity, deteriorated serotoninergic, noradrenalinergic and dopaminergic neurotransmission, impaired neurogenesis, neurodegeneration and so on (96, 103, 208). It has been found that chronic dietary omega-3 PUFAs deficiency led to a significant reduction in 5-HT and NA content, increased production of kynurenine, along with HPA

TABLE 1 Experimental design and results summary of animal studies in references.

References	Year	Animals	Experimental model	Omega-3 Dose	Effects	Molecular change
Song et al. (95)	2009	Sprague Dawley rats	Olfactory bulb resection depression model	1% EPA diet	Water maze: spatial memory↑	mRNA expression and activity of cPLA2↓; Serum IL-1β and PGE2 concentrations↓; CRF mRNA expression and blood corticosterone concentration↓; NGF expression in the hippocampus↑;
Ferraz et al. (102)	2011	Wistar rats	Restraint stress induced depression model	3.0 g/kg animal weight of an oral compound containing 12% of EPA and 18% of DHA	FST: immobility frequency↓; swimming frequency↑; climbing frequency↑; Water maze test: mean latency time↓; percentage of spent time in target quadrant↑; percentage of entries into closed arms↓; EPM: percentage of entries into open arms↑; percentage of time spent in closed arms↓; percentage of time spent in the open arms↑	None
Labrousse et al. (204)	2012	C57Bl6/J mice	Control diet non-depression model	An isocaloric LCω3 PUFA supplemented diet containing a mixture of rapeseed oil, high-oleic sunflower oil, palm oil and tuna oil resulting in a 10% EPA and 7% DHA diet	Spatial recognition: Spatial memory deficit↓	AA/dGLA↑; EPA and DHA in the brain↑; (dGLA+EPA)/AA↑; microglia-dependent activation↓; proinflammatory cytokines production in microglia↓; CD11b mRNA expression↓; TNF-α expression mRNA↓; IL-6 mRNA expression↓; IL-1β expression↓; length of astrocytic processes in aged mice↑; c-Fos positive cells↑; microglia-dependent activation↓; proinflammatory cytokines production↓
Balvers et al. (193)	2012	C57BL/6 mice	i.p. LPS induced depression model	1% or 3% fish oil	None	DHEA↑; EPEA↑; endocannabinoids↓; NAEs↓; DGLEA↓; adipose tissue levels of SEA↑; plasma levels of SEA↓; ARA↓; DHA↑; EPA↑; oxylipins↓; LTB4 in ileum and adipose tissue↓; LTB4 in liver↑; Lipoxin A4↑
Larrieu et al. (205)	2014	C57BL/6 mice	Chronic social defeat stress induced depression model	3.1% lipids	Number of social explorations↓ OFT: time spent exploring the center↓	Simplification of apical dendritic tree on pyramidal neurons of the dlPFC and dmPFC↓; total corticosterone elevation↓; HPA axis hyperactivity↓; neuronal atrophy↓

(Continued)

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TABLE 1 (Continued)

References	Year	Animals	Experimental model	Omega-3 Dose	Effects	Molecular change
Wu et al. (92)	2016	Sprague Dawley rats	Depressive model induced by intraperitoneal injection of doxorubicin	EPA: DHA 3:2; EPA 510mg/kg; DHA 360mg/kg	Weight loss↓ OFT:Number of crossings↑; number of rearing↑; latency time↓; FST: swimming time↑; immobility time↓	MDA in prefrontal cortex↓; MDA in hippocampus↓; SOD in hippocampus↑; IL-1 mRNA expression in prefrontal cortex↓; IL-6 mRNA expression in prefrontal cortex↓; IL-6 mRNA expression in hippocampus↓; TNF-α mRNA expression in hippocampus↓; protein level of NF-κB↓; protein level of iNOS↓; Number of nuclear pyknosis↓; Apoptotic index TUNEL-positive cells↓gene expression of Bcl-xl↑; gene expression of Bcl-2↓.
Larrieu et al. (103)	2016	C57BL6/J mice	Mifepristone subcutaneous implantation non-depression model	Containing 6% of rapeseed oil	Number of social interaction↑; OFT: Center time ↑	Plasma corticosterone levels ↓; the total apical dendritic material in both dlPFC and dmPFC ↑
Abdel-Maksoud et al. (153)	2016	Sprague-Dawley rats	Control diet non-depression model	EPA: DHA 3:2; EPA 180mg; DHA120mg	None	BDNF gene expression↑; serum total cholesterol↓; triacylglycerol↓; serum glucose level↓; HOMA index↓; triacylglycerol levels↓
Morgese et al. (98)	2017	Wistar rats	Control diet non-depression model	Containing 6% total fat in the form of only rapeseed oil (n-3 enriched, rich in linolenic acid 18:3n-3)	FST: immobility frequency↓; swimming frequency↑; struggling frequency↑; OFT: time of performing self-grooming↓	Cortical 5-HT concentrations↓; CRF content↑; corticosterone levels↑; plasmatic Aβ levels ↑; NA↑
Tang et al. (104)	2018	Sprague-Dawley rats	Control diet non-depression model	Fish oil (20 g/ kg)	FST: immobility frequency↓; SPT: sucrose preference↑	Protein expressions of glucocorticoid receptor ↑
Cigliano et al. (206)	2019	MRL/lpr mice	Non-depression model	An oral dose (30 mg) of FO (85%) containing 16 and 9,5 mg of DHA and EPA	None	Double-stranded DNA (anti-dsDNA) IgGs↓; TNF-α↓; PPAR-γ↑; DHA concentration in the brain↑; BDNF↑; SynaptophysinI↑; SynaptotagminI↑; SynapsinI↑; compensatory hyperactivation of phase 2 enzymes (GSR, G6PD) activities↓; GCL↓; GSR mRNA levels↓; Nrf2 ↓
Yang et al. (183)	2019	Sprague-Dawley rats	CUMS induced depression model	Fish oil (20 g/kg)	FST: Immobility times↓; SPT: sucrose preference↑; OFT: number of locomotor crossing↑; number of rearing↑	5-HIAA↓; DOPAC↑; HVA↓; VMA↓; GLN↑; DA turnover rate 2↓; NE turnover rate 1↓; NE turnover rate 2↓; DA/NE between-metabolite ratio 1↑

(Continued)

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TABLE 1 (Continued)

References	Year	Animals	Experimental model	Omega-3 Dose	Effects	Molecular change
Choi et al. (107)	2020	Wistar rats	Pup separation-induced depression model	EPA:DHA 5:3; EPA 450mg; DHA260mg	FST: immobility time↓; climbing time↑; Sucrose preference index↑; Pup retrieval test: Latency of the first contact↓; Latency to retrieve↓	Adrenocorticotropic hormone↓; corticosterone↓; hypothalamic corticotrophin releasing factor↓; hippocampal miRNA-218↓; prostaglandin E2↓; TNF-α↓; IL-6↓; miRNA-155↑; serotonin↑; serotonin-1A receptor↑; cAMP response element binding protein (CREB)↑; pCREB; brain-derived neurotrophic factor↑; miRNA-182↑.
Cutuli et al. (144)	2020	C57BL/6 mice	icv. mu-p75-saporin induced depression model	EPA: DHA 5:4 300 mg/kg	EPM: expected aversion↓; NORT: total object contact time↓	Preserved hippocampal volume; neurogenesis in the dentate gyrus↑;astrogliosis in the hippocampus↓
Peng et al. (207)	2020	Sprague Dawley rats	CUMS induced depression model	1% ethyl-EPA (96% pure) or 1% DHA (96% pure)	SPT: Sucrose consumption↑; FST: immobility time↓; OFT: numbers of locomotor crossing↑; numbers of rearing↑	Arachidonic acid (AA) level in the brain↓; docosapentaenoic acid in the brain↑; total cholesterol level ↓; serum corticosterone ↓; NE ↑; 5-HT ↑; NE/MHPG↑; IL-1β↓; IL-6↓; TNF-α↓; CD11b expression↓; p75NTR expression↓; GDNF expression↑; NF-KB and p38 expression↓; bax expression↓; bcl-2↑; bax/bcl-2↓
Carabelli et al. (185)	2020	Wistar rats	i.p. LPS induced depression model	3.0 g/kg (approximately 3.0 mL/kg) of fish oil containing 18% of EPA and 12% of DHA	Weight loss↓; FST: swimming frequency↑; immobility time↓	5-HT↑; 5HIAA/5-HT↓; IDO expression↓
Choi et al. (110)	2021	Wistar rats	CMS+ovariectomy induced depression model	EPA: DHA 3:2; EPA 300mg/kg; DHA260mg/kg	FST: swimming time↑; immobility time↓; SPT: sucrose preference index↑	Brain endocannabinoid/oxylipin levels↑; blood levels of adrenocorticotropic hormone and corticosterone↓; tumor necrosis factor-α, interleukin (IL)-6, IL-1β, and prostaglandin E2↓; brainstem serotonin levels and hippocampal expression of the serotonin-1A receptor, cAMP response element-binding protein (CREB), phospho-CREB, and brain-derived neurotrophic factor↑

"↑" Indicates increased levels or protein expression of factor substances *in vivo* after treatment with omega-3 compared to controls. "↓" Indicates decreased levels or protein expression of factor substances *in vivo* after treatment with omega-3 compared to controls. FST, Forced Swimming Test; SPT, Sucrose Preference Test; OFT, Open Field Test; EPM, Elevated Plus Maze; NORT, New Object Recognize Test; NGF, Nerve growth factor; LTB4, Leukotriene B4; MDA, Malondialdehyde; HOMA index, Homeostatic model assessment index; HVA, Homovanillic acid; VMA, Vanillylmandelic acid; GLN, glutamine.

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axis hyperactivity, higher proinflammatory cytokine production associated with higher expression of TLR2 and TLR4 and increased expression of oligomeric Aβ in hippocampus of female rats (209).

Both clinical and pre-clinical evidences have shown that the alterations of many different aspects of the CNS are involved in the anti-depressant effect of omega-3 PUFAs supplementation (63, 88, 89, 130, 184, 205, 206, 208, 210–213). Therefore, the six antidepressant mechanisms of omege-3 PUFAs that we summarized probably act synergistically but not separately. However, there is currently no clear conclusion on how these mechanisms are linked or how they interact, and whether there are causal links. All these questions require further studies to be answered.

Based on existing evidence, we summarized a variety of central mechanisms of omega-3 PUFAs anti-depressant actions, from molecular mechanisms to cellular mechanisms to neurobiological mechanisms. **At the molecular level,** omega-3 PUFAs directly changes lipid profiles, regulating membrane fluidity and membrane-associated cellular processes such as the assembly of membrane protein complexes and lipid valves; neurotransmitters and neuroendocrine exocytosis as well as microglia phagocytosis. Through metabolism and acting on the plasma membrane or intracellular receptors, omega-3 PUFAs can improve total antioxidant capacity; prevent lipid peroxidation: produce anti-inflammatory metabolites and regulate inflammatory signal pathways. **At the cellular level,** omega-3 PUFAs indirectly affect a wide range of cellular activities, such as the cell resistance to stress damage; various signaling transduction pathways; the neurotransmitter systems; the whole-genome expression profile; cell proliferation, differentiation, growth, development, senescence, apoptosis and so on. Based on its molecular and cellular mechanisms **at the neurobiological level**, omega-3 PUFAs exert a widespread and far-reaching influence on the mood regulating function of the central nervous system. Omega-3 PUFAs can improve neuroinflammation; dysfunction of neuroendocrine (HPA axis); oxidative stress; neurodegeneration; neuroplasticity; neurotransmitters system and so on. All these effects may play roles in the prevention and improvement of depression. Abbreviations: TRPV4, Transient receptor potential vanilloid 4; ROS, Reactive oxygen species; EGFR, Epidermal growth factor receptor; GPR120,G-protein coupled receptor 120; PPARγ, Peroxisome proliferator-activated receptor-gamma; TLR4, Toll-like receptor 4; COX-2, Cyclooxygenase-2; BDNF, Brain-derived neurotrophic factor; CREB, cAMP-response element binding protein; PPAR, peroxisome proliferator-activated receptor; Nrf2, nuclear factor-erythroid 2-related factor 2; 5-HT, 5-hydroxytryptamine; NE, Norepinephrine; CB, Cannabinoids; GC, Glucocorticoid; NF-κB, nuclear factor kappa-B; JNK, c-Jun N-terminal kinases; p38MAPK, p38 mitogen-activated protein kinase.

Future directions

The pathological mechanisms of depression have been found to be closely associated with multiple aspects of neural functions. Currently, omega-3 PUFAs are a kind of molecules of diverse biological activities, capable of producing multiple antidepressant effects in the CNS. The six possible mechanisms summarized in this review are probably interconnected in complex manner and can function synergistically to produce the anti-depressant effects. However, there is a critical need for well-designed systematic researches to identify the eventual unitary anti-depression mechanism from various different actions of omega-3 PUFAs.

Although there have been numerous studies published that have demonstrated the regulation of various physiological functions by omega-3 PUFAs in depressive disorders, there are still insufficient reports related to the causal mechanisms of omega-3 PUFAs anti-depressant action. Omega-3 PUFAs can have diverse regulatory effects on neurogenesis, synaptic plasticity, oxidative stress, neuroendocrine, and neurotransmitter transduction, but the specific molecular regulatory pathways remain largely unclear. In addition, it is also unclear to how these PUFAs affect depressive symptoms from the molecular to the behavioral level. To answer this question may depend on the thorough understanding about the role of omega-3 PUFAs in human life as well as the pathophysiological nature of depression.

It is still unclear which ones are direct or indirect mechanisms; which ones are the primary effects and which ones are the secondary mechanisms of the anti-depressant effect of omega-3 PUFAs. Clarifying these issues which will help establish the central pharmacological action and pharmacodynamics of omega-3 PUFAs.

In order to facilitate translation to application, future research may need to elucidate the anti-depressant mechanism of omega-3 PUFAs action by using quantitative systems pharmacology and to identify the clinical biomarkers and the antidepressant-response biomarkers in target subgroups of depressed patients.

Moreover, omega-3 PUFAs may play different roles in different depressed patients with different constitutions. Further studies should be conducted to explore the potential different mechanisms of the action of omega-3 PUFAs on depression in children, adolescents, postpartum women, and eldly adults or depressed patients with concomitant physical diseases such as cardiovascular disorders. This will help the personalized application of omega-3 PUFAs in different subgroups of MDD.

In addition, according to ISNPR's 2019 practice guideline for the assisted treatment of depression with omega-3 PUFAs, omega-3 PUFAs are found to be more effective as an adjuvant treatment than monotherapy for MDD treatment. So, what are the specific mechanisms by which omega-3 PUFAs can

accelerate or enhance effects of other antidepressants? This requires further studies to explore the exact mechanisms underlying greater efficacy of clinical antidepressants in combination with omega-3 PUFAs. This may be the good news for clinical use of antidepressants that act quickly but are often associated with side effects, or work too slowly, or do not work significantly.

Conclusions

This article provides a review of the neurobiological mechanisms underlying the antidepressant effects of omega-3 PUFAs. Based on the accumulated evidence from recent publications, we identified six potential mechanisms, including: (1) anti-neuroinflammatory; (2) anti-oxidative stress; (3) modulation of HPA axis; (4) anti-neurodegeneration; (5) neuroplasticity and synaptic plasticity; and (6) modulation of neurotransmitter systems. All these antidepressant mechanisms may be based on the molecular action and cellular effects of omega-3 PUFAs, however, how these processes work remains largely unknown. Although neurobiological mechanisms are probably interconnected and interdependent, the multiple sites of action of omega-3 PUFAs are still needed to be clarified. This review contributes to a better understanding the potential mechanisms of benefit of omega-3 PUFA and may provide useful references for the development of new strategies for the treatment of depressive disorder with omega-3 PUFAs.

Author contributions

J-TZ was responsible for the study conception and design and the writing and revising of the manuscript. LZ performed the collection, the writing of the manuscript, and provided the technique support. BL made revisions and polishing to the paper and provided the funding support. J-YX and Y-QC made material support and grammar checking. All authors contributed to and have approved the final manuscript.

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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.

Publisher's note

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Low carbohydrate and psychoeducational programs show promise for the treatment of ultra-processed food addiction

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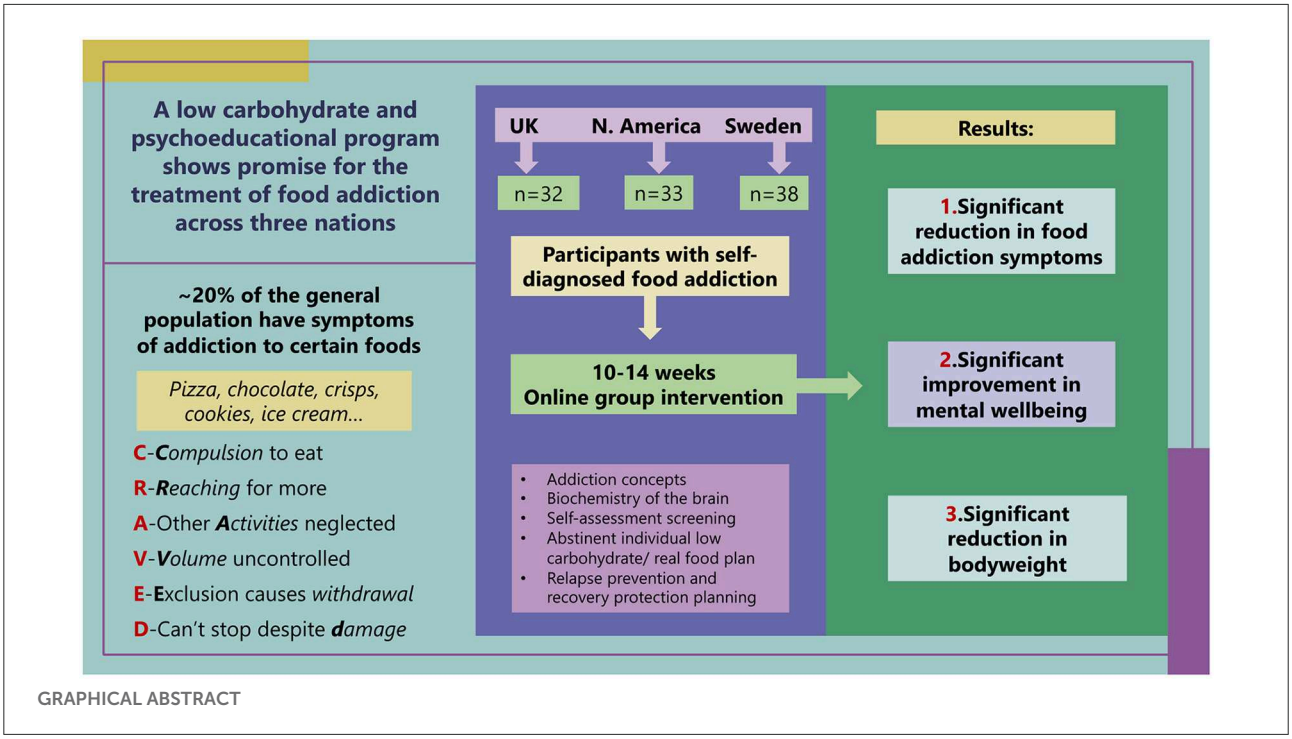
Food addiction, specifically ultra-processed food addiction, has been discussed in thousands of peer-reviewed publications. Although 20% of adults meet criteria for this condition, food addiction is not a recognized clinical diagnosis, leading to a dearth of tested treatment protocols and published outcome data. Growing numbers of clinicians are offering services to individuals on the basis that the food addiction construct has clinical utility. This audit reports on clinical teams across three locations offering a common approach to programs delivered online. Each team focused on a whole food low-carbohydrate approach along with delivering educational materials and psychosocial support relating to food addiction recovery. The programs involved weekly sessions for 10–14 weeks, followed by monthly support. The data comprised pre- and post- program outcomes relating to food addiction symptoms measured by the modified Yale Food Addiction Scale 2.0, ICD-10 symptoms of food related substance use disorder (CRAVED), mental wellbeing as measured by the short version of the Warwick Edinburgh Mental Wellbeing Scale, and body weight. Sample size across programs was 103 participants. Food addiction symptoms were significantly reduced across settings; mYFAS2 score −1.52 (95% CI: −2.22, −0.81), CRAVED score −1.53 (95% CI: −1.93, −1.13) and body weight was reduced −2.34 kg (95% CI: −4.02, −0.66). Mental wellbeing showed significant improvements across all settings; short version Warwick Edinburgh Mental Wellbeing Scale 2.37 (95% CI: 1.55, 3.19). Follow-up data will be published in due course. Further research is needed to evaluate and compare long-term interventions for this complex and increasingly burdensome biopsychosocial condition.

KEYWORDS

addiction, sugar, processed-food, low-carbohydrate diet, ketogenic diets



GRAPHICAL ABSTRACT

Introduction

Food addiction (FA) was first described in 1956 (1). Considerable debate has continued and it remains unresolved if FA is a distinct disorder warranting official recognition (2–4). To date, FA has not been classified in the Diagnostic and Statistical Manual of Mental Disorders (5) (DSM-5) or in the International Classification of Diseases (6) (ICD-10). There is also ongoing discussion amongst clinicians as to how to refer to this disorder. For the purposes of this paper, we will use the term food addiction to refer to dependency behaviors relating to sugar and processed foods, although it is increasingly being referred to as ultra-processed food addiction (7).

FA is operationalized using the Yale Food Addiction Scale (YFAS) originally published in 2009 (8) and more recently the YFAS 2.0 (9). In 2015, Schulte et al. reported pizza, chocolate, chips (crisps), cookies (biscuits) and ice cream as the five most problematic foods for those with FA symptoms (10). In recent years, increasing numbers of articles have described FA symptoms (11), prevalence (12), and possible mechanisms (13, 14) in both animals and diverse human populations worldwide. The most recent estimates suggest that the worldwide prevalence of FA is ~20% and that it positively correlates with BMI and eating disorders (15).

The symptoms of FA are captured using the 11 criteria for substance use disorder (SUD) from the DSM-5 (5) and applying those to foods high in refined carbohydrates/sugar, fat, and salt. Two or three symptoms indicate mild SUD, four or five is moderate and six or more indicates severe SUD. The criteria include:

- Consuming the substance in larger amounts or for longer than intended.
- Efforts to cut down or stop using the substance but not managing to.
- Time spent getting, using, or recovering from the substance.
- Cravings and urges to use the substance.
- Not managing to perform at work, home or school because of substance use.
- Continuing to use the substance despite causing problems in relationships.
- Giving up important social, occupational, or leisure activities because of substance use.
- Using the substance repeatedly despite harmful consequences.
- Continuing to use the substance despite physical or psychological problem caused or worsened by the substance.
- Needing more of the substance to get the desired effect.
- Development of withdrawal symptoms which are relieved by consumption of substance.

Similarly, there are six criteria from the ICD-10 (6), where three or more symptoms indicate SUD:

- "Craving," a strong desire or urge to use the substance.
- Difficulty controlling the onset, duration, amount, and termination of substance use.
- Increasing priority of substance use over other activities over time.
- Increased tolerance and the need to increase consumption over time.
- Physiological features of withdrawal when trying to abstain.
- Continued use of the substance despite mental or physical harm.

Clinicians who work with persons with type 2 diabetes, obesity, and metabolic syndrome will likely recognize these behaviors in their patients, particularly those who struggle to follow nutrition and lifestyle advice consistently. It has been shown that an understanding of addiction-like eating behavior can shift the blame narrative away from assumptions of "personal responsibility" and thereby reduce stigma associated with eating behavior (16, 17).

Prevalence estimates of FA are consistently highest in clinical samples of eating disorders (EDs), which has led some authors to urge for ED screening and careful assessment before determining proper diagnosis and treatment (18). Specifically, individuals with bulimia nervosa (BN) have the highest prevalence of FA (48–95%), followed by binge eating disorder (BED; 55–80%), and then anorexia nervosa (AN; 44–70%) (15, 18–20). It has been suggested that efforts to restrain eating, engage in compensatory behaviors (e.g., purging), or maintain body weights below normal might lead to increases in self-reported FA scores (7). Meanwhile, it can be established that FA symptoms exist independently of ED symptoms, thus it can be conceptualized as a distinct disorder warranting targeted interventions (7, 18). More research is needed in this area.

Several neurobiological mechanisms have been proposed to explain FA. Wiss et al. stated that "evidence is accumulating on the overlap of neural circuitry and commonalities between drug abuse and FA in humans" (13). These authors propose that FA in humans is similar to nicotine or caffeine addiction and that hyperpalatable foods can "hijack" reward centers in the brain, impairing decision-making processes in ways that can be subtle or quite obvious to the person (and those close to them). Similarly, Lindgren et al. found support for the concept of FA *via* overlapping neural mechanisms with drug and alcohol addiction: a dampening of dopamine signaling and downregulation of the μ-opioid receptor, "coupled with impairment of prefrontal regions that are involved in inhibitory control" (14). The authors add that further research is needed on the complex interaction between these processes and the hormones that modulate feeding behavior. Their discussion points to the challenge of designing interventions for FA because unlike other SUDs, total abstinence from food is not an available option.

A range of possible interventions for FA symptoms have been proposed including medications (21), cognitive behavioral therapy (22), brain stimulation (23), psychoeducation (24), bariatric surgery (25), low-calorie diets (26), probiotics (27), and "infra slow" brain training (28). No data have been presented for medication (21), cognitive behavioral therapy (22) or brain stimulation (23). Eleven obese women reported reduced cravings after infra slow brain training, however there was no follow up (28). A 6-week uncontrolled psychoeducational program for 66 women with BN showed FA severity can improve but still found 73% FA post intervention (24). A study of 44 people undergoing bariatric surgery showed a reduction of 32–2% with food addiction symptoms at 6 months (25). A low-calorie diet in 11 people with obesity and FA was found to normalize brain activation compared to people with obesity without FA. However, follow up was only 3 months and no details of the diet were given (26). In a randomized trial of probiotics for women with obesity and FA, the active treatment led to greater improvements in oxytocin levels and eating behavior, however there was no follow up.

Several authors affirm that low-carbohydrate approaches have therapeutic potential for treating FA symptoms (29). They propose that ultra-processed, refined, or high-glycemic index carbohydrates are a possible "trigger" mediating neurochemical response that is similar to that seen in addictions. The carbohydrate-insulin model of obesity supports observations of these foods triggering abnormal blood sugar and insulin spikes subsequently leading to changes in metabolic and neurobiological signaling (30). Carmen et al. published a case series of three patients with obesity, BED, and FA managed over 6–7 months on a low-carbohydrate ketogenic approach with no adverse effects (31). They were followed up over 9–17 months. Both binge eating and FA symptoms improved, accompanied by a 10–24% body weight loss. Interventions for FA must be able to demonstrate sustainable changes to symptoms and mental wellbeing. FA recovery can be achieved without overemphasis on weight which can detract from the clinical utility of the construct as a behavioral disorder (7).

In a recent poll of an online food addiction professional group, we found that 20 out 25 practitioners recommend low-carbohydrate or ketogenic food plans as part of their interventions (unpublished data). Although this proportion is subject to selection bias, it clarifies that carbohydrate restriction is a common clinical practice for the treatment of FA. Other practitioners include grains and fruit in their plans. No previous audits of practice outcomes in food addiction have been published to our knowledge. The current audit describes the pre- and post-intervention data from practices in three different countries offering online group interventions for people self-identifying as having FA, including an "abstinent" low-carbohydrate "real food" approach and biopsychosocial education focused on addiction and recovery.

Materials and methods

Clinics in three locations [the United Kingdom (UK); North America (NA); Sweden (SE)] already offering similar online programs for people with FA used the same measures for screening and follow up. The ethics protocol for the National Health Service in the UK was reviewed and indicated that since the project was an audit of pre-existing routine practice and participants were self-referred, formal ethical review was not required.

Participants

Participants in the programs typically made contact *via* social media and mailing list advertisements by the authors. Participants were screened through online interviews by the appropriate clinician to confirm self-identified FA symptoms. None of the programs accepted people under 18 years of age, pregnant, having serious mental health problems requiring ongoing specialist psychiatric support, or any doctor requesting exclusion. Each participant was given information about the program and audit and the opportunity to ask questions. Participants completed a consent form as part of the initial data collection to affirm that their anonymized data could be used in the audit of the programs. Participants' data were identified by a unique code to ensure anonymity. An information sheet (UK) and protocols are included as Supplementary materials. Participants paid a reduced fee (NA, SE) or donation (UK) to participate.

Power calculation

Data collection points were scheduled before and after the online group and at 6 months, 1 year, 18 months and 2 year follow up. The current paper audits the data available to date, which is the initial pre- and post- active intervention data as of June 2022. Power calculations using the main outcome measures of the mYFAS2 (32) and the short version of the Warwick Edinburgh Mental Wellbeing Scale (33) (SWEMWBS) indicated that 26 participants were needed to complete the 2-year follow-up in each location, for a total of 78 total participants. Each location aimed to have 60–70 participants complete baseline data to ensure adequate numbers at 2-year follow-up. The total sample size at the time of this audit is $n = 103$ (UK $n = 32$; NA $n = 33$; SE $n = 38$).

Measures

The mYFAS2 is a short version of the YFAS 2.0 (34). The mYFAS2 includes 13 items: one item for each of the 11 FA criteria in the DSM-5 for SUD and two items for the assessment of clinically significant impairment or distress. One example item is: I ate until I was physically ill. There are eight frequency choices from never to every day. The mYFAS2 has good reliability and convergent and discriminant validity (34). The scale can be scored as total number of criteria met (0–11, reported here) or as an indication of a clinical diagnosis and severity.

A brief screening tool for FA symptoms based on the six ICD-10 criteria for SUD (6) was developed by HG and JU as a simple tool for clinicians. CRAVED, which has not been formally validated, is described and included in the Supplementary materials. Participants were asked to rate whether they had experienced the symptom in the last month (yes or no, possible score 0–6). An example item is: I had such a strong desire or sense of compulsion at the thought of eating these foods, that I could not resist the urge to eat them. A score of 3 or more out of six indicates a potential SUD according to ICD-10 (6).

The SWEMWBS is a short version of the Warwick-Edinburgh Mental Wellbeing Scale (34). The scale was developed to monitor mental wellbeing in the general population and for the evaluation of programs designed to improve mental wellbeing. There are seven statements relating to functioning such as I've been thinking clearly with five response categories from none of the time to all of the time. The measure has good construct and external validity and test-retest reliability (34). Scores range from 7 to 35, higher scores indicating more positive wellbeing. The England population mean is 23.6 (34).

The following data were also collected: age, gender, and weight (kg). The online survey took ∼10 min to complete.

Programs

The programs consisted of 10–14 weeks of 90–120-min sessions in groups of 11–40 participants. The variation is due to each location having their own set of program materials and methods. Sessions consisted of educational content delivered live or pre-recorded, coaching discussions, and assigned reflections. The content of the programs included: understanding addiction concepts and biochemistry, self-assessment screening and reflection, abstinent low-carbohydrate individualized "real food" plan, imagining life beyond FA, new habits and tastes, resilience, relapse prevention planning, and personal lifestyle planning. A comparison of the three group programs and an example food plan (UK) are included in the Supplementary materials. Abstinence from sugar, grains, processed food and any foods the individual participants were unable to moderate (e.g., peanut butter) was emphasized. Following the active program phase, participants joined a monthly 60-min facilitated online

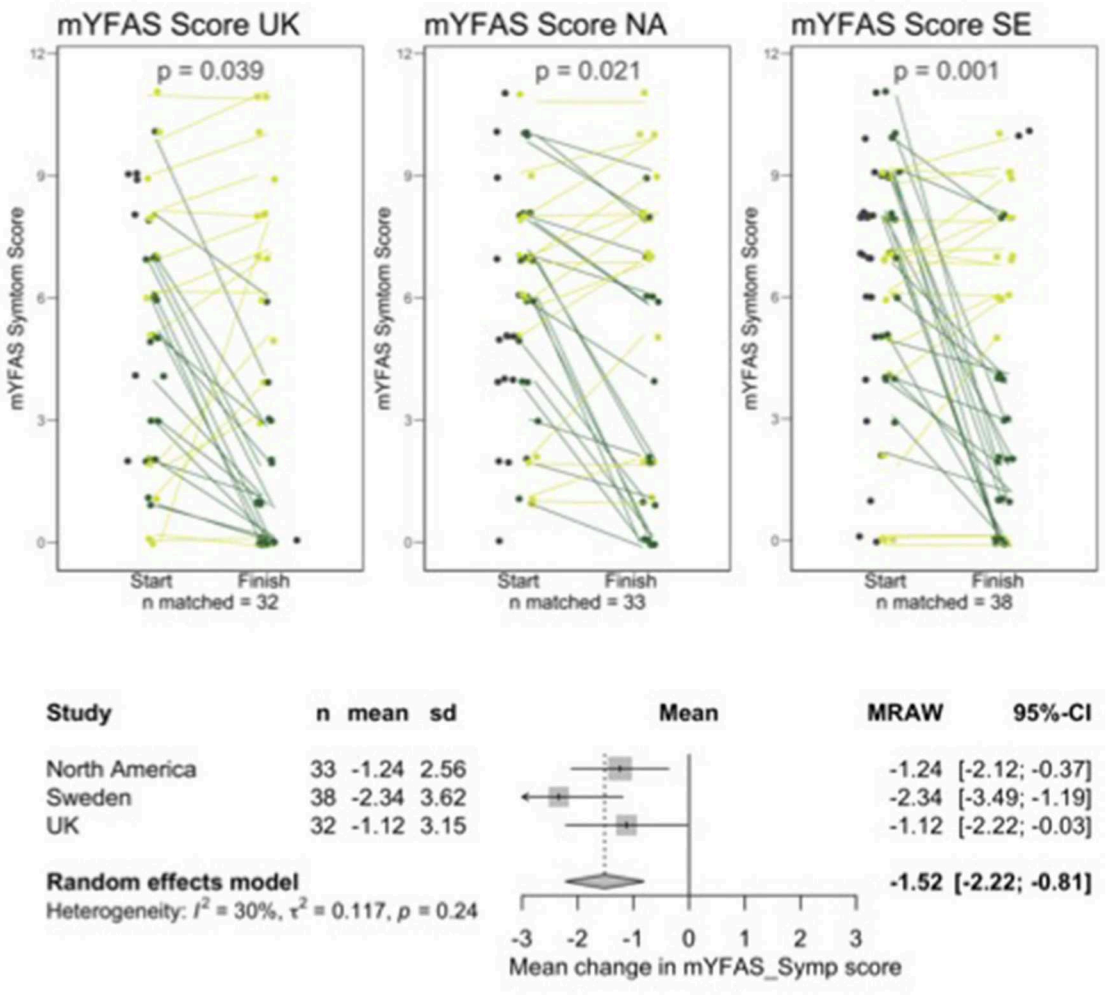


FIGURE 1
Line and forest plots for mYFAS2 symptom score. Dark green indicates improved scores, light green indicates worsening score or no change. Dark gray data points without a line represent people who started but did not finish or who completed a follow up questionnaire but could not be matched with a starting questionnaire.

support group, which will continue for 2 years. All groups also established independently their own support group chats and online meetings.

Data collection and analysis

Participants entered their data into online forms which were analyzed using R v4.0.2. *P*-values were calculated using the Wilcoxon rank sum test with continuity correction, and a value below 0.05 was considered statistically significant. Summary statistics were calculated using random effects models and the DerSimonian-Laird estimate (35) and visualized as forest plots using the meta package, version 4.13-0 and the metamean function.

Results

Not all participants were available for follow-up and a small number of participants who completed follow-up data could not be matched to baseline data due to them entering unidentifiable codes. There were 32, 33, and 38 sets of matched data for UK, NA, and SE, respectively. Graphs shown in Figure 1 through Figure 4 show all available data points for pre -and post-intervention data, including participants who were not available to follow up and unmatched participants but all analyses of the change from pre- to post-intervention were carried out on the matched pairs of data. Table 1 shows retention data to date.

The mean age of UK participants was 50 years (SD = 12), in NA 49 (SD = 12) and in SE 47 (SD = 9.8). Participants were predominantly female (91% UK, 97% NA, and 100% SE).

TABLE 1 Data recruitment and retention.

	UK	NA	SE
Expressed an interest	49	136	138
Screened	41	115	98
Accepted	40	82	83
Baseline data	40	71	60
Average group size	13.3	26.6	30
Sessions completed	33	34	42
Post-intervention data available	33	33	40
Matched pairs for analysis	32	33	38

TABLE 2 Summary data for UK participants.

Value	*N*	Median Q1Q3	Mean SD	*P*-value for pre-post-
Age (years)	32	50 (41, 60)	50 (12)	
Height (cm)	32	165 (160, 170)	165 (6.9)	
Weight pre (kg)	32	88 (72, 99)	88 (19)	
Weight post	32	82 (71, 95)	85 (20)	0.022*
Weight loss	32	2.5 (-1.2, 5.5)	2.8 (6.5)	
mYFAS2 symp pre	32	5.0 (2.0, 7.0)	4.9 (3.2)	
mYFAS2 symp post	32	3.0 (0.0, 7.0)	3.8 (3.7)	0.039*
mYFAS2 symp loss	32	1.0 (-1.0, 3.0)	1.1 (3.1)	
CRAVED pre	32	5.0 (4.0, 6.0)	4.9 (1.1)	
CRAVED post	32	3.5 (1.8, 5.0)	3.2 (2.0)	<0.001***
CRAVED loss	32	2.0 (0.0, 3.0)	1.7 (2.1)	
SWEMWBS pre	32	20 (19, 21)	20 (2.9)	
SWEMWBS post	32	23 (21, 25)	23 (4.6)	<0.001***
SWEMWBS loss	32	−3.1 (−4.9, −1.4)	−3.1 (3.2)	

*$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$.

Table 2 summarizes the UK data. Decrease in mYFAS2 scores was significant (mean reduction 1.1, SD 3.1, $p = 0.039$). Reduction in CRAVED was significant (mean reduction 1.7, SD 2.1, $p < 0.001$), as was increases in SWEMWBS (mean increase 3.1, SD 3.2, $p < 0.001$). Reduction in weight was also significant (Mean loss 2.5 kg, SD 6.5, $p = 0.02$).

Table 3 summarizes the NA data. Reduction in mYFAS2 scores was significant (mean reduction 1.2, SD 2.6, $p = 0.021$). Reduction in CRAVED was significant (mean reduction 1.8, SD 2.2, $p < 0.001$), as were increases in SWEMWBS (mean increase 1.6, SD 3.2, $p = 0.008$). Reduction in weight was also significant (mean loss 4.4 kg, SD 9.4, $p = 0.001$).

Table 4 summarizes the SE data. Reduction in mYFAS2 scores was significant (mean reduction 2.3, SD 3.6, $p = 0.001$). Reduction in CRAVED was significant (mean reduction 0.2, SD 1.2, $p < 0.001$), as was increases in SWEMWBS (mean increase 2.4, SD 3.3, $p < 0.001$). Reduction in weight was also significant (mean reduction 1.2 kg, SD 4.7, $p = 0.01$).

TABLE 3 Summary data for NA participants.

Value	*N*	Median Q1Q3	Mean SD	*P*-value for pre-post-
Age (years)	33	48 (42, 58)	49 (12)	
Height (cm)	32	165 (159, 170)	165 (9.2)	
Weight pre (kg)	31	88 (71, 106)	91 (29)	
Weight post	32	81 (67, 96)	85 (28)	0.001**
Weight loss	30	2.5 (0.0, 5.6)	4.4 (9.4)	
mYFAS2 symp pre	33	6.0 (4.0, 8.0)	6.0 (2.8)	
mYFAS2 symp post	33	6.0 (1.0, 8.0)	4.8 (3.6)	0.021*
mYFAS2 symp loss	33	1.0 (−1.0, 2.0)	1.2 (2.6)	
CRAVED pre	33	5.0 (4.0, 6.0)	4.8 (1.2)	
CRAVED post	33	3.0 (1.0, 5.0)	3.0 (2.1)	<0.001***
CRAVED loss	33	1.0 (0.0, 4.0)	1.8 (2.2)	
SWEMWBS pre	33	22 (19, 23)	22 (3.0)	
SWEMWBS post	33	22 (21, 25)	23 (3.8)	0.008**
SWEMWBS loss	33	−0.9 (-2.4, 0.8)	−1.6 (3.2)	

*$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$.

TABLE 4 Summary data for SE participants.

Value	*N*	Median Q1Q3	Mean SD	*P*-value for pre-post-
Age (years)	38	46 (40, 56)	47 (9.8)	
Height (cm)	38	169 (163, 175)	169 (9.1)	
Weight pre (kg)	38	84 (75, 100)	87 (18)	
Weight post	37	83 (70, 97)	85 (19)	0.01*
Weight loss	37	1.3 (0.0, 4.0)	1.2 (4.7)	
mYFAS2 symp pre	38	7.0 (4.2, 9.0)	6.3 (2.9)	
mYFAS2 symp post	38	3.5 (1.0, 7.0)	4.0 (3.4)	0.001**
mYFAS2 symp loss	38	1.0 (0.0, 5.8)	2.3 (3.6)	
CRAVED pre	38	5.0 (4.2, 6.0)	5.0 (1.1)	
CRAVED post	38	4.0 (2.2, 5.8)	3.8 (2.0)	<0.001***
CRAVED loss	21	0.0 (0.0, 1.0)	0.2 (1.2)	
SWEMWB pre	38	20 (19, 23)	21 (2.7)	
SWEMWB post	38	23 (21, 25)	23 (3.3)	<0.001***
SWEMWB loss	38	−1.7 (−4.1, 0.0)	−2.4 (3.3)	

*P < 0.05; **P < 0.01; and ***P <0.001.

Figures 1–4 show line plots and forest plots for mYFAS2 score, CRAVED score, SWEMWBS score and weight. The line plot shows change over time for each participant across study locations. Improvement (e.g., decreased mYFAS2 score or increased SWEMWBS) is shown as dark green while the opposite change, or no change, is light green. Random effects forest plots calculate the overall change across all three settings.

All scores changed significantly from pre- to post-intervention. The mYFAS2 symptom score decreased, with

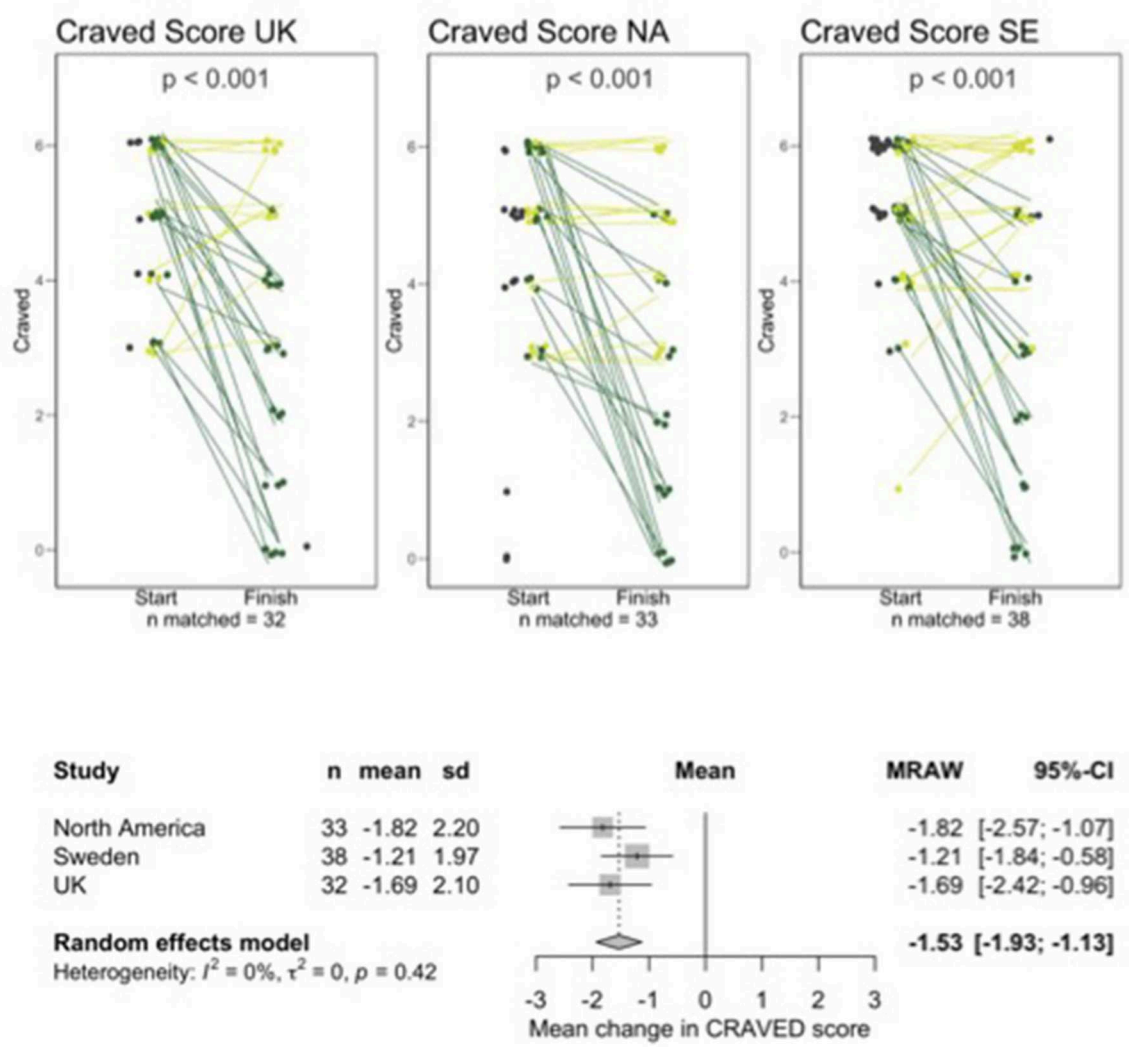


FIGURE 2
Line and forest plots for CRAVED. Dark green indicates improved scores, light green indicates worsening score or no change. Dark gray data points without a line represent people who started but did not finish or who completed a follow up questionnaire but could not be matched with a starting questionnaire.

a change of −1.52 (95% CI: −2.22, −0.81), CRAVED score decreased with a change of −1.53 (95% CI: −1.93, −1.13), SWEMWBS score increased with a change of 2.37 (95% CI: 1.55, 3.19) and weight decreased with a change of −2.34 kg (95% CI: −4.02, −0.66).

Discussion

There is a dearth of published data on any intervention outcomes for individuals struggling with addictive behaviors relating to food. Meanwhile, clinicians and coaches are providing services to some clients seeking help. The data presented here represent an audit of three online low-carbohydrate "real food" programs with psychoeducation and social support currently delivered in three locations in North America and Europe. The vast majority of participants were female (91–100%), which is higher than is reflected in prevalence studies. Praxedes et al. (15) found 27% of males with food addiction in their review. However, there were only two studies found. Further studies are needed to establish suitable interventions for male individuals with food addiction.

The number of people requesting participation in the programs was notable, demonstrating that such programs are in demand. It was interesting that people inquiring about

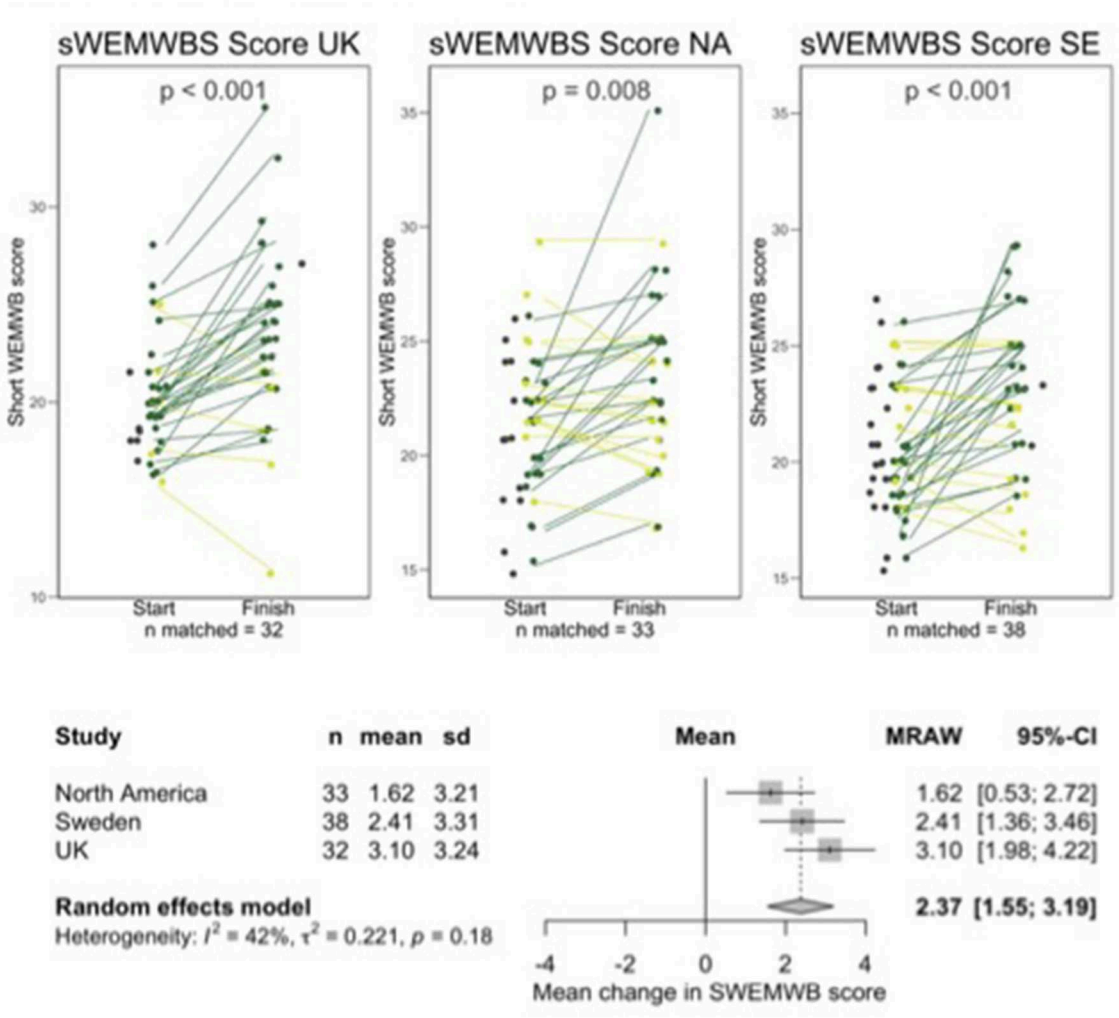


FIGURE 3
Line and forest plots for SWEMWBS. Dark green indicates improved scores, light green indicates worsening score or no change. Dark gray data points without a line represent people who started but did not finish or who completed a follow up questionnaire but could not be matched with a starting questionnaire.

the programs were self-identifying as "food addicts" despite a lack of formal recognition of this condition in the health care system. As shown by the pre-program data, participants appear able to judge this well. There were no screening tools for EDs which would help separate the FA "signal" from the "noise" of dietary restraint (18). All 32 participants in the UK scored 3 or more on the 6 WHO criteria (CRAVED score) prior to the intervention, indicating a probable substance use disorder.

Retention at the end of the group sessions (∼3 months) was 82.5, 48, and 70% for UK, NA, and SE, respectively. This is similar to other addiction programs such as those for smoking cessation where a meta-analysis showed an interquartile range of 68.5–89.5% for retention (36). NA retention is somewhat lower at this point. This difference cannot be attributed to larger group size as SE also ran larger groups. As more groups are audited further analysis of predictors of dropout such as higher weight or YFAS scores pre-program will be examined. Across all three countries participants independently set up support groups to share information between sessions, but no data were collected related to social support engagement. It appears that the interventions were accessible and acceptable to participants.

The significant improvements in FA symptoms across all three countries on both the mYFAS2 and CRAVED is encouraging, although this can be considered an early time point relative to the goal of evaluating outcomes after 2 years. Caution is required in interpretation of the results due to high

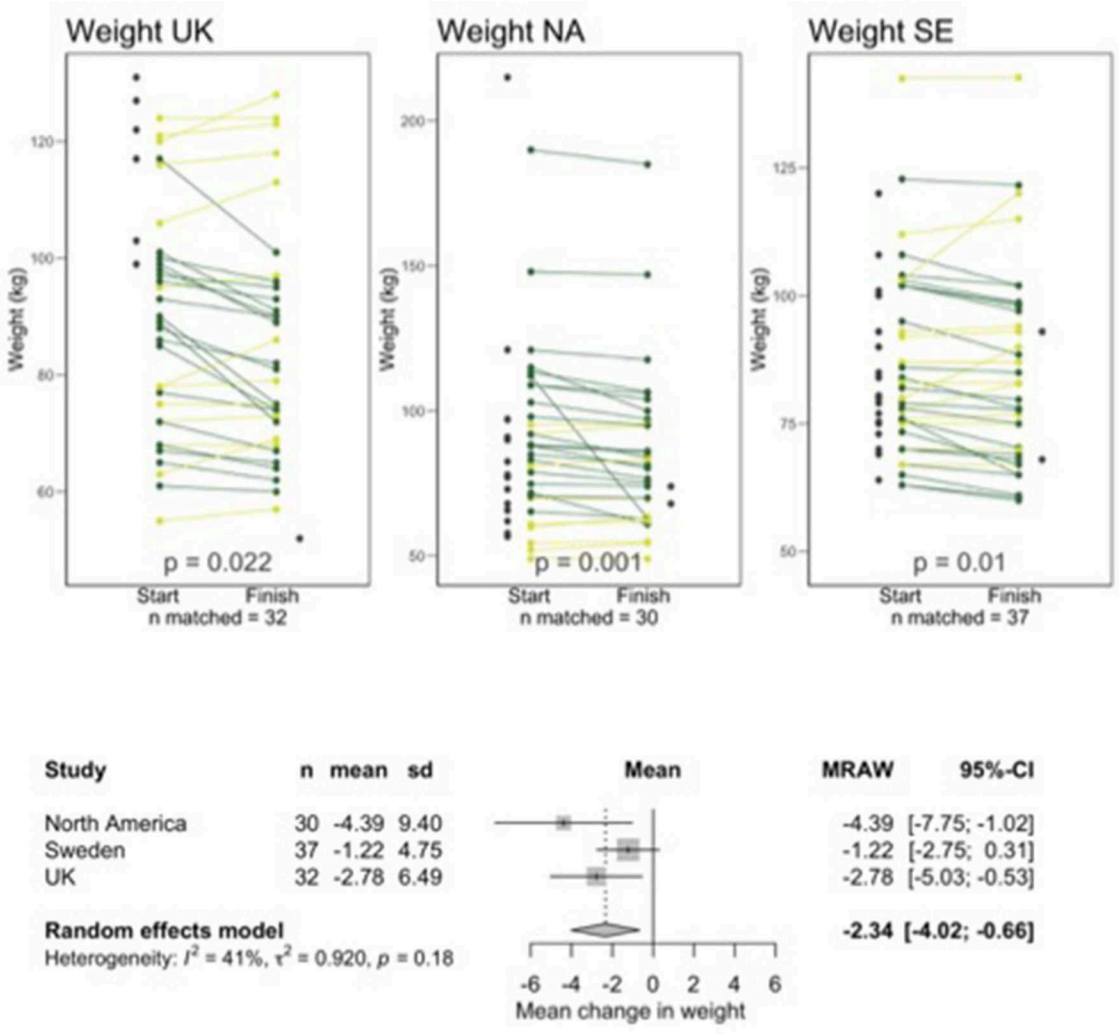


FIGURE 4
Line and forest plots for weight. Dark green indicates improved scores, light green indicates worsening score or no change. Dark gray data points without a line represent people who started but did not finish or who completed a follow up questionnaire but could not be matched with a starting questionnaire.

relapse rates in any addictive disorder (37). Follow-up data will be published in due course. The mYFAS2 asks for symptoms during the last year but only 3 months had elapsed at follow-up, demonstrating that responses are influenced by current symptom experience.

Diets high in refined sugar and carbohydrate have been associated with poorer mental health (22). Gangwisch et al. (38) found that women with higher refined carbohydrates in their diet were more likely to have depression 3 years later. Current participants' mental wellbeing was lower than the reported UK norms for the SWEMWBS prior to the intervention (mean 23.5, SD 3.9) (26). However, post-intervention scores were similar to population norms. Improved wellbeing has a range of known beneficial effects on health and quality of life (39). Again, caution is required in interpreting these audit results and it will prove meaningful to ascertain whether these improvements are maintained at longer-term follow-up.

Weight loss is not always a key outcome of FA treatment because 11.4% of people with FA are of normal weight or underweight (40). Another study found 5.5% of normal weight and 15% of underweight people have food addiction (41). However, people often pursue treatment in the hope of achieving this goal, which is one reason that many ED professionals criticize this field (7). Weight loss was significant across the study sites at this stage of follow-up despite it not being a focus of the programs.

Individual variation in results from interventions is often lost in large data sets. The line plots in Figure 1 through Figure 4 show each participant's data which allow us to see the heterogeneity in responses. We hope to qualitatively explore factors contributing to variations in outcomes.

This audit has some limitations. There is no control arm to compare participants not receiving the intervention. Participants not completing the program and follow-up data may have had poorer outcomes than those completing the sessions (attrition bias). When more data are collected, it will be possible to qualitatively examine factors predicting drop out or poor results. Furthermore, the intensive contact with the clinicians and fellow participants can be therapeutic regardless of the nutrition intervention. The study did not include screening for eating disorders. It is known that FA and eating disorders often co-occur (15, 18, 20). It is possible that some of the variability in outcomes could be explained by taking this into account in future prospective studies.

Conclusion

The current data are the first to demonstrate the short-term clinical effectiveness of a low-carbohydrate "real food" intervention delivered in an online group format with education and social support for individuals with FA symptoms. Larger, controlled and randomized intervention studies are urgently needed to continue to explore ways to help people with this serious and multi-faceted condition which often goes undiagnosed and untreated. It would be extremely useful to compare this approach to more inclusive "all foods fit" approaches among those with co-occurring FA and EDs, particularly BED.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JU produced the first draft of the manuscript. JU, HG, CK, MP, FS, and CS commented on the manuscript, contributed equally to the protocols, clinical program, and data collection. CD analyzed the data sets, produced the statistics, and commented on the manuscript. DW was advisor to the project and contributed to and commented on the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Authors HG, CK, MP, FS, CS, and DW have fee paying clients with food addiction. Author DW was employed at Nutrition in Recovery LLC.

The remaining 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1005523/full#supplementary-material

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Associations between adherence to the Taiwan Daily Food Guide and psychiatric morbidity: A population-based study in Taiwan

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Background: Mental health has become a public health concern worldwide, and the number of affected individuals is rising. Therefore, further research must be conducted to identify potential risk factors to develop optimal prevention strategies to mitigate mental health disorders.

Methods: Using Taiwanese Nutrition and Health Survey data collected from 2013–2016, we conducted a cross-sectional study to examine whether adherence to the Taiwan Daily Food Guide affects mental health conditions. Study participants were adults aged ≥19 years. The dietary assessment was conducted using a validated food frequency questionnaire. The presence of psychiatric morbidity was defined as a five-item Brief Symptom Rating Scale (BSRS-5) score of ≥10. Logistic regression models were used to determine whether Taiwan Daily Food Guide adherence was related to the presence of psychiatric morbidity.

Results: After adjusting for potential confounders, we observed protective associations between adherence to the Taiwan Daily Food Guide and psychiatric morbidity risk.

Conclusion: The Taiwan Daily Food Guide might reduce the risk associated with psychiatric morbidity and could be a reference for developing a national food guide for mental health.

KEYWORDS

mental health, psychiatric morbidity, psychiatric disorders, dietary guidelines, Daily Food Guide

Introduction

Mental health has become an increasingly burdensome public health challenge worldwide (1). The number of disability-adjusted life-years (DALYs) owing to mental disorders increased from 80.8 million in 1990 to 125.3 million globally in 2019 (2), remaining within the top ten causes of burden. Therefore, identifying possible risk factors is essential for developing effective prevention strategies against mental health conditions.

Dietary change might be a potential strategy for preventing mental health conditions. It is particularly attractive because it is a modifiable factor that can be controlled at all times. Previous studies revealed that certain dietary patterns are associated with a reduced risk of mental health conditions. For example, a meta-analysis suggested that a dietary pattern characterized by more frequent consumption of fruits and vegetables, whole grains, fish, olive oil, low-fat dairy, and antioxidants; and less frequent intake of animal foods was associated with reduced risk of depression. In contrast, frequent consumption of red and/or processed meat, refined grains, sweets, high-fat dairy products, butter, potatoes, and high-fat gravy; and less frequent intake of fruits and vegetables are associated with an elevated risk of depression (3). Some studies on Asian populations have revealed dietary patterns that are likely beneficial for mental health. For example, a cross-sectional study conducted in China revealed that after adjusting for age, gender, maternal and paternal education, family income, body mass index (BMI), and physical activity, consuming large amounts of snacks and animal foods increases the risk of mental disorders (4). Another cross-sectional study conducted in Japan showed that after adjusting for age, sex, workplace, marital status, BMI, job position, occupational physical activity, current smoking, non-job physical activity, history of hypertension and diabetes mellitus, and total energy intake, a dietary pattern characterized by more frequent consumption of vegetables and fruits, mushrooms, and soy products reduces the risk of depressive symptoms (5). Similarly, a case-control study among Korean adolescent girls indicated that after adjusting for menstrual regularity and energy intake, depression was significantly negatively associated with green vegetable and fruit intake. In contrast, depression was positively associated with the consumption of instant and processed foods (6). In summary, dietary patterns characterized by plant-based foods may benefit mental health.

Although certain dietary patterns might reduce the risk of mental conditions, governments and policymakers rarely state that a specific dietary pattern should be adopted. A general dietary guideline or daily food guide is usually adopted, such as those constructed by the US Department of Health and Human Services (DHHS), the US Department of Agriculture (USDA), and the World Health Organization (7, 8). This remains true in Taiwan. Although some Taiwanese studies have identified specific dietary patterns that affect health (9–11), it remains unclear whether Taiwan's daily food guide prevents disease. Further, the inclusion of particular recommendations may prevent some diseases but not others (12). In fact, some have argued that a dietary guideline may be more harmful than beneficial (13, 14). Therefore, instead of identifying a dietary pattern related to mental health, we aimed to examine whether adherence to the Taiwan Daily Food Guide reduced the risk of mental health conditions.

Materials and methods

The Nutrition and Health Survey in Taiwan (NAHSIT) 2013–2016 is a nationwide representative survey aimed at assessing the nutritional status of the general Taiwanese population. Survey methods employed have been described elsewhere (9, 15, 16). Briefly, study participants were selected *via* the application of three-stage probability sampling covering 359 townships or city districts. Throughout the first stage, the probability proportional to size sampling method was utilized to select eight primary sampling units (townships and city districts) and 160 townships or city districts. In the second stage, households were randomly selected to construct sampling clusters within each selected primary sampling unit. Finally, door-to-door visits were conducted by trained interviewers until the required number of sex and age groups were reached. Because seasonal variations may affect dietary consumption, the NAHSIT used a Latin square design to ensure that data collection times were spaced evenly throughout all four seasons. All participants were invited to a temporary health examination station and underwent a physical examination.

Study participants of NAHSIT 2013–2016 were contacted by door-to-door visits. In the NAHSIT survey, 11,072 participants aged 2 months and above were included. The response rate for the household visit was 77.2% in 2016. The present study restricted participants to adults aged ≥19 years (n = 5,770, 52.1%), a designation in accordance with the definition of an adult in the newest version of the Taiwan Daily Food Guide. Among them, 2,534 participants (43.9%) who had undergone physical examination and had complete demographic and dietary data were included in the final analysis. Demographic and lifestyle data, including age, sex, education, marital status, smoking status, alcohol intake, exercise, and self-reported medical history, were obtained *via* face-to-face interviews. The study protocol was approved by the China Medical University and Hospital Research Ethics Center (CRREC-108-136). The need for informed consent was confirmed by the research ethics center.

Psychiatric morbidity

A self-administered questionnaire (five-item Brief Symptom Rating Scale, BSRS-5) was used to determine the prevalence of psychiatric morbidity. The BSRS-5 is a five-item Likert scale that assesses the following: 1) difficulty falling asleep (insomnia), 2) feeling low in mood (depression), 3) feeling tense or keyed up (anxiety), 4) feeling easily annoyed or irritated (hostility), and 5) feeling inferior to others (inferiority) (17). Scores given for each item ranged from 0 to 4. According to a guideline in Taiwan, BSRS-5 scores were categorized as "mild" psychiatric morbidity with a score of 6–9, "moderate" with a score of 10–14, and "severe" with a score more than 15 (17, 18). The optimal

cut-off values were suggested in a validation study (19). Studies have indicated that the BSRS-5 is a high-quality assessment tool that may be used to detect psychiatric morbidity and suicidal ideation in both community and medical settings (20, 21). In the current study, the presence of psychiatric morbidity was defined as a BSRS-5 score $\geq$ 10, which indicates moderate to severe psychiatric morbidity that may require psychiatric counseling (22, 23).

Measurement of adherence to the Daily Food Guide

The Department of Health in Taiwan (now the Ministry of Health and Welfare in Taiwan) established the first edition of the Daily Food Guide in 1984 (24). The Ministry of Health and Welfare in Taiwan released the most recently updated edition of the Daily Food Guide in 2018, which included changes aimed at preventing nutrient deficiencies. The Taiwanese Daily Food Guide was constructed not only based on epidemiologic evidence but also to reduce the risk of chronic diseases. Guidelines recommend minimal servings for the following six food groups based on individual daily energy needs (15): 1) cereals and whole grains; 2) protein-rich foods (soybean, fish, egg, and meat); 3) dairy products; 4) vegetables; 5) fruits, and 6) fats, oils, and nuts. Face-to-face dietary interviews were performed by trained interviewers using a 79-item food-frequency questionnaire (FFQ). The FFQ was then divided into 23 food groups based on nutritional content and characteristics (25, 26). A similar simplified FFQ was validated by comparing it with data obtained by 24-h dietary recalls and nutritional biomarkers (10, 27) and showed good correlation coefficients.

Participant adherence levels to the Daily Food Guide were determined by a previously constructed Daily Food Guide index (15). Supplementary Table S1 shows the Taiwan Daily Food Guide (28), which was translated by the author. We calculated a single score for each study participant, which allowed us to rank their adherence levels to the Daily Food Guide (28). Because fat and oil intakes were not adequately assessed using the FFQ, we did not assess levels of adherence to fat and oil intake among study participants. The appropriate quantity of each food group that the participants should consume was determined by their estimated energy needs. Energy needs were estimated based on level of physical activity, resting metabolic rate, and healthy weight (28, 29). The score that a person received in any food category was determined by their consumption of an appropriate number of servings based on their daily energy needs (Supplementary Table S1). For example, a person who consumed the recommended number of servings from any food group received a score of 1 for that particular food group category. In contrast, a person who consumed no servings of a specific food group received a score of 0. Each score was calculated based on the proportion of recommended servings consumed (15).

Statistical analysis

Only participants with complete data were included in the final analysis. The participants were divided into five groups according to their Daily Food Guide index scores. If participants received a total score >6, they were placed in group 5, indicating that they had consumed more than the total number of recommended servings. The remaining participants who received scores $\leq$6 were then divided into four groups by the quartile of the Daily Food Guide index scores. The association between demographic characteristics and the prevalence of psychiatric morbidity was evaluated using chi-square or Fisher's exact tests (categorical variables). Potential confounding factors were selected based on prior knowledge and their relationship with exposures (adherence levels) and outcomes (the presence of psychiatric morbidity) (30). All the models were adjusted for age, sex, BMI, education level, alcohol intake, smoking status, marital status, family income, and physical activity.

A logistic regression model was applied to examine whether the Daily Food Guide index score was associated with the presence of psychiatric morbidity (present vs. not present). A p-value < 0.05 was considered statistically significant. All analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Results

A total of 2,534 participants with no missing data were included in the final analysis. Among them, 402 (15.9%) reported psychiatric morbidities. A comparison of the demographic characteristics of the two groups is listed in Table 1. Compared with those without psychiatric morbidity, participants who reported psychiatric morbidity were more likely to be women than men (60.95 vs. 49.62%, respectively), younger vs. older than 30 (22.39 vs. 12.34%, respectively), have a BMI value of <24 than $\geq$24 (56.47 vs. 50.00%, respectively), be married or live together than single (22.89 vs. 15.43%, respectively), and have median to high physical activity than low activity levels (67.41 vs. 59.89%, respectively).

Table 2 shows the relationship between the Daily Food Guide adherence score and the risk of psychiatric morbidity. After adjusting for age, sex, BMI, education level, alcohol intake, smoking status, marital status, family income, and physical activity, negative associations were found between Daily Food Guides adherence and psychiatric morbidity. The odds ratio (OR) for participants who were in the highest quartile

TABLE 1 Demographic characteristics of study participants ($n = 2,534$).

Variables	Participants without psychiatric morbidity $n = 2,132$	Participants with psychiatric morbidity $n = 402$	p-value
Sex			
Men	1074 (50.38)	157 (39.05)	<0.0001
Women	1058 (49.62)	245 (60.95)	
Age			
Age ≤ 30	263 (12.34)	90 (22.39)	<0.0001
40 ≥ age > 30	215 (10.08)	64 (15.92)	
50 ≥ age > 40	280 (13.13)	71 (17.66)	
65 ≥ age > 50	714 (33.49)	96 (23.88)	
Age > 65	660 (30.96)	81 (20.15)	
Body mass index (BMI)			
BMI < 24	1066 (50.00)	227 (56.47)	0.04
27 > BMI ≥ 24	558 (26.17)	84 (20.90)	
BMI ≥ 27	508 (23.83)	91 (22.64)	
Education			
Elementary school	1072 (50.28)	199 (49.5)	0.06
Junior high and high school	616 (28.89)	100 (24.88)	
College or above	444 (20.83)	103 (25.62)	
Drink			
No	1002 (47)	185 (46.02)	0.83
Rarely	856 (40.15)	161 (40.05)	
Frequently	274 (12.85)	56 (13.93)	
Smoke			
No	1,500 (70.36)	293 (72.89)	0.59
Ever smoke	313 (14.68)	54 (13.43)	
Current smoke	319 (14.96)	55 (13.68)	
Marital status			
Married or lived together	329 (15.43)	92 (22.89)	<0.001
Single	1486 (69.7)	250 (62.19)	
Divorced, separated, widowed, or refused to answer	317 (14.87)	60 (14.93)	
Family income			
Income < NT $10,000	173 (8.11)	37 (9.2)	0.26
NT $40,000>Income ≥ NT $10,000	449 (21.06)	85 (21.14)	
NT $80,000>Income ≥ NT $40,000	519 (24.34)	109 (27.11)	
Income ≥ NT $80,000	488 (22.89)	96 (23.88)	
Do not know or refuse to answer	503 (23.59)	75 (18.66)	
Physical activity			
Low	855 (40.1)	131 (32.59)	0.02
Median	1224 (57.41)	258 (64.18)	
High	53 (2.48)	13 (3.23)	

NT: The New Taiwan dollars.

TABLE 2 The relationship between the Daily Food Guide adherence score and the risk of psychiatric morbidity.

Variables	$n = 2,534$
Diet score	
Total servings equal to or lower than recommendation	
Group 1	**Reference**
Group 2	1.01 (0.73–1.41)
Group 3	0.77 (0.54–1.09)
Group 4	0.60 (0.41–0.87)
Total servings higher than recommendation	
Group 5	0.44 (0.30–0.63)
Sex	
Women	**Reference**
Men	0.52 (0.39–0.69)
Age	
Age ≤ 30	**Reference**
40 ≥ age > 30	0.77 (0.50–1.19)
50 ≥ age > 40	0.69 (0.44–1.09)
65 ≥ age > 50	0.38 (0.24–0.61)
Age > 65	0.26 (0.15–0.47)
Body mass index (BMI)	
BMI < 24	**Reference**
27 > BMI ≥ 24	0.89 (0.67–1.18)
BMI ≥ 27	0.96 (0.72–1.26)
Education	
College or above	**Reference**
Junior high and high school	1.08 (0.69–1.68)
Elementary school	0.92 (0.68–1.25)
Drink	
Non	**Reference**
Rarely	0.99 (0.77–1.28)
Frequently	1.29 (0.89–1.87)
Smoke	
Non	**Reference**
Ever smoke	1.36 (0.93–1.99)
Current smoke	0.90 (0.62–1.30)
Physical activity	
Low	**Reference**
Median	0.82 (0.60–1.13)
High	0.86 (0.43–1.71)
Marital status	
Married or lived together	**Reference**
Single	0.87 (0.59–1.29)
Divorced, separated, widowed, or refused to answer	1.15 (0.82–1.61)
Family income	
Income < NT $10,000	**Reference**
NT $40,000 > income ≥ NT $10,000	0.78 (0.50–1.22)
NT $80,000 > income ≥ NT $40,000	0.74 (0.46–1.17)
Income ≥ NT $80,000	0.71 (0.44–1.16)
Do not know or refuse to answer	0.54 (0.34–0.85)

NT: The New Taiwan dollars; All logistic models were adjusted for age, sex, BMI, education level, alcohol drinking, smoking status, physical activity, marital status, and family income.

TABLE 3 Relationships between adherence to individual food group index recommendations and the presence of psychiatric morbidity.

Variable	$n = 2,534$
Food group 1 (cereals and whole grains)	
Score < 0.5	**Reference**
0.5 ≤ score ≤ 1	0.56 (0.31–1.02)
Score > 1	0.86 (0.38–1.95)
Food group 2 (protein-rich foods)	
Score < 0.5	**Reference**
0.5 ≤ score ≤ 1	0.80 (0.63–1.02)
Score > 1	1.22 (0.77–1.94)
Food group 3 (dairy products)	
Score < 0.5	**Reference**
0.5 ≤ score ≤ 1	0.83 (0.62–1.10)
Score > 1	1.30 (0.69–2.44)
Food group 4 (vegetables)	
Score < 0.5	**Reference**
0.5 ≤ score ≤ 1	0.69 (0.51–0.95)
Score > 1	0.64 (0.46–0.88)
Food group 5 (fruits)	
Score < 0.5	**Reference**
0.5 ≤ score ≤ 1	0.79 (0.50–1.24)
Score > 1	0.80 (0.56–1.15)
Food group 6 (nuts)	
Score < 0.5	**Reference**
0.5 ≤ score ≤ 1	1.15 (0.71–1.84)
Score > 1	0.74 (0.49–1.11)

Score = 1 means that the participants consume recommended servings of the food group; score = 0.5 means that the participants consume half of recommended servings of the food group. All logistic models were adjusted for age, sex, BMI, education level, alcohol drinking, smoking status, physical activity, marital status, and family income.

for recommended total serving consumption was 0.60 [95% confidence interval (CI): 0.41–0.87] compared with those in the lowest quartile. Participants consuming a higher number of total servings than recommended were at reduced risk of psychiatric morbidity (OR: 0.44, 95% CI: 0.30–0.63). In addition, men (OR: 0.52, 95% CI: 0.39–0.69) aged 50–65 years (OR: 0.38, 95% CI: 0.24–0.61) or more than 65 years (OR: 0.26, 95% CI: 0.15–0.47), and those who did not know or refused to report their family income (OR: 0.54, 95% CI: 0.34–0.85) were at reduced risk of psychiatric morbidity.

Relationships between adherence to individual food group index recommendations and the presence of psychiatric morbidity are shown in Table 3. After adjusting for potential confounding factors, a negative association was found between adherence to food group 4 index recommendation (vegetables) and risk of psychiatric morbidity. ORs for participants with score between 0.5–1 and >1 were 0.69 (95% CI: 0.51–0.95) and 0.64 (95% CI: 0.46–0.88), respectively.

We tested whether the association between adherence levels and the risk of psychiatric morbidity was modified by age, BMI, and smoking status by introducing cross-product terms to the models. When there was a suggestive interaction effect (p-value < 0.10), stratified analysis was further conducted. However, we found no evidence that age, smoking, or BMI modified the relation between adherence levels and the risk of psychiatric morbidity.

Discussion

In this study, we observed that participants who reported good adherence to the Daily Food Guide were at reduced risk of psychiatric morbidity. A protective effect remained in participants who consumed more than recommended. This protective effect may be mainly due to increased levels of vegetable consumption. Consumption of cereals, whole grains, and fruits was also associated with reduced psychiatric morbidity risk; however, the findings were not statistically significant. In addition, men and older participants are likely at reduced risk of psychiatric morbidity. Although it is not clear why some participants have lower adherence levels, a study in Taiwan has suggested that people who were males, younger, less educated, divorced, separated or widowed, and had lower family income was associated with a lower adherence level to the Daily Food Guide (15). We suggest that health educators could develop educational programs focusing on different demographic groups to improve adherence levels. Future qualitative studies were recommended to better understand reasons for non-adherent behavior.

The findings of the present study are in line with those of previous studies that revealed that vegetable intake reduces the risk of mental health conditions, including depression and anxiety (3, 4, 31). Several studies have also suggested that the adoption of a Dietary Approach to Stop Hypertension (DASH) diet, which is characterized by high vegetable, fruit, and low-fat dairy product, and low saturated fat, total fat, and cholesterol recommendations, is protective of mental health (32–36). Observed associations are likely explained by the following: 1) increased consumption of vegetables that contain high levels of antioxidants might protect against depression. Previous studies have indicated that a reduced level of oxidative stress reduces the risk of neuronal damage in the hippocampus, consequently reducing the risk of developing depression (37, 38); or 2) mental health status might affect food preference. We could not determine which explanation is accurate owing to its cross-sectional study design. We also found a protective effect between adherence to food group 5 index recommendation (fruits) and risk of psychiatric morbidity. However, the effect was not significant. The reason underlying this finding might be that most fruits contain sugar, and a meta-analysis has shown that less healthy dietary patterns, including higher consumption of the sugar-sweetened beverage, were associated with severe mental illness (39).

This study has several strengths and limitations. A fair sample size allowed us to assess possible associations between adherence to the Daily Food Guide and the risk of psychiatric morbidity. In addition, the population-based design allowed us to generalize the findings to the general population of Taiwan. Psychiatric morbidity was assessed using a valid and effective screening tool. A limitation of this study included its cross-sectional design; therefore, causality could not be established. The associations warrant further prospective investigation to establish causality. Further, the use of a one-time dietary or psychiatric assessment may have introduced non-differential misclassification of exposures and outcomes. Further, the use of a one-time dietary or psychiatric assessment may have introduced non-differential misclassification of exposures and outcomes. For example, some participants might have serious psychiatric symptoms but were not willing to report them. As a result, they were classified into the control group and resulting in a misclassification of outcomes. However, non-differential misclassification usually biases toward the null hypothesis, tending to minimize the associations, which suggests that true effects might have been underestimated in this study.

Conclusions

In summary, adherence to the Taiwan Daily Food Guide may help reduce the risk of psychiatric conditions. The Taiwan Daily Food Guide might reduce the risk associated with psychiatric morbidity and can be a reference for developing a national food guide for mental health. Further prospective cohort studies will be needed to verify these findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary materials, further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the China Medical University and Hospital Research Ethics Center (CRREC-108-136). The patients/participants provided their written informed consent to participate in this study.

Author contributions

M-CL contributed to the conception and design of the study, performed the statistical analysis and organized the database, wrote the first draft of the manuscript, and contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1022892/full#supplementary-material

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Case report: Ketogenic diet acutely improves cognitive function in patient with Down syndrome and Alzheimer's disease

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Ketogenic diets have a century-long history as a therapeutic tool to treat intractable epilepsy. Recently, a renewed interest in neuroketotherapeutics has arisen, with ketogenic diets being explored for the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, as well as mental health conditions. Herein, we present a case report of a 47-year-old woman with Down syndrome diagnosed with Alzheimer's disease and absence seizures with accelerated cognitive decline over 6 years. A ketogenic diet restored her cognitive function over 6 weeks, with an increase in Activities of Daily Living Scale score from 34 to 58. A therapeutic ketogenic diet was associated with significant cognitive improvement in this patient with concurrent Down syndrome and dementia.

KEYWORDS

ketogenic, ketone, Down syndrome, Alzheimer's disease, cognition, episodic memory, executive function, mild cognitive impairment

Introduction

Alzheimer's disease (AD) occurs more commonly and at a younger age in people with Down syndrome. Furthermore, Down syndrome has a higher burden and density of senile plaques and neurofibrillary tangles (NFT) at a younger age. A child born today with Down syndrome has a life expectancy beyond the age of 60 (1), yet, the onset of AD presents much earlier, with a prevalence of 55% in the fifth decade and 77% in the seventh decade (2), compared to 8% of the 74.6 million US people in their seventh decade living with AD (3).

In 1948, Jervis described three patients with Down syndrome whose symptoms of dementia and neuropathological findings were similar to Alois Alzheimer's description

in euploid individuals with dementia (4). Since that case series, an extensive association between Down syndrome and AD shows early and numerous senile plaques, NFT, and neuronal loss within the hippocampus and amygdala (5).

The association of type 2 diabetes and Alzheimer's disease is well established. The accumulation of amyloid occurs not only in the brain, but also in the pancreas, and may play a role in diabetes itself (6). One study found that 81% of cases of Alzheimer's disease had type 2 diabetes or impairment in fasting glucose (7). Impaired utilization of the brain's glucose (8) and concomitant insulin signaling (9) within the brain may contribute to the etiology of AD. A randomized controlled trial in patients with AD showed that a ketogenic diet improved daily function and quality of life (10). Ketone bodies made in the liver freely cross the blood-brain barrier and are utilized to produce ATP by neurons and glial cells (11). Other evidence shows that providing the AD brain with sufficient ketone bodies—even from an exogenous source—may ameliorate the energy deficit (12, 13). Increased plasma ketone levels increase the brain's net energy uptake as defined by the combined energy uptake from ketones and glucose. When supplementing ketones, one study found no changes in total glucose uptake, suggesting that energy utilization from glucose remained constant, but uptake of ketones provided additional fuel for energy metabolism (14, 15). Other studies have found that supplemental ketones may result in improvement of cognition (16, 17).

Mechanisms of action to explain how and why ketosis results in improved cognitive function include the rescue of glucose hypometabolism, mitigation of neurotransmitter imbalances, reduction in oxidative stress, and reduced inflammation (18).

Case description

We present the case of a 47-year-old woman with Down syndrome diagnosed with AD 4 years prior to writing this report. We will refer to her as Mary. Before the onset of dementia symptoms, Mary's Down syndrome limited her ability to live independently or maintain employment. In 2014, Mary's body mass index (BMI) classified her as obese at 46.7 kg/m^2. She participated in many activities on the family hobby farm, including caring for the horses and dogs. One activity included going to the barn, removing the horses from their stalls, cleaning the stalls, and restoring the animals and tools to their proper places. She had substantial autonomy and could be unsupervised for up to 5 h without concern. She was able to perform basic activities of daily living, including choosing her clothes, showering without assistance, toileting without assistance, and completing household chores. Her communication skills never used words with three syllables but delivered her messages. Mary's weight prompted her family to support her commencing a "paleo" diet, which they described as only whole-food diet with <100 g total carbohydrates per day. Mary's mother, her primary caregiver, prepared her meals and measured carbohydrate intake using Cronometer, an app for tracking carbohydrates, protein, fat, and kilocalories.

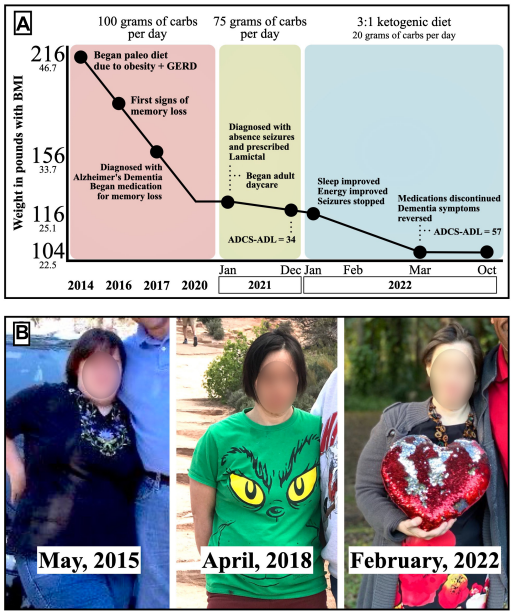

FIGURE 1
(A) Timeline of Mary's dietary patterns, weight loss, clinical symptoms, and ADCS-ADL scores. **(B)** Photos of Mary during the different dietary patterns.

In 2016, at age 41, Mary began exhibiting memory loss. She grew confused when she left the house and could not navigate back home. Her memory loss was associated with symptoms of fear and anxiety, and disruptive obsessive-compulsive behaviors. Her clothing pattern became restrictive, and her once widely varied wardrobe became reduced to one outfit worn over and over. She became paranoid about the water coming from the shower head and refused to shower. Because of her change in behavior, fear, and anxiety, she became largely housebound. Mary struggled with fatigue, took extended naps once or twice daily, and could no longer safely be left alone for extended periods (**Figure 1**).

In 2018, Mary's primary care physician referred her to a Memory Care Specialty center. Reversible causes of dementia were ruled out with normal thyroid studies, vitamin B12, and vitamin 25-OH D3. Her HbA1c measured 4.8% and ruled out untreated diabetes. Treatment began with daily paroxetine 20 mg, memantine 28 mg, and, as needed, alprazolam 0.5 mg.

Through adherence to a paleo diet with carb restriction to <100 g total per day between 2014 and 2020, Mary maintained a 90-pound weight loss, with BMI 27.2 kg/m^2. Despite her weight loss and medications, Mary continued to decline cognitively. She developed staring spells with lapses in awareness. These led to jerking movements of the hands and arms and the sudden loss of bladder control. She was diagnosed

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TABLE 1 ADCS–Activities of Daily Living Inventory and resources needed to care for Mary.

Before ketosis		ADL Previous 4 weeks	After ketosis	
Resources needed	**ADL**		**ADL**	**Resources needed**
Adult day care	2	1. Eating	3	Family support with activities
Complete bathing assistance	3	2. Walking	3	Locked refrigerator
Complete toileting assistance	1	3. Bowel and bladder function at the toilet	2	Nanny cams to monitor sleep
Adult incontinence undergarments	0	4. Bathing	2	Alprazolam once every 2–3 months
Locked cupboards	0	5. Grooming	3	
Locked refrigerator	2	6. (a) "Selecting" clothes; (b) Physically getting dressed.	3	
Locked garbage bins	3		4	
Door alarms	0	7. Telephone usage	0	
Nanny cams to monitor sleep	2	8. Television	3	
Geriatrician specializing in AD	2	9. Conversation	2	
Social worker	2	10. Cleaning dishes from table	3	
Caregiver support group	3	11. Finds personal belongings	3	
Alprazolam 2–3 times per week	1	12. Beverage	2	
	0	13. Meal or snack	0	
	2	14. Dispose of garbage or litter	3	
	2	15. Travel	3	
	1	16. Shopping a) choosing items; b) paying.	2	
	0		0	
	1	17. Appointments or meetings	2	
	0	18. Left alone	3	
	3	19. Talk about current events	3	
	0	20. Reading	0	
	1	21. Writing	1	
	2	22. Pastime, hobby, or game	3	
	1	23. Household appliance	4	
	34	**Total**	**57**	

with absence seizures. Treatment with lamotrigine 150 mg was initiated, and these symptoms decreased in frequency to 6–10 episodes per week.

In January 2021, Mary's carbohydrate intake was lowered to 75 grams daily to normalize weight into the non-overweight range to optimize her physical health. This resulted in another 10-pound weight loss with a BMI of 24.8 kg/m^2. Mary's cognition progressively declined, and her paranoia and social isolation worsened. She required adult day care when her ability to navigate obstacles was compromised. For example, when attempting to hand her mother an item when positioned on the opposite side of a table, Mary failed to navigate around the table without specific instructions. She began to require around-the-clock care when her reasoning skills diminished further, as evidenced by eating raw meat and other spoiled foods out of the trash.

In December 2021, an assessment using the Activities of Daily Living Scale (ADCS-ADL) (19) revealed a score of 34 out of a possible 78, with a lower score indicating greater severity of impairment and a 34/78 classifying her as "severely impaired" (Table 1).

The resources required to care for Mary at this time included the following: adult day care, complete bathing assistance, complete toileting assistance, adult incontinence undergarments, locked cupboards, locked refrigerator, locked garbage bins, door alarms preventing unnoticed entries or exits, nanny cams to monitor sleep, a memory-care team including geriatrician, social worker, and caregiver support group. Alprazolam was needed several times per week to help with anxiety. Mary's ADCS-ADL scores and the list of care resources before and after implementing a ketogenic diet are referenced in the Table 1.

In January 2022, Mary's mother began a ketogenic diet for her own health purposes, including self-education through a weekly physician-led ketogenic support group and confirmation of ketosis with daily measurements of serum ketones *via* fingerstick. With the support of Mary's

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TABLE 2 Sample menus with kcal and grams of carbs.

Day 1

	kcal	Grams of carbs
Breakfast: 7:00 a.m.		
2 Eggs Fried	155.0	1
Fried in bacon grease (1 Tbsp)	115.7	0
2 Slices Bacon	74.9	1
0.5 Avocado	182.4	12
Water/Sparkling Water		
Lunch: 12:30 p.m.		
2 Hamburger patties (1/4th pound each)	397.5	0
Fried in bacon grease (1 Tbsp)	115.7	0
5–6 dill pickle chips	3.9	0
1 TBSP Mustard	9.3	1
Water/Sparkling Water		
Snack: 4:00 p.m.		
1 cup Pork Rinds	159.0	0
3 TBSP Avocado Oil Mayonnaise	135.0	1.5
Water/Sparkling Water		
Daily total	1348.4	16.5
Protein:	74.8 g 23% of kcal	
Carbs:	16.5 g 4% of kcal	
Fat:	105.8 g 73% of kcal	

Day 2

	kcal	Grams of carbs
Breakfast: 7:00 a.m.		
2 Eggs Scrambled	155.0	1
Fried in bacon grease (1 Tbsp)	115.7	0
2 Tbsp Avocado Oil Mayonnaise	90.0	1
2 Sausage Patties	227.5	1
Water/Sparkling Water		
Lunch: 12:30 p.m.		
1 4 oz. can King Oscar Mackerel in Olive Oil	333.0	0
1 cup Cauliflower Mash	28.5	17
with Butter (1 Tbsp)	203.5	0
0.25 cup Raspberries	16.0	4
Water/Sparkling Water		
Snack: 4:00 p.m.		
1 cup Pork Rinds	159.0	0
3 TBSP Avocado Oil Mayonnaise	135.0	1.5
Water/Sparkling Water		
Daily total	1463.2	25.5
Protein:	65.8 g 21% of kcal	
Carbs:	25.5 g 4% of kcal	
Fat:	121.3 g 75% of kcal	

physicians, Mary's mother began a ketogenic diet for Mary as well in the desperate hopes that nutritional ketosis could benefit her suffering daughter. She had already noted that the restriction of carbohydrates to 75 g was insufficient for Mary to enter ketosis, with serum measurements reading less than or equal to 0.2 mmol/L. Mary's carbohydrate intake was limited to <20 total grams daily, with a subsequent rise in serum ketones to consistently 0.8–3.0 mmol/L, measured morning fasting. Specifically, Mary's diet consisted of 70–80% fat by calories, with sample menus provided in Table 2.

Several remarkable improvements occurred over the following 6 weeks.

First, Mary's seizure activity improved. Within two weeks, she was fully continent and no longer experienced dissociative episodes or displayed any further evidence of seizure activity. Mary's sleep and energy also improved. She awoke unprompted, stopped napping, enjoyed more energy, and her mood improved.

In the third week, Mary surprised her mother when she replied with these words, "Yes. I understand." This three-syllable word, "understand," had never been part of Mary's vocabulary. Her advanced articulation accompanied Mary's participation in conversations requiring short-term memory.

By the end of the fourth week, Mary regained interest in leaving the house, attending social events, and no longer required adult day care. Mary's paranoia about the showerhead abated, and she resumed unsupervised showers. Her obsessive-compulsive symptoms also resolved, and she resumed a varied wardrobe again. Mary's memory, concentration, and executive functions improved enough to resume her caring for the animals. She was able to walk the dog unaccompanied and free of anxiety.

After 6 months of starting a ketogenic diet, Mary's weight stabilized at 104 pounds, resulting in a BMI of 22.5 kg/m^2. Her doctor discontinued all medications, and her ADCS-ADL returned to her baseline score of 58/74. Thus, the diagnosis of presumed AD was removed from her chart.

Discussion

This case represents a dramatic improvement in symptoms of cognitive impairment in a woman with Down syndrome after starting a ketogenic diet. Mary's age of onset and rate of decline in overall function represented a typical presentation of Down syndrome with AD. Her ADCS-ADL decreased from her baseline of 57 to severe impairment of 34 in her fifth decade of life. Her cognition descended for 4 years despite standard medication therapy and weight loss of 100 pounds while on paleo and low-carbohydrate diets (<100 grams total carbs/day). Only when her diet resulted in a persistent state of ketosis

did she experience improvement in cognition and her activities of daily living.

Comparing euploid AD to Down syndrome brains, both show the same neuropathology and expected attrition in memory and overall function. The brain consumes 20–25% of total energy expenditure, of which neurons metabolize 70–80%. An estimated 20% energy deficit may be seen in AD, with increasing deficits of up to 50% as the disease progresses (20). Synaptic losses correlate with glucose hypometabolism and cognitive impairment in AD patients (21).

Weight loss tops the list of modifiable risk factors for dementia (22). Mary's hundred-pound weight loss using a low-carb diet failed to prevent her cognitive deterioration and ability to function. Her weight loss occurred over 6 years and coincided with the progressive symptoms of dementia. When Mary's carbohydrate restriction dropped to <20 g, her serum ketones increased to the 0.8–3.0 mmol/L range; thus providing an alternative source of fuel to her brain and possibly improving her brain energy metabolism. Additionally, ketone bodies have direct cell-signaling properties, acting on cell-surface G-protein couple receptors through signal transduction pathways, modifying epigenetics by acting as histone deacetylase inhibitors, and serving as substrate for direct post-translational modifications of intracellular proteins and enzymes (23, 24).

Some of the strengths associated with this case study include Mary's closely observed cognitive and health history prior to persistent ketosis. Multiple clinical visits thoroughly charted her baseline cognition, behavior, and mood, along with their decline and rise. Mary's meals were prepared and meticulously tracked by a reliable caregiver (her mother) and blood ketones were measured to confirm dietary adherence.

One likely criticism is that Mary's clinical improvement with the ketogenic diet may have been due to the resolution of seizures, as opposed to improvement in the pathology of AD itself. It is well-established that the ketogenic diet can be an effective treatment for seizures. Nonetheless, AD is often associated with the development of new-onset seizures, so these two diagnoses may not be distinct and inseparable.

Conclusion

In this case of a patient with Down syndrome and Alzheimer's disease, the patient and her family exhausted standard treatment options for 4 years while her cognitive and functional capacity continued to decline. Transition to a ketogenic diet of <20 g carbs per day improved her cognitive scores to baseline function, in association with improvements in behavioral and mood symptoms. Further research is warranted on the therapeutic use of ketogenic diets for Alzheimer's disease, including in patients with Down syndrome.

Patient perspective

Mary's mother wrote, "My daughter and I started the ketogenic diet to improve our health. It took some time for me to decide to go all the way to 20 total carbs or less with her because she loves food so much. I wondered if she would adjust to such a diet. Adding the ketone fingerstick tester was huge in helping us to know if we were achieving nutritional ketosis. Mary has adjusted to the new way of eating quite well. She loves the food we eat and so does our family. It takes supervision and the support of the family but it is very sustainable for us. Others in our family have had improved health outcomes as they adopted the diet after seeing the changes in our health and Mary's quality of life. We plan to eat this way for the rest of our lives."

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AB conducted participant interviews, reviewed the medical records, gathered, synthesized, and analyzed the data, and wrote and edited the manuscript. VL wrote the abstract, helped to organized the manuscript, and contributed to the discussion section. CP helped to organized and edit the manuscript. BS designed the graphics and tables. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AB receives royalties for the books *Anyway You Can, ketoCONTINUUM*, and *ketoCONTINUUM Workbook*, and the sales of products from BozMD.com. CP declares receiving royalties for a book, *Brain Energy*.

The remaining 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.

Publisher's note

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Associations between depression and the incident risk of obesity in southwest China: A community population prospective cohort study

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Objective: This study aimed to describe the incidence of obesity and investigate associations between depression and the risk of incident obesity among residents in Southwest China.

Methods: A 10-year prospective cohort study of 4,745 non-obese adults was conducted in Guizhou, southwest China from 2010 to 2020. Depression was assessed by the Patient Health Questionnaire-9 (PHQ-9) while the obesity was identified by waist circumference (WC) and/or body mass index (BMI). Cox proportional hazard models were used to estimate hazard ratios (HR), and 95% confidence intervals (CIs) of depression and incident obesity.

Results: A total of 1,115 incident obesity were identified over an average follow-up of 7.19 years, with an incidence of 32.66 per 1,000 PYs for any obesity, 31.14 per 1,000 PYs and 9.40 per 1,000 PYs for abdominal obesity and general obesity, respectively. After adjustment for potential confounding factors, risks of incident abdominal obesity for subjects with minimal (aHR: 1.22, 95% CI: 1.05, 1.43), and mild or more advanced depression (aHR: 1.27, 95% CI: 1.01, 1.62) were statistically higher than those not depressed, while there was no significant association with incident general obesity. The risks of any incident obesity among subjects with minimal (aHR: 1.21, 95% CI: 1.04, 1.40), mild or more advanced depression (aHR: 1.30, 95% CI: 1.03, 1.64) were significantly higher than those not depressed and positive association was found for PHQ score per SD increase (aHR: 1.07, 95%CI: 1.01, 1.13), too. The association was stronger significantly in Han Chinese (minimal: aHR: 1.27, 95% CI: 1.05, 1.52; mild or more advanced: aHR: 1.70, 95% CI: 1.30, 2.21) and farmers (minimal: aHR: 1.64, 95% CI: 1.35, 2.01; mild or more advanced: aHR: 1.82, 95% CI: 1.32, 2.51).

Conclusion: Depression increased the risk of incident obesity among adults in Southwest China, especially among Han Chinese and farmers. This finding suggests that preventing and controlling depression may benefit the control of incident obesity.

KEYWORDS

depression, obesity, prospective cohort study, community population, Chinese

1. Introduction

Obesity is one of the critical public health challenges worldwide. With socioeconomic growth and lifestyle changes, World Health Organization reported that the global age-standardized prevalence of overweight and obesity was high as 39 and 13% among adults in 2016 (1). As a significant risk factor for multiple chronic diseases such as diabetes, metabolic syndrome, musculoskeletal disorders, and some cancers, obesity caused 4 million deaths and 120 million disability-adjusted life years worldwide in 2015 (2, 3). However, extensive documentation indicated that the distribution of body mass index (BMI) and average waist circumference (WC) have shifted upward (4). Obesity incidence in America had increased more than 3-fold from 5.8 to 14.8% during 1950–2000 (5), while similar trends emerged in numerous low-income and middle-income countries (6). In China, the prevalence of overweight and obesity was 34.3 and 16.4%, which increased by 13.9 and 37.8% from 2012 to 2020 (7).

Overweight and obesity are influenced by socioeconomic status, diet, and environment (2, 8). Mental disorders were also frequently mentioned in recent studies (9). Several epidemiological studies have confirmed the complex mechanism of depression-to-obesity pathways, but the evidence was mixed and varied across regions or races. The role of gender was equivocal in the association between depression and obesity, which varied among Chinese adolescents, middle-aged residents, and American (10–12). Some studies found that non-Latino and white conferred a higher risk of comorbid obesity and mood disorders compared to Latino, African–American, and Asian Socio-cultural factors in different areas may also affect the relationship between obesity and depression (11–13). A meta-analysis found depressed persons had a 58% increased risk of becoming obese (14), while another Dutch study showed that the presence of baseline depressive symptoms was not prospectively associated with the development of obesity (15). Most studies on the association between depression and incident obesity were cross-sectional studies whose findings varied over age in China (10, 12, 13, 16, 17), which could not make the causal association between depression status and obesity.

To our knowledge, prospective cohort studies covering adults to evaluate the risk of incident obesity based on different depressive states have not been reported in China. Based on Guizhou Population Health Cohort (18), this study aimed to explore the association between depression and incident obesity by analyzing the discrepancies in obesity outcomes among people with different depression levels.

2. Materials and methods

2.1. Study design and population

The Guizhou Population Health Cohort Study (GPHCS) was a prospective community-based cohort conducted in Southwest China during 2010–2020 (18). Through the multistage proportional stratified cluster sampling method, 9,280 adult residents from 48 townships of 12 districts in Guizhou Province were recruited from November 2010 to December 2012. The inclusion criteria included: (1) Aged 18 and above; (2) Living in the study area and having no plans to move out; (3) Completing the questionnaire and blood sampling. All participants were subsequently followed up for major chronic diseases and vital status during 2016–2020, with a loss to follow-up rate of 12.04%. We further excluded 1,997 individuals with general and/or abdominal obesity at baseline (with BMI $\geq$ 28 kg/m^2 or having a waist circumference of $\geq$85 cm for women, or $\geq$90 cm for men), 1,245 missing BMI or WC at follow-up, and 176 without sufficient information on depression at baseline. Finally, the remaining 4,745 participants were eligible for the analysis (Figure 1). This study was approved by the Institutional Review Board of Guizhou Province Centre for Disease Control and Prevention (No. s2017-02), and written informed consent was signed by all subjects. All deaths were confirmed through the death registration information system and the essential public health service system.

2.2. Data collection

Baseline information included sociodemographic characteristics (age, gender, ethnicity, education level, residence, marital status, and occupation), lifestyle (tobacco and alcohol consumption, physical activity), and chronic medical history (hypertension, dyslipidemia, diabetes mellitus, and cardiovascular diseases), which was collected by trained investigators through structured questionnaires *via* face-to-face interview.

Physical examination data, including height, weight, waist circumference, and blood pressure, were collected by trained investigators through standard procedures. Standing height was measured to the nearest 0.1 cm without shoes using a portable stadiometer. Weight was measured to the nearest 0.1 kg using a digital weighing scale. WC was measured to the nearest 0.1 cm at the midpoint between the lowest rib margin and the iliac crest. Blood pressure data were taken as the average value of three consecutive measurements. Venous blood samples were obtained in the early morning for fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels after the participants had fasted for at least 8 h.

Above methods for data collection were same as baseline study during the follow-up study.

2.3. Assessments of depression and obesity

The Patient Health Questionnaire-9 (PHQ-9) was used to measure the levels of depression among participants according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV) (19). Subjects needed to answer nine questions which were graded from 0 to 3 and the total score ranged from 0 to 27, in which points = 0 was determined as non-depression, 1–4 points as minimal depression, and $\geq$5 points as mild or more advanced depression (20).

Body mass index (BMI) was calculated as weight in kg divided by height in m squared and general obesity was defined as BMI $\geq$ 28 kg/m^2. Abdominal obesity was defined as a waist circumference of $\geq$85 cm for women and $\geq$90 cm for men (21). Obesity was defined if either of them was met. Overweight was defined based on BMI (24.0–27.9 kg/m^2) or WC (80–85 cm for women and 85–90 cm for men).

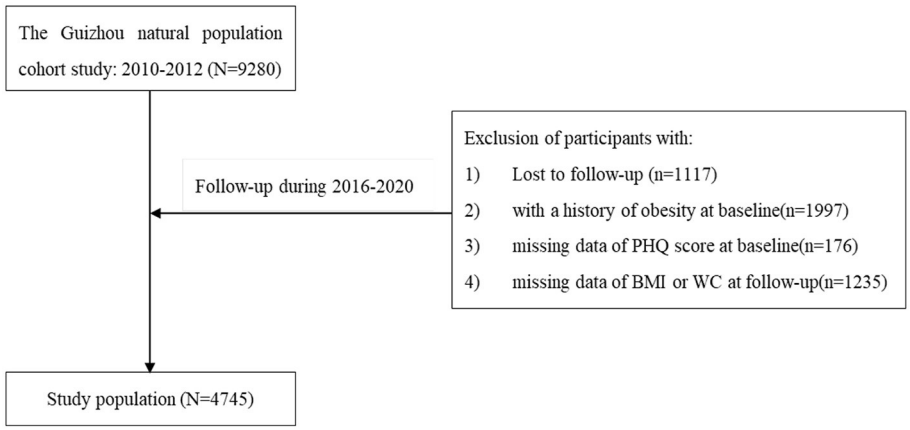

FIGURE 1
The flow chart.

2.4. Covariates

Alcohol consumption was defined as alcohol consumed at least once a month in the past 12 months. Physical activity was at least 150 min of moderate or high-intensity physical activity per week. Dietary habits were divided into two groups (light or greasy) according to whether participants consumed more than 5 g/day of salt or more than 25 g/ day of grease. Hypertension was defined as one of the following conditions: (1) systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg; (2) Self-reported physician diagnosis of hypertension or having received antihypertensive treatment (22). Diabetes mellitus (DM) was defined as one of the following conditions: (1) Fasting blood glucose ≥ 7.0 mmol/l; (2) 2-h postprandial blood glucose ≥ 11.1 mmol/l; (3) Glycosylated hemoglobin ≥ 6.5%; (4) Self-reported physician diabetes diagnosis or receiving hypoglycemic treatment (23). Dyslipidemia was diagnosed as one of the following conditions: (1) Total cholesterol (TC) ≥ 6.22 mmol/l; (2) Triglycerides (TG) ≥ 2.26 mmol/l; (3) High-density lipoprotein cholesterol (HDL-C) < 1.04 mmol/l; (4) Low-density lipoprotein cholesterol (LDL-C) ≥ 4.14 mmol/l; (5) Self-reported physician dyslipidemia diagnosis or having received lipid-lowering treatment (24).

2.5. Statistical analysis

Continuous variables were expressed in means and standard deviations, and categorical variables were as frequencies with proportions. χ^2 test and Kruskal-Wallis test were used to compare the group differences of variables. Person-year of follow-up was calculated from the baseline survey to the date of confirmed death, obesity appears, or completion of follow-up, whichever came first. We fitted four Cox proportional hazards regression models to estimate hazard ratio (HR), the adjusted HR (aHR), and corresponding 95% confidence interval (CI) to determine the association between depression and the risk of obesity. Model 1: without any adjustment for covariates. Model 2: adjusted for age (<30, 30–59.9, ≥60 years) and gender (male or female). Model 3: model 2 added education (10 years and above), occupation (farmer or other), physical activity (yes or no), marriage (unmarried, married, divorced), family relations (Good, general, poor), alcohol use (yes or no), dietary habit (yes or no). Model 4: model 3 added baseline diabetes (yes or no), baseline hypertension (yes or no), and baseline dyslipidemia (yes or no). We tested for interactions between all target and adjustment variables and further performed stratified analysis if significant interactions were observed. Model 4 was repeated after individuals with overweight at baseline were excluded for sensitivity analyses. Schoenfeld residuals were used to test the hazard proportionality assumption in Cox regression models and no violation of proportionality was found. Two-sided $P < 0.05$ was considered statistically significant. All statistical procedures were performed in R software (Version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Among 4,745 adults in this study, 3,510 were not considered depressed, 922 were minimal depression, and 313 were mild or more advanced depression. Details of the baseline characteristics are shown in Table 1. The average age of all participants was 44.09 ± 15.07 years, and nearly half (48.8%) were male. More than half of them were Han Chinese (59.8%), farmers (54.4%), or had received education for ≥9 years (45.1%). Most (80.8%) were married. Differences between the non-depressed and those with different grades of depression were statistically significant ($p < 0.05$) in terms of age, gender, ethnicity, education time, occupation, and family relationship (seen in Table 1).

3.2. Associations between baseline depression and incident obesity

Totally, 4,745 subjects were followed up for 34,138.66 person-years, with an average follow-up of 7.19 ± 1.15 person-years and a maximum of 9.54 person-years. One thousand one hundred fifteen incident obesity were identified with an incidence of 32.66 per 1,000

TABLE 1 General characteristics of Chinese adults without obesity at baseline over depression groups.

Characteristics	Total ($N = 4,745$)	Depression			*P*-value
		No ($N = 3,510$)	Minimal ($N = 922$)	Mild or more advanced ($N = 313$)	
PHQ-9 score	0.88 ± 2.04	0	2.12 ± 1.06	7.12 ± 2.77	<0.001
Age, years	44.09 ± 15.07	43.38 ± 15.04	46.40 ± 15.19	45.20 ± 15.28	<0.001
<30	1,004 (21.2)	796 (22.7)	158 (17.1)	50 (16.0)	
30–59.9	2,995 (63.1)	2,192 (62.5)	588 (63.8)	215 (68.7)	
≥60	746 (15.7)	522 (14.8)	176 (19.1)	48 (15.3)	
Men, %	2,315 (48.8)	1,777 (50.6)	411 (44.6)	127 (40.6)	<0.001
Han Chinese, %	2,839 (59.8)	2,055 (58.5)	584 (63.3)	200 (63.9)	0.010
Education ≥ 9 years, %	2,141 (45.1)	1,654 (47.1)	368 (39.9)	119 (38.0)	<0.001
Farmer, %	2,583 (54.4)	1,999 (57.0)	462 (50.1)	122 (39.0)	<0.001
Alcohol use, %	1,537 (32.4)	1,085 (30.9)	346 (37.5)	106 (33.9)	<0.001
Greasy diet, %*	3,135 (66.3)	2,338 (66.8)	609 (66.3)	188 (60.5)	0.078
Marriage, %					0.023
Unmarried	488 (10.3)	390 (11.1)	69 (7.5)	29 (9.3)	
Married	3,835 (80.8)	2,815 (80.2)	769 (83.4)	251 (80.2)	
Divorced	422 (8.9)	305 (8.7)	84 (9.1)	33 (10.5)	
Physical activity, %*	288 (6.1)	228 (6.5)	45 (4.9)	15 (4.8)	0.114
Family relation, %					<0.001
Good	3,908 (82.4)	3,012 (85.8)	716 (77.7)	180 (57.5)	
General	766 (16.1)	457 (13.0)	189 (20.5)	120 (38.3)	
Poor	71 (1.5)	41 (1.2)	17 (1.8)	13 (4.2)	
Hypertension, %	1,122 (23.6)	806 (23.0)	241 (26.1)	75 (24.0)	0.129
Diabetes, %*	358 (7.6)	258 (7.4)	73 (8.0)	27 (8.7)	0.620
Dyslipidemia, %	2,541 (53.6)	1,848 (52.6)	522 (56.6)	171 (54.6)	0.092
BMI, kg/m^2	22.10 ± 2.44	22.11 ± 2.44	22.10 ± 2.45	21.92 ± 2.39	0.402
WC, cm	74.31 ± 7.13	74.38 ± 7.15	74.26 ± 7.20	73.66 ± 6.68	0.220

*Missing value exists.
PHQ-9, Patient Health Questionnaire-9; BMI, body mass index; WC, waist circumference.

PYs, 1,063 (31.14 per 1,000 PYs) and 321 (9.40 per 1,000 PYs) for abdominal obesity and general obesity, respectively. The incidence of obesity was highest in subjects with mild or more advanced depression (38.01 per 1,000 PYs). As shown in Table 2, both model 1 (univariate cox model) and model 2 (adjusted for age and gender) showed that depression was associated with an increased risk of incident obesity. In the fully adjusted models, the aHR was 1.07 for abdominal obesity with per SD increase of PHQ score. Compared with those not depressed (PHQ score = 0), participants with minimal (aHR: 1.22, 95% CI: 1.05, 1.43) and mild or more advanced depression (aHR: 1.27, 95% CI: 1.01, 1.62) remained at higher risks of incident abdominal obesity. Risks of any incident obesity among subjects with minimal (aHR: 1.21, 95% CI: 1.04, 1.40), mild or more advanced depression (aHR: 1.30, 95% CI: 1.03, 1.64) were also significantly higher than those among not depressed participants (seen in Table 2).

3.3. Stratification analysis

The potential modification effects of age, gender, ethnicity, and occupation on the association of depression with incident obesity were explored in this study (seen in Figure 2). Associations between depression and incident obesity significantly varied over ethnicity and occupation (P for interaction = 0.001 and <0.001, respectively), and risks for incident obesity were statistically higher in Han Chinese or farmers. However, age and gender interactions were not observed.

In the sensitivity analysis, the corresponding effect estimates of baseline depression status on the incident obesity did not change substantially after excluding participants with overweight at baseline (seen in Figure 3).

TABLE 2 Associations between depression at baseline and incident obesity among Chinese adults.

Obesity	PHQ score	Cases, *n*	Incident rate/1,000 PYs	aHR (95% CI)			
				Model 1	Model 2	Model 3	Model 4
Abdominal obesity (WC)	PHQ-score (per SD increase)			1.09 (1.03, 1.15)**	1.06 (1.01, 1.12)*	1.07 (1.01, 1.14)*	1.07 (1.01, 1.14)*
	No (0)	754	29.77	1.00	1.00	1.00	1.00
	Minimal (1-4)	229	34.97	1.29 (1.12, 1.50)***	1.22 (1.05, 1.42)**	1.21 (1.04, 1.41)*	1.22 (1.05, 1.43)**
	Mild or more advanced (≥5)	80	35.36	1.30 (1.03, 1.64)*	1.19 (0.94, 1.50)	1.28 (1.01, 1.63)*	1.27 (1.01, 1.62)*
General obesity (BMI)	PHQ-score (per SD increase)			1.06 (0.95, 1.18)	1.05 (0.94, 1.16)	1.03 (0.93, 1.15)	1.03 (0.93, 1.15)
	No (0)	240	9.48	1.00	1.00	1.00	1.00
	Minimal (1-4)	55	8.40	1.01 (0.75, 1.35)	0.98 (0.73, 1.31)	0.93 (0.69, 1.25)	0.93 (0.69, 1.25)
	Mild or more advanced (≥5)	26	11.49	1.41 (0.94, 2.12)	1.34 (0.89, 2.01)	1.34 (0.87, 2.04)	1.33 (0.87, 2.03)
Obesity (WC or BMI)	PHQ-score (per SD increase)			1.09 (1.03, 1.15)***	1.06 (1.01, 1.12)*	1.07 (1.01, 1.13)*	1.07 (1.01, 1.13)*
	No (0)	792	31.27	1.00	1.00	1.00	1.00
	Minimal (1-4)	237	36.19	1.28 (1.10, 1.48)***	1.21 (1.04, 1.40)*	1.20 (1.03, 1.39)*	1.21 (1.04, 1.40)*
	Mild or more advanced (≥5)	86	38.01	1.34 (1.07, 1.67)*	1.23 (0.98, 1.54)	1.31 (1.04, 1.65)*	1.30 (1.03, 1.64)*

Model 1: Without any adjustment for covariates.
Model 2: Adjusted for age (<30, 30–59.9, ≥60 years), gender.
Model 3: Model 2 plus education, occupation, physical activity, marriage, family relations, alcohol use, dietary habit.
Model 4: Model 3 plus hypertension, diabetes mellitus, dyslipidemia.
*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$.
PHQ-9, Patient Health Questionnaire-9; PY, person years; HR, hazard ratio; BMI, body mass index; WC, waist circumference; 95% CI, 95% confidence interval; SD, standard deviation.

4. Discussion

Based on a prospective cohort study in Southwest China, we found that the incidence rate of incident obesity was high and depression was strongly associated with the risk of incident obesity among this community adult population, especially among Han Chinese and farmers. Our findings indicated that improving depression may help to prevent and control developing obesity.

The incidence rate of abdominal obesity (31.1/1,000 PYs) was higher than general obesity (9.4/1,000 PYs) in this study. Compared with another earlier cohort study whose incidence rate of general obesity was 6.97‰ in China (25), that was lower than our findings and may be driven by economic developments, sociocultural norms and policies with China's rapid urbanization and industrialization (26). Previous studies and WHO data have shown that the prevalence of obesity in many countries doubled and even quadrupled over the last 30 years (1, 27). The critical increase of obesity in China and worldwide called that more vigorous interventions should be implemented for obesity prevention and treatment.

Previous studies have demonstrated a positive association of depression and obesity (10, 28, 29). Apart from that, the limitation of BMI measures has been proven as unable to discriminate between fat percent and lean mass (30), so weight management guidelines in several countries suggested health professionals consider both BMI and WC to diagnose obesity (31). WC has confirmed exist higher accuracy in the measurement of depression-induced obesity compared with BMI due to the accumulation of visceral adipose (29). In this study, aHR of incident abdominal obesity was a 1.07 per SD (2.04 score) increase in PHQ score, which was comparable with that from two cohort studies in Norway and USA (32, 33). Several potential mechanisms on the association between depression and obesity were studied. Apart from the effect on individual perception of weight (34), impaired fat metabolism caused by abnormal secretion of the hypothalamic-pituitary-adrenal axis (32), and intake of antidepressants such as tricyclic and selective serotonin reuptake inhibitors may explain the mechanism of obesity (35, 36). Hyperphagia and hypersomnia have been proved to be critical features of atypical depression (37), which lead to weight gain through increased energy intake and circadian rhythm dysregulation (38). A twin study in Washington demonstrated that shared genetic risk might act upon depression and obesity (39), which also should be considered. However, this study did not observe a significant association between depression and incident general obesity.

Several researches indicated that the association between being obese and depressed mood tended to vary across ethnic groups (40), which suggested that the sociocultural differences or ethnicity moderation effects should be considered (36). The increased risk of incident obesity based on BMI and WC was more significant among Han Chinese and farmers in this study, where such ethnic variations may be explained by genetic background and other factors (40, 41). Miao and Bouyei were the main of the 1,906 minorities accounted for 40.2% in this study and their genetic background had been reported to exhibit significant differences compared with Han Chinese (42). One study conducted in Guizhou province also pointed

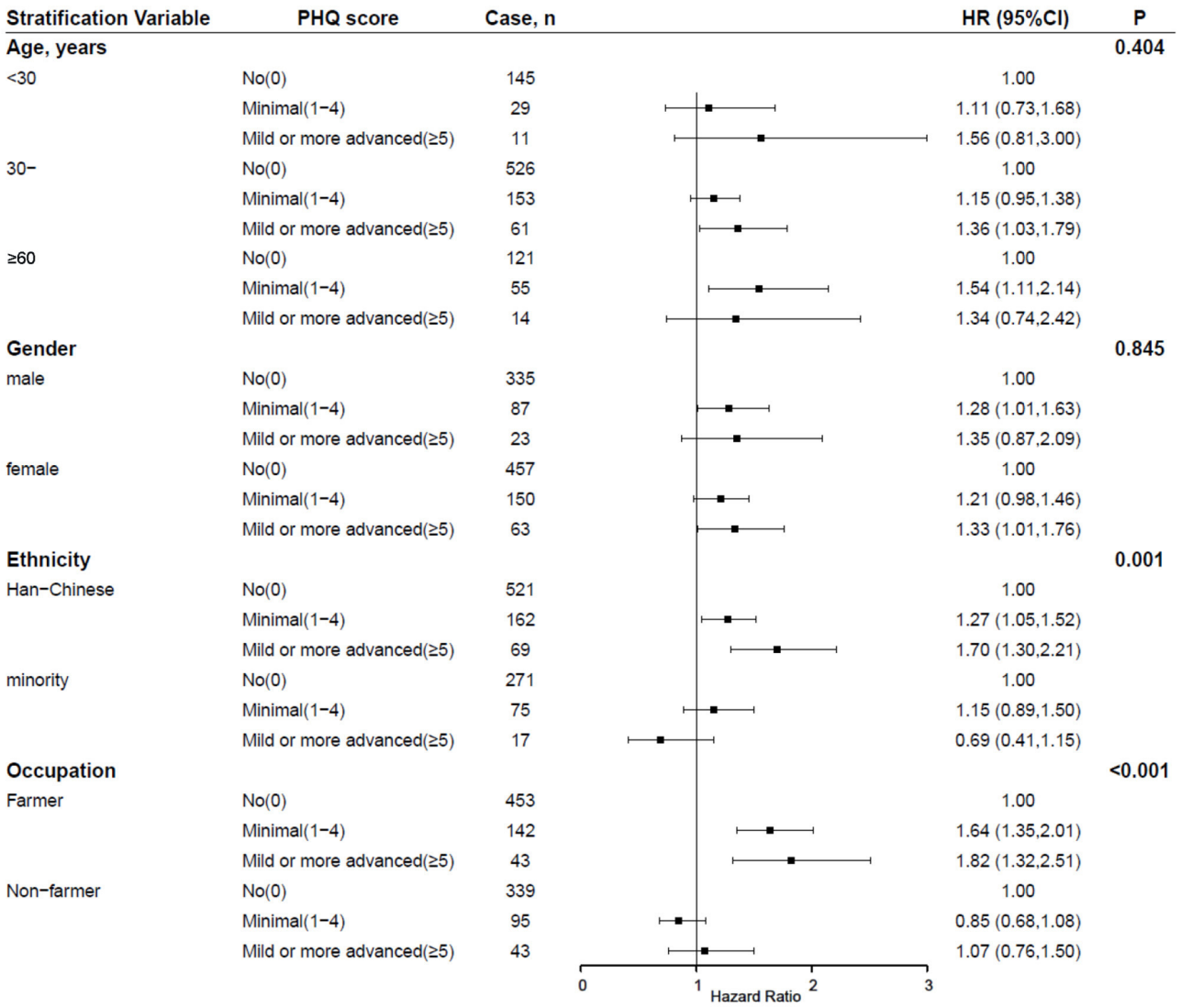

FIGURE 2
Interactions between depression and sociodemographic factors on the incident obesity among Chinese adults. Adjusted for age, gender, education, occupation, physical activity, marriage, family relations, alcohol use, dietary habit, hypertension, diabetes mellitus, and dyslipidemia. PHQ-9, Patient Health Questionnaire-9; aHR, adjusted hazard ratio; 95% CI, 95% confidence interval.

that Bouyei people had a lower prevalence of general (4.8 vs. 10.9%) and abdominal obesity (13.6 vs. 26.8%) compared with Han Chinese (43), which was similar to this study. The more significant association among farmers may be related to the low awareness of obesity and depression, and inadequate access to depression-related healthcare services while other occupational groups could be improved by timely management of depression-related symptoms (44). A French study showed that the prevalence of depression combined with obesity was higher in rural areas (45).

The presence of effect modification by gender has been reported for the association between depression and obesity, which was not observed in this study. A cohort study in Houston showed that depressed males had a 6-fold increased risk of obesity while another meta-analysis demonstrated that the association was more pronounced in adolescent females (28, 46). Accumulating evidence tends to hold a stronger correlation between depression and obesity among females (11). The divergences of psychological characteristics, interpersonal barriers, and physical predispositions might explain the association among females (39, 47, 48). Physiological studies indicated that the difference was a consequence of the combined action of stronger immune responses and more inflammatory markers caused by the increment of estrogen (49). Intense mood swings and emotional eating also act as mediators between depression and future weight gain, which were more common among the female (11, 48). However, no gender interaction was observed in this study.

To our knowledge, this was the first study to investigate the association between depression and incident obesity among the Chinese community population in southwest China. Strengths of this study were the prospective cohort design with the 10-year follow-up period and the relatively low loss to follow-up rate. Also, we explored the effects of depression on the risk of incident obesity with anthropometric indices through standardized measurements rather than self-report. Of course, this study had some notable limitations. First, baseline depression was assessed by the PHQ-9

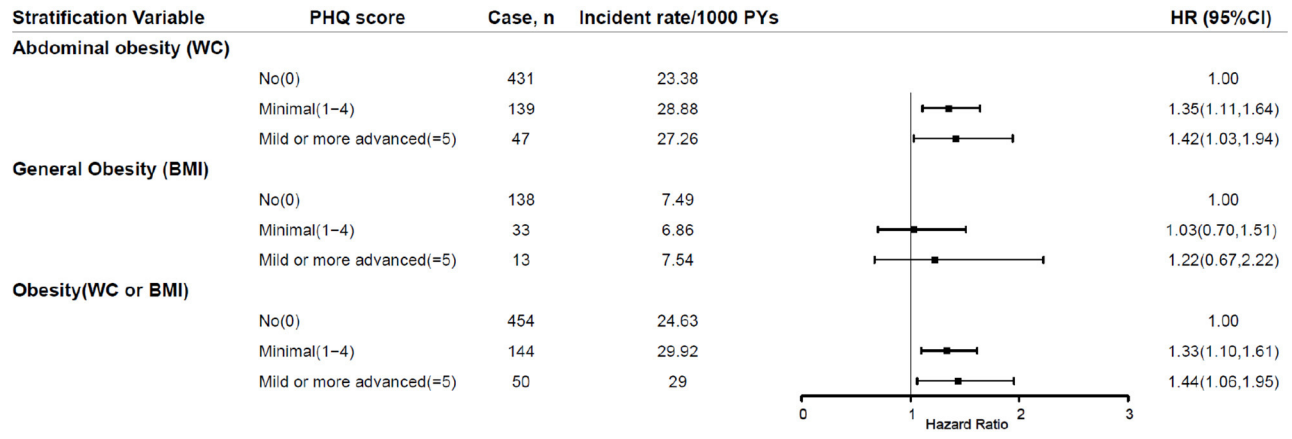

FIGURE 3
Sensitivity analyses after exclusion of individuals with overweight at baseline. PHQ-9, Patient Health Questionnaire-9; PY, person years; HR, hazard ratio; BMI, body mass index; WC, waist circumference; 95% CI, 95% confidence interval.

scale without clinical diagnoses. Second, data on depression status and antidepressant use were not collected during the follow-up survey, both of which may bias the findings of this study. Third, some possible confounding factors such as the family history, genetic variants of obesity and energy intake were not collected and controlled well in this study, which should be considered in future studies. Our findings in this southwest Chinese population need to be confirmed by more prospective or intervention studies over different populations. Further studies on clinically diagnosed depression and repeated measures of depression are required to confirm the complex bidirectional association between depression and obesity among Chinese population.

5. Conclusions

In conclusion, the long-term prospective study demonstrated that there were high risks in the incident obesity among the Chinese community population in southwest China, and both minimal and mild or more advanced depression increased the risk of developing obesity, especially in Han Chinese and farmers. Our findings further suggest that improving healthcare for depression may benefit to prevent and control the developing obesity, especially for abdominal obesity, in the community settings. Government departments and medical institutions, especially community health service centers should pay more attention to farmers' mental health issues, and developing appropriate community-based depression intervention services to improve their obesity control.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of (or Ethics Committee) Guizhou Province Centre for Disease Control and Prevention (No. S2017-02). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TL and BW: conceptualization, methodology, formal analysis, validation, writing—original draft, and visualization. YC: methodology, data curation, writing—review, and editing. YY and JZ: conceptualization, methodology, supervision, funding acquisition, writing—review, and editing. NW and KX: conceptualization, methodology, data curation, writing—review, and editing. CF: conceptualization, methodology, supervision, resources, writing—review, and editing. All authors contributed to manuscript revision, read, and approved the submitted version.

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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.

Publisher's note

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Association of metabolic syndrome with depression in US adults: A nationwide cross-sectional study using propensity score-based analysis

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Background: The association of metabolic syndrome (MetS) with depression has been previously reported; however, the results are ambiguous due to imbalanced confounding factors. Propensity score-based analysis is of great significance to minimize the impact of confounders in observational studies. Thus, the current study aimed to clarify the influence of MetS on depression incidence in the U.S. adult population by using propensity score (PS)-based analysis.

Methods: Data from 11,956 adults aged 20–85 years from the National Health and Nutrition Examination Survey (NHANES) database between 2005 and 2018 were utilized. Using 1:1 PS matching (PSM), the present cross-sectional study included 4,194 participants with and without MetS. A multivariate logistic regression model and three PS-based methods were applied to assess the actual association between MetS and depression incidence. Stratified analyses and interactions were performed based on age, sex, race, and components of MetS.

Results: After PSM, the risk of developing depression in patients with MetS increased by 40% in the PS-adjusted model (OR = 1.40, 95% confidence interval [CI]: 1.202–1.619, $P < 0.001$), and we could still observe a positive association in the fully adjusted model (OR = 1.37, 95% CI: 1.172–1.596, $P < 0.001$). Regarding the count of MetS components, having four and five conditions significantly elevated the risk of depression both in the PS-adjusted model (OR = 1.78, 95% CI: 1.341–2.016, $P < 0.001$ vs. OR = 2.11, 95% CI: 1.626–2.699, $P < 0.001$) and in the fully adjusted model (OR = 1.56, 95 CI%: 1.264–1.933, $P < 0.001$ vs. OR = 1.90, 95% CI: 1.458–2.486, $P < 0.001$). In addition, an elevation in MetS component count was associated with a significant linear elevation in the mean score of PHQ-9 ($F = 2.8356$, $P < 0.001$). In the sensitivity analysis, similar conclusions were reached for both the original and weighted cohorts. Further interaction analysis revealed a clear gender-based difference in the association between MetS and depression incidence.

Conclusion: MetS exhibited the greatest influence on depression incidence in US adults, supporting the necessity of early detection and treatment of depressive symptoms in patients with MetS (or its components), particularly in female cases.

KEYWORDS

metabolic syndrome, depression, propensity score-based analysis, positive association, cross-sectional study

Introduction

Major depression, characterized by limited psychosocial function and a reduction in the quality of life, is expected to become the third largest cause of the overall disease burden worldwide (1). In the past 30 years, the number of global depression cases increased by 49.86% (2), causing a huge economic burden. Previous studies indicated several risk factors associated with depression, including old age, female gender, low education level, cognitive impairment, central obesity, physiological abnormalities, and a chronic medical history (3–5). A deeper excavating of the impact of risk factors on depression is of advantage to effective prophylaxis and cure. Aside from these traditional risk factors, the influence of metabolic syndrome (MetS) on the development of depression should be studied.

MetS has been proposed as a risk factor for cardiovascular disease (CVD). Patients diagnosed with MetS are at a greater risk of CVD (2–3 times) and type 2 diabetes (five times) (6). Insulin resistance (IR) is thought to be the core mechanism of MetS. Patients with depression could also show IR and glucose intolerance (7). Meanwhile, arterial stiffness (AS), a key mediator of CVD, was confirmed to be associated with middle-aged depression (5). Patients with mental illness have a higher prevalence of MetS, ranging from 29.4 to 67.9% (8). In Brazil's general population, the risk of MetS in patients with psychiatric disorders was 1.58 times higher (8, 9). All these findings suggested that there should be a link between MetS and depression.

Recently, several scholars have paid attention to the depression–MetS relationship, but the results obtained were still ambiguous. A few studies supported the independent correlation of MetS with elevated depression risk, even after adjusting for related factors (10–12), whereas other studies have not found any positive association between mental distress and MetS (13, 14). Scholars have frequently utilized traditional regression models to control for confounding. However, such methods may cause bias due to unmeasured or residual confounders, while including all available variables may cause the model to overfit, preventing the effective identification of the association between exposures of interest and outcome (15). The adjustment method based on the propensity score (PS) is of great significance to limit confounding in observational studies. It was pointed out that adjusting PS is important to eliminate biases caused by all observational covariates (16, 17). Scholars have attempted to introduce weighting, regression adjustment, and matching as PS-based adjustment methods (17).

The present study aimed at evaluating the actual association between MetS and depression incidence using PS-based analysis in US adults aged 20–85 years, utilizing data from the National Health and Nutrition Examination Survey (NHANES) over the period 2005–2018.

Abbreviations: MetS, metabolic syndrome; NHANES, National Health and Nutrition Examination Survey; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; AS, arterial stiffness; AA, Associate of Arts; GED, General Equivalent Diploma; CVD, cardiovascular disease; CHF, congestive heart failure; CHD, coronary heart disease; OR, odds ratio; CI, confidence interval; Ref, reference; PS, propensity score; IPTW, inverse probability of treatment weight.

Methods

Study design and data source

The data of this study were obtained from NHANES, as previously described (18). The NHANES survey contained two parts; a family interview covering demographics, socioeconomic, nutritional, and health concerns; and a routine physical examination completed at the Mobile Examination Center (MEC) involving medical, dental, physiological measures, and laboratory testing. More details on NHANES can be obtained from the database.

Seven cycles of continuous NHANES data (2005–2018) were pooled in this cross-sectional study to produce sizable samples for analysis. Of the 70,190 subjects, we first eliminated individuals younger than 20 years (n = 30,441), followed by those who had missing data for MetS components (n = 23,318), depression questionnaire (n = 1,181), and other confounding factors (n = 3,294). Finally, this study contained 11,956 eligible subjects. The flowchart for choosing eligible subjects is displayed in Figure 1. The NCHS Research Ethics Review Committee gave its approval for all data collection, and all participants gave their written informed permission.

Assessment of depressive symptoms

We utilized the Patient Health Questionnaire-9 (PHQ-9) scores to evaluate depressive symptoms (19). A total score of ≥ 10 was used as the cutoff to define depression according to a previous study (19).

Assessment of metabolic factors

We evaluated waist circumference with the assistance of trained NHANES staff through procedures designed for this target. Blood pressure was measured by an automatic sphygmomanometer at rest, and the mean value of three right-arm readings was recorded. Laboratory data for fasting glucose, HDL-C, and triglyceride levels were determined from fasting plasma samples using routine methods. More information on sample collection and processing instructions can be obtained from the NHANES Laboratory Procedures Manual.

Definition of metabolic syndrome

According to the revised National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria (20), MetS was defined as having at least three of the following conditions: (1) abdominal obesity, defined as a waist circumference of at least 102 cm for men and at least 88 cm for women; (2) hypertension, defined as an SBP of ≥130 mmHg or a DBP of ≥85 mmHg, or pharmacological therapy; (3) hypertriglyceridemia, defined as a triglyceride level of ≥150 mg/dL or fibrates being used; (4) low HDL-C level, defined as an HDL-C of <40 mg/dL in men and <50 mg/dL in women or having recently used lipid-lowering drugs; (5) hyperglycemia, defined as a fasting plasma glucose level of ≥100 mg/dL or currently using insulin or oral hypoglycemic drugs (20).

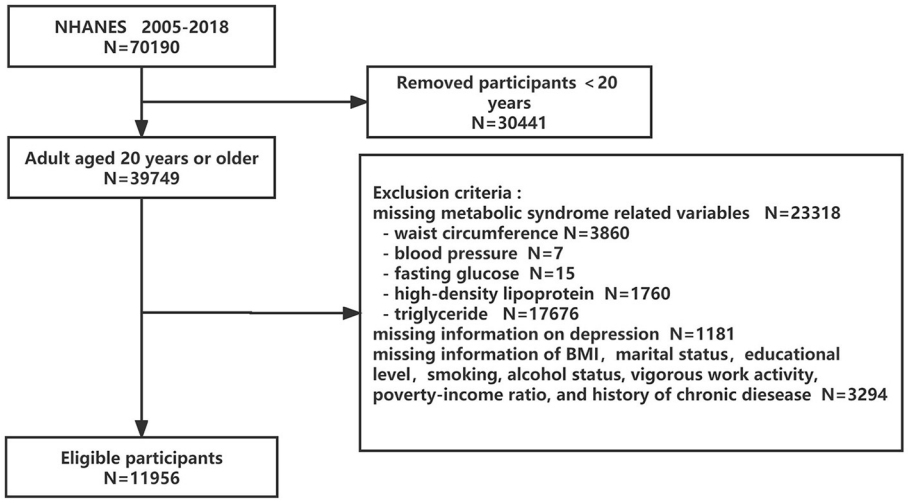

FIGURE 1
Flowchart of the eligible participant selection process. NHANES, National Health and Nutrition Examination Surveys.

Collection of confounding factors

As potential confounders, the sociodemographic factors, lifestyle factors, and the health examination of subjects were collected, which including age, sex, race, marital status, education level, poverty-to-income ratio (PIR), smoking status, alcohol status, vigorous work activity, and history of chronic diseases [congestive heart failure (CHF), coronary heart disease (CHD), angina, heart attack, hypertension, diabetes mellitus, hyperlipidemia, and stroke]. PIR was stratified as $\leq$1.3, 1.3–1.85, and >1.85, based on data from the original survey. Smoking status was categorized as current, former, and never based on participants' answers to the following questions: "Have you smoked more than 100 cigarettes in your lifetime?" and "Do you smoke now?" Alcohol status was regarded as positive if participants consumed $\geq$12 alcoholic drinks per year. Vigorous work activity was defined in terms of responses to participation in the vigorous-intensity activity. A history of chronic diseases was based on self-reports of physician diagnoses.

Statistical analysis

Continuous variables were presented as the mean±standard deviation (SD), and comparison between groups was made using the two-sample *t*-test; the expression of categorical variables was undertaken as percentages, and the statistical differences between groups were measured using the Rao-Scott chi-square test.

PS analysis matched all confounding variables listed in Table 1 between MetS and non-MetS groups, and a single group, involving subjects with similar covariates, was formed. A non-parsimonious multivariable logistic regression model was utilized to estimate PS, in which MetS and 14 confounding variables were regarded as independent variables and covariates, respectively. A 1:1 greedy nearest neighbor matching without replacement (greedy matching algorithm) was performed in this study, and the caliper width was set to 0.01. Standardized difference (SD) was calculated as the evaluation index of the covariate balance in these matched participants. For a given covariate, a SD <10.0% represents a relatively little imbalance (21, 22). Detailed information on PSM is provided in Supplementary Table 1 and Supplementary Figure 1. In addition, an assessment of differences in the PHQ-9 mean score was undertaken using Fisher's exact method by counting MetS components.

In our study, a robust estimation method was applied to control confounding variables and to evaluate the actual association between MetS and depression incidence. Specifically, the multiple logistic regression model and three PS-based models were used, including PS matching, PS adjustment, and inverse probability of treatment-weighted (IPTW) models were employed. First, the multiple logistic regression models were designed by adjusting for covariates in the PS-matched cohort. Second, PS adjustment was defined as a multivariate-adjusted regression model with adjustment for PS in the PS-matched cohort (17, 23). Third, for sensitivity analyses, an estimation of PS was undertaken for the calculation of IPTW. For instance, 1/PS was regarded as the weight of MetS, while 1/(1–PS) was attributable to the weight of non-MetS. The creation of a weighted cohort was undertaken *via* the IPTW model (24, 25). Using two relationship inference models (both in the original and weighted cohorts), sensitivity analysis was conducted. In addition, because PSM could only control the influence of measured confounders, if there are still unmeasured confounding factors, this will bring invisible bias. The E-value was calculated to assess the possibility of unmeasured confounders affecting the observed association between MetS and depression (26).

To further determine the robustness of our results in the diverse subgroups, stratified analysis based on age, sex, race, and components of MetS was also performed using stratified multivariate regression models. Each stratification was adjusted for PS in the PS-matched cohort. Exploration of modifications and interactions of subgroups was carried out using likelihood ratio tests. The STROBE statement was utilized to report the findings (27). R programming (version 4.1.3) and Empower Stats 4.1 software were applied for

TABLE 1 Baseline characteristics of MetS and non-MetS participants before and after propensity score matching.

Variables	Before Matching				After Matching			
	MetS	Non-MetS	SD (100%)	*P*-value	MetS	Non-MetS	SD (100%)	*P*-value
Participants	4,719	7,237			4,194	4,194		
Age, years	55.62 ± 15.92	44.94 ± 17.48	63.9	<0.001	53.82 ± 15.70	52.94 ± 17.08	5.3	0.014
Sex			1.6	0.383			3.4	0.121
Men, *n* (%)	2,305 (48.85)	3,594 (49.66)			2,072 (49.40)	2,143 (51.10)		
Women, *n* (%)	2,414 (51.15)	3,643 (50.34)			2,122 (50.60)	2,051 (48.90)		
Race			17.1	<0.001			9.3	0.001
Mexican American, *n* (%)	763 (16.17)	1,095 (15.13)			678 (16.17)	748 (17.84)		
Non-Hispanic black, *n* (%)	901(19.09)	1,432 (19.79)			822 (19.60)	761 (18.15)		
Non-Hispanic white, *n* (%)	2,310 (48.95)	3,257 (45.00)			2,027 (48.33)	1,918 (45.73)		
Other Hispanic, *n* (%)	449 (9.51)	665 (9.19)			390 (9.30)	418 (9.97)		
Other race or multi-racial, *n* (%)	296 (6.27)	788 (10.89)			277 (6.61)	349 (8.32)		
Marital status			36.3	<0.001			4.8	0.184
Married/living with a partner, *n* (%)	2,952 (62.56)	4,357 (60.20)			2,642 (63.00)	2,688 (64.09)		
Widowed, *n* (%)	517 (10.96)	376 (5.20)			399 (9.51)	354 (8.44)		
Divorced/separated, *n* (%)	751 (15.91)	922 (12.74)			669 (15.95)	637 (15.19)		
Never married, *n* (%)	499 (10.57)	1,582 (21.86)			484 (11.54)	515 (12.28)		
Education level			28.1	<0.001			11.3	<0.001
Less than high school, *n* (%)	1,347 (28.54)	1,543 (21.32)			1,117 (26.63)	1,208 (28.80)		
High school graduate/GED or equivalent, *n* (%)	1,170 (24.79)	1,540 (21.28)			1,026 (24.46)	979 (23.31)		
Some college or AA degree, *n* (%)	1,378 (29.20)	2,107 (29.11)			1,267 (30.21)	1,096 (26.13)		
College graduate or above, *n* (%)	824 (17.46)	2,047 (28.29)			784 (18.69)	911 (21.72)		
Poverty-income ratio			11.7	<0.001			2.0	0.651
≤1.3	1,602 (33.95)	2,122 (29.32)			1,372 (32.71)	1,405 (33.50)		
>1.3, ≤1.85	645 (13.67)	908 (12.55)			572 (13.64)	581 (13.85)		
>1.85	2472 (52.38)	4207 (58.13)			2250 (53.65)	2208 (52.65)		
Smoking status			20.7	<0.001			0.9	0.919
Current smoker, *n* (%)	953 (20.19)	1,535 (21.21)			889 (21.20)	884 (21.08)		
Former smoker, *n* (%)	1,443 (30.58)	1,571 (21.71)			1,191 (28.40)	1,208 (28.80)		
Never smokers, *n* (%)	2,323 (49.23)	4,131 (57.08)			2,114 (50.41)	2,102 (50.12)		
Alcohol status, *n* (%)	3,260 (69.08)	5,374 (74.26)	11.5	<0.001	2,958 (70.53)	2,991 (71.32)	1.7	0.428
Vigorous work activity, *n* (%)	900 (19.07)	1,674 (23.13)	10.0	<0.001	852 (20.32)	938 (22.37)	5.0	0.022
History of chronic diseases								
CHF, *n* (%)	251 (5.32)	100 (1.38)	22.0	<0.001	150 (3.58)	98 (2.34)	7.3	<0.001
CHD, *n* (%)	298 (6.31)	166 (2.29)	19.9	<0.001	208 (4.96)	162 (3.86)	5.3	0.014
Angina, *n* (%)	197 (4.17)	97 (1.34)	17.4	<0.001	124 (2.96)	96 (2.29)	4.2	0.056
Heart attack, *n* (%)	311 (6.59)	157 (2.17)	21.7	<0.001	201 (4.79)	154 (3.67)	5.6	0.011
Stroke, *n* (%)	257 (5.45)	162 (2.24)	16.7	<0.001	183 (4.36)	151 (3.60)	3.9	0.074

AA, Associate of Arts; MetS, metabolic syndrome; GED, General Equivalent Diploma; CHF, congestive heart failure; CHD, coronary heart disease.

TABLE 2 Adjusted odds ratios for the prevalence of depression according to the presence of metabolic syndrome and its components in the PS-matched cohort.

Variable	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
MetS						
NO	Ref		Ref		Ref	
YES	1.41 (1.211-1.630)	<0.001	1.37 (1.172-1.596)	<0.001	1.40 (1.202-1.619)	<0.001
Components of MetS						
<3	Ref		Ref		Ref	
3	1.12 (0.933-1.338)	0.2284	1.14 (0.945-1.372)	0.1722	1.12 (0.933-1.339)	0.2266
4	1.66 (1.354- 2.035)	<0.001	1.56 (1.264-1.933)	< 0.001	1.78 (1.341-2.016)	<0.001
5	2.16 (1.676- 2.776)	<0.001	1.90 (1.458-2.486)	<0.001	2.11 (1.626-2.699)	<0.001
P-value for the trend		<0.001		<0.001		<0.001

OR, odds ratio; CI, confidence interval. Model 1 no adjustement for other covariates. Model 2 adjusted for age, sex, race, marital status, educational level, PIR, smoking status, alcohol status, vigorous work activity, congestive heart failure, coronary heart disease, angina, heart attack, and stroke. Model 3 adjusted for propensity score.

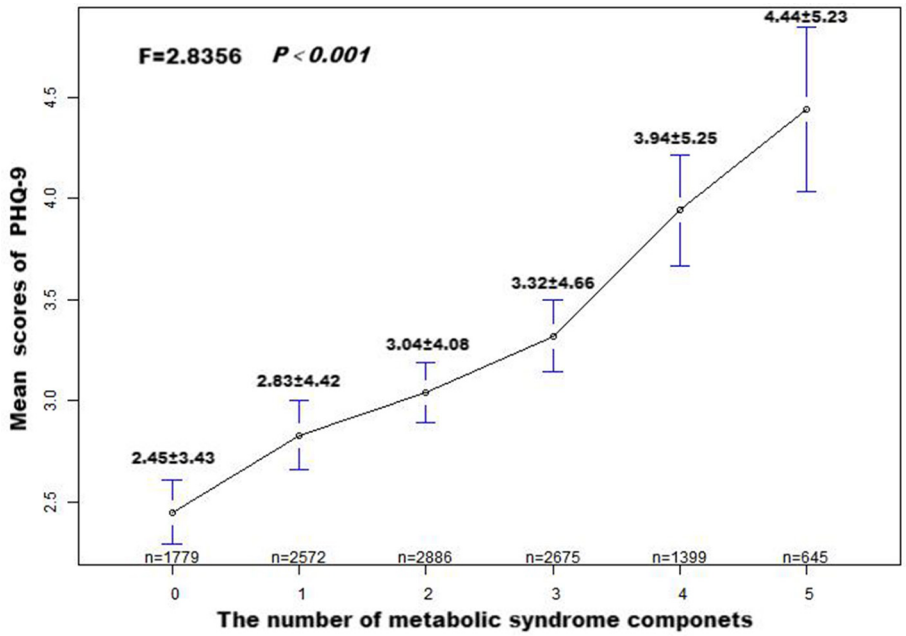

FIGURE 2
Patient Health Questionnaire-9 (PHQ-9) means score and standard error, according to the number of metabolic syndrome components. *P*-values were obtained by Fisher's exact test.

statistical analysis, and P < 0.05 was considered for defining statistical differences.

Results

Baseline characteristics

In this study, we enrolled 11,956 eligible subjects, whose mean age was 49.15 [17.67] years. Among them, 1,003 (8.4%) suffered from depression, with 369 (6.3%) and 634 (10.5%) being men and women, respectively. Before PSM, between the MetS group versus the non-MetS group, we identified significant differences in several confounding variables (Table 1). Patients with MetS appeared to be older, widowed, or divorced, with a lower PIR and education level, had a higher prevalence of cardiac–cerebral vascular diseases, and were more likely to be former smokers and drinkers. In general, 4,194 patients with MetS were successfully matched with non-MetS subjects by using a 1:1 PSM. Except for educational level, almost computation of standardized differences (SDs) indicated a rate of <10% for almost all covariates, exhibiting a well-matched after PSM.

MetS and its components exhibited a correlation with depression

We utilized multiple logistic regression models to clarify whether MetS is correlated with depression incidence after PSM. In the non-adjusted model, patients with MetS presented with a higher risk of depression (Model 1: OR: 1.41, 95 CI%: 1.211–1.630, $P < 0.001$; Table 2). After adjusting for all confounding factors, the results of Model 2 (OR:1.37, 95 CI%: 1.172–1.596, $P < 0.001$) were similar

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TABLE 3 Association of MetS and its components with depression in the original and the weighted cohorts.

Variable (A)	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Non-MetS	Ref		Ref		Ref	
MetS	1.69 (1.482-1.920)	<0.001	1.49 (1.291-1.713)	0.0010	1.44 (1.247-1.659)	<0.001
Components of MetS						
<3	Ref		Ref		Ref	
3	1.32 (1.124-1.556)	<0.001	1.22 (1.024-1.447)	0.0255	1.19 (1.004-1.420)	0.0452
4	2.04 (1.700–2.443)	<0.001	1.75 (1.444-2.131)	<0.001	1.69 (1.390-2.058)	<0.001
5	2.53 (2.007- 3.194)	<0.001	2.07 (1.617-2.660)	<0.001	1.94 (1.507-2.496)	<0.001
P-value for the trend		<0.001		<0.001		<0.001
Variable (B)	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Non-MetS	Ref		Ref		Ref	
MetS	1.64 (1.436-1.867)	<0.001	1.46 (1.267-1.674)	<0.001	1.43 (1.241-1.642)	<0.001
Components of MetS						
<3	Ref		Ref		Ref	
3	1.29 (1.115-1.490)	<0.001	1.20 (1.026-1.392)	0.0217	1.19 (1.017-1.381)	0.0291
4	2.00 (1.709- 2.334)	<0.001	1.74 (1.477-2.059)	<0.001	1.70 (1.440-2.010)	<0.001
5	2.53 (2.104- 3.045)	<0.001	2.17 (1.779-2.648)	<0.001	2.07 (1.697-2.535)	<0.001
P-value for the trend		<0.001		<0.001		<0.001

A: In the original cohort; B: in the weighted cohort. OR, odds ratio; CI, confidence interval. Model 1 no adjustement for other covariates. Model 2 adjusted for age, sex, race, marital status, educational level, PIR, smoking status, alcohol consumption status, and vigorous work activity. Model 3 adjusted for age, sex, race, marital status, educational level, PIR, smoking status, alcohol consumption status, vigorous work activity, congestive heart failure, coronary heart disease, angina, heart attack, and stroke.

to those of Model 1. Even in the PS-adjusted model, the incidence of depression was still higher in patients with MetS (Model 3: OR: 1.40, 95 CI%: 1.202–1.619, $P < 0.001$). In addition, we also found a greater risk of depression among those cases whose count of MetS components was higher. Compared with those who had less than three MetS components, participants who had four or five components of MetS were 1.56 and 1.90 times, respectively, more likely to develop depression after full adjustment (Model 2: OR: 1.56, 95% CI: 1.264–1.933, $P < 0.001$ vs. OR: 1.90, 95% CI: 1.458–2.486, $P < 0.001$). The association still existed after adjusting for PS (Model 3: OR: 1.78, 95 CI%: 1.341–2.016, $P < 0.001$ vs. OR: 2.11, 95% CI: 1.626–2.699, $P < 0.001$). To ensure the robustness of our results, we also handled the count of MetS components as a continuous variable and observed the same trend (*P* for the trend<*0.001*).

The patients' mean PHQ-9 score, based on MetS components count, is presented in Figure 2. It was noted that an elevation in MetS components count was associated with a significant linear elevation in the mean score of PHQ-9 ($F = 2.8356$, $P < 0.001$).

Sensitivity analysis

This study applied sensitivity analysis to further confirm the association between MetS and the incidence of depression in the two mentioned cohorts (Table 3). We utilized the estimated PS to form a weighted cohort *via* developing an IPTW model. In addition, we attempted to use the non-adjusted, partially adjusted, and fully adjusted models in both cohorts. A greater risk of developing depression was strongly related to patients with MetS in the cohorts. After adjusting all covariates, a greater risk of MetS was noted in those cases with MetS (Model 3: OR: 1.44, 95% CI: 1.247–1.659, $P < 0.001$) in the original cohort, and the results (Model 3: OR: 1.43, 95% CI: 1.241–1.642, $P < 0.001$) remained marked in the weighted cohort. MetS components count and the increased incidence of depression exhibited an independent relationship in the two cohorts. After adjusting all covariates, patients in the two cohorts with four (Model 3: OR: 1.69, 95% CI:1.390–2.058, $P < 0.001$ vs. OR: 1.70, 95% CI: 1.440–2.010, $P < 0.001$) or five (Model 3: OR: 1.94, 95% CI:1.507–2.496, $P < 0.001$ vs. OR: 2.07, 95% CI: 1.697–2.535, $P < 0.001$) components of MetS had a significantly elevated risk of depression than those without.

Moreover, the sensitivity of unmeasured confounders was estimated *via* the calculation of the E-value. The E-value was 2.15 (lower confidence limit, 1.68), indicating that there is less likely to be an unmeasured confounding factor that can affect the current association between MetS and depression incidence.

Subgroup analysis

We attempted to carry out a stratified analysis to assess the robustness of our findings in the diverse subgroups after PSM. Figure 3 indicates that stratified analysis based on the age, sex, race, and components of MetS yielded consistent outcomes. The interaction analysis revealed a clear gender-based difference in the relationship between MetS and depression incidence. After adjusting for possible confounders, the risk of depression in female participants with MetS was 1.63 times higher than those without (OR:1.63, 95

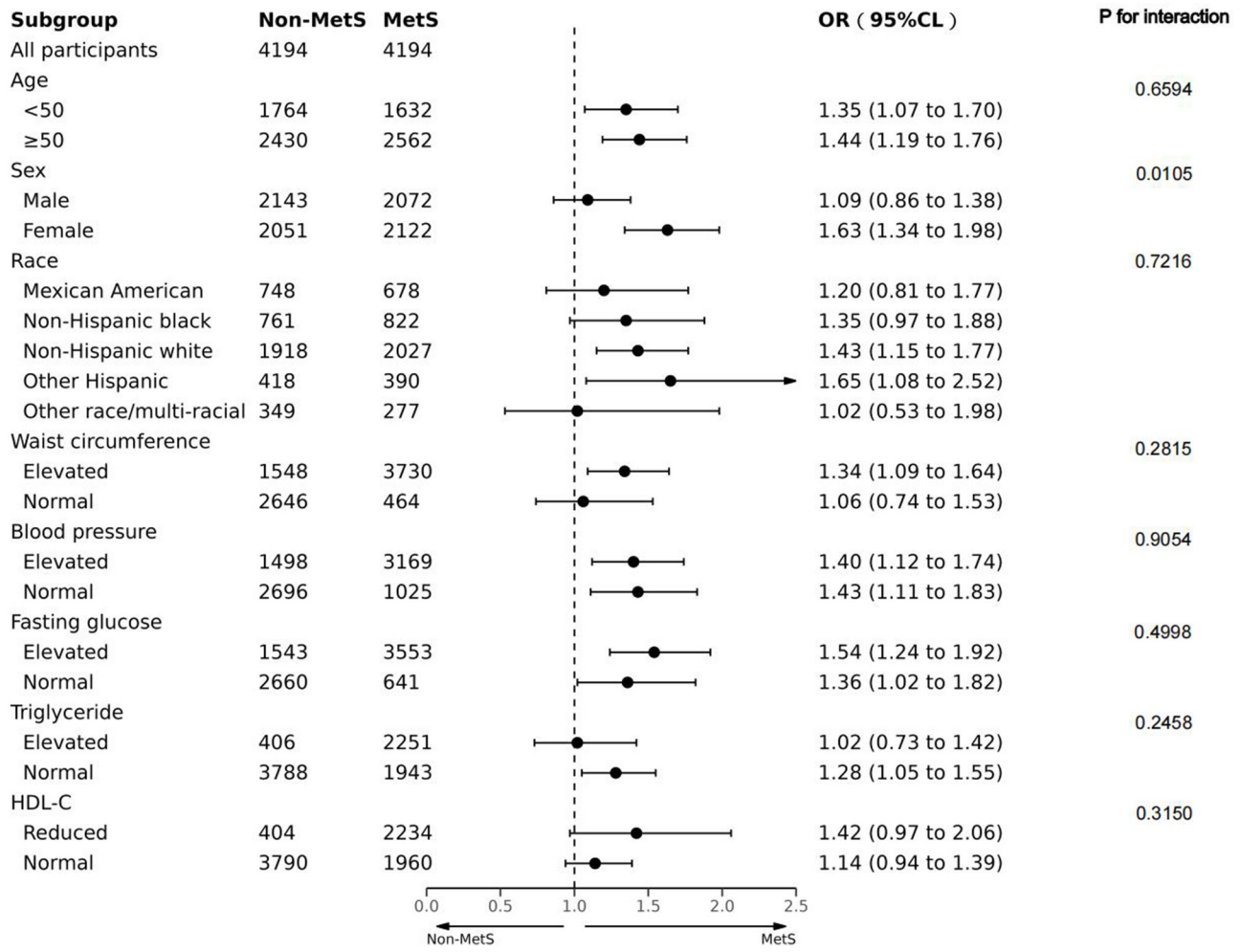

FIGURE 3
Forest plot of the association between MetS and depression in terms of age, sex, race, and components associated with MetS in the PS-matched cohort. Adjusted for PS.

CI%: 1.34–1.98). However, the association did not reach a statistical difference between male participants with MetS and depression (*P* for the interaction < 0.05). No noticeable interaction was identified for age, race, or components of MetS.

Discussion

Depression is one of the most prevalent mental illnesses affecting adults, seriously impacting public health in the USA (28). To date, the concept of MetS has been assessed, and was related to a greater likelihood of CVD and all-cause mortality (29). Previously, few studies have attempted to determine the association between MetS and the prevalence of depression. In this PSM cohort study, we observed a positive association between MetS and depression incidence in US adults: Patients with MetS had a 40% elevated risk of developing depression after adjusting for PS, and the association still existed after adjusting for all confounders. In addition, an elevated MetS components count was positively associated with a greater risk of developing depression after PSM. In the sensitivity analysis, similar conclusions were reached for both the original and weighted cohorts. Even after adjusting for PS, subgroup analysis stratified by the chosen variables yielded consistent findings. Further interaction analysis revealed a clear gender-based difference in the relationship between MetS and depression risk.

As a comorbid factor of multiple diseases, depression has been associated with all-cause mortality (30) and adverse health outcomes (31). Scholars have pointed out a link between depression and MetS. In a recent meta-analysis, a bi-directional association between the two was detected in prospective cohort studies (32), consistent with two other cross-sectional studies, which showed a link between depression and MetS in Korean adults (12) and the rural Chinese population (3). In another longitudinal cohort study, the utilization of antidepressants and elevated depressive symptoms exhibited a link with short-term metabolic dysregulation (33). In the current study, the positive association of MetS with depression occurrence was also observed. The interaction between MetS and depression may be regulated by multiple mechanisms. First, the pathophysiology of depression and Mets shared similar biological processes, involving central obesity (34), insulin resistance (35), and chronic inflammation

(36); thus, the occurrence and development of MetS may increase the risk of depression. Second, according to the vascular depression hypothesis, vascular damage in the brain may be a predisposing factor to depression in the elderly population (37). Third, the common unhealthy lifestyle related to depression and MetS, such as poor diet and sleep, smoking and alcohol use, as well as physical inactivity, may contribute to the promotion and development of each (38, 39). Fourth, antidepressants may have direct impacts on MetS components, for example, the use of tricyclic antidepressants (TCA) is related to abdominal obesity; conversely, a negative self-perception due to abdominal obesity may increase the risk of depression (40). In short, the mechanisms underlying this interrelationship are complex and unclear, and more research is needed, which will be essential for the prevention and treatment of both conditions.

The current study demonstrated that MetS and depression incidence exhibited a positive relationship. In this study, after PSM, the odds ratio for depression in patients with MetS was 1.40 (95% CI = 1.202–1.619), within the range of 1.23 to 1.52, which was provided as the odds ratio of patients with MetS for developing depression in a systematic review (33), confirming the importance of early detection and treatment of depression in patients with MetS. In terms of MetS components count, we observed a positive relationship of elevated OR for depression with MetS components count. Consistently, a study from the Korean NHANE (2007–2013) showed that MetS components count and the increased risk of depression exhibited a relationship (10). In addition, previous studies have also shown that the greater the MetS components count, the higher the mean PHQ-9 score (12, 35) or the severity of depression (12). The findings indicated that active treatment of depression should not only be aimed at those diagnosed with MetS but also those with a higher number of MetS components.

In addition, a sex difference in the association between MetS and depression occurrence was detected in the current study. The finding that the association was more remarkable in female patients with MetS agreed with previous studies (41–43). Physiological hormone differences (44), distinct lifestyle habits (45), and the use of a self-reported symptom scale for depression may partly explain the sex difference in this association. Men were more likely to under-report the severity of their depression, resulting in a classification bias.

Although a growing body of evidence has well-established the cross-sectional relationship between psychopathology and metabolic dysregulation, our study was the first conducted to explore the association between MetS and depression incidence by using the PS-based method. In addition, we attempted to conduct a sensitivity analysis to prove that our findings were robust. Moreover, our results may be more convincing due to the national representation and large sample size of NHANES. Lastly, age, sex, race, and components of MetS were selected for stratified analysis to analyze in more detail the effects of different populations diagnosed with MetS on depression incidence. However, the shortcomings of the present study should be acknowledged. First, the validity of the results might be influenced because no structured diagnostic scale was utilized to identify depression. Second, no longitudinal causal relationship could be determined between MetS and depression, attributable to the cross-sectional design. Third, some information (smoking status, physical activity, and alcohol consumption) was based on the participants' self-reports, highlighting the inevitability of bias risk.

Conclusion

In summary, MetS and depression incidence exhibited a positive relationship in a large, nationally representative study. The results highlighted the ongoing necessity for the early screening and management of depression in patients with MetS (or its components), particularly in female cases.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: http://www.cdc.gov/nhanes.

Ethics statement

The studies involving human participants were reviewed and approved by the NCHS Research Ethics Review Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LZ and JX contributed to the drafting of the manuscript, the analysis, interpretation of the data, read, and approved the final manuscript. LZ contributed to the conception, critical revision of the manuscript, analysis, interpretation of data, and approved the final version of the submitted manuscript. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1081854/full#supplementary-material

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The current state of research for psychobiotics use in the management of psychiatric disorders–A systematic literature review

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The need to find new therapeutic interventions in patients diagnosed with psychiatric disorders is supported by the data suggesting high rates of relapse, chronic evolution, therapeutic resistance, or lack of adherence and disability. The use of pre-, pro-, or synbiotics as add-ons in the therapeutic management of psychiatric disorders has been explored as a new way to augment the efficacy of psychotropics and to improve the chances for these patients to reach response or remission. This systematic literature review focused on the efficacy and tolerability of psychobiotics in the main categories of psychiatric disorders and it has been conducted through the most important electronic databases and clinical trial registers, using the PRISMA 2020 guidelines. The quality of primary and secondary reports was assessed using the criteria identified by the Academy of Nutrition and Diabetics. Forty-three sources, mostly of moderate and high quality, were reviewed in detail, and data regarding the efficacy and tolerability of psychobiotics was assessed. Studies exploring the effects of psychobiotics in mood disorders, anxiety disorders, schizophrenia spectrum disorders, substance use disorders, eating disorders, attention deficit hyperactivity disorder (ADHD), neurocognitive disorders, and autism spectrum disorders (ASD) were included. The overall tolerability of the interventions assessed was good, but the evidence to support their efficacy in specific psychiatric disorders was mixed. There have been identified data in favor of probiotics for patients with mood disorders, ADHD, and ASD, and also for the association of probiotics and selenium or synbiotics in patients with neurocognitive disorders. In several domains, the research is still in an early phase of development, e.g., in substance use disorders (only three preclinical studies being found) or eating disorders (one review was identified). Although no well-defined clinical recommendation could yet be formulated for a specific product in patients with psychiatric disorders, there is encouraging evidence to support further research, especially if focused on the identification of specific sub-populations that may benefit from this intervention. Several limitations regarding the research in this field should be addressed, i.e.,

the majority of the finalized trials are of short duration, there is an inherent heterogeneity of the psychiatric disorders, and the diversity of the explored Philae prevents the generalizability of the results from clinical studies.

KEYWORDS

probiotics, prebiotics, synbiotics, schizophrenia, major depressive disorder, neurocognitive disorders, substance use disorders, autism spectrum disorders

1. Introduction

The communication between the gut microbiome (GM) and the central nervous system (CNS) involves multiple neuro-immune and metabolic circuits *via* the vagal pathway or through the GM-synthesized metabolites, gut hormones, and endocrine peptides (1). Therefore, maintaining a healthy GM is currently explored as an essential factor for preserving mental health. The administration of prebiotics, synbiotics, or probiotics has been researched in patients with vulnerability toward-, or well-established diagnoses of psychiatric disorders and also in preclinical models of these conditions (1).

The diversity of GM and taxa abundance changes have been explored in clinical settings, and the results support the existence of a difference between patients (e.g., those diagnosed with depressive disorders, psychotic disorders, substance use disorders, etc.) and the general population (2–4). The association between GM changes and the onset or persistence of psychiatric disorders is difficult to explain because most of the discoveries related to GM composition are made after the onset of a specific pathology. To make things even more complicated, several psychotropics have been associated with changes in GM diversity, e.g., antipsychotics may exert a dose-related negative effect on the Shannon index and phylogenic diversity (5). Also, antidepressants exert *in vitro* changes in the representation of various GM species, most of their effects being antimicrobial (6).

High relapse rates, various types of disability, increased non-adherence, and treatment resistance have been reported across the spectrum of psychiatric disorders (7, 8). These negative prognosis factors indicate the need to find new therapeutic interventions for patients diagnosed with psychiatric disorders and even for the prophylaxis of such disorders. In order to validate the current state of knowledge regarding the efficacy and adverse events profile of psychobiotics in the treatment and/or prevention of psychiatric disorders, a review of the literature was conducted. Within this review, the category of "psychobiotics" includes probiotics (bacteria), prebiotics (non-digestible oligosaccharides), and synbiotics (various combinations of the previous products) (9). The definition of psychobiotics, according to Dinan et al. (10), is "a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness." Adding the dimension of GM modulation, Del Toro-Barbosa et al. (11) consider that "psychobiotics are defined as probiotics that confer mental health benefits to the host when ingested in a particular quantity through interaction with commensal gut bacteria." Also, the good tolerability of psychobiotics makes them more useful for a population with well-known adverse events to their ongoing medication (e.g., weight gain, diabetes, dyslipidemia, extrapyramidal manifestations, etc.) (11, 12). It is expected that psychobiotics would be a viable add-on option for patients diagnosed with psychiatric disorders due to their low risk of secondary effects, allergies, or dependence (11). *Probiotics* are considered "viable microorganisms, sufficient amounts of which reach the intestine in an active state and thus exert positive health effects" (9). There are many strains used in probiotic food, especially fermented milk products, e.g., lactobacilli, bifidobacteria, enterococci, streptococci, strains of Escherichia coli, etc. *Prebiotics* are "selectively fermented ingredients that allow specific changes both in the composition and/or activity in the gastrointestinal microflora that confer benefits upon host wellbeing and health" (9). From this category of psychobiotics, bifidogenic, non-digestible oligosaccharides are the most extensively explored products (9). *Synbiotics* are synergistic combinations of pro- and prebiotics (9).

The exact mechanisms by which psychobiotics exert their action are incompletely described, but induction of immunomodulatory mechanisms, protective effects against physiological stress, inhibition of pathogens growth, microbiome modulation, and improvement of the barrier function of the colonic epithelium have been explored (13).

A series of challenges have been reported by researchers investigating the effects of psychobiotics in clinical practice. The high heterogeneity of the microorganisms investigated and products administered during various clinical and preclinical studies, the paucity of well-designed clinical trials, especially of long duration, as well as the need to better define target subpopulations are but a few of the challenges faced by the research of psychobiotics (13, 14).

2. Objectives

The main objective was to evaluate the efficacy and tolerability of pre, pro, and synbiotics in different psychiatric disorders, based primarily on data derived from quantitatively and mixed (quantitatively and qualitatively) research.

A secondary objective was defined as the possibility of formulating a clinical recommendation for the use of psychobiotics in patients with psychiatric disorders in accordance with evidence found for their efficacy and tolerability.

3. Methodology

Due to the relative novelty of the subject, the methodology was conceived to include the largest pool of data available, meaning preclinical and clinical research derived from both primary and secondary reports (i.e., different types of studies or clinical cases and various types of reviews).

3.1. Design and search strategy

A systematic review focused on the efficacy and adverse effects of pre, pro, and synbiotics in the case of psychiatric disorders was conducted, based on PRISMA 2020 guidelines (15). The main electronic databases (PubMed, Cochrane, EMBASE, Clarivate/Web of Science) were included. Also, the register of clinical trials run by the US National Library of Medicine (NLM)[1] was searched for potential data regarding finalized studies dedicated to this subject.

The search paradigm used was "prebiotics" OR "probiotics" OR "synbiotics" OR "psychobiotics" AND "mood disorders" OR "major depression" OR "bipolar disorder" OR "schizophrenia" OR "substance use disorders" OR "anxiety disorders" OR "eating disorders" OR "neurocognitive disorders" OR "autism" OR "ADHD" OR "psychiatric disorders." All papers published between January 1990 and July 2022 were included in the primary search.

The checklist for the PRISMA criteria has been presented in **Supplementary Table 1**.

3.2. Inclusion and exclusion criteria

All reports referring to clinical or cohort studies, case reports, reviews, meta-analytic investigations, and preclinical research were allowed. Interventions assessed were probiotics, prebiotics, and/or synbiotics, without limitations regarding their composition or duration of administration. Patients diagnosed with any psychiatric disorder were allowed as participants if the diagnoses were based on specified criteria. Also, for preclinical studies, the model of a psychiatric disorder should be specified. The outcomes were assessed on psychometric validated scales or clinical observation for clinical trials and secondary reports and on specific behavioral manifestations for preclinical studies. Studies reporting gut microbiome changes, anthropometric markers, and/or biological variables (e.g., pro-inflammatory markers, brain-derived neurotrophic factor- BDNF, etc.) were also reviewed. Only reports written in English, for which the full paper could be accessed were included.

Exclusion criteria refer to studies without a clearly specified methodology (e.g., duration, methods of assessment, inclusion/exclusion criteria), participants without a psychiatric disorder or without a well-defined behavioral model for a psychiatric disorder in the case of preclinical studies, interventions other than those previously mentioned (e.g., fecal microbiota transplant), reports written in other languages than English, and purely qualitative research (e.g., expert opinion, perspectives, conceptual analyses).

1 www.clinicaltrials.gov

3.3. The assessment of evidence quality

The quality of evidence was based on criteria identified by the Academy of Nutrition and Diabetics for primary and secondary reports (16). These criteria are derived from the Agency for Healthcare Research and Quality guideline on rating systems for the strength of scientific evidence (17). The checklist for each research includes four relevance questions and 10 validity questions (17, 18). This methodology was preferred because it refers to both human trials and animal studies, and it includes criteria for the quality evaluation of observational, interventional, prospective, and retrospective studies, case reports, meta-analyses, and reviews. The quality of each research is scored "positive" (no risk of bias identified, very good methodology), "neutral" (the research is neither very accurate nor extremely weak), or "negative" (the main methodological aspects have not been adequately assessed), based on the quality criteria checklist (16). The reports are classified as "A" (randomized controlled/crossover trials), "B" (prospective/retrospective cohort study), "C" (non-randomized controlled/crossover trials, case-control studies), "D" (non-controlled studies, case studies, other descriptive research), "M" (meta-analyses, systematic reviews), "R" (narrative reviews, consensus statements) or "X" (medical opinions) (16).

4. Results

The primary search identified 1,062 reports, but only 43 remained after filtering them out according to the inclusion and exclusion criteria (**Supplementary Figure 1**). When distributed to different categories of psychiatric disorders, a degree of overlap between studies was detected because several reports included outcomes referring to multiple psychiatric manifestations (**Table 1**). Reports about the effects of psychobiotics on mood disorders were identified in 12 sources, while data about the modulation of anxiety manifestations through this type of intervention was found in nine sources (partially overlapping). References about schizophrenia spectrum disorders (SSD), substance use disorders (SUDs), neurocognitive pathology, and eating disorders were included in five, three, seven, and one reports, respectively. The impact of psychobiotics in patients with autism spectrum disorders (ASDs) or ADHD was also assessed in six and three reports, respectively.

The quality of the research is presented in **Supplementary Table 2**. Most of the results were gathered from the research of moderate (n = 18) or high (n = 20) quality, but low-quality reports were also identified (n = 5). The majority of the analyzed data originated in primary reports (i.e., clinical and preclinical studies, cohort studies, and case reports) (n = 34). Still, secondary reports were also identified and assessed (i.e., reviews or meta-analytic research) (n = 9).

4.1. Major depressive disorder and bipolar disorders

In most trials dedicated to patients diagnosed with depressive disorders, a decreased α-diversity of the GM has been found vs.

TABLE 1 Identified reports on the efficacy and tolerability of psychobiotics in patients with psychiatric disorders and their overall quality of evidence.

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
Mood disorders									
(20)	A systematic review of human studies (n = 13 trials)	Adults with MDD/BD	Probiotics *(Bifid.* and *Lact.* spp.)	Depressive symptoms	4-24 weeks	Seven trials concluded in favor of the intervention, and six did not.	Three positive results studies on *Lact. gasseri* were conducted by the same group of researchers. Not all probiotic bacteria could be efficient in decreasing depression severity.	M	ø
(21)	Systematic review (n = 3 trials) and meta-analysis (n = 2 RCTs)	713 women in the systematic review and 545 in the meta-analysis, all were pregnant at baseline	Probiotics *(Lact.* and/or *Bifid.* spp.) vs. placebo	EPDS scores	4-24 weeks	No significant difference was recorded in the active vs. placebo groups regarding the main outcome, or in the global mental health scores.	Anxiety levels were reduced more by the probiotics vs. placebo.	M	+
(23)	DBRCT	423 women, 14-16 weeks of gestation at baseline	Probiotics *(Lact. rhamnosus)* vs. placebo	EPDS and STAI-6 scores	∼24 weeks	Decreased depression/anxiety scores more in the active vs. placebo participants at the endpoint.	The number of women with clinically significant levels of anxiety was lower in the active group.	A	+
(24)	Systematic review (n = 62 trials) and meta-analysis (n = 50 RCTs)	Adults	Pre *(Lact., Bifid., Bacillus, Cl., Lactococcus, Strep., Weisella, Lacticaseibacillus),* pro, or synbiotics vs. placebo	Depressive symptoms measured on a validated scale	Variable, but most of the trials included had a duration of < 24 weeks	The results favored the active intervention based on the main outcome.	Effect sizes for synbiotics were larger than for prebiotics or probiotics.	M	+
(25)	OLT	Adults, 40 participants with MDD	*Cl.butyricum* + *ADT* (SSRIs or duloxetine)	HDRS-17, BDI, and BAI scores	8 weeks	70% response rate, 35% remission rate. The overall tolerability was good. No SAE was reported.	All enrolled patients were completers.	D	ø

(Continued)

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(26)	Cross-sectional populational study	Adult subjects (N = 18019)	Probiotic foods, probiotic supplements	PHQ-9 scores	Variable exposure (at least 30 days prior to one of the two study visits)	The use of probiotics was correlated with a diminished risk of depression according to the unadjusted data. After data adjustment, the prophylactic effect of the probiotics was no longer significant.	The monitoring period was 8 years (2005–2012).	D	-
(27)	DBRCT	Adults with MDD (N = 110)	Probiotics *(Lact. helveticus, Bifid. longum)* or prebiotic (galactooligosaccharide) vs. placebo	BDI scores	8 weeks	No significant difference at the endpoint between groups for prebiotics. Probiotic supplementation improved significantly the primary outcome vs. placebo.	The Trp/Ile increased significantly during the prebiotic administration vs. placebo.	A	+
(28)	DBRCT	Adults with moderate and severe mood symptoms, currently not under ADT treatment (N = 79)	Probiotics *(Lact. helveticus, Bifid. longum)* vs. placebo	MADRS scores	8 weeks	No significant difference at the endpoint between groups.	Baseline vitamin D level moderated the treatment effect on multiple outcome measures.	A	+
(29)	DBRCT	MDD patients (N = 40)	Probiotics *(Lact., Bifid.)* vs. placebo	BDI scores, multiple biological variables	8 weeks	The BDI scores significantly improved vs. placebo. Insulin, HOMA-IR, and serum hs-CRP levels also decreased significantly in the active group vs. placebo	The glutathione levels increased significantly in patients receiving probiotics. No change was reported for fasting plasma glucose, insulin sensitivity check index, lipid profiles, or other metabolic parameters.	A	+

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(30)	Permuted block RCT	Type 1 BD patients ($N = 38$)	Probiotics *(Bifid., Lact.)* vs. placebo	HDRS and YMRS scores	8 weeks	No significant differences at the endpoint between groups in the primary outcome, but a trend toward superiority for probiotics was reported.	Small sample size, and possible interactions between mood stabilizers and probiotics.	A	ø
(31)	Triple-blind RCT	Adults with depressive symptoms ($N = 71$)	Probiotics (a mixture of *Bifid.* spp., *Lacto.* spp., *and Lactococcus lactis*)	BDI, BAI, LEIDS-R, DASS-21 scores	8 weeks	No significant effect of probiotics on depressive or anxiety severity.	High attrition rate (34%).	A	ø
(32)	DBRCT	Patients undergoing hemodialysis ($N = 75$)	Synbiotic and probiotic *(Lact. acidophilus, Bifid.* spp.) vs. placebo	HADS-ANX, BDNF serum level HADS-DEP,	12 weeks	Synbiotics determined a significant decrease in HADS-DEP scores in patients with depressive symptoms vs. placebo and vs. probiotics. Also, synbiotics decreased HADS-DEP scores in all patients vs. placebo.	In patients with depressive symptoms, BDNF levels increased significantly in the synbiotic group vs. placebo and vs. probiotic groups.	A	+
Anxiety disorders									
(22)	Systematic review ($n = 3$ trials) and meta-analysis ($n = 2$ RCTs)	713 participants in the systematic review and 545 in the meta-analysis, women during pregnancy	Probiotics *(Lact., Bifid.)*	STAI-6 scores	4-24 weeks	Anxiety levels were reduced more by the probiotics vs. placebo.	Depression scores were not significantly improved by the probiotics vs. placebo	M	ø
(35)	Pilot, DBRCT	Pregnant women with severe depressive and/or anxiety manifestations ($N = 40$)	Probiotics *(Lact, Lactococcus, Bifid.)* vs. placebo	EPDS, LIDS- R, PRAQ-R, STAI, PES, EPL, MAAS, and MPAS scores	8 weeks	No significant difference was reported between groups at the endpoint regarding any of the outcome measures. The tolerability of probiotics was good.	This was a pilot trial so a low number of subjects were randomized in each arm.	A	ø
(31)	Triple-blind RCT	Adults with depressive symptoms ($N = 71$)	Probiotics (a mixture of *Bifid., Lacto., and Lactococcus lactis*)	BDI, BAI, LEIDS-R, DASS-21 scores	8 weeks	No significant effect of probiotics on anxiety severity.	High attrition rate (34%).	A	ø

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(36)	A systematic review (n = 12 studies)	Adults with a high level of stress, anxiety, or depression	Probiotics (*Bifid., Lact., Strep. salivarius/ termophilus, Cl. butyricum, Lactococcus* spp.), prebiotics, and/or synbiotics vs. placebo	Different scales for anxiety, stress, and depression	3-8 weeks	Anxiety levels were decreased by the probiotics.	Only two studies confirmed the efficacy of probiotics in patients with anxiety. Five trials did not support any improvement in this domain.	M	ø
(37)	DBRCT	Healthy volunteers (N = 150)	Probiotic mixture *(Strep. thermophiles, Bifid., and Lact.* spp.) vs. placebo	HAMA	12 weeks	The HAMA score decreased significantly vs. the placebo	The status of IL-1 beta rs 16944 carrier correlated with a favorable effect during probiotics administration.	A	+
(38)	DBRCT	Patients with GAD (N = 48)	Probiotic mixture *(Bifid.* spp., *and Lact. acidophilus)* vs. placebo + sertraline	HAMA	8 weeks	The primary outcome measure was improved by probiotic use vs. placebo.	The quality of life was not affected by the probiotic intervention.	A	+
(32)	DBRCT	Patients undergoing hemodialysis (N = 75)	Synbiotic and probiotic *(Lact. acidophilus, Bifid.* spp.) vs. placebo	HADS-ANX, HADS-DEP, BDNF serum level	12 weeks	Synbiotics did not improve significantly HADS-ANX scores vs. placebo, but all patients had a favorable evolution when compared to baseline. Patients with depressive symptoms also presented a favorable evolution vs. baseline during synbiotics use.	HADS is a self-evaluated scale, and no other validated scales have been used.	A	+
(39)	DBRCT	Healthy volunteers (N = 60)	Probiotics (various brands, composition not reported) vs. placebo	BAI and other scales validated for anxiety measurement	4 weeks	Probiotics improved panic anxiety, neurophysiological anxiety, negative affect, and worry.	Patients with a high level of distress had a better evolution during the probiotic administration. A ceiling effect is possible in this study for the anxiety-related variables.	A	+

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(40)	DBRCT	Adults with moderate stress levels (N = 111)	Probiotics *(Lact. plantarum)* vs. placebo	DASS-42 scores, multiple biological markers (e.g., plasma cortisol, cytokines levels, etc.)	12 weeks	The probiotics significantly decreased manifestations of stress, anxiety, and total psychological scores starting from week 8 vs. the placebo	Psychological functions, cognitive health, and memory are improved by probiotics in stressed adults.	A	+
Schizophrenia spectrum disorders									
(49)	Meta-analysis (n = 28 RCTs)	Patients with SCHZ	Psychobiotics, antibiotics, and antimicrobials vs. placebo as add-on	PANSS scores as the main outcome	12-24 weeks for the psychobiotics trials	No significant improvements during probiotic use were observed in the domain of negative symptoms. Vitamin D + probiotics may be superior to the placebo for negative symptoms management. Cognitive symptoms may be improved vs. placebo at 24 weeks. The tolerability of probiotics was similar to placebo.	Only three trials included pre/probiotics, one of which did not assess the negative symptoms.	M	ø
(50)	DBRCT	Patients with chronic SCHZ (N = 58)	Probiotics *(Lact. rhamnosus, Bifid. animalis)* vs. placebo as an add-on	Serum proteins related to immunity level determined in the blood, and BDNF serum level	14 weeks	Probiotics led to tvon Willebrand factor, **|** MCP-**l**,**t** BDNF, **t** RANTES, and **t** MIP-ip	Probiotics might exert their effects by regulating immune and intestinal epithelial cell functions via IL-17.	A	ø
(51)	DBRCT	Outpatients with SCHZ with moderate-severe symptoms (N = 65)	Probiotics *(Lact.* and *Bifid.* spp.) vs. placebo	PANSS scores	14 weeks	No significant difference in the PANSS total scores was detected between groups at the endpoint.	Patients treated with probiotics developed less frequently severe bowel symptoms during the trial.	A	ø
(52)	OLT	Outpatients with SCHZ (N = 29)	Probiotics *(Bifid. breve)*	HADS, PANSS - anxiety/ depression scores	4 weeks, FU visit at week 8	HADS and PANSS- anxiety/ depression scores decreased significantly after 4 weeks; 12 patients were responders.	Responders also presented fewer negative symptoms and a higher relative abundance of *Parabacteroides* in the GM vs. non-responders.	C	ø

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(53)	DBRCT	Patients with chronic SCHZ (N = 60)	Vitamin D3 and probiotics vs. placebo as add-on	PANSS total and general scores, antioxidant markers, metabolic and inflammatory variables	12 weeks	PANSS scores improved after 12 weeks.	Antioxidant markers increased vs. placebo. Metabolic and inflammatory parameters improved vs. placebo.	A	+
Substance use disorders									
(55)	An animal model study, C57BL/6 mice	Chronic binge alcohol exposure	Synbiotic vs. placebo	GM composition, hepatocyte lesions	10 days	In female mice who received chronic-binge ethanol feeding for ten days, the GM decreased its abundance and diversity, and the hepatocytes were more damaged than in mice receiving gavage with saline solution.	The synbiotics administered in mice exposed to alcohol use reduced the impact of this drug on the GM and liver endothelial barrier integrity.	A	ø
(56)	An animal model study, C57BL/6 mice	Chronic binge alcohol exposure	Synbiotic (*Faecalibacterium prausnitzii*+ potato starch) vs. fecal slurry	Hepatic inflammatory markers and oxidative stress variables	10 days	A decreased hepatic steatosis was induced by alcohol exposure when synbiotics were concomitantly administered.		A	ø
(57)	An animal model study, Wistar rats		A normal liquid diet +/- synbiotic or an ethanol liquid diet +/- synbiotic supplementation	Hepatic inflammatory markers and oxidative stress variables	12 weeks	The addition of a synbiotic attenuated the plasma endotoxin, hepatic triglyceride, and TNF-α levels, and increased the hepatic IL-10 concentration.	The synbiotic also protected against alcohol-determined increased permeability of the intestine and higher concentration of *Bifid.* and *Lacto.* in the feces.	A	ø
Neurocognitive disorders									
(62)	Meta-analysis (n = 3 RCTs)	Patients with AD (N = 161)	Probiotics (*Lacto. and Bifid.* spp.) and synbiotics	Psychometric measurements and metabolic variables	12 weeks	No significant cognitive improvement was reported during the administration of the probiotic.	The quality of evidence was very low for the cognitive outcome.	M	+

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(63)	OLT	Patients with AD (N = 16)	Probiotics (fermented milk supplement containing *Acetobacter* spp., *Lact.* spp., *Enterococcus faecium, Leuconostoc* spp., *Candida* spp.)	MMSE and other seven validated instruments for the assessment of cognitive functioning, cytokines serum levels, and oxidative processes markers.	90 days	Improvements in memory, visual-spatial/abstraction abilities, and executive/language functioning were observed at the end-point, and the level of several inflammatory cytokines and oxidative stress markers decreased.	No control group using other probiotics, and a very small sample size	C	ø
(64)	DBRCT	Healthy elders (N = 49)	Synbiotics (fructooligosaccharide + *Lact.* spp., *Bifid. lactis*) vs. placebo	GDS-15, MMSE, and inflammatory and oxidative stress markers	24 weeks	The effects of synbiotics on depressive symptoms and cognitive functioning were modest at six months vs. placebo.	GDS-15 scores reflected a slight worsening of depressive symptoms in both groups and a slight improvement in the MMSE scores.	A	+
(65)	DBRCT	Patients with AD (N = 79)	Probiotics (*Lact.*+ *selenium, Bifid.* spp.)+ selenium vs. selenium vs. placebo	Inflammatory and metabolic markers	12 weeks	Probiotic+selenium led to a significant reduction of hs-CRP and an increase in total antioxidant capacity and total glutathione vs. selenium as monotherapy or placebo. Serum levels of triglycerides, VLDL, LDL, and total-/HDL-cholesterol, were significantly reduced by this combination of selenium and probiotics vs. selenium as monotherapy and placebo.		A	+
(66)	DBRCT	Older adults with MCI (N = 80)	Probiotics *(Bifid. breve)* vs. placebo	RBANS and JMCIS scores	16 weeks	The cognitive functioning improved significantly in individuals using probiotics vs. placebo at the endpoint. Immediate memory, visuospatial/constructional, and delayed memory were significantly improved, as well as the global cognitive score.		A	+

(Continued)

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(67)	DBRCT	Healthy participants (N = 63)	Probiotics *(Bifid.* spp.)	Cognition and mood symptoms, GM composition, BDNF serum level	12 weeks	The relative abundance of GM species with pro-inflammatory roles decreased significantly during probiotic treatment. Mental flexibility and stress scores were also improved by probiotics vs. placebo. BDNF levels increased also in the active intervention group.		A	+
(68)	DBRCT	Elderly individuals with cognitive complaints (N = 121)	Probiotics *(Bifid. breve)* vs. placebo	RBANS and MMSE scores	12 weeks	A significant improvement was recorded in both groups, without differences between interventions. Immediate memory was, however, more improved under probiotics vs. placebo, both according to the RBANS and MMSE tests, but only in subjects with low RBANS scores at baseline. The tolerability of probiotic supplementation was good.		A	+
Eating disorders									
(73)	Review (n = 28 RCTs)	Patients with obesity	Pre, pro, and synbiotics vs. placebo	Metabolic and anthropometric parameters	6-28 weeks	Prebiotic use had a neutral effect on BW, with the possible reduction of inflammatory markers. Probiotics had a significant minor impact on BW and metabolic parameters.	Changes in GM were reported irregularly with pre or probiotics.	R	+
Autism spectrum disorders									
(78)	Systematic review (n = 14 controlled and uncontrolled clinical trials)	Children with ASD (sample sizes from 10 to 85)	Pro and/or prebiotics, or FMT	Behavioral outcomes measured on specific, validated scales	3 weeks-6 months	Probiotics did not influence positively the GM on RCTs. Prebiotics and synbiotics may be efficacious in improving specific behavioral symptoms, based on data from non-randomized controlled trials.	Only five RCTs had high methodological quality.	M	+

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(76)	Narrative review (n = 5 controlled and uncontrolled trials)	Children with ASD (N = 117)	Probiotics *(Lact.* spp., *Bifid.* spp., *Strep.),* mostly blended formulations compared or no with placebo	Behavioral and general symptoms using validated scales and clinical reports, GM composition	3 week-4 months	Probiotics may be helpful for ASD patients, and they may alter the GM or urine metabolites in a beneficial direction while reducing the ASD symptoms severity.	The available data are of poor methodological quality and allow for multiple confounding factors.	R	ø
(79)	DBRCT	ASD children (N = 22)	Probiotics *(Lacto. plantarum)* vs. placebo	DBC scores, GM composition, diary with clinical symptoms	3 weeks, with a monitoring period of 12 weeks	Probiotics were associated with significant changes in DBC scores. Probiotics also led to a substantial increase of lactobacilli and enterococci groups while significantly decreasing *Cl. cluster XIVa* vs. placebo.	A very high rate of dropouts was reported, and a higher inter-individual variability was detected.	A	ø
(80)	OLT	Autistic children (N = 30)	Probiotic supplementation *(Lacto.* spp., *Bifid. longum)*	ATEC scores, GM composition, clinical gastrointestinal symptoms using a structured assessment, anthropometric parameters	3 months	BW decreased significantly, ATEC scoresimproved, and gastrointestinal symptoms severity was reduced vs. baseline.	An increase in the *Bifid.* and *Lacto.* levels in the stool of these patients was observed. Small sample size.	C	ø
(81)	Case report	A 12-year-old boy, diagnosed with ASD and severe cognitive disability	Probiotic (a mixture of ten species- *Bifid.* spp., *Lact.* spp., *Strep.* spp.) as an add-on	ADOS-2	4 weeks, FU visit at week 8	The severity of gastrointestinal symptoms decreased, and the core symptoms of ASD also significantly improved after a few weeks of probiotic administration. The Social Affect" dimension scores of the ADOS improved after eight weeks, and the favorable evolution continued after another two months.	Repetitive behaviors did not improve during probiotic administration.	D	-

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TABLE 1 (Continued)

References	Study type	Population	Intervention	Outcomes	Duration of treatment	Results	Observations	Class	OQR
(82)	Case-control study	Children with ASD (N = 10), siblings (N = 9), and healthy children (N = 10)	Probiotic supplement *(Lacto, Bifid., Strep.)*	GM composition, CARS scores, gastrointestinal symptoms (parents' reports)	16 weeks	The *Bacteroidetes/Firmicutes* ratio normalized, and the representation of *Desulfovibrio* spp. and *Bifid* spp. improved also, in medication-free children with ASD.	The *Bacteroidetes/Firmicutes* ratio was lower in ASD children vs. healthy controls.	C	-
Attention-deficit/hyperactivity-disorder									
(85)	DBRCT	Children and adults with ADHD (N = 182)	A synbiotic *(Pediococcus pentasaceus, Lact.* spp. + inulin, β-glucan, pectin, and resistant starch) vs. placebo as an add-on	ADHD symptoms severity determined through validated scales	9 weeks	The synbiotic improved sub-threshold ASD manifestations in children and emotion regulation in goal-oriented behaviors in adults.	A high baseline sVCAM-1 level in adults was associated with significant improvement in emotion regulation. In children, it was associated with a reduction of the total score of autism symptoms and restricted, repetitive, and stereotyped behaviors. Concomitant medication may interfere with the effects of synbiotics.	A	+
(86)	OLT	Children with ADHD (N = 30)	Probiotics (*Bifid. bifidum)*	ADHD symptoms, BW, BMI, GM composition	8 weeks, FU at 12 weeks	During the treatment period, inattention and hyperactive/impulsive symptoms improved, while the GM composition changed, with *Firmicutes/Bacteroidetes* ratio significantly decreasing.	The BW and BMI of the participants increased during the trial. No control group, either a placebo or an active comparator, and a small sample overall. ADHD symptoms were subjectively determined.	C	-
(87)	Longitudinal, observational trial	Healthy infants (N = 75)	Probiotics *Lacto. rhamnosus*) vs. placebo	GM composition, clinical evaluation	6 months, 13 years FU	ADHD or Asperger syndrome was diagnosed in significantly more children who received placebo.	The number of the *Bifidobacterium* in the GM during the first six months of life was significantly lower in children who subsequently developed psychiatric disorders. High rates of drop-out, multiple factors that might influence the results and have not been controlled for.	D	-

AD, Alzheimer's disease; ADHD, attention-deficit/hyperactivity disorder; ADOS, Autism Diagnostic Observation Scale; ADT, antidepressants; ASD, autism spectrum disorders; ATEC, Autism Treatment Evaluation Checklist; Bifid., Bifidobacterium; BAI, Beck Anxiety Inventory; BD, bipolar depression; BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; BW, body weight; CARS, Childhood Autism Rating Scale; Cl., Clostriodioides; DASS-21/42, Depression Anxiety Stress Scale-21/42; DBRCT, double-blind, randomized controlled trial; EPDS, Edinburgh Postnatal Depression Scale; EPL, Everyday Problem List; FMT, fecal microbiota transplantation; FU, follow-up; GAD, generalized anxiety disorder; GDS, Geriatric Depression Scale; GM, gut microbiota; HADS, Hospital Anxiety and Depression Scale; HDRS-17, Hamilton Depression Rating Scale-17; Ile, isoleucine; JMCIS, Japanese version of the MCI Screen; Lacto., Lactobacillus; LIDSR, Leiden Index of Depression Sensitivity-Revised; MAAS, Maternal Antenatal Attachment Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MCI, mild cognitive impairment; MDD, major depressive disorder; MCP-1, monocyte chemotactic protein-1; MIP-1β , macrophage inflammatory protein-1 beta; MPAS, Maternal Postnatal Attachment Scale; OLT, open-label trial; OQR, Overall quality rating; PANSS, Positive and Negative Syndrome Scale; PES, Pregnancy Experience Scale; PHQ-9, Patient Health Questionnaire; PRAQ-R, Pregnancy-Related Anxiety Questionnaire-Revised; RANTES, regulated on activation, normal T cell expressed and secreted; RBAN, Repeatable Battery for the Assessment of Neuropsychological Status; RCT, randomized c[illegible]; SAE, serious adverse event; SCHZ, schizophrenia; SSRIs, selective serotonin reuptake inhibitors; STAI-6, State-Trait Anxiety Inventory-6; sVCAM-1, Circulating Vascular Cell Adhesion Molecule-1; Strep., Streptococcus; Trp, tryptophan; YMRS, Young M[illegible]cale.

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the general population, and the family *Ruminococcaceae*, genus *Roseburia*, and *Faecalibacterium* were especially affected (19). However, it is yet impossible to certainly attribute this lower diversity of GM to a vulnerability toward or to an effect of depression (20). Another important aspect is the inconsistent reporting of this phenomenon across trials in all individuals with depression (19). GM is also involved in synthesizing monoaminergic neurotransmitters and BDNF, which are presumed to be involved in the pathogenesis of mood disorders (20).

According to a systematic review (n = 13 trials), probiotics containing *Bifidobacterium* and/or *Lactobacillus* spp. may exert a positive effect on depressive symptoms, although this conclusion is not unanimously supported (seven trials agreed on the beneficial result, while six did not find significant improvement in depressive scores during probiotic supplementation) (19).

In a meta-analysis, probiotic use in pregnancy was associated with favorable results, but these were not statistically significant (n = 2 randomized controlled trials, N = 545 participants) (31). The sub-population which benefited most from the addition of probiotics was represented by pregnant women with a lower score for depression (31). Still, a randomized, placebo-controlled trial explored the effects of *Lactobacillus rhamnosus* in pregnant women and during the postpartum period on symptoms of depression and anxiety (N = 423 women, recruited at 14–16 weeks of gestation) (21). The participants received this probiotic or a placebo up to 6 months postpartum (21). Participants receiving the active intervention had significantly lower depression and anxiety severity than those in the placebo group (21).

A meta-analytic research targeting the effects of psychobiotics on the severity of depressive symptoms in the adult population vs. an inactive comparator or placebo identified 50 studies that supported statistically significant benefits for pre, pro, or synbiotics (22). A favorable evolution was observed in individuals with and without depression (22). However, the authors considered the trials included in this analysis as having heterogeneous quality and likely publication bias (22). It is also worth mentioning that individual studies rarely reported major benefits, probably because the monitoring of depressive symptoms was considered only a secondary outcome (22).

An 8 weeks open-label trial evaluated the effects of probiotics (*Clostridioides butyricum* MIYAIRI 588, 60 mg/day) as add-ons to antidepressants (mainly selective serotonin reuptake inhibitors and duloxetine) in adults presenting major depressive disorder (MDD) (N = 40 participants) (23). The improvement of depressive symptoms was significant on all scales- Hamilton Depression Rating Scale (HDRS-17), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) (23). At the final study visit, 70% of the participants were responders, while 35% were remitters (23). The overall tolerability was good, and no serious adverse events were reported (23).

A large cross-sectional U.S. population-based study evaluated the odds of developing depression in adult subjects who consumed probiotics versus the general population (N = 18,019 participants), and a Patient Health Questionnaire (PHQ-9) score of more than 10 was used to establish the existence of depression (24). The probiotic foods included in this analysis were yogurt, kefir milk, buttermilk, and kimchi, and 152 different probiotic supplements were also included (24). The analysis suggests that individuals who consumed probiotics had a lower risk for depression, but after data adjustment, the effect was no longer significant (24).

In a randomized trial, 110 patients with depression received a probiotic (*Lactobacillus helveticus* and *Bifidobacterium longum*), a prebiotic (galactooligosaccharide), or an inactive product during 8 weeks (25). Depressive symptoms improved in patients undergoing probiotic supplementation, and at the end of the study, the BDI scores decreased significantly vs. placebo and prebiotic (25).

A trial that enrolled 79 participants with mood symptoms self-evaluated as being of at least moderate severity, randomly assigned to a probiotic (*Lactobacillus helveticus* and *Bifidobacterium longum*) or an inactive compound, in a double-blind, 8 weeks trial (26). The results were not supportive of the efficacy of probiotics vs. placebo on any outcome psychological measures or biomarkers (26). At the endpoint, 23% of the subjects randomized on probiotics were responders, according to the Montgomery-Asberg Depression Rating Scale (MADRS) scores evolution vs. 26% in the placebo group (26).

A double-blind, placebo-controlled trial enrolled 40 MDD patients, randomly assigned to probiotic supplementation (*Lactobacillus acidophilus, Bifidobacterium bifidum,* and *Lactobacillus casei*) or placebo for 8 weeks (27). The improvement of BDI scores was significantly superior to the placebo after 8 weeks, and insulin, HOMA-IR, and serum hs-CRP levels also diminished in participants receiving active therapy vs. placebo (27). The glutathione levels increased significantly in patients receiving probiotics (27).

In a randomized trial, 38 patients with type 1 bipolar disorder (BD) received probiotics (*Bifidobacterium bifidum, lactis, langum,* and *Lactobacillus acidophilus*, 1.8×10^9 CFU/capsule) or placebo, and they were monitored for 2 months (28). At the last study visit, no significant changes were observed on the Young Mania Rating Scale (YMRS) or HDRS between groups, although a trend toward superiority in participants treated with probiotics was reported (28).

A triple-blind, placebo-controlled trial enrolled 71 individuals who were randomized on either a probiotic or placebo for 8 weeks (29). The active intervention correlated with a significantly higher reduction in cognitive functioning vs. placebo, but probiotics did not induce any significant modification of the gut microbiota in depressed patients (29). All participants presented at endpoint improvements in depressive symptoms, which raises the possibility of non-specific therapeutic factors involved in this phenomenon (i.e., frequent visits to the clinic) (29).

Synbiotic (15 g prebiotics, 5 g probiotic- *Lactobacillus acidophilus, Bifidobacterium bifidum, B. lactis, B. longum*, 2.7×10^7 CFU/g each) or probiotic (5 g probiotics as mentioned previously + 15 g placebo) supplementation in 75 hemodialysis-undergoing patients was compared with placebo (20 g maltodextrin) for 3 months (30). Synbiotics or probiotics were superior to placebo regarding the improvement of the Hospital Anxiety and Depression Scale (HADS)–Depression subscale score in patients with initial depressive symptoms, compared to placebo and probiotics interventions (30). All participants improved their depressive severity scores compared to placebo during synbiotics administration (30).

In conclusion, based on mostly moderate and high-quality data derived from eight clinical trials, one population study, and

three systematic reviews/meta-analyses, the use of probiotics was associated with more positive than negative results, while prebiotics administration was not supported. The majority of the trials evaluated were short-term, included a low number of patients, the intervention was heterogenous, and the population was also very diverse (e.g., the severity of depressive manifestations at baseline, the type of mood disorder, the age).

4.2. Anxiety disorders

Anxiety disorders are a heterogeneous group and different reports about GM changes in patients diagnosed with this pathology exist in the literature. In one such study, generalized anxiety disorder (GAD) patients presented a significant difference in microbiota diversity and richness vs. healthy controls, with *Fusicatenibacter* and *Christensenellaceae* spp. being significantly lower vs. controls (65). Systematic reviews found inconsistencies in the reported α and β diversity in patients with anxiety disorders, but an increased abundance of proinflammatory species and lower short-chain fatty acid (SCFAs)-synthesizing species were more frequently signaled across studies (66).

The results of a meta-analysis (n = 2 trials, N = 543 patients) confirmed that the administration of probiotics (*Lactobacillus* spp., *Bifidobacterium* spp.) during pregnancy decreased the severity of anxiety (assessed on the STAI-6 questionnaire) when compared to placebo, although this improvement was moderate if more rigorous criteria were used (31).

Pregnant women (N = 40) with low-risk pregnancies and severe depressive and/or anxiety symptoms received a probiotic (*Bifidobacterium bifidum, lactis* spp., *Lactobacillus acidophilus, brevis, casei, salivarius, Lactococcus lactis* spp.) or placebo, starting from 26–30 weeks of gestation until delivery, in a randomized, double-blind controlled trial (32). After 8 weeks of treatment, no major change was found in the efficacy outcomes (Edinburgh Postnatal Depression Scale, Leiden Index of Depression Sensitivity-Revised, Pregnancy-Related Anxiety Questionnaire-Revised, State-Trait Anxiety Inventory, Pregnancy Experience Scale, Everyday Problem List, The Maternal Antenatal Attachment Scale, and The Maternal Postnatal Attachment Scale) when the two groups were compared (32). The number of adverse and serious adverse events was similar in the two groups (32).

In a previously mentioned, triple-blind, randomized, placebo-controlled trial, the probiotic intervention did not induce any significant modification of the GM in patients presenting anxiety symptoms associated with depression (N = 71 participants) (28).

A systematic review (n = 12 studies) found that probiotics (*Bifid., Lact., Strep. salivarius/termophilus, Cl. butyricum,* and *Lactococcus* spp.) may be useful in the management of elevated stress, anxiety, or depression in adults (33). Probiotics have been found in the reviewed controlled and uncontrolled trials to reduce depression (n = 6 studies) and anxiety (n = 2 studies) (28). It should be noted that the same review found five trials that did not report any improvement in anxiety or depression vs. placebo.

In a randomized trial, 150 healthy volunteers received probiotic oral suspension (3 g/day, containing *Streptococcus thermophiles, Bifidobacterium animalis subsp. lactis, Bifidobacterium bifidum, Lactobacillus bulgaricus, L. lactis, L. acidophilus, L. plantarum, L. reuteri*) or placebo for 3 months, and the HAMA total score was significantly reduced in the active vs. control group (34). The carriers of IL-1β rs16944 single nucleotide polymorphism (related to high proinflammatory cytokine levels, depression, and neurodegenerative diseases) presented a moderate risk of having anxiety at baseline (43 vs. 11.4% in non-carriers), but the administration of probiotics helped in decreasing the HAMA score in this subgroup, while in the non-carriers the effect of probiotics was not significant (34).

In a randomized trial, 48 patients without current psychotropic treatment, diagnosed with generalized anxiety disorder, received probiotics (18×10^9 CFU *Bifidobacterium longum, B. bifidum, B. lactis,* and *Lactobacillus acidophilus*) or placebo, administered in combination with 25 mg sertraline for 8 weeks (35). The efficacy of sertraline + probiotic intervention was superior to placebo on the anxiety symptoms, according to the evolution of the scores on the HAMA and State-Trait Anxiety questionnaires, but the reported quality of life was similar in the two groups at the endpoint (35).

In a previously mentioned trial, the administration of synbiotic or probiotic supplementation in patients undergoing hemodialysis was compared with a placebo, and no superiority of the active intervention was detected at the endpoint regarding the improvement of the HADS–Anxiety subscale score (30). However, synbiotics significantly improved these scores vs. baseline values in all subjects, and also in those participants with depression at baseline (30).

The administration of probiotics was associated with improvements in panic, neurophysiological anxiety, negative affect, and worry in a group of healthy students participating in a double-blind, placebo-controlled trial (36). Patients with a high level of distress had more dimensions improved (BAI, Positive and Negative Affect Schedule, Penn State Worry Questionnaire, Negative Mood Regulation, Anxiety Control Questionnaire-revised) vs. those with normal distress, signaling a ceiling effect (36).

A randomized, double-blind, placebo-controlled study included 111 adults with moderate stress levels who received probiotics (*Lactobacillus plantarum* DR7) or a placebo for 3 months (37). The probiotics significantly decreased symptoms of stress and anxiety, starting from week 8 vs. placebo, as observed during the monitoring of the DASS-42 questionnaire scores (37). Plasma cortisol and pro-cytokines levels were reduced in subjects receiving probiotics, while cognitive and mnestic functioning improved in healthy, mature subjects vs. placebo and young adults (37).

In conclusion, based on nine reports identified in the literature, consisting of seven trials and two reviews of moderate and high quality, the effect of probiotics in decreasing anxiety manifestations was supported by several good-quality studies but invalidated by others. Synbiotics were not associated with significant results in this population. The overall tolerability of probiotics was good, but very few studies reported on this dimension.

4.3. Schizophrenia spectrum disorders

Therapeutic approaches to SSD are limited to antipsychotics with different metabolic or neurological adverse events, while

psychotherapy and other types of explored interventions have very limited benefits (3, 67, 68). Therefore, new treatments for these patients are necessary in order to improve their prognosis and overall functionality. Alterations in metabolites (e.g., SCFAs), changes in neurotransmission (e.g., GABA, glutamate, serotonin) and neurotrophic factors, and immunity impairments (e.g., altered blood T-cell numbers) have been suggested as intermediary stages between GM dysbiosis and the onset of SSD (3). Still, the correlations between specific GM changes and schizophrenia have not yet been validated, and antipsychotics have been associated with the potential to cause metabolic dysfunctions *via* microbiome alteration (69). A study using germ-free C57BL/6J mice showed that olanzapine potentiated a change toward a diathesis vulnerable to obesity in GM (64). Also, olanzapine has antimicrobial activity *in vitro* against certain species of bacteria within the GM (e.g., *Enterococcus faecalis, Escherichia coli*) (64). However, in a GM analysis of 90 medication-free patients with schizophrenia vs. 81 controls, it was observed that the first group presented differences in SCFAs, and neurotransmitters degradation or synthesis; therefore, at least some changes exist prior to the onset of the antipsychotic treatment in schizophrenia (70). GM in schizophrenia may be associated with neurostructural changes, psychopathology severity, subclinical inflammatory processes, and higher cardiovascular risk (71). Germ-free mice receiving fecal microbiome transplants (FMT) from patients with SSD had lower glutamate and higher glutamine/GABA concentrations in the hippocampus vs. healthy controls (72). The authors of the same study concluded that schizophrenia-like behaviors might be related to hypo-glutamatergic function (72).

Biotherapeutic products, i.e., probiotics, prebiotics, and polyphenols, have been hypothesized as potential add-ons to the antipsychotic treatment in patients with SSD (73). The positive influence of these products on BDNF serum levels might represent the factor behind the improvement of clinical evolution in this population (73).

A meta-analysis of trials with psychobiotics, antibiotics, and antimicrobials as add-ons in schizophrenia (n = 28 studies) did not report significant improvements using probiotics (only one trial met the inclusion criteria) vs. placebo on the negative symptoms of schizophrenia (38). One study included in the same meta-analysis detected a trend toward efficacy vs. placebo when probiotics were combined with vitamin D (38). The overall tolerability of the explored add-on agents was similar to that of the placebo (38).

The supplementation of the current treatment in patients diagnosed with chronic schizophrenia with probiotics (*Lactobacillus rhamnosus* GG, *Bifidobacterium animalis* Bb12) vs. placebo for 14 weeks (N = 31 vs. 27 participants) led to the significant reduction of von Willebrand factor and increased borderline significant the MCP-1 (monocyte chemotactic protein-1), BDNF, RANTES, and MIP-1β (macrophage inflammatory protein-1β) levels (39). A distinct analysis showed that probiotics might exert their effects by regulating immune cell function and intestinal epithelial cell activity (39).

Outpatients diagnosed with schizophrenia (N = 65) who presented moderately severe psychotic manifestations were distributed randomly to 14 weeks of double-blind add-on probiotic (*Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* Bb12) or placebo (40). The comparative analysis of the Positive and Negative Syndrome Scale (PANSS) total scores evolution did not detect differences between groups, but patients treated with probiotics developed less frequently severe bowel difficulty during the trial (40).

Another open-label trial enrolled 29 outpatients with schizophrenia who received probiotics (*Bifidobacterium breve* A-1) for 1 month, with a follow-up visit after another 4 weeks (41). Both the HADS total score and the mood scores on PANSS improved after 4 weeks, and 12 patients were considered responders (HADS reduction of more than 25%) at the endpoint (41). Responders also presented fewer negative symptoms and a more significant presence of *Parabacteroides* in the GM vs. non-responders (41). TRANCE and the expression of the IL-22 were significantly higher at 4 weeks after baseline in patients with a favorable response to the intervention (41).

Vitamin D3 (50,000 UI every 2 weeks) and probiotics (8×10^9 CFU/day) supplementation vs. placebo in 60 patients with chronic schizophrenia, administered for 12 weeks, were compared in a randomized, placebo-controlled trial (42). The total and general PANSS scores improved significantly after 12 weeks, and the total antioxidant capacity also increased vs. placebo (42). Malonaldehyde levels and hs-CRP levels decreased, and fasting plasma glucose, insulin concentration, triglycerides, and total cholesterol levels were reduced vs. placebo (42).

In conclusion, based on the results of five reports, i.e., four clinical trials and one systematic review, mostly of moderate quality, the recommendation for the administration of the probiotics in SSD could not be supported. However, several data about the potential benefits of this intervention on SSD-associated mood symptoms are encouraging, and the association of probiotics with vitamin D deserves more exploration.

4.4. Substance use disorders

The excessive use of alcohol may affect GM in human and animal models, leading to a dysbiosis that can represent an essential link in the pathogenesis of alcohol use disorders (AUD). Most of the data regarding this subject are derived from animal studies, which showed a connection between chronic alcohol use and increased oxidative stress, higher intestinal permeability to different bacteria-produced toxic factors, and the onset of alcoholic hepatitis (2, 74). Increased dysbiosis may determine systemic inflammation and endotoxemia, as well as specific organ pathologies, supporting, at a theoretical level, the usefulness of a probiotic or synbiotic modulation of the GM as prophylactic measures or therapeutic interventions in AUD (2).

In a preclinical model of chronic-binge alcohol exposure (CBAE), the addition of a synbiotic product (consisting of a butyrate-producing and anti-inflammatory commensal bacteria + a butyrate-yielding prebiotic) was explored from the perspective of GM composition changes and hepatocyte lesions (43). In C57BL/6 female mice who received CBAE for 10 days, the GM decreased its abundance and diversity, and the hepatocytes were more damaged than in mice receiving gavage with saline solution vs. synbiotic (43). The synbiotic administered in mice exposed to alcohol use reduced the negative effects on the GM and liver endothelial barrier integrity (43).

Another study conducted by the same team showed the superiority of the synbiotic administration (*Faecalibacterium*

prausnitzii + potato starch) by oral gavage vs. fecal slurry (fecal pellets) in C57BL/6 mice undergoing 10 days of chronic binge-eating alcohol when hepatic inflammation (TNF-alpha) and oxidative stress (4-HNE) were measured (44). Also, this study showed a decreased hepatic steatosis induced by alcohol exposure if synbiotics were concomitantly administered (44).

Another team of researchers demonstrated on male Wistar rats receiving either a normal liquid diet ± synbiotic or an ethanol liquid diet ± synbiotic supplementation for 3 months, that the addition of a synbiotic may reduce the plasma endotoxin, hepatic triglyceride, and TNF-α levels, and raise the hepatic IL-10 concentration (45).

In conclusion, the results of the three preclinical studies of moderate quality there is a possibility that probiotics may be of interest to human research of AUD in the near future.

4.5. Neurocognitive disorders

Changes in the GM can be considered between the potential pathogenic causes for the onset of neurocognitive disorders, for example, Alzheimer's dementia (75). In a study, fecal samples from patients with Alzheimer's disease and age-matched healthy controls were compared, and differences in GM were detected (e.g., *Bacteroides, Actinobacteria, Ruminococcus, Lachnospiraceae, Selenomonadales*) (76). Another study with a similar methodology reported a higher concentration of *Bifidobacterium, Sphingomonas, Lactobacillus,* and *Blautia* in patients with neurocognitive disorders, while *Odoribacter, Anaerobacterium*, and *Papillibacter* were reduced (77).

According to the results of a systematic review targeting trials dedicated to the effects of psychobiotics or FMT on cognitive functioning (n = 23 articles), probiotic supplementation improved the primary outcome (78). Most of the trials that enrolled healthy subjects communicated significant positive effects of probiotics in more than one performed cognitive task (78). In patients with cognitive impairments of different causes (Alzheimer's disease, hepatic encephalopathy, HIV-infected individuals, MDD, Parkinson's disease) the same adjuvants were associated with multiple favorable results on different cognitive tasks (78).

A meta-analysis dedicated to the effectiveness of probiotics and synbiotics on cognitive functioning in patients with dementia included three randomized controlled trials (N = 161 patients with Alzheimer's disease) (46). *Lactobacillus* and *Bifidobacterium* strains were not associated with beneficial effects on cognitive functioning when used as probiotic supplements (46). The quality of data was rated as very low for this outcome, but the probiotics improved plasma levels of triglycerides, VLDL, insulin resistance, and plasma malondialdehyde (46).

Probiotic-fermented milk supplementation (2 ml/kg/day, kefir synbiotic) for 3 months was investigated in individuals with Alzheimer's disease, in an open-label, uncontrolled trial (N = 16 participants) (47). Improvements in mnestic, visual-spatial, abstraction, executive and language functioning were observed, and the level of several inflammatory cytokines and oxidative stress markers decreased (47). Outcomes related to oxidative stress were also improved at the end-point (47).

In a study that enrolled 49 elders, synbiotic supplementation was compared to placebo, and the results support a favorable change in both groups regarding the percentage of body fat, TNF-alpha level, and serum diamine-oxidase (48). The IL-6, Geriatric Depression Scale-15 items version (GDS-15) score, and Mini-Mental State Examination (MMSE) score increased in both groups (48). IL-10 increased only during the synbiotic treatment, and lipopolysaccharide (LPS) decreased only in the placebo group (48). In conclusion, the effects of synbiotic vs. placebo on depressive symptoms and cognitive functioning were modest at 6 months in a group of apparently healthy elders (48).

In a randomized, controlled trial (N = 79 patients diagnosed with Alzheimer's disease), selenium (200 μg/day) + probiotic (*Lactobacillus acidophilus, Bifidobacterium bifidum, Bifido bacterium longum*, 2×10^9 CFU/day each) was compared to selenium as monotherapy (200 μg/day) or placebo for 3 months (49). Probiotic + selenium intake led to the reduction of the hs-CRP levels and an increase in the overall antioxidant capacity and total glutathione (GSH) vs. selenium as monotherapy or placebo (49). Also, lower insulin levels and HOMA-IR and higher QUICKI (quantitative insulin sensitivity check index) were associated with combined treatment vs. placebo or selenium monotherapy (49). Serum levels of triglycerides, VLDL, LDL, and total-/HDL-cholesterol, were significantly reduced by this combination of selenium and probiotics vs. selenium as monotherapy and placebo (49).

In a randomized, placebo-controlled trial, elders diagnosed with MCI (N = 80 otherwise healthy participants) received either a daily probiotic (*Bifidobacterium breve* A1, 2×10^{10} CFU) or a placebo for 4 months (50). The cognitive functioning improved significantly in individuals using probiotics vs. placebo after 16 weeks of treatment, using a structured assessment scale (Repeatable Battery for the Assessment of Neuropsychological Status, RBANS) (50). Immediate memory, visuospatial/constructional, and delayed memory were significantly improved, as well as the global cognitive score, at the end-point (50).

Another randomized, placebo-controlled trial explored the effects of probiotics (*Bifidobacterium bifidum* and *Bifidobacterium longum*) on cognition and mood in older adults (N = 63 healthy participants) for 12 weeks (51). At the end-point, the relative abundance of GM species involved in inflammation pathogenesis decreased significantly in patients undergoing probiotic treatment, while the same patients presented greater improvement in mental flexibility tests and stress scores vs. placebo (51). Probiotics increased serum BDNF levels and changed the composition of the GM (mainly *Eubacterium* and *Clostridioides* representation) (51).

In a randomized, placebo-controlled trial, *Bifidobacterium breve* A1 supplementation was added for 3 months in 121 elderly individuals with cognitive complaints (52). The neuropsychological tests (RBANS, MMSE) scores supported a significant improvement in both groups, without differences between interventions (52). Immediate memory was, however, more improved under probiotics vs. placebo, both according to the RBANS and MMSE tests, but only in subjects with low RBANS scores at baseline (52). The tolerability of probiotic supplementation was good during the entire period of the study (52).

In conclusion, the results of six clinical trials and one meta-analysis, mostly of moderate quality, support the necessity of further exploration for probiotics (eventually associated with selenium) and synbiotics in patients with MCI and neurocognitive

disorders. Although currently there is not enough data to recommend their use in this population, there are several encouraging results, both on specific cognitive dimensions, and on modification of the GM composition, that could reduce inflammation and oxidative stress. The tolerability of psychobiotics, assessed in very few reports, was good.

4.6. Eating disorders

Eating disorders have been associated with high risks for overall health status, quality of life, and general functionality (4, 79). Dietary, probiotics/prebiotics/synbiotics administration, and FMT have been conceptualized as possible interventions for patients diagnosed with anorexia nervosa (AN) (80). The modulation of weight gain in these patients' recovery involves GM changes, but the specific interaction between these two variables has not been elucidated (80). An analysis of the GM composition and diversity in AN patients vs. healthy controls revealed higher interindividual variation in the first group, suggesting altered GM functioning (81). Lower levels of serotonin, GABA, dopamine, butyrate, and acetate in AN patients' feces were detected when compared to healthy controls (81). A longitudinal analysis of AN patients' symptoms, BMI, and GM composition and metabolites, did not support a correlation between the BMI increase/symptoms improvement, on the one hand, and short-chain fatty acids, neurotransmitters profile, and GM composition, on the other (81).

Modulation of GM was investigated as an adjuvant in the treatment of obesity. Colonic dysbiosis may create a favorable terrain for neuroinflammation and behavioral changes, while obesity may be correlated with an important accumulation of persistent organic pollutants (50). Therefore, targeting GM could enhance the body detoxification process, and pre/pro/synbiotics could be helpful in this direction (82). A review of the randomized trials targeting the efficacy of psychobiotics in obese patients (n = 28 trials) suggests the prebiotics have a neutral impact on body weight, decreased fasting and postprandial glucose, improved insulin sensitivity, and lipid profile, with the possible reduction of inflammatory markers (53). The same source showed that probiotics have significant minor effects on body weight and metabolic parameters, and the changes in GM were not constantly reported during pre or probiotic use (53).

In patients with obesity (N = 101 participants), the analysis of GM showed a decrease in *Akkermansia* and *Intestimonas* distribution and an increase in *Bifidobacterium* and *Anaerostipes* (63). The same study showed low affect balance, impairments in inhibition and self-regulation, and increased emotional and external eating in patients with binge eating disorder (BED) vs. controls (63).

In conclusion, the data is yet inconclusive for the support of psychobiotics use in specific eating disorders.

4.7. Autism spectrum disorders

Functional gastrointestinal disorders are frequently diagnosed as a comorbidity in cases of autism spectrum disorders (ASD), and a common origin in gut dysbiosis has been suggested for these disorders (83). Children with ASD are estimated to present a four times higher risk of experiencing gastrointestinal symptoms vs. children without ASD (55). Therefore, pre- and probiotic supplementation represents possible useful interventions in children with ASD, but the findings to support this hypothesis are rather limited, with potential benefits in reducing gastrointestinal discomfort, improving ASD behaviors, changing GM composition, and reducing the inflammatory diathesis (83). Administration of probiotics containing *Lactobacillus* and *Bifidobacteria* strains may favor gastrointestinal and behavioral symptoms in ASD patients with gastrointestinal disturbances (84).

A systematic review (n = 14 articles) investigated the efficacy of different interventions focused on GM modulation in ASD patients, with negative results for probiotic studies, while prebiotics and synbiotics may be efficacious in improving specific behavioral symptoms (54). Another narrative review (n = 5 articles, N = 117 participants) concluded that the available data are of poor methodological quality and allow for multiple confounding factors (e.g., diet, concomitant medication, different dosages or strains administered) (55). However, probiotics may be helpful for ASD patients, and they may alter the fecal microbiota or urine metabolites in a beneficial direction while reducing the ASD symptoms severity (55).

The administration of a prebiotic (*Lactobacillus plantarum* WCSF1) in 22 ASD children during a double-blind crossover trial with a 12 weeks duration led to significant differences in behavioral scores (assessed on Developmental Behavior Checklist) at the end-point vs. baseline (56). Probiotics also led to a substantial increase of *Lactobacilli* and *Enterococci* groups while significantly decreasing *Clostridioides* cluster XIVa vs. placebo (56). A very high dropout rate was reported, indicating the need to interpret these results with caution. Also, a high inter-individual variability involves the necessity to enroll more homogenous groups of patients with ASD (56).

After probiotic supplementation (each gram containing 100×10^6 CFUs of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Bifidobacteria longum*) in a study that enrolled 30 autistic children (5–9 years old), there was reported a higher level of *Bifidobacteria* and *Lactobacilli* in the stool (57). Also, their body weight decreased significantly, the Autism Treatment Evaluation Checklist (ATEC) scores improved, and gastrointestinal symptoms severity decreased vs. baseline (57).

In a single case report, a 12 years-old boy diagnosed with ASD and severe cognitive disability received 4 weeks of an add-on mixture containing 10 probiotics (VSL#3) (58). The diet was preserved during the 8 weeks of monitoring (58). The severity of digestive manifestations decreased, and the core symptoms of ASD also significantly improved after a few weeks of probiotic administration (58). The "Social Affect" dimension scores of the Autism Diagnostic Observation Scale (ADOS) improved after 8 weeks, and the favorable evolution continued after another 2 months (58).

The administration of a probiotic diet supplementation ("Children Dophilus," containing *Lactobacillus, Bifidobacteria*, and *Streptococcus*) three times daily for 12 weeks normalized

the *Bacteroidetes/Firmicutes* ratio, the representation of *Desulfovibrio* spp. (a suspected pathogenetic factor of autism) and *Bifidobacterium* spp. in feces of medication-free ASD children (N = 10) (59). These patients had at baseline a significantly lower *Bacteroidetes/Firmicutes* ratio, an increased representation of the *Lactobacillus* genus, and a tendency to increase *Clostridioides* class 1 abundance vs. the control group (59).

In conclusion, based on data derived from six reports of mostly moderate and low quality, consisting of two clinical trials, one case-control study, one case report, and two reviews, probiotics may be beneficial for associated gastrointestinal manifestations in patients with ASD. Regarding the effects of psychobiotics on core ASD manifestations, the data reviewed were inconclusive.

4.8. Attention-deficit/Hyperactivity disorder

Attention deficit hyperactivity disorder in children has been associated with a higher representation of *Bacteroidaceae* and *Neisseriaceae*, which may cause a significant decrease in GM heterogeneity (85). Neuroinflammation in ADHD patients, abnormal activation of microglia, and altered proportion between pro- and anti-inflammatory cytokines may alter the maturation of the prefrontal cortex and the neurotransmission systems, increasing the risk for ADHD onset (86).

A synbiotic was added to children and adults with ADHD (N = 182) for 9 weeks in a randomized, placebo-controlled trial, and the results were not significantly different in the primary outcome (ADHD symptoms severity) (60). Synbiotic 2,000 decreased sub-threshold ASD manifestations (restricted, repetitive, and stereotyped behaviors) in children and had a favorable impact on emotion regulation in goal-oriented behavior in adults (60). If a high level of sVCAM-1 were detected at baseline, in adults, the synbiotic significantly improved emotion regulation (60). In children, this product reduced the overall severity of autism symptoms and the sub-domains of ASD behaviors (60).

Probiotics supplements with *Bifidobacterium bifidum* (Bf-688) 5×10^9 CFUs/day were administered for 8 weeks in an open-label trial that enrolled 30 children diagnosed with ADHD (61). During the treatment period, inattention and hyperactive/impulsive symptoms improved, while the GM composition changed, with *Firmicutes/Bacteroidetes* ratio significantly decreasing (61). Also, the weight gain and BMI of the participants increased during the trial (61).

An interesting study followed longitudinally for 13 years a group of 75 infants randomized to receive *Lactobacillus rhamnosus* GG or a placebo during their first 6 months of life (62). At the end of the monitoring period, ADHD or Asperger syndrome was detected in 17% of the subjects in the placebo group vs. none in the probiotic-receiving group (62). The number of the *Bifidobacterium* in the GM during the first 6 months of life was significantly lower in children who subsequently developed psychiatric disorders (62).

In conclusion, based on two clinical trials and one cohort study, of heterogenous quality, synbiotics may improve associated autistic symptoms, and probiotics may decrease inattention and hyperactive/impulsive symptoms. Also, a potential prophylactic effect of probiotics in children, if administered early in life, was detected, but this conclusion is based on very limited support.

5. Conclusion

Regarding the main objective of this review, the data supporting the efficacy of psychobiotic, primarily probiotics, as adjuvants in the treatment of psychiatric disorders is mixed. According to mostly moderate and high-quality data derived from primary (n = 9) or secondary (n = 3) reports, the use of probiotics was associated with more positive than negative results, while prebiotics administration was not supported in the treatment of *uni- or bipolar depression*. There are some limitations of these trials because most of them were conducted on short-term, included a low number of patients, the intervention was heterogenous, and the population was also very diverse (e.g., the severity of mood manifestations at baseline, the type of depression, or the age). Based on primary (n = 7) and secondary reports (n = 2), of moderate and high quality, the effect of probiotics in decreasing *anxiety manifestations* was controversial, and the use of synbiotics did not lead to significant results in this population. No conclusive results for the efficacy of probiotics in patients with *SSD* as adjuvant treatment could be found, according to primary (n = 4) or secondary (n = 1) reports, mostly of moderate quality. Based on the results of three primary reports of moderate quality, there is currently no support for the benefit of psychobiotics in patients with *SUD*. Primary (n = 6) and secondary (n = 1) reports, mostly of moderate quality, probiotics ± selenium and synbiotics deserve more exploration in patients with *MCI* and *neurocognitive disorders*. There is insufficient data yet to elaborate on the usefulness of psychobiotics in *specific eating disorders*, with only one secondary, high-quality report being reviewed. Based on data derived from four primary and two secondary reports of mostly moderate and low quality, probiotics may be beneficial for associated gastrointestinal symptoms in individuals with *ASD*. Synbiotics may be efficient in patients with *ADHD* for improving associated autistic symptoms, and probiotics may decrease inattention and hyperactive/impulsive symptoms, according to the results of three heterogeneous quality primary reports. The overall tolerability of probiotics was good, but only a minority of studies reported on this dimension.

The secondary objective, which referred to the possibility of formulating a clinical recommendation for the use of psychobiotics in specific psychiatric disorders, the reviewed reports did not currently support such a strategy. The most promising data are for the patients with mood disorders, who may benefit from the administration of probiotics, but there is still much heterogeneity in the products used to enable a specific therapeutic add-on recommendation. Probiotics may be useful in patients with ASD (for associated symptoms, especially gastrointestinal) and ADHD (also for associated symptoms, but for core symptoms, too), but, again, it is too early to formulate specific recommendations.

Regarding new perspectives on the interplay between GM and psychiatric disorders, data in the literature reflect intense efforts to find different ways to modulate the microbiome in order to enhance stress resilience. Increasing resilience to stressors

by influencing GM through diet has been explored in animal models of depression, cognitive impairment, Parkinson's disease, ASD, and epilepsy (87). Anti-inflammatory effects mediated by the microbial metabolites of dietary fibers and polyphenols are considered responsible for the benefits of diet on GM (87). An increased abundance of diverse GM species able to produce SCFA, e.g., *F. prausmitzii, E. rectale, Roseburia*, and *A. mucinophilia*, has been associated with the use of the Mediterranean diet (87). Vagotomy has been reported to block depression-like phenotypes in rodents after FMT of the microbiome from depressed subjects, which involves a complex interplay between the GM, vagus nerve, stress resilience, and depression (88). Interventions aiming at the manipulation of GM during the first phases of development in order to prevent or decrease the effects of early-life stressors are still under investigation (89). This type of research could indicate the existence of epigenetic modulations through GM changes, which might open an entirely new perspective on stress resilience; this, in turn, could raise the possibility of increasing the chances of therapeutic and even prophylactic interventions for psychiatric disorders.

Although other literature reviews dedicated to this topic exist and were cited in the previous sections of this paper (18, 20, 22, 31, 33, 38, 54), the current research explored all the major psychiatric disorders both in adults, adolescents, and children, including primary and secondary reports, without restriction to the type of the psychobiotics administered. A meta-analysis targeting the effectiveness of probiotic supplementation in psychiatric disorders (n = 23 studies) concluded that probiotics might be useful in reducing depressive symptoms in a statistically significant proportion vs. placebo, but not in the case of schizophrenia, stress, and anxiety (90). These conclusions are similar to the current systematic review, stressing the potential beneficial role of probiotics in mood disorders. Even more, the previously cited meta-analysis concluded that parameters like the probiotic composition, the quality of ingested psychobiotics, and the trial length significantly modulate the results of the active intervention vs. placebo (90). Regarding the studies on prebiotics and synbiotics, the results of their administration in patients with psychiatric disorders were inconclusive, according to another systematic review (91). The need for more well-designed trials focused on specific probiotic strains, inter-individual GM variations, and more homogenous phenotypes of psychiatric disorders has been emphasized by other authors exploring this topic (91, 92).

Limitations of the review refer to the selection and assessment of the quality of data which was conducted by only one researcher, and to the limited duration of the primary reports which may prevent the observation of long-term effects of psychobiotics use. Also, the high heterogeneity of several psychiatric nosographic categories, e.g., mood disorders, anxiety disorders, or SSD, makes it difficult a signal detection of psychobiotics. Different interactions between pre-, pro-, or synbiotics and currently administered psychotropics is a difficult-to-eliminate bias factor.

Although the reviewed data could not be translated into clinical recommendations, there is enough evidence to grant further research, especially for the assessment of the efficacy of psychobiotics in patients diagnosed with mood disorders, ASD, and ADHD.

Data availability statement

The original contributions presented in this study are included in this article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

The author confirms being the sole contributor of this work, and has approved it for publication.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1074736/full#supplementary-material

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Breaking the vicious cycle: The interplay between loneliness, metabolic illness, and mental health

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Loneliness, or perceived social isolation, is a leading predictor of all-cause mortality and is increasingly considered a public health epidemic afflicting significant portions of the general population. Chronic loneliness is itself associated with two of the most pressing public health epidemics currently facing the globe: the rise of mental illness and metabolic health disorders. Here, we highlight the epidemiological associations between loneliness and mental and metabolic health disorders and argue that loneliness contributes to the etiology of these conditions by acting as a chronic stressor that leads to neuroendocrine dysregulation and downstream immunometabolic consequences that manifest in disease. Specifically, we describe how loneliness can lead to overactivation of the hypothalamic-pituitary-adrenal axis and ultimately cause mitochondrial dysfunction, which is implicated in mental and metabolic disease. These conditions can, in turn, lead to further social isolation and propel a vicious cycle of chronic illness. Finally, we outline interventions and policy recommendations that can reduce loneliness at both the individual and community levels. Given its role in the etiology of the most prevalent chronic diseases of our time, focusing resources on alleviating loneliness is a vitally important and cost-effective public health strategy.

KEYWORDS

loneliness, social isolation, metabolic syndrome, mental health, depression, chronic stress, HPA axis, mitochondria

Introduction

Even before the coronavirus pandemic limited in-person gatherings and social activities, U.S. Surgeon General Vivek Murthy called the growing "crisis of loneliness" plaguing the country a concerning public health epidemic (1). Loneliness, or perceived social isolation, is the subjective feeling of a mismatch between one's desired and actual levels of social connection (2). Loneliness differs from social disconnection in that the latter is an objective measure of connectivity, while the former is a subjective state (3, 4). Loneliness is widely recognized as a major risk factor for morbidity and premature mortality (5); by some estimates, lack of social connection increases the odds of death by as much as 50% (5–7). The prevalence of loneliness is alarming: according to a World Health Organization report, in 2021, nearly one-third of U.S. older adults felt lonely frequently (8).

Epidemiological studies have associated loneliness with some of the most pressing public health challenges of our time, namely, the epidemics of chronic diseases like mental illness and the metabolic syndrome (MetS), which includes hypertension, dyslipidemia, obesity, and insulin resistance. Loneliness is associated with an increased risk of developing myriad neuropsychiatric disorders, including major depressive disorder, anxiety disorders, and post-traumatic stress disorder (9–14). For example, by performing cross-lagged analyses on longitudinal data from middle-aged and older U.S. populations, Cacioppo and colleagues demonstrated that loneliness predicted subsequent increases in depressive symptoms, but not vice versa, suggesting that loneliness may play a causal role in the development of depression rather than being a side-effect (14). While most of the research into MetS has focused on the contribution of diet and physical activity, some epidemiological studies have also identified associations between conditions of MetS and loneliness or other measures of social integration (15, 16). Notably, a large longitudinal study revealed that individuals who reported increased levels of loneliness had greater odds of developing MetS, an effect that was partly mediated by depression (17).

Here, we characterize loneliness as a major chronic stressor common to the pathogenesis of both mental and physical disease through neuroendocrine, immune, and ultimately metabolic, dysregulation. Furthermore, we describe how these physiological consequences of loneliness can lead to further isolation in a vicious cycle. To counteract the pathophysiological consequences of loneliness, we suggest strategies and interventions that increase metabolic and mental resilience at an individual level and argue that improving social connection is an effective public health strategy to alleviate loneliness and the chronic diseases it may contribute to.

Loneliness leads to pathophysiological changes: A chronic stress model

From an evolutionary perspective, social connections are important for various survival-related behaviors, including foraging, protection against predation, and reproduction. Evolutionary pressures on social species have shaped our brains and endocrine systems, in part to promote cooperation and be reactive against social isolation. Accordingly, loneliness is thought to have evolved as an alarm signal, akin to hunger or thirst, to seek out social contact and promote survival (2, 18, 19). While adaptive in acute settings, chronic activation of this stress response by prolonged feelings of social isolation—or, chronic loneliness, hereafter referred to as loneliness—has long-term costs. As such, loneliness acts as a chronic stressor that taxes the neuroendocrine, immune, and metabolic systems of the body and leads to the chronic physical and mental diseases associated with social isolation.

Although the chronic stress of loneliness might lead to poor metabolic and mental health through numerous pathways—including dysregulation of sympathoadrenal or autonomic nervous system function [for reference, see Vitale and Smith (20)]—evidence for the effect of loneliness on these systems remains relatively scant and inconsistent (21). Here, we focus on the overactivation of the hypothalamic-pituitary-adrenal (HPA) axis and its downstream immunometabolic consequences, particularly as they relate to mitochondrial function dysregulation.

Lastly, MetS is a multi-parameter condition capturing the high-frequency co-occurrence of metabolic risk factors for type 2 diabetes mellitus and cardiovascular disease. Though the disorders of MetS have vastly different clinical presentations in isolation, all likely arise from common pathophysiological pathways including neurohumoral activation, insulin resistance, and chronic inflammation. For simplicity, and given their common pathophysiology and high frequency of comorbidity, here we do not explore differential pathways or interventions for each disorder of MetS, except when consideration of a condition in isolation serves an illustrative purpose.

Risk factors for loneliness

Various genetic, environmental, and demographic factors can increase an individual's susceptibility to loneliness. Evidence from twin studies suggest that loneliness is a moderately heritable trait, with estimates of heritability ranging from 0.4–0.5 (22). A recent analysis of large-scale genome-wide association study data not only identified unique genetic loci associated with loneliness, but also found shared genetic overlap between risk factors for loneliness, cardiovascular disease, and severe mental disorders (22). Functional analyses of these loci implicated biological processes related to the brain, immune system, and metabolism, and suggested that genetic risk for loneliness may increase the risk for both cardiovascular disease and mental illness (23).

Beyond genetics, marriage, having children, higher levels of education, and a larger number of siblings may protect against loneliness, while having a male gender, chronic work or social stress, and physical health symptoms may put one at greater risk (21, 24, 25). Though prevalent across all age groups, loneliness seems to be most common in adolescents and the elderly, with 80% of teens younger than 18 and 40% of adults over 65 reporting loneliness at least sometimes (3). Notably, loneliness may affect individuals in an age-dependent manner: a large combined longitudinal study investigating the effect of social relationships on health across the lifespan found, for example, that social isolation significantly increased the risk of abdominal obesity in adolescents, but hypertension in older adults (26). Despite these differences, the physiological impacts of loneliness emerge in adolescence and persist through life (26).

Psychosocial and behavioral changes in loneliness

Individuals experiencing prolonged loneliness exhibit a range of psychological and behavioral changes. Feelings of unsafety, which stem from loneliness, result in a chronic hypervigilant state, leading to increased anxiety, altered stress responsiveness, and social withdrawal (3, 21). Functional magnetic resonance imaging (fMRI) studies of the visual cortex and ventral striatal area revealed that lonely individuals are more likely to pay attention to and remember negative interactions and derive less reward from social

stimuli (3). Importantly, these negative cognitive biases in lonely individuals can thus perpetuate social isolation in a vicious cycle in which loneliness begets loneliness, irrespective of the presence of metabolic or psychiatric conditions. Lonely individuals get less salubrious sleep, have diminished executive function compared to non-lonely individuals, and are more likely to engage in impulsive and unhealthy behaviors (3, 18, 21, 27). Further, cross-sectional and longitudinal research shows that lonely individuals show poorer self-regulation and have fewer odds of engaging in regular exercise than non-lonely individuals (28).

In addition to exercise and poor sleep, loneliness is associated with substance use disorder (SUD). Though no substantial differences in prevalence or severity of loneliness are seen across users of different substances, higher severity and duration of substance dependence consistently predicts higher levels of loneliness (29). Whether cognitive patterns that predispose to loneliness overlap with those predisposing to SUD remains unclear, and longitudinal studies have yielded mixed results regarding the causal direction or dynamics of association between them (29). Rather, there appears to be a mutually reinforcing relationship between loneliness and SUD. On one hand, social stress, social isolation, and feelings of loneliness have consistently been identified as risk factors for the development and progression of SUD (29, 30). On the other hand, stigma associated with SUD, disruption of support networks in acute stages of the disease, and foregoing of old detrimental relationships in people recovering from SUD have all been found to further feelings of loneliness (29, 31). Regardless, loneliness remains intricately tied to substance use disorder.

Chronic loneliness may thus predispose individuals to metabolic and mental health disorders through increased stress sensitivity, reduced sleep quality, and less health-promoting behaviors, including substance misuse.

Neuroendocrine changes in loneliness

Hypothalamic-pituitary-adrenal axis in loneliness

The brain is the central organ for appraising and responding to psychosocial stressors like loneliness through the activation of neuroendocrine stress pathways such as the HPA and sympathetic-adrenal-medullary (SAM) axes (32), which exert broad effects on the body through glucocorticoid (cortisol in humans) release by the adrenal cortex and catecholamine release by the adrenal medulla, respectively. Circulating glucocorticoids (GC) constrain HPA axis activity through feedback inhibition and act on virtually every cell type in the body by binding to intracellular glucocorticoid receptors (GRs), which then migrate to the nucleus to regulate the transcription of hundreds of genes involved in glucose metabolism and inflammatory signaling (21). Although some studies suggest that loneliness also leads to SAM axis overactivation, findings remain less numerous and inconsistent relative to the literature on the HPA axis, which might be in part attributable to the role of SAM axis as modulator of the short-term response to stress (21).

Studies of loneliness and chronic social isolation in humans and animal models have consistently found an overactivation of the HPA axis, supported by findings of higher cortisol awakening responses (CAR), greater total GC output (area under the curve; AUC), and flattened diurnal cortisol rhythms in lonely individuals (33–39). Persistently high cortisol levels are associated with far-reaching physiological consequences, including hyperglycemia, increased vascular resistance, redistribution of body fat to the viscera, and accelerated biological aging (40). These changes can directly lead to insulin resistance and hypertension and thus represent a mechanism by which loneliness may drive the development of metabolic syndrome.

Several studies also suggest that prolonged HPA hyperactivity in loneliness is associated with greater GC resistance and thus, a corresponding disinhibition of proinflammatory gene expression (21, 34, 41, 42). DNA microarray analyses of circulating leukocytes from lonely individuals revealed an overexpression of NF-κB/Rel-driven genes involved in immune activation and cell proliferation, and an under-expression of anti-inflammatory glucocorticoid response elements, relative to socially connected controls (43). Indeed, loneliness has been associated with the up-regulation of pro-inflammatory cytokines like IL-6, IL-8, and TNF-a, as well as inflammatory transcriptional profiles in monocytes and microglia (42, 44). It is well-established that increased inflammation may contribute to the development of cardiometabolic diseases like T2DM and atherosclerosis, as well as mental health disorders like anxiety and depression (41). Perhaps as a consequence of these immunometabolic changes, loneliness has been linked to impaired humoral and cellular immunity as supported by weaker antibody response to flu vaccination, increased antiviral antibodies, and diminshed natural killer (NK) cell activity among individuals experiencing loneliness (3, 21, 42, 45–47). Thus, HPA axis overactivity and consequent glucocorticoid resistance in individuals experiencing loneliness can result in chronic inflammation and potentially lead to related sequalae, like conditions of MetS.

Oxytocin as a mediator between social connection and the HPA axis

While loneliness and social isolation may activate the HPA axis as a stressor, social connection may dampen this activation and impart anti-stress effects through the release of oxytocin. Oxytocin is released within the hypothalamus during positive social interactions and acts as both a neurotransmitter and hormone with far-reaching effects on the body (48). Importantly, oxytocin has a well-established role in suppressing HPA activity by inhibiting the release of corticotropin-releasing hormone from hypothalamic neurons. Thus, the absence of social interactions may increase HPA activation through a decrease in oxytocin-mediated neurotransmission. In animal studies, the direct administration of oxytocin protected against the behavioral and physiological effects of isolation (49). Beyond its action on the HPA axis, oxytocin also has well-established direct cardioprotective and neuroprotective effects as an anti-inflammatory and antioxidant hormone (50–52).

Mitochondrial dysfunction as a target and effector of stress signaling in loneliness

Mitochondria are both sources and targets of stress signals and thus play a critical role in both regulating and carrying out the stress response (53). They are sensitive to chemical stress mediators,

including glucocorticoids and oxytocin, and in response, modulate physiological adaptations to stress by releasing glucocorticoids and mitokines (54). These chemical adaptation signals of mitochondrial origin epigenetically regulate bioenergetic processes that make the stress response possible (55). Prolonged subjection to stressful stimuli and their corresponding metabolic oversupply leads to the accumulation of mitochondrial damage and disruption of structural and functional integrity, eventually reaching a threshold in which the energetic demands of the stress response can no longer be met efficiently (54, 56). For instance, sustained exposure to high GC levels diminishes mitochondrial calcium-buffering capacity, induces pathological production of reactive oxygen species, reduces mitochondrial membrane potential, alters mitochondrial morphology, and dysregulates mitochondrial fusion and fission (57, 58). This overall dysregulation of mitochondrial function from cumulative stress-related damage is termed mitochondrial allostatic load (MAL) (59). Social disconnection is associated with increased MAL through HPA overactivation in animal models (60).

The brain, consuming 20% of body energy despite accounting for 2% of total body mass (61), is highly susceptible to dampened energy production. Robust evidence from pharmacologic, genetic, molecular, and neuroimaging studies in both animal models and human's links mitochondrial dysfunction with psychiatric disorders [for a review, see (62)]. Elevated levels of circulating cell-free mitochondrial DNA (ccf-mtDNA), the most prominent marker of mitochondrial damage, have been associated with mental health conditions, including MDD (63). Compared to controls, individuals who recently attempted suicide were found to have higher ccf-mtDNA, with levels that correlated with HPA-axis hyperactivity (64). Translation abnormalities and alterations in mtDNA sequence and copy number have been found in individuals with MDD, bipolar disorder, substance use disorder, and schizophrenia (65).

Given their central role in cellular metabolism, the implication of mitochondrial dysfunction in the etiology of metabolic diseases is unsurprising but notable, with persistent hyperglycemia serving as an illustrative example. Chronic states of elevated blood glucose–whether caused by chronic stress, inflammation, or overnutrition–are associated with the accumulation of mtDNA damage and fragmented mitochondria (66, 67). Correspondingly, mtDNA mutational burden is associated with age-related chronic disease; mtDNA mutations typically increase with age, especially in patients with diabetes (68). Mitochondrial dysfunction, such as impaired energy production and altered dynamics, has been extensively described in diabetic cardiomyopathies (69), one of the main causes of death for patients with MetS. Similar associations between mtDNA damage and other conditions of MetS have been described extensively elsewhere (70–72).

To summarize, the long-term experience of loneliness becomes embedded in the body through chronic stress at the biobehavioral, neuroendocrine, and mitochondrial levels, impeding metabolic function and contributing to the onset of physical and mental chronic diseases (**Figure 1**).

Loneliness leads to a vicious cycle of illness

Loneliness is not only a cause but also a consequence of mental health and metabolic disorders. The causal pathways linking poor metabolic and mental health to social disconnection and loneliness are likely better understood at the biobehavioral and psychosocial levels.

A brief examination of depression illustrates how experiencing certain mental health disorders may lead to further social isolation and worsening feelings of loneliness. For example, when establishing novel relationships in the setting of an emerging social group, depressive symptoms at baseline predict fewer social interactions, more time spent with similarly-depressed individuals, and prioritizing novel dyadic interactions over broader group interactions (73). Once friendships are established, the ability to maintain positive relationships and terminate negative ones might be impaired (74). Difficulties in generating and maintaining social connections in depression might be explained by increases in rejection sensitivity, maladaptive social cognition, decreases in social self-efficacy, and disruptions in social skills, among other behaviors and predispositions (75–78). The stigma surrounding mental health might further exacerbate ostracism among individuals experiencing a mental health condition.

Beyond their association with psychiatric disease, considering certain conditions of MetS and potential mediators of their association with social isolation can begin to shed light on plausible mechanisms at a sociobehavioral level. For example, when compared to other individuals with obesity, those experiencing higher internalized weight bias and more frequent experiences of weight-related discrimination feel more lonely (79). This evidence suggests that obesity might lead to social isolation and subsequently loneliness through socio-normative pressures and the internalization of weight-related stigma (16). Other conditions of MetS, like CVD, might lead to social disconnection by reducing health fitness and limiting the individual's ability to socialize through sports and physically-demanding activities, a possibility that should be considered given the remarkable effects of group exercise on social connectivity and prosocial behavior (80). More generally, if the morbidity from conditions of the MetS is severe enough to lead to substantial disability and need for involved care, the strain placed on caregivers might lead to disruption of key social relationships central to the patient's wellbeing.

Thus, biobehavioral and psychosocial maladaptive changes associated with mental health conditions and poor metabolic health might expose individuals to acute social isolation, predispose individuals to fail to adapt to this acute stressor, and facilitate the progression and maintenance of the chronic stress of loneliness.

Interventions for treating and preventing loneliness

Akin to a viral pandemic, loneliness spreads through social networks *via* a contagious process (81, 82). Critically, loneliness appears in clusters of people closely interacting with one another and is more severe at the periphery of social networks (81).

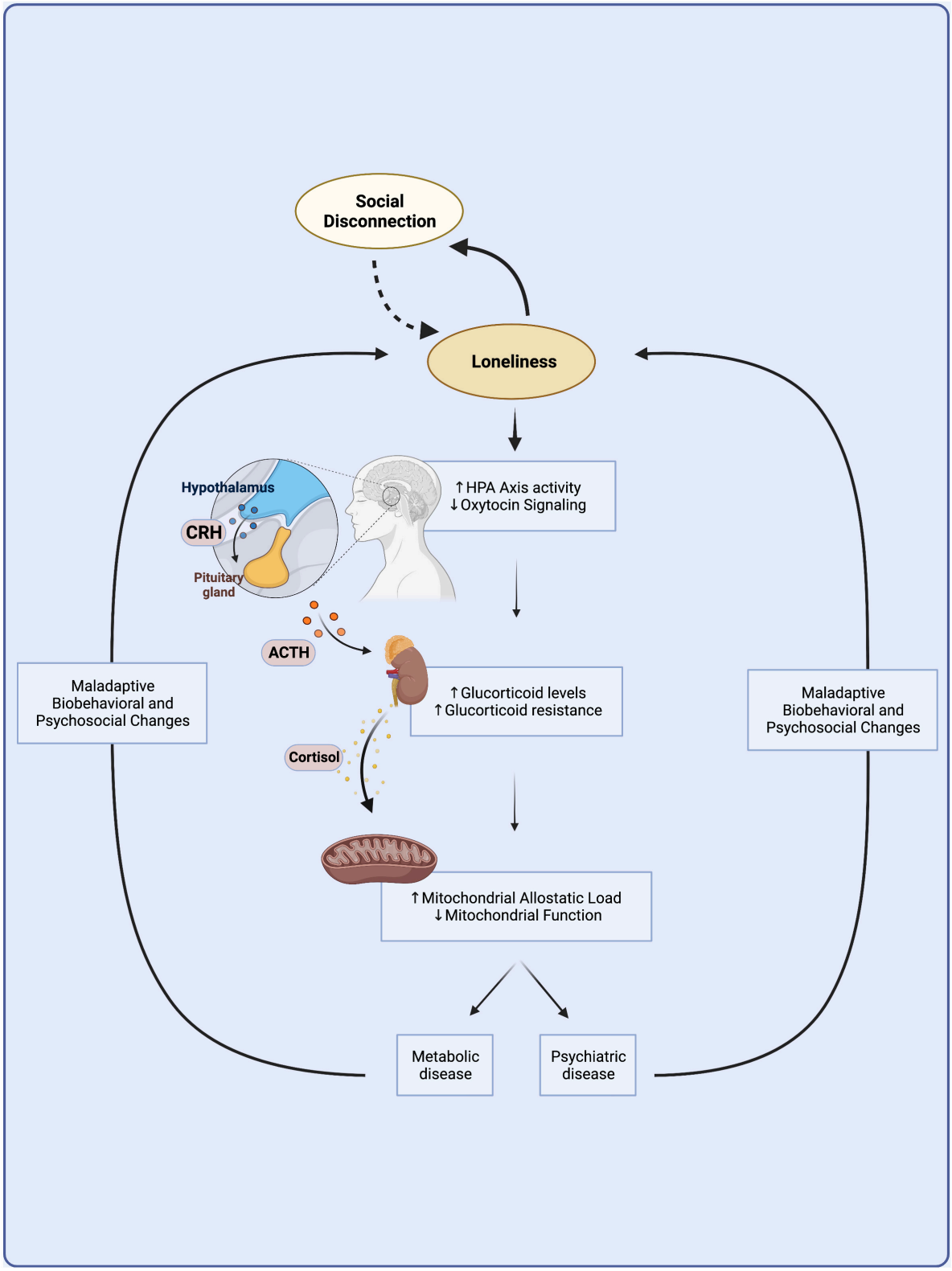

FIGURE 1
A vicious cycle links loneliness with metabolic and psychiatric disease. Loneliness arises from social disconnection as the discrepancy between desired and actual levels of social connection. Loneliness might lead to further social isolation through maladaptive biobehavioral changes and increased stress sensitivity in a vicious cycle independent of disease. Chronic loneliness is a prolonged psychosocial stressor that becomes embedded in the body through the overactivation of the hypothalamic-pituitary-adrenal axis, which leads to chronically elevated levels of circulating glucocorticoids. Chronic HPA axis hyperactivity leads to glucocorticoid resistance and mitochondrial dysfunction that culminate in immunometabolic changes common to the etiologies of many metabolic and mental illnesses. Biobehavioral and psychosocial changes observed in metabolic and mental illness might contribute to a vicious cycle furthering loneliness and its adverse downstream neuroendocrine and immunometabolic consequences. HPA, hypothalamic-pituitary-adrenal; CRH, corticotrophin releasing hormone; ACTH, adrenocorticotropic hormone. Created with BioRender.com.

These observations point to the multiplicative public health impact interventions might have if they lead to the strengthening and conservation of social connections, even at the individual and small community level. Thus, addressing loneliness resulting from widespread social disconnection emerges as an actionable, cost-effective, and influential target for intervention.

Keeping the chronic stress paradigm laid out above in mind, two general approaches to prevent the progression from social disconnection to loneliness and, furthermore, address the deleterious downstream effects of loneliness are (1) building psychological and bioenergetic capacity to adequately respond and adapt to stress and (2) removing or minimizing the stressor. While the former can be achieved most effectively through interventions at the individual level, the latter calls for interventions at the community and societal level. By building stress resilience at the individual level, increasing social connectedness at the community level, and advancing policies that support a public health infrastructure that increases connectedness at a societal level, the interventions recommended below might help break the vicious cycle linking social disconnection to the development and progression of metabolic and mental health disorders (Table 1).

TABLE 1 Interventions for treating and preventing loneliness.

Building stress resilience	Increasing social connectedness
Mental resilience	**Community level**
Practicing self-reflection	Seeking collective effervescence
Improving interoception	Religious gatherings
Improving stress management	Concerts and music festivals
Diaphragmatic breathing	Sports events
Meditation	Political demonstrations
Loving-kindness	Seeking shared experiences
Compassion	Peer support groups
Fomenting adaptive appraisals	Communal meals
Practicing self-compassion	Community gardening
Gratitude practices	House renewal
Cognitive strategies–including cognitive behavioral therapy	Visiting nature
Avoid upward contrast	Digital interventions
Considering role of FoMO	Other group activities
Increasing oxytocin signaling	**Policy level**
Skin-to-skin stimulation	Medicine
Gustatory stimulation	Loneliness screening guidelines
Positive human interactions	Support infrastructure to address loneliness
Interaction with pets	Social prescribing
Metabolic resilience	Increasing social connectivity
Increasing movement	Physical connectivity
Optimizing diet and nutrition	Digital connectivity
Ketogenic diet	Encouraging corporate wellness efforts
Intermittent fasting, caloric restriction	Spearheading educational interventions
Minimizing exposure to POPs	Address maladaptive social cognition

Interventions that (1) increase bioenergetic and psychosocial capacity to respond to stress and (2) remove the stressor of social disconnection will be protective against loneliness. By focusing on building metabolic and mental stress resilience at an individual level, increasing social connectedness at the community level, and prioritizing public policies that support society's key institutions in connecting the people they serve, we can begin to address the growing epidemic of loneliness and break the cycle linking it to poor metabolic and mental health.

Individual level: Building stress resilience by increasing psychological and bioenergetic capacity to respond to social disconnection

Mental resilience

Whether social disconnection turns into loneliness and the extent to which this perceived social isolation persists over time is ultimately determined by the psychological appraisal of our situation in relation to the rest of the world. Among other things, this process relies on self-efficacy, the subjective interpretation of environmental cues, interoceptive interpretations of internal sensations, the processing of feelings and emotions as they relate to social interactions, and belief systems and expectations surrounding the number and quality of social connections we ought to have (83–86). Hence, independent of objective changes to one's level of social connection, building mental resilience will protect against loneliness by facilitating adaptive appraisals of our place in relation to the rest of the world.

Practices that encourage self-reflection, like journaling, can help in identifying stress arising from loneliness by improving interoception and increasing self-awareness and emotional regulation (84). Journaling has been associated with decreased mental distress among general medical patients with anxiety symptoms in a preliminary randomized controlled trial (87). Once the stress state is identified, deploying relaxation and stress management techniques known to dampen the stress response, like diaphragmatic breathing or loving-kindness and compassion meditation, might improve emotional regulation and help prevent the progression of maladaptive physiological processes tied to loneliness (88, 89). Indeed, unlike control subjects, individuals practicing diaphragmatic breathing show reductions in cortisol levels following a single session (89). In a classic study, Fredrickson et al. found that practicing loving-kindness meditation is associated with increased social support in the long term, hinting at its potential value in addressing loneliness specifically (88).

Daily gratitude practices and writing exercises that encourage self-compassion predispose individuals to more adaptive appraisals of future social interactions (90). For example, self-compassion is associated with greater equanimity when resolving future relationship conflicts (91). Cognitive strategies tied to reductions in loneliness include avoiding social comparisons leading to upward contrast (85) and reflecting on the role of fear of missing out as a contributor to loneliness (92). Although several systematic reviews have highlighted the need for more rigorous assessments of the efficacy of interventions against loneliness, a meta-analysis

of 50 studies including young and older adults concluded that interventions combatting maladaptive social cognition, including multiple forms of cognitive behavioral therapy, are more effective than strategies focusing on increasing social skills and enhancing social support at reducing loneliness (93).

Experiences that increase oxytocin signaling increase stress resilience by contributing to the development and maintenance of the body's neuroendocrine stress buffering capacity. Examples of interventions found to increase oxytocin signaling include skin-to-skin stimulation like massages, gustatory stimulation, positive human interactions like cohabitation and safe, consensual sexual interactions, and interaction with pets (48). Notably, a systematic review and meta-analysis of 44 studies found that animal therapy is more effective than psychotherapy and occupational therapy, among other types of interventions, in reducing loneliness among older adults (94).

Metabolic resilience

The response to the stress arising from social disconnection, whether adaptive or maladaptive, is ultimately instantiated by the mitochondria. Mitochondrial dynamics involved in the stress response are energy-demanding, particularly when stress-buffering strategies at the psychosocial level are insufficient to prevent the progression from an adaptive response to stress arising from social disconnection to the chronic stress response tied to loneliness. Thus, interventions that build metabolic fitness, or mitochondrial bioenergetic capacity, will build stress resilience.

Movement, in the form of endurance exercises (95), resistance training (96), or yoga (97) induce protective changes in biogenesis, fusion rates, volume, structure, and function of mitochondria, increasing the body's overall bioenergetic capabilities (98). Notably, these changes, even when occurring most evidently within skeletal muscle, are also thought to underlie exercise-induced neuroprotection (99). At an epidemiological level, higher levels of physical exercise positively predict prosocial behavior among children and adolescents (100, 101).

Dietary changes that facilitate the maintenance of healthy blood glucose levels and help avoid chronic overnutrition will optimize mitochondrial function and build stress resilience. In particular, the ketogenic diet (KD), a high-fat, low-carbohydrate diet mimicking the metabolic state of starvation, improves several markers of mitochondrial redox status by inducing the production of antioxidants and detoxification enzymes (102, 103). Along those lines, caloric restriction and intermittent fasting (IF) induce protective changes in mitochondrial dynamics, reduce mitochondria-related oxidative stress, and improve the energetic output of mitochondrial respiration (104, 105). Reducing exposure to persistent organic pollutants (POPs), for example, by preferring organic food and filtering water and air, may further prevent mitochondrial damage (106).

Community level: Minimizing the stress of loneliness by increasing social connectedness

Beyond building stress resilience, seeking experiences that decrease loneliness by either increasing the number and quality of social connections, or a sense of connectedness to the world around us, will contribute to better mental and metabolic health. Here, we list a number of ways to increase connectedness at the community level.

Higher frequency of experiences of collective effervescence, or the sensation of shared sacredness and connection arising in group gatherings, confers significant protection against loneliness (107, 108). Although originally conceived as arising from religious gatherings, it is now understood that collective effervescence is also commonly brought about by more ubiquitous group experiences, including concerts, sports events, and political demonstrations (107, 109). Concerts and music festivals can further increase feelings of connection to other attendees through joint action and interpersonal coordination synchronized to the music rhythm (110).

Not surprisingly, shared experiences at the community level, even in the absence of collective effervescence, lead to reductions in loneliness (111, 112). Support groups, particularly those centered around common experiences of illness and peer-to-peer support, can increase feelings of connectedness while offering practical advice (113–115). In fact, a systematic review by Cattan et al. concluded that group interventions, particularly those targeting a specific group with a shared identity or experience, might be more effective at reducing loneliness than one-on-one strategies (116). Examples of other group community efforts that likely reduce loneliness include participating in communal meals and community gardening or house renewal projects, visiting nature sites with friends, and taking art or cooking classes (112, 117).

Digital interventions have gained popularity after the onset of the COVID-19 pandemic. Although still limited in their reach by disparities in access to technological resources such as high-bandwidth internet associated with lower socioeconomic status, certain digital interventions have proved to be effective at reducing loneliness across a wide range of demographic groups during the COVID-19 pandemic (118–120). For instance, in a series of four studies including over one thousand participants involving younger and older adults in Australia and the United Kingdom, GROUPS 2 CONNECT, a web-based intervention deploying a series of interactive screens inviting participants to engage in priority- and goal-setting around social relationships, was found to lead to improvements in self-reported quality of social connections and ability to stay connected over time (121). As digital interventions against loneliness will likely become a mainstay in the post-pandemic era, priority should be given to those that (1) take provisions to minimize accessibility concerns, (2) are developed based on a robust theoretical framework (122), (3) facilitate more frequent direct and meaningful (as opposed to fleeting) interactions among individuals (123), and (4) include a technology education component when targeting older adults (124).

Societal level: Minimizing the stress of loneliness by advancing community-building public policy

Public policies directly aiming to address loneliness can support society's key institutions—including health care systems, workplaces, religious and secular community organizations, schools, and colleges—in being more intentional and systematic about connecting the society members they serve.

In health care, screening for loneliness with objective measures at primary care appointments and developing an infrastructure for connecting individuals to programs, resources, and institutions focusing on addressing social disconnection should be considered. Currently, despite the negative health consequences of social isolation–which is comparable to risk factors that are screened routinely, like heavy drinking or smoking (125)–guidelines recommending screening for loneliness in the primary care setting are notoriously missing. Though standardized measures of social isolation and loneliness have been developed and are often used in research (i.e., Lubben Social Network Scale, Duke Social Support Index, UCLA Loneliness Version Scales), they are not currently used in the clinical care setting, in part due to a paucity of research on their efficacy as a preventive tool in the clinical setting. Moreover, whether any of these measures is robust enough to capture loneliness as a multidimensional construct remains an area of concern (29).

In addition to promoting the advancement of evidence-based screening guidelines, public health efforts should be devoted to developing and supporting interventions that bolster social connectivity among at-risk groups. Though further research is needed, social prescribing, or the use of non-clinical referral options by clinicians, is emerging as an effective paradigm for connecting individuals to programs, resources, and institutions focused on addressing loneliness (125, 126).

Increasing access to safe and adequately lit parks, bike lanes, public transportation, recreational activities, and high-speed internet access are all ways communities can enable physical and digital proximity that can facilitate social connection for its residents (127).

A variety of corporate wellness programs improve employees' physical and psychological health by fostering social connection in the workplace (128, 129). Policies that encourage the development and maintenance of such programs should be considered a public health priority.

Public health interventions with an educational focus might have a role in counteracting cognitive biases that further compromise social connection. In fact, educational interventions focused on addressing maladaptive social cognition are among the most effective types of interventions against loneliness (93). Such public education campaigns could be developed and implemented in partnership with K-12 schools, colleges, senior centers, workplaces, and government agencies.

Conclusion

Loneliness is a growing public health problem at the heart of the epidemics of mental health-related conditions and metabolic health-related conditions. Although not often considered a serious risk factor for chronic disease, loneliness is a major predictor of all-cause mortality and is associated with the development of both mental and cardiometabolic disease. The chronic stress brought about by loneliness may cause HPA axis hyperactivity and adverse downstream immunometabolic consequences fundamentally arising from mitochondrial dysfunction that may ultimately lead to further social isolation. Given its role in the etiology of the most prevalent chronic diseases of our time, alleviating loneliness is a vitally important and cost-effective public health strategy, and loneliness checks should be incorporated into routine patient care. Future work should identify scalable, evidence-based interventions to reduce loneliness and its deleterious health consequences.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

IC and MA contributed equally to the research and production of this manuscript from the conception and design to the research and writing. MM contributed to the conception of the original idea and provided the expert guidance on the theoretical framework for this manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Conflict of interest

MM was employed by Adamo Bioscience, Inc.

The remaining 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.

Publisher's note

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Associations between overweight, obesity, and mental health: a retrospective study among European adults aged 50+

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Background: The comorbidities associated with overweight and obesity have been well researched and scientifically proven while their relationship to mental health is still not verified.

Methods: This study is aimed at investigating reciprocal associations between obesity and mental health, and is intended to further analyze possible long-term effects using data from the Survey of Health, Ageing and Retirement in Europe (SHARE). In order to do that, waves 4 and 8, conducted in 2010 and 2019/20 of this survey, were analyzed in a cross-lagged panel approach including 16,184 adult Europeans (50+) using multiple linear regression analysis focusing on the Body Mass Index (BMI), depression status and quality of life (QoL).

Results: Findings yield significant cross-lagged effects in one direction regarding BMI predicting QoL and depression state, whereas depression state and QoL do not significantly predict BMI. Findings include people living with obesity, overweight, and underweight showing significantly decreased levels of QoL as well as increased depression scores compared to people of normal weight over a lag time of 10 years, where people living with obesity indicate the strongest effect.

Conclusions: However, results do not confirm reciprocal associations in the long term. Hence, there is a strong need to carry out further research on this issue.

KEYWORDS

mental health, obesity, overweight, long-term, association, body mass index, depression, quality of life

1. Introduction

Obesity is the fifth leading cause of death worldwide (1) and is therefore considered a global epidemic, demonstrating one of the major health-related issues not only in industrialized countries but also in developing countries (2, 3). According to the World Health Organization (WHO), overweight and obesity are defined as a BMI greater than or equal to 25, respectively, a BMI greater than or equal to 30 (4). Over recent decades, however, sedentary lifestyles have increased and calorie-rich foods have been consumed more frequently, leading to a substantial increase in body weight and BMI levels. Besides increased mortality rates and impaired QoL, obesity and its associated comorbidities such as cardiovascular events or diabetes mellitus have a significant impact on health care expenditures.

Additionally, mental disorders such as impairments of mood, thoughts as well as behavioral dysregulation contribute to burden of disease (5). According to the Global Burden of Disease (GBD)

study, mental disorders as well as disorders linked to substance use are considered the fifth leading cause of burden with respect to disability adjusted life years (DALYs) (6, 7). Both obesity and mental illness show increasing prevalence rates and are associated with numerous medical complications in vulnerable populations, as shown in several studies (8–11). Presumably, the coexistence of these conditions is more than just a random overlap. However, there is still a lack of knowledge in terms of linking mechanisms (12). People who live with severe mental disorders have a significantly shorter life expectancy of about 20 years compared to the general population. This may be due to a sometimes unhealthy lifestyle and the frequent occurrence of physical diseases (13), including cardiovascular issues (14–16). According to a global systematic review and meta-analysis on lifestyle patterns of people with mental disorders such as schizophrenia, bipolar disorder, and major depressive disorder, sedentary behavior and less physical activity was increasingly observed among those people. About 50% of individuals living with a mental disorder do not follow the general recommendation of at least 150 min of exercise per week (17). Furthermore, people with severe mental illness often show unhealthy eating habits, including a low consumption of fruits and high fiber food, but a high intake of junk food (18, 19). Additionally, people with mental disorders are more frequently heavy smokers than the general population (20–22).

First reports describing increased risks of obesity in patients with mental disease were established by Nicholson in 1946. Accordingly, Nicholson documented emotional tensions and psychoneurosis to be related to obesity (23). Since then, numerous studies on the relationship between these clinical conditions have been carried out leading to predominantly focus on a bi-directional association (24). In addition, individuals who have mental illnesses show a 2- to 3-fold increased risk of obesity. In contrast, people living with obesity are at a 30 to 70% higher risk of developing a mental illness (25). A North-American study found that about 80% of 10,000 people diagnosed with schizophrenia, bipolar disorder or depression were either affected by being overweight or lived with obesity (26). The reason for this high number of patients living with obesity and severe mental illnesses has been widely debated. Several studies state that complex interactions between genetic, environmental, disease-inherent factors, and the side effects of antipsychotic drugs appear to be responsible for gaining body weight (27). Others see the main reason for this increase in antipsychotic adverse events (28–31). It is generally assumed that weight gain, as a side effect of antipsychotic drugs, may emerge from multiple mechanisms, including the neurotransmission of hormones, such as serotonin, histamine and/or epinephrine (32). Active agents of antipsychotics act on neural pathways by modulating their activity. As a consequence, weight gain may be due to the blockade of specific receptors, which has an impact on regulatory mechanisms of appetite and body weight (33). Both antidepressants (34–39) and antipsychotic medications can cause increased BMI levels and may further lead to a greater cardiovascular risk, indicating an exponential rise in BMI scores and metabolic risk (40). Furthermore, different, sometimes unhealthy lifestyles such as smoking, lack of physical activity, and their effects, further complicate causal research (41, 42). Both mental illness and obesity are chronic conditions which are very prevalent. Besides, some examinations point out that these two events are linked to each other (43). Possible associations between obesity and physical and mental ill health have been widely discussed (44). Some examinations point out that individuals with psychiatric disorders are at a higher risk of developing obesity (45, 46) and people with mental illnesses are much more likely to live with either overweight or obesity than the average population (47). Depression, impaired mental health and poor quality of life are often associated with obesity (48). In addition, this co-occurrence seems to be particularly likely when people are affected by physical impairments as well. Thus, the relationship between obesity and mental health seems to be stronger in later life than in early periods of life or middle-aged individuals (43, 49). A systematic review and meta-analysis conducted by Mannan et al. suggests that depressive adolescents are at a 70% increased risk of obesity, and adolescent individuals with obesity are at a 40% greater risk of being depressed (50). The comorbidities related to overweight and obesity have been scientifically confirmed (51, 52), while knowledge of their association with mental health is still deficient (53) and inconclusive (45). Given that most of the studies have investigated the association between mental health and obesity only using measurements made at one time point (43), this work aims to contribute to a better insight into the nature of possible long-term relations, stimulate further discussion, and shed more light on possible reciprocal cause-effect relationships focusing on the mental health constructs depression and quality of life (QoL). Thus, the following hypotheses were formulated:

> *Null hypothesis (H_0): European female and male adults aged 50 years and older who live with either overweight or obesity show no significant positive bi-directional association between their depression score and body mass index (BMI), and also no significant negative bi-directional association between their quality of life (QoL) levels and body mass index (BMI) over a 10 year follow-up period.*

> *Alternative hypothesis (H_1): European female and male adults aged 50 years and older who live with either overweight or obesity show a significant positive bi-directional association between their depression score and body mass index (BMI), and also a negative significant bi-directional association between their quality of life (QoL) levels and body mass index (BMI) over a 10 year follow-up period.*

2. Materials and methods

2.1. Study design, survey method and samples

In this study, data from the Survey of Health, Ageing, and Retirement in Europe was used to investigate our research question aiming at analyzing a possible bi-directional association between the BMI of male and female individuals from wave 4 and mental health, including QoL and depression status, in wave 8 and vice versa, in the context of a longitudinal analysis using a two-wave cross-lagged panel approach over a defined time lag of 10 years.

The Survey of Health, Ageing and Retirement in Europe was conducted among 50+ individuals and started in 2004, including 11 countries within Europe. Baseline study in wave 1 involved Scandinavia (Denmark, Sweden), central Europe (Austria, France, Germany, Switzerland, Belgium, Netherlands) and the Mediterranean including Greece, Italy and Spain. At the end of 2004, Israel was additionally integrated into the survey. Estonia, Portugal, Slovenia and Hungary joined the third regular panel in wave 4 carried out in 2010, including 58,000 participants constituting the gross data basis for this study. Fieldwork for the eighth wave in October 2019 was interrupted

due to the COVID-19 pandemic in March 2020, resulting in a considerably shortened questionnaire. Therefore, the following countries were included: Austria, Belgium, Bulgaria, Cyprus, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Israel, Italy, Luxembourg, Poland, Spain, Sweden, Lithuania, Latvia, Malta, Finland, Switzerland, Slovenia, Hungary, Netherlands and Slovakia (54) resulting in a gross sample size of 46,733 of which 19,915 participants completed main interviews in the fourth wave.

The target population of the SHARE survey consisted of people who were 50 years of age or older at the time of the surveys and who had their regular residence in the relevant country of the survey. Persons who were either hospitalized, incarcerated, or out of the country for the entire duration of the interview were excluded from the interviews. Other exclusion criteria included insufficient language skills with regard to the respective national language or moving to an unknown address. All persons of a household born in 1960 or earlier (wave 4) and 1969 or earlier (wave 8) were admitted to interviews (55). The participation in the interviews was voluntary and confidential. All collected data from the survey interviews was linked to a wave-specific identifying variable (ID) (54).

All data was collected using computer-assisted personalized interviews (CAPI) and face-to-face interviews. This process was further enhanced by self-completed paper & pencil questionnaires (54). Each interviewer was using a laptop when conducting face-to-face interviews on which the CAPI tool was installed. Due to the need of executing various physical tests, this personalized approach was necessary for the survey. SHARE uses an ex-ante harmonization concept, that is, one general questionnaire is translated into the respective national languages. This is made possible through the use of an internet-based translation tool, which carries out an automatic translation into the CAPI instrument (55). Based on a significant dropout of several respondents over the time period of 10 years who either died, moved from their regular residence, could no longer be contacted, or refused to participate, we finally obtained a net sample of 16,184 from 19,915 individuals who participated in both wave 4 and wave 8 providing complete data without defined missing values for further analysis. Another reason for the withdrawal of participants in the eighth wave from the survey might have been the beginning of the COVID-19 pandemic in 2019/2020, which is why the study was discontinued.

2.2. Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and obtained approval from the Ethics Committee of the Medical University of Graz, Austria (Document Number 32-305 ex 19/20).

2.3. Measures

2.3.1. Central variables

Overweight and obesity were derived from the variable body weight and height of each respondent in the survey and desired BMI values were then calculated according to Quetelet's formula: Weight divided by height in meters squared, expressed in kg/m^2 (56). Accordingly, individual categories of BMI were defined (4) representing overweight as a BMI greater or equal to 25, and obesity classified as a BMI greater or equal to 30. Depression status was measured using the EURO-D scale, an instrument for assessing late-life depression in different countries across Europe consisting of 12 items. Respondents can reach a score between 0 and 12, where a higher score indicates a higher degree of depression. Accordingly, scores equal to or higher than 4 represent a case of depression while values less than 4 correspond to the "no depression" category (57). The mental health variable QoL was collected using the CASP-12, a 4-point Likert scale questionnaire, comprising 4 sub-scales, including control, autonomy, self-realization, and pleasure. All 12 items constitute an overall score ranging from a minimum of 12 to a maximum of up to 48, whereby higher scores represent higher levels of QoL (58).

2.3.2. Control variables

It is well recognized that both social and economic factors have an impact on people's mental health status, whereby natural and man-made problems and situations may affect their resilience (59, 60). Furthermore, social aspects may have an impact on gaining body weight (61). The influence of control variables such as age, sex, living situation, and educational level, acting as confounding factors, was investigated using multiple linear regression analysis.

2.4. Psychometric properties

Internal consistency reliability of mental health measures was calculated using Cronbach's alpha. The EURO-D scale which was applied in wave 4 and wave 8 resulted in values ranging from 0.62 to 0.78 and proved to be rather moderately internally consistent in all included European countries (62). Moreover, the abridged CASP-12 scale indicates sufficient Cronbach's alpha scores between 0.56 and 0.76 across different countries (63).

2.5. Preparation and data cleaning

The first step was to match relevant SHARE data sets including central characteristics from waves 4 and 8 as well as sociodemographic variables. The matching procedure was accomplished using a person identifier variable as a key variable. Given that some cases yielded data on wave 4 but not on wave 8, all following calculations, including respective hypotheses tests, refer entirely to the cases in which all data was available. Remaining, non-paired cases were excluded using a filter variable. The age of respondents was transformed into categories representing three age groups: "50–59", "60–74", "75+". Collected information on the "living situation" of respondents was transformed into a binary coded variable for "living alone," and "living with a partner." Furthermore, we created dummy variables of the categorical predictors, including sex, BMI, and educational level to allow the analysis of their impact on the respective outcome variables. Responses such as, "refuse," "do not know," "implausible or suspected wrong," were defined as missing values and were excluded from the analysis.

2.6. Statistical analysis

Statistical analysis was entirely performed using IBM SPSS statistical software (Version 26). Addressing the long-term effects,

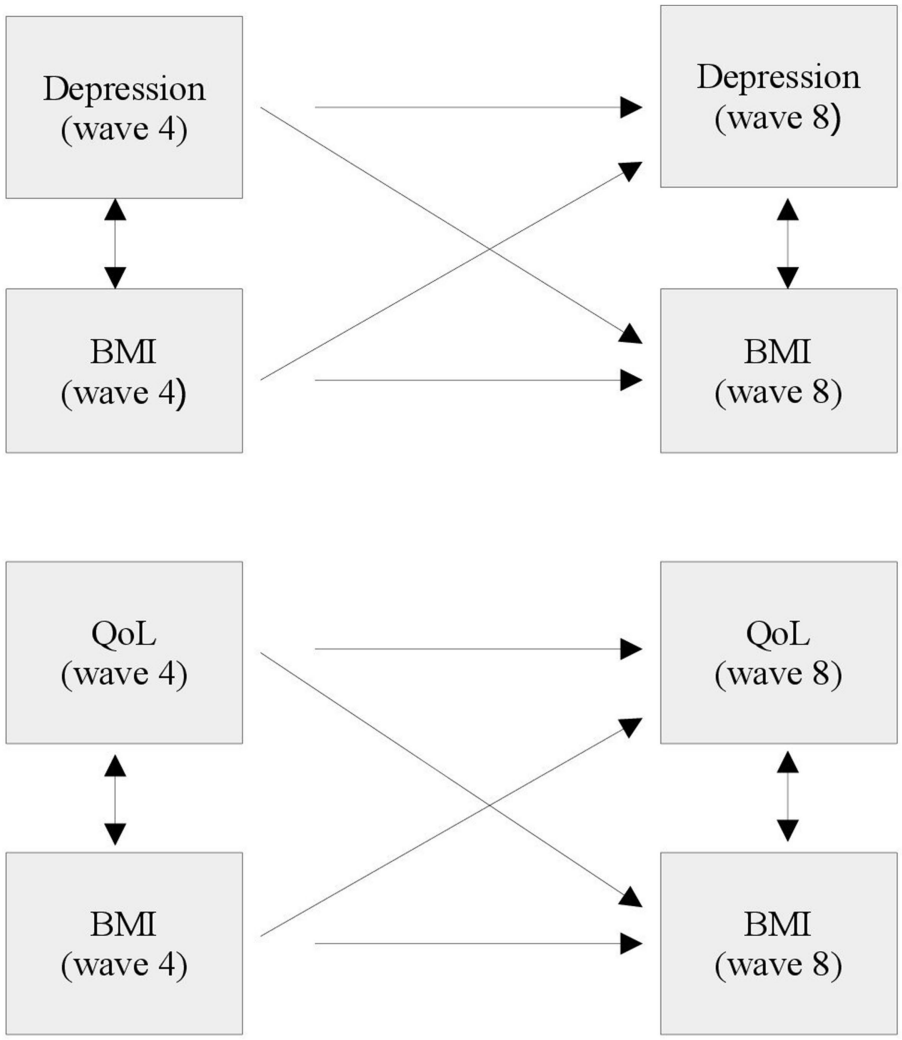

FIGURE 1
Overview of synchronicity, stability associations and cross-lagged pathways between central constructs: depression (EURO-D), QoL (CASP), and body mass Index (BMI). Single-headed arrows represent synchronous (cross-sectional) paths; double-headed arrows demonstrate stability (horizontal) and cross-lagged (diagonal) associations.

according to our hypothesis, was accomplished using multiple linear regression analysis to define associations between BMI categories and mental health variables, depression and QoL. The level of significance (value of p) was defined at $p < 0.05$ ($\alpha = 5\%$). In order to evaluate the association of predicting variables from wave 4 on outcome variables in wave 8, a two-wave-cross-lagged panel approach (64–66) with a time lag of about 10 years was conducted in the context of a longitudinal analysis. Central variables, BMI, depression status and QoL were measured at two different time points (wave 4 and 8) leading to six possible relations (65), which were analyzed using multiple regression analysis to determine stability (autoregressive) and cross-lagged effects, whereby synchronicity of constructs at both time points was assumed. Synchronicity, stability and cross-lagged associations of central variables in waves 4 and 8 result in two synchronous (cross-sectional), two stability (autoregressive), and two cross-lagged relations (65). In order to investigate the stability of the relation between BMI values at two time points, BMI was used as a metric predictor. Accordingly, autoregressive and cross-lagged effects between different measures in waves 4 and 8 were calculated simultaneously to determine the size of stability of each construct and reciprocal associations over time (Figure 1). Accordingly, the analysis of stability and cross-lagged effects resulted in 3 models (Table 1).

Based on these results, the impact of sociodemographic variables, including age, sex, living situation and educational level (ISCED-97) on respective outcome variables was analyzed. Additionally, further multiple linear regression analysis adjusting for sociodemographic characteristics was conducted.

3. Results

3.1. Demographics and health characteristics of participants

In the longitudinal analysis, 16,184 people (aged 50 and above) were included, consisting of 9,428 (58.3%) female and 6,756 (41.7%)

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TABLE 1 Overview of models analyzing stability and cross-lagged associations between central constructs.

Model	Stability path[a]	Cross-lagged path[b]
1	CASP CASP	underweight[b] CASP
DV: CASP		overweight[b] CASP
		living with obesity[b] CASP
2	EURO-D EURO-D	underweight[b] EURO-D
DV: EURO-D		overweight[b] EURO-D
		Living with obesity[b] EURO-D
3	BMI BMI	CASP BMI
DV: BMI		EURO-D BMI

[a]Autoregressive associations of constructs between wave 4 and wave 8.
[b]Crossed associations over a 10 year time lag.BMI, body mass index; CASP, QoL, EURO-D, depression; DV, dependent variable.

male respondents. The mean age of the participants was 63.6 years (SD = 8.1). The youngest participants were 50 and the oldest was 92 years of age. Most of the participants were from Estonia (13.1%) and the Czech Republic (10.1%). The majority of respondents reported living together with their partner (74.9%). In addition, 37.6% of the sample population indicate an upper secondary education (level 3) (Table 2).

The mean BMI score of the study population was 27.0 kg/m^2 (SD = 4.7). The majority of respondents were overweight (42.1%) followed by normal weight (35.2%) and people living with obesity (21.8%) – underweight people only account for a minority of 0.9%. The mean depression score according to the EURO-D scale was 2.2 (SD = 2.1) reflecting an overall non-depressed state of the population. After measuring QoL using the CASP-12 scale ranging from 0 to 12, mean values and standard deviations were calculated, indicating a mean QoL score of 38.4 (SD = 5.9) indicating a high level of QoL within the study population (Tables 3, 4).

3.2. Results of multiple linear regression analysis

All three models demonstrate good to high fit to the data. The first model (model 1) was significant in terms of the stability of QoL (CASP) scores and BMI categories predicting QoL over time in the eighth wave (F (4,16,179) = 1575.441, $p < 0.001$, $R^2 = 28.0\%$). As a result, QoL scores in wave 4 seem to significantly predict QoL scores (autoregressive path) at a second time point in wave 8 ($\beta = 0.515$, $p < 0.001$). This mental health characteristic indicates high stability over a lag time of about 10 years. Cross-lagged analysis of BMI categories predicting QoL indicates that people living either with overweight, obesity or underweight show significantly decreased levels of QoL in comparison to respondents of normal weight, where people living with obesity show the strongest effect ($\beta = -0.084$, $p < 0.001$).

Our second model (model 2) yields a significant result as well (F (4,16,179) = 820.656, $p < 0.001$, $R^2 = 16.8\%$). The Depression score proved significantly stable in the long term ($\beta = 0.403$, $p < 0.001$). The analysis of cross-lagged associations yields that BMI categories, underweight, overweight and obesity significantly predict depression

TABLE 2 Distribution of demographic characteristics in SHARE (n = 16,184).

Country	n	%
Austria	1,216	7.5
Germany	552	3.4
Sweden	739	4.6
Netherlands	906	5.6
Spain	701	4.3
Italy	945	5.8
France	1,588	9.8
Denmark	928	5.7
Switzerland	1,581	9.8
Belgium	1,153	7.1
Czech Republic	1,632	10.1
Poland	480	3.0
Hungary	679	4.2
Slovenia	967	6.0
Estonia	2,117	13.1
Sex		
Male	6,756	41.7
Female	9,428	58.3
Age group		
50–59	5,631	34.8
60–74	8,801	54.4
75+	1752	10.8
Partner in household		
Yes	12,116	74.9
No	4,068	25.1
Level of Education*		
ISCED-97 Code 1	2,262	14.0
ISCED-97 Code 2	2,906	18.0
ISCED-97 Code 3	6,090	37.6
ISCED-97 Code 4	960	5.9
ISCED-97 Code 5	3,837	22.9
ISCED-97 Code 6	129	0.8

*Code 1–6 of Education refers to the Level of 1–6 of Education: Primary education/first stage of basic education (ISCED-97 Code1), lower secondary education/s stage of basic education (ISCED-97 Code 2); upper secondary education (ISCED-97 Code 3), post-secondary, non-tertiary education (ISCED-97 Code 4), first stage of tertiary education (ISCED-97 Code 5), second stage of tertiary education (ISCED-97 Code 6).

TABLE 3 Distribution of BMI categories in SHARE (wave 4).

BMI Category	n	%
underweight	145	0,9
normal weight	5,701	35.2
overweight	6,815	42.1
living with obesity	3,523	21.8

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TABLE 4 Descriptive statistics of variables in SHARE (n = 16,184).

Variables	Mean	SD
BMI	27.0	4.7
CASP Index	38.4	5.9
Depression (EURO-D)	2.2	2.1
Age	63.6	8.1

TABLE 5 Overview of stability and cross-lagged coefficients-unadjusted linear regression model (n = 16,184).

Variables	CASP (wave 8)		EURO-D (wave 8)		BMI (wave 8)	
	β	p	β	p	β	p
CASP Index	0.515[b]	<0.001	–	–	0.000[c]	0.950
EURO-D	–	–	0.403[b]	<0.001	0.006[c]	0.266
underweight[a]	−0.026[c]	<0.001	0.020[c]	0.005	–	–
overweight[a]	−0.044[c]	<0.001	0.026[c]	0.001	–	–
obesity[a]	−0.084[c]	<0.001	0.063[c]	<0.001	–	–
BMI[d]	–	–	–	–	0.782[b]	<0.001
Adjusted R^2	28.0%		16.8%		61.2%	

[a]Normal weight is a reference category.
[b]Stability (autoregressive) coefficients over 10 year time lag.
[c]Cross-lagged coefficients over 10 year time lag.
[d]Metric scaled.–, not applicable.

status over time, resulting in increased scores of depression compared to people of normal weight. Again, with the strongest effect among individuals who live with obesity ($\beta = 0.063$, $p < 0.001$).

The third model (model 3) was also significant (F (3,16,180) = 820.656, $p < 0.001$, $R^2 = 61.2\%$) demonstrating a significantly stable association regarding the autoregressive path. The BMI score in wave 4 predicts the BMI score in wave 8, indicating high stability ($\beta = 0.782$, $p < 0.001$), whereas depression state and QoL do not significantly predict BMI over time (Table 5).

3.3. Results of multiple linear regression analysis adjusted for sociodemographic confounders

In order to investigate the impact of sociodemographic covariates on respective outcome variables, we performed a second run of analysis adjusting for baseline characteristics, including sex, age, living situation, and educational level. In addition, cross-lagged associations between central constructs and stability correlations were retested according to models 1 to 3 described above, including confounding predictors.

The first model examining the effect of BMI categories and confounding factors on QoL was significant (F (12,16,171) = 647.113, $p < 0.001$, $R^2 = 32.4\%$). The analysis reveals that respondents of older age indicate a significantly lower QoL, which comparably demonstrates the strongest effect among sociodemographic characteristics within this model in terms of predicting QoL ($\beta = -0.166$, $p < 0.001$). Moreover, our first adjusted model provides no evidence that sex of respondents significantly affects QoL over time. The education of respondents seems to significantly affect QoL. In fact, the higher the level of education the higher the QoL in the long term, while educational level 5, referring to tertiary education, represents the strongest educational predictor of QoL ($\beta = 0.118$, $p < 0.001$). Individuals who live with their partners show significantly higher QoL than those who live alone ($\beta = 0.032$, p < 0.001).

The second model examined the impact of confounding factors on depression scores, yielding a significant result (F (12,16,171) = 345.542, $p < 0.001$, $R^2 = 20.3\%$). Similar to model 1, age of respondents seems to play a significant role in predicting depression scores over time. People of older age show higher depression scores over a time-lag of about 10 years ($\beta = 0.138$, <0.001). Furthermore, females significantly indicate increased depression scores compared to males ($\beta = 0.091$, <0.001). The level of education seems to affect depression scores. More precisely, higher educated individuals indicate significantly lower depression levels over a 10 year period in contrast to individuals with low education. Again, tertiary educated individuals, who belong to educational level 5, show the strongest effect in terms of decreased depression scores ($\beta = -0.094$, $p < 0.001$), while living with a partner has no significant effect on depression status compared to living without a partner.

The third model proved to be significant as well (F (11,16,172) = 2421.248, $p < 0.001$, $R^2 = 62.2\%$). Interestingly, older respondents seem to have significantly lower BMI scores ($\beta = -0.100$, $p < 0.001$), whereas sex has no significant effect on BMI scores. With regards to education, in contrast to QoL and depression status, education levels 5 and 6 (tertiary education) make a significant contribution to the prediction of BMI ($\beta = -0.028$, $p < 0.001$; $\beta = -0.013$, $p = 0.008$). Thus, tertiary education seems to be negatively associated with BMI, indicating that tertiary educated individuals show decreased BMI scores. Overall, living situations, that is "living with a partner," does not significantly predict BMI (Table 6).

In summary, the stability of central constructs proved significant over a 10 year time period in all three models. Significant cross-lagged effects can be observed in one direction between BMI predicting QoL

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TABLE 6 Overview of stability and cross-lagged coefficients-adjusted linear regression model (n = 16,184).

Variables	CASP Index (wave 8)		EURO-D (wave 8)		BMI (wave 8)	
	β	p	β	p	β	p
CASP Index	0.487[c]	<0.001	–	–	−0.001[f]	0.856
EURO-D	–	–	0.378[e]	<0.001	0.003[f]	0.567
BMI category						
underweight[d]	−0.025[f]	<0.001	0.017[f]	0.014	–	–
overweight[d]	−0.031[f]	<0.001	0.025[f]	0.002	–	–
obesity[d]	−0.077[f]	<0.001	0.060[f]	<0.001	–	–
BMI[g]	–	–	–	–	0.779[e]	<0.001
Sex[a]	−0.009	0.168	0.091	<0.001	−0.004	0.414
Age	−0.166	<0.001	0.138	<0.001	−0.100	<0.001
Education						
ISCED-97 code 2[b]	0.025	0.006	−0.047	0.001	−0.002	0.720
ISCED-97 code 3[b]	0.089	<0.001	−0.077	<0.001	−0.004	0.588
ISCED-97 code 4[b]	0.052	<0.001	−0.050	<0.001	−0.000	0.997
ISCED-97 code 5[b]	0.118	<0.001	−0.094	<0.001	−0.028	<0.001
ISCED-97 code 6[b]	0.014	0.037	−0.010	0.153	−0.013	0.008
Living situation						
Partner in household	0.032	<0.001	0.006	0.434	−0.010	0.043
Adjusted R^2	32.4%		20.3%		62.2%	

[a]Female gender is a reference category.
[b]Primary educational level is a reference category.
[c]Living with a partner is a reference category.
[d]Normal weight is a reference category.
[e]Stability (autoregressive) coefficients over 10 year time lag.
[f]Cross-lagged coefficients over 10 year time lag.
[g]Metric scaled.–, not applicable.

and depression state, but not vice versa. Hence, people living with underweight, overweight or obesity show lower QoL and higher depression scores than people of normal weight, whereas obesity indicates the strongest effect regarding the prediction of both QoL and depression state over a lag-time of 10 years. Accordingly, results do not confirm any reciprocal association. The depression state and QoL do not significantly predict BMI in older adults. Moreover, attention has to be paid to the rather small strength of the respective cross-lagged effects.

Sociodemographic predictors such as educational level and age of respondents seem to significantly affect QoL, depression state, and BMI over time. Higher education seems to be associated with lower BMI and depression scores. More highly educated people show greater QoL levels than those with lower levels of education. Female gender obviously predicts increased depression scores, whereas no significant impact on QoL and BMI can be observed. The older age of respondents also proved to be a significant predictor for increased depression scores and decreased QoL, but is negatively associated with BMI scores, implying that older individuals display lower BMI scores. However, the effects are rather small.

4. Discussion

This study is grounded on the assumption that European female and male adults aged 50 years and older who live either with overweight or obesity show a significant positive bi-directional association between their depression score and body mass index (BMI), and a significant negative bi-directional association between their quality of life (QoL) levels and body mass index (BMI) over a 10 year follow-up period. Accordingly, this investigation was performed using longitudinal data from older individuals aged 50 years of age or above to determine possible associations in both directions using a two-wave cross-lagged panel approach. In order to investigate the associations between mental health constructs and overweight or obesity over a time-lag of about 10 years, multiple regression analysis was conducted focusing on answering the hypothesized research question. Mental health characteristics were measured by means of well validated questionnaires that demonstrate good to excellent psychometric properties and BMI scores were calculated constituting the foundation for our analysis.

With regard to our main research hypothesis, the findings of the investigation of possible associations between BMI levels and mental health variables yields indications of significant small effects in terms of predicting QoL and depression scores implying higher depression and lower QoL scores among those people who live with underweight, overweight or obesity compared to persons of normal weight. Accordingly, people living with obesity demonstrate the strongest effect regarding the prediction of both QoL and depression status. Despite significant results, the strength of these effects is rather small and should therefore be interpreted with caution in terms of

confirming any considerable association in the long term. The hypothesis of a one-directional association (25, 43, 48, 50) was grounded on the assumption that female and male adults aged 50+ who live with either overweight or obesity indicate a significant positive association between their BMI predicting depression score and a negative association between participants´ BMI and quality of life (QoL) levels in a 10 year follow-up. As a result, a significant one-directional cross-lagged effect can be observed regarding BMI scores predicting QoL and depression status. People who live with overweight and obesity are more likely to show increased depression scores and decreased QoL. Furthermore, regression analysis reveals that neither depression nor QoL predict BMI. However, we were not able to confirm any significant reciprocal associations between mental health and overweight or obesity.

Obviously, certain sociodemographic characteristics such as age, level of education, and sex are associated with mental health characteristics and BMI. In addition, living with a partner seems to slightly increase QoL and decline BMI. Female gender, in particular, seems to significantly predict increased depression scores. Another result of our study indicates that respondents of older age are more likely to show decreased BMI scores, which is consistent with suggestions by Wysokiński et al. who postulate that many older, even healthy individuals, experience weight loss, which may be associated with an age-related reduced food intake resulting from dysregulated appetite, especially among people of very advanced age referred to as "anorexia of aging" (67). The negative association between older age and reduced BMI scores, according to our study, may be due to the fact that our sample population also included some respondents of very advanced age. However, to the best of our knowledge, there is no clear evidence available for younger populations. As suggested by previous research (68, 69), anorexia of aging and the related loss of weight typically occurs among the older adults above 65 years of age who are either hospitalized, in long-term care facilities, or live with neurological disorders or inflammatory diseases. This effect is therefore thought to be an age-related condition emerging from metabolic changes, loss of appetite, and frailty, among other things (70). As a consequence, the decrease of weight and body fat is considered a typical late-life phenomenon (71). According to several studies on the risk of developing depression, demographic conditions such as female gender (72, 73) and older age (74, 75) are recognized risk factors for the development of this mental health condition. Regarding sociodemographic parameters, the findings of this study turned out to be in line with the results of previous studies (59, 76). In particular, social determinants including age, sex, and educational attainment seem to be associated with people's mental health (60). In line with our expectations, and consistent with prior research (72, 73), female gender appears to be more strongly associated with reporting higher depression scores compared to males, whereas sex of participants has no significant impact on QoL.

The main finding of this study that BMI significantly predicts depression state and quality of life levels, is partially consistent with suggestions from a systematic review and meta-analysis conducted by Mannan et al. who investigated bi-directional associations between obesity and depression (50). The results obtained by Mannan et al. suggest a significant depression-obesity link regardless of the direction of association, although the strength of association turned out to be more significant in terms of depression leading to obesity than vice versa (50). Nevertheless, findings obtained from multiple regression analysis are not in line with the suggestions made by McElroy et al. and Pickering et al. who stated that mentally ill individuals are at a higher risk of developing overweight and obesity (45, 46) since no significant link between mental illness leading to overweight or obesity can be observed with respect to depression status and QoL level. Yet, our findings indicate some similarities with the results from Luppino et al. who postulated that low QoL and depression often co-occurs with obesity and may be highly prevalent among older individuals who experience impaired physical conditions (48).

Furthermore, a meta-analysis of several longitudinal studies conducted by Luppino et al. found that obesity and depression are reciprocally associated (48). As a result, our findings are consistent with the suggestions by Luppino et al. who claim that depression, mental health issues, and poor quality of life (QoL) are frequently related to obesity (48). Moreover, our findings are in line with the suggestion by (43, 49) indicating that the association between obesity and mental health is more pronounced in older individuals (43, 49). In this regard, our results suggest that people at older age living with obesity and overweight indicate decreased QoL and higher depression levels in comparison to people of normal weight. Furthermore, results from multiple regression analysis are consistent with the statements of Avila et al. claiming that obesity is significantly associated with reduced QoL. In accordance with that, mental illnesses such as depression seem to be significantly associated with obesity and may also lead to a considerable decrease in QoL. In the case of co-occurrence of these two conditions, effects seem to amplify significantly. Despite the existing public awareness and corresponding efforts made, the rising prevalence of both mental illness and obesity is still a fundamental issue (12).

Correll et al. suggest that the majority of mentally ill individuals live with obesity, respectively overweight, hinting at a possible link between mental illness and obesity (26). Accordingly, our findings agree with previous research from Corell et al. in terms of identifying a significant relationship between BMI and depression status (26) in the sense that obesity leads to increased depression scores. However, results obtained from our investigation also reveal that people living with underweight show significantly reduced QoL and increased depression scores as well, even though the effect size is at its lowest here.

The core finding of this investigation is in line with the suggestions by De Hert and colleagues who postulate that people living with obesity are more likely to have a mental illness (25). However, this concordance, according to our result, may only apply to the constructs depression and QoL. Considering that the relationship between obesity and mental health seems to be more pronounced in older adults than in younger populations, our major finding, that is, BMI is significantly associated with increased mental health issues, is consistent with the claims made by (43, 49). However, when interpreting the results, especially with regard to the one-directional association between BMI and mental health variables, it should be taken into account that the participants were already over 50 years of age, and we do not have reliable data about the onset of obesity. In addition, the dichotomization into depressed/non-depressed does not account for the severity of depression. Another important point is the effect of taking psychotropic medication, that is, antidepressants (34–39) and antipsychotics, which are considered major leading factors causing obesity and may contribute to the outcome of this study. Hence, this might be a possible explanation for our result indicating BMI predicting mental health but not vice versa. Additionally, another explanation could be the fact that many respondents of advanced age

with a lower BMI were included in our study, which could also have an impact on this outcome.

4.1. Limitations and strengths of this study

In contrast to the performance of randomized control trials (RCTs) for investigating causal effects among study populations, longitudinal studies of observational data such as the Survey of Health, Ageing and Retirement in Europe (SHARE) offers the opportunity to study long-term, and hypothesized bi-directional associations over a defined time-lag. Although results can never prove complete causality. Nevertheless, this study provides a longitudinal design that is highly desirable in order to investigate cause-effect associations between mental health and overweight over time. Despite a large sample size, including respondents from all over Europe, this study does not account for further possible confounding factors such as physical activity, eating behavior, physical comorbidities or the use of psychotropic medication, which may substantially contribute to causing obesity and metabolic side effects (40).

In fact, information on the intake of psychotropic drugs of respondents may have an impact on results considering that prior research (34–39) suggests that certain antidepressants are suspected to potentially increase the risk of weight gain, in addition to antipsychotic drugs. Following the suggestions from an early review conducted by Fava, older antidepressants such as mirtazapine, within the subgroup of tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), may more frequently increase body weight compared to the newer generation of selective serotonin reuptake inhibitors (SSRIs) (35), which is also in accordance with suggestions by Serretti and Mandelli who claim in their meta-analysis that mirtazapine, among other antidepressants, is considered a cause of weight gain (36, 37, 39). Gaining weight from these medications may in some cases result from complex hormonal mechanisms, including the antihistaminergic effect of both antipsychotics and certain antidepressants on H_1 histamine receptors, and imbalances of the orexigenic and anorexigenic hormones ghrelin and leptin (77–79). Yet, it should be considered that the mechanisms through which antidepressants may potentially be associated with weight gain are unclear and poorly understood (80) assuming that these findings may not warrant causal inference, while the effect of residual covariates possibly contribute to overrate this association (81).

According to Rogosa, investigating long-term effects using a two-wave cross-lagged procedure is not useful for determining causal inference (82), whereas Selig and Little suggest that this panel design may generate more insight, better understanding of longitudinal associations, and stimulate further research (83). Another limitation of this study is that the anthropometric characteristic body weight was self-reported, which carries the risk of response bias. Moreover, we were not able to account for weight bias and stigmatization of people living with obesity, which obviously may affect people's mental health status. Individuals who live with obesity often experience weight bias and being targeted for jokes because of their body weight, especially via the media, which further promotes the stereotype that larger body size does not comply with the norm, and is socially not acceptable (84).

In fact, one strength of this study is that the analysis is based on observational data derived from a large-scale panel approach which may significantly contribute to generating an adequate sample population encompassing the older adults in their private household setting. The analysis of longitudinal data provides a reliable tool for identifying cause-effect- and bi-directional associations in the long term. Since data collection was performed on people of the general population from 15 European countries, the sample population is assumed to be representative and provides an appropriate sample size yielding generalizable results.

4.2. Outlook, implications for the future

Given that both mental illness and overweight are public health issues of great importance, gaining more insight into the complexity of their relationship and exploring the underlying nature of these two entities seem to be crucial in respect of disease prevention and developing innovative treatment strategies considering that mental health issues have often been overlooked in the past (85). The findings of this study should initiate further research focusing on this subject, accounting for links between mental health issues and their impact on body weight, and vice versa, particularly, in the older adults among whom overweight and obesity is highly prevalent. Thus, integrating mental health status into treatment strategies following a biopsychosocial approach and implementing new evidence in clinical settings could improve future treatment and prevention strategies.

In this regard, this study should encourage researchers to set up innovative investigations addressing associations between mental health and obesity, and further analyze interactions between common mental illnesses such as depression and anxiety, with respect to overweight and obesity, particularly with regard to bi-directional long-term effects and corresponding casualties in terms of a cause-effect principle. In fact, evidence on associations between mental health and obesity is still inconclusive (45) and most of the studies that have been carried out in the past are based on a cross-sectional approach, while prospective studies using repeated measurements of both mental illness and overweight are scarce. In particular, further large-scale investigations are required in order to provide profound studies by which potential cumulative effects can be analyzed and discussed in a broader sense. Moreover, generalizability of previous findings needs to be verified (43). Nowadays, both mental illness and obesity are among the greatest global public health challenges. Exploring and understanding the underlying nature of these complex relationships is crucial and highly desirable, considering that the associations between obesity and mental health highlight the importance of addressing both physical and mental health when treating obesity. By addressing mental health concerns, individuals with obesity may be better equipped to manage their weight and improve their overall health and well-being.

4.3. Contribution to the field

This work is intended to create stronger awareness and to stimulate further discussion on this issue. In particular, this research provides multiple measuring points within a panel approach, which is highly necessary to assess reciprocal interactions. Most of the prior research focusing on the relationship between obesity and mental health predominantly determines synchronous effects of a given population leading to results that are generally rather inconsistent (43). Our investigation provides a longitudinal design that allows us to estimate reciprocal interactions, which is quite rare in view of the

existing evidence. Since it is well known that both obesity and mental health issues do often occur among older individuals, indicating a highly prevalent issue, our findings provide valuable statements about the associations over a long period of time, and hint to possible causal influences that need to be further analyzed by future research activities. Moreover, most of the studies carried out previously yielded results that do not allow an overall conclusion to be drawn for all age groups, which may have an impact on respective results (48). This study contributes to obtaining a more detailed picture of long-term effects and interactions among older people, which is essential in terms of determining the direction of the relationship. On this foundation, treatment strategies and prevention programs could be further improved by identifying potential risk factors, considering that obesity may be a risk factor for the development of depression, interventions that target overweight and obesity may improve the prevention of depression and low QoL. Furthermore, the results of our investigation should serve as an important foundation for clinical practice suggesting that clinicians and professional care providers should account for mood monitoring in patients living with overweight and obesity, especially when treating older patients with long-term obesity, which may further facilitate the establishment of treatment guidelines.

In addition, we hope that the findings of this study strengthens public awareness about the importance of addressing both obesity and mental health in order to reduce stigmatization and encourage affected individuals to seek treatment. This work should further contribute to identifying early signs of pathological developments and improving interventions for people at a higher risk. We really hope that this research stimulates further scientific discussions and investigation to verify the nature of the relationship between mental health and obesity. Based on our findings, we do believe that further epidemiological research is warranted to determine these underlying mechanisms, notably with regard to possible moderators and confounding factors within the European population. Finally, we hope that our findings inform policy decisions related to public health.

5. Conclusion

In conclusion, cross-lagged, one-directional associations between BMI predicting mental health characteristics depression and QoL can be confirmed over a 10 year period. However, this study does not verify any considerable bi-directional associations in the long term corresponding to previous investigations on this topic (12, 45, 46, 48, 50). Even though models show significance regarding explained variances, overall corresponding beta coefficients proved to be rather small. These findings should be taken as weak evidence of a possible association, although this is not proof of a causal relationship. Generally, results should be seen as an impetus for further research on this topic. Gaining knowledge, not only among older populations, but also in terms of detecting early onsets of pathologies among younger populations involving children and adolescents seems to be crucial for preventing illnesses.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical University of Graz, Austria (Document Number 32-305 ex 19/20). The patients/participants provided their written informed consent to participate in this study.

Author contributions

GR, AG, and WF: conceptualization and writing—review and editing. GR and WF: methodology, formal analysis, interpretation of data, and visualization. GR: writing—original draft preparation. WF: supervision and project administration. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1206283/full#supplementary-material

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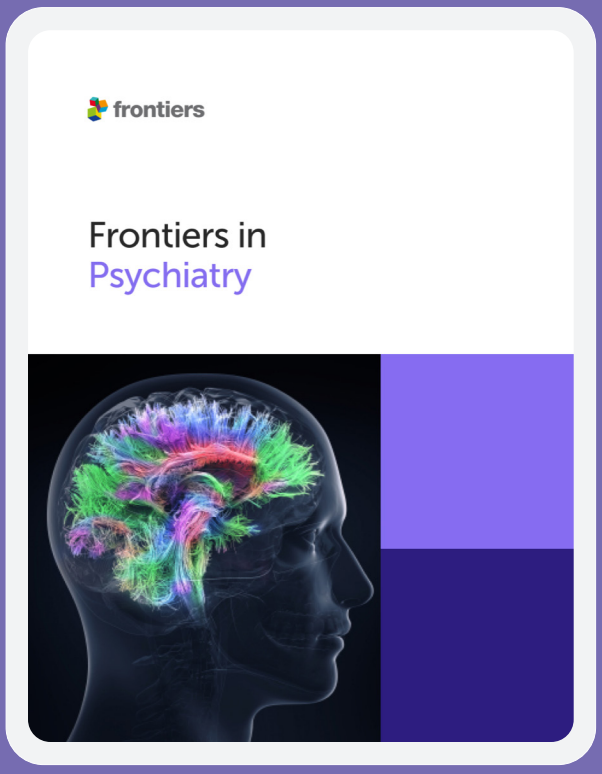

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