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Efficacy of an adjuvant non-face-to-face multimodal lifestyle modification program for patients with treatment-resistant major depression: A randomized controlled trial

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ABSTRACT

Background: The high prevalence of depression is partly attributable to the poor response of patients to first-line antidepressants. Multimodal programs that promote a healthy lifestyle are successful in treating depression when used as a complementary therapy, but their medium- and long-term benefits have not been demonstrated for patients with treatment-resistant depression (TRD). The main aim of this study was to compare the effectiveness of a lifestyle modification program (LMP) with mindfulness-based cognitive therapy (MBCT) and a placebo-control (written suggestions for lifestyle changes) in Spanish patients with TRD.

Methods: This controlled clinical trial randomized 94 patients with TRD into 3 arms. The primary outcome was the Beck Depression Inventory-II (BDI-II) score at baseline, 2, 6 and 12 months. The secondary outcomes were changes in scores that evaluated quality-of-life, adherence to the Mediterranean diet, physical activity, and social support.

Results: Relative to the placebo group, the LMP and MBCT groups had significantly better quality of life ($p = 0.017$; $p = 0.027$), and the LMP group had significantly better adherence to the Mediterranean diet ($p<0.001$) and reduced use of antidepressants ($p = 0.036$). However, the three groups showed no significant differences in BDI-II score.

Limitations: Only about half of the planned 180 patients were recruited, in part due to the COVID-19 pandemic.

Conclusions: There was no evidence that the LMP treatment significantly reduced symptoms of depression relative to the other groups during the COVID-19 lockdown.

1. Introduction

Recent estimates indicated that about 186 million people worldwide live with major depressive disorder (MDD) (Global Health Data Exchange, 2021). Many of these patients have poor prognoses because of difficulties in diagnosis, limited access to effective treatments, and

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unsatisfactory responses to first-line antidepressants (Silverman et al., 2015; Hidaka, 2012; Mueller et al.,1996). In particular, there is evidence that more than one-third of patients with MDD do not respond to conventional antidepressants and do not achieve lasting remission (Malhi et al., 2020; Rush et al., 2006; Silverman et al., 2015; Voineskos et al., 2020). It is likely that many of these patients would benefit from psychosocial treatments that have proven effectiveness (Ijaz et al., 2018; Lopresti et al., 2013; Sarris et al., 2014).

MDD is usually considered treatment-resistant depression (TRD) when treatments with at least two antidepressants have been unsuccessful (Conway et al., 2017a; Brown et al., 2019; Daly et al., 2018; Rush et al., 2006; Schosser et al., 2012). Nevertheless, researchers have proposed more than 100 different definitions of TRD (Brown et al., 2019), indicating a lack of consensus on what constitutes TRD (Conway et al., 2017b; Brown et al., 2019; Gaynes et al., 2020).

To address the enormous individual and public health burden of MDD, there is a need for new, effective, well tolerated, and safe alternative treatments (Pérez-Sola et al., 2021). MDD has a complex etiology and is a multifactorial disease; hence, a variety of lifestyle factors may affect its development and progression, as well as the efficacy of different treatments (Gómez-Gómez et al., 2020; Haapasalo et al., 2018; Lopresti et al., 2013; Sarris et al., 2014). There is compelling evidence that a variety of lifestyle factors may protect against a depressive mood (Gómez-Juanes et al., 2017; Sarris et al., 2020; Wang et al., 2021). For example, encouraging patients to adopt lifestyle changes may be an effective approach for managing and treating depression (Goracci et al., 2016; Sarris et al., 2014).

Lifestyle medicine (LM), which encourages patients to make changes in their lifestyle, has emerged as an approach for managing numerous health problems (Egger et al., 2009). LM combines environmental, behavioral, and psychological principles with a therapeutic and preventive approach to improve physical and emotional well-being. Diet, physical activity, and sleep are the major targets of these interventions (Egger et al., 2009; Sarris et al., 2014). Previous reviews found that diet, exercise, and social interaction were the three primary lifestyle factors that affected the course of TRD (Lopresti et al., 2013). Some other studies emphasized the importance of sleep, sun exposure (García-Toro et al., 2012; Serrano Ripoll et al., 2015), and stress management (Wong et al., 2021).

Some evidence suggests that a LM intervention that focuses on a single factor could be effective for patients with MDD (Gómez-Gómez et al., 2020). Other studies used LM interventions that targeted multiple factors, based on the assumption that different lifestyle factors may interact (Hidaka, 2012; Sarris et al., 2014). A recent meta-analysis reported that multi-component LM interventions appeared to be effective in reducing MDD symptoms in the short-term (Gómez-Gómez et al., 2020; Wong et al., 2021). Nevertheless, controversy remains regarding the long-term efficacy of these multi-component lifestyle programs, mostly related to difficulties in maintaining patient adherence (Castro et al., 2021; Serrano Ripoll et al., 2015; Wong et al., 2021). Consequently, some researchers suggested the importance of increasing patient support and encouraging patient commitment and motivation to make behavioral changes, such as through of group psychotherapy (Serrano Ripoll et al., 2015). A multi-component program that considers these many issues could help patients with TRD, but studies using LM interventions have heretofore only examined the impact of certain specific lifestyle changes on patients with TRD (Mota-Pereira et al., 2011).

More research is needed to evaluate the feasibility and efficacy of LM interventions that address multiple lifestyle factors in patients with MDD, and to assess their short and long-term impacts. Well-controlled trials that control for bias are needed to examine this topic, because the placebo effect can be significant in patients with MDD and TRD (Jones et al., 2021). For instance, some studies on treatments for MDD used patients on a waiting list as a control group, which can lead to bias that favors the intervention group (Leichsenring et al., 2022). Additionally, when evaluating a novel psychotherapeutic intervention, a comparison with a previously established intervention is often recommended. To make such a comparison, however, it is crucial to avoid biases by using interventions that have similar formats, sessions with similar durations, and similar prescriptions for daily tasks outside the therapy sessions. Mindfulness-based cognitive therapy (MBCT) is an intervention with a format similar to multi-component LM programs, and has a well-established effect on preventing new episodes of recurrent depression (McCartney et al., 2021). MBCT has also shown to be effective during episodes of MDD, even in patients with TRD (Cladder-Micus et al., 2018; Eisendrath et al., 2016; Foroughi et al., 2020).

The effect of the COVID-19 pandemic on mental health is mostly unknown, but it is likely to have had deleterious effects, at least in part because it greatly disrupted the lifestyles of so many people (Cervera-Martínez et al., 2021). The psychological impact of quarantine can be substantial and long-lasting (S. K. Brooks et al., 2020). Studies have found associations between the COVID-19 pandemic and increased prevalences of anxiety and depression (Huang et al., 2020) and depressive disorders (Santomauro et al., 2021). The COVID-19 pandemic led to changes in health care, including mental health care. In particular, there was a shift toward remote care because of lockdowns, and many patients received psychological therapies using a computer, tablet, or smart phone for management of depression, subjective well-being, and other conditions (Fischer et al., 2020). Recent meta-analyses concluded that several evidence-based psychological non-face-to-face treatments were effective for treatment of depression (Andersson and Cuijpers, 2009; Andrews et al., 2010; Castro et al., 2020), although self-guided multi-component online interventions appear to be less effective than standard in-person therapies (Fischer et al., 2020). In addition, guided online interventions appear to be more effective than self-guided online interventions (Fischer et al., 2020).

The main objective of the present study of patients with TRD was to compare the effectiveness of a lifestyle modification program (LMP) with MBCT and with a placebo treatment (written recommendations for a healthy lifestyle). The primary hypothesis was that patients randomized to the LMP group would show greater improvement in a clinical measure of depression than those in the placebo group, and no less improvement than those in the MBCT group. The secondary hypotheses are that measures of quality-of-life and healthy lifestyle (diet, physical activity, social support) in the LMP group would be higher than those in the placebo-control group, and no less than those in the MBCT group.

2. Materials and methods

2.1. Study design

This study was a pragmatic, parallel, randomized, and controlled clinical trial with three treatment arms: Placebo-control (placebo), Mindfulness-Based Cognitive Therapy (MBCT), and Lifestyle Modification Program (LMP). Each intervention was administered for 8 weeks. Data were collected at baseline (T0), and at 2 months (T1), 6 months (T2), and 12 months (T3). The details of the main study methods and procedures were published previously (Navarro et al., 2020).

This study was registered at ClinicalTrials.gov (NCT04428099; 11/6/2020). Ethical approval was provided by the Research Ethics Committee of the Balearic Islands (IB3925/19PI; 29–5–2019). The study design was developed in accordance with the Helsinki Declaration. All participants provided written informed consent for participation after receiving comprehensive explanations of the study protocol.

2.2. Participants and procedures

Patients from the Balearic Islands diagnosed with an episode of TRD were recruited by mental health workers by phone and using social media. After a participant was deemed eligible and provided with information about the study, informed consent for participation was

obtained either in person at Health Research Institute of the Balearic Islands (IdISBa) or using a web platform. Because the COVID pandemic had been declared, a psychologist administered the baseline questionnaires by phone. Each eligible patient was randomly allocated in a 1:1:1 ratio to one of three groups (placebo, MBCT, or LMP). Randomization was concealed using a computer-generated random assignment sequence. Each intervention was implemented remotely using an online platform due to the COVID-19 pandemic. Recruitment started on January 22, 2020 and ended on February 8, 2021. All interventions were free-of-charge to the patients.

2.3. Inclusion and exclusion criteria

The inclusion criteria were age ≥18 years-old; diagnosis of an episode of TRD, defined by MDD based on DSM-5, the Mini-International Neuropsychiatric Interview (MINI) criteria, and at least two failures or refusals of treatment using a psychopharmacological treatment; previous care by a psychologist or psychiatrist for at least 1 month; sufficient physical ability and cognitive aptitude to understand and participate in the study; and access to technologies and knowledge needed to engage in online videoconferences at home.

The exclusion criteria were inability to speak the Spanish language; presence of another disease that affects the central nervous system (*e.g.*, organic brain pathology, traumatic brain injury, or dementia); another psychiatric diagnosis or severe psychiatric illness by MINI criteria (*e.g.*, substance dependence or abuse, history of schizophrenia or other psychotic disorders, eating disorders, severe anxiety or a severe personality disorder); presence of a serious or uncontrolled medical, infectious, or degenerative illness that may interfere with the affective symptoms; presence of delirium or hallucinations; pregnancy or breast-feeding; high risk of suicide; and presence of any medical, psychological, or social condition that could seriously interfere with participation in the study.

2.4. Sample size

A 17% reduction in the Beck Depression Inventory-II (BDI-II) score (Beck et al., 1996) is considered clinically relevant (Button et al., 2015). Based on our previous study (García-Toro et al., 2012), the statistical power was calculated so that a reduction of 6 points or more in the BDI-II score at the 12-month follow-up could be detected. Considering a dropout rate of 25%, α risk of 0.05, and β risk of 0.15 in a bilateral comparison, 60 subjects were required for each group. Thus, the total required sample size was estimated to be 180.

2.5. Intervention

Each participant received treatment as usual (TAU) prescribed by the mental health team. The LMP consisted of treatments prescribed by the mental health team, written suggestions for lifestyle changes, and an 8-week lifestyle promotion program. The MBCT consisted of treatment prescribed by the mental health team, written suggestions for lifestyle changes, and an 8-week on-line MBCT program. The placebo treatment prescribed by the mental health team consisted of written suggestions for lifestyle changes.

All therapists were trained mental health experts who reviewed patient engagement and provided one-to-one support online or by chat, and less frequently by telephone calls. The psychologist was certified as an MBCT instructor, and the nurse was trained in mindfulness-based programs. Both had training and experience in applying lifestyle-based programs to patients with mental disorders. If either one detected signs that a patient's mental state deteriorated during the intervention, they coordinated a telephone-based assessment if necessary, and the research team determined the approach to be used.

2.8. Measures and study outcomes

Four trained psychologists administered the MINI (Ferrando et al., 2000) by telephone to ensure that all enrolled patients met the inclusion criteria.

At baseline, demographic and clinical variables were obtained by telephone interview. At baseline and at the 12-month follow-up, data on psychopharmacological prescriptions were collected. Several self-reporting instruments (see below) were administered at four time points (T0, T1, T2, T3). The follow-up was completed on March 22, 2022.

Primary Outcome:

The primary outcome was depression severity, as determined by the BDI-II (Beck et al., 1996). This is a self-reporting instrument that measures the severity of depression using 21 multiple-choice questions, with each answer scored from 0 to 3. Previous research validated the reliability of the Spanish version of the BDI-II, with Cronbach's alpha of 0.89 (Sanz, 2005).

Secondary outcomes:

There were four secondary outcomes, each based on measurements at 12 months (T3).

The three-level European quality-of-life 5 dimension questionnaire (EQ-5D-3 L) was used to measure health-related quality-of-life (Brooks et al., 1996). In this test, a patient marks a point on a line (visual analogue scale, VAS) that best reflects a personal assessment of his/her current global health status (Badia et al., 1999).This VAS is a quantitative health outcome measure that reflects the patient's own judgment. Cronbach's alpha coefficient for this scale indicated satisfactory reliability in some disease-specific populations (Brooks et al., 1996; Badia et al., 1999).

The 14-item Mediterranean diet adherence screener (MEDAS), which was developed by the PREDIMED study group (Martínez-González et al., 2010), was used to measure adherence to the Mediterranean diet. The total score ranges from 0 to 14, with a higher score indicating better adherence (Schröder et al., 2011).

The international physical activity questionnaire-short form (IPAQ-SF) was used to measure physical activity (Kim et al., 2013).This scale assesses the level of habitual physical activity during the previous 7 days. It has 7 items, and activity is rated at 4 levels (vigorous intensity, moderate intensity, walking, and sitting). The validated Spanish language version was used (Roman-Viñas et al., 2010).

The medical outcomes study social support survey (MOS-SS) (Sherbourne and Stewart, 1991) was used to measure social support. This self-reporting instrument has 4 subscales (emotional/informational, tangible, affectionate, and positive social interaction) that indicate overall functional social support. The validated Spanish language version was used (Revilla Ahumada et al., 2005).

2.9. Statistical analysis

All statistical analyses were performed using SPSS version 26 (SPSS/IBM, Chicago, IL, USA) according to a predefined analysis plan (Navarro et al., 2020).

Per protocol (PP) analysis and intention to treat (ITT) analysis were used to analyze clinical outcomes. All results were reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines extension for cluster trials (Campbell et al., 2012).

The effectiveness of the intervention on depression symptoms (BDI-II) was assessed using a general linear model (ANOVA) for continuous measures at 2, 6, and 12 months. A sensitivity analysis was performed in 55 patients who had TRD based on more restrictive diagnostic criteria; specifically, these patients were treated by a psychiatrist and/or psychologist for at least 2 months, had tried two antidepressants from different pharmacological groups for at least one month each, and had used the maximum tolerated dose of each drug within the therapeutic range (Conway et al., 2017; Voineskos et al., 2020).

Multiple imputations were used for the main analysis, because this method generally provides less biased estimates of an effect than a complete case analysis. Missing outcomes were accounted for using multiple imputation with a chained equation (White et al., 2011).

3. Results

3.1. Patient characteristics

Ninety-four eligible patients were included in this study, fewer than planned because of difficulties in recruitment during the COVID-19 pandemic (Fig. 1, Table 1). Thirty-four patients were randomly allocated to the LMP group, 29 to the MBCT group, and 31 to the placebo group. Most patients were female (74.5%) and the average age was 48.15 years (SD = 13.05, range: 20–75 years). A total of 34% were single, 53.2% had a secondary education, and 26.6% had paid employment. Fifty-nine patients (62.8%) reported a family history of depression. The mean duration of the depressive episode was 10 months, and all patients were initially treated in primary health care and there were also treated by a psychologist or psychiatrist for at least 1 month.

A total of 94 patients were initially randomized (T0), 73 patients (77.65%) completed the evaluation at 8 weeks (T1), 66 patients (90.41%) completed the evaluation at 6 months (T2), and 59 (89.39%) completed the evaluation at 12 months (T3). Thus, 35 patients (37.3%) were lost during follow-up.

The session attendance rate was 79.3% in the LMP group and 66.81% in the MBCT group. There were no relevant adverse effects or significant safety issues attributable to the interventions, and no patients were excluded due to a worsening of depressive symptoms.

3.2. Primary outcome

The PP analysis and ITT analysis indicated the three groups had no statistically significant differences in mean BDI-II scores at 2 months, 6 months, or 12 months (Table 2).

Analysis of the severity of depression symptoms (mean BDI-II score) showed that each group had severe depression at study onset, with the severity declining over time (Fig. 2). This decline was 16.8 points in the LMP group, 15.96 points in the MBCT group, and 13.07 points in placebo group. Pairwise comparisons of these groups at each time point indicated no statistically significant differences.

3.3. Secondary outcomes

The results for secondary outcomes using a PP analysis with adjustment for baseline data showed that the LMP group ($P = 0.017$) and

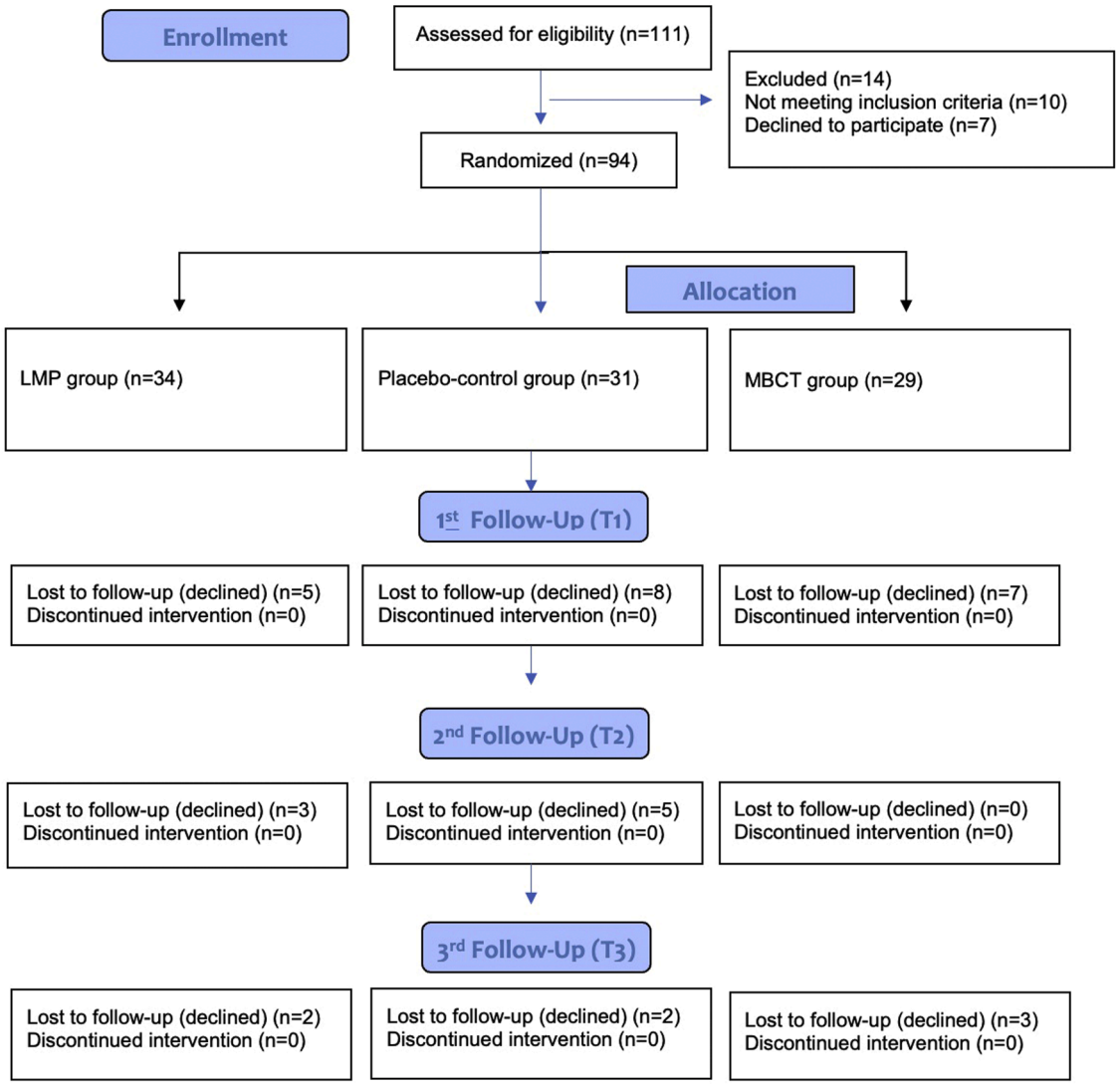

Fig. 1. CONSORT flow diagram.

Table 1
Baseline sociodemographic and clinical characteristics of the study population[a].

	Total (n = 94)	Placebo (n = 31)	LMP (n = 34)	MBCT (n = 29)
Age, mean (SD) in years	48.15 (13.055)	47.84 (11.978)	45.47 (13.150)	51.62 (13.684)
Sex, n (%)				
Male	24 (25)	9 (9.6)	11 (11.7)	4 (4.3)
Female	70 (75)	22 (23.4)	23 (24.5)	25 (26.6)
Family status, n (%)				
Single	32 (34)	12 (12.8)	11 (11.7)	9 (9.6)
Married	16 (17)	3 (3.2)	7 (7.4)	6 (6.4)
Divorced	23 (24.4)	7 (7.4)	5 (5.3)	11 (11.7)
Widowed	4 (4.2)	1 (1.1)	2 (2.1)	1 (1.1)
Others	18 (19.1)	7 (7.4)	9 (9.5)	2 (2.1)
Educational level, n (%)				
None	6 (6.4)	2 (2.1)	0 (0)	4 (4.3)
Primary	13 (13.8)	4 (4.3)	4 (4.3)	5 (5.3)
Secondary	50 (53.2)	15 (16)	20 (21.3)	15 (16)
University	25 (26.6)	10 (10.6)	10 (10.6)	5 (5.3)
Work Status, n (%)				
Not working	46 (48.9)	14(14.9)	17(18.1)	15 (16)
Working	25 (27.2)	8 (8.5)	11(11.7)	6(6.4)
Sick leave	23 (25)	9 (9.6)	6(6.4)	8 (8.5)
Family history of depression, n (%)				
Yes	59 (62.8)	17 (18.1)	23 (24.5)	19 (20.2)
No	35 (37.2)	14 (14.9)	11 (11.7)	10(10.6)
Number of previous episodes, mean (SD)				
	4.89 (6.63)	3.42 (2.14)	5.72 (5.58)	5.43 (10.38)
Length of current episode, mean (SD) in weeks				
	43.28 (36.65)	51.93 (39.28)	39.17 (34.19)	38.38 (36.03)
Age at onset of depression, mean (SD) in years				
	27.2 (12.56)	28.47 (11.73)	24 (12.49)	29.11 (13.26)
Baseline BDI-II score, mean (SD)				
	34.90 (11.27)	37.26 (11.50)	33.03 (10.56)	34.59 (11.76)
Antidepressant type, n				
SSRI	38	7	17	14
SNRI	39	13	11	15
Other antidepressant	36	11	15	10
Anxiolytic	50	16	18	16
Other psychopharmacology agent	23	7	10	6

[a] Results are for all 94 enrolled patients except "Number of episodes" (n = 74), "Length of current episode" (n = 85), and "Age at onset of depression" (n = 90).

Abbreviations: BDI-II, Beck Depression Inventory II; SSRI, selective serotonin uptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

MBCT group ($P = 0.027$) had higher EQ-5D-3 L scores than the placebo group at 12 months (Table 2). However, these differences were not significant in the ITT analysis (both $P > 0.05$). In addition, the PP analysis indicated that the LMP group had a higher MEDAS score than the placebo group at 12 months ($P < 0.001$), but there was only a tendency for significance in the ITT analysis ($P = 0.082$). The two groups did not differ significantly from the placebo group in IPAQ-SF score or MOS-SS score in the PP analysis and ITT analysis (all $P > 0.05$).

Analysis of antidepressant prescriptions (data not shown) showed that 3 patients in the LMP group increased their doses and 21 did not, 7 patients in the placebo group increased their doses and 7 did not, and 6 patients in the MBCT group increased their doses and 10 did not. These differences were statistically significant (x^2: 6.63; df: 2; $P = 0.036$).

The sensitivity analysis with 55 patients who had TRD based on more restrictive criteria showed similar results (data not shown).

4. Discussion

The present study found that TRD patients in the placebo, MBCT, and LMP groups all experienced declines in depressive symptoms from baseline, but there were no significant differences between groups. This

Table 2
Primary and secondary outcomes in the three groups[a].

Variable	Placebo	MBCT			LMP			ITT Analysis		ITT Analysis		
	mean ± SD	mean ± SD	Beta (95% CI) MBCT *vs.* Placebo*	p	mean ± SD	Beta (95% CI) LMP *vs.* Placebo*	p	Imputed Beta (95% CI) MBCT *vs.* Placebo**	p	Imputed Beta (95% CI) LMP *vs.* Placebo**	p
BDI-II											
2 months (n = 74)	24.87±14.2	19.95±12.0	−3.75 (−10.23,2.73)	0.252	17.34±10.8	−5.18 (−11.24,0.88)	0.092	−2.37 (−8.37,3.63)	0.438	−3.99 (−9.76,1.77)	0.174
6 months (n = 66)	23.17±17.3	19.41±11.0	−2.70 (−10.85,5.45)	0.511	16.85±13.3	−4.03 (−11.99,3.92)	0.315	−2.37 (−9.33,4.59)	0.504	−2.79 (−9.96,4.37)	0.443
12 months (n = 59)	23.33±15.3	19.47±14.9	−3.46 (−13.11,6.20)	0.476	19.87±15.9	−0.83 (−10.14,8.48)	0.859	−5.24 (−14.44,3.97)	0.262	−1.85 (−1.52,7.83)	0.705
EQ-5D VAS	45.27±26.8	62.58±19.7	18.44 (2.21,34.67)	**0.027**	63.50±25.2	19.00 (3.55,34.45)	**0.017**	10.90 (−5.34,27.14)	0.185	9.91 (−4,51,24.33)	0.176
MEDAS	5.27±1.5	6.22±1.3	0.11 (0.68,0.91)	0.777	7.40±1.5	1.52 (0.75,2.28)	**<0.001**	−0.19 (−0.99,0.61)	0.644	0.7 (−0.09,1.50)	0.082
IPAQ	1966.67 ±2851.7	1823.50 ±1571.64	−408.67 (−2156.15,1338.81)	0.637	1717.83 ±1306.54	−522.30 (−2044.54,999.94)	0.490	−236.58 (−1529.04,1055.87)	0.719	−327.59 (−1476.26,821.07)	0.575
MOS-SS	70.62±16.91	64.28±21.80	0.364 (−11.95,12.67)	0.953	73.77±18.20	3.56 (−7.92,15.04)	0.536	−0.99 (−9.99,8.01)	0.953	3.56 (−7.63,14.75)	0.533

[a] General linear model (GLM) with adjustment for baseline values. Missing outcomes were accounted for using multiple imputation by baseline score and group, with a chained equation.

Abbreviations: BDI-II, Beck Depression Inventory-II, EQ-5D VAS, Visual Analogue Scale of European Quality of Life-5 Dimensions Questionnaire; IPAQ-SF, International Physical Activity Questionnaire-Short Form; MBCT, Mindfulness-Based Cognitive Therapy; MEDAS, Mediterranean Diet Adherence Screener; MOS-SS, Medical Outcomes Study Social Support Survey.

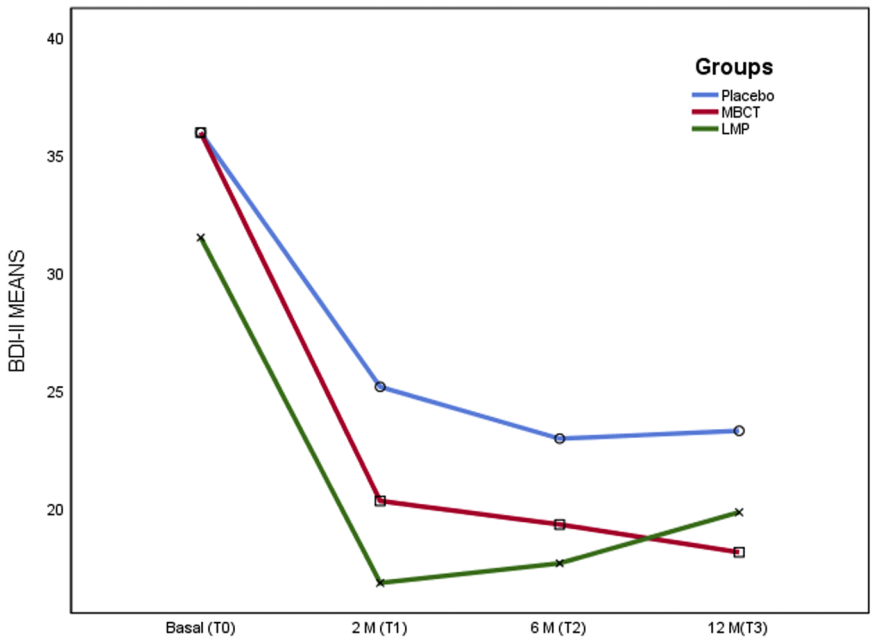

Fig. 2. Changes over time in the mean BDI-II score in the three groups. Means are from all participants who completed the questionnaire at each time.

result differs from a previous study which showed that a similar online lifestyle intervention significantly reduced non-resistant MDD compared with a control group (Meyer et al., 2009). Although the inter-group differences in the present work were not significant, all changes in depression were in the direction we hypothesized and were clinically relevant.

As hypothesized, our PP analysis showed that health-related quality-of-life was significantly greater in the LMP and MBCT groups than the placebo group at 12 months, in accordance with similar studies (Montero-Marín et al., 2016). These findings showed that both of these treatments could be effective in improving the long-term quality-of-life of patients with TRD, and thus contribute to a reduced burden of suffering and disability in these patients (Gili et al., 2020).

The LMP group also showed increased adherence to the Mediterranean diet relative to the placebo group at 12 months. Previous research suggested a beneficial effect of an intervention that targets diet in patients with depression, although some studies reported discordant results, possibly because of the clinical heterogeneity of depression (Sánchez-Villegas et al., 2013; Wardle et al., 2000; Vreijiling et al., 2021). Our results indicated no significant differences between the groups in physical activity, perhaps reflecting poor compliance. Other studies showed the efficacy of mild or moderate aerobic exercise for patients with MDD, but used closer monitoring of patients to improve compliance (Dunn et al., 2005). Furthermore, our results are similar to those obtained in a randomized-controlled trial of physical activity in MDD, which found a non-significant effect of exercise that was attributed to a very low effect size (Kruisdijk et al., 2019). Our LMP program also had no impact on the perception of social support. Taken together, we believe that our LMP program would have been more effective if we had taken more measures to improve patient adherence (Castro et al., 2021).

Patient adherence is a major issue during treatment for depression (Pampallona et al., 2002). In the present study, only 63% of participants completed assessments at the final time-point, and only 46% completed all 8 sessions. These percentages are slightly higher than reported in some previous systematic reviews and meta-analyses, which showed only about 53% of enrolled patients had adequate adherence to lifestyle interventions (Castro et al., 2021). Adherence to our interventions was most likely adversely affected by the COVID-19 pandemic. Hence, our study suggests that it may be necessary to more rigorously ensure patient adherence to obtain results similar to those of other studies that examined non-resistant depression (Lopresti et al., 2013; Sarris et al., 2014).

We initially planned to perform this study using face-to-face interventions, but restrictions imposed during the COVID-19 pandemic made us change to an online format, which likely influenced our results. It is possible that confinement to the home reduced patient adherence to the lifestyle interventions. Given the uniqueness of the COVID-19 pandemic, no previous studies were performed under these conditions, thus preventing comparisons of our results with previous studies. Due to the pandemic, our options in February 2020 were to halt the study with some patients already recruited and confined, or to administer the study online. We chose the second option because there were some interesting precedents regarding the feasibility of administering mindfulness and lifestyle interventions online (Gili et al., 2020). However, we acknowledge that the exceptional conditions in which the study was performed likely affected the results, for example by reducing patient adherence. Importantly, the COVID-19 pandemic prevented recruitment of the intended 180 patients.

We previously mentioned the lack of consensus regarding the diagnostic criteria for TRD (Conway et al., 2017). Therefore, we chose "soft" diagnostic criteria that would allow us to enroll more patients, because patient enrollment during the pandemic was very difficult. However, we did a sub-group analysis using more rigorous diagnostic criteria for TRD, and the results also showed had no significant differences among the three groups.

Successful treatment of TRD may require different biomedical methods, such as combinations of psychopharmacological agents, brain neurostimulation techniques, and even powerful new drugs such as ketamine (Capuzzi et al., 2021; Nuñez et al., 2022). However, these treatments can have problems of acceptance, tolerance, and safety, and there is also the problem of maintaining long-term efficacy (Eduardo et al., 2022). Given that some previous studies of psychosocial interventions in some TRD patients have reported efficacy with good tolerance and safety, we believe non-pharmacological interventions should be considered for suitable patients (Ijaz et al., 2018). Nevertheless, our results showed no clear benefit of a multimodal LMP as an adjuvant treatment for patients with TRD in the context of a pandemic with lockdowns. Adjuvant lifestyle modification programs for TRD should be tested face-to-face in routine clinical practice to clarify whether this type of adjuvant therapy has beneficial and long-term

effects in these specific patients. Extending the duration of LMP to more than two months could improve treatment efficacy.

4.1. Limitations

The present study had some limitations. First, because of the COVID-19 pandemic, our sample size was smaller than originally planned (Navarro et al., 2020) and was also smaller than that used in similar previous studies (Meyer et al., 2009). Replicating our analyses in a larger sample is therefore necessary. Second, as discussed above, it is likely that the COVID-19 pandemic adversely affected engagement in physical exercise, social activities, and other activities. It also seems likely that the COVID-19 pandemic influenced the evolution of depressive symptomatology, perhaps by increasing patient anxiety and uncertainty. In addition, we had to change the modality of the intervention from face-to-face to online, therefore the findings may not be generalisable, compromising external validity. Finally, the online modality may have made it difficult for older people to participate because they are less familiar with new technologies, which may have introduced a bias. Notwithstanding, the mean age (48.15±13.05 years) was similar to that of previous studies with face-to-face recruitment and intervention (Garcia-Toro, 2012; Serrano-Ripoll, 2015).

5. Conclusions

The results of the present study of patients with TRD showed that the group which received LMP as an adjunctive online program did not achieve a better outcome in terms of depressive symptoms than the MBCT or placebo groups. However, the results of our PP analysis showed that the LMP group had improved adherence to the Mediterranean diet and better quality-of-life at 12 months, and also used lower doses of antidepressants. However, the COVID-19 pandemic likely influenced our results, making it necessary to reexamine this topic in the absence of a pandemic lockdown.

CRediT authorship contribution statement

AGR, AY, MBV, CN, JS, OI, RGJ, MJSR, BO, MG, MR, PR and MGT designed the study. AGR, AY, MBV, CN, JS, OI, RGJ, MJSR and MGT wrote the protocol. AGR, AY, MBV, AAL, JMM and MGT conducted the literature searches and analyses. AGR, AY, MBV and MGT undertook the statistical analyses. AGR, AY, MBV and MGT wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

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Declaration of Competing Interest

All authors declare have no potential conflicts of interest.

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