Effect of multi-nutrient supplementation and food-related behavioral activation therapy on prevention of major depressive disorder among overweight or obese adults with subsyndromal depressive symptoms: the MooDFOOD randomized clinical trial

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Key points

Question What is the effect of multinutrient supplementation and food-related behavioral activation therapy on prevention of a new episode of major depressive disorder among overweight or obese adults with depressive symptoms?

Findings: In this 2x2 factorial randomized clinical trial that included 1025 adults, there was no significant difference in episodes of major depressive disorder over 1 year follow-up with multinutrient supplementation vs placebo (54 (10.5%) vs 51 (9.9%)) or with food-related behavioral activation therapy vs no therapy (48 (9.4%) vs 57 (11.1%)).

Meaning: These findings do not support the use of multinutrient supplementation or food-related behavioral activation therapy for prevention of major depressive disorder.

Abstract

Importance: Effects of nutritional interventions on the prevention of major depressive disorder (MDD) in overweight adults are unknown.

Objective: To examine the effect of two nutritional strategies (multi-nutrient supplementation, food-related behavioral activation (F-BA) therapy) and their combination for prevention of a new MDD episode in overweight adults with subsyndromal depressive symptoms.

Design, setting, participants: This multicenter 2x2 factorial randomized clinical trial included overweight adults (BMI 25-40kg/m^2) aged 18-75years with elevated depressive symptoms (Patient Health Questionnaire-9 (PHQ-9) scores≥5) not meeting criteria for MDD episodes in the past 6 months from 4 European countries. 1025 adults were randomized between July-30-2015 and October-12-2016, and followed for 1 year (until October-13-2017).

Interventions: Daily multi-nutrient supplements (1412mg omega-3 fatty acids, 30µg selenium, 400µg folic acid, and 20µg D-3 vitamin plus 100mg calcium) versus placebo (blinded), and/or 21 individual and group F-BA sessions versus no F-BA (blinded to researchers), for one year. Participants were allocated to placebo without F-BA (n=257), placebo with F-BA (n=256), supplements without F-BA (n=256), and supplements with F-BA (n=256).

Main Outcomes and Measures: Primary outcome was cumulative 1-year onset of MDD measured with the Mini International Neuropsychiatric Interview after 3, 6 and 12 months. Logistic regression using effect-coded variables (-1 indicating control, +1 indicating intervention) evaluated intervention effects both individually and in combination (interaction) on MDD onset.

Results: Among 1025 participants (mean age 46.5y; 772 (75%) women; mean BMI 31.4kg/m^2), 779 (76%) completed the trial.

During 12 month follow-up, 105 (10%) developed MDD (placebo without F-BA: 25 (9.7%), placebo with F-BA: 26 (10.2%), supplements without F-BA: 32 (12.5%), supplements with F-BA: 22 (8.6%).. Neither

supplements (odds ratio (OR)=1.06; 95%-confidence interval (CI)=0.87-1.29), F-BA (OR=0.93; 95%CI=0.76-1.13), nor their combination (OR=0.93; 95%CI=0.76-1.14, p for interaction=0.48) affected MDD onset. Number of deaths/hospitalizations were for placebo without F-BA (n=0,n=24), placebo with F-BA (n=0,n=24), supplements without F-BA (n=0,n=26) and supplements with F-BA (n=1,n=24), respectively.

Conclusions and Relevance: Among overweight or obese adults with depressive symptoms, multi-nutrient supplementation compared with placebo and food-related behavioral activation therapy compared with no therapy did not reduce episodes of major depressive disorder during 1 year. These findings do not support the use of these interventions for prevention of major depressive disorder.

Trial registration: https://www.clinicaltrials.gov/ct2/show/NCT02529423. August-2015.

Introduction

Major depressive disorder (MDD) is a common psychiatric disorder (lifetime prevalence 17%),[1] ranking as the second leading contributor of years lived with disability.[2] Prevention may offer an important opportunity to reduce the global disease burden of MDD.[3]

One preventive strategy for MDD might be to modify diet. Prospective studies have found that better adherence to higher quality diets is associated with reduced future onset of depressive symptoms.[4] Food-related behaviors, like unhealthy eating styles,[5] have been cross-sectionally related to increased depressive symptoms. Recent randomized clinical trials (RCTs) found that dietary improvement strategies reduced depressive symptoms in depressed adults relative to control conditions,[6,7] but there remains a clear lack of RCTs testing dietary strategies to prevent depression.[8]

Similarly, observational studies have suggested that lower levels of specific nutrients (e.g. omega-3 polyunsaturated fatty acids, folic acid, vitamin D, selenium) are related to higher levels of depressive symptoms. [9,10] Some - but not all - nutritional supplement intervention studies have indicated that nutrient supplementation may reduce depressive symptoms in those with MDD.[11]

To date, few experimental studies have directly evaluated the effect of changing diet, food-related behavior or nutrients on preventing MDD[8,12] and none to our knowledge have specifically targeted overweight and obese individuals, who are a particularly relevant population, given their increased risk for MDD and the key role of diet in these conditions.[13] Therefore, the MooDFOOD depression prevention trial examined the effect of two different nutritional strategies (multi-nutrient supplementation, food-related behavioral activation therapy) and their combination for prevention of a new MDD episode in overweight people with subsyndromal depressive symptoms.

Methods

Study design

This study was a 2x2 factorial RCT performed between July 30 2015 and October 13 2017 in four European countries (Germany, Spain, United Kingdom and The Netherlands). For full details of trial design and protocol see Roca et al.[14] and Supplement 1. Ethics approval was provided by the Human Research Ethics Boards of the four study sites. All participants provided written informed consent. This manuscript reports on primary and secondary mental health outcomes as assessed up to 12 months.

Recruitment and eligibility criteria

Participants were recruited to participate in a study investigating new strategies to improve mood and wellbeing through changes in diet and lifestyle by the study sites (located in Leipzig; Palma de Mallorca; Exeter, UK; Amsterdam). Main eligibility criteria were age 18-75 years, body mass index (BMI) between 25-40 kg/m^2, having at least mild depressive symptoms as operationalized by Patient Health Questionnaire (PHQ-9) scores of ≥5,[15] but having no current MDD episode (in past 6 months; Mini International Neuropsychiatric Interview 5.0 (MINI 5.0)[16] (see Appendix 1 in Supplement 2 for recruitment details and eligibility). All eligible participants were invited to visit one of the study sites for a baseline interview, physical measurements, and blood sampling conducted by trained research assistants/nurses, and the completion of self-report questionnaires. Follow-up assessments took place at 3, 6 and 12 months.

Randomization

At the end of the baseline interview, participants were randomized with equal probability to: (1) placebo supplements without F-BA; (2) placebo supplements with F-BA; (3) multi-nutrient supplements without F-BA; or (4) multi-nutrient supplements with F-BA by a permuted block randomization (block sizes ranging from 8-12; https://www.sealedenvelope.com). Randomization was stratified by study site and participants' lifetime history of depression status. After randomization, researchers dispensed supplements to participants according to unique randomization codes. Participants, therapists, and

researchers were blind to supplement allocation. Participants of the F-BA intervention were contacted directly by the therapist, ensuring that researchers assessing follow-up outcomes remained blind to F-BA intervention status. Statistical analyses on the primary outcome and the reported secondary outcomes in which participants were analyzed according to their randomization group were carried out blinded for randomization.

Interventions

Multi-nutrient supplements

Patients received either multi-nutrient supplements (1412mg of eicosapentaenoic and docosahexaenoic omega-3 poly unsaturated fatty acids (PUFAs) (ratio 3:1), 30µg selenium , 400µg folic acid, and 20µg vitamin D3 coupled with 100mg calcium) or placebo, each provided in two pills per day, taken daily for one year (see Appendix 2 in Supplement 2 for details).

Food-related behavioural activation therapy (F-BA)

F-BA consisted of a protocol-based intervention that incorporated standard BA approaches. BA is effective in depression treatment,[17] and includes self-monitoring, functional analysis, and activity scheduling. F-BA applied these proven techniques to improve mood by changing dietary habits, food-related behaviours (e.g., snacking), increasing positive behaviours and emphasising a Mediterranean-style diet, which has been related to reduced depression onset.[4] F-BA was provided in up to 21 sessions (15 individual, 6 group) for one year (see Appendix 3 in Supplement 2 for F-BA details). No active (e.g. attention) control condition was provided in those receiving no F-BA.

Outcomes

Primary outcome

Primary outcome was the 12-month cumulative onset of an episode of MDD, defined according to standard psychiatric Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, and measured with the depression section of the MINI 5.0[16] at 3, 6, and 12 months.

Secondary outcomes

Secondary trial outcomes were depression severity (PHQ-9, range 0-27 with higher values indicating higher severity ,[15] Inventory of Depressive Symptomatology; IDS30-SR, range 0-84 with higher values indicating higher severity),[18] anxiety severity (Generalized Anxiety Disorder-7; GAD-7, range 0-21 with higher values indicating higher severity),[19] health-related quality of life (utility, EuroQol instrument EQ-5D-5L[20] using the value sets for England[21], range 0-1, with higher values indicating better health utility), eating behavior (three factor eating questionnaire; TEFQ-R18, all three factors ranging from 0-100 with higher values indicating poorer eating behaviour)[22] food behavior, food intake (GA2LEN food frequency questionnaire[23]), physical activity and sedentary behavior (short questionnaire to assess health-enhancing physical activity; SQUASH[24]), and body weight perception (Stunkard[25]). This article paper reports on the mental health secondary outcomes depression severity (PHQ-9,[15] IDS30-SR),[18] anxiety severity (GAD-7),[19] and utility (EQ-5D-5L; Appendix 4 in Supplement 2).[20,21] Time to onset of first MDD episode was included for post-hoc analyses.

Other measures

Good adherence to interventions (attending ≥8 of 21 sessions for F-BA, and taking ≥70% of the supplements during the 12 months for supplements) was defined a priori. A detailed description of these and other measures can be found in Appendix 5 and 6 in Supplement 2.

Sample size

Sample size was based on the primary outcome and accounted for the 2x2 factorial design. At the time the trial was designed, effective preventive interventions in high-risk groups were found to reduce the onset of depression by 25–50 %.[3] Assuming a 33% reduction of MDD onset between active (20% MDD onset) versus control conditions (30% MDD onset),[26,27] 392 participants (196 in each of the four possible intervention combinations) were needed to evaluate the main effect of each of the two nutritional interventions (versus respective control) assuming a 2-sided test at α=0.05 and a power of (1−β)=0.90. Assuming a follow-up attrition rate of 22%, 250 participants per intervention combination were needed. This corresponds to an absolute difference of 10%, which is consistent with the assumed clinically relevant difference in depression onset, estimated by consulting clinical experts and stakeholders (e.g. health insurance companies), reported in a previous depression prevention trial.[28]

Statistical methods

Participants were analyzed according to their randomization group, including all participants randomized regardless of intervention actually received or study withdrawal. The two nutritional interventions were effect coded (-1 indicating control and +1 indicating intervention) and jointly modelled to efficiently study main effects and interactions as recommended for factorial designs.[29] All analyses were adjusted for study site and history of MDD. Missing data for the trial endpoints were accounted for using multiple imputation under the missing at random (MAR) assumption into 100 datasets. Results were pooled using Rubin's rules.[30]

Logistic regression analyses were conducted to estimate effects of the interventions on the primary outcome. Cox proportional hazard modelling was used to study intervention effects on time to first MDD onset (3, 6 or 12 months for either MDD onset or last available measurement) as post-hoc analysis. Scaled Schoenfeld residuals were used to test the proportionality of hazard assumption, which was met ($p>0.05$). For secondary outcomes, Generalized Estimating Equations (GEE) longitudinal analysis of

covariance (ANCOVA) with an exchangeable correlation structure was used,[31] modelling outcomes at 3, 6, and 12 months as dependent variables, and adjusting for their corresponding baseline values. Overall follow-up effects (including all follow-up assessments) and 12-month effects of the interventions for these secondary follow-up outcomes were tested.[31] Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. Effect modification of study site and history of MDD was investigated with their corresponding interaction terms with the interventions. Similarly, effect modification by baseline symptom severity was included as post-hoc analyses.

As GEE are known to be robust for missing data, GEE longitudinal ANCOVA without multiple imputation was carried out as sensitivity analyses. Cohens' D was calculated for each baseline-12-month follow-up difference in secondary outcome between the intervention groups,[32] using multiple imputed data. Furthermore, Complier Average Causal Effect (CACE) analyses[33-34] were carried out with the multiple imputed data using structural equation modelling within STATA, to provide an estimate of intervention effects taking into account good adherence with the interventions, whilst retaining the benefits of randomization for both primary and secondary 12-months follow-up outcomes (Appendix 7 in Supplement 2). Analyses were conducted with R (version 3.4.4), the packages geepack, and mice, were used for the GEE analyses, and multiple imputation, respectively. The 2-sided significance threshold was set at p=0.05.

Results

Description of participants

Between July-30-2015 and October-12-2016, 5965 individuals visited the online screening questionnaire, 2235 participants fulfilled the key inclusion criteria, 1773 participants completed the subsequent

telephone screening, and 1250 were deemed eligible for the trial. After subsequent exclusion of individuals not willing/able to participate, 1025 adults were randomly allocated to receive placebo without F-BA (n=257), placebo with F-BA (n=256) multi-nutrient supplements without F-BA (n=256) and multi-nutrient supplements with F-BA (n=256). Table 1 shows the baseline characteristics of the intervention groups, the flow chart is described in Figure 1.

Follow-up attrition

The number of participants not taking part in follow-up assessment at 3, 6, and 12 months, was 194 (19%), 254 (25%), and 246 (24%), respectively. Figure 1 shows numbers and main reasons for lost-to-follow-up (defined as having no 12-months follow-up measurement, n=246). In total, 239 (23%) participants dropped out before the 12-month follow-up or before the main endpoint (onset of MDD) occurred. Missing rates for the primary outcome did not differ between the four intervention groups at 3 months (p=0.47), 6 months (p=0.62), and 12 months (p=0.91). Missing rates for the secondary outcomes of depressive symptoms, anxiety symptoms and health utility scores obtained through self-report questionnaires were slightly higher: number of individuals with missing data at 0, 3, 6, and 12 months ranged from 29-32, 206-210, 275-278, and 268 for these outcomes, respectively. These missing rates did not differ across intervention groups.

Adherence to interventions

Appendix 8 in Supplement 2 describes adherence for each intervention group. Of all 12-month follow-up participants, pill weight data indicated that 77% of participants had adherence of >70% to the supplements/placebo. Of those randomized to F-BA, 71% attended ≥8 of 21 sessions. A median of 14 out of 15 individual sessions were attended (interquartile range IQR 6-15), and a median of 0 out of 6 group sessions (IQR 0-4) were attended, indicating that adherence to individual sessions was highest.

Onset of MDD

105 participants (10%) developed a MDD episode during the 12-months follow-up (Table 2). The number of individuals developing MDD was 25 (9.7%) in those receiving placebo without F-BA, 26 (10.2%) in those receiving placebo with F-BA, 32 (12.5%) in those receiving supplements without F-BA, and 22 (8.6%) in those receiving supplements with F-BA. Considering the main effect of each intervention the numbers of participants who developed MDD were 51 (9.9%; 1.1 per 100 person-months) in those receiving placebo, 54 (10.5%; 1.2 per 100 person-months) in those receiving supplements, 57 (11.1%; 1.3 per 100 person-months) in those not receiving F-BA and 48 (9.4%; 1.0 per 100 person-months) in those receiving F-BA. Logistic regression using effect-coded intervention variables (-1,1) showed no significant effect of supplements (OR=1.06, 95%CI 0.87-1.29, p=0.57) or F-BA (OR=0.93, 95%CI 0.76-1.13, p=0.47) or significant supplements-by-F-BA interaction (OR=0.93, 95%CI 0.76-1.14, p for interaction=0.48) on the onset of MDD. There was no significant effect of supplements (HR=1.05, 95%CI 0.86-1.27, p=0.65) or F-BA (HR=0.91, 95%CI 0.75-1.10, p=0.32) or significant supplements-by-F-BA interaction (HR=0.91, 95%CI 0.75-1.11, p for interaction=0.36) on the time to first onset of MDD (Table 2).

Depressive symptoms, anxiety symptom and health-related quality of life

Figure 2 shows boxplots and means of the secondary outcome scores at baseline, 3, 6 and 12 months stratified by F-BA and supplement groups (see Appendix 9 in Supplement 2 for figure stratified by the four intervention combinations) . There were no significant supplement-by-F-BA interactions for any of the secondary outcome scores (p-values for interaction ranging from 0.41 to 0.98). Table 3 presents effects on secondary outcomes. F-BA was significantly related to lower anxiety GAD scores at 12 months follow-up (adjusted mean difference=-0.48, 95%CI-0.84 to -0.12,p=0.01; unadjusted baseline GAD for no F-BA=5.8), unadjusted baseline GAD for F-BA=5.8, unadjusted 12-month follow-up GAD for no F-BA=3.9,

unadjusted 12 month follow-up GAD for F-BA=3.2), but not on other secondary outcomes. There was a significant effect of supplements on overall follow-up measures of the PHQ (adjusted mean difference=0.65, 95%CI 0.25-1.06,p=0.002), IDS (adjusted mean difference=1.20, 95%CI 0.29-2.10,p=0.01) and GAD (adjusted mean difference=0.50, 95%CI 0.16-0.84,p=0.004) scores, and on PHQ scores at 12 months follow-up (adjusted mean difference=0.56, 95%CI 0.11-1.01,p=0.02; unadjusted baseline PHQ for placebo=7.3), unadjusted baseline PHQ for supplements=7.5, unadjusted 12-month follow-up PHQ for placebo=4.1, unadjusted 12-month follow-up PHQ for supplements=4.9), showing *less improvement* in depressive and anxiety symptoms relative to placebo.

Effect modification and sensitivity CACE analyses

Appendix 10 in Supplement 2 shows the results of post-hoc effect modification analyses by study site, history of depression and baseline symptoms scores. These analyses suggested that 1) the effect of F-BA on PHQ at 12 months follow-up was more favorable (larger reduction) when baseline PHQ depression severity was higher, 2) use of supplements resulted in higher follow-up anxiety scores when baseline anxiety severity scores were higher, and 3) that the effect of F-BA on health utility scores at 12-month follow-up was larger in the United Kingdom compared to the Netherlands. Sensitivity analyses for depression, anxiety, and health utility scores without multiple imputed data gave comparable effect estimates (Appendix 11 in Supplement 2). The results of the CACE analyses were consistent with the original analyses, finding no effect of supplements on the primary outcome, and similar effects for secondary outcomes (Appendix 12 in Supplement 2). CACE analyses found a significant effect of F-BA on the primary outcome (OR 0.78; 95% CI 0.64-0.95), accounting for treatment adherence.

Adverse events and concealment

98 participants were hospitalized and 1 participant died during the 12-month follow-up, these events were judged as unrelated to interventions (Appendix 8 in Supplement 2). Those receiving placebo were less likely to believe they were taking multi-nutrients compared to those receiving multi-nutrients (placebo without F-BA 8.2%, placebo with F-BA 10.4%, multi-nutrients without F-BA: 25.5%, multi-nutrients with F-BA 43.7%, $p<0.001$; Appendix 13 in Supplement 2). 40.4% reported that they did not know their allocation.

Discussion

This multi-center trial conducted in 1025 overweight individuals with subsyndromal depressive symptoms showed no effect of multi-nutrient supplements, F-BA, or their combination on the 1-year cumulative onset of MDD.

To our knowledge, this is the first randomized trial evaluating the effectiveness of two nutritional strategies and their combination for the prevention of depression in a high-risk group of overweight people. Despite our large sample size and selection of people with elevated depressive symptoms, the onset of MDD was lower than expected, which reduced the statistical power to detect a statistically significant effect. Comparisons of intervention effects with other trials are difficult due to methodological and sample differences: compared to previous trials testing preventative psychological strategies for depression that found significant effects,[35] our sample had on average lower initial levels of depressive symptoms, and lower likelihood of having a history of MDD, making them less vulnerable for MDD onset.

The adherence to both interventions was adequate, with about three quarters fulfilling predefined adherence criteria for the interventions. For F-BA, the individual sessions in the first six months were well attended, but the group sessions in the subsequent six months were not.

This study showed that multi-nutrient supplements containing omega-3 PUFAs, vitamin D, folic acid and selenium neither reduced depressive symptoms, anxiety symptoms, nor improved health utility measures. In fact, they appear to result in slightly poorer depressive and anxiety symptoms scores compared to placebo. Despite substantial evidence of observational studies linking lower nutrient levels to higher depressive symptoms, similar to our findings, a review of nine RCTs found no support that vitamin D could prevent depression in older adults.[12] For omega-3 PUFAs, one RCT in mild to moderately depressed individuals – a population that is somewhat comparable to our sample - also showed no favorable effect of omega-3 PUFAs on depressive symptoms.[36] No effect of folic acid combined with

vitamin B6 and B12 was found on the onset of depression in older men[37] and older women.[38] Furthermore, Rayman et al.[39] found no effect of selenium on mood in older adults. Overall, the studies available thus far, including our own trial, do not support the use of nutritional supplementation in the prevention of depression.[12]

F-BA had a significant effect on reduction in anxiety symptoms at 12 months, but not on any of the other secondary mental health outcomes. When accounting for a priori defined intervention adherence (i.e. attending ≥8 of 21 sessions), F-BA was related to lower MDD onset, with an effect size comparable to that reported in (meta-analytic) studies of psychological interventions for depression.[35,28,40] In a post hoc analysis, a more beneficial effect of F-BA on depressive symptoms for those with higher baseline depression scores was observed. This suggests that with sufficient dose and a higher risk sample, F-BA might prevent depression, although this requires further study. It would be relevant to study which characteristics make participants more likely to adhere to the intervention, to identify persons who may benefit from this intervention.

Strengths of this study are its randomized 2x2 factorial design, inclusion of participants from four countries with different background characteristics and dietary patterns, its large sample size compared to other prevention studies of depression,[35] intervention and follow-up period of one year, efficient testing of multiple nutrients, blinded design, measurement of multiple outcome assessments, and active adherence monitoring.

Limitations

This study has several limitations. First, the onset of MDD was lower than expected, which resulted in lower power to detect significant effects, if present. However, as placebo outperformed supplements for some secondary outcomes, it is unlikely that inclusion of an adequately powered sample would favor supplements for the prevention of depression. Second, a considerable number of participants (about a quarter) was lost to follow-up. Although this number was balanced between

intervention groups, attrition bias cannot be ruled out. Third, those who received placebo were less likely to believe they were taking multi-nutrients, which suggests that the blinding of participants was not optimal. Fourth, participants were not selected based on deficiencies in the specific nutrients provided. It is conceivable that deficient individuals will be more likely to benefit from supplementation, but studies addressing this are scarce.[12] Fifth, no active control group for the F-BA component was present. Sixth, the pre-defined follow-up time of this study was one year, which might have been too short to detect an effect.

Conclusions

Among overweight or obese adults with subsyndromal depressive symptoms, multinutrient supplementation compared with placebo and food-related behavioral activation therapy compared with no therapy did not reduce episodes of major depressive disorder during 1 year. These findings do not support the use of these interventions for prevention of major depressive disorder in this population.

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MooDFOOD Prevention Trial Investigators

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Conflicts of interest

No conflicts of interest for Mariska Bot, Ingeborg A. Brouwer, Elisabeth Kohls, Ed Watkins, Gerard Van Grootheest, Mieke Cabout, Margalida Gili, Matthew Owens, and Marjolein Visser. Miquel Roca received in the last three years research funding from Janssen and Lundbeck (not related to the MooDFOOD project). Ulrich Hegerl was in the last three years an advisory board member for Lundbeck, Janssen and

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Roles

MB was the lead author on the manuscript and MB/EW/MO analyzed the data. All interpreted the data. MV and IAB obtained funding for the MooDFOOD project, designed the MooDFOOD prevention trial and together with MC coordinated the MooDFOOD project. BWP, MB and EW contributed to the design of the MooDFOOD prevention trial. EW led the development and training of the MooDFOOD Food-related behavioural activation intervention. EK and UH coordinated the recruitment, interventions and follow-ups at the trial center in Germany, University Leipzig. BWP and MB coordinated the recruitment, interventions and follow-ups at the trial center in the Netherlands, Amsterdam UMC Vrije Universiteit Amsterdam. EW and MO coordinated the recruitment, interventions and follow-ups at the trial center in the United Kingdom, University of Exeter. MR and MG coordinated the recruitment, interventions and follow-ups at the trial center in Spain, University of Balearic Islands. GvG set up the logistics for the trial's data collection. All authors contributed to the writing of the manuscript and approved the final version.

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Table 1. Baseline sample characteristics of the trial stratified by intervention group

	Placebo without Food-related behavioural activation	Placebo with Food-related behavioural activation	Supplements without Food-related behavioural activation	Supplements with Food-related behavioural activation
N	257	256	256	256
Sex				
Females, n (%)	180 (70.0)	193 (75.4)	193 (75.4)	206 (80.5)
Males, n (%)	77 (30.0)	63 (24.6)	63 (24.6)	50 (19.5)
Age in years, mean (SD), median (IQR)	45.7 (13.2), 47 (36-55)	46.1 (12.8), 47 (37-55)	47.2 (13.3) 48 (38-58)	47.1 (12.7) 47 (38-56)
Site, n (%)				
Germany	70 (27.2)	67 (26.2)	69 (27.0)	71 (27.7)
United Kingdom	64 (24.9)	63 (24.6)	64 (25.0)	63 (24.6)
Spain	64 (24.9)	64 (25.0)	62 (24.2)	62 (24.2)
The Netherlands	59 (23.0)	62 (24.2)	61 (23.8)	60 (23.4)
Education, n (%)[a]				
Low	25 (9.7)	21 (8.2)	31 (12.1)	26 (10.2)
Middle	124 (48.2)	141 (55.1)	120 (46.9)	113 (44.1)
High	108 (42.0)	94 (36.7)	105 (41.0)	117 (45.7)
History of major depressive disorder, n (%)	83 (32.3)	89 (34.8)	88 (34.4)	83 (32.4)
2 or more episodes, n (%)	59 (23.0%)	53 (20.7%)	62 (24.2%)	58 (22.7%)
Current smoker, n (%)	53 (20.6)	50 (19.5)	35 (13.7)	47 (18.4)
Alcohol use (drinks/week), median (IQR)	1.0 (0.2-3.7)	1.0 (0.2-3.7)	1.0 (0.2-3.7)	1.0 (0.2-3.7)
Total physical activity (in hours/day), median (IQR)[b]	7.8 (6.1-9.5)	7.8 (5.6-10.0)	7.9 (5.9-10.2)	7.5 (5.3-9.7)
BMI kg/m^2, mean (SD)	31.4 (4.1)	31.2 (3.9)	31.3 (4.0)	31.7 (3.9)
Depression severity (PHQ-9), mean (SD), median (IQR)[c]	7.3 (4.1) 7 (4-10)	7.3 (4.4) 6 (4-10)	7.9 (4.4) 7 (5-10)	7.1 (4.0) 6 (4-9)
Depression severity (IDS), mean (SD), median (IQR)[d]	21.3 (9.8) 20 (14-27)	21.6 (10.5) 21 (13-29)	22.8 (10.2) 21 (15-30)	21.4 (9.8) 20 (14-28)
Anxiety severity (GAD-7), mean (SD), median (IQR)[e]	5.8 (4.4) 5 (3-7)	6.2 (4.5) 5 (3-9)	5.7 (3.8) 5 (3-7)	5.4 (3.8) 5 (3-7)
Health utility[f] (EQ5D5L), mean (SD), median (IQR)[f]	0.87 (0.11) 0.88 (0.82-0.94)	0.86 (0.13) 0.87 (0.81-0.95)	0.86 (0.12) 0.87 (0.81-0.94)	0.86 (0.12) 0.88 (0.81-0.94)
MooDFOOD diet score, mean (SD)[g]	51.7 (7.6)	51.9 (6.9)	51.6 (6.8)	51.4 (6.9)
Prior (multi)-nutrient supplement use, n (%)	77 (30.0)	86 (33.6)	78 (30.5)	79 (30.9)

Abbreviations: EQ5D5L: EuroQol 5 dimension 5 level, GAD-7: Generalized Anxiety Disorder-7, IDS: Inventory of Depressive Symptomatology, IQR: Interquartile range,
PHQ-9: Patient Health Questionnaire-9

[a] low = no education, primary education or lower secondary education; middle = upper secondary education, post-secondary non-tertiary education, short-cycle tertiary education; high = Bachelor, Master, Doctoral or equivalent level.

[b] Total activity represents the number of hours/day spent on commuting (walking and cycling), work-related, household, leisure time and sport activities.

[f]

[c]PHQ-9 score ranges from 0 to 27, with higher values indicating higher depression severity. PHQ score >=5 indicates mild depression. PHQ score >=10 indicates moderate depression.
[d]IDS score ranges from 0 to 84, with higher values indicating higher depression severity. IDS score >=14 indicates mild depression. IDS score >=26 indicates moderate depression.
[e]GAD-7 score ranges from 0 to 21, with higher values indicating higher anxiety severity. GAD score >=5 indicates mild anxiety. GAD score >=10 indicates moderate anxiety.
[f]EQ5D5L score ranges from 0 to 1, with higher values indicating higher health utility (0 equaling death, 1 equaling full health). Health utility is based on the tariff of England, which is an algorithm that can be used to attach values to all health states derived from the health-related quality-of-life EQ5D5L instruments, reflecting a country-specific preference on health states.
[g]MooDFOOD diet score ranges from 0 to 77, with higher values indicating better adherence to the Mediterranean-style diet that was promoted in the F-BA group. The MooDFOOD diet score consisted of 11 components, and the median self-reported intake of each component was: vegetables (2.8 times/day), fruit (1.9 times/day), fish (1.5 times/week), legumes/pulses (1 times/week), meat (5 times/week), whole grain products (67% of total grains), low-fat dairy (0.9 times/day), olive oil (33% of total dressings, cooking oils and fats), soft drinks (0.14 times/day), processed food (1.6 times/day), and alcohol (0.14 times/day).

Table 2. Effect of supplements and food-related behavioural activation (F-BA) therapy on MDD onset

Primary outcome: 12 month MDD onset					
	N	**Number of events**	**No. of follow-up dropouts** [a]	**Imputed OR (95% CI)**[b]	**p**[b]
Placebo[c]	513	51	113	Ref	
Supplements[d]	512	54	126	1.06 (0.87-1.29)	0.57
No F-BA[e]	513	57	122	Ref	
F-BA[f]	512	48	117	0.93 (0.76-1.13)	0.47
Supplements by F-BA[g]	NA	NA	NA	0.93 (0.76-1.14)	0.48
Post-hoc outcome: time to MDD onset					
	Time to event or censoring (person months)	**Number of events**	**No. of follow-up dropouts** [e]	**HR (95% CI)**	**p**
Placebo	4656	51	113	Ref	
Supplements	4488	54	126	1.05 (0.86-1.27)	0.65
No F-BA	4503	57	122	Ref	
F-BA	4641	48	117	0.91 (0.75-1.10)	0.32
Supplements by F-BA[g]	NA	NA	NA	0.91 (0.75-1.11)	0.36

Models were adjusted for interventions, site and history of MDD. F-BA and pills were effect-coded (-1,1). CI=confidence interval, HR=hazard ratio, MDD=major depressive disorder, NA=not applicable, OR=odds ratio.

[a] n that did not complete 12 months follow-up and had no MDD at previous follow-up measurements

[b] derived from multiply imputed data.

[c] Events/Total (%): Placebo without F-BA 25/257 (9.7%); Placebo with F-BA 26/256 (10.2%)

[d] Events/Total (%): Supplements without F-BA 32/256 (12.5%); Supplements with F-BA 22/256 (8.6%)

[e] Events/Total (%): Placebo without F-BA 25/257 (9.7%); Supplements without F-BA 32/256 (12.5%)

[f] Events/Total (%): Placebo with F-BA 26/256 (10.2%); Supplements with F-BA 22/256 (8.6%)

[g] interaction between F-BA and supplements

Table 3. Effect of supplements and food-related behavioural activation (F-BA) therapy on secondary outcomes

Outcomes		Overall follow-up effect using all follow-ups[a]		Effect at 12 month follow-up[b]		
		Estimate (95% CI)	P	Estimate (95% CI)	P	Cohens' D
PHQ	Supplements vs Placebo (ref)	0.33 (0.12 to 0.53)	0.002	0.28 (0.05 to 0.50)	0.02	0.10
	F-BA vs no F-BA (ref)	-0.13 (-0.33 to 0.07)	0.19	-0.17 (-0.39 to 0.06)	0.14	-0.02
IDS	Supplements vs Placebo (ref)	0.60 (0.15 to 1.05)	0.01	0.36 (-0.19 to 0.90)	0.20	0.05
	F-BA vs no F-BA (ref)	-0.23 (-0.67 to 0.22)	0.32	-0.28 (-0.83 to 0.27)	0.31	0.006
GAD	Supplements vs Placebo (ref)	0.25 (0.08 to 0.42)	0.004	0.14 (-0.04 to 0.33)	0.13	0.10
	F-BA vs no F-BA (ref)	-0.16 (-0.32 to 0.01)	0.06	-0.24 (-0.42 to -0.06)	0.01	-0.07
Utility	Supplements vs Placebo (ref)	-0.006 (-0.012 to 0.000)	0.052	-0.002 (-0.008 to 0.005)	0.61	-0.07
	F-BA vs no F-BA (ref)	0.002 (-0.003 to 0.008)	0.44	0.004 (-0.002 to 0.009)	0.23	0.08

The two interventions and their interactions were modelled together. All models were adjusted for study site, history of MDD, and for the baseline value of the corresponding outcome measure. F-BA and pills were effect-coded (-1,1), Supplement-by-F-BA interaction effects were not included in the model because none of the interactions were significant.

estimate= unstandardized regression coefficient, CI=confidence interval, NA=not applicable, SE=standard error,

, GAD=Generalized Anxiety Disorder-7, IDS=inventory of depressive symptomatology OR=odds ratio, PHQ-9=Patient Health Questionnaire-9.

To obtain adjusted mean differences in outcomes between the intervention conditions, the estimates and 95% confidence interval should be multiplied by 2.

Cohen's D calculated from baseline and 12 month follow-up means and pooled standard deviations obtained from multiple imputed data.

[a]Estimates were obtained from generalized estimating equations longitudinal GEE analyses using effect-coded interventions based on multiply imputed data.

[b]Estimates were obtained from robust linear regression analyses based on multiply imputed data.

Figure titles and legends

Figure 1. Flow chart of the MooDFOOD depression prevention trial

BMI=body mass index, PHQ=Patient Health Questionnaire

Figure 2. Course of depressive symptoms, anxiety symptoms and health utility per intervention group

The boxplot inner horizontal lines represent the median, the boxes represent the interquartile range (25% and 75%), the vertical whiskers represent the 1.5 interquartile range beyond the 25th and 75th percentiles, and the dots represent all other values. The diamonds represent the means, which were connected with orange/blue lines.
N represents the number of persons that completed the secondary outcomes at the different time points. Data shown are the available data.