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Effect of Multinutrient 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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IMPORTANCE Effects of nutritional interventions on the prevention of major depressive disorder (MDD) in overweight adults are unknown.

OBJECTIVE To examine the effect of 2 nutritional strategies (multinutrient supplementation, food-related behavioral activation therapy) and their combination for prevention of a new MDD episode in overweight adults with subsyndromal depressive symptoms.

DESIGN, SETTING, AND PARTICIPANTS This multicenter 2 × 2 factorial randomized clinical trial included overweight adults (body mass index, 25-40) with elevated depressive symptoms (Patient Health Questionnaire-9 [PHQ-9] scores ≥5) and no MDD episode in the past 6 months from 4 European countries. A total of 1025 adults were randomized (July 30, 2015-October 12, 2016) and followed up for 1 year (October 13, 2017).

INTERVENTIONS Daily multinutrient supplements (1412-mg omega-3 fatty acids, 30-μg selenium, 400-μg folic acid, and 20-μg vitamin D_3 plus 100-mg calcium) vs placebo and 21 individual or group therapy sessions vs none (blinded to researchers) for 1 year. Participants were allocated to placebo without therapy (n = 257), placebo with therapy (n = 256), supplements without therapy (n = 256), and supplements with therapy (n = 256).

MAIN OUTCOME AND MEASURES Cumulative 1-year onset of MDD via the Mini International Neuropsychiatric Interview at 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, 46.5 years; 772 women [75%]; mean BMI, 31.4), 779 (76%) completed the trial. During the 12-month follow-up, 105 (10%) developed MDD: 25 (9.7%) patients in the placebo without therapy, 26 (10.2%) in the placebo with therapy, 32 (12.5%) in the supplement without therapy, and 22 (8.6%) in the supplement with therapy group. None of the treatment strategies affected MDD onset. The odds ratio (OR) for supplements was 1.06 (95% CI, 0.87-1.29); for therapy, 0.93 (95% CI, 0.76-1.13); and for their combination, 0.93 (95% CI, 0.76-1.14; *P* for interaction, .48). One person in the supplementation with therapy group, died. Twenty-four patients in each of the placebo groups and 24 patients in the supplementation with therapy group were hospitalized, and 26 patients in the supplementation-only group were hospitalized.

CONCLUSIONS AND RELEVANCE 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.

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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 unhealthful 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 (eg, 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 of MDD and the key role of diet in these conditions.[13] Therefore, the MooDFOOD depression prevention trial examined the effect of 2 different nutritional strategies (multinutrient 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 2 × 2 factorial RCT performed between July 30, 2015, and October 13, 2017, in 4 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. For the statistical analysis plan, see Supplement 2. Ethics approval was provided by the human research ethics boards of the 4 study sites. All participants provided written informed consent. This article 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 well-being through changes in diet and lifestyle by the study sites (located in Leipzig, Germany; Palma de Mallorca, Spain; Exeter, United Kingdom; and Amsterdam, the Netherlands). Main eligibility criteria were age between 18 and 75 years, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) between 25 and 40, having at least mild depressive symptoms as operationalized by Patient Health Ques-

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 subsyndromal depressive symptoms?

Findings In this 2 × 2 factorial randomized clinical trial that included 1025 adults, there was no significant difference in episodes of major depressive disorder over 1 year of 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.

tionnaire (PHQ-9) scores of 5 or higher[15] but having no current MDD episode in past 6 months (Mini International Neuropsychiatric Interview 5.0 [MINI 5.0]).[16] (See eAppendix 1 in Supplement 3 for recruitment details and eligibility.) All eligible participants were invited to visit one of the study sites for a baseline interview. The interview, physical measurements, blood sampling were conducted by trained research assistants or nurses. Furthermore, participants completed 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 therapy; (2) placebo supplements with therapy; (3) multinutrient supplements without therapy; or (4) multinutrient supplements with therapy 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 (**Figure 1**). After randomization, researchers dispensed supplements to participants according to unique randomization codes. Participants, therapists, and researchers were blinded to supplement allocation. Participants of food-related behavioral activation intervention therapy were contacted directly by the therapist, ensuring that researchers assessing follow-up outcomes remained blind to this 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

Multinutrient Supplements

Patients received either multinutrient supplements (1412 mg of eicosapentaenoic and docosahexaenoic omega-3 polyunsaturated fatty acids [PUFAs]; ratio, 3:1), 30 μg of selenium, 400 μg of folic acid, and 20 μg of vitamin D_3 coupled with 100 mg of calcium) or placebo, each were provided in 2 pills per day, taken daily for 1 year (see eAppendix 2 in Supplement 3 for details).

Figure 1. Flow of Participants Through the MooDFOOD Depression Prevention Trial
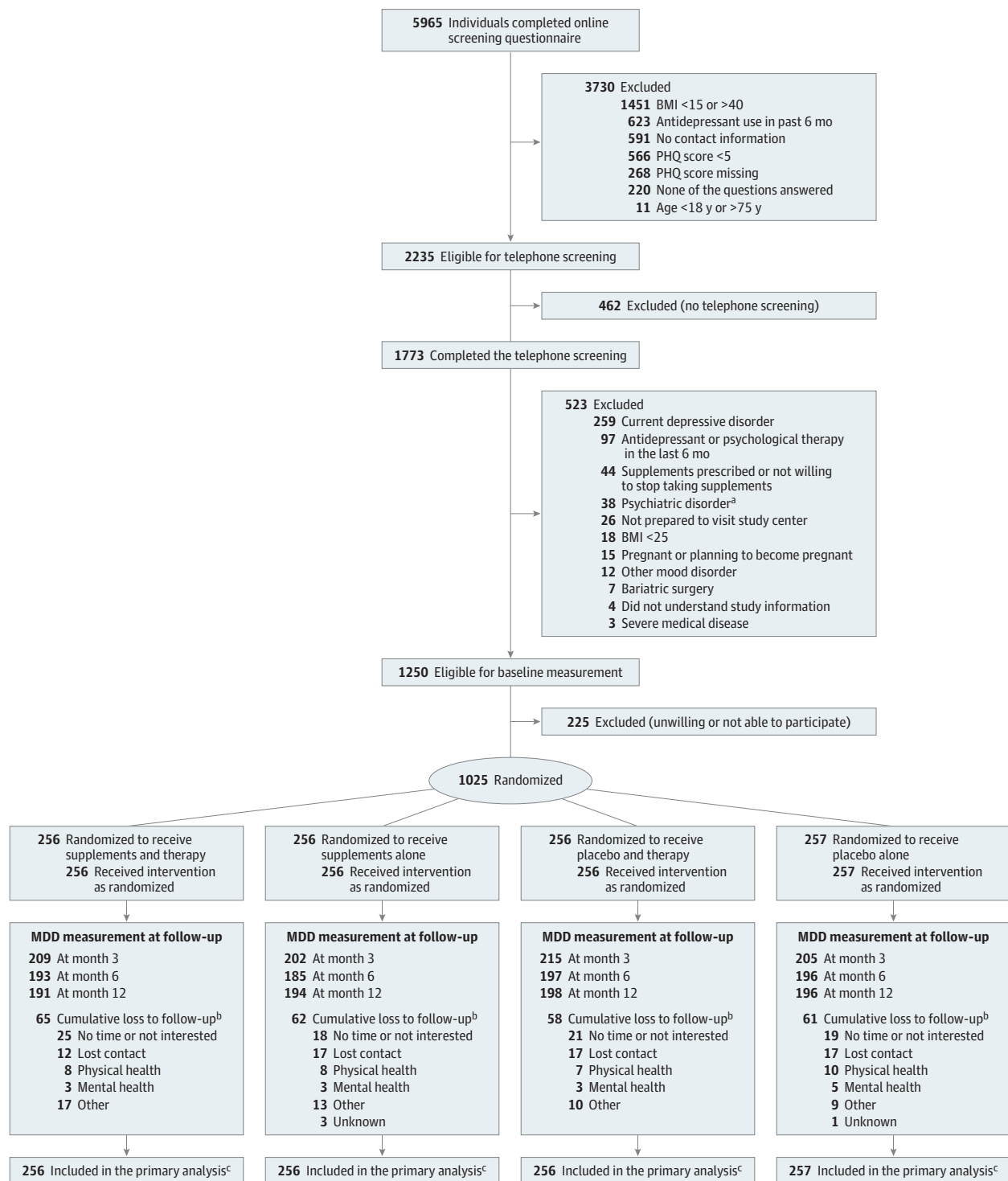
[a] Bipolar disorder, schizophrenia, psychosis, eating disorder, anxiety disorder, alcohol, drug, or substance addiction.

[b] Cumulative loss to follow-up is defined as having no MDD measurement at month 12.

[c] The primary analysis included all participants according to their randomization

group, including all participants randomized regardless of the intervention actually received or of study withdrawal. Missing data were multiple imputed.

BMI indicates body mass index; MDD, major depressive disorder; PHQ, Patient Health Questionnaire.

Food-Related Behavioral Activation Therapy

Food-related behavioral activation therapy consisted of a protocol-based intervention that incorporated standard behavioral activation approaches. Behavioral activation is effective in depression treatment[17] and includes self-monitoring, functional analysis, and activity scheduling. Food-related behavioral activation applied these proven techniques to improve mood by changing dietary habits, food-related behaviors (eg, snacking), increasing positive behaviors, and emphasizing a Mediterranean-style diet, which has been related to reduced depression onset.[4] A maximum of 21 sessions were provided (15 individual, 6 group) for 1 year (see eAppendix 3 in Supplement 3). No active (eg, attention) control condition was provided in those receiving no therapy.

Outcomes

Primary Outcome

The 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) criteria and was 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 Item Scale [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 (3-factor eating questionnaire [TEFQ-R18], all 3 factors ranging from 0-100, with higher values indicating poorer eating behavior)[22] food behavior, food intake (Global Allergy and Asthma European Network [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 et al[25]). This article 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; eAppendix 4 in Supplement 3).[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 therapy sessions, and taking ≥70% of the supplements during the 12 months) was defined a priori. A detailed description of these and other measures can be found in eAppendixes 5 and 6 in Supplement 3.

Sample Size

Sample size was based on the primary outcome and accounted for the 2 × 2 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% to 50%.[3] Assuming a 33% reduction of MDD onset between active (20% MDD onset) vs control conditions (30% MDD onset),[26,27] 392 participants (196 in each of the 4 possible intervention combinations) were needed to evaluate the main effect of each of the 2 nutritional interventions (vs respective control) assuming a 2-sided test at α = .05 and a power of (1−β) = .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 (eg, 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 2 nutritional interventions were effect coded (−1 indicating control and 1 indicating intervention) and jointly modeled 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 end points were accounted for using multiple imputation under the missing at random assumption into 100 data sets. Results were pooled using the Rubin rules.[30]

Logistic regression analyses were conducted to estimate effects of the interventions on the primary outcome. Cox proportional hazard modeling 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 ($P > .05$). For secondary outcomes, generalized estimating equations (GEE) longitudinal analysis of covariance (ANCOVA) with an exchangeable correlation structure was used,[31] modeling 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 I error due to multiple comparisons, findings for analyses of secondary end points 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. A Cohen D value 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 modeling within STATA, to provide an estimate of intervention effects taking

Table 1. Baseline Sample Characteristics of the Trial Stratified by Intervention Group

	No. (%) of Participants			
	Placebo		Supplements	
	Without Food-Related Behavioral Activation Therapy (n = 257)	With Food-Related Behavioral Activation Therapy (n = 256)	Without Food-Related Behavioral Activation Therapy (n = 256)	With Food-Related Behavioral Activation Therapy (n =256)
Sex				
Men	77 (30.0)	63 (24.6)	63 (24.6)	50 (19.5)
Women	180 (70.0)	193 (75.4)	193 (75.4)	206 (80.5)
Age, y				
Mean (SD)	45.7 (13.2)	46.1 (12.8)	47.2 (13.3)	47.1 (12.7)
Median (IQR)	47 (36-55)	47 (37-55)	48 (38-58)	47 (38-56)
Site				
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[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 MDD	83 (32.3)	89 (34.8)	88 (34.4)	83 (32.4)
≥2 Episodes	59 (23.0)	53 (20.7)	62 (24.2)	58 (22.7)
Current smoker	53 (20.6)	50 (19.5)	35 (13.7)	47 (18.4)
Alcohol use, median (IQR), drinks/wk	1.0 (0.2-3.7)	1.0 (0.2-3.7)	1.0 (0.2-3.7)	1.0 (0.2-3.7)
Physical activity, median (IQR), h/d[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, mean (SD)	31.4 (4.1)	31.2 (3.9)	31.3 (4.0)	31.7 (3.9)
Depression severity				
PHQ-9[c]				
Mean (SD)	7.3 (4.1)	7.3 (4.4)	7.9 (4.4)	7.1 (4.0)
Median (IQR)	7 (4-10)	6 (4-10)	7 (5-10)	6 (4-9)
IDS[d]				
Mean (SD)	21.3 (9.8)	21.6 (10.5)	22.8 (10.2)	21.4 (9.8)
Median (IQR)	20 (14-27)	21 (13-29)	21 (15-30)	20 (14-28)
Anxiety severity[e]				
Mean (SD)	5.8 (4.4)	6.2 (4.5)	5.7 (3.8)	5.4 (3.8)
Median (IQR)	5 (3-7)	5 (3-9)	5 (3-7)	5 (3-7)
Health utility[f]				
Mean (SD)	0.87 (0.11)	0.86 (0.13)	0.86 (0.12)	0.86 (0.12)
Median (IQR)	0.88 (0.82-0.94)	0.87 (0.81-0.95)	0.87 (0.81-0.94)	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	77 (30.0)	86 (33.6)	78 (30.5)	79 (30.9)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; EQ5D5L, EuroQol 5 dimension 5 level; GAD-7, Generalized Anxiety Disorder 7; IDS, Inventory of Depressive Symptomatology; IQR, interquartile range; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire 9.

[a] Low represents no education, primary education, or lower secondary education; middle, upper secondary education; postsecondary nontertiary education, short-cycle tertiary education; high, bachelor's degree or higher or equivalent level.

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

[c] Higher values (range, 0-27) indicate greater severity (≥5 indicates mild depression; ≥10, moderate depression).

[d] Higher values (range, 0-84) indicate greater severity (≥14 indicates mild depression; ≥26, moderate depression).

[e] Higher values (range, 0-21) indicate greater severity (≥5 indicates mild anxiety; ≥10 moderate anxiety).

[f] Higher values (range, 0-1) indicate higher health utility (0, death; 1, 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] Higher values (range, 0-77) indicate better adherence to the Mediterranean-style diet. The median intakes of each of the 11 MooDFOOD diet score components were vegetables (2.8 times per day), fruit (1.9 times per day), fish (1.5 times per week), legumes or pulses (1 times per week), meat (5 times per week), whole grain products (67% of total grains), low-fat dairy (0.9 times per day), olive oil (33% of total dressings, cooking oils, and fats), soft drinks (0.14 times per day), processed food (1.6 times per day), and alcohol (0.14 times per day).

Table 2. Effect of Supplements and Food-Related Behavioral Activation Therapy on Major Depressive Disorder Onset

	No. of Patients	No. of Events	No. of Follow-up Dropouts[a]	Imputed OR (95% CI)[b]	P Value[b]
Primary Outcome: 12-mo MDD Onset					
Placebo[c]	513	51	113	1 [Reference]	
Supplements[d]	512	54	126	1.06 (0.87-1.29)	.57
Food-related behavioral activation therapy					
No[e]	513	57	122	1 [Reference]	
Yes[f]	512	48	117	0.93 (0.76-1.13)	.47
Supplements by therapy[g]	NA	NA	NA	0.93 (0.76-1.14)	.48
Post Hoc Outcome: Time to MDD Onset					
	Time to Event or Censoring (Person-Months)			HR (95% CI)	
Placebo	4656	51	113	1 [Reference]	
Supplements	4488	54	126	1.05 (0.86-1.27)	.65
Food-related behavioral activation therapy					
No	4503	57	122	1 [Reference]	
Yes	4641	48	117	0.91 (0.75-1.10)	.32
Supplements by therapy[g]	NA	NA	NA	0.91 (0.75-1.11)	.36

Abbreviations: HR, hazard ratio; MDD, major depressive disorder; NA, not applicable; OR, odds ratio.

[a] No. that did not complete 12 mo follow-up and had no MDD at previous follow-up measurements.

[b] Derived from multiple imputed data. Models were adjusted for interventions, site and history of MDD. Food-related behavioral activation therapy and pills were effect-coded (–1,1).

[c] Twenty-five of 257 participants (9.7%) in the placebo without therapy group and 26 of 256 (10.2%) in the placebo group with therapy.

[d] Thirty-two of 256 participants (12.5%) in the supplements without therapy group and 22 of 256 (8.6%) in the supplements without therapy group.

[e] Twenty-five of 257 participants (9.7%) in the placebo group without therapy and 32 of 256 (12.5%) in the supplements without therapy group.

[f] Twenty-six of 256 participants (10.2%) in the placebo with therapy group and 22 of 256 (8.6%) in the supplements with therapy group.

[g] Interaction between therapy and supplements.

into account good adherence with the interventions, while retaining the benefits of randomization for both primary and secondary 12-month follow-up outcomes (eAppendix 7 in Supplement 3). Analyses were conducted with R (version 3.4.4), using the packages geepack for the GEE analyses and mice for multiple imputation. The 2-sided significance threshold was set at P = .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 or able to participate, 1025 adults were randomly allocated to the 4 groups: placebo without therapy (n = 257), placebo with therapy (n = 256), multinutrient supplements without therapy (n = 256), and multinutrient supplements with therapy (n = 256) (Figure 1). **Table 1** shows the baseline characteristics of the intervention groups.

Follow-up Attrition

The number of participants not taking part in follow-up assessment were 194 (19%) at 3 months, 254 (25%) at 6

months, and 246 (24%) at 12 months (Figure 1). In total, 239 participants (23%) dropped out before the 12-month follow-up or before the onset of MDD (the main outcome) occurred. Missing rates for the primary outcome did not differ between the 4 intervention groups at 3 months (P = .47), 6 months (P = .62), and 12 months (P = .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 baseline was 29 to 32, at 3 months 206 to 211, at 6 months 275 to 278, and at 12 months 268 for these outcomes. These missing rates did not differ across intervention groups.

Adherence to Interventions

Adherence for each group is described in eAppendix 8 in Supplement 3. Of all 12-month follow-up participants, pill weight data indicated that 77% of participants had adherence of more than 70% to the supplements or placebo. Of those randomized to the therapy groups, 71% attended 8 or more of the 21 sessions. A median of 14 of 15 individual sessions were attended (interquartile range [IQR], 6-15), and a median of 0 of 6 group sessions (IQR, 0-4) were attended, indicating that adherence to individual sessions was highest.

Onset of MDD

One hundred five participants (10%) developed an MDD episode during the 12-month follow-up (**Table 2**): 25 partici-

Figure 2. Course of Depressive Symptoms, Anxiety Symptoms, and Health Utility per Intervention Group

A Supplements

B Food-related behavioral activation therapy
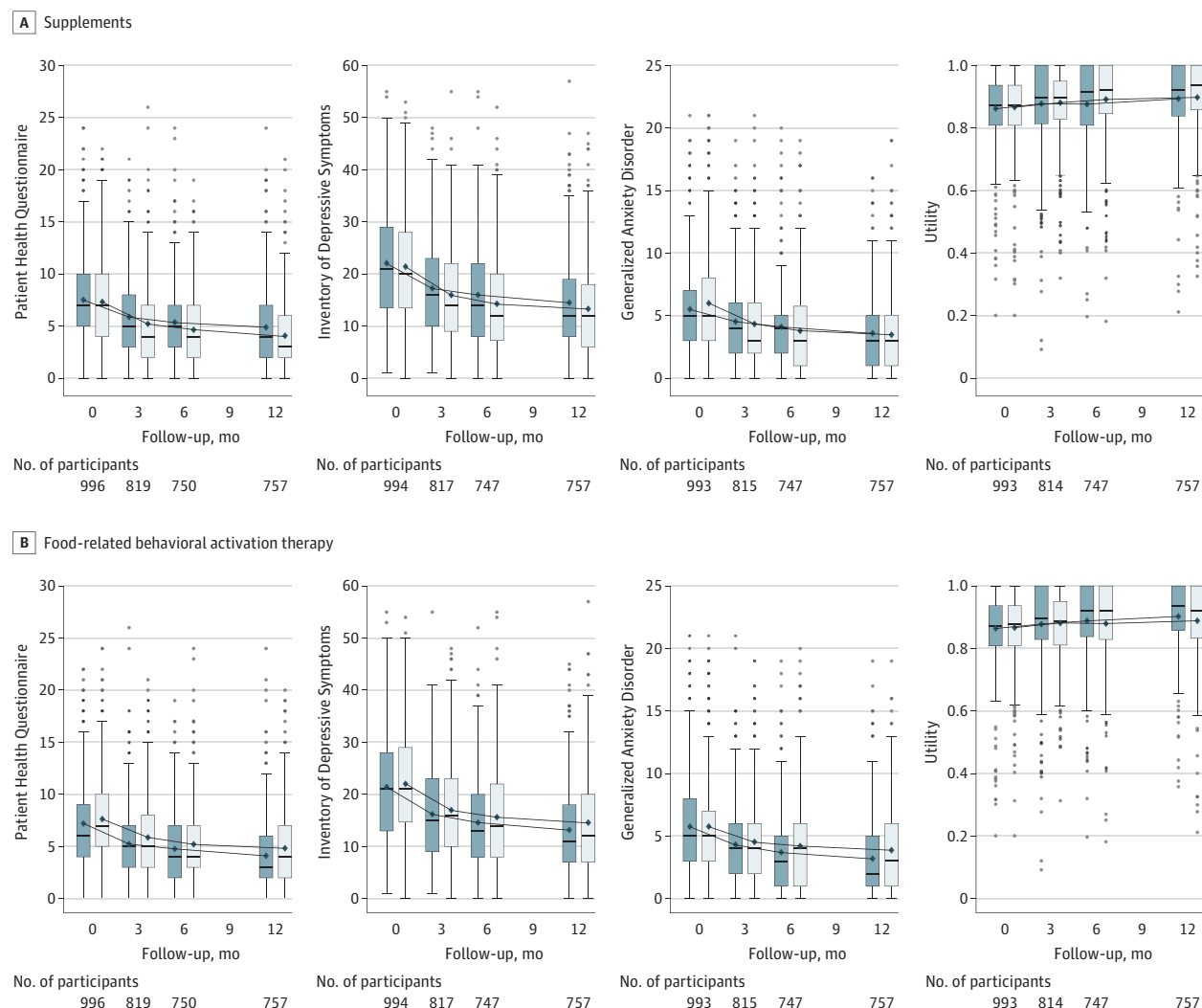
The boxplot inner horizontal lines represent the median, the boxes represent the interquartile range (25% and 75%), the vertical whiskers represent the 1.5 interquartile range beyond the 25th and 75th percentiles, and the dots represent all other values. The diamonds represent the means. The dark blue bars indicate the intervention; the light blue bars, control. The No. of participants represents the number of persons who completed the secondary outcomes at the different time points. Data shown are the available data.

pants (9.7%) receiving placebo alone, 26 (10.2%) receiving placebo with therapy, 32 (12.5%) receiving supplements alone, and 22 (8.6%) receiving supplements with therapy. Considering the main effect of each intervention, the numbers of participants who developed MDD were 51 participants (9.9%; 1.1 per 100 person-months) receiving placebo, 54 (10.5%; 1.2 per 100 person-months) receiving supplements, 57 (11.1%; 1.3 per 100 person-months) not receiving therapy, and 48 (9.4%; 1.0 per 100 person-months) receiving therapy. 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 = .57) or food-related behavioral activation therapy (OR, 0.93, 95% CI, 0.76-1.13; P = .47) or significant supplements × therapy interaction (OR, 0.93; 95% CI, 0.76-1.14, P for interaction, .48) on the onset of MDD. There was no significant effect of supplements (HR, 1.05; 95% CI,

0.86-1.27; P = .65) or therapy (HR, 0.91; 95% CI, 0.75-1.10; P = .32) or significant supplements × therapy interaction (HR, 0.91; 95% CI, 0.75-1.11; P for interaction, .36) on the time to first onset of MDD (Table 2).

Depressive Symptoms, Anxiety Symptoms, and Health Utility

Figure 2 shows boxplots and means of the secondary outcome scores at baseline and at 3, 6, and 12 months stratified by food-related behavioral activation and supplement groups (see eAppendix 9 in Supplement 3 for figure stratified by the 4 intervention combinations). There were no significant supplement × food-related behavioral activation therapy interactions for any of the secondary outcome scores (P values for interaction ranged from .41 to .98). **Table 3** presents effects on secondary outcomes. Food-related behavioral activation

Table 3. Effect of Supplements and Food-Related Behavioral Activation Therapy on Secondary Outcomes[a]

Outcomes	Overall Follow-up Effect Using All Follow-ups[b]		Effect at 12 Month Follow-up[c]		
	Estimate (95% CI)[d]	P Value	Estimate (95% CI)[d]	P Value	Cohen D Value[e]
Patient Health Questionnaire 9					
Supplements vs placebo	0.33 (0.12 to 0.53)	.002	0.28 (0.05 to 0.50)	.02	0.10
With vs without food-related behavioral activation therapy	−0.13 (−0.33 to 0.07)	.19	−0.17 (−0.39 to 0.06)	.14	−0.02
Inventory of Depressive Symptomatology					
Supplements vs placebo	0.60 (0.15 to 1.05)	.01	0.36 (−0.19 to 0.90)	.20	0.05
With vs without food-related behavioral activation therapy	−0.23 (−0.67 to 0.22)	.32	−0.28 (−0.83 to 0.27)	.31	0.006
Generalized Anxiety Disorder 7					
Supplements vs placebo	0.25 (0.08 to 0.42)	.004	0.14 (−0.04 to 0.33)	.13	0.10
With vs without food-related behavioral activation therapy	−0.16 (−0.32 to 0.01)	.06	−0.24 (−0.42 to −0.06)	.01	−0.07
Utility					
Supplements vs placebo	−0.006 (−0.012 to 0.000)	.052	−0.002 (−0.008 to 0.005)	.61	−0.07
With vs without food-related behavioral activation therapy	0.002 (−0.003 to 0.008)	.44	0.004 (−0.002 to 0.009)	.23	0.08

Abbreviation: estimate, unstandardized regression coefficient.

[a] The 2 interventions were modeled together. All models were adjusted for study site, history of major depressive disorder, and for the baseline value of the corresponding outcome measure. Food-related behavioral activation therapy and pills were effect-coded (−1,1), supplement × food-related activation interaction therapy interaction effects were not included in the model because none of the interactions were statistically significant.

[b] Estimates were obtained from generalized estimating equations

longitudinal (GEE) analyses using effect-coded interventions based on multiple imputed data.

[c] Estimates were obtained from robust linear regression analyses based on multiple imputed data.

[d] To obtain adjusted mean differences in outcomes between the intervention conditions, the estimates and 95% CIs should be multiplied by 2.

[e] The Cohen D value was calculated from baseline and 12-month follow-up means and pooled standard deviations obtained from multiple imputed data.

therapy was significantly related to lower GAD scores at 12 months (adjusted mean difference, −0.48; 95% CI, −0.84 to −0.12; P = .01). The unadjusted baseline GAD score for both the therapy and nontherapy group was 5.8. At 12 months, the unadjusted score was 3.9 for the nontherapy group vs 3.2 for the therapy group. No effect of therapy on other secondary outcomes was found.

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 = .002), the IDS (adjusted mean difference, 1.20; 95% CI, 0.29-2.10; P = .01), and the GAD (adjusted mean difference, 0.50; 95% CI, 0.16-0.84; P = .004) scores. There was also a significant effect on PHQ scores at the 12-month follow-up (adjusted mean difference, 0.56; 95% CI, 0.11-1.01; P = .02). The unadjusted baseline PHQ for those taking placebo was 7.3 vs 7.5 for those taking supplements. The unadjusted 12-month PHQ score for placebo was 4.1 vs 4.9 for supplements. This indicates less improvement in depressive and anxiety symptoms for supplements relative to placebo.

Effect Modification and Sensitivity Analyses
The eAppendix 10 in Supplement 3 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 food-related behavioral activation therapy on PHQ at 12 months was more favorable (larger reduction) when the baseline PHQ depression severity was

higher, (2) the use of supplements resulted in higher follow-up anxiety scores when the baseline anxiety severity scores were higher, and (3) that the effect of food-related behavioral activation on health utility scores at 12 months was larger in the United Kingdom than in the Netherlands. Sensitivity analyses for depression, anxiety, and health utility scores without multiple imputed data gave comparable effect estimates (eAppendix 11 in Supplement 3). The results of the Complier Average Causal Effect (CACE) analyses were consistent with the original analyses, finding no effect of supplements on the primary outcome, and similar effects for secondary outcomes (eAppendix 12 in Supplement 3). The CACE analyses found a significant effect of food-related behavioral activation therapy on the primary outcome (OR, 0.78; 95% CI, 0.64-0.95), accounting for treatment adherence.

Adverse Events and Concealment
Ninety-eight participants were hospitalized and 1 participant died during the 12-month follow-up, these events were judged as unrelated to interventions (eAppendix 8 in Supplement 3). Those receiving placebo were less likely to believe they were taking multinutrients than did those receiving multinutrients (placebo without therapy, 8.2%; placebo with therapy, 10.4%; multinutrients without therapy, 25.5%; and multinutrients with therapy, 43.7%; P < .001; eAppendix 13 in Supplement 3). Of those completing the questions on concealment at the 12-month follow-up, 40.4% reported that they did not know their allocation.

Discussion

This multicenter trial involving 1025 overweight individuals with subsyndromal depressive symptoms showed no effect from multinutrient supplements, food-related behavioral activation therapy, or their combination on the 1-year cumulative onset of MDD.

To our knowledge, this is the first randomized trial evaluating the effectiveness of 2 nutritional strategies and their combination for the prevention of depression in a high-risk group of overweight people. Despite the 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 with previous trials testing preventive 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 to MDD onset.

The adherence to both interventions was adequate, with about three-quarters fulfilling predefined adherence criteria for the interventions. For food-related behavioral activation, the individual sessions in the first 6 months were well attended, but the group sessions in the subsequent 6 months were not.

This study showed that multinutrient 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 appeared to result in slightly poorer depressive and anxiety symptoms scores compared with placebo. Despite substantial evidence of observational studies linking lower nutrient levels to higher depressive symptoms, similar to our findings, a review of 9 RCTs found no support that vitamin D could prevent depression in older adults.[12] For omega-3 PUFAs, one RCT involving mild to moderately depressed individuals—a population that is somewhat comparable with our sample—also showed no favorable effect of omega-3 PUFAs on depressive symptoms.[36] No effect of folic acid combined with vitamin B_6 and B_{12} 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 trial, do not support the use of nutritional supplementation in the prevention of depression.[12]

Food-related behavioral activation therapy 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 (ie, attending ≥8 of 21 sessions), food-related behavioral activation therapy was related to lower MDD onset, with an effect size comparable with that reported in (meta-analytic) studies of psychological interventions for depression.[28,35,40] In a post hoc analysis, a more beneficial effect of food-related behavioral activation therapy on depressive symptoms for those with higher baseline depression scores was observed. This suggests that with sufficient dose and a higher-risk sample, food-related behavioral activation therapy 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 it.

The strengths of this study are the randomized 2 × 2 factorial design, the inclusion of participants from 4 countries with different background characteristics and dietary patterns, the large sample size compared with other prevention studies of depression,[35] the intervention and follow-up period of 1 year, the efficient testing of multiple nutrients, the blinded design, its measurement of multiple outcome assessments, and the 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, because 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 multinutrients, 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 food-related behavioral activation therapy component was present. Sixth, the predefined follow-up time of this study was 1 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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