Supplementary Online Content

Bot M, Brouwer IA, Roca M, et al: Effect of mulitnutrient supplementation and food-related behavioral activationa therapy on prevention of major depressive disorder among overweight or obeses adults with subsyndromal depresive symtoms: the MooDFOOD randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.0556

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplement 3

eAppendix 1. Recruitment and eligibility criteria

Recruitment strategies included websites, local advertisements in social media and newspapers, mailings to registered subjects in the general practice setting or in other registers (e.g. municipality registers), and MooDFOOD brochures as well as posters in public areas. Participants interested in this study were directed to the online screening tool on the study website [http://www.moodfood-vu.eu], which provided further information and included questionnaires to assess key eligibility criteria (see below). Those individuals who passed the online screening and indicated an interest in the study were followed up by a telephone interview, which consisted of screening questions on mental and somatic health to confirm eligibility for the trial.

Eligibility criteria

Inclusion criteria assessed with the online screening tool consisted of age 18-75 years, body mass index (BMI) between 25-40 kg/m^2, and having at least mild depressive symptoms as operationalized by a Patient Health Questionnaire (PHQ-9) score of ≥5.[1] Exclusion criteria (assessed during telephone interview) were a current episode of MDD (in the past 6 months, according to psychiatric DSM-IV criteria), as determined in the structured Mini International Neuropsychiatric Interview 5.0 (MINI 5.0),[2] use of antidepressant drugs or psychological interventions in the past 6 months; current eating disorder; history of psychosis, bipolar disorder, substance dependence or other severe psychiatric disorder that required specialized clinical attention; history of or planned bariatric surgery; current pregnancy or breastfeeding; current severe, life-threatening physical disease; severe cognitive impairment sufficient to limit the conduct of the study as assessed through research staff evaluation of participant's ability to complete the screening instruments in an adequate manner; or not able/willing to stop using dietary supplements that contained one of the nutrients of the MooDFOOD multi-nutrient supplement intervention.

eAppendix 2. Multi-nutrient supplements

Patients received either multi-nutrient supplements or placebo's provided in two pills per day, to be taken daily for one year. Multi-nutrient supplements were specifically prepared for the study and consisted of omega-3 fatty acids, 1412 mg of eicosapentaenoic acid and docosahexaenoic acid (ratio 3:1) provided as a clear slightly yellowish oil encapsulated in a clear soft gelatin shell of non-porcine origin (supplement 1), and a pill containing selenium (30µg), folic acid (400µg), and vitamin D3 (20µg) coupled with calcium (100mg) (supplement 2).

To match the two multi-nutrient supplements, placebo 1 contained sunflower oil (57% linoleic acid, 30% oleic acid) provided as a clear slightly yellowish oil encapsulated in a clear soft gelatin shell of non-porcine origin, and placebo 2 consisted of a pill with filling materials (microcrystalline cellulose; corn starch; polyvinylpyrrolidone; crosslinked carboxymethylcellulose sodium; magnesium stearate and magnesium silicate). Each pair of multi-nutrient supplement and corresponding placebo was identical to one another in shape, color, and package. Participants received packages of supplements during the interviews and were instructed not to chew the capsules.

As described previously,[3] these nutrients were selected from epidemiological studies suggesting associations between deficiencies or low levels of these nutrients and depression risk, or clinical intervention studies showing effects of nutrient supplementation on depressive symptoms. Observational as well as meta-analytic evidence suggest that some specific nutrients, especially omega-3 fatty acids, vitamin D, folic acid, and selenium could have beneficial impact on depression.[4,5,6] Several - but not all - systematic reviews[7,8,9,10] suggested that omega-3 fatty acids could be effective at reducing depressive symptomatology for depression. A recent meta-analysis suggests that doses of 0.6–4.4 g of eicosapentaenoic acid (EPA) plus 0.2–2.2 g of docosahexaenoic acid (DHA) may be efficacious compared to placebo in reducing depressive symptoms in depressed patients.[11]. In people with depression or with higher depression scores, lower levels of vitamin D were found.[12,4] Several trials have found that vitamin

D supplementation improves mood scores[13] and reduces depressive symptoms in obese people,[14] although other trials found no benefit of vitamin D supplementation depressive symptoms in general population samples[15,16,17] For folic acid, a systematic review found preliminary evidence to suggest that folate supplementation may reduce depressive symptoms in the treatment of depression.[18] Depression was associated with lower selenium blood levels[19,20,21] and low levels of selenium intake were also associated with an increased risk for depression.[22]

The selected nutrients were combined to study their joined effect. Contents of selenium, EPA and DHA of supplements were tested and confirmed in duplicate for 6 supplements and 5 placebo's in an independent laboratory (Chemisch Biologisch Laboratorium Bodem, Wageningen University, The Netherlands), giving an average of 30 ug, (SD 0.4) of selenium, 67.9 g/100g fatty acids methyl esters (FAME) (SD 0.85) EPA, and 14.6 g/100g FAME (SD 1.55) DHA g/100g FAME for the supplements, and 0.03 ug/kg (SD 0.03) selenium and <0.1 gram EPA and DHA for the placebo's.

eAppendix 3. Food-related behavioural activation intervention

Little is known about the effectiveness of food-related behavioural elements incorporated in behavior activation for the prevention of depression. The F-BA consisted of specific nutritional advice on improving food-related behaviors (e.g. having regular meals per day; reducing snacking; mindful eating) and making dietary shifts towards a healthy Mediterranean style diet. This MooDFOOD diet recommended the following intakes for ten different food groups: 300-400 g/day vegetables, 2-3 pieces of fruit/day, 3 times fish/week, reduction to 300 g/week for meat, 3 times/week pulses or legumes, choosing whole grain products, 3 servings/day of low-fat dairy products, olive oil as principal source for cooking, limiting processed foods, limiting soft drinks, and alcoholic beverages in moderation. The F-BA intervention consisted of up to 21 sessions (up to 15 individual sessions of 30 min, provided in single or double (1-hour) meetings at first weekly and then every two weeks; followed by 6 group-based sessions of up to 10 people lasting approximately 1 hour, occurring monthly and then bimonthly). The intervention was delivered by trained psychologists familiar with BA, and a dietician was available for advice at all study sites.

eAppendix 4. Minimally clinically important difference (MCID) for the reported secondary outcomes when used in a treatment instead of a prevention setting

Instrument	MCID and cut-offs	References
PHQ-9	The MCID is 2 to 3 points (using 1-standard error of measurement (SEM) approach), up to 4 to 6 points (using the more conservative 2-SEM approach) (Kroenke et al., 2016) PHQ-9 scores of 5, 10, 15 and 20 are taken as the cut-off points for mild, moderate, moderate-severe and severe depression, respectively (Kroenke et al., 2001)	Kroenke K, Wu J, Yu Z, Bair MJ, Kean J, Stump T, Monahan PO. (2016). The patient health questionnaire anxiety and depression scale (PHQ-ADS): initial validation in three clinical trials. Psychosomatic medicine, 78(6), 716. Kroenke K. Spitzer RL, Williams JB. (2001). The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine, 16(9), 606-613.
IDS-SR30	No MCID reported. IDS-SR30 scores of 14, 26, 39, and 49 are taken as the cut-off points for mild, moderate, severe, and very severe depression, respectively. (ids-qids.org)	http://www.ids-qids.org
GAD-7	The MCID is 2 to 3 points (using 1-standard error of measurement (SEM) approach, up to 4 to 6 points (using the more conservative 2-SEM approach) (Kroenke et al., 2016) GAD-7 scores of 5, 10, and 15 are taken as the cut off points for mild, moderate, and severe anxiety, respectively. (Spitzer et al. 2006)	Kroenke K, Wu J, Yu Z, Bair MJ, Kean J, Stump T, & Monahan PO. (2016). The patient health questionnaire anxiety and depression scale (PHQ-ADS): initial validation in three clinical trials. Psychosomatic medicine, 78(6), 716. Spitzer RL, Kroenke K, Williams JB, Löwe B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine, 166(10), 1092-1097.
Health utility (EQ5D5L)	The MCID is 0.074.	Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005;14(6):1523–32.

Abbreviations: EQ5D5L: EuroQol 5 dimension 5 level, GAD-7: Generalized Anxiety Disorder-7, IDS-SR30: Inventory of Depressive Symptomatology, self-report, MCID: Minimally Clinically Important Difference, PHQ-9: Patient Health Questionnaire-9, SEM: standard error of measurement.

eAppendix 5. Rationale for compliance rate cut-off for food-related behavior activation therapy (F-BA)

The pre-specified criterion of 8 out of 21 F-BA sessions was chosen because:

(a) ***Research into psychological therapies for current major depression including behavioural activation (BA) and cognitive-behavioural therapy (CBT), which explicitly inform the F-BA intervention, robustly find significant treatment effects between 4-8 sessions.*** The majority of intervention effects (i.e., change in depressive symptoms) typically occur during the first 2-8 sessions of CBT or BA, including so-called "sudden gains" and "rapid early response"- with this effect robustly found across multiple trials and being replicated multiple times, especially for CBT (e.g., Delgadillo et al., 2014; DeRubeis et al., 2005; Ilardi & Craighead, 1994; Masterson et al., 2014; Stulz et al., 2007; Tang & DeRubeis, 1999; Vittengl et al., 2016), with evidence of good treatment effects for anxiety and depression at an average of 6 sessions (Salomonsson et al., 2018). This number of sessions is also consistent with existing psychological service delivery for individuals with mild-to-moderate symptoms of depression (as consistent with the sample in the MooDFOOD trial) receiving behavioural activation interventions, most notably in the Improving Access to Psychological Treatment services in the UK NHS.

(b) ***Similar levels of compliance have been typically used in treatment trials for major depression, whereas participants in the MooDFOOD trial all have sub-threshold depressive symptoms and no major depression at the time of randomization.*** For example, the COBRA trial comparing BA and CBT for major depression, in which participants could receive up to 20 sessions of therapy, attending 8 treatment sessions or more was operationalized as the threshold for compliance representing a minimally clinically sufficient dose of therapy (Richards et al., 2016). Twelve sessions of CBT have been recommended for the acute treatment of common mental disorders such as current major depression (National Institute for Health & Clinical Excellence [NICE], 2011: one may expect fewer sessions to be

necessary for preventive effects for sub-threshold levels of depressive symptoms as in MooDFOOD relative to acute intervention in major depressive disorder.

(c) ***It reflected the distribution and focus of the treatment sessions.*** The intervention protocol specified that participants could receive up to 21 treatment sessions over 12 months, starting with up to 15 individual face-to-face sessions occurring at first weekly then fortnightly and monthly, followed by up to 6 group sessions each lasting approximately one hour, occurring at first monthly and then every two months. The individual face-to-face sessions were designed to provide the detailed psychoeducation, identification of patient goals, and detailed functional analysis to change mood and food-related habits (i.e., the most active part of the therapy), with the group sessions then designed as booster and maintenance sessions to consolidate gains over the remaining six months. The 15 individual sessions were hypothesized to be the most active and important in the treatment effect, and assuming that participants would progress through the majority of individual sessions before progressing to group sessions, attending 8/21 sessions would mean that participants would receive at least half of the individual face-to-face sessions, which is in line with results from dose-response research in psychotherapy and also with the classical EC50 curve, applied in pharmacological research.

(d) ***The lowest effective minimum dose would increase the feasibility and acceptability by the general population.*** Ultimately, we are aiming for the F-BA intervention, if effective, to be easily implementable into existing treatment services, feasible to deliver and acceptable to the general population. With this in mind, we set our a priori level of compliance at a level we thought would be most feasible to deliver and for patients to attend, whilst still being effective, which meant testing the lowest minimum number of sessions that could be justified by the literature.

References:

Delgadillo J, McMillan D, Lucock M, Leach C, Ali S, Gilbody S. (2014). Early changes, attrition, and dose–response in low intensity psychological interventions. *British Journal of Clinical Psychology*, *53*(1), 114-130.

DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, O'Reardon JP, Lovett ML, Gladis MM, Brown LL, Gallop R. (2005). Cognitive therapy vs medications in the treatment of moderate to severe depression. *Archives of General Psychiatry*, *62*(4), 409-416.

Ilardi SS, Craighead WE. (1994). The role of nonspecific factors in cognitive-behavior therapy for depression. *Clinical Psychology: Science and Practice*, *1*(2), 138-156.

Masterson C, Ekers D, Gilbody S, Richards D, Toner-Clewes B, McMillan D. (2014). Sudden gains in behavioural activation for depression. *Behaviour Research and Therapy*, *60*, 34-38.

National Institute for Health & Clinical Excellence [NICE], Depression in adults, Quality standard, 2011, https://www.nice.org.uk/guidance/qs8, Accessed January 2, 2019.

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Stulz N, Lutz W, Leach C, Lucock M, Barkham M. (2007). Shapes of early change in psychotherapy under routine outpatient conditions. *Journal of Consulting and Clinical Psychology*, *75*(6), 864-874.

Tang TZ, DeRubeis RJ. (1999). Sudden gains and critical sessions in cognitive-behavioral therapy for depression. *Journal of Consulting and Clinical Psychology*, *67*(6), 894-904.

Vittengl JR, Clark LA, Thase ME, Jarrett RB (2016).Defined symptom-change trajectories during acute-phase cognitive therapy for depression predict better longitudinal outcomes. *Behaviour Research and Therapy, 87*, 48-57.

eAppendix 6: Description of compliance and other measures

Other measures

Sex, age, education level, smoking, alcohol intake (Alcohol Use Disorders Identification Test (AUDIT[23]), physical activity (SQUASH[24]), BMI (kg/m^2), and past month supplement use were assessed at baseline.

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. Participants were instructed to return all pill jars (used and not used) at each visit. Good adherence to the supplements was based on weights of provided and returned jars, to indicate the number of supplements taken divided by the total of supplements received. In addition, self-reported supplement use (i.e. frequency and % of time supplements were taken) after 3, 6, 9 and 12 months (kappa for agreement 0.73 and 0.70 for supplement 1 and 2, respectively), and the 4-item Morisky Medication Adherence Scale (MMAS-4)[25] were used as indicators for adherence.

Furthermore, change in measured body weight (kg, absolute and relative), MooDFOOD diet quality score and serum nutrient status were assessed (12 month minus baseline). Dietary intake was assessed with the 250-item GA2LEN food frequency questionnaire.[26] Intake of the eleven MooDFOOD diet quality food groups were summed to obtain the MooDFOOD diet quality score (range: 0 indicating poor adherence, 77 indicating optimal adherence). At baseline and 12 months, in a subset of participants (n=211 to 331, 22-32%) non-fasting blood samples were collected, stored in aliquots (-80°C until analysis) to assess serum selenium, folic acid and 25-hydroxyvitamin D levels by the Reference Laboratory (Barcelona, Spain).

Hospitalizations, deaths and concealment

Hospitalizations (derived from a question in all follow-up interviews, or when reported as reason for drop-out) and deaths (when reported as reason for drop-out) were registered. After 12 months, participants were asked whether they believed they were allocated to supplements, placebo or whether they did not know.

eAppendix 7: Explanation of Complier Average Causal Effect (CACE) analysis

Complier Average Causal Effect (CACE) is a measure of the causal effect of an intervention on the people who received it as intended by the original group allocation. The CACE approach is intended to maintain the benefits of randomization for addressing measured and unmeasured confounders, whilst adjusting for rates of treatment compliance through the use of randomization as an instrumental variable.

The CACE method provides a "what would things be like" scenario of potential outcomes from a counterfactual scenario with respect to levels of compliance. For the provision of an intervention (e.g. F-BA), a percentage of those allocated to the intervention will be compliers (i.e., completing a sufficient dose of the intervention), and a percentage will be non-compliers. Before randomization to an intervention, it can be asked whether each individual will comply with the treatment or not if the person is randomized to the treatment condition. The same question can be asked for those who were randomized to the control condition – i.e., would they have complied with the treatment if it had been offered to them. We can directly observe the level of compliance in those who were allocated to the treatment condition, but we do not know what the level of compliance would have been if the participants in the control group had been offered the treatment; this is estimated using assumptions described below. CACE adjusts the observed intervention effect by taking into account the proportion of individuals who would be non-compliant to the treatment condition, whether they received it or not.

CACE assumes the following (for detailed description see Dunn et al., 2005 and Angrist et al., 1996):

a. There are two latent classes of participants: Compliers – who receive an adequate dose of intervention only if they are allocated to the intervention and non-compliers - who never receive an adequate dose of therapy regardless of allocation (i.e., would not comply sufficiently with treatment even if offered).

b. If randomization is properly done, there should be an equal probability of individuals likely to comply with any given intervention being allocated to the intervention condition versus the control condition, thus there should be a similar proportion of compliers in the control condition than as directly observed

in the intervention condition. Hence, the proportion of unobserved compliers in the control condition (e.g. no F-BA) is estimated by directly observing the proportion in the treatment condition (e.g. receiving F-BA).

c. Outcome is independent of randomization ("exclusion restriction"): randomization does not have a direct link with outcome but is instead dependent on intervention receipt status (whether an individual received a dose of intervention), which in turn is dependent on randomization. Hence, one can assume that the proportion of non-compliers in the control condition will be the same as observed in the treatment condition.

In CACE, randomization is used as an instrumental variable (as a factor with only an indirect effect on outcome, via its effect on intervention receipt) in a structural equation model analysis. Hence, randomization and the full sample is retained in the analysis, maintaining the same benefits of an intention to treat-based analyses for addressing measured and unmeasured confounders on outcome, which would be lost in a per protocol approach to examine intervention compliance. The CACE analysis estimates the difference in the outcome variable between the compliers in the intervention condition and the compliers in the control condition. This estimate is the ratio of the original intervention effect estimate to the proportion of compliers in the treatment arm.

References:

Angrist JD, Imbens GW, Rubin DB. Identification of Causal Effects Using Instrumental Variables. *J Am Stat Assoc*. 1996;91(434):444-455. https://dash.harvard.edu/handle/1/3382969. Accessed March 8, 2016.

Dunn G, Maracy M, Tomenson B. Estimating treatment effects from randomized clinical trials with noncompliance and loss to follow-up: the role of instrumental variable methods. *Stat Methods Med Res*. 2005;14(4):369-95.

eAppendix 8. Description of adherence to interventions, serious adverse events, and change in diet score, weight and blood nutrient levels

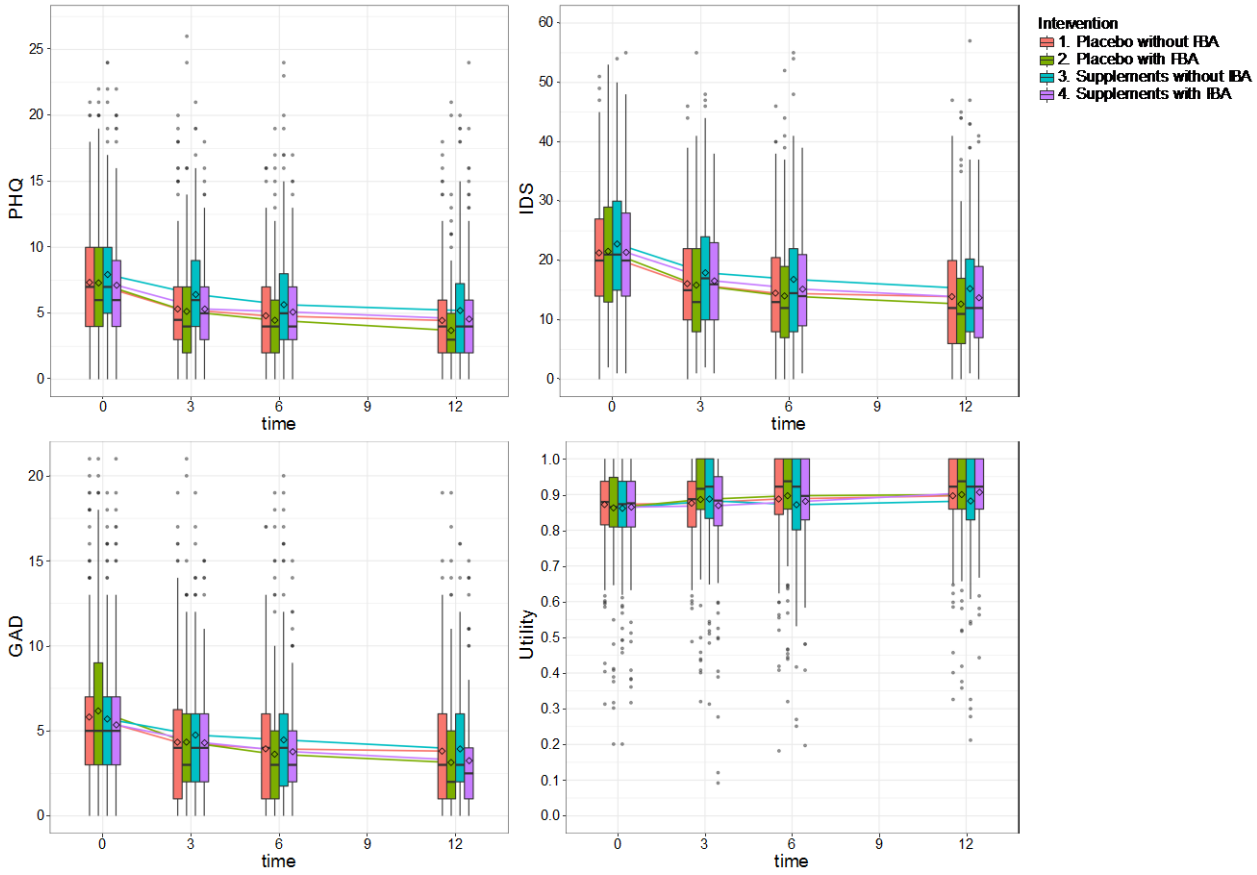
	N	Placebo without F-BA	Placebo with F-BA	Supplements without F-BA	Supplements with F-BA
Adherence					
Multinutrient adherence ≥70% from pill weight*	666	135 (76.7%)	134 (78.8%)	126 (75.0%)	120 (78.9%)
Multinutrient adherence ≥70% from self-report*	855	164 (77.7%)	165 (74.3%)	155 (73.8%)	151 (71.2%)
Omega adherence ≥70% from pill weight*	652	133 (76.9%)	133 (81.1%)	126 (76.8%)	120 (79.5%)
Omega adherence ≥70% from self-report *	855	163 (77.3%)	164 (73.9%)	156 (74.3%)	152 (71.7%)
Morisky score (average), median (IQR)	856	1 (0.50-1.50)	1 (0.50-1.75)	1 (0.50-1.50)	1 (0.50-1.75)
Number of F-BA sessions attended ≥8	512	NA	71.9%	NA	70.7%
Number of F-BA sessions attended, median (IQR)	512	NA	15 (6-18)	NA	15 (6-19)
Number of individual F-BA sessions attended, median (IQR)	512	NA	14 (6-15)	NA	14 (6-15)
Number of group F-BA sessions attended, median (IQR)	512	NA	0 (0-3.3)	NA	0 (0-4)
Serious adverse events					
Deaths	NA	0	0	0	1
Number of persons hospitalized	NA	24	24	26	24
Change in weight, diet, and nutrients					
Delta MooDFOOD diet score T12-T0	719	0.8 (5.3)	3.6 (5.9)	1.8 (5.2)	3.4 (6.4)
Delta weight (kg) T12-T0	766	-0.3 (4.9)	-0.8 (4.9)	-0.3 (5.0)	-0.4 (5.1)
Delta % weight (%kg from baseline weight) T12-T0	766	-0.1 (5.4)	-0.8 (5.6)	-0.3 (5.6)	-0.5 (5.6)
Delta Selenium (mcg/L) T12-T0, median (IQR)	335	1 (-6.3 to 7)	-1 (-5 to 5)	5 (-5 to 13)	5 (-3 to 12)
Delta Folic acid (ng/mL) T12-T0, median (IQR)	335	-0.1 (-1 to 1.3)	0.4 (-1.2 to 1.7)	6.2 (0.6 to 10.6)	5.9 (2.8 to 10)
Delta Vitamin D (ng/mL) T12-T0, median (IQR)	335	0 (-2.3 to 3.0)	1 (-2 to 5)	7 (3 to 13)	6 (1 to 11)
Delta Eicosapentaenoic acid (mcmol/L) T12-T0, median (IQR)	334	2.5 (-11 to 20)	3 (-19 to 13)	32 (5 to 81)	30.5 (6.8 to 89.5)

IQR=interquartile range, T0=baseline, T12=12 month follow-up

*average Morisky score over the four follow-up moments. Calculated when at least 1 follow-up value was available

**Kappa for pill weight and self-report adherence for multinutrient=0.73 and omega=0.70.

Appendix 9. Course of depressive symptoms, anxiety symptoms and health utility for each of the intervention combinations



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 lines colored to represent each intervention combination. Data shown is the available data.

eAppendix 10. Moderation effects of interventions with site, history of depression and baseline severity scores

The effects on the reported primary and secondary outcomes were not moderated by history of MDD. A significant F-BA by baseline PHQ depression severity interaction was present, indicating that the effect of F-BA on PHQ at 12 months follow-up were more favorable (larger reduction) when baseline PHQ depression severity was higher (Supplemental table A). Furthermore, a significant supplement-by-baseline anxiety severity (measured by GAD) was present, indicating that supplements resulted in higher follow-up anxiety scores when baseline anxiety severity scores were higher (Supplemental table B). Finally, a significant F-BA by site interaction effect was present for health utility scores, indicating 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 (Supplemental table C).

A. Interaction between F-BA and depression severity for PHQ-9 score after 12-month follow-up

	B	95% CI		p
Supplements	0.046	-0.399	0.490	0.841
F-BA	0.288	-0.155	0.731	0.203
The Netherlands	ref			
Spain	-0.480	-1.161	0.202	0.168
United Kingdom	0.275	-0.373	0.923	0.405
Germany	0.233	-0.396	0.862	0.468
History of depression	-0.536	-1.036	-0.036	0.036
Baseline PHQ-9	0.322	0.265	0.379	<0.001
F-BA: Baseline PHQ-9	-0.064	-0.118	-0.01	0.020
Supplements: Baseline PHQ-9	0.032	-0.023	0.086	0.259

PHQ-9=Patient Health Questionnaire-9

B. Interaction between supplements and overall anxiety severity follow-up

	B	95% CI		p
Supplements	-0.107	-0.384	0.17	0.45
F-BA	-0.054	-0.329	0.221	0.703
The Netherlands	ref			
Spain	0.107	-0.424	0.520	0.694
United Kingdom	0.117	-0.371	0.638	0.637
Germany	0.058	-0.401	0.606	0.804
History of depression	-0.317	-0.698	0.063	0.102
Baseline GAD-7	0.464	0.409	0.52	0
F-BA * Baseline GAD-7	-0.016	-0.068	0.036	0.554
Supplements * Baseline GAD-7	0.062	0.009	0.115	0.022

GAD-7=Generalized Anxiety Disorder-7

C1. Interaction between F-BA and research site for health utility score after 12-month follow-up

	B	95% CI		p
Supplements	0.000	-0.012	0.012	0.952
F-BA	-0.006	-0.018	0.006	0.313
The Netherlands	ref			
Spain	0.005	-0.012	0.022	0.548
United Kingdom	-0.014	-0.031	0.003	0.097
Germany	0.011	-0.006	0.027	0.198
History of depression	0.009	-0.003	0.022	0.148
Baseline health utility	0.498	0.438	0.558	<0.001
F-BA * The Netherlands	ref			
F-BA * Spain	0.016	-0.001	0.032	0.066
F-BA * United Kingdom	0.017	0.001	0.033	0.041
F-BA * Germany	0.006	-0.01	0.022	0.452
Supplements: The Netherlands	ref			
Supplements * Spain	-0.006	-0.023	0.011	0.499
Supplements * United Kingdom	-0.001	-0.018	0.016	0.907
Supplements * Germany	0.002	-0.014	0.017	0.850

C2. Subgroup analysis for United Kingdom for health utility score after 12-month follow-up

	B	95% CI		p
Supplements	0.000	-0.012	0.011	0.944
F-BA	0.013	0.001	0.024	0.033
History of depression	0.007	-0.016	0.03	0.559
Baseline health utility	0.738	0.62	0.856	<0.001

C2. Subgroup analysis for the Netherlands for health utility score after 12-month follow-up

	B	95% CI		p
Supplements	0.000	-0.012	0.012	0.935
F-BA	-0.007	-0.019	0.005	0.267
History of depression	-0.005	-0.031	0.021	0.697
Baseline health utility	0.509	0.400	0.619	<0.001

eAppendix 11. Effect of supplements and F-BA on secondary outcomes – no multiple imputation

		Overall follow-up effect using all follow-ups*		Effect at T12**	
		B (95% CI)	P	B (SE)	P
PHQ	Suppl vs Placebo (ref)	0.30 (0.11 to 0.49)	0.002	0.28 (0.11)	0.013
	F-BA vs no F-BA (ref)	-0.14 (-0.34 to 0.05)	0.14	-0.22 (0.11)	0.052
	F-BA * Supplements	-0.01 (-0.20 to 0.18)	0.94	0.02 (0.11)	0.84
IDS	Suppl vs Placebo (ref)	0.55 (0.11 to 0.99)	0.01	0.28 (0.28)	0.30
	F-BA vs no F-BA (ref)	-0.26 (-0.70 to 0.18)	0.25	-0.36 (0.28)	0.20
	F-BA * Supplements	-0.01 (-0.45 to 0.43)	0.96	0.12 (0.28)	0.66
GAD	Suppl vs Placebo (ref)	0.24 (0.08 to 0.40)	0.004	0.17 (0.09)	0.07
	F-BA vs no F-BA (ref)	-0.16 (-0.32 to 0.00)	0.06	-0.26 (0.09)	0.005
	F-BA * Supplements	0.04 (-0.13 to 0.20)	0.66	0.03 (0.09)	0.74
Utility	Suppl vs Placebo (ref)	-0.006 (-0.011 to 0.000)	0.055	-0.001 (0.003)	0.66
	F-BA vs no F-BA (ref)	0.002 (-0.004 to 0.007)	0.51	0.004 (0.003)	0.23
	F-BA * Supplements	-0.002 (-0.008 to 0.003)	0.42	0.001 (0.003)	0.65

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). B= 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.

*Estimates (unstandardized regression coefficients) were obtained from generalized estimating equations longitudinal GEE analyses.

**Estimates (unstandardized regression coefficients) were obtained from robust linear regression analyses.

eAppendix 12. The effect of CACE analysis on the intervention estimates

	F-BA CACE[1]	Supplements CACE[2]
	OR (95% CI)	OR (95% CI)
MDD onset	0.78 (0.64 to 0.95)*	0.84 (0.67 to 1.07)
	B (95% CI)	B (95% CI)
PHQ	-0.22 (-0.59 to 0.15)	0.43 (0.08 to 0.77)*
IDS	-0.42 (-1.24 to 0.40)	0.47 (-0.33 to 1.27)
GAD	-0.31 (-0.60 to -0.02)*	0.18 (-0.11 to 0.47)

All models were derived from multiple imputation data and adjusted for site and history of MDD. The MDD analysis reported here refers to a logistic regression with MDD at any follow up as the outcome. PHQ, IDS and GAD analyses refer to ANCOVA models assessing the effect of intervention on each symptom score at 12-month follow up, adjusting for the respective baseline scores. F-BA and Supplements were effect-coded (-1,1).

B= unstandardized regression coefficient, CI=confidence interval, GAD=Generalized Anxiety Disorder-7, IDS=inventory of depressive symptomatology OR=odds ratio, PHQ-9=Patient Health Questionnaire-9.

[1]F-BA compliance = 8/21 sessions

[2]Supplement compliance of Omega-3 supplement >=70%;

*Denotes $p<0.05$, **$p<0.01$

eAppendix 13. Multi-nutrient supplement concealment (n=759)

	Placebo without F-BA		Placebo with F-BA		Supplements without F-BA		Supplements with F-BA	
	N	%	N	%	N	%	N	%
Thought to be allocated to:								
Placebo	95	48.7	84	43.5	66	35.1	43	23.5
Multi-nutrient supplements	16	8.2	20	10.4	48	25.5	80	43.7
I don't know	84	43.1	89	46.1	74	39.4	60	32.8

$p<0.001$

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