

## MooDFOOD Analysis Plan Prevention Trial Data

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Data wave:	T0, T3, T6, T9, T12 MooDFOOD prevention trial
Where will the analyses be done:	Amsterdam
Publication or internship thesis:	Publication
<b>Short description of the research proposal</b>	
Research question:	To examine the feasibility and effectiveness of two different nutritional strategies (multi-nutrient supplement and food-related behavioral change) to prevent depression in high-risk overweight persons with subsyndromal symptoms of depression.
Brief background and rationale:	<p>Major depressive disorder (MDD) is a common psychiatric disorder (lifetime prevalence 17%; Kessler, 2005) with a significant personal and public health burden. MDD is ranked as second leading contributor of years lived with disability by the WHO's Global Burden of Disease studies (Vos, 2012). MDD is related to excess mortality (Cuijpers, 2012), and increases the risk of somatic conditions such as diabetes mellitus (Mezuk, 2008), cardiovascular disease (Nicholson, 2006) and obesity (Luppino, 2010).</p> <p>Recently, depression has been linked to poorer dietary intake and deficiencies in several nutrients. Increased depressive symptoms were associated with a higher consumption of processed foods and lower adherence to a more Mediterranean style dietary pattern (Opie 2015; Sánchez-Villegas, 2009; Akbaraly 2009; Ruusunen 2014), which might partially explain the higher rates of obesity in persons with depression. In addition, depressive symptoms were related to perceived barriers to healthy eating, and food-related behavior such as meal skipping, and more disordered eating (Goodman and Whitaker, 2002; Fulkerson, 2004). Studies linking depression and dietary intake were largely based on observational data. However, a recent randomized controlled clinical trial that studied the efficacy of a dietary improvement program for the treatment of depression (compared to a social support intervention), showed that dietary improvement resulted in a significant decrease in depressive symptoms (Jacka, 2017).</p> <p>In addition to the established relationships of depression with dietary patterns, observational studies and systematic reviews suggest that some specific nutrients (e.g. omega-3 polyunsaturated fatty acids, folic acid, vitamin D, selenium and calcium) could affect mood (Grosso 2016; Milaneschi 2014; Sarris 2016; Connor</p>

	<p>2014). Several studies show that these nutrient levels are lower in persons with depressive symptoms compared to persons without depressive symptoms. Some - but not all - intervention studies indicate that supplementation of nutrients such as omega-3 polyunsaturated fatty acids may improve depressive symptoms (Appleton 2012, Bloch 2012; Mocking 2016).</p> <p>There are several evidence-based treatment options available for MDD, including cognitive behavioral therapy, antidepressant medication, and behavioral activation. However, the outreach and efficacy of these treatments is limited. Therefore, prevention may offer an important opportunity to reduce the disease burden associated with MDD (Cuijpers, 2012). The established relationship between depression and diet raises the possibility that diet and nutrition may offer key modifiable targets for the prevention of MDD (Opie 2015b; Sarris 2016).</p> <p>As of yet, few experimental studies have directly intervened on diet, food-related behavior and nutrients to examine their effects on preventing depression, and none have specifically targeted overweight individuals who are at increased risk for MDD (Luppino 2010). Therefore, the MooDFOOD prevention trial examines the feasibility and effectiveness of two different nutritional strategies (multi-nutrient supplementation and food-related behavioral activation therapy) to prevent a new episode of MDD in overweight persons with subsyndromal symptoms of depression.</p>
<p>Determinant(s):</p>	<p>Multi-nutrient supplement (A) Food-related behavioral change therapy (B)</p>
<p>Outcome(s):</p>	<p><b>Primary:</b> cumulative onset of MDD since T0 (yes/no) measured with the Mini International Neuropsychiatric Interview (MINI) 5.0 plus MDD section (Sheehan, 1998) - MDD yes = 1 = MDD episode between T0-T12 (MDD positive at T3, T6, or T12) - MDD no = 0 = no MDD episode between T0-T12 (MDD negative at T3, T6, and T12)</p> <p><b>Secondary:</b> continuous depressive symptoms as measured by: - Patient Health Questionnaire-9 (PHQ-9) score (T3,T6,T12) - Inventory of Depressive Symptomatology (IDS30-SR) (T3,T6,T12) Other: - Anxiety symptoms (Generalized Anxiety Disorder-7; GAD-7) - Health related quality of life (HRQoL; EuroQol instrument EQ-5D-5 L)</p>
<p>Covariates:</p>	<p>In all analyses, the stratification variables will be used as covariates, because this results in more valid inferences (Kahan &amp; Morris, 2012)(CONSORT 2010): - History of MDD (yes, no) measured with the MINI at T0. - Center (AMS, LEI, EXE, MAL)</p>

	<p>We do not by default adjust for other covariates in the primary analyses, but this can be done in secondary analyses (Kraemer, 2015).</p>
<p>Statistical analyses:</p>	<p>First, in a flow chart we will show the numbers of persons screened, randomized, allocated to each intervention, followed-up and analysed. The data analyst is blinded for the original coding.</p> <p>Second, we will describe the baseline characteristics (T0) of the study sample (age, sex, years of education, income, center, history of MDD, no of chronic illnesses, smoking, alcohol use, physical activity, body mass index, depression severity, anxiety severity, HRQoL, dietary score from FFQ, eating behaviour, medication/supplement use) in a table with four columns representing each of the intervention combinations.</p> <p>Third, descriptives of adherence to therapies (self-reported compliance Morosky scale, % of multinutrient pills taken, reasons for non-compliance, number of sessions attended; change in food-related behaviour; start of other ‘therapies’ during the trial) will be given. As an additional measure of compliance to the multinutrient supplement, T6 and T12 blood levels of vitamin D, selenium, folic acid, n-3 PUFA (EPA;DHA) will be compared across the intervention groups in longitudinal data analysis, with the corresponding T0 blood concentration as covariate. Furthermore, as a measure of compliance to the FBC therapy, food-related behaviour (T3, T6 and T12) and dietary intake (FFQ,T6,T12) will be compared across the intervention groups in longitudinal data analysis, with the corresponding T0 data as covariate.</p> <p>Fourth, logistic regression analyses will be done to estimate the effect of each intervention on our primary outcome (new major depressive episode). Odds ratio’s and 95% CI along with p values will be presented. The two interventions will be effect coded (Collins et al., 2014) and we will report their main effects and interactions. For the secondary outcomes, the effect of each intervention will be studied in mixed models or Generalized Estimating Equations. Here, regression coefficients and 95% CI along with p values will be presented. For the secondary outcomes, in addition to the earlier mentioned covariates adjustment for T0 depression scores will be done to increase precision (European Medicines Agency, 2013; Twisk 2008) For T12 continuous outcomes, standardized mean differences (95% CI, p values) between groups will be displayed.</p> <p>Fifth, adverse events and side effects will be described for the groups.</p> <p>Sixth, we will report the successfulness of blinding of the multinutrient supplement (which type of intervention thought to received).</p> <p>Statistical analyses will be conducted with SAS or R. For all statistical tests the 2-sided significance threshold will be set at p 0.05.</p>

**General analysis principle**

The primary analyses will be conducted according to the Intention-To-Treat (ITT) principle. In case of incomplete compliance to the intervention, ITT analysis will underestimate the efficacy of an intervention. Therefore, as a secondary analysis we will conduct Complier Average Causal Effect (CACE) analysis, which takes into account the level of compliance to the intervention whilst retaining the benefits of randomization (Dunn, Maracy, & Tomenson, 2005)(Angrist, Imbens, & Rubin, 1996). CACE analysis seeks to compare outcomes for individuals in the intervention condition who complied with treatment with individuals in the control group who would have complied with treatment given the opportunity to do so.

Good compliance to the interventions is defined as:

- At least 70% of the supplements was taken during the 12 months. This number is based on the weighted jars, or if not available, by the self-reported supplement use (averaged over T3, T6, T9 and T12).
- At least 8 out of 21 sessions attended during the 12 months.

**Interaction of the intervention strategies for our primary outcome**

We will additionally test the interaction between the two interventions for our main outcome.

- Test for statistical interaction (interaction as deviation on a multiplicative scale) will be done by entering the interaction term A\*B to the logistic regression model in addition to the independent variables (and covariates).
- Furthermore, it could be possible that the two interventions result in a better prognosis for depression compared to the sum of the individual interventions effects. For example, the combination of interventions could result that nutrient levels cross a certain threshold that is needed to prevent depression that is more than the sum of the effect of the individual interventions. Therefore, as a sensitivity analysis we will also study the possibility of biological interaction (interaction as departure from additivity of relative risks) by calculating the relative excess risk due to interaction (RERI). A RERI >0 is indicative of a deviation from additivity (Andersson, 2005). The RERI will be obtained from a linear odds ratio model, and likelihood-based 95% confidence intervals will be calculated according to the procedure described in Richardson and Kaufman (Richardson & Kaufman, 2009). To obtain valid estimates, the preventive conditions will be recoded such that the stratum with the assumed lowest risk becomes the reference category when both conditions are considered jointly (Knol, 2011).

**Secondary analysis**

As a secondary analysis, we will study the effect between the two nutritional strategies on the time to onset of MDD using Cox regression analysis. Results will be expressed in hazard ratio's (HR) and 95% confidence intervals along with p-values.

**Effect modification**

As a secondary analysis, we will test effect modification for the two stratification variables (History of depression and Center), leaving the other potentially effect modifying variables for a separate paper.

Testing for effect modification will be done by entering the interaction terms of the variables to the logistic regression model that also includes both intervention variables. For example, A\*MDD history, and B\*MDD history will be added to the logistic regression model that also includes A, B, and MDD history (and center). Significant effect modification will be measured as statistical interaction and is present when one of these interaction terms result in a  $p < 0.05$ .

Effect modification will be either shown in tables (e.g. stratified analyses) or in the text (e.g. “we found evidence for significant effect modification by history of MDD, in a way that the preventive effect of the intervention was stronger for those with a history of MDD (statistics)”).

#### **Missing data and drop-out**

Missing data introduces potential biases in the comparison of the treatment groups. There may be differences in causes and rates of drop-out between the study arms, which could result in biased estimates of the effects. We therefore will inspect the frequency and nature of the missing data. Full information maximum likelihood (FIML) or multiple imputation (MI) will be used where appropriate (Enders, 2006). In case of MI, 100 datasets will be created to impute missings of the primary outcome under the assumption of missing at random (MAR) (Little et al., 2012). The multiply imputed estimates will be combined in a single estimate using Rubin's rules (Rubin, 2004). Given that the assumptions for the missing data mechanism (e.g. MAR) cannot be validated, sensitivity analyses will be conducted and reported (Little et al., 2012).

#### **Outliers and distributions**

We will first investigate the nature of the outlier (e.g. impossible values). If the outlier can be corrected, this will be done. For other outliers, we will run sensitivity analyses with and without these outliers to study the influence on the study outcomes. Furthermore, we will apply (log) transformations if there are violations in the statistical model assumptions due to non-normal distribution of data.