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The MooDFooD randomized controlled trial: the data and its implications for the theory

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The MooDFooD trial is a large randomized controlled trial (RCT) that investigated the effects of food-related behavioral activation (FBA), multi-nutrient supplementation, and their combination on the prevention of depression. The results of this one-in-a-kind trial proof that the interventions have no effect on the primary and secondary outcomes, depression onset, and depressive symptoms, respectively (Bot et al., 2019). Secondary analyses of these data were recently published in *Psychological Medicine*. Vreijling et al. (2021) investigated whether the interventions had an effect on distinct depressive symptom profiles and individual symptoms. The work was guided by a theory in which increases in weight and a suboptimal nutritional status are gateways/mediators through which depression can unfold (Bot et al., 2019; Milaneschi, Lamers, Berk, & Penninx, 2020). The theory entails the existence of a so-called *immuno-metabolic form of depression*. A formal definition of this type of depression does not exist. We infer that it constitutes a *clustering of immunometabolic biological dysregulations and specific behavioral symptoms* (Milaneschi et al., 2020, p. 369).

Vreijling et al. find that FBA led fewer people to self-report an increase in weight and appetite (Vreijling et al., 2021). Based on this, the authors conclude that '… *food-related behavioral interventions are most beneficial to alleviate somatic symptoms and symptoms of the atypical energy-related symptoms profile linked to an immune-metabolic form of depression.*' In the authors' theory, weight change is a possible mediator for depression to unfold: intervention → weight change → depression. This chain of events is not what the data show. FBA led fewer people to self-report an increase in weight, without a contingent effect on mood, or anhedonia and sadness (Vreijling et al., 2021); the core symptoms of depression. Objective changes in weight were not observed in the FBA arm (Paans et al., 2020) and *immunometabolic biological dysregulations* were not assessed. Self-reported weight change, or lack thereof, seems to be equated with *immuno-metabolic depression*. This is a mistake. Weight gain is no (mood) disorder and it occurs outside the depression context. For example, in the Netherlands, where part of the trial took place, weight gain occurs more frequently as depression does (Dutch Central Bureau of Statistics, 2023). The theory predicting that increases in weight are a gateway to depression is in need of an update and the conclusion regarding FBA efficacy can be formulated less complexly. Concluding that *FBA is beneficial in alleviating self-reported increases in weight gain* rests on fewer assumptions and describes the data to the point.

Multi-nutrient supplementation was also tested in the study as a depression determinant (Roca et al., 2016). The data obtained in this arm of the trial are surprising. Multi-nutrient supplementation led people to *more* often self-report symptoms in the *mood-cognition* and *energy-related symptom profiles*. In the discussion section, this effect is set aside as representing merely an association [… *it was found that multi-nutrient supplementation* (*versus placebo*) *was associated with a higher severity on mood/cognition and energy-related symptom profiles …* (Vreijling et al., 2021, p. 3586)]. The positive effects of FBA on self-reported weight gain are presented as being causal [… *the beneficial effect of food-related behavioral activation on somatic and energy-related symptoms …* (Vreijling et al., 2021, p. 3585)]. This surprises us since the findings regarding the multi-nutrient supplementation are methodologically stronger (i.e. placebo controlled) than the findings regarding FBA (i.e. not placebo controlled). We expected that the authors would suggest an update of the theory that led them to test the clinical efficacy of the multi-nutrient supplements as their data show that this theory has it backwards. The MooDFooD trial is the largest and probably the best-performed RCT on these topics after all.

Author contributions. All authors contributed equally

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Conflict of interest. Patricio Molero reports to have received research grants from the Ministry of Education (Spain), the Government of Navarra (Spain), the Spanish Foundation of Psychiatry and Mental Health and AstraZeneca; he is a clinical consultant for MedAvantéProPhase and has received lecture honoraria from or has been a consultant for AB-Biotics, Guidepoint, Janssen, Novumed, Roland Berger, and Scienta. Florian Thomas-Odenthal and Marc Molendijk declare no competing interests.

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