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Invited Letter Rejoinder

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The MooDFOOD randomized controlled trial: the data and its implications for the theory – Authors' reply

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With great interest we have read the letter to the editor by Thomas-Odenthal, Molero, and Molendijk (2023) and we thank them for their insightful comments on the implications of our earlier published findings from the multi-center randomized controlled MooDFOOD depression prevention trial (Vreijling et al., 2022). Among overweight adults with subsyndromal depressive symptoms, we found that dietary interventions have a differential impact on the severity of specific depressive symptom profiles. Somatic and atypical, energy-related symptoms of depression were found to improve more from a food-related behavioral activation (F-BA) intervention *v.* no intervention, while mood/cognitive and atypical, energy-related symptoms of depression improved less from multi-nutrient supplementation *v.* placebo supplementation. First, Thomas-Odenthal et al. (2023) ask for caution against generalizing the effects of F-BA on self-reported increased weight and appetite to depression, and particularly 'immuno-metabolic depression'. Second, they wonder about the implications of the effectiveness of multi-nutrient supplements for the prevention of depression.

Before addressing these points, please let us re-iterate on the concept of immuno-metabolic depression. From the extensive literature in this field, it is clear that alterations in inflammatory and metabolic pathways (e.g. low grade inflammation, higher body mass index [BMI] and obesity/metabolic syndrome rates, and dyslipidemia (Howren, Lamkin, & Suls, 2009; Jung et al., 2017; Vancampfort et al., 2014)) are associated with depression, most consistently and strongly with the depression symptom profile that we have labeled 'atypical, energy-related' (Milaneschi, Lamers, Berk, & Penninx, 2020). This profile includes reversed neurovegetative or atypical symptoms that may reflect an altered energy homeostasis, i.e. increased appetite, weight gain, hypersomnia, fatigue, leaden paralysis. The *clustering* of inflammatory and metabolic alterations with these specific depression symptoms is what we refer to as immuno-metabolic depression. It is important to note that our article focused solely on symptom profiles, while the concept of immuno-metabolic depression involves biological dysregulations as well; we do thus not equate self-reported weight gain with depression or immuno-metabolic depression. We must further highlight that with this concept we do not aspire to establish a new binary type of depression, but to propose a potentially clinically relevant dimensional profile that may be present in depression and related disorders to varying degrees.

We agree with the statement of Thomas-Odenthal et al. (2023) that increased appetite and weight gain are depressive symptoms and part of the DSM criteria for depression, but without the core depressive symptoms 'depressive mood' or 'loss of interest' these symptoms may indeed be unrelated to depression. However, MooDFOOD participants were selected based on an above average score on a depressive symptom questionnaire and thus endorse more (severe) depressive symptoms compared to the general population (Bot et al., 2019). In addition, their overweight status (on average BMI ~31 kg/m2) puts them at risk for depression. Obesity and depression have been found to have a longitudinal bidirectional relationship, i.e. obesity increases risk for depression and vice versa (as reviewed in Milaneschi, Simmons, van Rossum, & Penninx, 2019). Moreover, previous Mendelian randomization studies provided evidence that the genetic liability for higher BMI is likely causal for depression (Tyrrell et al., 2019) and specifically for depression with increased appetite (Pistis et al., 2021). Perhaps we could have emphasized a bit more that our findings apply to a population of high-risk individuals who were selected to take part in a prevention study. Changes in 'increased appetite' and 'weight gain' in this particular population are therefore more likely be linked to the development of depression, and potentially manifest as part of immuno-metabolic depression.

We agree with Thomas-Odenthal et al. (2023) that presenting our findings as effects rather than associations would provide a more accurate interpretation of the results on multi-nutrient

supplements and a better balanced reporting. As we found that the use of supplements *v.* placebo resulted in increased mood/cognitive symptoms, the authors ask for more discussion regarding the theory that proposes supplements to be an effective prevention strategy for depression. This is however beyond the scope of our article as we tested the efficacy of supplements on depressive symptom profiles and not on the prevention of depression in general. The best available evidence regarding the use supplements for the prevention of depression in this population is provided in the JAMA publication by Bot et al. (2019) indicating no effect of supplements on depression prevention and even slightly poorer depressive symptoms scores in the supplement *v.* placebo group (effect size for the total score on patient health questionnaire was similar [$d = 0.10$] as for mood/cognitive symptoms [$d = 0.09$]). A comprehensive discussion regarding the theoretical implications of the MooDFOOD findings is available as well (Owens et al., 2020). In addition, in a previous response to guidelines of the International Society for Nutritional Psychiatry Research Practice (Guu et al., 2019), our group argued that the current evidence from randomized clinical trials, including MooDFOOD, is too limited to support the use of omega-3 fatty acids supplementation for the prevention of depression (Thesing, Lamers, Bot, Penninx, & Milaneschi, 2020).

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