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Diet and depression: future needs to unlock the potential

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TO THE EDITOR:

In line with our previous responses to Dr Molendijk's correspondences (e.g., ref. [1]), we reassert that, although there are limitations in the current literature that require further investigation (as highlighted in our review and in previous work in the field), both observational and randomized controlled trial (RCT) data, supported by extensive preclinical data, are supportive of a role for diet in the aetiology and adjunctive treatment of depression. Indeed, Dr Molendijk and colleagues' own meta-analysis of prospective studies shows a 0.64–0.78 odds ratio reduced risk of depressive symptoms with improved diet quality. Although their subgroup analysis of 3 (of 17) effect sizes reported no significant effect when controlling for baseline depressive symptoms, this is in contrast to a more recent meta-analysis that used a rigorous harmonized analysis to address between-study heterogeneity [2].

Regarding the emerging RCT data, findings of meta-analyses suggest a small but significant effect of dietary interventions on depressive symptoms in largely non-clinical populations (see ref. [3] and Thomas-Odent et al. 2020, cited in the original letter). Moreover, three existing RCTs in those with current depression show evidence of efficacy from dietary interventions [4–6], along with relationships between degree of dietary change and mood improvements, and—where investigated—cost-effectiveness due to benefits that extend beyond symptom improvement (e.g., see ref. [7]). With regards to the prevention of incident depression, the results of the most recent and largest study on this are consistent with a prevention effect. To explain: despite the 2019 MoodFOOD trial reporting a null result in their primary outcome, possibly owing to the lower-than-expected incident depression cases and a minimal average change in diet, the trial reported a reduction in the risk for incident depression in people who were classified as adherent to the dietary 'food-related behavioural activation therapy' intervention, an effect that was more pronounced in those with higher depressive symptoms at baseline [8]. In addition, a recent analysis of the MoodFood trial suggests that the dietary intervention may have also improved somatic and energy-related profiles of depressive symptoms [9]. Furthermore, although also limited by lower-than-expected transition to incident depression, a second prevention study showed that coaching to improve dietary habits was as efficacious as problem-solving therapy in reducing the transition to case-level depression in older Americans, with benefits that were sustained over 2 years [10]. Given Dr. Molendijk and colleagues' previous comments regarding expectation bias as the explanation for the positive findings in our SMILES trial [1], it is notable that the nutrition education intervention in this study was in fact the control condition and there was no expectation

on the part of the investigators that dietary change would have any impact on depression outcomes.

It should also be emphasized that the cited limitations in Dr. Molendijk and colleagues' letter speak to the complexity of conducting non-pharmacological interventions more generally. Indeed, due to the nature of lifestyle interventions, whether it is dietary, physical activity, or otherwise, it is inherently difficult to incorporate clinical trial features such as double-blinding or placebo controls compared to pharmacotherapy interventions. Investigating mental health outcomes such as depression further compounds these challenges, as there are currently no objective biomarkers to measure clinical outcomes, necessitating a reliance on subjective measures. The inherent methodological challenges of nutrition research are also of relevance here. Partly for these reasons, we are currently conducting large-scale pragmatic trials to ascertain 'real-world' effectiveness and cost-effectiveness of dietary interventions in mental health. Given the focus of our review, the limitations of the existing diet-depression evidence base were not expanded upon; however, these have been addressed in other publications (e.g., see ref. [11]).

Given the growing evidence base regarding efficacy and cost-effectiveness, and the increasing recognition of the importance of addressing diet and other lifestyle behaviours in mental health treatment, now reflected in official Australian clinical treatment guidelines (Mahli et al. [12]), it is entirely appropriate to posit how diet may modulate depression. To this end, the current review provided a detailed overview of selected mechanisms of action that are implicated in mental health and where the existing data suggest that they may be modulated by dietary intervention. We do not suggest that the data are unequivocal regarding the mechanisms of actions by which diet may exert its influence on mental health outcomes, because no clinical trial has been powered to examine this but rather, and as we have stated in our review, these are proposed mechanisms that require further investigation and this requires large-scale RCTs that facilitate their examination.

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WM and FNJ drafted the manuscript. All authors provided feedback on the draft and approved of the final manuscript.

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COMPETING INTEREST

KW, ST, AS-V, HA and TA declare no competing interests.

ADDITIONAL INFORMATION

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