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Change in Ultra-Processed Food Consumption Moderates Clinical Trial Outcomes in Depression: A Secondary Analysis of the SMILES Randomised Controlled Trial

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Abstract: Background: In this secondary analysis of the Supporting the Modification of Lifestyle In Lowered Emotional States (SMILES) randomised controlled trial, we investigated if the beneficial effects of a dietary intervention on clinical depression were driven, in part, by reducing the consumption of foods classified as ultra-processed. **Methods**: The SMILES trial enrolled 67 adults with major depressive disorder, randomly assigning them to either a 12-week modified Mediterranean dietary intervention or a social support control. Our analysis included 44 participants with non-missing dietary data and at least one valid Montgomery–Åsberg Depression Rating Scale (MADRS) assessment at 12 weeks of follow-up. The Nova food classification system was used to estimate the proportion of ultra-processed foods in the overall diet (percentage of grams) based on data from seven-day food diaries. We fitted linear regression models under blinded conditions to determine whether ultra-processed food intake-change from baseline to 12 weeks moderated the dietary intervention effects on depressive symptoms. We estimated mean differences in depressive symptoms along with ninety-five per cent confidence intervals (95%CIs). **Results**: For participants in the dietary intervention, there was an additional 2.5-point improvement in MADRS scores for each 10% reduction in the dietary share of ultra-processed foods compared to participants in the control group (between-group mean differences in depressive symptoms: −2.46, 95%CIs −4.71 to −0.20, p=0.039, η_p^2 of 0.10). **Conclusions**: These preliminary findings suggest that the therapeutic benefit of a dietary intervention for depression may stem, at least in part, from reductions in the dietary share of ultra-processed foods. **Trial Registration**: Australia and New Zealand Clinical Trials Register (ANZCTR): ACTRN12612000251820. Registered on 29 February 2012.

Keywords: ultra-processed food; Nova food classification system; major depressive disorder; nutritional psychiatry; secondary analysis; randomised controlled trial

Introduction

Depression is a common mental disorder that can be difficult to treat. [1] Despite increases in the availability of treatments, a recent Global Burden of Disease Study reported there has been little reduction in the burden of mental disorders, including depression, since 1990. [2] Lifestyle treatments such as adjunctive dietary interventions may optimise the effects of current therapeutics. This notion is supported by four clinical trials involving human participants. [3-6] These trials have demonstrated the efficacy of adjunctive dietary interventions in reducing both depressive symptoms and clinical depression, especially among individuals with higher levels of depression at baseline. [3-6] One such trial was the Supporting the Modification of Lifestyle In Lowered Emotional States (SMILES) trial. This was the first experimental study to show that a dietary intervention comprising seven individual nutritional consulting sessions and delivered by a clinical dietitian was efficacious in reducing symptoms of clinical depression compared to a control condition (social support). [3] Over 12 weeks of follow-up, the reductions in depression observed in the dietary intervention group correlated strongly with the degree to which participants adhered to a modified Mediterranean diet. [3,7] Despite the novelty and compelling nature of the SMILES trial results overall, it remains uncertain as to whether the dietary intervention effects were partly driven by participants' decreased consumption of highly refined, ultra-processed foods.

A contemporary food classification system that is widely used to help identify such foods is known as Nova. Nova was designed to classify foods according to the nature, extent, and purposes of industrial processing they have undergone. [8] This system includes four incrementally processed categories: minimally or un/processed foods (group 1); processed culinary ingredients (group 2); processed foods (group 3); and, ultra-processed foods (group 4). Nova defines the latter group, ultra-processed foods, as being manufactured through various industrial processes and predominantly comprised of high-yield and inexpensive ingredients. [8] These ingredients may include components extracted from foods and derived from further processing of foods, as well as compounds 'never or rarely used in kitchens, or classes of additives whose function it is to make the final product palatable or more appealing'. [8] Despite the harms linked to the dietary share of ultra-processed foods, [9-11] recent country-specific purchase data show that for many food systems globally, an increasing trend in the variety and quantity of ultra-processed foods continues to grow. [12]

Our recent systematic reviews and meta-analyses indicated that across 28 countries, ultra-processed foods accounted for between 17% to 56% of total daily energy intake. [9,10] We also showed through separate meta-analyses of cross-sectional and prospective cohort studies direct associations between greater consumption of ultra-processed foods and higher risks of both the prevalence and incidence of depressive outcomes, respectively. [10] However, the depression incidence meta-analysis was limited to just two prospective cohort studies that were available at the time of publication. [13,14] Since this meta-analysis, several other prospective cohort studies have been published. Two of these studies included adults from Australia and the United Kingdom and both reported that greater ultra-processed food consumption was associated with a higher risk of subsequent depressive outcomes. [15,16] One other study was conducted in a Brazilian sample of young adults and showed no association. [17] Although it remains important to further investigate associations across the lifespan, particularly in young adults, the existing evidence largely and directly links the consumption of ultra-processed foods to depressive outcomes. It thus stands to reason that the beneficial dietary intervention effects observed in the SMILES trial might have been driven, at least in part, by reductions in ultra-processed food intake. The aim of the study was to examine this using a secondary analysis approach.

Methods

Pre-registration and Ethics Approval

We prospectively registered this study with the Open Science Framework (OSF) registry (internet archive link: https://archive.org/details/osf-registrations-us5t7-v1), and we reported this study in concordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

[18] The St Vincent's Hospital, Barwon Health and Deakin University Human Research Ethics Committees provided approval for the original SMILES trial protocol, and written consent to participate was provided by the participants. [19] Approval for exemption from ethical review for the current study, in accordance with the National Statement on Ethical Conduct in Human Research (2007, updated 2018) Section 5.1.22, was provided by the Deakin University Human Research Ethics Committee (project number: 2022-050).

The study protocol for the original SMILES trial has been published elsewhere. [19] In brief, SMILES (2013-15) was a 12-week, parallel-group, single-blind, randomised controlled trial that tested the effect of an adjunctive dietary intervention in the treatment of moderate to severe depression (pre-registration via Australia and New Zealand Clinical Trials Register: ACTRN12612000251820). The inclusion criteria were assessed at the time of screening and included participants who: (1) had the capacity to give informed consent and were 18 years old or more; (2) met the criteria for a major depressive episode (MDE) diagnosis (as per the Diagnostic and Statistical Manual of Mental Disorders-4th edition [DSM-IV]); (3) had a Dietary Screening Tool score equal to or less than 75/104 (i.e., were considered to have scope for dietary improvement); and, (4) had a Montgomery–Åsberg Depression Rating Scale (MADRS) score equal to or more than 18/60. [3] The exclusion criteria included participants who: (1) within the two weeks prior to screening, had started treatment for depression (e.g., pharmacotherapy or psychotherapy); (2) had antidepressant therapy for the current MDE that had been unsuccessful at or above two times; (3) were involved in any dietary or physical activity intervention; (4) had serious aversions, allergies or intolerances to food; (5) had a substance use disorder and/or personality disorder as a primary clinical diagnosis; (6) had bipolar I or II disorder as a coexisting diagnosis; (7) had a systemic disease (known or suspected) that was not stable; and, (8) were pregnant. [3]

In the original SMILES trial, a total of 67 individuals were enrolled (dietary intervention, $n = 33$; control, $n = 34$). [3] A clinical dietitian (Accredited Practising Dietitian) delivered the dietary intervention that was based on a modified Mediterranean diet model involving seven nutritional consulting sessions. [3] A research assistant delivered the control condition, which included a social support ('befriending') protocol that had the same visit schedule and length as the dietary intervention. [3] The primary outcome was depression symptom levels (MADRS scores) at 12 weeks. [3] To address our main aim of determining whether ultra-processed food intake-change from baseline to 12 weeks moderated the therapeutic benefit of the dietary intervention for depression compared to the control, participants who had food diary data and MADRS assessment across the trial duration were included ($n = 44$).

Dietary Assessment of Ultra-Processed Food

In the week leading up to the baseline and follow-up assessment, detailed information on foods and fluids consumed was collected for each participant using seven-day food diaries. [19] For this study, all food diary items were classified according to the Nova food classification system as unprocessed or minimally processed foods (Nova group 1), processed culinary ingredients (Nova group 2), processed foods (Nova group 3), and ultra-processed foods (Nova group 4). Examples of Nova's classification of unprocessed or minimally processed foods (group 1) include fresh, squeezed, chilled, frozen or dried: fruits, grains, legumes, seeds, nuts, and vegetables, as well as milk (pasteurised or powdered) and natural yogurt (no artificial sweeteners or added sugar); [20] processed culinary ingredients (group 2) include butter, honey, lard, sugar, salt, and vegetable oils; [20] and, processed foods (group 3) are made from adding group 2 substances to group 1 foods, including bottled or canned: fruits, fish, legumes, and vegetables, as well as breads, cheeses, sugared or salted seeds and nuts, and smoked and salted meats. [20] Examples of Nova's classification of ultra-processed foods (group 4) include carbonated drinks, confectionary (lollies or candy), biscuits (cookies), 'instant' noodles and soups, packaged buns, breads and snacks (savoury and sweet) and ready-to-eat or -heat and shelf-stable meals. [20] Further details regarding the Nova food classification system have been specified elsewhere. [8] We included all participants with food diary records (complete or

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incomplete), with the majority providing six- to seven-day records at baseline (89%) and follow-up (96%), respectively. Using the average of food diary records, the mean daily contribution of each Nova food group (listed above) to intake of total energy (kilojoules) and weight (grams) was calculated based on the AUStralian Food and NUTrient (AUSNUT) 2011-13 database that contains information for 5,740 foods and beverages. [21]

Depressive Symptoms

The interviewer-rated MADRS was used to assess depressive symptoms at baseline and follow-up. MADRS assessment at 12 weeks follow-up was the primary outcome. The MADRS is the most widely used rating scale for depression, being a robust and psychometrically sound interviewer-rated instrument. [22] It consists of 10 items, each measured on a six-point scale and scores range from 0 to 60; greater symptom severity is reflected by higher MADRS scores. [22]

Assessment of Covariates

An *a priori* approach to identifying covariates was undertaken by assessing previous relevant literature. [23-25] These covariates were measured at baseline via a structured interview and included: 1) sociodemographic characteristics: sex (men, women), age (continuous; years), highest level of education (pre-secondary education, post-secondary education), and household income (below $80,000 per year, at or above $80,000 per year); 2) lifestyle and health related behaviours: physical activity (continuous; a total Metabolic Equivalent of Task (MET) score was calculated for each participant as a summary of minutes per week of walking as well as moderate and vigorous physical activity), [26] smoking status (never smoked, current smoker, former smoker), alcohol intake (continuous; grams per day), and modified Mediterranean diet (Mod*i*MedDiet) score (continuous; a total criterion-based score that comprised a maximum estimate of 120 and was calculated using prespecified absolute or normative goals for intakes of specific foods items, which were independent of individual-level characteristics); [7] and, 3) body mass index (continuous; calculated as kilograms divided by the square of participants' height in metres). Sociodemographic characteristics and lifestyle and health-related behaviours were considered as potential confounders, whereas body mass index was hypothesised as an intermediate on the causal pathway (see below).

Statistical Analysis

Participant characteristics at baseline were described using frequency and percentage for categorical variables and mean and standard deviation (SD) for continuous variables. As per previous ultra-processed food studies, [27-30] we aimed to better represent intakes of ultra-processed foods that provided nil to minimal amounts of energy (e.g., non-sugar sweetened beverages). As such, we used the proportion of ultra-processed foods in weight (% grams per day) and adjusted for energy intake by using Willett's residual method [31] to model our ultra-processed food intake variable in 10% increments. Analyses were performed according to modified intention-to-treat principles, [3] in which randomised participants were included if they had at least one valid follow-up MADRS assessment and non-missing food diary data.

Prior to running the main model, preliminary analyses via linear regression investigated a cross-sectional association between the consumption of ultra-processed food and MADRS scores at baseline (adjusted for sociodemographic characteristics and lifestyle and health-related behaviours as potential confounders), as well as whether baseline ultra-processed food intake moderated the dietary intervention effects on depressive symptoms at 12 weeks. For the main analysis, we examined via linear regression whether ultra-processed food intake-change from baseline to follow-up moderated the dietary intervention effects on depressive symptoms at 12 weeks. The outcome was follow-up MADRS scores, and the independent variables were randomly allocated treatment groups (dietary support, social support) and ultra-processed food intake-change from baseline to 12 weeks.

A two-way interaction term between changes in ultra-processed food intake and treatment groups estimated the additional effects of the dietary intervention on improved MADRS scores arising from each 10% reduction in ultra-processed food consumption. The change from baseline to 12 weeks in ultra-processed food intake was included in the model as a continuous variable. As part of an exploratory post-hoc investigation aimed at enhancing interpretability and visual representation (not intended as a formal hypothesis test), we presented marginal mean estimates and graphical plots based on tertiles (categories) of changes in ultra-processed food intake. In this exploratory post-hoc analysis, the first tertile denotes the most substantial decrease in ultra-processed food intake, while the third tertile represents the least reduction. While the main analysis adjusted for baseline MADRS scores, further adjustment for potential confounders formed part of our additional sensitivity analyses (see below) given that we anticipated no or minimal baseline imbalances owing to randomisation. [32]

Finally, sensitivity analyses were undertaken by i) controlling for relevant baseline confounding variables (i.e. sex, age, education, household income, smoking status, alcohol intake, physical activity and Mod*i*MedDiet score), ii) excluding participants with a comorbid disorder(s) (n = 29/44) and, iii) imputing missing data for participants without food diary data at follow-up (n = 12/56) using multi-imputation methods; the results of these sensitivity analyses were compared with our main mediation analysis. Body mass index has been implicated as a potential intermediate in the ultra-processed food-depression relationship. [25,33] Given that 1) the total 'effect' of our ultra-processed food moderator variable on the relationship between treatment groups and MADRS scores at follow-up was of primary interest, and 2) body mass index did not qualify as a confounder, body mass index was thus not adjusted for as part of our sensitivity analyses. [34]

Mean differences in depressive symptoms for each 10% reduction in ultra-processed food consumption were estimated along with ninety-five per cent confidence intervals (95%CIs). As strongly recommended in the literature, [35-38] and as per our pre-registered analysis plan, instead of relying on an arbitrary probability (*p*-)value threshold, we analysed the direction and magnitude of effect estimates and their corresponding 95%CIs, along with precise *p*-values, to evaluate the robustness of our findings. In addition, partial eta squared (η_p^2) was estimated as an effect size measure. The effect sizes were interpreted using the following conventions: small ($\eta_p^2 \geq 0.01$), medium ($\eta_p^2 \geq 0.06$) and large ($\eta_p^2 \geq 0.14$). [39]

All analyses were undertaken using R version 4.2.1 (2022-06-23) [40] and by the first (MML) and second (ML) authors who were blinded to group allocation.

Results

Of the 67 participants enrolled in the SMILES trial, 56 completed the MADRS assessment at baseline and 12 weeks follow-up, and of these, 44 participants with both baseline and follow-up food diary data were included. Table 1 details the participants' characteristics by group allocation at baseline. Participants in the dietary intervention group were, on average, more likely to be female, younger, consume more alcohol and engage in less physical activity than participants in the control group. Participants in the dietary intervention group also had lower Mod*i*MedDiet scores on average than the social support control group at baseline. This is similar to the results reported in the original SMILES trial results paper, [3] and is in line with the greater average consumption of ultra-processed food observed for participants in the dietary intervention group versus control group (calculated as the percentage contribution to the overall diet in weight [% grams] per day).

Table 1. Descriptive Characteristics of the Study Population at Baseline.

Variable	Dietary support intervention group	Social support control group	Total
n – Frequency	31	28	59
MADRS (0-60) – Mean (SD)	26.3 (5.0)	24.0 (4.2)	25.2 (4.7)

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Female – n (%)	25 (80.6%)	18 (64.3%)	43 (72.9%)
Age – Mean (SD)	37.6 (10.9)	42.3 (15.1)	39.8 (13.2)
Post-secondary school education – n (%)	20 (64.5%)	19 (67.9%)	39 (66.1%)
Household income above $80,000/year – n (%)	6 (19.4%)	5 (17.9%)	11 (18.6%)
Current smoker – n (%)	2 (7.1%)	6 (21.4%)	8 (14.3%)
Alcohol (g/d) – Mean (SD)	11.5 (22.4)	5.8 (7.4)	8.8 (17.2)
Physical activity (total MET score) – Mean (SD)	2,270.3 (2682.7)	2,852.1 (2767.9)	2,550.0 (2,713.0)
Body mass index (kg/m2) – Mean (SD)	30.3 (9.6)	28.0 (6.1)	29.2 (8.2)
Mod*i*MedDiet Score (0-120) – Mean (SD)	35.7 (13.0)	46.6 (14.0)	40.8 (14.4)
Total proportion of ultra-processed food (% g/d) – Mean (SD)	31.3 (21.4)	22.5 (10.2)	27.1 (17.5)

Note: MADRS (0-60), Montgomery-Åsberg Depression Rating Scale; kg/m2, kilograms/metres2; Mod*i*MedDiet, modified Mediterranean diet; g/d, grams per day; kJ/d, kilojoules per day.

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In our initial analyses, baseline ultra-processed food consumption was not associated with baseline MADRS scores (mean depressive symptoms: 0.59, 95%CIs −0.28 to 1.45, p=0.188, η_p^2 = 0.04), nor did baseline ultra-processed food consumption moderate the dietary intervention effects at follow-up (between-group mean differences in depressive symptoms: −1.40; 95%CIs −3.94 to 1.14, p=0.287, η_p^2 = 0.03). In our main analysis, and for participants in the dietary intervention, there was an additional 2.5-point improvement in MADRS scores for each 10% reduction in ultra-processed food consumption compared to participants in the control group (between-group mean differences in depressive symptoms: −2.46, 95%CIs −4.71 to −0.20, p=0.039). The effect size for this interaction was medium to large, with a η_p^2 of 0.10. Table S1 shows the average within-group and between-group differences in MADRS scores and ultra-processed food consumption during the trial.

The exploratory post-hoc analysis, including estimates and graphical plots, supported our primary finding and highlighted a dose-response relationship (Figure 1). This relationship pertained to the tertiles of decreasing ultra-processed food consumption. Moving from the most substantial reduction in ultra-processed food to the least, there were between-group marginal mean differences in MADRS scores of: 6.67 (95%CIs −3.39 to 10.45), 6.59 (95%CIs −2.72 to 8.38), and 0.30 (95%CIs −3.11 to 9.59) for tertiles one through three, respectively.

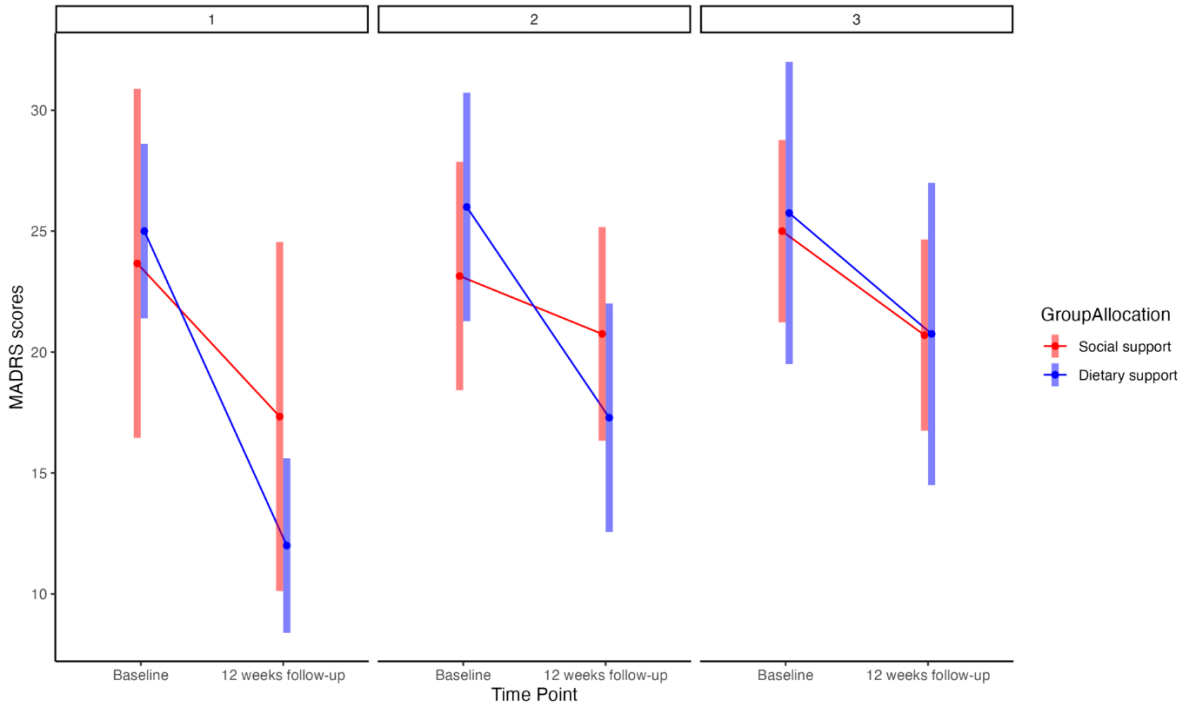

Figure 1. Note: MADRS (0-60)=Montgomery-Åsberg Depression Rating Scale; panels 1, 2, and 3=tertiles one, two and three (highest, middle range, and lowest reduction in ultra-processed food intake, respectively).

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Sensitivity Analyses

Our main finding that ultra-processed food intake-change from baseline to follow-up partly moderated the dietary intervention effects on MADRS scores at follow-up remained relatively stable across sensitivity analyses that controlled for relevant baseline confounding variables (i.e. sex, age, education, household income, smoking status, alcohol intake, physical activity and Mod*i*MedDiet score) (between-group mean differences in depressive symptoms: −3.44, 95%CIs −6.09 to −0.79, p=0.018, η_p^2 = 0.23). The direction and magnitude of our main result also remained stable after imputing missing data for participants without food diary data at follow-up (between-group mean differences in depressive symptoms: −2.26, 95%CIs −4.8 to 0.32, p=0.093). After excluding individuals with comorbid disorder(s) (n = 29/44), the effect size was reduced (between-group mean differences in depressive symptoms: −1.06, 95%CIs −4.74 to 2.61, p=0.583, η_p^2 = 0.03). In both multiple imputation and exclusion sensitivity analyses, the confidence interval widened and included the null.

Discussion

We conducted a secondary analysis of the SMILES randomised controlled trial and primarily sought to assess whether the therapeutic benefits of a dietary intervention on clinical depression were at least partly driven by changes in ultra-processed food intake. We found that reductions in the dietary share of ultra-processed foods moderated the relationship between the dietary intervention and the improvement in depressive symptoms. This suggests that the beneficial effect of the dietary intervention on depressive symptoms was, in part, a result of the decrease in ultra-processed food intake.

The finding that changes in ultra-processed food intake moderated the dietary intervention effects on clinical depression over a reasonably brief period (12 weeks) highlights ultra-processed food consumption as a viable intervention target. It also suggests that recommendations for modifying dietary habits should include a specific focus on reducing the consumption of ultra-processed foods. This notion is further supported by compelling evidence from epidemiological studies and meta-analyses, which have demonstrated strong associations between greater ultra-processed food consumption and higher risks of both the prevalence and incidence of depressive outcomes. [9,10,13-16] It is also supported by the fact our results most notably held after controlling for relevant baseline confounding variables (i.e. sex, age, education, household income, smoking status, alcohol intake, physical activity and Mod*i*MedDiet score). Although we did not further adjust for body mass index as part of our sensitivity analyses (as per the rationale outlined in our Methods section), it is worth highlighting that on average no between-group differences at baseline were observed (see Table 1), nor were there any changes to body mass index within or between-groups at follow-up (see Table S1 and [3]). This is consistent with the SMILES' *ad libitum* and weight-neutral dietary approach and findings, where dietary improvement without weight loss was the focus and where improvements in depressive disorders occurred independently of weight changes. [3]

Participants in the dietary intervention achieved an additional 2.5-point improvement in MADRS with each 10% reduction in ultra-processed consumption across the trial duration compared to participants in the control group. This is on top of the average 7-point between-group difference in MADRS reported in the SMILES' primary results paper. [3] When taking into account a previously established minimal clinically important difference threshold of 2 points in MADRS, [41] this finding underscores clinically meaningful decreases in depressive symptoms that arise from overall dietary improvement—and decreases in ultra-processed food consumption in particular.

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There are several biological mechanisms of action by which a reduction in ultra-processed food consumption may influence depressive symptoms. The Nova system does not classify foods based on their respective nutritional composition. [8] However, numerous ultra-processed food items contain nutrient-poor profiles, in addition to non-nutritive components produced via or used during intensive food processing, that may elicit the prevalence, development and symptom severity of depression through various pathways, including oxidative stress, inflammation and the gut microbiota. [42-49] Indeed, ultra-processed food consumption has been implicated in altering the gut microbiota composition [50] and prospectively [51] and cross-sectionally [24,52-54] associated with inflammation and oxidative damage in Australian, Brazilian, Portuguese and Iranian populations. Both the nutritive and non-nutritive aspects of foods classified as ultra-processed and the proposed mechanisms of action they have been associated with will require further investigation in large-scale human trials.

Strengths and Limitations

One strength of our study is that we measured depressive symptoms using the interviewer-rated MADRS tool rather than relying on self-reported methods, which approximately 65% of other ultra-processed food-mental disorder studies have done [10] and where less precision in estimates remains possible. [55] The prospective nature of the data collection in the context of a rigorous clinical trial is a further strength. Another strength of our study includes the use of food diary data to calculate ultra-processed food consumption, which can provide greater precision over food frequency questionnaires, [56] as well as the application of a rigorous method to classify food diary data according to the Nova system following Machado et al (2019). [57] In addition to the benefit of food diary data measured at the start and end of the trial (which allowed us to assess change in ultra-processed food intake), these measurement-related factors may have increased the sensitivity of our models, while also permitting us to provide descriptive estimates in a confirmed clinical population.

A limitation of our study is that the SMILES trial originally recruited participants with major depression on the basis of existing poor-quality dietary intake. This means that the generalisability of the current secondary analysis may not translate to the broader population of people with a depression diagnosis. However, we observed that average ultra-processed food intake at the beginning of the trial contributed 27 per cent to total food intake in weight (% grams per day) (see Table 1). This estimate is comparable to our recent population-based cohort study assessing longitudinal associations between ultra-processed food and depression in Australian adults (25% grams per day), [15] as well as various general and diseased populations in other high-income countries such as the United Kingdom and the United States of America. [58] This suggests that (poor) dietary quality appears to be relatively concordant between the wider population and individuals with depressive illness and that our results may have reasonable external validity.

As discussed as a key limitation in the original results paper, [3] we also cannot rule out the possibility of expectation bias and that the inability to blind participants to their intervention may account for the associations between dietary intake, including ultra-processed food consumption, and depressive symptoms. However, this is a limitation of the field in general where it is difficult to blind participants in non-pharmacotherapeutic-based intervention studies involving nutrition, physical activity and psychotherapeutics. [59] Another limitation is that ultra-processed food consumption was not registered as a secondary outcome in the original trial registration. This is because its concept at the time of designing the SMILES trial in 2013 was relatively unknown, with details and principles of the Nova food classification system, along with its concept of ultra-processed food, first published in 2009. [60]

Notably, however, we sought to protect against publication bias by prospectively pre-registering our analysis plan with the OSF registry (see Methods section).

Finally, our study was a secondary analysis of existing data from a trial with a small sample size and the observed results indicate associations that may not necessarily be causal. To assess the causal effects of ultra-processed food intake on depressive symptoms and understand how these effects may unfold over time, prospective randomised studies with mechanistic investigations are needed. Such studies will play a critical role in establishing causality and confirming whether the therapeutic benefit of dietary intervention for depression is driven, in part, by reductions in ultra-processed food consumption, as implied by our findings. However, while we acknowledge the preliminary nature of our secondary analysis findings, the insights gained can serve as valuable groundwork and justification for conducting future research on the causal effects of ultra-processed food on depressive symptoms, with a more targeted and controlled approach. Indeed, secondary analyses, in general, can provide insights that may be used to inform the development of research questions, study designs and sample size calculations for prospective randomised trials specifically focused on examining causality. [61] Relatedly, our relatively small sample size is another limitation, particularly for the preliminary analyses that showed point estimates in the expected direction but were not statistically significant, with further larger studies needed.

Conclusions

In a secondary analysis, we report that the degree of change in the dietary share of ultra-processed foods appeared to moderate the effect of the dietary intervention on mood improvements across the trial duration. Our secondary analysis suggests that measures of ultra-processed food consumption should be considered when analysing the outcomes of novel lifestyle treatments for depression. It also provides preliminary experimental evidence that the benefits of dietary improvement as an adjunctive treatment for major depressive disorder may be partly driven by reductions in the dietary share of ultra-processed foods. To support causal inference, future sufficiently powered prospective randomised controlled trials ought to focus on replicating our findings, as well as testing whether and how reducing ultra-processed foods may independently facilitate reductions in depressive symptoms.

Supplementary Materials:

Funding: This research received no external funding.

Institutional Review Board Statement: The current study was approved for exemption from ethical review in accordance with the National Statement on Ethical Conduct in Human Research (2007, updated 2018) Section 5.1.22 by the Deakin University Human Research Ethics Committee (project number: 2022-050). The study protocol for the original SMILES trial was approved by St Vincent's Hospital, Barwon Health and Deakin University Human Research Ethics Committees.

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