EDITORIAL

Diet and Depression—From Confirmation to Implementation

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Over the past decade, nutritional psychiatry has developed into a promising research area in a field with great unmet need.[1] The early research has advanced from cross-sectional epidemiological studies reporting associations between diet quality and mental health outcomes, including depression and anxiety,[2] to longitudinal and mechanistic studies.[3] Observational findings have been extensively replicated and documented in meta-analyses[4] and are supported by intervention studies examining the efficacy of dietary improvement as a treatment for depression; recently, 2 preliminary trials of dietary interventions for depression have yielded similar positive findings.[5,6] A new meta-analysis confirms that dietary interventions significantly reduce depressive symptoms, although nearly all studies to date have involved nonclinically depressed populations; that is, individuals with subsyndromal depressive symptoms, metabolic disorders, other somatic conditions, or healthy adults recruited from the general population.[7] Thus, for the findings from these studies to serve as catalysts for clinical change, additional independent and methodologically rigorous interventions targeting depression are essential. In this issue of *JAMA*, 2 randomized trials[8,9] provide important results that focus on the emerging field of nutritional psychiatry.

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Bot and colleagues,[8] from the European MooDFOOD consortium, report findings from a clinical trial of a nutrition-focused prevention intervention for major depression, involving 1025 overweight and obese adults with elevated depression symptoms but not meeting criteria for major depression. In this 1-year study, using a 2 × 2 factorial design, the investigators compared both a dietary intervention focused on improving dietary behaviors and promoting a Mediterranean-style diet (referred to as food-related behavioral activation therapy), and a dietary intervention involving supplementation with a multinutrient formulation, which included omega-3 fatty acids, selenium, folic acid, vitamin D_3, and calcium vs placebo. Neither the therapy nor the diet supplementation, alone or in combination, prevented the primary outcome of major depressive disorder (MDD) at 1 year. The rates of MDD development were 10% for placebo supplementation without therapy, 9.7% for placebo supplementation with therapy, 10.2% for multinutrient supplementation without therapy, and 8.6% for multinutrient supplementation with therapy. The rates of transition to MDD in all treatment groups were substantially lower than the rates the investigators anticipated (MDD onset estimated at 20% in the active treatment group and 30% in the control group).

Among the secondary outcomes, a signal for improved anxiety was detected in the food-related behavioral activation therapy groups, and another signal suggested that more symptomatic individuals derived greater benefit from the therapy intervention, a finding concordant with most of the depression literature showing greater efficacy in more unwell individuals. However, the multinutrient supplementation group did worse on a number of measures including self-rated depression. Concordant with the results of this study, a recent study of a multinutrient formulation for the treatment of depression not only failed to benefit participants but also performed significantly worse than placebo.[10] These results offer a note of caution about the liberal and mostly non-evidence-based use of nutrient supplement combinations for psychiatric disorders.

Prevention of MDD is difficult to study. There are issues with statistical power because only a small subset of participants with subsyndromal depressive symptoms will develop depression in the follow-up period (approximately 10% in the study by Bot et al). The diverse and multiple nature of risk factors for depression, each with a small effect, also complicates prevention endeavors. Nutrition research involves additional methodological challenges relating to expectation effects, whereby study participants or raters in trials may have expectations of benefit that affect outcomes and dietary adherence, which is notoriously low and fleeting. In the food-related behavioral activation therapy group in the study by Bot et al, only 71% attended more than 8 of the 21 offered sessions, and how many followed the dietary recommendations is unclear. Nevertheless, an additional preplanned analysis showed a significant reduction in risk of depression among those attending at least 8 of the therapeutic sessions, which is consistent with findings from recent treatment trials in which dietary adherence correlated with symptom improvement.[5,6] However, it is also possible that the factors that assist adherence, such as personality and social support, may be driving other adaptive health behaviors that led to reduced risk of depression, a possibility that requires further investigation.

In another report, Ma and colleagues[9] in the RAINBOW trial evaluated the effects of an integrated collaborative care intervention, with depression and body mass index (BMI) as coprimary outcomes. This well-powered, parallel-group clinical trial compared usual care (n = 205) with a behavioral weight loss treatment plus problem-solving therapy (n = 204), and antidepressant medications when indicated, for depression in adults with obesity (BMI >30) and depression. At 12 months, the expected modest benefits for weight were found (between-group difference in BMI, −0.7; 95% CI, −1.1 to −0.2), whereas the more novel result was a significant, although again modest, reduction in depression (between group difference, −0.2 points; 95% CI, −0.4 to 0.0) on the Depression Symptom Checklist 20-item scores (range, 0-4), A secondary outcome

response, defined as a 50% reduction in depression symptoms, occurred in significantly more patients (31% vs 16%) in the intervention group; this is consistent with a clinically meaningful result. However, antidepressant prescription rates may be an explanatory factor, as prescription rates increased in the intervention group and declined in the control group.

The study is similar to a previous smaller study involving patients with comorbid obesity and depression (n = 161), showing a significant reduction in Beck Depression Inventory II scores at 6 months of −12.5 in the experimental group vs −9.2 in the control condition (P = .005) but not in weight.[11] Similarly, the recent SMILES trial (n = 67) showed significant benefits (P < .001) on symptoms of clinical depression without any significant weight change; however, in contrast to this trial, the dietary protocol in that study focused on improving diet quality and not weight loss.[5] Importantly, the RAINBOW trial was implemented in primary care settings, which provides a pragmatic clinical service framework to translate these findings into improved health outcomes and also supports previous work using such collaborative care models.

Depression is a common and potentially disabling disorder that can be complex to manage effectively and often responds only modestly to both pharmacotherapy and psychotherapy; consequently, many patients, even with treatment, have residual depressive symptoms and impairments in functioning and quality of life. Although the extent of the potential benefits of diet for depression is yet to be confirmed, given the modest effect sizes in these studies—notwithstanding larger ones in previous studies[5,6]—dietary change is not likely to be a sole treatment for depression. Rather, these recent findings highlight that an integrated care package incorporating first-line psychological and pharmacological treatments, along with evidence-based lifestyle interventions addressing smoking cessation, physical activity, and diet quality, may have a more robust effect on this burdensome disorder. These approaches also may be more cost-effective than other approaches.[12,13]

Mood and numerous noncommunicable disorders are commonly comorbid and share common risk factors and pathophysiological pathways.[14] Obesity and depression, for example, interact in a bidirectional manner[15] with lifestyle factors including poor diet as shared contributing factors. The new studies by Bot and colleagues[8] and by Ma and colleagues[9] pave the way to new therapeutic interventions that address common mental health disorders and noncommunicable physical disorders simultaneously, recognizing common risk determinants and shared end points.[16]

ARTICLE INFORMATION

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