

Letters

COMMENT & RESPONSE

A Closer Look at Ketogenic Diet Effects in Depression

To the Editor In their randomized clinical trial published in *JAMA Psychiatry* of a ketogenic dietary intervention for treatment-resistant depression, Gao and colleagues¹ reported a modest between-group advantage for ketogenic therapy on the 9-item Patient Health Questionnaire (PHQ-9) at 6 weeks (mean difference, -2.18; 95% CI, -4.33 to -0.03; $P = .05$). The between-group difference at 12 weeks was not statistically significant. This letter highlights 3 interpretive issues relevant to diet trials in depression.

First, the PHQ-9 includes several somatic and behavioral items (sleep, appetite, energy, psychomotor change) that could plausibly shift over short intervals with structured dietary interventions independent of core affective pathology.² In this context, an overall PHQ-9 difference of approximately 2 points could reflect preferential movement on somatic items rather than clinically meaningful change in depressed mood or anhedonia. Item-level analyses (or separation of somatic vs cognitive/affective components) would clarify which symptom domains drove the primary outcome and whether any signal concentrates in core depressive features.

Second, if ketosis per se is hypothesized as a primary mechanism, the absence of a clear dose-response association between ketone levels and symptom change warrants careful consideration. Although participants in the ketogenic arm achieved measurable ketosis, greater ketone exposure was not clearly associated with greater improvement in depressive symptoms.¹ This pattern complicates a straightforward mechanistic interpretation in which ketosis mediates antidepressant effects. When between-group differences are modest and within-group improvements substantial, clarifying the link between biological targets and clinical outcomes becomes especially important. Future trials should prespecify mechanistic hypotheses, incorporate rigorous assessment of target engage-

ment, and formally test whether changes in ketone levels mediate symptom improvement.

Third, the primary result sits on the statistical threshold with a confidence interval that narrowly excludes 0. In a post hoc sensitivity analysis using an alternative error model, the 6-week effect was no longer statistically significant.¹ Sensitivity analyses for missing primary-outcome data yielded P values greater than .05 under prespecified scenarios (eg, $P = .06$ to .08).¹ When effects are small relative to within-group change, conclusions can be fragile to analytic choices and missing-data assumptions. Future trials should prespecify and foreground robustness analyses (including alternative missingness models and estimands).

The next-step studies should incorporate clinician-rated end points, symptom-domain or item-level outcomes, rigorous assessment of target engagement, and prespecified robustness frameworks, while equalizing treatment framing and support intensity, to determine whether ketogenic interventions yield specific improvements in core depressive psychopathology.

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Editorial Note: This letter was shown to the corresponding author of the original article, who declined to reply on behalf of the authors.

1. Gao M, Kirk M, Knight H, et al. A ketogenic diet for treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. Published online February 4, 2026. doi:[10.1001/jamapsychiatry.2025.4431](https://doi.org/10.1001/jamapsychiatry.2025.4431)

2. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. doi:[10.1046/j.1525-1497.2001.016009606.x](https://doi.org/10.1046/j.1525-1497.2001.016009606.x)