Reviewer's report

Title: Mediterranean dietary pattern and depression: the PREDIMED randomized trial

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Reviewer: Ian Colman

Reviewer's report:

This interesting study on the Mediterranean diet and depression is notable for some impressive strengths. The authors point out that randomized controlled trials are a necessary next step in the study of diet and mental health, and they provide one with a very large sample size. Unfortunately their study is limited by some important methodological flaws, some of which can not be remedied. The biggest problem may be that the control group in the study also received a positive diet intervention, which could have masked a larger true effect.

The outcome used in the study is problematic. A structured assessment would be preferred. Physician diagnosis is biased by treatment-seeking behaviour, as is antidepressant treatment. Furthermore, factors associated with treatment-seeking behaviour may be associated with other lifestyle factors that confound the association between diet and mental health (or could even be associated with the intervention). Even if there is no bias, under-estimating the true rate of depression in the follow-up period undermines the statistical power of the study, which makes interpretation of the results difficult. Unfortunately, there is nothing the authors can do about this.

The exclusion of 1,870 individuals who had less than three years of follow-up is unexplained and seems unnecessary in the analytical framework. Is there a biological reason why it would take three years of diet change before an effect on mental health could be observed? This must be discussed in more detail, especially given that mechanisms linking diet and mental health have been proposed but not conclusively defined. From an analytical point of view, there is no reason to exclude these individuals. In the Cox model individuals would be censored at the time at which their follow-up finishes. The authors mention wanting to avoid reverse causality, but I'm not sure how this is possible in an RCT.

Related to this, it's not clear why these individuals do not have three years of follow-up. Are they lost to follow-up? If so, an analysis of predictors of missingness is necessary, particularly given that drop-out appears to differ by group, and drop out is likely related to the outcome.

It's awkward to say that "although not significant, a decrease in depression risk was observed". It's true that the observed hazards were lower, but the confidence interval suggests no meaningful difference. Consequently, the term
"risk" should be avoided, as should discussion of differences. This follows right through to the conclusion.

The results on those with diabetes are interesting and make for a good and well-reasoned discussion, but they could also be a result of a type I error considering the number of different sensitivity analyses.

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests