Author's response to reviews

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

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Version: 4 Date: 23 July 2013

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The paper has been significantly improved and will make an important contribution to the literature, particularly given the fact that it is a high quality RCT.

There is only one issue that was not adequately addressed in the revised manuscript - the exclusion of the first three years of follow-up to avoid reverse causality. The authors make a compelling case in their response to the reviews that the key issue is that participants who are depressed at baseline are less likely to comply to the prescribed diet. However, they don’t make this link between compliance and follow-up times in the manuscript. They only mention wanting a "sufficiently long induction period". This phrase suggests that there is a prolonged biological mechanism that links the intervention to the outcome, not that it is a methodological issue.

1) We have included a new sentence in the text of the discussion section explaining that:

"We assumed this 3-year period because we believed likely that participants with undetected (subclinical) depression at baseline may receive a delayed diagnosis of depression during the first, second or even the third year of follow-up. On the other hand, we considered unlikely that in these participants with true but undiagnosed depression at baseline this depression may remain undetected during the first 3 years of follow-up and, in spite of that, they might yet receive a delayed diagnosis only at the fourth year of follow-up or later."

Usually, to minimize the influence of possible “reverse causation” owing to the presence of undiagnosed disease at baseline, a methodological approach in cohort studies assessing other hypotheses has been to exclude cases occurring during the first three (Zheng et al. N Engl J Med 2011;364:719-29) or five (Pischon et al. N Engl J Med 2008;359:2105-20.) years of follow-up. Our follow-up period was not sufficiently long as to allow us to exclude cases occurring during the first 5 years. That is the reason why we decided to exclude early cases occurring during the first 3 years.

2) "Induction" period. You are right and we admit that our sentence might be misunderstood because we were not meaning any specific and known biological mechanism which may need exactly 3 or more years to exert its causal role. Therefore, to comply with your suggestion, we have now erased the term "induction" in the new version.