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Letters to the Editor

Regarding the Robustness of Results for "Association of Tryptophan Metabolites with Incident Type 2 Diabetes in the PREDIMED Trial: A Case–Cohort Study"

To the Editor:

An update to the primary PREDIMED study was recently published to take into account some departures from the individual randomization protocol affecting only a small subset of participants *(1)*. Specifically, (*a*) some participants were not individually randomized because they were members of the same household of a previous participant and they were allocated during the duration of the trial to the same arm as their previously randomized relative (the household was considered as a cluster), and (*b*) in 1 of the 11 recruiting centers, a subset of participants did not undergo individual randomization, but they were allocated to each arm of the trial in small clusters (these clusters were the clinics). The new analyses for the primary end point of the PREDIMED study used robust variance estimators to account for intracluster correlation, as well as adjustment for propensity scores predicting randomization to account for small between-group imbalances at baseline.

In our observational analysis published in *Clinical Chemistry* entitled "Association of Tryptophan Metabolites with Incident Type 2 Diabetes in the PREDIMED Trial: A Case–Cohort Study," we examined the association between plasma metabolites and type 2 diabetes using data from the PREDIMED trial *(2)*. Obviously, in this case, the independent variable was not the intervention but rather plasma concentrations of tryptophan and other metabolites. Therefore, randomization was not an issue, given that we followed an observational design. We emphasize that the study design, data collection, data analysis, and interpretation of results were performed under the assumption that the independent variables (plasma concentrations of metabolites) were not randomly distributed among participants. Nevertheless, we have conducted additional sensitivity analyses for the main findings of our article using robust estimates of the variance to correct for potential intracluster correlations and to adjust for propensity scores (built with 30 predictors of allocation) for the ancillary analyses examining the association of the intervention with changes in metabolite levels *(1)*.

The overall results are extremely robust, and they remain intact. Our finding that tryptophan concentrations may initially increase at diabetes onset and then shift downstream as disease severity progresses is unchanged.

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