

The Intention to Treat Principle, and the Potential Impact of Excluding Data from the Analysis of Clinical Trial Data

Dear Editor,

We write to comment on the article by Nelson et al. (1). The authors conducted an experiment to examine the impact of a supplemental dose of 20 $\mu\text{g}/\text{d}$ vitamin D on serum 25-hydroxyvitamin D [25(OH)D] concentrations in 112 women ages 19–35 y. This study addresses an important research need. However, we have some concerns about the conduct and analysis of the study that may inadvertently affect the interpretability of the results.

First, participants were withdrawn from the data analysis because some dropped out of the study at various points after beginning, others were found to not meet eligibility criteria, and others did not adhere to the study protocol. The specific reasons for withdrawal from the analysis were as follows: 1) Ten participants withdrew from the study (5 before and 5 after randomization) and were excluded from the analyses. The period prior to randomization is important because it was used to establish an increase in 25(OH)D due to sunlight only. 2) Five participants were excluded because their 25(OH)D concentrations were outside of the range (22.5–175 nmo/L) established for inclusion. It was not clear when this exclusion took place. 3) Twelve female participants who either began or quit using contraceptives during the study were excluded from the analyses. In addition, 4) Fifteen participants “tanned” during the study against instructions in the protocol. Four were in the “Placebo” group and 11 were in the “Supplement” Group. These individuals were *included* in the analyses.

We are concerned that these “exclusions” and “inclusions” may compromise the interpretability of what otherwise would be a very useful study. In addition, although not everyone agrees with the “Intention-to-Treat” procedure for analyzing data from a clinical trial, where all data are included in the data analysis (2), we are concerned that excluding participants from the analysis can and has been shown to result in biased results (3). If participants are to be withdrawn from the data analysis, the burden rests with the investigator(s) to convince the scientific community that the analysis has not been biased (3). From our reading of the article, the authors have not offered that assurance.

As a result, we would like to suggest that the authors report the results of the trial, i.e., the comparison of mean 25(OH)D

concentrations between treatment and placebo groups, as follows: 1) including all the data; 2) including all the data adjusted for covariance using an analysis of covariance model; and 3) looking at subgroups to assess the impact of the withdrawals. As noted by Friedman et al. (3, p. 288), “If the analyses from all the enrolled participants and from the subgroups agree, the interpretation of the results... is clear. If the results differ, however, investigators must be very cautious in their interpretation.” We further suggest that the results for the entire group should be emphasized because for them the results are always valid (3).

Second, the authors mentioned that 5 participants developed hypercalciuria that was not clinically relevant or important (1). Because hypercalciuria is commonly used as an indicator of vitamin D toxicity, more discussion of this finding would be useful. Finally, because the authors are expert in this area, we further suggest that they should have taken this opportunity to discuss the general issue of how monitoring for clinical side effects in vitamin D and calcium trials should be conducted, especially in studies where the supplemental doses are much larger than in their present study.

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Literature Cited

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