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In Reply Our Editorial accompanied the report of the VITAL-DKD trial.[1,2] The focus of that article and our Editorial was the lack of benefit of vitamin D supplementation over placebo for prevention of chronic kidney disease end points. We concluded that the VITAL-DKD and D2d trials "provide strong clinical trial-grade evidence against … kidney-protective effects of routine vitamin D_3 supplementation in the vast majority of patients with prediabetes or established type 2 diabetes," and emphasized the discrepancy between the "negative" results of these trials relative to previous observational studies that suggested benefits of higher vitamin D levels.

Drs Grant and Boucher dispute our conclusion that the RCTs failed to confirm prior results of observational studies. They cite nominally significant results from a small selection of the many secondary subgroup and post hoc analyses presented in the original reports of the parent VITAL trial and the D2d trial that suggest possible benefits of vitamin D treatment for prevention of cancer, cardiovascular events, and type 2 diabetes.[3,4]

We respectfully disagree. It is not uncommon to identify subgroups in RCTs that seem to benefit from an intervention that otherwise failed to meet its primary end point in the overall study population. However, such results must be interpreted cautiously. When statistical significance is set at $P < .05$, 1 in 20 tests may occur by chance alone. In the setting of numerous comparisons, including many other subgroups that could be presented but are not, the false-positive rate increases to unknown levels.[5] Furthermore, determining whether randomization is maintained in smaller subgroups would require assessment of a series of tables of baseline characteristics that are rarely if ever presented. In their absence, the extent to which imbalances in baseline characteristics account for nominally "positive" findings in subgroups cannot be known.[5]

Grant and Boucher also cite a secondary analysis of breast cancer incidence based on 2 RCTs and 1 nonrandomized prospective cohort study in which the primary exposure was levels of achieved vitamin D rather than vitamin D treatment vs no treatment. Inferring benefits of vitamin D from these results is even more problematic. Although it used data from RCTs, this was a purely observational study in which it is impossible to disentangle whether observed differences in risk could be attributed to vitamin D itself or to the baseline levels of health that permitted certain patients to achieve higher vitamin D levels while simultaneously avoiding breast cancer.

All types of clinical research aimed at improving health are important, but subgroup analyses of trials and results from observational studies should assume their rightful positions in the data hierarchy—not as substitutes for RCT data, but rather as hypothesis-generating findings that stimulate new RCTs, which the community would welcome.

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Conflict of Interest Disclosures: Dr Wolf reported receiving personal fees from Akebia, AMAG, Amgen, Ardelyx, Diasorin, and Pharmacosmos. No other disclosures were reported.

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CORRECTION

Typographical Error: In the Clinical Review titled "Nonalcoholic Steatohepatitis: A Review,"[1] published in the March 24, 2020, issue of *JAMA*, the legend for Figure 1 had a typographical error. The sentence describing stenosis with hepatocyte ballooning and lobular inflammation should have read that such "patients are considered to have NASH." This article was corrected online.

1. Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA, Ikramuddin S. Nonalcoholic steatohepatitis: a review. *JAMA*. 2020;323(12):1175-1183. doi:10.1001/jama.2020.2298

Data Error in Viewpoint on COVID-19 in Italy: In the Viewpoint titled "Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy" published online March 23, 2020, in *JAMA*,[1] a data error appeared in the eighth paragraph. The number of women included in the chart review of 355 patients should have been reported as 106 (not 601). This article has been corrected online.

1. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. Published online March 23, 2020. doi:10.1001/jama.2020.4683