Statistical Considerations Are Necessary in Assessing Associations between Micronutrient Intake and Times to Clinical Events

Dear Editor,

Recently, de Oliveira Otto et al. (1) studied the associations of incidence of three clinical conditions with intake of certain micronutrients. The authors used Cox regression analysis to model times to metabolic syndrome (MetS), Type 2 diabetes, and cardiovascular disease (CVD) given baseline characteristics, including nutrient intake based on responses to an FFQ. To test for linear trends between nutrient intake and the outcomes, they treated intakes as continuous variables using the medians for each quintile. However, the baseline nutrient intake and follow-up biological measurements may be subject to substantial error. Mismeasured covariates in Cox models may lead to biased estimates, and hence, misleading inference (2,3).

Statistical literature considers traditional methods that fail to account for covariate error as “naïve” and recommends several methods for modeling of time-to-event data and covariates measured with error (4). Two-stage joint-modeling methods such as those used by Dafni and Tsiatis (3) model the covariate process using a mixed effects model and the time-to-event outcome by a Cox model based on the predicted covariate values. Many are approximate, requiring regression calibration (RC). Tsiatis and Davidian (5) propose a conditional score estimator that relaxes the assumption of normal random effects. Others capture extraneous variability via latent variables or latent classes, which may be useful for heterogeneous populations with potentially different baseline hazards. In the Nutrition Prevention of Cancer trials, Lin et al. (6) use latent class joint-modeling to investigate the association between selenium and prostate cancer. Simulation extrapolation (SIMEX) has also been used recently. RC is preferable to SIMEX when there is substantial measurement error, but it is not robust to mis-specification of the measurement error distribution (7,8). When measurement error is understated, RC underestimates risk; when measurement error is overstated, RC overestimates risk (7). Two-stage joint models may be implemented in software such as SAS using standard procedures for mixed models and Cox models (4). Lin et al. (6) are willing to provide code in S Plus. Joint models are generally less biased and more powerful than naive approaches (3,5).

Therefore, some conclusions by de Oliveira Otto et al. (1) may be suspect. Random measurement error, which biases estimates toward the null, is especially acute in nutritional epidemiological studies. Joint modeling may illuminate significant associations that were biased toward the null in the study by de Oliveira Otto et al. (1). Examples include the associations in model 2 of MetS with vitamin E and zinc as well as of CVD with zinc from red meat, adjusted for total heme iron. There may also be bias away from the null. A covariate that should be highly predictive of the event may carry residual error that artificially inflates the effect of another covariate. Consequently, the reported significant associations in the study by de Oliveira Otto et al. (1) may in fact be spurious and nonsignificant in a joint model. Dafni and Tsiatis (3) simulated an HIV treatment independent of AIDS progression after adjusting for CD4 counts, a highly variable biomarker predictive of the event time. Estimates ignoring error in CD4 counts were biased away from the null, incorrectly highlighting a treatment effect. Analyzing the data in the study by de Oliveira Otto et al. (1) with methodology that accounts for covariate measurement error constitutes better statistical practice and would strengthen the validity of the study.

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Letters to the Editor

Literature Cited