Bias attributable to the use of a composite outcome in evaluating a cocoa extract supplement.

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Dear Editor:

Composite Outcomes (COs) are frequently used in clinical trials to increase the number of events to analyze in cardiovascular research (1). Sesso and colleagues evaluated cocoa extract supplementation to prevent cardiovascular disease (CVD) in older adults (2). The primary outcome was a composite including seven components: myocardial infarction (MI), stroke, coronary revascularization, cardiovascular death, carotid artery disease, peripheral artery surgery, and unstable angina. In intention to treat analysis, Sesso et al. did not find a significant reduction in total CVD risk. However, cocoa extract supplementation was associated with a 27% significant reduction of cardiovascular mortality. The difference in these effects indicates that there may be a bias attributable to the use of the CO.

We compared the relative risks of the CO (RR_c) and cardiovascular death (RR_d) by estimating the index of bias attributable to CO (BACO)(3). The RR_c for primary CO was 0.90 (95% CI: 0.79 to 1.02), the RR_d of cardiovascular death was 0.73 (95% CI: 0.54 to 0.98), and the BACO index was 0.34 (95% CI: -0.06 to 0.74; p <0.001). A BACO index <1 indicated that the use of CO underestimated the effect of cocoa extract supplementation on the prognosis. This result suggested that the inclusion of several components in the outcome diluted the stronger association observed for cardiovascular death.

Sesso et al. also analyzed a not prespecified composite outcome “major cardiovascular events”, with only three components: MI, stroke, and CVD death, the RR_c was 0.84 (95% CI: 0.71 to 0.99). In this case, the effect on prognosis was not significantly underestimated (BACO index 0.56; 95% CI: 0.07 to 1.05; p=0.08).

These findings exemplify that the more components included in CO, the higher probability of diluting an effect on prognosis. The COs can mix different mechanisms by having events associated with medical decisions (e.g., revascularization or surgery) and severity indicators (e.g., MI, stroke, or death). This diversity of phenomena can introduce bias and misinterpretation of clinical trials (4,5). Therefore, CO components should be carefully selected based on a robust biological rationale. Moreover, treatment effects should be expected to be similar to all the component endpoints (6–8).

Regarding the study of cocoa extract supplementation, we consider that the result of the BACO index would support the main conclusion focusing on the effect on cardiovascular mortality.

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