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

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 (2) evaluated cocoa extract supplementation to prevent cardiovascular disease (CVD) in older adults. The primary outcome was a composite including 7 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. (2) 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, 1.02), the RR_d of cardiovascular death was 0.73 (95% CI: 0.54, 0.98), and the BACO index was 0.34 (95% CI: –0.06, 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. (2) also analyzed a not prespecified composite outcome, "major cardiovascular events," with only 3 components: MI, stroke, and CVD death; the RR_c was 0.84 (95% CI: 0.71, 0.99). In this case, the effect on prognosis was not significantly underestimated (BACO index 0.56; 95% CI: 0.07, 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.

Supported by the National Council for Scientific and Technological Development–CNPq (Fellowship for Research Productivity 312656/2019-0 to FAD-Q).

The authors' responsibilities were as follows – all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Paula C Ramírez
Fredi Alexander Diaz-Quijano

From the School of Physical Therapy, Universidad Industrial de Santander, Bucaramanga, Colombia (PCR, e-mail: pcramire@uis.edu.co), and School of Public Health, Department of Epidemiology, Laboratório de Inferência Causal em Epidemiologia (LINCE-USP), University of Saõ Paulo, Saõ Paulo, Brazil (FAD-Q).

References

1. Armstrong PW, Westerhout CM. Composite end points in clinical research. Circulation 2017;135(23):2299–307.
2. Sesso HD, Manson JE, Aragaki AK, Rist PM, Johnson LG, Friedenberg G, et al. Effect of cocoa flavanol supplementation for the prevention of cardiovascular disease events: the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized clinical trial. Am J Clin Nutr 2022;115(6):1490–500.
3. Diaz-Quijano FA. Estimating and testing an index of bias attributable to composite outcomes in comparative studies. J Clin Epidemiol 2021;132:1–9.
4. Ferreira-González I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ 2007;334(7597):786–8.
5. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA 2003;289(19):2554–9.
6. Montori VM, Permanyer-Miralda G, Ferreira-González I, Busse JW, Pacheco-Huergo V, Bryant D, et al. Validity of composite end points in clinical trials. BMJ 2005;330(7491):594–6.
7. Choi SW, Cheung CW. The case of the misleading composite—one outcome is better than two. Anaesthesia 2016;71(9):1101–3.
8. Palileo-Villanueva LM, Dans AL. Composite endpoints. J Clin Epidemiol 2020;128:157–8.

doi: https://doi.org/10.1093/ajcn/nqac185.

Reply to PC Ramírez and FA Diaz-Quijano

Dear Editor:

We appreciate the opportunity to respond to Ramírez and Diaz-Quijano regarding the challenges of defining and analyzing a composite outcome of total cardiovascular disease (CVD) for COSMOS (the COcoa Supplement and Multivitamin Outcomes Study) (1). We do not believe that differences in results for our composite outcome of total CVD events compared with its 7 individual components constitute any bias. The HR estimates for the composite outcome of CVD death are different not because of bias, but because the corresponding estimands are different; the true intention-to-treat (ITT) effect of the cocoa extract treatment on the composite outcome compared with the true ITT effect of treatment on CVD death, respectively. The composite outcome provides a reasonable summary measure, because the cocoa extract intervention had a similar influence across all 7 individual CVD outcomes with all

 Printed in USA. © The Author(s) 2022. Published by Oxford University Press on behalf of the American Society for Nutrition. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

7 HR estimates ≤ 1 [Figure 2 in Sesso et al. (1)]. Post hoc analyses did not provide any evidence supporting a differential influence across outcomes ($P = 0.85$ from a 6-df test for the interaction between randomized cocoa extract group and outcome) (2).

Thus, the protocol-specified composite outcome was a reasonable summary for the overall influence of cocoa extract on CVD, and there was no valid statistical evidence to suggest that the HR estimates for the composite outcome and CVD death statistically differed ($P = 0.13$ for the difference in log-HR-estimates using the robust-sandwich estimator for the variance-covariance matrix) (2). However, our primary endpoint may have lacked sufficient power, because overall rates of CVD were lower than projected. Also, in COSMOS, the nonsignificant HR for our ITT analysis of the cocoa extract intervention and total CVD could have reflected a less restrictive and less rigorous composite CVD outcome that combined clinical events and vascular procedures, whereas endpoints showing greater risk reductions tended to be more rigorously defined.

The definition and interpretation of composite outcomes require mechanistic assumptions and raise analytic challenges. Critical to their validity is their prespecification; a post hoc determination of which components should be included threatens the validity of the findings. Although the differences in HRs for composite outcomes noted by Ramírez and Diaz-Quijano suggest areas for future inquiry in COSMOS and other studies, the primary results as originally reported remain the most reliable information available.

The authors' responsibilities were as follows—HDS, JEM, AKA, PMR, and GLA: wrote the reply; and all authors: contributed to the revision of the reply and read and approved the final manuscript.

Howard D Sesso
JoAnn E Manson
Aaron K Aragaki
Pamela M Rist
Lisa G Johnson
Georgina Friedenberg
Trisha Copeland
Allison Clar
Samia Mora
M Vinayaga Moorthy
Ara Sarkissian
William R Carrick
Garnet L Anderson
For the COSMOS Research Group

From the Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA (HDS, e-mail: hsesso@hsph.harvard.edu; JEM; PMR; GF; TC; AC; SM; MVM; AS); Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA (HDS; JEM; PMR); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA (AKA; LGJ; WRC; GLA); and Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA (SM).

The COcoa Supplement and Multivitamin Outcomes Study (COSMOS) is supported by an investigator-initiated grant from Mars Edge, a segment of Mars dedicated to nutrition research and products, which included infrastructure support and the donation of study pills and packaging. Pfizer Consumer Healthcare (now Haleon) provided support through the partial provision of study pills and packaging. COSMOS is also supported in part by grants AG050657, AG071611, EY025623, and HL157665 from the National Institutes of Health, Bethesda, MD. The Women's Health Initiative (WHI) program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, and 75N92021D00005. Neither company had a role in the trial design or conduct, data collection (other than blinded assays supported by Mars Edge and completed independently), data analysis, or manuscript preparation or review

HDS and JEM reported receiving investigator-initiated grants from Mars Edge, a segment of Mars Incorporated dedicated to nutrition research and products, for infrastructure support and donation of COSMOS study pills and packaging, and Pfizer Consumer Healthcare (now Haleon) for donation of COSMOS study pills and packaging during the conduct of the study. HDS additionally reported receiving investigator-initiated grants from Pure Encapsulations and Pfizer Inc. and honoraria and/or travel for lectures from the Council for Responsible Nutrition, BASF, NIH, and American Society of Nutrition during the conduct of the study. The other authors report no conflicts of interest.

Abbreviations used: COSMOS, COcoa Supplement and Multivitamin Outcomes Study; CVD, cardiovascular disease; ITT, intention-to-treat.

References

1. Sesso HD, Manson JE, Aragaki AK, Rist PM, Johnson LG, Friedenberg G, et al. Effect of cocoa flavanol supplementation for the prevention of cardiovascular disease events: the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized clinical trial. Am J Clin Nutr 2022;115(6):1490–500.
2. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Stat Assoc 1989;84(408):1065–73.

doi: https://doi.org/10.1093/ajcn/nqac187.