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Letter to the Editor

Reply to W Willett

Dear Editor:

We appreciate the opportunity to respond to Dr Willett's comments on our 2 papers. These papers used serum and urine metabolomics profiles in a Women's Health Initiative (WHI) feeding study to propose biomarkers for the densities of total fat [1] and major fatty acid categories [2] and applied these via regression calibration in disease association studies of WHI cohorts.

The need for objective measures of dietary intake has been recognized for decades. The long-standing double-labeled water biomarker for total energy [3] reveals strong systematic biases for the food frequency questionnaire (FFQ) and other self-reported total energy assessments in WHI [4], but few biomarkers have been established for macronutrients.

Our novel feeding study design [5] attempts to fill this gap by providing food and beverages over a 2-wk period that approximated each participant's usual diet. Serum and 24-h urine metabolomics profiles were used to identify correlates of the provided diet, with a cross-validated correlation of 0.6 used as a biomarker criterion (this compares with correlations of ~0.7 for double-labeled water and energy and 0.6 for urinary nitrogen and protein). Participant characteristics were included in biomarker equations to allow for variations in metabolite response to dietary intake among subpopulations, although correlational biomarker criteria may need to adapt to such inclusions as Willett suggests. As with multidimensional regression models in other settings, multiple combinations of predictor variables may yield similar correlations, including metabolites that are negatively correlated with the targeted intake. In fact, our fat density biomarker reflects negative correlations with carbohydrate and protein densities for which metabolomics-based biomarker equations were readily developed [6]. This biomarker led to fat density estimates by calibrating FFQ fat density, yielding hazard ratio (HR) estimates for a reduction in fat density equal to the randomization group difference in the WHI low-fat diet trial. These HRs agreed with the clinical trial results, identical for invasive breast cancer [1]. The HRs reflect a low-fat dietary pattern, and as Willett notes, the HR for breast cancer was closer to the null after adjusting for variables, such as saturated fat and fiber density, that contributed to the studied low-fat dietary pattern.

Willett asks why we do not use FFQ intakes at times after the WHI baseline in our HR analyses. Although averaging estimates of intake can reduce HR attenuation resulting from random measurement error in outcome analyses that lack measurement error correction, it should be noted that our calibration procedure makes a rather comprehensive allowance for this noise component of measurement error. Also, further statistical research would be needed to adapt our calibration procedure to bring in postenrollment FFQs because FFQs were available at baseline and 3 y in the WHI Observational Study, but more frequently on a different schedule in the low-fat diet trial cohort.

When we could not directly develop a biomarker meeting the correlational criteria for total fat density [7], we turned to biomarkers for major fatty acid classes [2], for which metabolite combinations with correlations of $\geq$0.6 were identified for each SFA, MUFA, and PUFA [2]. We agree with some points raised by Willett about the potential fatty acid biomarkers that emerged, and we were circumspect in our interpretation of the resulting HRs for SFA and PUFA. As indicated [2], biomarkers need to have substantial sensitivity and specificity, in addition to substantial correlation with intake, which are both difficult to assess with high-dimensional metabolite predictors. For various reasons, including the study of comparative HRs with and without biomarker calibration, we are continuing the work on fatty acid biomarkers by focusing on specific fatty acids within the SFA, MUFA, and PUFA categories. These analyses also consider measured serum fatty acid concentrations while building biomarker models. An important study by the Fatty Acids and Outcomes Research Consortium (FORCE) examines specific serum fatty acid concentrations related to clinical outcomes [8,9], although, as the authors acknowledge, these profiles reflect both intake and metabolism, not intake alone.

The nutritional research community is still in the early stages of integrating objective measures into nutritional epidemiology disease associations, and we appreciate Dr Willett's perspectives on the considerations and refinements that may be needed to bring this important work to maturity.

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Conflicts of interest statement

RTC receives personal fees from Novartis, AstraZeneca, Pfizer Amgen, Genentech, Puma, and Up-To-Date. The other authors report no conflicts of interest.

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References

[1] R.L. Prentice, S. Vasan, L.F. Tinker, M.L. Neuhouser, S.L. Navarro, D. Raftery, et al., Metabolomics-based biomarker for dietary fat and associations with chronic disease risk in postmenopausal women, J. Nutr. 153 (9) (2023) 2651–2662, https://doi.org/10.1016/j.tjnut.2023.05.021.

[2] R.L. Prentice, S. Vasan, L.F. Tinker, M.L. Neuhouser, S.L. Navarro, D. Raftery, et al., Metabolomics biomarkers for fatty acid intake and biomarker-calibrated fatty acid associations with chronic disease risk in postmenopausal women, J. Nutr. 153 (9) (2023) 2663–2677, https://doi.org/10.1016/j.tjnut.2023.05.003.

[3] D.A. Schoeller, J.M. Hnilicka, Reliability of the doubly labeled water method for the measurement of total daily energy expenditure in free-living subjects, J. Nutr. 126 (1996) 348S–354S.

[4] R.L. Prentice, Y. Mossavar-Rahmani, Y. Huang, L. Van Horn, S.A. Beresford, B. Caan, et al., Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers, Am. J. Epidemiol. 174 (5) (2011) 591–603, https://doi.org/10.1093/aje/kwr140.

[5] J.W. Lampe, Y. Huang, M.L. Neuhouser, L.F. Tinker, X. Song, D.A. Schoeller, et al., Dietary biomarker evaluation in a controlled feeding study in women from the Women's Health Initiative cohort, Am. J. Clin. Nutr. 105 (2) (2017) 466–475, https://doi.org/10.3945/ajcn.116.144840.

[6] R.L. Prentice, M. Pettinger, C. Zheng, M.L. Neuhouser, D. Raftery, G.A.N. Gowda, et al., Biomarkers for components of dietary protein and carbohydrate with application to chronic disease risk in postmenopausal women, J. Nutr. 152 (4) (2022) 1107–1117, https://doi.org/10.1093/jn/nxac004.

[7] C. Zheng, G.A.N. Gowda, D. Raftery, M.L. Neuhouser, L.F. Tinker, R.L. Prentice, et al., Evaluation of potential metabolomics-based biomarkers of protein, carbohydrate and fat intakes using a controlled feeding study, Eur. J. Nutr. 60 (8) (2021) 4207–4218, https://doi.org/10.1007/s00394-021-02577-1.

[8] J.H.Y. Wu, M. Marklund, F. Imamura, N. Tintle, A.V. Ardisson Korat, J. deGoede, et al., Omega-6 fatty acid biomarkers and incident type 2 diabetes: pooled analysis of individual–level data for 39,740 adults from 20 prospective cohort studies, Lancet. Diabetes. Endocrinol. 5 (12) (2017) 965–974.

[9] W.S. Harris, N.L. Tintle, F. Imamura, F. Qian, A.V.A. Korat, M. Marklund, et al., Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies, Nat. Commun. 12 (1) (2021) 2329.