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Does Simplified Estimation of Total Fruit and Vegetable Intake Pave the Way for Accurate Biomarkers of the Same?

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Diet and lifestyle represent important modifiable risk factors in many chronic diseases such as obesity, type 2 diabetes, cardiovascular disease, and cancer. Much evidence on the role of diet in chronic disease is based on observational data from large cohort studies. Dietary assessment in such studies often relies on self-reported data obtained through FFQs or 24-h recalls. These methods are prone to random measurement errors and biases that cause uncertainty and risk of misleading results (1, 2). Despite the enormous development in science and technology over the past decades, it is remarkable that accurate estimation of dietary intake of individuals remains an unresolved scientific challenge. This hampers the fundamental understanding of the role of diet in health and disease and calls for complementary techniques that could provide more objective reflection of dietary intake. Biomarkers of specific food intakes or food patterns may offer such an alternative as they provide complementary, orthogonal information that could be used to improve the reflection of the intake (3). Fast development in the field of nutritional metabolomics, along with recent large collaborative scientific efforts, has led to the discovery of many putative biomarkers of commonly consumed foods and specific dietary patterns of importance to health (4). Both single-biomarker molecules and a combination of several biomarkers (biomarker panels) have been shown to reflect individual foods and dietary patterns (5–8). However, much work is still needed both to validate such putative dietary biomarkers and to develop methods for their integration with traditional and evolving methods of dietary assessment.

In the current issue of the *Journal of Nutrition*, Owen et al. (9) highlight the need for development of accurate biomarkers reflecting total fruit and vegetable intake and methods combining such biomarkers with dietary assessment that capture total fruit and vegetable intake through assessment of a minimal optimal selection of individual fruits and vegetables. As pointed out by the authors, there is compelling evidence on the beneficial role of the intake of fruit and vegetables on all-cause mortality, but the optimal daily intake remains inconclusive, which is also reflected in differences in the official dietary guidelines across countries. Further research to better understand the dose response is warranted to allow more effective public health recommendations. Access to biomarkers that accurately reflect total fruit and vegetable intake could aid such research. As a first step, the authors aimed to derive a concise (small) number of fruit and vegetables that were predictive of total fruit and vegetable intake. They suggest that such a prediction model could be used to guide the development of biomarkers of total fruit and vegetable intake, or at least of individual fruit and vegetables that together could predict total fruit and vegetable intake with high precision. Currently, no single biomarker or any biomarker panel accurately reflects the total fruit and vegetable intake, despite many attempts to come up with such (8).

To derive a useful predictive model of total fruit and vegetable intake based on individual fruit and vegetables, the authors used 4-d food diary–derived data from years 5–6 and years 7–8 of the cross-sectional intakes of the National Diet and Nutrition Survey (NDNS) rolling program (9). Data from 1746 individuals aged >11 y were used for modeling. In total, daily intakes of 96 fruits and vegetables were calculated and used as potential predictors of modeled total fruit and vegetable intake, using a forward stepwise regression approach. Three pragmatically determined selection criteria were used: a standard error of the estimate ≤80 g of a fruit and vegetable serving, variance in total fruit and vegetable intake (R^2 >0.7), and the number of predictors in the model <10.

For validation of the final total fruit and vegetable prediction model, an independent validation data set from the NDNS years 7–8 with 1865 participants aged >11 y was used. Results from predictions of total fruit and vegetable intake were compared with observed intakes using correlation analyses and Bland–Altman plots to address the agreement.

It was found that inclusion of 7 fruits and vegetables (tomatoes, apples, carrots, bananas, pears, strawberries, and onions) provided a prediction model that met the criteria and showed an excellent agreement between predicted and observed total fruit and vegetable intake ($r = 8.4$, $P < 0.001$, with 95% of the residuals within the limits of agreement from the Bland–Altman plot). This is an interesting approach to reduce the information needed to be collected through dietary assessment to simplify the estimation of total fruit and vegetable intake. However, the question is to what extent the established prediction model could be applied with similar performance in other populations and to what extent it is

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Abbreviation used: NDNS, National Diet and Nutrition Survey.

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unaffected by typical confounding factors associated with the specific fruit and vegetable intakes. A subanalysis among vegans and vegetarians showed similar performance, and this provides a positive indication about the generalizability, but the model needs to be evaluated in different populations before wider use (9).

A more pressing question is to what extent total fruit and vegetable intake represented by 7 specific food items could provide a useful route for discovery of biomarkers reflecting total fruit and vegetable intake or the individual foods that predict the total intake. This question remains unresolved in the current study, in which no biomarker data were included but useful perspectives on biomarkers were discussed.

Finding individual biomarkers or biomarker panels reflecting total fruit and vegetable intake that are robust across different populations would be attractive but is hampered by the fact the proportions of the individual fruit and vegetables vary across populations and consequently also the molecules that specifically reflect the foods. Finding specific biomarker molecules that reflect tomatoes, apples, carrots, bananas, pears, strawberries, and onions may be useful to predict total fruit and vegetable consumption in the current population but of limited use in a population where other fruit and vegetables are consumed to a greater extent. Moreover, combining already existing biomarkers of specific fruits and vegetables may be useful to improve the use of biomarkers to assess total fruit and vegetable intake, but only a few studies have so far used this approach (8).

An alternative strategy to derive potential biomarkers of total fruit and vegetable intake could be to apply untargeted metabolomics profiling on plasma or urine samples from individuals with a controlled and diverse fruit and vegetable intake. An optimal minimum number of molecules (i.e., a putative biomarker panel) that reflect total fruit and vegetable intake could be derived using machine learning such as random forest algorithms or Partial Least Squares regression. This approach has been successively used to derive candidate biomarker panels that reflect specific foods or dietary patterns in free-living individuals (10, 11), but it also needs to be validated in different populations before implementation.

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