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Editorial

Controlled dietary interventions with individual's habitual diet are warranted to shed light on the performance of dietary biomarkers

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Despite enormous advances in science during the last 50 y, accurate assessment of an individual's habitual diet remains a grand challenge. Much evidence regarding diet-disease relationships stem from observational studies where diet has been assessed by food frequency questionnaires (FFQs) that can be subject to measurement errors. Even if FFQs have been pivotal for the conduct of large prospective cohort studies paving the way for the development of nutritional recommendations globally, their shortcomings have also led to concerns about the overall quality of the evidence provided in nutritional epidemiology [1,2]. Thus, there is a great need for new complementary methods.

Dietary biomarker may represent such instruments [3]. Traditionally, dietary biomarkers have been divided into recovery biomarkers, concentration biomarkers, replacement biomarkers, and predictive biomarkers [4] but other classifications have also been suggested more recently [5]. Recovery biomarkers, such as doubly labeled water for energy expenditure and urinary nitrogen excretion for total protein intake have a special position, because they reflect the intake without being affected by interpersonal variation in absorption and disposition, and therefore could be used to study and correct for dietary measurement error in epidemiologic studies [4]. Unfortunately, only a few recovery biomarkers exist. Concentration biomarkers, on the other hand, correlate with food intake and can rank individuals with respect to food intake, but metabolism and other characteristics may affect their measured level [4]. Concentration biomarkers are typically molecules derived from specific foods or their metabolites and their concentrations are measured in plasma or other biofluids, for example alkylresorcinols in plasma reflecting whole grain intake, proline-betaine reflecting citrus fruits, etc. Most dietary biomarkers fall into this category. Rapid development in metabolomics, i.e. comprehensive analysis of small molecules in biological sample, has led to discovery of many new candidate dietary biomarkers [6]. Different validation schemes have been developed to facilitate the evaluation of their usefulness and applicability [7]. Strikingly, the correlation between biomarker concentrations and habitual intake from self-reported data are often weak to modest at best [6]. Using observational data for biomarker validation has benefits, such as reflecting real-life conditions under which a biomarker will be used, but a severe limitation is that it is difficult to disentangle to what extent poor to modest correlations with intake are because of the biomarker or imperfect measurements of the diet. Thus, high-quality feeding studies are needed for comprehensive validation of promising dietary biomarker candidates [8], but such studies are rare.

In this issue of the *American Journal of Clinical Nutrition*, Playdon et al. [9] present data from exactly such a study in a large number of participants who were provided their emulated habitual diet. Comprehensive metabolomics assessment of urine and serum were conducted to investigate how provided foods were reflected in the metabolome. The study included 153 women from a substudy of the Women's Health Initiative. Participants were provided a 14-d controlled diet designed to mimic their usual diet that was first assessed by a 4-d weighed food record and the reported intakes were provided as rotating 4-d menus. Estimated intakes of 65 food groups were averaged over the period of 14 d and used as exposure measurements. A comprehensive set of ~1300 metabolites in 24 h urine and ~1110 metabolites in serum were analyzed in samples collected at the end of the 14-d period using LC-MS/MS platforms at Metabolon Inc. Foods were correlated with metabolites adjusted for confounders and it was also evaluated whether multiple metabolites compared with single metabolites could improve prediction.

In total, ~170 Bonferroni-significant diet-metabolite correlations were found from urine and reflected 21 foods, beverages, and supplements associated with 157 unique metabolites. The corresponding number from serum was 62 diet-metabolite correlations and 55 unique metabolites. The data confirmed that a 24-h urine collection may offer a more comprehensive reflection of the diet than a serum sample, but it also showed that serum metabolites performed better than what has

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been shown in other studies. Very few studies have access to 24-h collections, and it is yet unclear how a spot urine sample would perform. Remarkably strong diet-metabolite correlations were found for citrus ($r = 0.80$), broccoli ($r = 0.63$), and dairy ($r = 0.65$) with specific metabolites. Moderate correlations were found for avocado, fish, garlic, onion, and poultry ($r = 0.5$–0.6). For beverage, the strongest correlations were found for coffee and urinary metabolites ($r > 0.85$) and for alcohol, a previously dismissed biomarker, urinary ethyl glucuronide, was shown to perform surprisingly well ($r = 0.69$). The overall strong correlations found in this study points to an important uniqueness compared with many other studies: this study had carefully controlled food intake and did not rely on self-reported assessment by questionnaires. On the other hand, the study also used averaged intakes over 14 d and the dietary assessment thus reflected the averaged controlled intake over a relatively short time window that is likely more closely correlated with food metabolites in urine and serum, which all have short half-lives. Promising biomarker candidates reflecting important foods, such as whole grain from different cereals, were not included in the commercial panels, which highlights the need for further development of metabolite panels specifically targeting diet.

The results from the study by Playdon et al. [9] may open new avenues for the use of concentration biomarkers in nutritional epidemiologic studies. Concentration biomarkers reached correlations at a similar magnitude as recovery biomarkers in previous studies [9], which raises the question whether they may be used to correct for self-reported questionnaire-based measurement errors by regression calibration, as suggested by Lampe et al. [10]. With the example of coffee, Playdon et al. [9] showed that metabolites could differentiate between preparation methods, which represent important complementary information that would be difficult to get from a questionnaire. In contrast to what has been frequently suggested [6], the study did not show stronger diet-metabolite associations for metabolite panels than for single metabolites.

In summary, the results from the study by Playdon et al. [9] clearly show stronger potential of dietary biomarkers than previous studies, but reflection of long-term habitual diet remains a challenge. Repeated sampling may be a solution, even for short-lived biomarkers. To be feasible, such an approach would require access to cheaper and simpler assays, which are yet lacking. Hopefully, the rapid development of self-sampling techniques coupled with new assays of comprehensive dietary biomarker panels could offer new possibilities to address these issues as well as allow wider use of the most promising biomarkers in nutrition and health studies.

Author contributions

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Conflict of interest

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