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The elephant in the room: using nutritional biomarker cutoffs to assess status

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The value of a nutritional biomarker rests in its ability to accurately assess the nutritional status of an individual or population. This has both clinical and public health implications. The correct identification of individuals or groups who have low or deficient status allows them to be targeted for treatment or for the design of appropriate public health interventions. Accurate assessment of nutritional status also allows for the monitoring of response to nutritional interventions over time, both at the individual and population levels. Such assessments depend on the assumptions that an intake-response relation exists between the nutrient of interest and the biomarker of status, that the biomarker can be measured reliably and accurately, and that biomarker cutoffs accurately identify individuals or groups at risk of inadequacy.

It is well accepted that different methods for analyzing nutritional biomarkers (or any biomarker for that matter) can and do produce substantially different results. A case in point is the measurement of folate status. There are a multitude of folate assays, including radioprotein-binding assays, chemiluminescence immunoassays, analytic chemistry assays, and microbiological assays, each with its own limitations and biases. Comparison studies have shown that differences between the assays can be >30%, with the degree of difference depending on many factors, including the methods being compared, the biological samples examined (e.g., plasma/serum or red blood cells), and the calibrators used, to name a few (1).

Despite intermethod differences, cutoffs for the assessment of nutritional adequacy have mostly been established by using a single method but are applied broadly in clinical and research settings. The WHO has endorsed a suite of cutoffs to assess population folate status, established with the use of 1 of 2 methods. They include folate deficiency cutoffs based on hematologic (microbiological assay) or metabolic indicators (radioimmunoassay adjusted for comparability to microbiological assay) and a cutoff for higher risk of neural tube defect (NTD)–affected pregnancies (microbiological assay) (2, 3). These cutoffs are applied to data produced from many other methods and used to estimate the prevalence of inadequate folate status or to assess folate status of individuals in the clinic.

In this issue of the Journal, Pfeiffer et al. (4) make a clear case for why the application of folate status cutoffs mismatched for the method used to produce the data being analyzed risks considerable misinterpretation. They provide illuminating examples in which the use of method-unadjusted cutoffs produces prevalence estimates of folate inadequacy that are drastically different from the method-adjusted estimates. Of note, particular subgroups within the population are more likely to be affected by misinterpretation depending on where they fall on the status distribution; for example, groups with a low prevalence of low folate status were more likely to have a larger extent of misinterpretation.

It is clear that cutoffs for folate status must be appropriately applied to accurately estimate the prevalence of nutritional adequacy. But at the end of the day, for right or wrong, researchers can only use what is available to them while acknowledging methodologic limitations. I say this from experience: I used the cutoff for NTD risk to estimate the prevalence of Canadian women of childbearing age who may be at risk of folate-responsive NTDs in Canada with data produced by using an immunoassay (5). A conversion factor has since been developed (6), but at the time I had to choose between not reporting the data or reporting the data with acknowledgment of their methodologic limitations. Studies such as mine and others are not valueless. They allow for the identification of determinants of higher or lower nutritional status, and estimates of prevalence can be interpreted with caution assuming the limitations are reported transparently.

These issues have broad implications. Public health programs and initiatives depend on accurate data to ensure that the right people are getting the right intervention. We cannot assess the effectiveness of public health interventions if we cannot accurately assess population nutritional status across time. And at the bedside, individuals may be misclassified, resulting in an inappropriate treatment of a nutritional deficiency that does not exist or the nontreatment of one that does. Until a systematic comparison of the variable and widely used methods and platforms is performed, and conversion factors are developed, the reality is that researchers will continue to use established cutoffs with the data they have, for better or worse. As a field, we have a choice: we can continue acknowledging methodologic limitations and rely on potentially inaccurate interpretation of our data or we can do something about it. Investments must be made in the pursuit

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of comprehensive method comparison studies and the derivation of intermethod conversion factors. And, in the case of methods that are egregiously inaccurate and cannot be improved, we need to make the move away from them.

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REFERENCES

1. Yetley EA, Pfeiffer CM, Phinney KW, Fazili Z, Lacher DA, Bailey RL, Blackmore S, Bock JL, Brody LC, Carmel R, et al. Biomarkers of folate status in NHANES: a roundtable summary. Am J Clin Nutr 2011;94 (Suppl):303S–12S.
2. WHO. Serum and red blood cell folate concentrations for assessing folate status in populations. Vitamin and Mineral Nutrition Information System. Geneva (Switzerland): World Health Organization, 2012.
3. WHO. Guideline: optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects. Geneva (Switzerland): World Health Organization, 2015.
4. Pfeiffer CM, Sternberg MR, Hamner HC, Crider KS, Lacher DA, Rogers LM, Bailey RL, Yetley EA. Applying inappropriate cutoffs leads to misinterpretation of folate status in the US population. Am J Clin Nutr 2016;104;1607–15.
5. Shi Y, De Groh M, MacFarlane AJ. Socio-demographic and lifestyle factors associated with folate status among non-supplement-consuming Canadian women of childbearing age. Can J Public Health 2014;105: e166–71.
6. Colapinto CK, Tremblay MS, Aufreiter S, Bushnik T, Pfeiffer CM, O'Connor DL. The direction of the difference between Canadian and American erythrocyte folate concentrations is dependent on the assay method employed: a comparison of the Canadian Health Measures Survey and National Health and Nutrition Examination Survey. Br J Nutr 2014;112:1873–81.

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