TECHNICAL NOTE

Assessing the relationship between dietary nutrient intake and nutrient biomarker data in population surveys

FEBRUARY 2024

Nutrient biomarkers are used in population surveys to assess nutritional status. Nutrient biomarkers typically collected in nutrition surveys have been termed 'concentration' biomarkers' and are not directly related to absolute nutrient intake because they are tightly controlled metabolically (National Cancer Institute a). These are different from the few 'recovery' biomarkers for nutrients, which have a direct relationship with nutrient intake and can be used as measures of dietary exposure. The relationship between dietary intake and concentration biomarkers is not simple and detecting a significant correlation between the two should not be assumed.

This brief describes the issues with assessing the relationship between dietary nutrient intake and nutrient concentration biomarkers (hereby termed biomarker) in population surveys. General issues will be described first and then four specific nutrients will be reviewed.

Using dietary nutrient intake as a predictor variable in biomarker outcome regression analyses in population surveys

Population nutrition surveys typically collect data on dietary intakes for one or two days, which is sufficient to estimate a population distribution of usual intake but not an individual's usual intake. Nutrient intakes vary from day to day in an individual. Statistical modeling is needed to use the information learned about within-person (or day-to-day) variability in the individuals with 2 days of dietary data to construct a population-level usual intake distribution that reflect only between-person variability.

However, specific statistical modeling can be done to estimate a continuous nutrient intake predictor variable for diet-biomarker regression analyses using the technique of regression calibration to correct the slope of the regression coefficient in the specific diet-biomarker model for which the intake predictor was estimated for. An important requirement is that the same set of covariates for the biomarker outcome model must be used in the usual intake model to create the predictor variable.

Intake is a Center for Dietary Assessment at FHI 360, established in 2016 with funding from the Bill & Melinda Gates Foundation. *Intake* aims to strengthen policies and programs to improve nutritional status in low- and middle-income countries (LMICs) by increasing the availability, quality, comparability, and use of dietary data. Intake provides flexible, on-demand technical assistance to governments for collecting, analyzing, and using dietary intake data for evidence-based decision-making in LMICs; develops tools and technology to facilitate dietary data collection and analysis; and carries out research to advance dietary assessment methods and develop validated metrics of diet quality.

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The NCI usual intake method and series of SAS macros can be used to conduct the usual intake modeling and estimation of the nutrient intake predictor (National Cancer Institute b). The Intake Program for Usual Diet Assessment[1] implements the NCI method and SAS macros in an integrated fashion, conducts linear or logistic regression with biomarker (or other) outcomes to estimate changes in the biomarker outcome along specified points on the usual intake distribution, and performs repeated analyses to correctly estimate variance around the estimate of the regression coefficient or odds ratio.

Issues with dietary nutrient intake–biomarker outcome regression analyses in population surveys

Population surveys are typically a cross-sectional design. While associations may be determined by cross-sectional surveys, causality cannot.

Biomarkers should be reflective of current intake of the respective nutrient to expect a potential association between the two variables. However, this is not always the case. For example, serum folate is reflective of current intake, but RBC folate is more reflective of longer-term intake (Bailey et al. 2015).

One measure of a biomarker is generally used for assessment at the individual or population level but not all biomarkers that are used for population assessment are very sensitive at the individual level, most notably zinc (King 2018). However, when examining associations between diet and biomarkers, the individual value is used and thus must be a good indicator of status at the individual level.

Biomarkers are determined by additional factors other than dietary intake that may or may not be able to be accounted for. Infections are known to affect levels of some biomarkers, notably iron and vitamin A (Namaste et al. 2020, Tomkins 2003). Absorption and metabolism in the body affects the level of biomarker in the blood and these factors vary among individuals.

Bioavailability, how much of the nutrient is absorbed and utilized by the body, can be dependent on other factors in the diet and is a known issue with dietary iron and zinc. Inadequacy of dietary iron and zinc is often more easily assessed by using a dietary requirement that has been adjusted for a presumed level of bioavailability, rather than adjusting the amount of dietary iron or zinc that is bioavailable due to lack of agreement on or availability of algorithms to do so.

Population surveys may not capture use of nutrient supplements or quantify total nutrient intakes from supplements. Supplement intake may be more likely to be associated with biomarkers given the typically higher dose of nutrients in a supplement than in food. This issue could also apply to fortification if nutrient values of foods are not accurately captured in a food composition table.

For these reasons, the expectation of detecting significant associations between dietary intake and biomarker outcomes should be tempered. If no association is found, it cannot be concluded that dietary intake is not a determining factor for nutritional status in that population.

1 The *Intake* Program for Usual Diet Assessment was developed by *Intake* to streamline the implementation of the National Cancer Institute (NCI) method to estimate usual dietary intakes of dietary components (foods, food groups and nutrients) using quantitative dietary intake data. It consists of four modules: Create Bootstrap Weights (to conduct bootstrap sampling procedures to produce confidence intervals); Distribution Run (to estimate usual intake distribution of a dietary component); Ratio Run (to jointly estimate two dietary components and a usual intake distribution of a ratio of the two components); and Regression Run (to estimate associations between usual intake of a dietary predictor and a health outcome). The *Intake* Program for Usual Diet Assessment is currently available to users upon request. The Program will be available on the *Intake* website once the accompanying User Manual is complete.

Examples of biomarkers commonly used in population nutrition surveys and their potential for association with dietary nutrient intakes

IRON

Commonly used measures of iron status in population surveys include serum or plasma transferrin receptor and serum ferritin or a ratio of the two. Serum ferritin is a measure of iron storage, although it represents only a small fraction of the body's ferritin pool it is proportional to the body's iron stores (Lynch et al. 2018). Serum ferritin is inflated in the presence of infection or inflammation, and accounting for these conditions is necessary for interpretation of serum ferritin (Larson et al. 2017). Transferrin receptor is bound to transferrin, which binds iron in the circulating plasma and extracellular tissue. The serum transferrin receptor/serum ferritin ratio may be more reliable than either measure alone and has been shown to be the most sensitive indicator of iron status following iron supplementation (Lynch et al. 2018).

Iron bioavailability depends on dietary factors, such as the form of iron and inhibitors of absorption such as phytates and polyphenols (Lynch et al. 2018). Heme iron is well absorbed, but most dietary iron is the non-heme form which has very low absorption. Several algorithms are available to estimate the amount of absorbable iron from a diet and more recently algorithms incorporate a measure of iron status (by biomarker). Issues with available algorithms include difficulty in accurately capturing all enhancers and inhibitors of absorption in dietary data, varying assumptions about the absorption of non-heme iron, development of the algorithm for one population group may not be representative of a different population, and the results have been shown to underestimate bioavailability and differ greatly using different algorithms (Lynch et al. 2018). Therefore, population assessment of adequacy of dietary iron intake typically uses an average requirement that is adjusted for assumed iron bioavailability based on characteristics of the diet such as high amounts of meat or cereal grains, thereby assuming the same level of bioavailability for all individuals in the population.

A EURRECA summary of systematic reviews of randomized-controlled trials examining impacts of iron intake on iron status reported significant effects of iron supplementation on serum ferritin and transferrin receptor (Harvey et al. 2013). One of the reviews also found effects of iron as a fortificant on serum ferritin. Iron intake in the absence of supplementation or fortification was not examined.

EFSA did not consider serum biomarkers of iron status in establishing Dietary Reference Values due to their lack of sensitivity to iron intake (EFSA NDA Panel 2015a).

The expectation of detecting significant associations between dietary iron and serum biomarkers of iron status is low.

ZINC

Serum or plasma zinc is endorsed as a useful biomarker to assess the risk of zinc deficiency in populations (IZiNCG 2012, 2018) despite that only a small amount of the total body zinc is present in circulating blood. At a population level, the prevalence of low plasma zinc and inadequate dietary zinc intakes have been found to correspond. At the individual level, the association is poor due to issues of bioavailability, metabolism, and physiological states such as pregnancy (King et al. 2016).

Several studies have found increases in plasma zinc when zinc was provided in a supplement but not when the same amount of zinc was provided in a zinc-fortified food, indicating that zinc may be metabolized differently when consumed as a food or supplement (King et al. 2016).

EFSA did not consider serum zinc to establish Dietary Reference Values due to its lack of sensitivity to dietary zinc intake (EFSA NDA Panel 2014a).

The expectation of detecting significant associations between dietary zinc and serum zinc is low.

A
Vitamin A

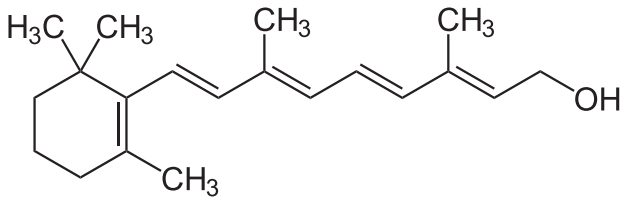
VITAMIN A

Serum retinol is commonly used as a measure of vitamin A status in population surveys, but it is under homeostatic control and reflects liver stores only when they are very low (Tanumihardjo et al. 2016). Serum retinol binding protein (RBP) correlates with serum retinol and is easier and cheaper to measure (Tanumihardjo et al. 2016). Both serum retinol and RBP are affected by infection and inflammation (Larsen et al. 2017). While liver reserves are the 'gold-standard' of vitamin A assessment given that most of the body's vitamin A is stored in the liver. The modified-relative dose response (MRDR) test is a measure of release of RBP from the liver in response to a dose of vitamin A (Tanumihardjo et al. 2016). The MRDR test is more sensitive to changes in vitamin A status than serum retinol concentrations alone. The MRDR test can be used in a randomly selected subset of individuals in population surveys.

Serum retinol remains stable across a wide range of adequate vitamin A intakes (Palmer et al. 2012). However, fortification of sugar with retinol has been shown to increase serum retinol concentrations (Arroyave et al. 1981). The MRDR test responds better in vitamin A interventions when liver reserves change from marginal to adequate (Tanumihardjo et al. 2016).

EFSA did not consider serum retinol in establishing Dietary Reference Values due to the homeostatic control and confounding factors such as infection and inflammation (EFSA NDA Panel 2015b).

The expectation of detecting significant associations between dietary vitamin A and serum biomarkers of vitamin A status is low.



B9
Folate

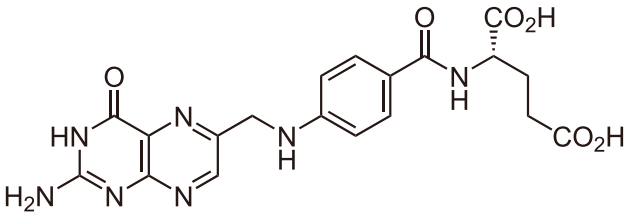
FOLATE

Serum folate reflects recent folate intake, while red blood cell (RBC) folate reflects longer term intake representing the accumulation in RBCs during their formation in the preceding 120 days (i.e., the half-life of RBCs) (Bailey et al. 2015). Both serum and RBC folate have been shown to be responsive to fortification with folic acid (Bailey et al. 2015).

An analysis of US national survey data reported that dietary folate (in dietary folate equivalents or DFE) was significantly associated with both serum and RBC folate (Bailey et al. 2017). A study of adults in Ireland reported higher correlation between RBC folate and folic acid than food folate (Hoey et al. 2007) and supports the use of dietary folate equivalents to account for better utilization of supplemental folic acid than food folate (Bailey et al. 2015).

EFSA considered serum folate and RBC folate in establishing Dietary Reference Values because they are sensitive indicators of intake and status (EFSA NDA Panel 2014b).

The expectation of detecting significant associations between dietary folate and serum folate and/or RBC folate is moderate-high.



Summary

Most common biomarkers of nutrition status used in population surveys are not directly related to dietary nutrient intake. Of the four nutrients reviewed, only folate has biomarkers that are feasible for use in population surveys and are sensitive enough to intake to be useful in establishing dietary recommendations and to have reasonable expectation of detecting associations with intakes.

If diet-biomarker regression analyses are conducted for nutrients where a relationship is expected, such as folate, appropriate statistical techniques should be applied to account for measurement error in dietary assessment.

If diet-biomarker regression analyses for other nutrients such as iron, zinc, and vitamin A are undertaken, the likelihood of finding significant associations is low. Furthermore, the interpretation is unclear, as it cannot be concluded that dietary intake of the nutrient is not a determining factor for nutritional status.

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