Best Practices for Dietary Supplement Assessment and Estimation of Total Usual Nutrient Intakes in Population-Level Research and Monitoring

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ABSTRACT
The use of dietary supplements (DS) is pervasive and can provide substantial amounts of micronutrients to those who use them. Therefore when characterizing dietary intakes, describing the prevalence of inadequacy or excess, or assessing relations between nutrients and health outcomes, it is critical to incorporate DS intakes to improve exposure estimates. Unfortunately, little is known about the best methods to assess DS, and the structure of measurement error in DS reporting. Several characteristics of nutrients from DS are salient to understand when comparing to those in foods. First, DS can be consumed daily or episodically, in bolus form and can deliver discrete and often very high doses of nutrients that are not limited by energy intakes. These characteristics contribute to bimodal distributions and distributions severely skewed to the right. Labels on DS often provide nutrient forms that differ from those found in conventional foods, and underestimate analytically derived values. Finally, the bioavailability of many nutrient-containing DS is not known and it may not be the same as the nutrients in a food matrix. Current methods to estimate usual intakes are not designed specifically to handle DS. Two temporal procedures are described to refer to the order that nutrient intakes are combined relative to usual intake procedures, referred to as a “shrinking” the distribution to remove random error. The “shrink then add” approach is preferable to the “add then shrink” approach when users and nonusers are combined for most research questions. Stratifying by DS before usual intake methods is another defensible option. This review describes how to incorporate nutrient intakes from DS to usual intakes from foods, and describes the available methods and fit-for-purpose of different analytical strategies to address research questions where total usual intakes are of interest at the group level for use in nutrition research and to inform policy decisions. Clinical Trial Registry: NCT03400436. J Nutr 2019;149:181–197.

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Introduction
Accurate nutrient exposure assessment is critical for the 2 main functions in nutritional epidemiology: characterizing the intake distributions and relating dietary intakes to health outcomes. Traditionally, studies investigating diet and health relations have failed to include nutrient exposures from dietary supplements (DS). However, more than half of US adults and one-third of children use DS and the majority of these products contain essential nutrients (1–5).

DS are defined in the US under the 1994 Dietary Supplement Health and Education Act as any product, other than tobacco, intended to supplement the diet which is not a conventional food. DS ingredients include micronutrients, macronutrients, herbs, botanicals, phytochemicals, zoochemicals, as well as many other concentrates, metabolites, constituents, extracts, or combinations (e.g., probiotics, glucosamine, and melatonin). Multivitamin-mineral (MVM) DS are the product that is most commonly used; however, no legal or regulatory definition of the term “micronutrient supplement” or MVM exists (6).

For example, different reports have characterized MVMs as products containing ≥3 vitamins, ≥3 vitamins + ≥1 mineral, and ≥9 or ≥10 total micronutrients (1, 3, 5, 7, 8).

Although the effects of DS on diet-related health promotion efforts, chronic disease prevention, and treatment remain unclear (9), it is evident that these products meaningfully contribute to nutrient exposures, providing nearly 100% of the...
Measuring DS use

Currently no standardized methods are available to assess the prevalence of use and nutrient exposures from DS. Supplement use has been measured by methods that focus solely on supplements, such as frequency-based questionnaires (FBQ), supplement inventories, and short screening tools. Their use has also been measured in conjunction with food and beverage intake, using methods such as 24-h dietary recalls (24HRs), FFQs, food diaries or records, and in some screening tools, all of which may query intake of foods, beverages, and supplements. Daily Value for some nutrients, such as vitamins C, D, E, and many of the B vitamins.

Thus, characterizing nutrient intakes from diet alone provides an incomplete assessment of total nutrient intakes and provides biased estimates of population prevalence estimates, so that nutrient-disease associations in studies may be misleading. However, there are unique challenges involved when incorporating DS-nutrients in the estimation of total nutrient intakes, particularly when usual intakes are the primary objective.

Usual or habitual intakes (i.e., long-term average daily intakes) are, in general, the most relevant nutrition indicator for research and monitoring of a population (10). Dietary recommendations are intended to be met over time because nutrients can be stored in the body, making it unnecessary to achieve nutrient intake recommendations each day (11). Long-term nutrient intake, as opposed to intake on a given day, is the ideal measure to determine whether a group or population is meeting or exceeding the Dietary Reference Intakes (12) and to determine links with health outcomes that manifest over time. However, difficulties arise when attempting to use dietary assessment methods to inform decisions about long-term, usual intake because they are prone to measurement error. Furthermore, the challenges with DS are different from those with foods; unlike foods, DS usage patterns can substantially vary over time (13). It is therefore simplistic and incorrect to assume that what is good for measuring foods is equally as good for measuring DS. Research is needed to understand the measurement error structure of usual nutrient intakes from DS, especially at the group or population level (13).

This article reviews the methods of assessing usage patterns of DS and the databases available to analyze their content, with an emphasis on the US context. Also discussed are the challenges encountered and suggested best practices for measuring and estimating total usual nutrient intakes that include the contributions of DS at the group or population level when long-term or habitual intakes are of primary interest. Mobile applications and web-based platforms have also been used to measure DS.

Little is known about the accuracy, reliability, and measurement error structure of DS assessment methods. However, consideration of the rich literature that explores and quantifies the measurement error inherent in dietary assessment and specifying the similarities and differences between traditional dietary assessment and DS assessment can inform an understanding of the error that can be expected to be inherent in DS assessment. Dietary assessment methods are subject to different types of measurement error for quantifying energy and nutrients from the diet (see section on measurement error below). The 24HR is the least-biased method to assess energy intakes from foods (i.e., inclusive of beverages) when compared to other measures, but both recalls and frequency methods underestimate true dietary intakes as assessed by recovery biomarkers (14–16). Yet, the extent and distortion that dietary and DS measurement error contribute to estimates of total nutrient intake and relation with health outcomes have not been characterized. Most 24HR methods have the ability to collect data on DS use (17). Some modules facilitate collection and coding for any DS reported, but must be used in conjunction with the assessment of foods and beverages whereas others offer a standalone method to query only DS (17). The collection of DS data as part of the 24HR adds a time burden for both the participant and interviewer. The Automated-Self-Administered 24HR has recently been used with a DS module, and was validated against a traditional 24HR over the phone (18). The Automated-Self-Administered 24HR reduces interviewer burden, allows the participant to answer questions at his or her own pace, reduces data transcription errors, and is available to the research community without cost.

Most large epidemiological studies use a FFQ to obtain information about dietary intake, and many include items on DS. However, the FFQs most commonly used in the US differ markedly in how they query DS. They inquire about different DS or product categories and use differing methods for assigning the default values for nutrients and other bioactive constituents. The DS questions on various FFQs differ from one another in the number of products listed, frequency of use responses, duration of use categories, and the dosages, making comparisons of intakes across studies difficult, if not impossible (19). Rios-Avila et al. (19) performed a qualitative examination of the specific modalities employed by some of the most widely used FFQs in large epidemiological cohorts and found tremendous variation in the way FFQs assess DS use including the Diet History Questionnaire II (20), the Harvard (Willett) FFQ (21), the 2014 Block FFQ and physical activity screener (22), the Women’s Health Initiative FFQ (23), the Vitamins and Lifestyle FFQ (24), and the Multiethnic Cohort Study FFQ and the additional supplement questionnaire used to validate the Multiethnic Cohort’s FFQ supplement data (25–27). The FFQs differed on number of DS queried with a range of 3 to 49 supplements, and the questions varied considerably on the types of DS: 1 FFQ did not ask about multivitamin with minerals, 4 did not ask about herbal/botanicals, and 2 did not ask about nonvitamin/nonmineral supplements. The “dosage” or amount of nutrients consumed were not uniformly queried, if queried at all. Considerable variation was also noted in the questions about product use duration. FFQs are particularly problematic for assessing herbs and botanical supplements because they rarely provide detail on the product and the bioactive constituents may be unknown. At present the best

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Abbreviations used: 24HR, 24-h dietary recall; DS, dietary supplement; DSLD, Dietary Supplement Label Database; DSMQ, Dietary Supplements and Prescription Medicine Questionnaire; EAR, Estimated Average Requirement; FBQ, frequency-based questionnaire; ISU, Iowa State University; NCI, National Cancer Institute; NHANES, National Health and Nutrition Examination Survey; NHANES-DDD, NHANES Dietary Supplement Database; SPADE, Statistical Program to Assess habitual Dietary Exposure; UL, Tolerable Upper Intake Level.
solution to these problems is to use a FFQ with DS questions that have been validated for the population under study.

**Issues with measuring DS use**

Many issues can arise when collecting DS data: the data may be incomplete or missing; it may be impossible to collect detailed information; only product types may be queried (e.g., MVM on an FFQ); participants may not recall desired details necessary to identify the product; and, errors may be introduced when recording information from the product label. All of these factors can prevent identifying the exact product used by a participant. In these cases, default formulations must be assigned to reported products, and the manner in which the default is chosen may introduce error.

All self-reported nutrient intake assessment methods rely on databases for estimates of nutrient content. Maintaining the currency and accuracy of DS databases is challenging because of the sheer number of products on the market (at least 85,000 products on the market at a given time) and the reformulation and rapid turnover of DS products, estimated to be about a third of products annually. Brand specificity of formulations, and even changes in the same brand over time, provide another challenge to accurate assignment of nutrient contents to reported DS. Similar issues may arise for dietary reporting if the database does not capture important differences among brands. However, the amount of error that may be introduced by matching a particular product to a more general product for DS as a default, compared with foods, has the potential to be magnified because of the vastly greater ranges in nutrient content in DS compared with foods. Thus, even if accurate information on the brand is collected through reporting, photographing of the product label, or scanning the Universal Product Code (although many Universal Product Codes are generalized and reused over time), erroneous information may still result if the product database does not include those brands or is not current.

**DS use in the US**

This section presents information on DS use obtained from nationally representative data sources and other indicators of DS use such as sales data.

**The National Health and Nutrition Examination Survey**

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative, cross-sectional Federal program of studies designed to describe the health and nutritional status of the noninstitutionalized resident population of the US (28). NHANES collects data via interviews in participants’ homes; augmented by a dietary interview and physical examination with the collection of biospecimens, such as blood and urine, in a mobile examination center; and, a follow-up telephone interview.

Data on DS use have been collected as part of NHANES since the early 1970s (4). The NHANES protocol for DS assessment includes an in-home inventory method in which participants show trained interviewers the containers/bottles of all DS that they used in the 30 d before the interview. The interviewer records information from the product label, including product name, manufacturer, strength for many single nutrient products, and form (e.g., tablet, powder, or liquid). The inventory is collected in tandem with the Dietary Supplements and Prescription Medicine Questionnaire (DSMQ), which assesses more details such as the amount typically taken, the frequency taken in the past 30 d, how long the product or a similar product was taken, and the motivation(s) for taking the product. This level of detail is quite unusual for recording supplement use, but it is critical to obtain the most accurate information, especially if the goal is to estimate an average daily exposure of nutrients from all dietary supplements taken. Since 2007, DS information has been collected as part of an additional module at the end of the interview consisting of two 24HRs, in addition to the inventory and DSMQ collected in the home. During the in-person and telephone 24HR, conducted approximately 3-10 d apart, the interviewer asks the participants if they used the products reported in the home inventory and DSMQ or any new products in the previous 24 h.

The NHANES DSMQ data indicate that estimated use of any DS has increased among adults from before to after the Dietary Supplement Health and Education Act, that is, from NHANES III (1988–1994) to the continuous NHANES (i.e., 1999 and beyond) (29, 30). Use has remained generally stable since the early 2000s with about half of US adults reporting regular use of at least 1 DS (1, 2, 3). Use of DS is lower among US infants and children than among adults, with about one-third of children (2–18 y) routinely taking them (3, 4, 31). Across time in both adults and children, MVM supplements account for the vast majority of total DS use. Limited national estimates exist on the use of DS during pregnancy and lactation, but it has been estimated that 77% of US pregnant females take a prenatal vitamin, with use being highest in the third trimester (32). Older adults are the highest users of DS across all age groups, with about 70% taking at least 1 DS and almost 30% taking ≥4 products (33). Some subgroups of the population have very high use of dietary supplements. These include athletes, members of the armed forces, and others with an interest in physical performance, those with chronic and other diseases, and users of other complementary and alternative medicines. But NHANES is unlikely to capture these specific population subgroups in sufficient numbers to make meaningful estimates.

Much less is known about DS use in NHANES from both the 24HR and the DSMQ. Including both the short term (i.e., the previous 24 h) and the long term (i.e., the previous 30 d) may provide an ideal measurement tool to ensure capturing both habitual and episodic DS use. Nicastro et al. recommend using both methods to best assess MVM use because prevalence estimates are lower on the 24HR alone than on the DSMQ in both men and women (34). The majority of those who used MVM (63%) did so daily. The results for other users seem to reflect a potential digit-preference bias because the estimated numbers of days on which supplements were used were multiples of 5 (34). Interestingly, those who used DS less frequently, as estimated from the DSMQ (1–9 d during a 30-d period), were more likely to use MVM on any given day, as estimated from the 24HR; whereas more frequent MVM use was associated with a similar proportion of use on a given day. Most MVMs (67%) were used in a 30-d period and on a given day, but a higher percentage of default values were assigned using the estimates for a given day (26%) when compared to the estimates for a 30-d period (12%) or both time periods (9%) (34). Although these findings provide some insights on methods differences for the 24HR and the DSMQ, it should be noted that the 24HR interviewer specifically asks participants...
whether he/she took a product reported in the home interview; thus, more research is needed to garner specific details of how DS reporting may differ based on method.

In NHANES, data are collected on DS of all types, but detailed quantitative estimates are made only for nutrient-containing DS. Quantitative information on intakes cannot be assessed for many other types of supplements for reasons mainly related to not having a comprehensive analytic composition database and having to rely on what is declared on the product label. These issues include lack of knowledge of what the bioactive(s) ingredients actually are, lack of analytical data on known bioactive ingredients, lack of information on the label about the amounts of the presumed bioactive(s) listed in proprietary blends, and other issues (35–37).

The National Health Interview Survey
The National Health Interview Survey (NHIS), conducted by the National Center for Health Statistics, is a nationally representative, cross-sectional, household-based survey designed to describe the health of the noninstitutionalized resident population (38). NHIS has been collecting data on the health of the US population since 1957. Whereas NHANES incorporates both examination and household interview components in a smaller nationally representative sample, the NHIS includes only a household interview with a larger nationally representative sample. This allows for an increase in the scope of the questions asked regarding DS. NHIS does not collect detailed data on DS from the product label or detailed information on the frequency of consumption or amount typically taken. Also, it does not collect dietary intake (foods and beverages). However, NHIS can be used to estimate the prevalence of use of selected types of DS. It has the advantage of a very large sample (i.e., 35,000 households containing about 87,500 persons per year), so estimates for less commonly used products are possible. As a result, the NHIS is commonly used to estimate prevalence of herbal and botanical supplements in complementary health practices.

In 2002, 2007, and 2012, the Child and Adult Alternative Health supplement module was administered in NHIS to randomly selected participants to assess nutrient and nonnutrient DS use (39, 40). The DS module is included approximately once or twice a decade as funds permit. Estimates from NHIS indicate that nonvitamin and nonmineral supplements (e.g., herbal and botanical supplements) remain the most common form of complementary health practice in adults (18.9% in 2002, 17.7% in both 2007 and 2012) (39). Although the prevalence of these general types of DS has remained unchanged over time, the specific type of nonmineral, nonvitamin DS has changed (41).

Other indicators of DS use
DS sales data are available from the Nutrition Business Journal and other sources to monitor consumer expenditures on DS. They are not useful for estimating the prevalence of DS use directly because they provide estimates in dollar amounts; thus, products with a low prevalence of use but a very high price would appear to be similar in dollars expended to products used widely with very low prices. Moreover, data are presented by marketing category, such as performance supplement or memory supplements rather than by more objective criteria. However, the data can be used to forecast trends in product types and monitor patterns in the sales of products or categories. Also, some products, such as sports bars and energy drinks that may not actually be DS from the regulatory standpoint are included in the aggregate numbers. Therefore, care must be taken in disaggregating the true DS from other products that are also listed. Sales data are released annually and provide an up-to-date barometer of changes in the marketplace. According to Nutrition Business Journal, total supplement sales in 2016 were $41.2 billion, with the majority being composed of micronutrient supplements (42).

DS Databases
High-quality DS composition databases are essential to assign nutrient values to products reported in surveys and studies (43). However, this has been and continues to be a difficult task because of the ever-evolving marketplace (44). In addition, some existing products are reformulated and others drop out of the market, complicating the currency of DS databases.

The NHANES Dietary Supplement Database
The NHANES Dietary Supplement Database (NHANES-DSD) provides information on the nutrient values of DS reported by NHANES respondents since 1999. The NHANES-DSD was developed because no freely available and comprehensive DS database existed. The database contains label information from prescribed and over-the-counter DS, nonprescription antacids containing calcium and/or magnesium (although these are not DS based on the definition provided in Dietary Supplement Health and Education Act), and default and generic formulations of products. The current NHANES-DSD provides product information for products reported in NHANES from 1999 to 2014. It includes products that may no longer be on the market or have been reformulated, thus allowing researchers to use the database to retroactively assign nutrient values for studies that were conducted in the past.

As previously discussed, many issues can arise when collecting DS data including assigning of default formulations to reported products. NHANES assigns defaults through use of the most common product formulation and the most common strength/doses. These default formations are also included in the NHANES-DSD for researchers to use when analyzing NHANES, and can be used in other studies. More information on the NHANES-DSD can be found elsewhere (45).

Dietary Supplement Label Database (DSLD)
In 2013, the Dietary Supplement Label Database, a federal effort of the National Institutes of Health, sponsored by the Office of Dietary Supplements and National Library of Medicine, was released online. This database contains labels and product information of currently marketed DS, as well as labels since 2012 of products no longer available, with the goal to eventually contain all DS marketed in the US. This important tool allows researchers to analyze data collected over various time points. The functions and potential of the DSLD are described elsewhere (46).

The Dietary Supplement Ingredient Database
Both the NHANES-DSD and DSLD provide DS composition data from labeled values. However, nutrient amounts on labels can differ from analytically derived values, especially for certain nutrients (47–49). The USDA Nutrient Data Laboratory, in collaboration with the Office of Dietary Supplements, has been working to compare the labelled amounts of nutrients to the actual amounts in products (50). This effort has included studies on products such as adult MVMs, children’s MVMs,
The Concept of Usual and Total Nutrient Intakes

As previously stated, usual intakes represent the long-term average intake patterns of a group, and are generally more salient when evaluating nutrient adequacy and excess or when examining diet and disease relations. However, it should be noted that there are certain research questions for which short-term intakes are of interest. For example, in NHANES, sodium and potassium intake from the first 24HR and blood pressure are both measured on the same day at the medical examination; thus, to assess the relation of intakes to blood pressure, where a short temporal association is assumed, usual intakes would not be of interest, rather relating recent intakes would be relevant (52). Similarly, the timing of consumption of a dietary supplement may be of interest. For example, NHANES participants who consumed folic acid during the time period when they were instructed to refrain from eating foods had much higher concentrations of the biomarker unmetabolized folic acid than those who did not take the supplement (53).

Total nutrient intakes

The phrase “total nutrient intake” refers to the concept of capturing nutrients obtained from all sources, including diet and DS. Exposure to nutrients comes not only from well-recognized sources such as foods, beverages, and DS, but may also come from often overlooked sources such as prescription drugs (e.g., niacin or ω-3 fatty acids) and over-the-counter medications (e.g., antacids), and minerals found in tap and bottled water (e.g., sodium or other minerals), all of which are captured in NHANES. It is important to capture intakes from all of these sources because they may be quite large (54–57).

Total nutrient intake estimation methods are an important research goal. Without inclusion of nutrients derived from DS, the prevalence of inadequacy may be overestimated and the prevalence of intakes above the Tolerable Upper Intake Level (UL) may be underestimated when assessing the intakes of population groups (57–62). Furthermore, characterizing total usual nutrient intake would aid understanding of how cumulative nutrition exposures can influence health and clarify the relation between nutrient exposure and health.

Challenges to Estimation of Usual and Total Nutrient Intakes

In this section we describe the types of challenges encountered in estimating total usual nutrient intakes, including those shared with diet (e.g., measurement error, skewness, various consumption patterns), as well as those unique to combining the 2 components of intake (e.g., “spikes” in the distribution from uniform dosages of DS).

Measurement error

All dietary assessment methods have measurement error that complicates estimation of usual or habitual intakes. Any deviation between measurement and “truth” (e.g., the true intake) is referred to as measurement error. This error may be either random or systematic. Validation studies evaluating self-report dietary assessment methods (e.g., FFQs, records, and 24HR) against recovery biomarkers have consistently found that diet assessment methods are subject to both random and systematic error (14, 63, 64). Both types of errors, whether associated with estimation of the intake distribution (Figure 1), or of the relations between diet and some health parameter, can bias the obtained distribution and therefore research results. However, the random error component for the 24HR contributes a larger share relative to the total error than does the FFQ, which displays considerably more systematic error. FFQs, although intended to capture longer-term intakes than the 24HR or records, are subject to systematic error for which no mitigating statistical methods have been developed. Nevertheless, even if the 24HR provides a good, relatively unbiased measure of intake on a single day, because of a great deal of random error from the variability in what people eat, it cannot provide a reliable estimate of an individual’s usual nutrient intakes or exposures unless many 24HRs on random days are averaged across days of the week and season of the year, which is generally impractical (13, 65, 66). Statistical methods to model certain characteristics of usual nutrient intakes using small numbers of replicated short-term assessments to mitigate random error, are described in detail in the section on methods for estimating usual intakes from food sources.

Biomarkers to estimate measurement error.

Recovery biomarkers exhibit a direct relation with consumed foods and beverages, but are limited to energy, potassium, sodium, and protein. Thus, our knowledge of the structure of measurement error in dietary assessment methods comes from studies using recovery biomarkers. Although less is known about how well self-report instruments measure other dietary components beyond that for recovery biomarkers (67), these findings provide additional justification for 24HR rather than FFQ as the instrument of choice for population surveys to measure foods and beverages, with the caveat that more complicated methods may need to be used in analysis to adjust for random error. However, because so little is known about measurement error associated specifically with DS at present (68, 69), it is recommended that multiple types of information be combined when possible (34, 70).

Concentration biomarkers are thought to reflect dietary intakes and can be used to compare nutrient “status” to an endpoint of interest, but they are not necessarily useful for assessing measurement error (71–73). For example, in US adults, usual total folate intakes followed the same patterns of distribution as serum and red blood cell folate indicating rank order comparability; but, less agreement was garnered when cutpoints were applied to classify risk of inadequacy (74). In contrast, unlike folic acid that is almost ubiquitously consumed in the US because of fortification, much less agreement has been observed between the biomarker (serum 25-hydroxyvitamin D) and dietary intakes for vitamin D, especially in terms of the prevalence of risk of inadequacy, potentially because vitamin D is highly concentrated in DS, is not uniformly found in the food supply, and can be synthesized from UV exposure (56, 75, 76). Many issues exist with the use of cutpoints for nutritional biomarkers and should be considered when interpreting findings such as these, as reviewed elsewhere (77).

No methods exist to estimate the bioavailability and bioaccessibility of nutrients specifically from DS (78). Issues to consider regarding bioavailability from foods, compared
with DS, differ from nutrient to nutrient, and by other factors, as reviewed elsewhere (78). Briefly, bioavailability is impacted by the dissolvability and dissolution of the actual supplement, the form of the nutrients and their matrix, timing and coadministration with foods, and many other factors. Metabolomics may be useful to future understanding of the bioavailability of nutrients from supplements (79).

**Random error.**
Day-to-day variation in intakes make it unlikely that a single day’s intake, even if captured perfectly, is a reliable reflection of habitual or usual intake. This error in within-person variability is generally thought of as a “random” or “classical” measurement error because the average of many single-day intakes for an individual is, by definition, usual intake for that individual. If assessments are subject only to random error and this error is ignored, the estimate of the variance of the distribution is inflated; this leads to estimates of inadequate or excess intake that are too high (66). Furthermore, when assessing diet-disease relations, the presence of random error leads to attenuation or other aberrations from the true relation.

Dietary intakes vary from day to day because of variation in the types of foods consumed as well as the amounts consumed. Additional random error can be introduced by, for example, estimation errors in amounts consumed or food-to-nutrient conversion errors. In contrast, DS intakes are expected to have much less random error than food intakes, if consumed almost every day. Still, random variation in DS assessment can arise from taking partial doses, changing DS formulations, or not consuming the DS on a given day.

**Systematic error.**
As opposed to random error, if a measure has “systematic” error, or bias, the average of many repeated measures does not yield an estimate of true usual intake. If usual intake is assessed using a measure that systematically under- or overreports intake of a nutrient by a fixed amount, the estimated usual intake distribution will have the correct shape but will be shifted to the left (under) or right (over) (16).

Systematic error may reflect i) general additive bias (i.e., a constant source of over- or underreporting), ii) intake-related bias, which is related to the individual’s true intake, or iii) person-specific bias, which is associated with an individual’s personal characteristics such as age or social desirability. Systematic errors at the group level are generally in the direction of underreporting (16), especially for energy intake, but systematic errors at the individual level can go in either direction. Other forms of systematic error, such as underreporting by a fixed fraction of true intake, will cause other distortions. It is important to note that additive bias that does not vary from person-to-person does not impact diet-outcome relations. For example, in a group of people who were all taking 2000 IU of vitamin D/d, the relation with vitamin D and the outcome would not be impacted by assuming they were all taking 1000 IU of vitamin D/d, as the ranking of individuals would not change. Of course, if the goal was to make an inference on the dose of vitamin D that should be consumed for health benefit, this information on actual dose would be relevant.

The impact of intake-related bias on estimating a distribution is dependent on the direction of the bias. It can be shifted left and have a narrower distribution than true intake when intakes are consistently reported as a proportion of true intakes (e.g., 10% less). In contrast it may be shifted right and have a wider distribution, when reported intakes are consistently overreported by some proportion (e.g., 10% more). Sometimes, intake-related bias and general additive bias occur together, resulting in the “flattened slope” phenomenon, where individuals with low true intake tend to overreport while individuals with high intakes tend to underreport. In such cases, the shift could be either right or left, but the effects on variance are still determined by the intake-related bias. With regard to diet-outcome relations, if intakes are proportionally underreported, then the relation between diet and the outcome will be exaggerated in various ways; if they are proportionally overreported, the relation will be attenuated. Assuming that doses are not missed (which, of course, they sometimes are), it seems unlikely that DS users would exhibit much intake-related bias, as DS doses tend to be constant over time.

**FIGURE 1** Hypothetical nutrient distributions with different types of measurement error and the impact on estimation of population prevalence (%) of meeting or exceeding the Dietary Reference Intake guidelines. EAR, Estimated Average Requirement; UL, Tolerable Upper Intake Level.
Person-specific bias has similar effects to that of random error, that is greater variability that can lead to excess estimates of the proportion of individuals in the tails of a distribution and attenuation of diet-outcome relations. It is anticipated that the types of person-specific biases for DS might be similar to that seen for foods and nutrients, but at present the magnitude and direction of reporting errors for dietary supplements is unknown.

Challenges with DS are different from those with foods; unlike foods, DS usage patterns can substantially vary over time (13). It is therefore simplistic and incorrect to assume that what is good for measuring foods is equally as good for measuring DS. Research is needed to understand the measurement error structure of usual nutrient intakes from DS, especially at the group or population level (13).

Skewness in the distribution
Distributions of nutrient intakes from foods and beverages, although generally continuous, rarely conform to a normal or Gaussian distribution and are typically right-skewed, with some people consuming large amounts. However, because the normal distribution is described by its mean and variance, and it has other desirable statistical properties, dietary data are often transformed to approximate normality for analysis. When data are right-skewed, distributions that pull in the tail are used, such as power transformations. The Box-Cox transformation is commonly used because of its equivalence with the natural log distribution for a parameter of 0. For many nutrients, simple normality transformations are effective and useful analysis tools.

The additive nature of nutrient intakes from DS can only compound the skewness phenomenon, by allowing even larger total intake amounts than would be seen from foods and beverages alone. Because nutrient intakes from DS are not constrained by energy intakes in the same way as those from foods and beverages, their contribution to skewness can be extreme. Even with the power transformation, it is typically not a normal distribution.

Spikes in the distribution
The distributions from nutrients from foods are not as dramatically spiked because most nutrients are consumed, typically from multiple food sources, with certain exceptions such as vitamin A. When considering the distributions of nutrient intakes solely from DS, individuals who do not use DS provide a “spike” at zero. Also, because the nutrient dosages in the most commonly used DS often cluster around specific amounts, such as multiples of the RDA, 100% of the Daily Value, or round numbers (e.g., 1000 mg), distributions of intakes from DS tend to be “spiky” or discrete, rather than continuous. Depending on the number, placement, and magnitude of the spikes in the DS distribution, the distribution of total intakes can be multimodal. Box-Cox or similar transformations retain these multiple modes; therefore, the transformed data will not approximate a (unimodal) normal distribution.

As illustrated in Figure 2, the raw distribution of calcium intakes from foods alone (Figure 2A) is easily transformed to approximate normality (Figure 2B). Almost all individuals in a population consume calcium from a variety of foods, but not every person uses a calcium supplement. Furthermore, unlike many nutrients that are aggregated across a large number of foods and beverages, nutrients from supplements usually come from 1 or 2 products for an individual, most manufacturers offer similar labeled doses across products (e.g., vitamin D is typically available in 400, 1000, or 2000 IU, but not 1100 IU), and individuals usually consume the same amount of them on days when they take them. These factors therefore lead to spikes in the intake distributions from supplements.

When supplements are taken at much higher doses than typically are consumed in the diet, a multimodal distribution can arise. Typical power transformations, such as the Box-Cox, can handle right-skewed data rather easily; however, a transformation cannot smooth a spike or multimodal distribution. This is illustrated in Figure 2. The calcium found in MVMs is generally around 150–200 mg, whereas a calcium supplement tends to be around 600 mg (Figure 2C). Therefore, the application of traditional power transformations will not result in a normal unimodal distribution (Figure 2D). Rather, adding calcium supplements to the food-based intakes alters the distribution, especially when they are consumed at these constant, fixed doses. In addition, when modeling supplements separately, a large spike at zero occurs when many persons in the sample do not use supplements, and this must be modeled appropriately.

Consumption patterns
DS consumption patterns differ from those of foods. Energy and most nutrients are consumed daily by nearly all people, but some foods, nutrients, or other bioactives are consumed episodically by some or many people. Nutrients found in more restricted sets of foods might be consumed episodically (i.e., not every day) by most people and never consumed by some people. Similarly, some people never use DS, and those who use DS tend to consume them daily whereas others do so only episodically. For example, people may use vitamin C episodically (e.g., when they feel ill); these 2 different supplements may be used at different times and often along with a daily MVM. In addition, just as certain foods may be consumed only when in season, some people may use DS seasonally, or perhaps only when they are ill. For example, people may use vitamin D only in the winter months.

According to NHANES data, about 70% of MVM users use them regularly (i.e., 21–30 times during a given 30-d period) (80). Among older adults (≥60 y) in NHANES 2011–2014, 84% of MVM users reported daily consumption (33). Nationally representative estimates for Canadians (aged ≥1 y) suggest that supplemental nutrients are generally consumed daily 80–86% of the time (81). Another study among a racially diverse group of older adults reported that regular use of DS over a 30-d period was more common in individuals who consumed fewer DS per day (82). In addition, some people consume multiple DS daily, which is called “stacking.” This phenomenon is common in older adults (33) and military and tactical populations (83), and can present additional challenges based on frequency and the large combinations of nutrients that can result from different products being used, especially when MVMs are combined with other single-nutrient DS.

Issues unique to combining dietary and supplement data
Measurement error, as described earlier, is a problem not only for estimating dietary intake but also for estimating intakes from DS. The combination of 2 quantities measured with different error structures presents additional challenges for estimating total usual intake distributions. Furthermore, supplement information is typically collected via a questionnaire, and the average daily exposure estimated from this assessment is added to the nutrient estimates from food. Therefore, a constant is added to each recall day. Although within-person variation is not affected by this calculation, between-person variation increases. From a biological perspective, this variation may be
FIGURE 2  Calcium intake distributions from foods (A and B) and from dietary supplements (C and D) in the original (A and C) and transformed scale (B and D).

accurate. However, because a constant value is assumed for the supplement (e.g., 400 IU of vitamin D for all supplement users), the estimate of variation may not be random enough. In statistics, this is referred to as Berkson error, where the true intake is more variable than the measured intake. In addition, adding large supplement amounts to intakes can result in “spikes” in the data. Both of these lead to difficulties in statistical modeling. When supplement intake is measured with a 24HR, the reported amount is added to each day. Although this also leads to spikes in intake amounts, Berkson error is less likely because of the more specific information on supplement formulations (e.g., some supplements have 400 IU of vitamin D, whereas others have 2000 IU), and information that is specific to a given day as opposed to an average across days.

Correlation between DS use and dietary intake.
DS contribute considerably to the intakes of individuals who use these products. Interestingly, adult DS users tend to have higher nutrient intakes from the diet alone across a range of nutrients (58, 59, 84, 85); however, this phenomenon is not seen in children and adolescents (60). In addition, use of nutrient-containing DS is associated with private health insurance, higher self-assessed health, higher educational attainment and income, more frequent exercise, and lower likelihood of smoking. This has been described previously as the “healthy user” effect, and may introduce a potential source of differential measurement error leading to confounding of associations between total nutrient intakes and health outcomes. Conversely, DS use can also be very high in certain population groups, such
as cancer survivors or those newly diagnosed with cancer (86–88).

Database considerations.
As previously described, accurate estimates of nutrients from DS rely on up-to-date products and formulas in databases. Furthermore, default values in databases are used when not enough information is collected on the products reported and may introduce an additive source of measurement error. In some cases, the number of defaults can be very large. Any deviation in nutrient estimates consumed from DS and the default value represents another source of measurement error, the type (random, intake-related, or person-specific bias) and degree of which are largely unknown.

Application of dietary reference intakes
Nutrient adequacy at the group level is typically assessed using the Estimated Average Requirement (EAR). Several nutrients have insufficient scientific evidence to determine an EAR, particularly among infants; and for these cases, an Adequate Intake has been established, defined as the amount consumed by apparently healthy individuals (89). The RDA is set at 2 SD above the EAR, and is typically used for individual level purposes. The UL is the Dietary Reference Intake value that is typically used to define intakes that are potentially excessive (i.e., the highest intake not associated with adverse effects).

Assessment of nutrient intakes from both diet and DS is essential for determining prevalence of nutrient inadequacies or excesses in a group or population. Without inclusion of DS, the population prevalence of inadequacy (i.e., < EAR) may be overestimated, and the population prevalence of intakes > UL for nutrients may be underestimated. Although DS help users to achieve the EAR, children and adults who use DS are much more likely to have exposures > UL than those who do not (54, 55, 57, 84, 90). Indeed, for some nutrients, the proportion of total intake from DS may be quite large. For example, very few foods provide vitamin D, with the exceptions of fortified milk and fatty fish; but very large amounts of vitamin D may be obtained from DS. Alternatively, for other nutrients, some individuals may get both large amounts from their diet and large amounts from DS.

The comparison of population intakes to the Dietary Reference Intake may present challenges, some of which are specific to the inclusion of DS, as illustrated by 3 examples (Table 1). First, some nutrients in foods and DS exist in a variety of chemical forms (e.g., folic acid and folate) that, given their different bioactivities, must be converted to a standard measure before total intake is determined. Second, for the nutrients folic acid, niacin (vitamin B3), and magnesium, the UL only pertain to intakes from DS and from enriched or fortified foods. In such situations, excess consumption may only be identified in a population when nutrient intakes from DS are quantified. The third example pertains to vitamin A. Food and DS labels typically list preformed vitamin A (retinol found in animal-based foods) combined with provitamin A carotenoids (found in plant-based foods). However, the UL only applies to retinol. Therefore, the combination of vitamin A forms on some product labels may not be helpful in determining the proportion of the population exceeding the UL for this nutrient (Table 1).

Methods for Examining Usual Intakes from Food Sources
As mentioned previously, because of within-person variation in dietary intake, direct assessment of usual intake would require many daily observations (36, 91). However, it is impractical to collect such large numbers of replicate 24HRs or records. For this reason, several procedures have been developed to estimate the distribution of usual intakes when only a small number of 24HRs are available per individual (92–96). These methods use statistical modeling to approximate the distribution that would be obtained by averaging many 24HRs per person.

When multiple 24HRs are not available for all people, and if a replicate is available on a representative subset, usual intake procedures can still be estimated. For example, in the 2016 Feeding Infants and Toddlers Study, one 24HR was available for all participants and a replicate recall in 25% of participants was used with the National Cancer Institute (NCI) method to produce usual total nutrient intakes (61, 97). When only one 24HR is available, it is possible to use external estimates variance components from a different, but similar group as has been done with different cycles of NHANES data with the Iowa State University (ISU) method (98). This concept of “borrowing” variance components has also been used to adjust biomarker data from various cycles of NHANES (99, 100).

Usual intake methods vary considerably in their complexity, strengths, limitations, and fitness-for-purpose, and they are reviewed in depth elsewhere (66, 95). These methods, typically applied to data from food frequency questionnaires, generally assume that (1) 24HRs are generally assumed to have random error, and (2) transformations to correct for skewed data will result in normal distributions. Assumption 1 implies that the average of 24HR intakes approximates the mean of the usual intake distribution, but the distribution of intakes from one 24HR per person has more spread than that of the usual intake distribution.

The underlying framework of all of the usual intake methods is illustrated in the 4 panels of Figure 3. The distribution of the nutrient exposure from a single day is typically skewed to the right and needs to be transformed to approximate normality (the process from panels A → B). Transformed single-day intakes are assumed to arise as the result of adding a normally distributed within-person error term to a normal distribution that exhibits between-person variation. After estimating the within-person and between-person variance components, the within-person variability is removed, “shrinking” the distribution of the data. Shrink is the term used because the tails of the usual intake distribution are pulled in closer to the mean relative to the unadjusted distribution with random error (see Figure 1 (B1)). Next, the normal distribution, reflecting only between-person variance (Figure 3C), is used as the basis for the remaining step, where a “back transformation” derived from the initial normality transformation and the within-individual variance component, is applied to approximate the distribution of usual intakes in its original, conventional units (the process from Figure 3C→D). In this way the data can be used in the scale which they were collected to provide meaningful comparisons and descriptions. Note that only the top 2 panels in Figure 3 represent actual observations; the bottom 2 are based on a hypothetical normal distribution with estimated mean and variance. Estimation of this hypothetical distribution is operationalized by randomly generating 100 simulated individuals for each sample person, sometimes referred to as “pseudo-people,” to determine true intakes for the population with this mean and variance. To accommodate more complex modeling, involving covariates (see below), this simulation approach uses each sample person as the basis for simulated intakes for pseudo-people, which now reflects the usual intakes at the population level based on the distribution of covariates in the population as sampled. The real people represent the real distribution of covariates that exist overall. Thus, it is the population distribution of usual intakes that is estimated from this approach, rather than the distribution of usual intakes for particular individuals.

The first such approach, developed by Beaton, was proposed in 1986 and published in a report by the National Research Council (92). Future, independent iterations permitted different transformations and included
covariates in the models (see below). These include the bias-corrected best power method, ISU Method, the NCI Method, the European Food Consumption Validation Consortium’s Multiple Source Method, and the Statistical Program to Assess habitual Dietary Exposure (SPADE). Currently the ISU and NCI methods are most frequently used by researchers in the US, and SPADE and the Multiple Source Method are more frequently used in Europe. The ISU method is implemented as a standalone program that can run on Linux or Windows operating systems; whereas the NCI method is implemented in sets of macros that require the SAS software. The Multiple Source Method is accessed through a dedicated website that performs analysis of user-uploaded data, whereas SPADE was developed for use with R software.

Some of the methods described above can also be of use when interest centers on relating some outcome to (unobservable) usual intake. Using an error-prone measure (e.g., a single 24HR) as a surrogate for usual intake in a (linear, Cox, or logistic) regression model produces biased estimates of the relations between intake and outcome. Some of the usual intake software implementations can produce inputs to a regression program that yield (approximately, in all but the linear case) unbiased parameter estimates when they are used as the predictor variable. It is crucial to note that these inputs are not intended to approximate individual usual intakes, and thus should not be used to make judgments about particular individuals.

All of the usual intake methods mentioned above can be applied to analyze a single dietary component consumed nearly every day by almost all members of a population. Some of the methods can also handle analysis of an episodically consumed dietary component, where a sizable fraction of the observed data is zero (i.e., no intake is reported). For such analysis, usual intake is conceptualized as the product of the probability to consume on a given day and the usual amount consumed on reported intake days.

Covariates

The ability to explicitly incorporate covariates into usual intake models is a very powerful addition to usual intake methods that is particularly important when considering DS use. Covariates are generally incorporated into the model for 3 purposes (94). First, they can be entered to account for factors that may affect intake, such as day of the week (commonly weekday compared with weekend). Second, nuisance effects, such as sequence effects or data collection modality of the 24HRS, may also be used as covariates to mitigate their effect. Finally, they may be used to account for individual level effects, such as sex-age groups or supplement consumers compared to nonconsumers.

Methods for Examining Total Usual Nutrient Intakes

Extensions of the usual intake models from foods, as described above, make it possible to estimate not only the group means, but also the distribution of total usual nutrient intakes inclusive of DS. These models are appropriate for estimating total usual intakes at the group level because they more accurately reflect the true distribution of intakes. They can also accommodate additional goals, such as estimating the proportion of the population meeting or exceeding certain Dietary Reference Intake cutpoints or for estimating intake at certain percentiles of the population distribution.

The methods that exist for incorporating nutrient intakes from DS with nutrient intakes from foods and beverages are provided in Table 2. Methods exist to examine populations with users and nonusers combined as a group as well as users and nonusers divided or stratified by DS use. The method of choice is dependent on the research question or the purpose of the analysis and the dietary assessment method. The models presented here are intended to be used at the group level. This section describes the available methods for estimating total usual intakes evoking the 24HR and DSMQ that are available from NHANES 2007 and beyond; but these methods can be applied with different data sources. These assumptions are commonly associated with the methods that may not consistently be found: 1) reported nutrient intakes from food source from 24HRS are unbiased, meaning that they capture usual intake with only random error; 2) self-reported DS intake reflects true long-term DS intake; and, 3) label declarations on DS and database estimates are accurate.

Group mean method

The group mean method refers to the calculation of the mean of the added nutrients from DS and adding them to nutrient intakes from foods without the use of usual intake procedures. This is only

### Table 1: Nutrients that have special considerations when applying the DRI framework

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Conversion factors</th>
<th>EAR, AI</th>
<th>DRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (retinol and provitamin A carotenoids)¹</td>
<td>1 IU retinol = 0.3 μg retinol or 0.3 μg RAE</td>
<td>Includes retinol, α- and β-carotene, and β-cryptoxanthin</td>
<td>Only retinol from all sources</td>
</tr>
<tr>
<td>Vitamin E²</td>
<td>1 IU = 0.67 mg for α-tocopherol (natural form)</td>
<td>For α-tocopherol alone (the single form that occurs naturally in foods and the 4 stereoisomeric forms that occur in fortified foods and supplements)</td>
<td>Applies to all forms of α-tocopherol, including the 8 stereoisomers present in synthetic vitamin E</td>
</tr>
<tr>
<td>Folate, folic acid</td>
<td>1 μg DFE = 1 μg food folate = 0.6 μg folic acid from fortified foods or supplements consumed with foods = 0.5 μg folic acid from supplements taken on an empty stomach</td>
<td>Includes DFE from all sources</td>
<td>Only DFE from fortified foods and supplements (which is in the form of folic acid)</td>
</tr>
<tr>
<td>Niacin vitamin B3</td>
<td>1 mg (NE) = 1 mg niacin = 60 mg tryptophan</td>
<td>Includes NE from all sources</td>
<td>Only niacin from fortified foods and supplements; listed in mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>None; ensure database provides amount of elemental magnesium</td>
<td>Includes magnesium (mg) from all sources</td>
<td>Only magnesium from supplements and pharmacological agents</td>
</tr>
<tr>
<td>Calcium</td>
<td>None; ensure database provides amount of elemental calcium</td>
<td>Includes calcium (mg) from all sources</td>
<td>Calcium from all sources, including food, supplements, water, and pharmacological agents (such as antacids)</td>
</tr>
</tbody>
</table>

¹ AI, Adequate Intake; DFE, dietary folate equivalents; DRI, Dietary Reference Intake; EAR, Estimated Average Requirement; NE, niacin equivalents; RAE, retinol activity equivalents; UL, Tolerable Upper Intake Level (12).

² New labels on foods and dietary supplements that become mandatory in 2020 will replace the measure of vitamin A in IU with μg RAE and the measure of vitamin E in IU with mg.
appropriate when the goal of the analysis is to estimate the mean intake of a group. For NHANES analysis, to estimate the population mean total intake, we recommend adding the average nutrient intakes from food sources to the average intake of nutrients from DS. Ideally the DS nutrients should be used from the DSMQ because the reported DS use is lower on the 24HR than that of the DSMQ (34), and the DSMQ captures use in a more rigorous way (i.e., home inventory) and thereby facilitates estimation of episodically consumed DS. Ignoring the DSMQ data and relying only on 24HR will introduce an unquantifiable source of bias. For example, if a person uses a calcium supplement 15 of 30 d/mo, it is conceivable that that calcium supplement may or may not be consumed on the day(s) the 24HR is performed. Problems also arise when the frequency data on DS use are not collected at all. Indeed, many researchers only have 1 or 2 d of 24HR, so decisions must be made on how to calculate the average nutrient intake from DS in such circumstances. In this scenario, imputation techniques, such as hot deck (101) or sequential regression tree (102), should be considered to estimate the group nutrient intakes from DS.

The Group Mean Method can be applied with both the combined and stratified approaches. However, this method is not without limitations and, as such, researchers should acknowledge potential bias in the interpretation of their results and consider how it may have an impact on application of the findings. With only a limited number of 24HRs or records, it is difficult to accurately assess nutrient intakes from episodically consumed DS. Finally, this method assumes that intakes measured from both sources are unbiased, which is generally not the case. Therefore, it is always preferred to use usual intake procedures if they are available.

**Group distribution methods**

When the total usual intake distribution is the primary goal for analysis, rather than just a group mean, it is necessary to move beyond the Group Mean Method and incorporate usual intake procedures. Two temporal procedures have been described to refer to the order in which nutrient intakes are combined relative to the usual intake procedures, referred to here as a “shrink” to the distribution (81). The available methods that exist to estimate usual total intake distributions will be described in this and the following sections: the combined “shrink then add” method, combined “add then shrink” method, the stratified “add then shrink” method, stratified “shrink then add” method, and a 3-part method, which is a hybrid of combined and stratified methods.

**Combined method: shrink then add.**

The preferred application of the combined group approach, in which users and nonusers of DS are analyzed together as 1 group, is referred to as the “shrink then add” framework and incorporates DS use as a covariate. In this method, the nutrients from food sources are first processed through the usual intake procedures for the entire sample, employing an indicator variable for reported supplement use (i.e., user or nonuser) from the DSMQ or a FBQ, if available. Next, an “adjustment” incorporates the estimated usual intakes of DS to the adjusted distribution of nutrients from food sources to produce a final...
distribution of usual total nutrient intake. This adjustment occurs after the model parameters are estimated, during the generation of “pseudo-
people.” Then, in the second step after the pseudo-people are generated, each will have a designation from their covariate as to whether or not they are supplement users. If they are supplement users, then the supplement use from the DSMQ is added to each pseudo-person based on covariates employed.

The “shrink then add” combined approach guarantees that the estimated mean of usual intake will recover a similar mean for the Group Mean Method (81). In addition, with this method, the prevalence of usual intake < EAR from food sources alone is always greater than or equal to the estimated prevalence of usual intake < EAR from foods and supplements, which in theory should always be the case (103).

The “shrink then add” combined approach, when applied to methods that use covariates, has 2 advantages that are salient for nutrients from DS. First, it allows for different means of subpopulations to be generated while pooling information about the variance components. This is critical because some (58, 59, 84, 85, 104) but not all reports (60, 105) suggest that DS users have higher intakes of nutrients from their diets alone than nonusers. Using this method, adding nutrient intakes from supplements after adjusting the nutrient intake distribution from foods, allows for less-complicated transformations in the usual intake procedures. By avoiding creation of data that violate key assumptions of the shrinkage methods, the “shrink then add” approach is thus preferable to “add then shrink” (81).

Combined method: add then shrink.

The “add then shrink” technique, in which intakes from foods and DS are added together before shrinkage methods are applied, may not be the correct application at the combined group level and employing it may yield inconsistent population distributions and may evoke a similar group mean to exist for users and nonusers of DS (81, 103). The “add then shrink,” although easier from a programming standpoint, tends to create a bimodal distribution (1 mode for users and 1 for nonusers) that cause the shrinkage methods (i.e., usual intake procedures) not to perform as expected because these methods assume a unimodal distribution. Furthermore, “add then shrink” can cause a dramatic widening of the range of the distribution as well as introduce spikes, which impacts the estimate of between-person variation in intake causing it to be too large because the modes artificially inflate the variance. As a result, the “add then shrink” method does not guarantee that the mean will match the Group Mean Method or that the prevalence < EAR from food sources will be ≤ prevalence from foods and supplements because of the possibility of dramatically different estimates of within- and between-person variance components in the “before-” and “after-summation” data sets. When this distribution is widened, it results in a greater prevalence of intakes < EAR if a covariate for DS use is not employed (106).

When you stratify users and nonusers this problem is eliminated; however, the use of DS as a covariate to the “add then shrink” method, may in some circumstances, also alleviate this problem.

The choice of when to use DS use as a covariate and when to stratify users and nonusers into 2 groups for analysis depends on many factors, including, but not limited to, the sample size, the proportion of the group that uses DS, and the variance components of nutrient intakes from food sources, which can vary from nutrient to nutrient. If the food source variance components are similar, use of the indicator variable from DS is appropriate; however, if the variance components are different, examining users and nonusers with the stratified method is appropriate.

### Stratified methods.

Stratifying refers to dividing the group into supplement users and nonusers before applying the usual intake methods. Researchers often examine users and nonusers of DS as 2 different groups because their nutrient intakes from food sources can differ. This model has the advantage that the nutrient intakes from the 2 sources (food and DS) can be distinguished, given the data are good enough (e.g., not too many nonconsumers, that is, the “zero inflation” is not too large) (107, 108).

For nonusers, because the group is stratified, estimating usual intakes does not differ from the foods alone procedures outlined above. For “users,” the safest approach to produce total usual intakes is to proceed with the “shrink then add” approach (81). However, when examining users and nonusers as 2 distinct groups, DS can sometimes be added to the nutrients from foods before usual intake procedures (i.e., “add then shrink”) depending on the sample characteristics (81).

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**TABLE 2** Analysis strategies and details for methods available to estimate total usual intakes inclusive of nutrients from all sources

<table>
<thead>
<tr>
<th>Analysis strategy</th>
<th>Group Mean Method</th>
<th>Combined method</th>
<th>Stratified method</th>
<th>Hybrid method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add average 24HR food source intake to average DS intake OR Add DS intake to each 24HR food source intake, then average</td>
<td>Add nutrient intake distribution from food source first and then add usual DS intake</td>
<td>Adjust nutrient intake distributions separately for DS users and nonusers</td>
<td>For DS users, jointly model food source intake and DS frequency from respective 24HRs, add modeled DS dose to adjusted food source intake, for DS nonusers, just adjust food source intake.</td>
<td></td>
</tr>
<tr>
<td>DS assessment</td>
<td>DS FBQ and/or DS amounts from 24HR</td>
<td>DS FBQ and/or DS amounts from 24HR</td>
<td>DS FBQ and/or DS amounts from 24HR</td>
<td>N/A</td>
</tr>
<tr>
<td>Shrinkage procedure</td>
<td>N/A</td>
<td>Shrink then add OR Add then shrink</td>
<td>Shrink then add OR Add then shrink</td>
<td>DS user/nonuser questionnaire, plus DS amounts from 24HR</td>
</tr>
<tr>
<td>Strength Limitations</td>
<td>Simplicitic</td>
<td>Covariates</td>
<td>Covariates</td>
<td>Covariates</td>
</tr>
<tr>
<td>Limitations</td>
<td>Cannot be used to assess the population distribution intakes (i.e., &lt; EAR or &gt; UL)</td>
<td>Frequency information may not be available to include as a covariate in some data sets</td>
<td>Separate estimation for DS users more likely (but not guaranteed) to meet assumptions</td>
<td>As with stratified model, with added complexity and possible instability of joint modeling</td>
</tr>
</tbody>
</table>

124HR, 24 hour dietary recall; DS, dietary supplement; FBQ, frequency-based questionnaire that captures frequency and type of dietary supplements.

2The preferred assessment is always a frequency-based method.

3Depending on sample characteristics.

4Add then shrink should only be used if a covariate is sufficient to reduce the bimodal distribution.

5This method has not been used with the NHANES data.

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124HR, 24 hour dietary recall; DS, dietary supplement; FBQ, frequency-based questionnaire that captures frequency and type of dietary supplements.
Three-part method.

A 3-part mixed effect extension of the “shrink then add” approach, developed using a modified NCI method, is currently available in R but not in SAS (106). This model estimates and combines the usual intake distributions from food alone among nonsupplement users (part 1), food alone among supplement users (part 2), and nutrients from DS obtained from a frequency questionnaire with imputed doses from the nutrient distributions from 24HR (part 3).

The 3-part model may be thought of as combining elements from the combined and stratified methods. Similar to the combined “shrink then add” approach and stratified method, it separates DS users from nonusers. In this case, DS users are defined as those who either report intake on a frequency questionnaire in the past 30 d or report intake on nonusers. In this case, DS users are defined as those who either report intake on a frequency questionnaire in the past 30 d or report intake on nonusers. Parts 2 and 3 are modeled jointly, allowing correlation between nutrients from food sources and DS sources (106). Part 1 can be modeled using the food sources methods described above to obtain a distribution of usual intake for pseudo-people who are DS nonusers. Parts 2 and 3 are modeled jointly with correlated random effects to obtain a distribution of pseudo-people with predicted nutrient intake from food sources and probability of DS use on a given day. The amount of DS use is assumed to be known; specifically, Verkaik-Kloosterman et al. used the mean of DS consumption days to estimate the amount (106). This value was then multiplied by the probability of supplement use, and added to nutrient intake from food sources to obtain total nutrient usual intake distributions for DS users. Finally, percentiles of total nutrient usual intake for the whole population were obtained from the full set of distribution data for nonusers and users. Because 100 pseudo-people are generated for each actual person in the data set, the proportions of users and nonusers are represented in the full data set. The same or different covariates can be added to each part of the model.

Choosing between models

There is no one “right” method to model total usual nutrient intakes at the group level. Whatever method is chosen should be driven by the research question and is dependent on the sample characteristics, total sample size, and proportion of that sample that is using DS. The study of a large sample with many supplement users should include a plan with strategies to estimate total usual nutrient intakes, while understanding the caveats that exist (Box 1). By avoiding creation of data that violate key assumptions of shrinkage methods, the “shrink then add” approach is preferable to “add then shrink.”

Text Box 1.

Caveats with dietary supplements (DS)

- There is tremendous variation in the dietary assessment methods used for DS.
- Assessments for DS may query usage over a time period different from those for foods.
- No single comprehensive analytical database exists; this is an ever-evolving marketplace.
- Nutrient amounts in DS databases rely on label declarations, which have varying accuracy and tend toward overages.

- Default product types are typically assigned (depending on assessment method), which may or may not accurately reflect the nutrient content estimates.
- Dissolution and dissolvability are not equivalent to bioavailability, which can bias exposure estimates.
- The form (unit) on the DS label can differ from those of foods.
- Limited database values are available for botanical and herbal DS.
- DS can be consumed daily, episodically, or seasonally.
- Some users take multiple DS with varying frequencies.

In general, the “shrink then add” procedure is the preferred approach for estimating total usual nutrient intakes with the combined group approach. Separation of users from nonusers mitigates some of the issues that can occur when DS amounts are added to the nutrients from foods before usual intake procedures (i.e., the “add then shrink” procedure). However, even with this separation, it is important to proceed with caution and to examine the group characteristics before using the “add then shrink” method.

Figure 4 compares the Group Mean Method (i.e., no adjustment) with the combined and stratified group approach for both the “add then shrink” and “shrink then add” procedures through use of the NCI method to estimate calcium intake among 14–18-y-old girls from NHANES 2007–2008 (11). The mean intakes from users and nonusers combined are generally consistent for all 3 approaches; however, the “add then shrink” procedure forces the group means to be similar, resulting in the same total mean intake for those who take and those who do not take calcium supplements, and, as a result, produces similar prevalence of the group < EAR. Importantly, the Group Mean Method (i.e., “no adjustment”) overestimates the proportion < EAR for the group and for DS users because there is no adjustment for the random error of within-person variation. Although each nutrient behaves differently, it should be noted that this phenomenon has also been observed for vitamin D (106) and vitamin C (81).

The “shrink then add” approach at the combined group level, when applied to methods that use covariates, has 2 advantages that are relevant for nutrients from DS. First, it allows for different means of subpopulations to be generated while pooling information about the variance components, which is salient because DS users tend to have higher nutrient intakes from their diets alone than nonusers. Using this procedure, adding nutrient intakes from supplements after adjusting the nutrient intake distribution from foods, allows for less complicated transformations. The “shrink then add” procedure has been used with the NCI method in NHANES, incorporating research-specific covariates, such as income and DS use, at the combined group level (62).

However, it should be noted that few methods comparisons have been published comparing usual intake methods with inclusion of nutrients from DS with the NCI method; but, the ISU and SPADE reports have issued similar recommendations as we do for the NCI method (81, 106).

Summary and Conclusions

Assessment of nutrient intakes from both diet and DS is essential for determining prevalence of nutrient inadequacies or excesses in a population and for estimating true exposures to relate to health outcomes. However, currently no standardized methods are available to assess the prevalence of use and nutrient exposures from DS. Researchers and policymakers should be aware that when comparing estimates of DS and MVM use between NHANES and other studies, important differences in methodology and product definitions can impact those prevalence estimates obtained (5). FBQs and FFQs vary considerably on the types/brands and frequency of consumption questions from 1 questionnaire to another, making comparisons difficult if not impossible (19). Furthermore, online surveys...
for assessing DS use tend to report much higher prevalence estimates when compared with NHANES (109, 110).

This review described the major challenges that should be considered when estimating usual total nutrient intakes, including DS, in research studies; described statistical approaches that have been used; and offers a lessons-learned approach to help researchers handle many issues that may arise when working with DS data. Understanding the major challenges in working with DS will provide insights to improving methods to estimate usual total nutrient intakes. Challenges with supplements differ from those with foods so we cannot simplistically assume that what is good for measuring foods is equally good for measuring DS. Furthermore, the measurement error from traditional dietary assessment for foods and beverages (e.g., energy underreporting, difficulty in estimating portion size, and issues of social desirability) is likely to differ considerably from error in measuring DS use. DS add nutrients to the diet that are not bound by energy intakes, leading to severely skewed multimodal distributions with spikes corresponding to discrete doses delivered in DS, complicating traditional methods to estimate usual intakes.

Future directions
Future directions in this field should include studies to identify and characterize the structure of measurement error of nutrient intakes from DS. Standardized FBQs are needed both as standalone DS assessment methods, but also as part of FFQs. Comprehensive databases with analytically derived values are also needed, and best practices for the appropriate handling of assigning default values are critical; this is especially important for FFQ and FBQ methods of DS assessment. Examination of the total usual intake methods discussed should be further investigated for nutrients beyond what has been observed for calcium, vitamin D, and vitamin C. Future work should also seek to develop new methods to estimate total usual nutrient intakes at both the group level with both combined and stratified approaches. In that vein, the previous models developed to incorporate episodically consumed foods (107, 108), conditional on being a consumer, may possibly be applied to a DS.

Finally, a note of caution, because so little is known on properties and measurement error associated specifically with DS at present, it is simply premature to assume that the use of 24HR alone without a FBQ is sufficient to adequately capture DS use. Challenges with DS are different from those with foods, thus it is inappropriate to assume that best practices from measuring foods and beverages are equivalent for measuring DS.

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