

# Use of the Predictive Sugars Biomarker to Evaluate Self-Reported Total Sugars Intake in the Observing Protein and Energy Nutrition (OPEN) Study

Nataša Tasevska<sup>1,2</sup>, Douglas Midthune<sup>3</sup>, Nancy Potischman<sup>1</sup>, Amy F. Subar<sup>1</sup>, Amanda J. Cross<sup>2</sup>, Sheila A. Bingham<sup>4</sup>, Arthur Schatzkin<sup>2</sup>, and Victor Kipnis<sup>3</sup>

## Abstract

**Background:** A *predictive* biomarker for intake of total sugars was recently developed under controlled conditions. We used this biomarker to assess measurement error (ME) structure in self-reported intake of total sugars in free-living individuals.

**Methods:** The Observing Protein and Energy Nutrition (OPEN) study involved 484 participants aged 40 to 69 years. Diet was assessed using two administrations of a food frequency questionnaire (FFQ) and two nonconsecutive 24-hour dietary recalls (24HDR). Two 24-hour urine samples checked for completeness were analyzed on sucrose and fructose. We applied the biomarker calibrated in a feeding study to OPEN data to assess the ME structure and the attenuation factors (AF) for intakes of absolute total sugars and sugars density for the FFQ and 24HDR.

**Results:** The AFs for absolute sugars were similar for a single FFQ and 24HDR, but attenuation decreased with repeated 24HDRs. For sugars density, the AFs for FFQ (men: 0.39; women: 0.33) were greater than for single 24HDR (men: 0.30; women: 0.24), and similar to two 24HDRs (men: 0.41; women: 0.35). The attenuation associated with both instruments was greater in women than in men.

**Conclusions:** Both the FFQ and 24HDR were found to be biased; hence, incorporation of the sugars biomarker in calibration studies within the cohorts may be necessary to more reliably estimate associations of sugars and disease.

**Impact:** In this article, we propose a new dietary reference instrument based on the recently defined class of *predictive* biomarkers. Using sugars biomarker, we quantify ME in the FFQ- and 24HDR-reported absolute total sugars and total sugars density. *Cancer Epidemiol Biomarkers Prev*; 20(3); 490–500. ©2011 AACR.

## Background

Positive associations between sugars and cancer have long been postulated in nutritional epidemiology (1), yet difficult to study, due to unreliability of self-reported intake. Measurement error (ME) associated with self-reported added sugars, which are particularly prone to misreporting (2–5), may substantially distort estimated

disease risk and reduce statistical power to detect an effect (6). Wide recognition of the problem of ME in self-reported diet (7, 8) has raised interest in development and use of dietary biomarkers (9–11), which are objective measures of intake that do not depend on a person's capacity or motivation to accurately report their diet.

In the late 1990s, Kaaks and colleagues (12) defined 2 classes of dietary biomarkers: *recovery* and *concentration* biomarkers. *Recovery* biomarkers are based on a "known quantitative relationship between intake and output" (16) over a certain period of time and therefore qualify as reference instruments in validation/calibration studies, given that they can be translated into absolute estimates of intake. Unfortunately, only few recovery biomarkers have been identified so far, including 24-hour urinary nitrogen for protein intake (13), doubly labeled water (DLW) for total energy intake (14), and possibly 24-hour urinary potassium for potassium intake (15). *Concentration* biomarkers measure concentrations of specific compounds in blood, adipose, or other tissues (e.g., serum carotenoids or vitamin C, adipose tissue fatty acids, etc.; ref. 12). These biomarkers "do not have the same

**Authors' Affiliations:** <sup>1</sup>Applied Research Program, Division of Cancer Control and Population Sciences, <sup>2</sup>Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, and <sup>3</sup>Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; and <sup>4</sup>MRC Dunn Human Nutrition Unit, Cambridge, United Kingdom

Dr. Sheila A. Bingham sadly passed away on June 15, 2009.

Dr. Arthur Schatzkin sadly passed away on January 20, 2011.

**Corresponding Author:** Nataša Tasevska, Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, 6130 Executive Blvd, EPN/3121, Bethesda, MD, 20892. Phone: 301-496-8550; Fax: 301-435-3710. E-mail: tasevskan@mail.nih.gov

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quantitative relationship with intake for every individual in a given study population" (16). In addition, they do not have a time dimension, and their between-subject variation "is generally determined not only by dietary intake of a given compound, but also by variations in digestion and absorption, distribution over body compartments, endogenous synthesis and metabolism, and excretion" (16). Thus, although concentration biomarkers are correlates of dietary intake, it is not yet clear how to use them in validation/calibration studies, even though when combined with dietary measures, they were shown to help in the investigation of diet–disease relationships by increasing the statistical power to detect an effect (17).

Recently, the sum of urinary sucrose and fructose in 24-hour urine was proposed as a dietary biomarker for total sugars intake on the basis of data from 2 feeding studies (18). In the study of constant diets, the biomarker responded to intake in a dose–response and time-sensitive manner, and in the habitual diet study, the 30-day mean of the biomarker was highly correlated with 30-day mean of intake of total sugars ( $r = 0.84$ ). Yet, the overall urinary recovery of the sugars ( $\sim 0.05\%$  of intake) was much lower than that for 24-hour urinary nitrogen or potassium (both  $\sim 80\%$  of intake). Given that the sugars biomarker showed more complex relationship with intake than with recovery biomarkers, but, unlike concentration biomarkers, its relationship with intake was much stronger, relatively stable, time-related, and sensitive to intake in a dose–response manner, the authors proposed a new class, which they called *predictive* biomarkers (18). To our knowledge, the sugars biomarker is so far the only member of this class, and its statistical modeling for validation/calibration purposes has not yet been defined.

This article has two aims. First, we propose a novel ME model for *predictive* biomarkers. With the parameters of the model estimated from feeding studies, the *predictive* biomarker can be calibrated to meet the requirements for a reference instrument in validation/calibration studies. Second, we apply this novel ME model to the urinary sugars biomarker to investigate misreporting of intake of total sugars in the Observing Protein and Energy Nutrition (OPEN) study (19). Under the assumption that the urinary sugars biomarker conforms to the ME model for *predictive* biomarkers, we first use data from the feeding study in which this biomarker was developed to estimate the model parameters and to calibrate the biomarker. Then, we apply the calibrated biomarker in the OPEN study to estimate the ME structure and the attenuation related to intakes of absolute total sugars and total sugars density reported on a food frequency questionnaire (FFQ) and 24-hour dietary recall (24HDR).

## Material and Methods

### Feeding study

The development of the sugars biomarker in the feeding study is described elsewhere (18). Briefly, the feeding

study was a 30-day intervention applied to 7 men and 6 women aged 23 to 66 years residing in a metabolic suite under strictly controlled conditions while consuming their usual diet. Prior to the intervention, participants were asked to keep 7-day estimated food diaries for 4 consecutive weeks while living at home. These data were then used to provide participants with their usual diet during the intervention. Continuous 24-hour urine collections were made throughout the 30 days. In total, 386 urinary measurements of sucrose and fructose, and 389 days of dietary measurements were available for analysis.

### The OPEN study design

The OPEN study was conducted by the National Cancer Institute (NCI) from September 1999 to March 2000. Details on the study design have already been reported (19). Briefly, 261 men and 223 women aged 40 to 69 years who were healthy volunteers from Montgomery County, Maryland, took part in the study. Each participant was asked to complete an FFQ and 24HDR twice. The FFQ was first administered within 2 weeks of visit 1, and then approximately 3 months later, within a few weeks of visit 3. The 24HDR was administered at visit 1, and approximately 3 months later at visit 3. Participants provided two 24-hour urine collections at least 9 days apart and within 2 weeks following visit 1, verified for completeness by the PABAcheck method. The DLW was administered for 2 weeks from visit 1 to visit 2, and the protocol was repeated for 14 male and 11 female volunteers.

### Dietary assessment

The FFQ used in this study was the NCI Diet History Questionnaire, which is a self-administered semiquantitative FFQ with 124 food items that queried participants about their usual diet over the previous 12 months (20). A question in the FFQ also inquired whether participants usually drank sugar-free- or regular calorie-type beverages, and what kind of sweetener they usually added to coffee and tea (sugar or honey, equal or aspartame, saccharin or Sweet'N Low, or other sweetener). The food items, sex-specific portion sizes, and nutrient database for the FFQ were generated using data from the U.S. Department of Agriculture (USDA) Continuing Survey of Food Intake by Individuals (CSFII) 1994–1996, as described by Subar and colleagues (21). The 24HDR was a standardized 5-pass method, developed by the USDA for use in national dietary surveillance (22). It was conducted by in-person interview, where interviewers used highly standardized probes, food models, and coding. On the basis of the responses from the 24HDR, daily intake was calculated using the Food Intake Analysis Systems (version 3.99), which obtains its database from updates to the USDA CSFII 1994–1996 (23). Individual monosaccharides and disaccharides were estimated using Nutrition Data System for Research software version 5.0\_35 (2004), developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN. The group of

total sugars was defined as the sum of monosaccharides (glucose, fructose, and galactose) and disaccharides (sucrose, lactose, and maltose).

### Dietary biomarkers

**Biomarker for sugars intake.** Twenty-four-hour urine samples were preserved with boric acid (up to 2 g/L) during collection. The completeness of the collections was assessed by urinary recovery of three 80-mg tablets of PABA (*para*-aminobenzoic acid) taken by the participants on the urine collection day (PABAcheck, Laboratories for Applied Biology; ref. 24). PABA concentration in urine was measured by a colorimetric technique (24). Urine collections with less than 70% recovery of the oral dose of PABA were considered incomplete and were excluded from the analyses. Those with PABA recovery of 70% to 85% were retained; but, the content of analytes was proportionally adjusted to 93% PABA recovery (25). In case of recovery of greater than 110%, PABA was measured by high-performance liquid chromatography, to distinguish between PABA and chemically similar compounds, such as acetaminophen, a drug commonly taken by participants (26, 27).

Sucrose and fructose in urine were quantitatively determined using a colorimetric method on the Olympus AU640 clinical chemistry analyzer. The method used Olympus glucose reagent, whereas sucrose and fructose reagents and calibrators, and a glucose calibrator were prepared in house (Quotient Bioresearch Ltd.). Control material was prepared using a Fluka fructose standard and Sigma glucose and sucrose standards (1,000 mg/L). Lower and upper limits of quantification were 4 and 133 mg/L for sucrose, and 1.2 and 88 mg/L for fructose, respectively.

Using the daily urine volume and sucrose and fructose concentration in urine, we estimated daily excretion of urinary sucrose and fructose. The sum of the 2 was used as a predictive biomarker of total sugars intake to estimate the ME structure of FFQ- and 24HDR-reported total sugars in the OPEN biomarker study.

**Biomarker for energy intake.** We used the DLW biomarker, which measured total energy expenditure (TEE) over 2 weeks, as a reference measure of participants' energy intake. The DLW protocol, measurement of isotopes, and calculation of TEE have been previously reported in detail (19).

### Statistical methods

**Modeling the predictive sugars biomarker.** A general model for predictive sugars biomarker data of fitting this model to the sugars biomarker data from the feeding study where this biomarker was developed (19) are described in the Appendix.

Simplifying notations used in the Appendix, for individual  $i$ , where  $i = 1, \dots, n$ , let  $T_i$  denote logarithm of true usual (i.e., long-term average) intake of sugars;  $T_{ij}$  denote the logarithm of true intake on day  $j$ ; and  $M_{ij}$  denote the log-transformed sugars biomarker value on day  $j$ . As

detailed in the Appendix, analyzing the feeding study data, we determined that the relationship between  $M_{ij}$  and true intake  $T_{ij}$  can be approximated by the following model,

$$M_{ij} = \beta_{M0} + \beta_{MT}T_{ij} + \beta_{MX}A_i + u_{Mi} + \varepsilon_{Mij} \quad (A)$$

where  $A_i$  is a log-transformed age,  $u_{Mi}$  is a person-specific bias (random effect), and  $\varepsilon_{Mij}$  is within-person random error. Under certain assumptions discussed in the Appendix, one can use model A to specify the relationship between  $M_{ij}$  and true usual intake  $T_i$ . In the feeding study, we estimated this relationship to be

$$M_{ij} = 1.67 + 1.00 \times T_i + 0.02 \times S_i - 0.71 \times A_i + u_{Mi} + \varepsilon_{Mij}$$

where  $S_i$  is an indicator variable that equals 0 for men and 1 for women. As follows from equations A8, A11, and A12 in the Appendix, the calibrated biomarker values that are calculated as

$$M_{ij}^* = M_{ij} - 1.67 - 0.02 \times S_i + 0.71 \times A_i \quad (B)$$

satisfy the following ME model:

$$M_{ij}^* = T_i + u_{Mi} + \varepsilon_{Mij}$$

We also used the feeding study to estimate the ratio of the variance of  $u_{Mi}$  to the variance of  $T_i + u_{Mi}$

$$\kappa = \frac{\sigma_{uM}^2}{\sigma_T^2 + \sigma_{uM}^2} = 0.218 \quad (C)$$

It is assumed that both the parameters of the calibration equation B and the ratio C are relatively stable and do not change substantially from population to population. Yet, the biomarker ME parameters used here were estimated on the basis of only one feeding study with a limited sample size. More such studies, preferably conducted across different populations, are needed to investigate the stability of the parameters used in this analysis.

**Estimating the ME structure in self-reported intake in the OPEN study.** For intake of sugars, we used an ME model, which is a modification of the model described by Kipnis and colleagues (8). For individual  $i$ , where  $i = 1, \dots, n$ , let  $Q_{ij}$  and  $R_{ij}$  denote log-transformed reported intake on the  $j$ th application of the FFQ and 24HDR, respectively. Denoting by  $\mathbf{X}_F$ , the vector of potential covariates that may affect the relationship between an instrument  $F = Q, R$  and true usual intake, the ME model is given by:

$$Q_{ij} = \beta_{Q0} + \beta_{QT}T_i + \beta_{QX}X_{Qi} + u_{Qi} + \varepsilon_{Qij}, \quad (D)$$

$$R_{ij} = \beta_{R0} + \beta_{RT}T_i + \beta_{RX}X_{Ri} + u_{Ri} + \varepsilon_{Rij}, \quad (E)$$

$$M_{ij}^* = T_i + u_{Mi} + \varepsilon_{Mij}, \quad (F)$$

where, for a self-reported instrument  $F = Q, R$ ,  $\beta_{F0}$  is the overall population intercept and represent constant

biases at the population level; slope  $\beta_{FT}$  reflects intake-related bias; slope  $\beta_{FX}$  defines the association of the respective measure with the corresponding vector of covariates;  $u_{Fi}$  is person-specific bias with mean zero and variance  $\sigma_{u_f}^2$ ; and  $\varepsilon_{Fij}$  is within-person random error with mean zero and variance  $\sigma_{\varepsilon_f}^2$ . Although FFQ queries about diet over the previous year whereas 24HDR measures diet on a particular day, we consider both instruments to be measures of usual intake, which is the average intake over 15 months. The 24HDR will then have a greater within-person random error than the FFQ due to additional day-to-day variation in intake. We assume that the person-specific biases for the FFQ and 24HDR (i.e.,  $u_{Qi}$  and  $u_{Ri}$ , respectively) are correlated with each other but are independent of the person-specific bias for the calibrated biomarker  $u_{Mi}$  and that all 3 are independent from other random variables in the model whereas the within-person random errors are independent of each other and of all other variables in the model. The log-transformed biomarker was calibrated using equation B. However, the ME model allows within-person random errors  $\varepsilon_{Qij}$ ,  $\varepsilon_{Rij}$ , and  $\varepsilon_{Mij}$  to be correlated if measurements are taken very close in time. Otherwise, the within-person errors are assumed to be independent of each other and of all other variables in the model. In the OPEN study, the first 24HDR and the first urinary sugars biomarker were taken at least 2 days apart, so we initially fitted a model that allowed  $\varepsilon_{Ri1}$  and  $\varepsilon_{Mi1}$  to be correlated. Given that the estimated correlation was small and not statistically significantly different from zero ( $P$  value = 0.95 for men and 0.30 for women), in the final model, we assumed they were uncorrelated.

For energy intake, we used the ME model of Kipnis and colleagues (8), which is the same as models D to F, except that the DLW biomarker on the log scale does not need any calibration and satisfies equation F with no person-specific bias.

For all dietary and urinary variables on the log scale, we excluded values which were below the 25th percentile minus twice the interquartile range or above the 75th percentile plus twice the interquartile range. For each variable and each dietary instrument, no more than 9 outlying values for men and 7 for women were excluded from the analyses. Under the assumption that data were missing at random, we used the maximum likelihood method, which includes all available data for each subject to produce unbiased estimates of the model parameters.

As was recently suggested by Willett (28), an evaluation of an FFQ could be invalid unless heterogeneity in the study population due to gender, age, and body size was adjusted for. To address this issue, we stratified the analysis of the ME structure in the FFQ and 24HDR by gender and also included log-transformed age and body mass index (BMI) in the ME model for self-reported intakes of sugars and energy as components in the covariate vector  $\mathbf{X}_Q = \mathbf{X}_R$ .

Taking the fixed value of ratio C into account, we used the method of maximum likelihood to estimate the para-

meters in ME models D to F for intakes of sugars and energy simultaneously under the assumption of normality of the random effects and within-person errors in the models. The simultaneous fitting of ME models for sugars and energy allows one to improve the efficiency of the estimates and to obtain the ME parameters for both absolute and energy-adjusted intake estimates (29). We used the nutrient density method for energy adjustment, where intake of sugars was expressed in grams per 1,000 kcal of total energy intake.

**Estimation of the attenuation factors for the FFQ and 24HDR and the Pearson correlation coefficients between self-reported and true intake.** When using self-reported dietary intake  $F$  measured with error to investigate the association between diet and disease, the observed log relative risk (RR) will be biased (7–9). On an appropriate scale, to a very good approximation, the bias is multiplicative so that the observed log RR will be the product of the bias factor and the true log RR. The bias factor is given by the slope  $\lambda_{F|X}$  for reported intake in the multiple linear regression of true intake on self-reported intake  $F$  and covariates  $\mathbf{X}$  in the ME model for  $F$ . In dietary studies, the value  $\lambda_{F|X}$  is usually between 0 and 1 so that ME leads to underestimation (attenuation) of the true RR and  $\lambda_{F|X}$  is called the attenuation factor (AF; ref. 30). Values closer to zero indicate more serious attenuation of risk.

The AF for a dietary assessment instrument  $F = Q, R$  was calculated from the parameters in ME models D to F as

$$\lambda_{F|X} = \frac{\text{cov}(T, F|\mathbf{X})}{\text{var}(F|\mathbf{X})} = \frac{\beta_{FT}}{\beta_{FT}^2 + \sigma_{u_f}^2/\sigma_{T|\mathbf{X}}^2 + \sigma_{\varepsilon_f}^2/\sigma_{T|\mathbf{X}}^2} \quad (\text{G})$$

When the disease model involves intake categorized into quantiles (e.g., quintiles), the observed log RR between any 2 quintiles will be attenuated by the partial Pearson correlation coefficient between the self-reported and true intakes (31). The partial correlation between the reported intake  $F = Q, R$  and the true intake can be calculated from the parameters in ME models D to F as follows:

$$\begin{aligned} \rho_{F,T|\mathbf{X}} &= \frac{\text{cov}(T, F|\mathbf{X})}{\sqrt{\text{var}(T|\mathbf{X})\text{var}(F|\mathbf{X})}} \\ &= \frac{\beta_{FT}}{\sqrt{\beta_{FT}^2 + \sigma_{u_f}^2/\sigma_{T|\mathbf{X}}^2 + \sigma_{\varepsilon_f}^2/\sigma_{T|\mathbf{X}}^2}} \end{aligned} \quad (\text{H})$$

For the FFQ and 24HDR, we estimated the AF and correlation with true intake by substituting the estimated parameters from fitting ME models D to F into equations G and H for  $F = Q, R$ .

## Results

Four hundred seventy-nine participants in the OPEN study completed the FFQ and 24HDR on 2 occasions. Valid DLW data were available from 450 of 484 participants. In total, seven hundred four 24-hour urine

collections were considered complete and were available for analysis. Of those, 51 collections had PABA recovery between 70% and 85% and the analytes were readjusted to 93% PABA recovery; 41 of 51 collections were from unique individuals, whereas 10 collections came from 5 participants. For 73 and 90 urine samples, fructose and sucrose values were below the limit of quantification (<1.2 mg/L for fructose and <4 mg/L for sucrose). To retain those samples, we set their respective values to half the limit of quantification. We also conducted a sensitivity analysis wherein we excluded values below the limit of quantification, which produced virtually the same estimates. Thus, the findings from the analysis which included all the values are reported here.

The geometric means of total sugars and total sugars density by gender as estimated by the 2 instruments and the biomarker, as well as of urinary sucrose and fructose, are presented in Table 1. Reported intake of total sugars was about 13.5% lower on the FFQ for both men and women than the biomarker-based estimate. Intake of sugars reported from 24HDRs was slightly higher than the biomarker in men and nearly identical for women. The self-reported total sugars density intakes as estimated by the FFQ and 24HDRs were greater than the biomarker by approximately 32% and 20%, respectively, for both men and women. It is important to note that the group means indicate the validity of instruments to measure intakes of absolute total sugars on a group level only and do not necessarily invalidate the use of these self-reported dietary instruments in a cohort study. If participants in a cohort misreport to the same extent and direction, then the instrument would still serve the

purpose of ranking individuals with regard to their intake of total sugars. The greatest contributors to intake of total sugars in our participants were soft drinks (18%) and fruits (15%), as measured by FFQ, and soft drinks (22%) and cookies, cakes, and pies (13%), as measured by 24HDR.

ME parameters for the FFQ and 24HDR are given in Table 2. The slope  $\beta_{RT}$  in the regression of reported intake  $R$  on true intake represents part of bias of the instrument associated with true intake, also called intake-related bias:  $\beta_{RT} = 1$  means no such bias in the instrument, whereas  $\beta_{RT} < 1$  indicates a tendency to underreport high and overreport low intake (a flattened slope phenomenon) that results in inflation of the risk estimate (32). As shown in Table 2, the slopes for the FFQ were somewhat smaller (less favorable) than for the 24HDR and for both instruments were much smaller in women than in men. No change in the slopes was observed with energy adjustment. The variance of the person-specific bias was greater for the FFQ than for the 24HDR absolute intake estimates and was similar between men and women (Table 2). In men, the variance of the person-specific bias in the FFQ, but not in the 24HDR, was greater than the variance of true intake, whereas in women, for both instruments, it was smaller than the variance of true intake. Energy adjustment reduced the person-specific bias in both instruments, although considerably less so in the 24HDR, and made it similar in magnitude between the two. Nevertheless, in all instances, the person-specific bias was still substantial and statistically significantly different from zero. We observed a strong positive correlation between the person-specific biases of the FFQ

**Table 1.** Geometric means and 95%CI for total sugars intake and total sugars density as assessed by FFQ, 24HDR, and urinary sugars biomarker in the OPEN study

	Instrument	Men (n = 261)		Women (n = 223)	
		n	Geometric mean (95% CI)	n	Geometric mean 95% CI
Intake of total sugars, g/d	FFQ1	259	107.8 (101.1–115.0)	220	94.3 (88.2–100.8)
	FFQ2	259	99.4 (93.2–106.1)	218	87.5 (82.6–92.8)
	24HDR1	259	128.2 (119.6–137.5)	223	104.6 (97.5–112.1)
	24HDR2	260	121.8 (113.4–130.7)	220	100.7 (94.0–107.9)
	Biomarker <sup>a</sup>	225	119.2 (108.9–130.6)	188	105.8 (94.9–117.9)
Total sugars density, g/1,000 kcal	FFQ1	257	55.1 (52.7–57.7)	220	61.9 (59.0–64.9)
	FFQ2	257	54.4 (52.0–57.0)	218	62.4 (59.9–65.0)
	24HDR1	259	50.7 (48.0–53.6)	223	54.5 (51.3–57.8)
	24HDR2	257	49.7 (46.9–52.7)	220	54.9 (51.8–58.2)
	Biomarker <sup>a,b</sup>	209	41.2 (37.7–45.0)	174	47.4 (42.7–52.7)
Urinary excretion, mg/d	Sucrose	226	28.8 (25.9–32.0)	188	21.6 (19.1–24.5)
	Fructose	226	11.4 (10.0–12.9)	190	13.7 (11.7–15.9)

<sup>a</sup>Estimated on the basis of the ME parameters generated from the feeding study (18).

<sup>b</sup>Expressed on energy intake estimated by DLW measurement of TEE.

**Table 2.** ME structure for total sugar intake and total sugars density as assessed by FFQ and 24HDR by gender on log scale

	Gender	Variance of true intake ( $\sigma_T^2$ )	Instrument	Slope in regression of reported on true intake ( $\beta_{QT}$ or $\beta_{RT}$ )	Variance of person-specific bias ( $\sigma_{uQ}^2$ or $\sigma_{uR}^2$ )	Correlation of person-specific biases ( $\rho_{uQ,uR}$ )	Variance of within-person error ( $\sigma_{\varepsilon_Q}^2$ or $\sigma_{\varepsilon_R}^2$ )
Intake of total sugars, g/d	Male	0.12 (0.04 <sup>a</sup> )	FFQ	0.66 (0.16)	0.17 (0.02)	0.81 (0.08)	0.06 (0.005)
			24HDR	0.82 (0.18)	0.08 (0.02)		0.16 (0.01)
	Female	0.25 (0.06)	FFQ	0.16 (0.06)	0.16 (0.02)	0.72 (0.09)	0.07 (0.01)
			24HDR	0.22 (0.08)	0.08 (0.02)		0.18 (0.02)
Total sugars density, g/1,000 kcal	Male	0.08 (0.03)	FFQ	0.65 (0.17)	0.08 (0.01)	0.82 (0.09)	0.03 (0.002)
			24HDR	0.82 (0.19)	0.05 (0.02)		0.12 (0.01)
	Female	0.22 (0.05)	FFQ	0.16 (0.06)	0.07 (0.01)	1.00 (0.08)	0.04 (0.003)
			24HDR	0.21 (0.07)	0.06 (0.01)		0.12 (0.01)

NOTE: All the parameters were estimated using FFQ- and 24HDR-ME models adjusted for BMI and age, and biomarker ME model adjusted for age.

<sup>a</sup>Standard error (all values in parenthesis).

and 24HDR, which remained after energy adjustment and, in women, became even stronger. As expected, the variance of the within-person error was greater in the 24HDR than in the FFQ. The within-person error in 24HDR was also closer to the between-person variation than that in the FFQ. After energy adjustment, the within-person error was somewhat reduced.

In Table 3, we present the AFs for reported intake and the correlation coefficients between true and reported intakes for FFQ, single 24HDR, and for the average of two 24HDRs. The AF for FFQ for intake of absolute total sugars was rather small and more favorable in men ( $\approx 0.3$ ) than in women ( $\approx 0.2$ ). The AF for a single 24HDR was

only slightly greater than that for the FFQ but further increased when the average of 2 repeat 24HDRs was used. Similar to the FFQ, the AF for 24HDR was greater in men than in women. Energy adjustment improved the attenuation associated with the FFQ; the AFs somewhat increased, but still remained substantially smaller than 1, whereas for the 24HDR, some improvements were observed in women but none in men. After energy adjustment, the AFs for a single FFQ were only slightly lower than for two 24HDRs. When we used the 24HDR as a reference instrument for total sugars density, the estimated AFs for the FFQ were considerably closer to 1 compared with the biomarker-based estimates

**Table 3.** Correlations of true and reported total sugars intake and total sugars density on log scale and AFs for reported total sugars intake and total sugars density on log scale from an ME model for the urinary sugars biomarker

	Instrument	Men (n = 261)		Women (n = 223)	
		AF	Correlation with true intake	AF	Correlation with true intake
Intake of total sugars, g/d	FFQ	0.283 (0.058 <sup>a</sup> )	0.431 (0.069)	0.169 (0.068)	0.163 (0.064)
	Single 24HDR	0.304 (0.056)	0.499 (0.067)	0.196 (0.069)	0.206 (0.070)
	Average of two 24HDR	0.407 (0.074)	0.577 (0.076)	0.291 (0.102)	0.252 (0.085)
Total sugars density, g/1,000 kcal	FFQ	0.385 (0.093)	0.500 (0.090)	0.331 (0.129)	0.231 (0.087)
	Single 24HDR	0.301 (0.069)	0.496 (0.079)	0.238 (0.089)	0.225 (0.080)
	Average of two 24HDR	0.410 (0.092)	0.578 (0.091)	0.346 (0.128)	0.271 (0.096)

NOTE: All the parameters were estimated using FFQ- and 24HDR-ME models adjusted for BMI and age, and biomarker ME model adjusted for age.

<sup>a</sup>Standard error (all values in parenthesis).

(men: 24HDR-based AF = 0.68 vs. biomarker-based AF = 0.39; women: 24HDR-based AF = 0.71 vs. biomarker-based AF = 0.33).

The results for the correlation coefficients between true and reported intake of sugars were qualitatively similar to the results for the AFs. For absolute intake of sugars, they were greater in men than in women, greater for a single 24HDR than for the FFQ, and further increased with two 24HDRs. The correlations of FFQ estimates with true intake improved after energy adjustment but were still lower than the correlations yielded by two 24HDRs. Similarly, the estimated correlation coefficients between the FFQ and true sugars density based on 24HDR suggest that using 24HDR as a reference may lead to considerable overestimation of FFQ validity with respect to intake of sugars, especially in women (men: 24HDR-based  $\rho = 0.79$  vs. biomarker-based  $\rho = 0.50$ ; women: 24HDR-based  $\rho = 0.83$  vs. biomarker-based  $\rho = 0.23$ ).

In further sensitivity analysis (data not shown), after adding smoking and education as covariates in the ME model, the AFs and correlation coefficients between reported and true intake of sugars remained virtually the same in men and only slightly increased in women. Furthermore, replacing the continuous covariate BMI with a categorical one in the ME model produced virtually unchanged results. We also attempted stratified analyses of the ME model by age, BMI, smoking status, and alcohol intake. The estimated AFs and correlation coefficients were not statistically significantly different between strata at the nominal level for any of the investigated variables, except for the correlation coefficients stratified by age in men. Nonetheless, these differences became statistically nonsignificant after adjustment for multiple testing. We emphasize though that the OPEN study was not powered for such stratified analyses. In the future, it would be important to investigate whether differences by characteristics, such as age, BMI, and race, do exist should larger validation studies become available.

## Discussion

In this report, we propose an ME model for *predictive* biomarkers and show how it could be calibrated using estimates from feeding studies. The important qualities of a *predictive* biomarker are that its person-specific bias is uncorrelated with the person-specific biases in the self-report instruments and that the biomarker ME parameters are reasonably similar for all individuals across different categories in the study population. Although we acknowledge that level of predictive biomarkers' may be affected by genetic, physiologic, pathologic, or other determinants besides diet only (as potential sources for person-specific bias), they ought not to explain a significant portion of the variability in the biomarker and their effect estimates (calculable from a feeding study) ought to be stable. Although they also may be associated with intake-related and covariate-related bias, their associa-

tion to intake should be quantifiable, stable, and time-sensitive (i.e., refer to certain period of intake). After calibration and given that their person-specific bias is stable compared with their intake-related bias (ratio given in equation A10 in the Appendix), *predictive* biomarkers, similar to *recovery* biomarkers, can be used as reference instruments in validation/calibration studies to estimate the ME structure in self-reported intake and/or adjust estimated diet-disease relationships for ME. In fact, *recovery* biomarkers can be considered a special class of *predictive* biomarkers, which are known to have no bias.

In this report, we also apply the developed ME model for *predictive* biomarkers to the recently developed *predictive* biomarker for intake of sugars to investigate misreporting in FFQ and 24HDR in the OPEN study. On the basis of the physiologic mechanisms by which sugars biomarker occur in urine (18), it is plausible to assume that errors in the calibrated sugars biomarker are independent of errors in the self-reporting instruments, that is, of subject's capacity or motivation to give an accurate response to the traditional dietary assessment methods, and that it has less nondietary determinants than concentration biomarkers. In general, urinary measures may be better candidates for *predictive* or *recovery* biomarkers, as their levels are less likely to be affected by the complex homeostatic and metabolic mechanisms and lifestyle factors that affect blood or tissue measures. Although a study of participants on constant diets showed a certain level of between-subject variability in the urinary sugars biomarker (18), a second study of participants consuming their usual varying diet showed that dietary intake of sugars explained a large proportion of the variance in sucrose and fructose excretion (72% of the variance in 30-day mean urinary sucrose and fructose was explained by 30-day mean intake of sugars; ref. 18), suggesting that it is very likely that this would be the case in other populations too. The fact that no effect of several commonly investigated characteristics, such as sex, BMI, or physical activity, was found on the relationship between the biomarker and true total intake of sugars further suggests that the assumption of stability of the biomarker ME parameters is plausible. It must be stressed though that the sample size of the feeding study was small and the power to detect moderate effects was relatively low. However, another feeding study confirmed the independence of the sugars biomarker from individuals' BMI (33).

Sucrose and fructose occur in urine in very small amounts; urinary sucrose is possibly a fraction of dietary sucrose that escapes enzymatic hydrolysis in the small intestine, and once in the blood stream is excreted in the urine, whereas urinary fructose is a portion of fructose, either from dietary fructose or from sucrose, that escapes fructose hepatic metabolism. Thus, any person-specific differences in absorption, hepatic metabolism, or renal excretion of these two nutrients, determined by genetic factors, physiologic or medical conditions, would be possible sources of person-specific bias and may differ

between different populations. For instance, altered intestinal disaccharidase activity (34), gastric damage (35), or high intraluminal concentration of sucrose (36) may facilitate sucrose leakage through the gut and increase its excretion. Although age was found to statistically significantly affect the biomarker–diet relationship in the feeding study, in our sensitivity analysis, excluding age in the biomarker ME model did not significantly affect the biomarker-based attenuation and correlation estimates for the self-report instruments in the OPEN study (data not shown), suggesting that even a simple ME model may be robust enough for validation purposes.

By using the sugars biomarker, we found reports of sugars on both FFQ and 24HDR to be associated with intake-related and person-specific biases. These biases have opposing effects on risk estimates; while intake-related bias leads to inflated estimated risk, person-specific bias attenuates risk (37). In our analysis, intake-related bias was somewhat greater in the FFQ than in the 24HDR and much greater in women than in men. Yet, the relative variances of the person-specific bias and the within-person error in women were still substantial and overrode the effect of the intake-related bias resulting in AFs well below 1. While person-specific bias was greater in the FFQ, as expected, the within-person error was greater in the 24HDR due to day-to-day variability in intake.

The AFs, as well as person-specific biases, for the FFQ improved after energy adjustment, meaning that errors in FFQ estimates of total sugars and energy were correlated; hence, energy adjustment diminished the effect of ME, although it still remained substantial. From the AF estimates shown in Table 3, it can be calculated that in analyses with energy-adjusted FFQ intake, true RR of 2, 1.5, or 1.2 would be observed as 1.3, 1.2, or 1.1, respectively. On the other hand, energy adjustment had very little effect on the attenuation or on the person-specific bias associated with 24HDR, suggesting that errors in estimates of sugars were independent of errors in energy reporting. It is therefore possible that errors in estimates of sugars from 24HDR and FFQ reports may have different sources or that in our data, sugars were major contributors to energy as reported on FFQ but not as reported on 24HDR. It is also possible that the interrelation of errors among reported macronutrients (i.e., the energy contributors) is different in the FFQ compared with the 24HDR. Yet, the person-specific biases in the two instruments remained highly correlated even after energy adjustment, which makes questionable the use of 24HDR as a reference instrument for absolute or energy-adjusted sugars reported on the FFQ.

In both men and women, the AFs for self-reports of absolute sugars were somewhat better for one 24HDR than for one FFQ and they further improved with repeated 24HDR. Although, compared with the FFQ, the AFs for 24HDR did not improve much with energy adjustment, these values for two 24HDRs were still greater (more favorable) than the AFs for the FFQ. More-

over, as seen from equation G, with added 24HDR repeats, the AF will further improve. We also note that the attenuation associated with both instruments was greater in women than in men. In earlier studies, energy underreporting was found to be more common in women than in men (38, 39).

From earlier analysis using *recovery* biomarkers, ME structures for self-reported energy and protein showed somewhat similar patterns with what we are seeing for sugars (7, 31, 40). The attenuation associated with misreporting of intake of sugars was similar to that of protein and smaller (better) than that of energy. One might expect that misreporting of sugars would be greater than misreporting of protein because of the tendency to misreport foods high in added sugars (2–5). Yet, the sugars biomarker measures not only added sugars (i.e., used as ingredients in processed and prepared foods, or added at the table) but also naturally occurring sugars from fruits and vegetables. It may be that error from possibly underreporting food with high in added sugars is in part canceled out by overreporting fruits and vegetables.

In summary, using the newly developed sugars biomarker, we showed that absolute and energy-adjusted total sugars reported on both the FFQ and 24HDR in the OPEN study were associated with substantial error. On the basis of our findings, in a disease model with intake of absolute total sugars, two 24HDRs would provide more accurate risk estimate for the sugars effect than FFQ, whereas in analysis with energy-adjusted intakes, the FFQ seems to perform similarly to two 24HDRs. Women tended to misreport sugars more than men on both instruments. Hence, problematic assessment of sugars in nutritional epidemiology may have prevented us from detecting a causal link between sugars and cancer. As both instruments were found to be biased, incorporation of the sugars biomarker in calibration studies within large cohorts (which will allow for adjusting the risk estimates for ME) may be necessary to obtain more definite answers for the role of sugars in cancer.

It is important to note that the ME structure of the self-report instruments was assessed on the basis of biomarker ME parameters estimated from only one feeding study with a limited sample size. More feeding studies across different populations are necessary to investigate the stability of the sugars biomarker ME parameters used in this analysis.

## Appendix: ME Model for Predictive Biomarkers

For person  $i = 1, \dots, n$ , daily measurement  $j = 1, \dots, J$ , let  $T_{ij}$  represent true intake of a food/nutrient. Define true usual intake as the within-person mean of daily intakes  $T_i = E(T_{ij}|i)$ . Consider the following model relating appropriately transformed biomarker measurements  $g_M(M_{ij})$  to appropriately transformed true daily intakes  $g_T(T_{ij})$ :

$$g_M(M_{ij}) = \beta_{M0} + \beta_{MT}g_T(T_{ij}) + \beta_{MX}^t \mathbf{X}_i + u_{Mi} + \varepsilon_{Mij} \quad (A1)$$



where  $\mathbf{X}_i$  is a vector of covariates that may affect the relationship between the biomarker and true intake;  $\beta_{M0}$ ,  $\beta_{MT}$  are the scale parameters that define overall population and intake-related biases, respectively, in biomarker measurements;  $\beta_{MX}$  is the vector of parameters that define covariate-related bias;  $u_{Mi}$  is the person-specific bias with mean zero and variance  $\sigma_{uM}^2$  that represents the difference between within-person bias and its intake-related and covariate-related components; and  $\varepsilon_{Mij}$  is within-person random error with mean zero and variance  $\sigma_{\varepsilon M}^2$ . We assume that random variables  $T_{ij}$ ,  $u_{Mi}$ ,  $\varepsilon_{Mij}$  are mutually independent and that  $u_{Mi}$ ,  $\varepsilon_{Mij}$  are independent from vector  $\mathbf{X}_i$ . Because for a given person  $i$ , the biomarker measurements are taken on consecutive days, components of vector  $\varepsilon_{Mi} = (\varepsilon_{Mi1}, \dots, \varepsilon_{Mij})^t$  may be correlated with the variance-covariance matrix  $\Sigma_\varepsilon$ .

Let  $\delta_{ij}$  denote within-person deviations of transformed daily intakes for person  $i$  from the within-person mean  $\mu_i = E[g_T(T_{ij}) | i]$ , that is,

$$g_T(T_{ij}) = \mu_i + \delta_{ij}, E(\delta_{ij} | i) = 0 \quad (\text{A2})$$

Note that the deviations  $\delta_{ij}$  are uncorrelated with any personal characteristic  $V_i$ , including  $g_T(T_i)$  and  $\mathbf{X}_i$ , as

$$\text{cov}(V_i, \delta_{ij}) = E[\{V_i - E(V_i)\}\delta_{ij}] = E(E[\{V_i - E(V_i)\}\delta_{ij} | i]) = 0$$

For nonlinear transformation,

$$\mu_i = E[g_T(T_{ij}) | i] \neq g_T[E(T_{ij} | i)] = g_T(T_i)$$

In general, the difference  $v_i = \mu_i - g_T(T_i)$  could depend on true transformed usual intake, as well as the covariates in the model. Regressing  $v_i$  onto  $g_T(T_i)$  and  $\mathbf{X}_i$ , we have

$$v_i = \gamma_0 + \gamma_T g_T(T_i) + \boldsymbol{\gamma}_X^t \mathbf{X}_i + \xi_i, \text{cov}(\xi_i, g_T(T_i)) = \text{cov}(\xi_i, \mathbf{X}_i) = 0 \quad (\text{A3})$$

so that

$$\mu_i = \gamma_0 + (1 + \gamma_T)g_T(T_i) + \boldsymbol{\gamma}_X^t \mathbf{X}_i + \xi_i \quad (\text{A4})$$

Substituting expression (A2) into model A1 with  $\mu_i$  specified according to regression (A4), it follows that the model relating biomarker measurements to transformed true usual intake is given by

$$g_M(M_{ij}) = \tilde{\beta}_{M0} + \tilde{\beta}_{MT} g_T(T_i) + \tilde{\boldsymbol{\beta}}_{MX}^t \mathbf{X}_i + \tilde{u}_{Mi} + \tilde{\varepsilon}_{Mij}, \quad (\text{A5})$$

where

$$\begin{aligned} \tilde{\beta}_{M0} &= \beta_{M0} + \beta_{MT}\gamma_0, \tilde{\beta}_{MT} = \beta_{MT}(1 + \gamma_T), \\ \tilde{\boldsymbol{\beta}}_{MX} &= \boldsymbol{\beta}_{MX} + \beta_{MT}(\boldsymbol{\gamma}_X), \tilde{u}_{Mi} = u_{Mi} + \beta_{MT}\xi_i, \\ \tilde{\varepsilon}_{Mij} &= \varepsilon_{Mij} + \beta_{MT}\delta_{ij} \end{aligned}$$

If  $g_T(\cdot)$  is the log transformation, then under certain conditions, equation A5 simplifies. We have

$$\log T_{ij} = \log T_i + v_i + \delta_{ij}$$

or

$$T_{ij} = T_i \exp\{v_i + \delta_{ij}\}$$

Since, by definition,  $T_i = E(T_{ij} | i)$ , it follows that

$$E(\exp\{v_i + \delta_{ij}\} | i) = 1$$

and

$$v_i = -\log\{E(e^{\delta_{ij}} | i)\} \quad (\text{A6})$$

Under the assumption that  $E(e^{\delta_{ij}} | i)$  is a constant, which would be the case if the  $\delta_{ij}$  are identically distributed, it follows that  $v_i$  is a constant. Denoting this constant by  $v$ , it follows from equation A5 that

$$g_M(M_{ij}) = (\beta_{M0} + v) + \beta_{MT} \log(T_i) + \boldsymbol{\beta}_{MX}^t \mathbf{X}_i + u_{Mi} + \varepsilon_{Mij} \quad (\text{A7})$$

It is assumed that model A5 is stable by satisfying the following requirements:

- (i) parameters  $\tilde{\beta}_{M0}$ ,  $\tilde{\beta}_{MT}$ ,  $\tilde{\boldsymbol{\beta}}_{MX}$  are the same for individuals across different populations and can be evaluated in the feeding studies;
- (ii) the ratio  $\kappa = \sigma_{uM}^2 / (\tilde{\beta}_{MT}^2 \sigma_{g(T)}^2 + \sigma_{uM}^2)$  of the variance of the person-specific bias to the variance of the intake-related and person-specific biases is nearly the same for individuals across different populations and can be evaluated in the feeding studies; and
- (iii) person-specific bias  $\tilde{u}_{Mi}$  and within-person random error  $\tilde{\varepsilon}_{Mij}$  are independent of any personal characteristics and of self-reported intakes from dietary assessment instruments.

Under assumptions (i) to (iii), using the parameters evaluated in the feeding studies, the *predictive* biomarker could be calibrated to remove intake-related and covariate-related biases by calculating

$$M_{ij}^* = \frac{g_M(M_{ij}) - \tilde{\beta}_{M0} - \tilde{\boldsymbol{\beta}}_{MX}^t \mathbf{X}_i}{\tilde{\beta}_{MT}} \quad (\text{A8})$$

Denoting  $T_i^* = g_T(T_i)$ , the calibrated *predictive* biomarker follows the model

$$M_{ij}^* = T_i^* + u_i^* + \varepsilon_{ij}^*, u_i^* = \frac{\tilde{u}_i}{\tilde{\beta}_T}, \varepsilon_{ij}^* = \frac{\tilde{\varepsilon}_{ij}}{\tilde{\beta}_T} \quad (\text{A9})$$

with the ratio

$$\kappa = \frac{\sigma_{uM}^2}{(\tilde{\beta}_{MT}^2 \sigma_{g(T)}^2 + \sigma_{uM}^2)} = \frac{\sigma_{u^*}^2}{(\sigma_{T^*}^2 + \sigma_{u^*}^2)} \quad (\text{A10})$$

estimated from the feeding studies, all the parameters of model A9 are uniquely identifiable in any biomarker validation study, and the calibrated *predictive* biomarker  $M_{ij}^*$  could be used as a reference instrument to estimate

the ME structure of dietary assessment methods such as the FFQ and 24HDR.

### Developing the biomarker of calibrated sugars in the feeding study

We first used data from the feeding study in which this biomarker was developed (18) to evaluate the appropriate scales for the biomarker and true daily intakes of sugars, covariates  $X_i$  related to biomarker-intake relationship, and the covariance structure of within-person errors for ME model A1. We used the SAS MIXED procedure to fit the model by the method of maximum likelihood under the assumption that random effect and within-person error are normally distributed.

After considering various transformations to approximate the linear relationship between true daily intake and biomarker level in model A1, we chose both  $g_M(M_{ij})$  and  $g_T(T_{ij})$  to be the logarithmic transformation. Figure 1 shows the association between log-transformed daily urinary sucrose and fructose measurements and log of daily intake of total sugars in the 13 participants. In a previous report of these data (18), the authors used 30-day means of urinary sucrose and fructose and intake of total sugars to assess the characteristics of the biomarker, whereas in this analysis, we use all 30 daily measurements of urinary and dietary sugars per participant. Using all daily measurements, we analyzed a set of potential covariates  $X_i$  in model A1 including gender, age, BMI, and true intakes of fat, carbohydrates, protein, and total energy. Only log-transformed age,  $A_i$  was identified as a statistically significant covariate in the regression of urinary on dietary sugars ( $P = 0.003$ ), which was therefore included in the ME model as a single covariate  $X_i = A_i$ .

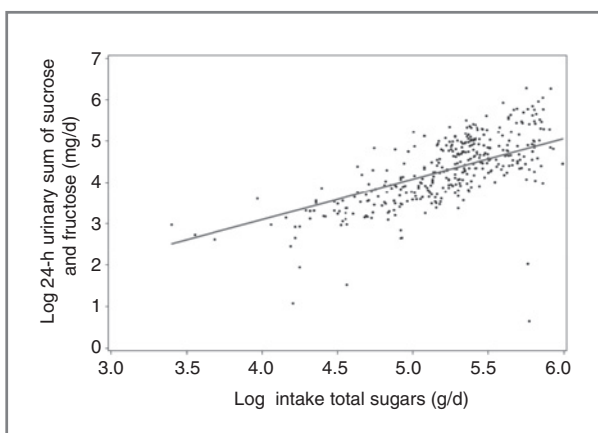


Figure 1. Association between urinary sucrose and fructose and intake of total sugars in the 30-day feeding study ( $n = 13$ ; 13 subjects  $\times$  thirty 24-hour urine collections and 13  $\times$  30 days of diet; ref. 19)

We considered 2 correlation structures for the variance-covariance matrix  $\Sigma_\varepsilon$ : (i) the first order autoregressive structure and (ii) the Toeplitz structure of orders 2 to 4 (41). The second-order Toeplitz structure, which assumes that any 2 consecutive within-person errors  $\varepsilon_{ij}, \varepsilon_{ij+1}$  are correlated with the same correlation coefficient but nonconsecutive within-person errors are uncorrelated, produced the best fit based on the Akaike information criterion (42) and was chosen for model A1.

The estimated parameters for thereby specified model A1 were as follows:  $\beta_{M0} = 1.71$ ,  $\beta_{MT} = 1.00$ ,  $\beta_{MX} = -0.71$ ,  $\sigma_{u_M}^2 = 0.060$ , and  $\sigma_{T^*}^2 = 0.215$ .

In the feeding study, we checked the assumption that  $E(e^{\delta_{ij}}|i)$  is a constant and found that the mean  $E(e^{\delta_{ij}}|i)$  depends on participants' gender. Stratifying by gender, the individual means  $E(e^{\delta_{ij}}|i)$  were not exactly the same but the differences from the overall gender-specific mean were very small with  $\text{var}(v_i) = 0.0006$  for both genders. We further fitted regression (A3) to estimated values  $v_i$  from equation A6. None of the considered covariates was statistically significant in the model. Slope  $\gamma_T$ , although statistically significantly different from zero, was very small at 0.03 compared with  $\beta_{MT} = 1.00$  and the residual variance was 0.0003. Substituting those values into equation A5 did not produce any material difference compared with model A7. We, therefore, proceeded by using estimated parameters from model A7 with the gender-specific parameter  $v$  as follows: for women, this parameter was estimated as  $\bar{v} = 0.020$  and, for men, as  $\bar{v} = 0.039$ .

As a result, the fitted in the feeding study ME model for predictive sugars biomarker is given by

$$\log M_{ij} = 1.67 + 0.02 \times S + 1.00 \times \log T_i - 0.71 \times A_i + u_{Mi} + \varepsilon_{Mij} \quad (\text{A11})$$

where  $S = 0$  for men and  $S = 1$  for women. The estimated ratio of person-specific bias to the sum of person-specific and intake-related biases is given as follows:

$$\kappa = \frac{0.060}{0.275} = 0.218 \quad (\text{A12})$$

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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