Validity Coefficient of Repeated Measurements of Urinary Marker of Sugar Intake Is Comparable to Urinary Nitrogen as Marker of Protein Intake in Free-living Subjects

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ABSTRACT

Background: Studies do not show consistent relationships between self-reported intake of sugar and outcome of disease. To overcome the drawbacks of self-reported intake methods, we investigated whether there is an agreement in ranking of individuals between their self-reported sugar intake and urinary sucrose and fructose.

Methods: We used data of 198 Dutch adults (106 women) from the DUPLO study. Sugar intake of all foods and drinks consumed over 24-hour period was estimated by collecting duplicate portions (DP) and 24-hour recalls (24hR), telephone (24hRT) and Web-based (24hRW), while sugar excretion was based on 24-hour urine samples. Sugar content of 24hR was calculated using a newly developed sugar database and sugar content of DPs and urine samples was calculated using high-performance liquid chromatography–atomic emission spectrometry and LC/MS-MS, respectively. Measurement error models assessed validity coefficients (VC) and attenuation factors (AF). Coefficients were compared with those of protein biomarker.

Results: The VC for the marker, using DP as reference, showed comparability with substantially better ranking of participants (0.72 for women and 0.93 for men), than 24hRT (0.57 and 0.78) or 24hRW (0.70 and 0.78) as reference in the sucrose models. The VC of the sucrose models was within 10% of the protein models, except for the model with 24hRT as reference, among women. The AF started at higher values and increased by a greater factor compared with the VC.

Conclusions: Repeated measurements of urinary sucrose and fructose as a marker of daily sucrose intake had a ranking performance comparable to urinary nitrogen as marker of protein intake in free-living Dutch adults.

Impact: The validation of the sugar biomarker in a free-living population with three different dietary assessment methods and its comparable ranking ability with a good recovery biomarker (i.e., protein biomarker) have important research applications. The biomarker may be used for validating dietary assessment methods, for monitoring compliance in human feeding studies, for monitoring the effect of public health interventions, and as a surrogate for ranking subjects according to sucrose intake when information on sucrose in food composition databases is lacking.

Introduction

The World Health Organization (WHO) recommends to reduce the intake of sugar throughout the life course. The intake in both children and adults should not amount to more than 10% of total energy intake and preferably to less than 5% (1). While diets high in sugar are suspected to increase the risk of overweight and related chronic diseases (2–6), and the prevalence of dental caries (7, 8), the evidence is labeled by WHO as "moderate quality evidence," which can be attributed to the research methodology used in the studies.

Observational studies do not show consistent relationships between self-reported intake of "sugar" and outcome of disease (9–12). A drawback of these studies may be the use of methods that rely on self-reported dietary intake and that "sugar" is often loosely defined. Self-reports may contain measurement errors (ME) such as recall and reactivity bias, selective underreporting of foods perceived as being unhealthy, and difficulties in estimating portion sizes by the participants, which may have distorted the relationships under investigation (13). The lack of consistency observed may also be due to the fact that information on sucrose and fructose is often absent in food composition databases or may be unreliable due to frequent changes in food product formulation by the manufacturers. Therefore, a biomarker of sugar intake may be an objective and useful measure to either evaluate the level of self-reported intake or to rank individuals according to their intake. Excretion of fructose and sucrose in the urine was first proposed as a predictor of sucrose intake in 1996 (14).

On the basis of highly controlled feeding studies in adult subjects, Tasevska and colleagues suggested the use of 24-hour urinary sugar (i.e., the sum of urinary sucrose and free fructose) as a so-called predictive biomarker of sugar intake (15). Predictive biomarkers are a class of dietary biomarkers intermediate to concentration and recovery

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biomarkers. This type of marker shows a dose–response relationship with intake, but a low recovery, and the relationship may be more dependent on subject characteristics, resulting in lower correlations with intake (15, 16).

Later studies under controlled conditions showed that 24-hour urinary excretion levels of sucrose and fructose were significantly correlated with extrinsic sugar (sucrose) intake (i.e., sugar added to foods during processing or home preparation), but not with intrinsic sugar intake (i.e., sugar that is naturally enclosed in the food matrix; ref. 17). Urinary excretion levels of sucrose and fructose were not affected by body mass index (BMI) of the study participants (18). Studies in adolescents showed that urinary excretion of sugar was significantly associated with sugar intake (19). In addition, spot urine samples showed significant associations with self-reported sugar intake in a prospective subcohort of the EPIC study (20), and in a study of self-reported sugar intake from multiple 24-hour recalls (24hR) in children and adolescents showing validity coefficients (VC) > 0.6 (21).

We aimed to assess the validity of the urinary biomarker of sugar intake in a free-living population with a Dutch food pattern, in an existing well-designed validation study (DUPLO study; ref. 22). Our main objective was to investigate the agreement in the ranking of individuals between their sugar (sucrose plus fructose) intake, sucrose intake, or mono- and disaccharides intake, according to duplicate portions (DP) or 24hRs, and urinary excretion of sucrose and fructose. Moreover, we compared the performance of the sugar biomarker with that of urinary nitrogen as a biomarker of protein intake, which is considered to be a good recovery biomarker of dietary exposure (23).

Materials and Methods

Study population and study design

The DUPLO study, which is a subsample of the Nutrition Questionnaires plus (NQplus) study (24), investigated 200 healthy Dutch adults (108 women and 92 men) ages 20–70 years old. The recruitment and study set-up are described in detail elsewhere (22). The study was conducted according to the guidelines in the Declaration of Helsinki, and all data collection was approved by the Ethical Committee of Wageningen University (Wageningen, the Netherlands). All participants gave written informed consent and their data were handled according to privacy legislation.

The study design and the time frame of data collection are presented in **Fig. 1**. Briefly, between July 2011 and July 2014, preceded by verbal and written guidance, each participant randomly collected two DPs, two 24-hour urine samples, between 0 and 8 telephone-based 24-hour dietary recalls (24hRT), and between 0 and 10 Web-based 24-hour dietary recalls (24hRW). Data collection with the different methods did not exactly cover the same time period. Within a time frame of 3 years each participant collected two DPs (~5 months apart) and two urine samples (~1 year apart). The 24hRTs were administrated approximately 4 months apart and the 24hRWs approximately 3 months apart. A varying number of 24hR per person was available because participants were enrolled in different substudies of the NQplus study. However, to be consistent with the number of two DPs available, only the first two 24hRs collected per participant were used. In addition, in 70 of the 200 DUPLO study participants, total energy expenditure was determined using the doubly labeled water

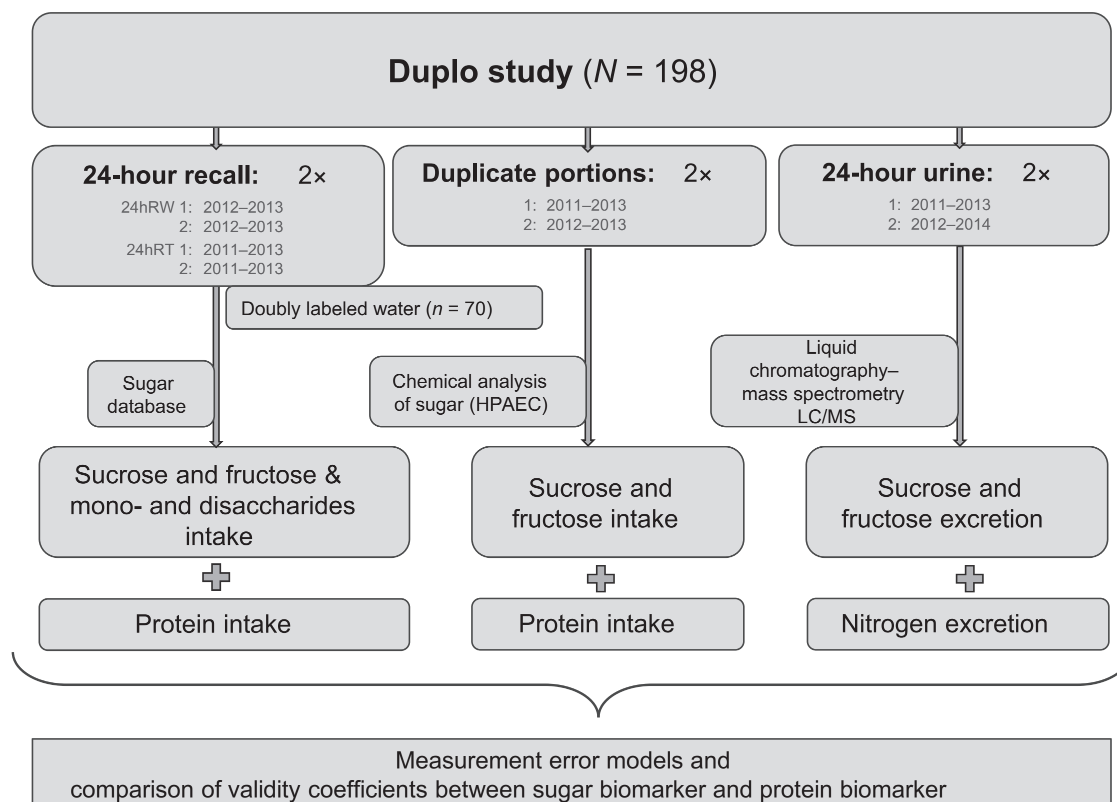

Figure 1.

Study design and the time frame of data collection. Within a time frame of 3 years each participant randomly collected two DPs (~5 months apart) and two urine samples (~1 year apart). The 24hRTs were administrated approximately 4 months apart and the 24hRWs approximately 3 months apart. A subsample of participants had total energy expenditure determined using the DLW method.

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method (DLW; refs. 25, 26). Two participants got pregnant during the study and were, therefore, excluded from analysis of this study, because it was suspected that they had changed their habitual dietary intake, energy expenditure, and urinary excretions.

Data collection

DP collection and analytic methods

Participants collected twice (~5 months apart) an identical portion of all foods and drinks consumed over a 24-hour period (26). Subjects received a monetary reimbursement for the foods collected. The DPs were stored in a cool box (5°C) and picked up from the participants' home 1 day after collection. At the study center, the samples were weighed and homogenized in a blender (Waring Commercial model 34BL22) with the addition of an antioxidant (2.5 mL of 0.02% tert-butylhydroquinone in ethanol per kg of sample; BHQ, E319). The homogenized samples were stored within 1 hour at −20°C, and part of the sample was freeze-dried. The mono- and disaccharides were extracted from the freeze-dried samples, and then chemically analyzed by high-performance anion exchange chromatography with pulsed amperometric detection, as described previously (27), to obtain sucrose and fructose content.

24-hour dietary recalls

Total mono- and disaccharides, and sucrose and fructose intake assessed by 24hRT and 24hRW was calculated using the Dutch Food Composition Database NEVO of 2011 (28), and the newly developed Food Composition Database, which linked data on sucrose and fructose to the food codes in the NEVO database (29). In both DP and 24hR, sugar was expressed as the sum of sucrose plus fructose.

24hRs were either filled out online by the participants after an unannounced email invitation (24hRW; ~3 months apart) or collected by a telephone interview (24hRT; ~4 months apart) by trained dieticians. Both methods were based on the five-step multiple pass method (30). The 24hRW was performed and processed using the software program Compl-eat, consisting of a recall and a calculation module, which was developed at Wageningen University (Wageningen, the Netherlands; ref. 31). Portion sizes of foods or recipes were reported using household measures, standard portion sizes, weight in grams, or volume in liters. Recalls were checked for completeness and for unusual or missing values; if necessary, adjustments were made using a standard protocol. The 24hRTs were coded and also processed using the calculation module of Compl-eat (32–34).

Urine sampling and urinary sugar analysis

Participants collected two 24-hour urine samples (~1 year apart). The urine collection started after discarding the first voiding on the morning of the collection day and finished after the first voiding on the morning of the next day. Three 80 mg tablets of para-aminobenzoic acid (PABA) were ingested during breakfast, lunch, and supper to check for completeness of urine collection. The preservative, lithium dihydrogen phosphate (25 g), was added to the collection containers. This was done to allow metabolomics analysis in the urine samples in a substudy of the NQplus study. At the study center, the urine collections were mixed, weighted, aliquoted, and stored at −20°C until further analyses.

PABA was measured by means of high-performance liquid chromatography (HPLC) after alkaline hydrolysis of the urine samples to convert PABA metabolites into PABA (35). Considering a minimum of 78% PABA recovery as a cut-off point for complete urine collection, which is proposed if PABA is analyzed by HPLC (35), 18.4% of the urine samples were judged incomplete.

Urinary sucrose and fructose concentrations were determined by LC/MS-MS. Quantification of sucrose and fructose was achieved over the range 0.1–1,000 μmol/L with the inclusion of stable isotope-labeled internal standards (^{13}C12-sucrose and ^{13}C6-fructose, Sigma-Aldrich). Prior to analysis, urine samples were thawed at 4 °C, and then a 100 μL aliquot was transferred to an Eppendorf tube to which 100 μL internal standard solution containing ^{13}C12-sucrose and ^{13}C6-fructose was added. This was vortex mixed and centrifuged at 13,000 × g for 10 minutes and the supernatant was transferred into a 96-well plate for LC/MS-MS analysis. Separation was performed on a Waters Acquity UPLC Instrument using a BEH Amide Column (Waters) coupled to a Quattro Ultima tandem quadrupole Mass Spectrometer (Micromass). The mass spectrometer was operated with positive electrospray ionization using multiple reaction monitoring mode (transitions monitored for fructose were 197.9 > 162.9 and 197.9 > 144.9 and for sucrose were 359.9 > 144.9 and 359.9 > 162.9).

Sucrose or fructose concentrations below the detection limit (0.1 μmol/L) were estimated to be 0.05 μmol/L, assuming that concentrations below the detection limit were normally distributed. Concentrations were transformed into g/L. Urinary sugar was expressed as the sum of urinary sucrose plus urinary fructose.

DLW

Total energy expenditure over a 2-week period was assessed by DLW method in 70 participants. Data from one participant were excluded because of physiologically implausible body water changes between repeated measurements, while body weight remained stable. Thus, data of 37 men and 32 women were included and 29 of these participants completed a second DLW measurement. We used the average energy expenditure per person from DLW method if two measurements were available; otherwise the single DLW estimate was used. A detailed description of the DLW method applied in the DUPLO study can be found elsewhere (26).

Statistical analysis

Baseline population characteristics are presented as mean and SD. Categorical data are reported as percentages of total. Dietary and urinary data were checked for normality by executing Shapiro–Wilk tests and histograms, and because of their skewed distribution, are presented as median with interquartile range (IQR), and a square root transformation was applied. Participants with missing data for one or more of the methods were included in the analysis because they provided information for the other methods. The significance level was set at a two-sided P value of 0.05. R Software version 3.4.3 (R Development Core Team) and SAS Software version 9.4 for Windows (SAS Institute Inc) were used to analyze the data.

ME models

We considered DP, 24hRT, or 24hRW, each as reference methods of dietary intake. We assumed dietary intake assessed by the reference methods to be unbiased estimates of the "true" unknown intake, T (36), and not to vary within the duration of the study, as well as to have a linear relationship with the biomarker.

In our ME model, i is the person and j indicates the occasion; α_M the constant bias; β_M the proportional scaling bias; w_{Mi} the person-specific bias; ε_{Mij} the random within-person error with mean zero and constant variance for the biomarker (M) and εX_{ij}, similarly for the reference

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method X (either DP, 24hRT, or 24hRW). Repeated measurements (replicates) of biomarker contributed to the estimation of $w_{Mi.}$

$$\text{Reference method model: } X_{ij} = T + \varepsilon X_{ij} \quad \text{(A)}$$

$$\text{Biomarker model}: Mij = \alpha_M + \beta_{M*} T + w_{Mi} + \varepsilon_{Mij} \quad \text{(B)}$$

The constant bias, α_M, showed a high correlation with β_M, which hindered us from adequately estimating β_M and, in some cases, caused models to fail to converge. Therefore, we removed the term α_M and assumed absence of constant additive systematic error in the biomarker model (equation B). Age, BMI, and gender were added to the models to account for possible confounders. Except for gender, none of the possible confounders seemed to influence the model outcomes; therefore, gender-specific ME models are reported.

The reference method model (equation A) was modeled with three different dietary intake components: sucrose, sugar (i.e., sucrose plus fructose), or mono- and disaccharides. The reference method model was related to the biomarker model (equation B), for which the input was urinary sugar data (i.e., urinary sucrose plus urinary fructose).

With the estimates obtained from the ME models, we calculated the VC, ρ_{MT} (equation C), and the attenuation factor (AF), λ_M (equation D). The VC assesses the loss of statistical power to detect a diet–disease association and the ability to rank participants according to their intake, whereas the AF provides the attenuation of the diet–disease associations by using the biomarker instead of the true sugar intake. Note that the closer to 1, the better the VC is, and that the AF is not only influenced by ME, but also by β_M, the regression coefficient of biomarker measurement on true intake.

$$\text{Validity coefficient}: \rho_{M,T} = \sqrt{\frac{\beta_M^2 * \textit{variance } T}{\beta_M^2 * \textit{variance } T + \frac{\textit{variance } \varepsilon_{Mij}}{\kappa} + \textit{variance } w_{Mi}}} \quad \text{(C)}$$

$$\text{Attenuation factor}: \lambda_M = \frac{{\rho_{M,T}}^2}{\beta_M} \quad \text{(D)}$$

where, *variance T* is the variance of the "true" intake, *variance* ε_{Mij} denotes the variance of the random within-person error, *variance* w_{Mi} is the variance of the person-specific bias, and k the number of replicates of the biomarker. We assessed the theoretical case of obtaining an infinite (∞) number of biomarker measurements, in which within-person variation ($\frac{\textit{variance } \varepsilon_{Mij}}{\kappa}$) cancels out from the equations.

Protein models and sugar biomarker evaluation

Considering that organic urinary nitrogen is a good recovery biomarker of dietary protein intake (23), it was used to evaluate the performance of the sugar biomarker, which was considered as "good" if the difference of its VCs deviated less than 10% from those of protein. Therefore, we also performed the previously proposed ME models and calculated the VC and AF between protein intake and urinary nitrogen data, which were also collected in the same participants within the DUPLO study framework (22). Protein intake assessed by 24hRT and 24hRW was calculated using the Dutch Food Composition Database NEVO of 2011 (27). Detailed methodology of protein intake and urinary nitrogen data assessment was described previously elsewhere (22). Furthermore, assuming independence of the errors in the reference method and in the biomarker, the VC calculated for the sugar biomarker can be considered as a lower boundary for the true value of the VC.

Sensitivity analyses

A sensitivity analysis was performed comparing the model outcomes from the complete urine dataset with the model outcomes after exclusion of the urine samples with PABA recovery <78% (35). ME model outcomes did not differ substantially when no urine samples were excluded compared with excluding urines with PABA recovery <78%. We, therefore, reported the results on the basis of the complete set of urine samples.

A second sensitivity analysis with a subset of 69 participants substituting absolute intakes by densities of sugar intake (calculated on the basis of the energy expenditure assessed by DLW) did not substantially affect the model outcomes. Thus, models with absolute intakes were reported.

Finally, a sensitivity analysis including all 24hRW and 24hRT measurements available, instead of up to two replicates per participant, did not substantially affect the model outcomes. As a result of that, and also to improve the comparability of the models with 24hRT or 24hRW as reference method with the models with DP as reference method, for which a maximum of two measurements per individual were available, models with a maximum of two 24hRs per participant were reported.

Intraclass correlation coefficients

We also evaluated the reproducibility of the biomarker using intraclass correlation coefficients (ICC) between the two biomarker measurements of each participant with linear mixed models.

$$\text{ICC} = \frac{\textit{Between}-\textit{individual variance}}{(\textit{Between}-\textit{individual variance} + \textit{within}-\textit{indiviudal variance})} \quad \text{(E)}$$

Results

At baseline, participants ($n = 198$) were on average 55.7 (SD, 10.2) years old, had mean BMI of 25.1 kg/m^2 (SD, 3.7), and 18.7% were classified as low educated (primary or lower education), while 52.5% were classified as high educated (university or college degree; **Table 1**).

Table 1. Baseline characteristics of the study population, Wageningen, the Netherlands, July 2011–July 2014 (mean value ± SD or absolute number and proportion).

	Total ($N = 198$)	**Women ($n = 106$)**	**Men ($n = 92$)**
Age (years)	55.7 (±10.2)	53.8 (±10.6)	58.0 (±9.3)
BMI (kg/m^2)	25.1 (±3.7)	24.6 (±3.8)	25.8 (±3.5)
BMI, *n* (%)			
<25 kg/m^2	110 (55.6%)	68 (64.2%)	42 (45.7%)
25–30 kg/m^2	67 (33.8%)	27 (25.5%)	40 (43.5%)
>30 kg/m^2	21 (10.6%)	11 (10.4%)	10 (10.9%)
Education level, *n* (%)			
Low[a]	37 (18.7%)	23 (21.7%)	14 (15.2%)
Intermediate[b]	57 (28.8%)	32 (30.2%)	25 (27.2%)
High[c]	104 (52.5%)	51 (48.1%)	53 (57.6%)

[a]Primary or lower education.
[b]Secondary or higher vocational education.
[c]University or college.

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Median intake and urinary excretion of sugars are presented in **Table 2**. Median sucrose, fructose, and sugar estimated with the three dietary assessment methods were somewhat different. The 24hRT estimated the highest median intake of sucrose (39.6 g; IQR, 29.1), while DP estimated the highest median fructose intake (50.6 g; IQR, 35.3) and sugar intake (74.5 g; IQR, 38.5) among all participants. The lowest median sucrose, fructose, and sugar intake was assessed by 24hRW. A similar pattern in estimated intake was found among gender subgroups, with men and women having comparable median intakes by all three dietary assessment methods used. Mono- and disaccharides intake was only assessed by 24hRT and 24hRW, with an overall median intake of 99.6 g (IQR, 43.0) and 89.7 g (IQR, 55.3), respectively. Median intake of mono- and disaccharides was higher in both women (98.2 g; IQR, 35.0) and men (100 g; IQR, 52.3) using the 24hRT. Median urinary excretion of sugar was 34.4 mg (IQR, 33.9) among all participants, with sucrose accounting for the majority of it (21.6 mg; IQR, 23.7). Median urinary sucrose was 17.8 mg (IQR, 22.4) in women and 27.8 mg (IQR, 29.0) in men.

The VCs and AFs are presented in **Table 3**. VCs and AFs varied depending on the dietary component studied (either sucrose, sugar, or mono- and disaccharides), reference method used (either DP, 24hRT, or 24hRW), and gender analyzed. The VCs and AFs increased when the number of replicates was raised from one up to infinite, with the AFs starting at higher values and increasing by a greater factor with raising number of replicates compared with the VCs. Men showed higher VCs and AFs than women in all dietary component models, regardless of the reference method. All VCs of the sugar and mono- and disaccharides component models were smaller than the corresponding VC in the sucrose component model, for all reference methods and for both genders, indicating that the biomarker's ranking ability is best for sucrose intake. In the sucrose component model, the highest VCs for infinite replicates were found with DP as the reference method (0.72 for women and 0.93 for men), while in the sugar component model, the highest coefficients were found with 24hRW as the reference method for women (0.56) and 24hRT as the reference method for men (0.71). When mono- and disaccharides were modeled, the VCs were comparable for the 24hRT and 24hRW reference methods for women (0.48 vs. 0.46, respectively), and were moderately different for men (0.53 vs. 0.62, respectively; **Table 3**).

Variance of "true" intake (variance *T*) ranged between 0.82 (sucrose component model for women, with DP as the reference method) up to 1.85 (mono- and disaccharides component model for men, with 24hRW as the reference method). Variance of person-specific bias (variance w_i) varied between 0.02 and 0.04. Variance of within-person error (variance ε_{ij}) was constant across all models, consistent with the methodology. Proportional scaling bias (β_M), which means less bias when closer to 1, varied to a similar extent for both genders (range, 0.01–0.04; **Table 4**).

The VCs for protein component models (see **Table 5**), in the theoretical scenario of infinite replicates, were compared with the VCs for the sucrose, sugar, and mono- and disaccharides component models (see **Table 3**). The component models in which VCs differed more than 10% from the respective protein component model were: (i) sucrose component model with 24hRT as the reference method, for women; (ii) all sugar component models, except for the model with 24hRW as the reference method for men; and (iii) all mono- and disaccharides component models. However, despite not presenting comparable VCs for infinite replicates, in some of those models, the VCs for three replicates were comparable to the VCs of the respective protein component model with only one replicate. These models were the sugar component model, with 24hRW as the reference

Table 2. Median intakes and excretion of sucrose, fructose, sugar[a], and mono- and disaccharides, in grams, per gender, as measured by DP, 24hRT, 24hRW, and urinary marker of sugar intake (M), as measured by LC/MS-MS, among 106 women and 92 men ages 20–70 years, Wageningen, the Netherlands, July 2011–July 2014 (median value and IQR).

			Total ($N = 198$)				Women ($n = 106$)				Men ($n = 92$)			
	n	Total number of measurements	Sucrose median (IQR)	Fructose median (IQR)	Sugar[a] median (IQR)	Mono- and disaccharides median (IQR)	Sucrose median (IQR)	Fructose median (IQR)	Sugar[a] median (IQR)	Mono- and disaccharides median (IQR)	Sucrose median (IQR)	Fructose median (IQR)	Sugar[a] median (IQR)	Mono- and disaccharides median (IQR)
Intake (g/day)														
DP	198	396	19.7 (24.5)	50.6 (35.3)	74.5 (38.5)	—	17.9 (22.7)	51.8 (31.3)	71.3 (34.7)	—	24.4 (27.9)	49.7 (36.8)	77.7 (52.4)	—
24hRT	155	302	39.6 (29.1)	15.9 (14.9)	61.6 (27.2)	99.6 (43.0)	41.4 (27.7)	15.9 (13.0)	61.8 (26.8)	98.2 (35.0)	37.5 (31.4)	15.4 (17.1)	59.0 (33.1)	100 (52.3)
24hRW	194	384	21.1 (23.1)	10.9 (11.1)	34.8 (30.3)	89.7 (55.3)	20.8 (21.0)	11.0 (8.9)	33.7 (21.5)	84.7 (50.5)	23.0 (25.1)	10.5 (13.2)	35.7 (39.0)	93.7 (62.2)
Urinary excretion (mg/day)	195	380	21.6 (23.7)	9.3 (13.9)	34.3 (33.9)	—	17.8 (22.4)	7.9 (13.1)	27.3 (27.7)	—	27.8 (29.0)	11.4 (13.9)	42.7 (42.6)	—

Note: Data were first averaged on the individual level and then overall median was obtained.
[a]Sugar, sucrose plus fructose.

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Table 3. VCs and AFs of the urinary marker of sugar intake[a] (M) for sucrose, sugar[b], and mono- and disaccharides intake, per gender, in grams, on square root scale, with the DP, 24hRT, or 24hRW as the reference method[c] (X), among 106 women and 92 men ages 20–70 years, Wageningen, the Netherlands, July 2011–July 2014 (estimate and SE).

		Women (n = 106)[d]			Men (n = 92)[d]		
	k	Sucrose intake estimate (SE)	Sugar intake[b] estimate (SE)	Mono- and disaccharides intake estimate (SE)	Sucrose intake estimate (SE)	Sugar intake[b] estimate (SE)	Mono- and disaccharides intake estimate (SE)
VC ($\rho_{X,M}$)							
DP	1	0.43 (0.07)	0.28 (0.04)	—	0.60 (0.05)	0.42 (0.04)	—
	2	0.53 (0.09)	0.35 (0.05)	—	0.71 (0.06)	0.49 (0.04)	—
	3	0.57 (0.10)	0.38 (0.05)	—	0.77 (0.07)	0.52 (0.05)	—
	∞	0.72 (0.14)	0.49 (0.09)	—	0.93 (0.11)	0.62 (0.07)	—
24hRT	1	0.34 (0.04)	0.30 (0.04)	0.27 (0.03)	0.49 (0.06)	0.45 (0.06)	0.33 (0.05)
	2	0.41 (0.06)	0.36 (0.05)	0.34 (0.04)	0.59 (0.07)	0.54 (0.07)	0.39 (0.06)
	3	0.45 (0.06)	0.40 (0.05)	0.37 (0.05)	0.64 (0.07)	0.58 (0.07)	0.43 (0.07)
	∞	0.57 (0.10)	0.51 (0.09)	0.48 (0.09)	0.78 (0.11)	0.71 (0.11)	0.53 (0.10)
24hRW	1	0.43 (0.05)	0.33 (0.05)	0.28 (0.04)	0.51 (0.06)	0.45 (0.06)	0.42 (0.04)
	2	0.52 (0.06)	0.41 (0.07)	0.34 (0.05)	0.60 (0.07)	0.53 (0.06)	0.50 (0.05)
	3	0.57 (0.07)	0.44 (0.07)	0.37 (0.05)	0.65 (0.08)	0.57 (0.07)	0.53 (0.05)
	∞	0.70 (0.11)	0.56 (0.11)	0.46 (0.08)	0.78 (0.11)	0.68 (0.09)	0.62 (0.07)
AF ($\gamma_{X,\ M}$)							
DP	1	4.46 (1.60)	4.08 (1.17)	—	8.80 (1.70)	7.77 (1.49)	—
	2	6.57 (2.29)	6.10 (1.78)	—	12.4 (2.26)	10.6 (2.05)	—
	3	7.79 (2.73)	7.30 (2.21)	—	14.3 (2.67)	12.1 (2.43)	—
	∞	12.4 (4.92)	12.1 (4.74)	—	20.8 (5.02)	16.9 (4.15)	—
24hRT	1	4.40 (1.24)	4.05 (1.10)	4.46 (1.10)	7.95 (1.99)	7.79 (2.07)	5.49 (1.85)
	2	6.49 (1.84)	6.00 (1.66)	6.70 (1.73)	11.3 (2.76)	11.2 (2.94)	7.92 (2.71)
	3	7.71 (2.25)	7.15 (2.06)	8.04 (2.21)	13.1 (3.26)	13.0 (3.51)	9.30 (3.25)
	∞	12.4 (4.56)	11.6 (4.38)	13.4 (5.18)	19.4 (5.75)	19.6 (6.32)	14.2 (5.77)
24hRW	1	5.08 (1.35)	3.79 (1.34)	4.25 (1.29)	5.91 (1.49)	5.88 (1.55)	8.58 (1.71)
	2	7.33 (1.86)	5.59 (1.94)	6.22 (1.89)	8.30 (2.01)	8.17 (2.07)	11.7 (2.32)
	3	8.60 (2.21)	6.63 (2.32)	7.35 (2.30)	9.59 (2.34)	9.38 (2.39)	13.3 (2.72)
	∞	13.1 (4.08)	10.6 (4.31)	11.6 (4.41)	13.9 (3.97)	13.3 (3.84)	18.3 (4.51)

Abbreviations: k, number of biomarker replicates; ∞, infinite.
[a]M, urinary marker, urinary sucrose plus fructose.
[b]Sugar, sucrose plus fructose.
[c]X, reference method.
[d]Gender-specific estimates were obtained using model equations (C) and (D).

method for women and 24hRT as the reference method for men, and the mono- and disaccharides component model, with 24hRW as the reference method for men. This suggests that, with an increased number of replicates, these models showed similar performance to the respective protein component model with a single replicate. Furthermore, in comparison with protein component models, increasing the number of marker replicates (from one up to infinite) led to larger improvements in VCs for the sucrose, sugar, and mono- and disaccharides component models.

ICC of repeated urinary biomarker measurements for sucrose was 0.47 [95% confidence interval (CI), 0.36–0.58], while for urinary fructose was 0.38 (95% CI, 0.26–0.51) and for urinary sugar was 0.41 (95% CI, 0.29–0.53). Within-individual variance was larger than between-individual variance, indicating large day-to-day variance in the biomarker measurements (**Table 6**).

Discussion

The primary aim of this project was to investigate the agreement in ranking of individuals between their sugar intake and urinary excretion of sucrose and fructose in a sample of Dutch individuals from the DUPLO study. Our second aim was to compare the performance of the sugar biomarker with the protein biomarker. We found that repeated measurements of urinary sucrose and fructose ranked individuals almost comparable to their daily sucrose intake as urinary nitrogen does to their protein intake. To our knowledge, this is the first study to validate the sugar biomarker with three different dietary assessment methods in a free-living population and compare its ranking ability with a good recovery biomarker (i.e., protein biomarker) in the same study population. Moreover, we had the unique availability of DPs, in which the amount of sucrose and fructose was measured instead of calculating using a sugar composition database.

We found differences in the median intake assessed by the three dietary assessment methods (DP, 24hRT, and 24hRW). Estimated median sucrose intake was roughly two times higher than fructose intake when assessed by 24hRT compared with DP, while fructose intake was more than three times higher than sucrose intake when assessed by 24hRT and 24hRW compared with DP. This could be explained by differences between the methods, for instance, selective reporting (24hR) and/or selective collection (DP), and mismatch of documented sugar contents (e.g., data from food composition databases in 24hR and data analyzed in DP). In addition, 24hR estimated

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Table 4. ME estimates of the urinary marker of sugar intake[a] (M) for sucrose, sugar[b], and mono- and disaccharides intake, per gender, with DP, 24hRT, or 24hRW as reference method, per gender, in grams, on square root scale, among 106 women and 92 men ages 20–70 years, Wageningen, the Netherlands, July 2011–July 2014 (estimate and SE).

	Women ($n = 106$)[c]			Men ($n = 92$)[c]		
	Sucrose intake estimate (SE)	Sugar intake[b] estimate (SE)	Mono- and disaccharides intake estimate (SE)	Sucrose intake estimate (SE)	Sugar intake[b] estimate (SE)	Mono- and disaccharides intake estimate (SE)
Variance of "true" intake (var_T)[d]						
DP	0.82 (0.16)	1.12 (0.16)	—	1.50 (0.21)	1.69 (0.17)	—
24hRT	1.03 (0.15)	1.08 (0.14)	1.28 (0.15)	1.39 (0.19)	1.50 (0.21)	1.43 (0.24)
24hRW	0.95 (0.14)	0.90 (0.17)	1.23 (0.19)	1.02 (0.15)	1.16 (0.18)	1.85 (0.20)
Variance of person-specific bias (var_{wi})						
DP	0.03 (0.011)	0.04 (0.008)	—	0.02 (0.018)	0.04 (0.008)	—
24hRT	0.03 (0.009)	0.04 (0.008)	0.04 (0.008)	0.03 (0.011)	0.03 (0.01)	0.04 (0.009)
24hRW	0.03 (0.01)	0.04 (0.009)	0.04 (0.008)	0.03 (0.011)	0.04 (0.01)	0.04 (0.009)
Variance of within-person error ($var_{\varepsilon ij}$)						
DP	0.06 (0.004)	0.06 (0.004)	—	0.06 (0.005)	0.06 (0.005)	—
24hRT	0.06 (0.004)	0.06 (0.004)	0.06 (0.004)	0.06 (0.005)	0.06 (0.005)	0.06 (0.005)
24hRW	0.06 (0.004)	0.06 (0.004)	0.06 (0.004)	0.06 (0.005)	0.06 (0.005)	0.06 (0.005)
Proportional scaling bias (β_M)						
DP	0.04 (0.002)	0.02 (0.001)	—	0.04 (0.001)	0.02 (0.001)	—
24hRT	0.02 (0.001)	0.02 (0.001)	0.01 (0.001)	0.03 (0.001)	0.02 (0.001)	0.02 (0.001)
24hRW	0.03 (0.001)	0.03 (0.001)	0.01 (0.001)	0.04 (0.001)	0.03 (0.001)	0.02 (0.001)

[a]M, urinary marker, urinary sucrose plus fructose.
[b]Sugar, sucrose plus fructose.
[c]Gender-specific estimates were obtained using model equations (A) and (B).
[d]As measured by the reference method.

intake on the basis of sugar data linked to the Food Composition Database in 2011, and DP samples were collected between 2011 and 2014. Thus, it is possible that industrialized foods had their formulation or food labeling modified over that period of time (e.g., reduction of sugar content or partial substitution of sucrose by syrups, such as fructose-glucose syrup) or the actual sugar content could have been mislabeled or misinterpreted. The dietary assessments were performed randomly throughout the study period; therefore, it is unlikely that any changes in dietary patterns affected any method in particular. We estimate that the higher fructose intake based on analysis in DPs samples is not due to hydrolysis of sucrose. Sugar is stable in freeze-dried foods and because of its stability it is used for stabilizing protein in freeze-dried materials (37). So, there are a number of possible explanations for the differences observed in median intake, yet it is difficult to estimate and disentangle their influence on the results found.

We also observed differences in intake estimated by 24hRT and 24hRW. The 24hRW estimated intake of sucrose and sugar almost twice as low as the 24hRT. Both recalls had food items assigned to the same food groups, hence we were able to compare the number of times the intake of foods from certain food groups were reported by the participants. We observed that in the 24hRT, participants consumed 8% more from the food groups "sugar, confectionary, sweet fillings, and sweet sauces," 9% more "fruits," 16% more "vegetables," and 4% more "pastry, cakes, and biscuits" than in the 24hRW (Supplementary Table S1).

Nevertheless, the intake of mono- and disaccharides estimated by the Dutch National Food Consumption Survey (110 g/day; ref. 38), was rather comparable to what was found in this study.

The mean urinary sucrose and fructose assessed in our study (Supplementary Table S2) were smaller than what has been found by a highly controlled study when 13 participants were fed their usual diet and had their urinary sugars assessed by enzymatic assay (sucrose 36.6 vs. 29.6 mg/day in our study and fructose 61.8 vs. 13.0 mg/day in our study; ref. 15). Likewise, values higher than what we observed were found in a randomized cross-over feeding study, where 81 individuals following a low- and high-glycemic load diet had their urinary sugars assessed by gas chromatography (sucrose 16.9 mg/day and fructose 57.2 mg/day; ref. 39). In the latter study, considerable differences were observed between the enzymatic assay and the gas chromatography method, with correlation coefficients of 0.71 for fructose and 0.27 for sucrose. We estimated sucrose and fructose by LC/MS-MS, which has been shown to be a superior method with better sensitivity, accuracy, and precision (39). Moreover, considering the study design and the free-living conditions of our study, differences from controlled studies are to be expected.

The results from our ME models are in-line with what has been previously found in a study with free-living subjects (40). The Pearson correlation coefficient between self-reported and true intake for mono- and disaccharides intake in the OPEN study was 0.25 for women and 0.58 for men (based on the average of two 24hRs; ref. 40). Despite differences in study design and study population, the average VC of 24hRT and 24hRW in our study was 0.34 for women and 0.45 for men in the mono- and disaccharides component models.

In agreement with our findings, where BMI did not seem to influence our models' outcomes when added as a covariate in the sensitivity analysis, Joosen and colleagues did not find an interaction between sucrose or fructose urinary excretion and BMI (18). That could suggest that the application of the marker is valid regardless of the individual's BMI. This is an advantage over dietary assessment methods, in which reporting of intake is influenced by BMI. Such an

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Table 5. VCs and AFs of the urinary biomarker (M) for protein intake, per gender, in grams, on square root scale, with the DP, 24hRT, or 24hRW as the reference method[a] (X), among 106 women and 92 men ages 20–70 years, Wageningen, the Netherlands, July 2011–July 2014 (estimate and SE).

	k	Women ($n = 106$)[b] Estimate (SE)	Men ($n = 92$)[b] Estimate (SE)
VC ($\rho_{X,M}$)			
DP	1	0.60 (0.05)	0.73 (0.04)
	2	0.66 (0.06)	0.81 (0.04)
	3	0.69 (0.06)	0.84 (0.04)
	∞	0.75 (0.07)	0.92 (0.05)
24hRT	1	0.62 (0.07)	0.66 (0.07)
	2	0.69 (0.07)	0.74 (0.08)
	3	0.72 (0.08)	0.77 (0.08)
	∞	0.79 (0.09)	0.84 (0.09)
24hRW	1	0.55 (0.10)	0.55 (0.08)
	2	0.62 (0.11)	0.61 (0.09)
	3	0.65 (0.12)	0.64 (0.10)
	∞	0.71 (0.13)	0.70 (0.11)
AF with BM ($\gamma_{X,M}$)			
DP	1	0.33 (0.06)	0.46 (0.05)
	2	0.40 (0.07)	0.56 (0.06)
	3	0.43 (0.08)	0.61 (0.06)
	∞	0.52 (0.10)	0.72 (0.09)
24hRT	1	0.37 (0.08)	0.39 (0.09)
	2	0.45 (0.10)	0.49 (0.11)
	3	0.49 (0.11)	0.53 (0.12)
	∞	0.59 (0.14)	0.63 (0.15)
24hRW	1	0.28 (0.10)	0.26 (0.08)
	2	0.34 (0.13)	0.32 (0.10)
	3	0.37 (0.14)	0.35 (0.11)
	∞	0.45 (0.17)	0.42 (0.14)

Abbreviations: *k*, number of biomarker replicates; ∞, infinite.
[a]X, reference method.
[b]Gender-specific estimates were obtained using model equations (C) and (D) for protein.

influence of BMI on self-reported intake was previously seen in the DUPLO study population, where BMI was found to be consistently associated with misreporting of energy, protein, and potassium intake (41).

We found that repeated measurements of urinary sucrose and fructose ranked individuals comparable with their sucrose intake as urinary nitrogen does for protein intake, especially when DPs were used for assessing intake (**Tables 3** and **5**). As with protein, the VCs for urinary sugars were slightly lower for females than for males. For the 24hRs, the VCs for sugar and protein were similar in men (average VC of 24hRT and 24hRW was 0.77 and 0.78 for protein and sucrose, respectively), but the VC for sugar was slightly lower in women (average VC of 24hRT and 24hRW was 0.75 and 0.63 for protein and sucrose, respectively). However, such agreement was mostly seen when the number of sugar biomarker replicates was theoretically increased to represent the usual intake ($n = \infty$). Increasing the number of repeated measurements led to larger improvements in VCs in the sucrose, sugar, and mono- and disaccharides component models in comparison with protein models. In view of higher within-person variability in sugar intake compared with protein intake, larger improvements in VCs seem plausible (42) and seem to indicate the need for more replicates in research settings where urinary measurements are used as a proxy for sugar intake. Furthermore, the protein biomarker is a known good recovery biomarker (23), and both protein and sugar are short-term biomarkers, that is, a time window of 1 day. Moreover, even though dietary assessment methods may be more susceptible to underestimation of sugar-rich products than protein-rich products (43), the sugar biomarker appears to be comparable to the protein biomarker in our study.

Modeling the sucrose intake data provided the highest VCs among the three dietary intake components modeled (sucrose, sugar, and mono- and disaccharides). When compared with DP, the sucrose component models using 24hRW and 24hRT as reference methods showed a lower VC among women and more pronounced VC among men in the theoretical scenario of infinite replicates.

AFs for sugar biomarker showed remarkably high values when compared with protein models. AFs are influenced by the magnitude of the proportional scaling bias (β_M, i.e., β_M is the divisor of equation D). The AF can be used as a multiplicative factor to correct the RR estimate on the association between diet and disease. An AF higher than 1 suggests a possible over-correction, with a greater deviation from 1 indicating more over-correction. Proportional scaling bias ranged between 0.01 and 0.04 for sugar biomarker and between 0.48 and 0.63 for protein (44), and therefore, produced much lower AF for protein biomarker.

The sugar biomarker showed fair reproducibility in terms of ICC values (**Table 6**), which reflects the degree of correlation and the agreement between the biomarker measurements. We found a high within-person variation, suggesting a high variability in subject's day-to-day intake of sugar. Therefore, to capture individual habitual intake, one needs to cover many days of intake or multiple days of urine collection.

A weakness of our study is the limited generalizability of our findings to other populations, considering that we studied a group of individuals that is not representative of the general Dutch population; for example, they were more highly educated and were less overweight, and they were highly motivated (26). We screened our participants for diabetes mellitus and other chronic diseases; however, we cannot exclude the possibility of having prediabetic patients in our sample set, who could have had a different urinary fructose excretion as has been shown in patients with diabetes (45).

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Table 6. ICC of urinary marker measurements of sucrose, fructose, and sugar[a], square root transformed, among 106 women and 92 men ages 20–70 years, Wageningen, the Netherlands, July 2011–July 2014 (ICC and 95% CIs).

	Sucrose	Fructose	Sugar[a]
ICC (95% CI)	0.47 (0.36–0.58)	0.38 (0.26–0.51)	0.41 (0.29–0.53)
Within-individual variance	3.33	2.01	4.24
Between-individual variance	2.96	1.26	2.69

[a]Sugar, sucrose plus fructose.

Making assumptions was necessary to be able to estimate model parameters, even though not all of these assumptions may hold in practice. We made assumptions of negligible error correlation (between the biomarker and DP or 24hR and between replicates of the biomarker), and assumptions of absence of proportional scaling bias for the DP and 24hR. The assumption of uncorrelated errors between biomarker and DP or 24hR is likely to hold because the errors in biomarker measurements are assumed to be mostly physiologic, while the errors in DP and 24hR are related to the reporting of dietary intake. Moreover, the study design was designed for replicates to be taken independently with enough time in between and individual characteristics absorbed by the person-specific error terms.

A strength of our study is the use of data from a well-designed validation study, performed in a relatively large population, in free-living conditions. Even though some of the methods used to estimate intake and urinary excretion might be troublesome and costly, for example, collection of DPs and chemical analysis of sugars and assessment of urinary sugar by LC/MS-MS, they seem less prone to bias and more precise than other methods of choice.

Research applications of the sugar biomarker include its use for validating dietary assessment methods, for monitoring compliance in human feeding studies, for monitoring the effect of public health interventions, and as a surrogate for ranking subjects according to intake when information on sucrose in food composition databases is lacking.

Considering that, when compared with the protein biomarker, the sugar biomarker showed slightly lower VCs, we believe that the urinary sugar marker is also able to adequately rank sugar intakes in other populations. However, the biomarker might have a different performance in populations with very low or very high intakes, that is, if the relationship between intake and excretion is strongly nonlinear at very high or very low levels of intake, the ranking ability of the biomarker could be affected. Therefore, future research should focus on assessing the validity of the biomarker at wider ranges of intake.

In free-living conditions, repeated measurements of urinary sucrose and fructose ranked Dutch adults almost comparable to their daily sucrose intake, as urinary nitrogen does to their protein intake. This study adds to the literature on the use of urinary sucrose and fructose as a predictive biomarker of sugar intake.

Authors' Disclosures

P.J.M. Hulshof reports grants from Knowledge Centre Sugar and Nutrition (primary source of funding for the reported study) during the conduct of the study and Top Consortium Knowledge and Innovation (project: high pigment potatoes for a healthy lifestyle) outside the submitted work. J.H.M. de Vries reports grants from Knowledge Centre Sugar and Nutrition during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

T.C. Abreu: Formal analysis, investigation, writing–original draft, writing–review and editing. **P.J.M. Hulshof:** Conceptualization, methodology, project administration, writing–review and editing. **H.C. Boshuizen:** Conceptualization, methodology, writing–review and editing. **L. Trijsburg:** Investigation, methodology, writing–review and editing. **N. Gray:** Investigation. **J.H.M. de Vries:** Conceptualization, supervision, methodology, project administration, writing–review and editing.

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