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Original Research Article

Relative validity of habitual sugar and low/no-calorie sweetener consumption assessed by food frequency questionnaire, multiple 24-h dietary recalls and urinary biomarkers: an observational study within the SWEET project

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A B S T R A C T

Background: Studies investigating associations between sweeteners and health yield inconsistent results, possibly due to subjective self-report dietary assessment methods.

Objectives: We compared the performance of a food frequency questionnaire (FFQ), multiple 24-h dietary recalls (24hRs), and urinary biomarkers to estimate intake of sugars and low/no-calorie sweeteners (LNCSs).

Methods: Participants ($n = 848$, age 54 ± 12 y) from a 2-y observational study completed 1 semiquantitative FFQ and ≥ 3 nonconsecutive 24hRs. Both methods assessed intake of sugars (mono- and disaccharides, sucrose, fructose, free and added sugars) and sweetened foods and beverages (sugary foods, fruit juice, and sugar or LNCS-containing beverages [sugar-sweetened beverages and low/no-calorie sweetened beverages (LNCSBs)]); 24hRs also included LNCS-containing foods and tabletop sweeteners (low/no-calorie sweetened foods [LNCSFs]). Urinary excretion of sugars (fructose+sucrose) and LNCSs (acesulfame K+sucralose+steviol glucuronide+cyclamate+saccharin) were simultaneously assessed using ultrapressure liquid chromatography coupled to tandem mass spectrometry in 288 participants with 3 annual 24-h urine samples. Methods were compared using, amongst others, validity coefficients (correlations corrected for measurement error).

Results: Median (interquartile range) FFQ intakes ranged from 0 (0–7) g/d for LNCSBs to 94 (73–117) g/d for mono- and disaccharides. LNCSB use was reported by 32% of participants. Median LNCSB+LNCSF intake using 24hRs was 1 (0–50) g/d and reported by 58%. Total sugar excretions were detected in 100% of samples [56 (37–85) mg/d] and LNCSs in 99% of urine samples [3 (1–10) mg/d]. Comparing FFQ against 24hRs showed VCs ranging from 0.38 (fruit juice) to 0.74 (LNCSB). VCs for comparing FFQ with urinary excretions were 0.25 to 0.29 for sugars and 0.39 for LNCSBs; for 24hR they amounted to 0.31–0.38 for sugars, 0.37 for LNCSBs, and 0.45 for LNCSFs.

Conclusions: The validity of the FFQ against 24hRs for the assessment of sugars and LNCSBs ranged from moderate to good. Comparing self-reports and urine excretions showed moderate agreement but highlighted an important underestimation of LNCS exposure using self-reports.

Keywords: dietary intake, fructose, low/no-calorie sweetened beverages, measurement error models, non-nutritive sweeteners, sugar-sweetened beverages, sucrose, urine biomarkers

Abbreviations: 24hR, 24-h dietary recall; ADI, acceptable daily intake; AF, attenuation factor; FFQ, food frequency questionnaire; ICC, intraclass correlation coefficient; LNCS, low/no-calorie sweetener; LNCSB, low/no-calorie sweetened beverage; LNCSF, low/no-calorie sweetened food; MET, metabolic equivalent of task; NQplus, Nutrition Questionnaires plus; QC, quality control; SSB, sugar-sweetened beverage; VC, validity coefficient.

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Introduction

The global consumption of low/no-calorie sweeteners (LNCSs) strongly increased during the past decades [1,2]. Although LNCSs are considered safe from a toxicologic perspective [3], uncertainty remains about their long-term health impact [4]. Results from randomized controlled trials support a beneficial effect of replacing sugars by LNCSs on body weight [5,6], but observational data are more diverse [7–11].

These inconsistencies may be partly due to inaccurate estimates of dietary consumption in epidemiologic studies. To illustrate, many large-scale epidemiologic studies evaluated associations between LNCSs and health by comparing self-reported intakes of low/no-calorie sweetened beverages (LNCSBs) and sugar-sweetened beverages (SSBs) using food frequency questionnaires (FFQs) [7,9–12]. However, because LNCSs are also present in foods [13], solely assessing LNCSBs provides an incomplete assessment of LNCS intake. As 24-h recalls (24hRs) allow for a more detailed reporting of foods and portion sizes, comparing the performance of an FFQ against multiple 24hRs can provide valuable insights into measurement errors associated with an FFQ [14,15]. Still, both FFQs and 24hRs rely on self-reported data and are subject to reporting bias [16,17]. Moreover, as LNCSs are present in varying blends and amounts within similar categories of foods and beverages, their specific assessment is challenging when information on product brands is lacking in self-reports. Similarly, this information is currently lacking in most food composition databases. Using biomarkers as an additional approach could offer a more objective and detailed dietary assessment [18,19].

To date, total urinary excretion of sucrose and fructose has been established as a predictive biomarker of sugar intake [20–24], showing more coherent association with obesity than using self-reported sugar intake in several studies [25,26]. Although predictive biomarkers, unlike recovery biomarkers, can be influenced by individual characteristics, they still show a strong time-related and dose-response relationship with intakes and may be useful in assessing reporting errors [20]. A urinary biomarker approach for LNCS may also be promising in exploring reporting errors with traditional dietary assessment methods [27–29].

As part of the EU project SWEET (www.sweetproject.eu), we recently developed and validated a new ultrapressure liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) method to simultaneously measure urinary sugars (sucrose and fructose) and LNCSs (acesulfame K, saccharin, cyclamate, sucralose, and steviol glucuronide, a metabolite of steviol glycosides) [30]. With the increasing use of LNCSs as substitutes for sugar intake, simultaneously and objectively measuring both sugar and LNCSs may be particularly useful in evaluating self-reported dietary intake. However, a biomarker approach may not yet be optimal as, for example, not all LNCSs can be measured in urine (i.e., aspartame), emphasizing the utility of contrasting various approaches.

Therefore, this study aimed to compare the performance of an FFQ, multiple 24hRs, and urinary biomarkers to estimate intake of sugars and LNCSs in an observational study. Insight into the relative validity of these methods will help in the interpretation of previously observed associations of sugars and LNCSs with health outcomes.

Methods

Study population and study design

The Nutrition Questionnaires plus (NQplus) Study was a 2-y longitudinal observational study conducted among men and women aged 20–70 y living in the Gelderland and Utrecht provinces of The Netherlands [31], initiated as an extension of the National Dietary Assessment Reference Database project to facilitate the development of new high-quality FFQs and validation of existing FFQs [32]. Men and women who were able to speak and write Dutch were eligible to participate. In total, 2048 participants were recruited and included in the study between May 2011 and February 2013. At baseline, participants completed an FFQ and general and health questionnaires and were subjected to physical examinations. Participants completed multiple telephone-based 24hRs over the course of the study with ≥14 d in between each recall. Participants also provided 24-h urine samples at baseline, 1 y, and 2 y. The NQplus study was approved by the ethics committee of Wageningen University and conducted according to the Declaration of Helsinki. All participants provided written informed consent.

Population for the validation studies

The relative validity of the measurement methods was assessed in a subset of NQplus participants that completed an FFQ and 3 or more telephone-based 24hRs. Of 2048 participants, 1647 participants completed an FFQ at baseline, and 906 participants completed at least 3 24hRs during the 2-y follow-up. After excluding plausible energy intake misreporters (i.e., <500 and >3500 kcal for women and <800 and >4000 kcal for men [33]), 1627 participants were available with FFQ data, 904 with 24hR data, and 848 with both. In this subset, we evaluated the habitual intake of sugar and sugar or LNCS-containing foods assessed with an FFQ against the 24hR data. Subsequently, we compared the FFQ and 24hRs against urinary LNCS and sugar excretions in a subsample of 288 participants who had 3 repeated 24-h urinary collections, each ~1 y apart (see Supplemental Figure 1).

Data collection

Food frequency questionnaire

Habitual dietary intake was assessed using a 183-item semi-quantitative FFQ [32], which was based on a 104-item FFQ that was externally validated in a Dutch population against food records for total energy ($r = 0.84$) [34] or against 3 24hRs [35] for intakes of energy ($r = 0.65$), macronutrients (e.g., carbohydrate, $r = 0.80$), dietary fiber ($r = 0.82$), and a selected number of vitamins ($r = 0.46$–0.86). The FFQ was designed to cover ≥96% of the absolute level of food intake and ≥95% of the between-person variability of each nutrient under study as assessed in the Dutch National Food Consumption Survey from 1998.

Commonly eaten manufactured foods that appeared on the market after 1998 were selected from the Dutch National Food Consumption Survey of 2011 and included in the FFQ. Questions relating to the consumption frequency of the previous month were followed by answer categories ranging from "never" to "6–7 days per week." Questions related to SSB and LNCSB consumption were "How often have you drunk soda or fruit lemonade in the past month?" and "What types of soda have you drunk?," with categories "soda, lemonade, sport drink or energy drinks" and "light soda, light lemonade" and answer categories ranging from "rarely" to "always." Portion sizes were estimated using natural portion sizes and commonly used household measures [36]. Sugar intakes (mono- and disaccharides, fructose, sucrose, added sugars, and free sugars) were calculated by multiplying the consumption frequency by portion size and nutrient content (grams) using the Dutch food composition table of 2011 [37] and a developed sugar database [38] that connects information on specific sugars to food

codes of the Dutch composition table. As these food composition databases did not include information regarding LNCSs, specific amounts from reported items could not be calculated. The FFQ was self-administered and completed online (open-source survey tool LimeSurvey, LimeSurvey Project Team/Carsten Schmitz). Trained research dieticians conducted several quality checks to ensure the quality of the FFQ.

24-h dietary recalls

24hRs were conducted via telephone interviews by trained dieticians following a standard protocol and using the 5-step multiple-pass method [32]. Dates for telephone-based 24hRs were randomly selected with ≥2 wk between the recalls, scheduled regularly throughout the year, and proportionally evenly distributed over weekdays (±70%) and weekend days (±30%). Recalls were collected during the entire study period from baseline to 36 mo. If a participant denied or missed a recall attempt, the recall was rescheduled within 3–10 d. Portion sizes were assessed using commonly used household measures, weight/volume, and standard portions. Participants were not instructed to report specific product brands. Recalls were transcribed into the food codes of the Dutch food composition table of 2011 [37] using the software Compl-eat (Div. Human Nutrition and Health, Wageningen University), and intake levels of energy and nutrients were subsequently calculated [32]. The 24hRs were reviewed by trained dietitians for completeness, unusual portion sizes, and any notes. Any errors or notes were addressed using a standardized approach, which involved using standard portion sizes and recipes to make corrections. For example, if a participants reported consuming 125 cups of coffee, this was modified to 1 cup of 125 g. Participants completed at least 3 recalls and a maximum of 8 recalls. Of the 848 participants that completed the FFQ, 407, 58, 253, 104, 22, and 4, participants completed 3, 4, 5, 6, 7, and 8 24hRs, respectively.

Urine collection

At baseline and after each year of follow-up, participants collected a 24-h urine sample. The day before the collection, participants received verbal and written instructions and 2 urine containers (3 L) including the preservative lithium dihydrogen phosphate (25 g) and 3 para-aminobenzoic acid (PABA) tablets (80 mg) (PABAcheck, Elsie Widdowson Laboratory). Urine collection started after discarding the first voiding in the morning of the collection day and finished after the first voiding in the morning of the next day. The 3 PABA tablets were ingested during breakfast, lunch, and supper to check for completeness of urine collection. At the study center, the urine collections were mixed, weighed, aliquoted, and stored at −20°C until further analyses. At the first 2 time points, PABA was measured using HPLC after alkaline hydrolysis of the urine samples to convert PABA metabolites into PABA. A minimum of 78% PABA recovery was used as a cutoff point for complete urine collection [32]. However, excluding participants with incomplete urine collection did not affect the results, in line with previous observations [22]; thus, results of the complete sample are shown.

Urinary biomarkers analysis

Urinary sucrose, fructose, and LNCS concentrations (i.e., acesulfame K, sucralose, cyclamate, saccharin, and steviol glucuronide, a metabolite of steviol glycosides) were determined using a previously validated UPLC-MS/MS method [30]. Human urine samples were prepared by a simple 20-fold dilution step containing the internal standards in water, ammonia, and methanol. Separation was achieved on a Shodex Asahipak NH2P-40 hydrophilic interaction liquid chromatography column (Showa Denko Europe GmbH) using gradient elution. The UPLC-MS/MS system consisted of an Acquity H-Class Plus UPLC quarternary pump that was coupled to a Xevo TQ-S micro tandem mass spectrometer (Waters). Analytes were detected using negative ion mode electrospray ionization, and selective reaction monitoring was optimized to detect the [M-H]- ions. Concentrations in the urine extracts were quantified against calibration curves, which ranged from 34 to 19, 230 ng/mL for fructose and 1.8 to 1026 ng/mL for sucrose and LNCSs. Details on the method development and analytical validation can be found in the methods paper [30]. The validation included the evaluation of accuracy, precision, sensitivity limits of the analytical method, which showed that the method is suitable for the quantitative determination of the target analytes in human urine. Quality control (QC) samples were made by spiking known amounts of analytes to a pooled human urine sample and were included in each analytical batch to monitor the performance of the analytical method. The intrabatch coefficient of variation for the spiked QC samples ranged between 4.1% and 10.1%, with accuracies ranging between 79% and 99%.

After correcting for the 20-fold dilution, urinary concentrations (ng/mL) were multiplied by 24-h urine volumes and converted to daily excretions (mg/d). The urine data were then averaged across the 3 sampling days measures as a proxy of usual total sugar and LNCS excretion. Participants were identified as possible consumers if urinary excretion was detected. We also evaluated the total identified urinary excretion without urinary saccharin because this LNCS is present in many hygiene products. Because LNCSs are excreted to varying degrees in the urine, average absorption values from pharmacokinetic studies, as reported by Logue et al. [29], were used to approximate total LNCS consumption, i.e., 90% for acesulfame K, 88% for saccharin, 40% for cyclamate, 14.5% for sucralose, and 60.0% for steviol glycosides. These values were also used to calculate the proportion of acceptable daily intake (ADI) as follows: (estimated consumption of specific LNCS [mg]/body weight [kg]) / ADI × 100%.

Classification of sugar intake and low-calorie sweeteners across methods

The food item classifications from the FFQ and 24hRs are shown in Table 1. In addition to specific sugars calculated from the food compositions tables [mono- and disaccharides, sucrose, fructose, sugar intake (fructose + sucrose), free sugars, and added sugars], food items contributing to total sugar and LNCS were selected: sugary foods (table sugar, sweet toppings and fillings, candy, sweet snacks and desserts), SSBs, LNCSBs, and fruit juices and drinks. Because the 24hRs contained additional information regarding low/no-calorie sweetened foods (LNCSFs), including tabletop sweeteners, an additional food category was created. The total of LNCSB + LNCSF was compared to total urinary LNCS. Sugary foods, SSBs, and fruit juices were not compared with urinary biomarkers because urinary sugars are not specific predictive biomarkers for these food groups. As neither the FFQ nor the 24hRs allowed for a precise estimation of LNCS due to lack of information in the food composition tables or brand reporting (thus blends of LNCS could not be estimated), the sum of all urinary LNCS excretion was calculated, with and without calibration for average absorption.

Statistical analyses

Baseline characteristics were calculated as mean (SD), median (25^{th}–75^{th} percentiles), and number (percentage). To evaluate the

TABLE 1
Classification of sugars and low-calorie sweeteners in the FFQ, 24hRs, and urinary biomarkers used in the NQplus validation study

Dietary variable	FFQ	24hRs	Urinary biomarkers
Sugar intakes	• Sucrose • Fructose + sucrose • Mono- and disaccharide • Free sugar • Added sugar	• Sucrose • Fructose + sucrose • Mono- and disaccharide • Free sugar • Added sugar	Fructose + sucrose
Sugary foods	Candies, sweet snacks, sweetened chocolate products, sweet sauces & toppings, water-based sweets (ice), sugar added to drinks/yogurt during meal	Sugar, confectionary, sweet fillings, sweet sauces, pastry, cake, and biscuits, sugar added to drinks/yogurt during meal	—
SSBs	Soft drinks/lemonade (soda, lemonade or energy/sports drinks)	Soft drinks (carbonated soda), lemonade, sports/energy drinks, Iced tea	—
Fruit juice	Fruit juices (orange juice and other types)	Fruit and fruit drinks (100%, mixed or concentrated)	—
LNCSBs	Light soft drinks (soda, lemonade)	Soda, lemonade, energy drinks, or iced tea specified with "light", "no-sugar" or "with sweeteners"	acesulfame K + cyclamate + saccharin + steviol glycosides + sucralose
LNCSFs	—	Other food items specified with "light", "no-sugar" or "with sweeteners" e.g. yogurt, quark and dairy drinks, pudding, chocolate and candy, tabletop sweeteners, chewing-gum	acesulfame K + cyclamate + saccharin + steviol glycosides + sucralose

Abbreviations: 24hR, 24-h recall; FFQ, food frequency questionnaire; LNCSB, low/no-calorie beverage; LNCSF, low/no-calorie sweetened food; NQplus, Nutritional Questionnaires plus; SSB, sugar-sweetened beverage.

validity of the different assessment methods, a combination of statistical methods was applied: mean differences, Spearman correlation coefficients, quartile cross-classifications [17,39], validity coefficients (VCs), and attenuation factors (AFs) [40]. Spearman's rank correlation coefficients were calculated between the FFQ intakes and the mean intakes of the multiple 24hRs. Coefficients above 0.5 were considered good, between 0.20 and 0.49 moderate, and below 0.20 poor [39]. Cross-classifications were used to evaluate ranking agreement for nutrients and food groups across quartiles. For beverages, cross-classifications were performed across 4 categories due to the high proportion of nonconsumers in the sweet beverages groups (>50%), i.e., categories were defined as follows: category 1 = nonconsumers and categories 2 to 4 = tertiles of intake among consumers. If >50% of participants were correctly classified in the same or adjacent category and <10% were misclassified in the extreme opposite quartile or category, ranking agreement was considered good [39]. Weighted κ statistics were calculated as well.

VCs indicate how well a method ranks participants according to their unknown true intake and are also used to estimate the loss of statistical power to detect a diet–disease association [40,41]. To estimate VCs, we used measurement error models based on joined linear mixed models with random intercepts for participants to account for the multiple 24hRs or urine samples [40,42].

The following measurement error model was used (Equations *1* and *2*):

$$\text{Reference method (24hRs or biomarkers)} : X_{ij} = T_{ij} + \varepsilon xij \quad (1)$$

$$\text{FFQ (or 24hRs)}: Q_{ij} = \alpha_Q + \beta_Q T_{ij} + u_{Qi} + \varepsilon_{Qij} \quad (2)$$

where T indicates the "true" unobserved intake, i the person, and j the occasion; α_Q is the constant bias and β_Q indicates the proportional scaling bias (or intake-related related bias, less bias if value is close to 1), u is the person-specific bias, and ε is the random error.

Subsequently, the VCs (ρ_{QT}) were derived from the parameters of the models (Equation *3*) as the correlation between the measurement and true intake adjusted for within-person variation.

$$\text{Validity coefficient} : \rho_{QT} = \sqrt{\frac{\beta_Q{}^2 * var\ T}{\beta_Q{}^2 * var\ T + \frac{var\ \varepsilon_{Qij}}{k} (+var\ u_{Qi})}} \quad (3)$$

where var T is the variance of the unobserved true intake and varε_{Qij} is the variance of the random error; varu_{Qi} indicates the variance of the person-specific bias, and k is the number of replicates for the method assessed (i.e., k = 1 for FFQ and k = 3 for the 24hRs). As we only had one measure of the FFQ, the variance of the person-specific bias (u_{Qi}) could not be estimated because, as a single measurement, it cannot be differentiated from the within-person variance. The models above were also used to assess the 24hRs or FFQ against the urinary biomarkers.

When comparing the FFQ to the 24hRs, AFs were derived from the VC and proportional scaling bias (Equation *4*).

$$\text{Attenuation factor} : \lambda_Q = \frac{\rho_{QT}{}^2}{\beta_Q} \quad (4)$$

An AF <1.0 indicates an attenuation of the diet–disease association using the FFQ instead of the reference method, whereas an AF close to 1.0 indicates a better estimation. We did not calculate AFs when comparing self-reports to urinary biomarkers because the interpretation would be affected by the difference in units between 24hRs/ FFQ (g/d) and urinary excretions (mg/d).

For the beverage consumption (SSBs, fruit juice, and LNCSBs) estimated via 24hRs, measurement error models were additionally modified to take into account the large number of nonconsumers (zero-inflated models) with a 2-part model including a correlation between the random effect for the amount and the frequency of consumption [43,44]. The fitted 2-part models were used to simulate data containing both true intake and measured values. These were used to calculate the VC as the correlation between measured and true intake in the simulated data and

the AF by regressing the true intake on measured intake. The models used are described in detail in the Supplemental Material.

We calculated the intraclass correlation coefficient (ICC) for the multiple 24hRs and urinary biomarkers from measurement error models as follows: ICC = $varT^2$ / ($var\varepsilon^2_{xij}$ + $varT^2$). An ICC estimate closer to 1 represents greater reliability and less day-to-day variation [45].

When comparing the FFQ against the 24hRs, the absolute values and the energy-adjusted values of the nutrients and food groups were also compared using the residual method [46]. For nutrients, we used the residual method to adjust for n intake based on the logarithm scale because of skewness. For beverages, the density method (amount in g/1000 kcal) was used [46].

With all validation methods, we evaluated confounding and effect modification by adding sex, age, and BMI as covariates to the models used as well as performing stratified analyses (i.e., men and women, age <56 and ≥56 y (median split), BMI <25 and ≥25 kg/m^2). Analyses were conducted using SAS version 9.4 (SAS Institute, Inc) for the measurement error models (Proc NLMIXED) and RStudio version 1.3.959 (RStudio Team) with R version 4.0.2 (R Foundation for Statistical Computing) for all other analyses.

Results

General characteristics of the study population

Participants of the validation study (n = 848) had a mean age of 54 ±12 y, mean BMI of 26.0 ± 4.0 kg/m^2, 45% had normal weight, and 56% had higher education (Table 2). In the subsample with 3 urine collections (n = 288), participants were slightly older (55 compared with 53 y), more likely to be female (60% compared with 40%), have normal weight (51% compared with 41%) and lower waist circumference (90 compared with 93 cm), were less moderate physically active (648 compared with 898 metabolic equivalents of task [METs]-min/wk) and have slightly lower total energy intake (1975 compared with 2009 kcal/d) than participants with no urine samples.

Intakes and urinary excretions of sugar and LNCS

Median [25th–75th percentiles] absolute sugar intakes ranged from 16 [11–21] g/d for fructose to 94 [73–117] for mono- and disaccharides as reported by the FFQ, and mean differences compared to 24hRs were small (Table 3). Comparing mean and median values for food groups indicated skewness of their intake distributions. Differences in food groups between FFQ and 24hRs ranged from +6 g/d for sugary foods to −38 g/d for SSBs. The proportion of consumers also differed between the methods, e.g., 32% reported LNCSB use with the FFQ and 22% with 24hRs.

Median total urinary sugar excretion was 56.1 [37.2–84.8] mg/d, with fructose accounting for 29.2 [16.0–46.0] mg/d (Table 4). Median urinary LNCS excretions ranged from 0.0 [0.0–0.1] mg/d for sucralose (57% of participants) to 0.7 [0.0–4.4] mg/d for acesulfame K (83% of participants). Total urinary excretion was 3.0 [0.7–10.3] mg/d, and excretion was observed in 99% of the participants. Excretion of at least 3 LNCSs was observed in 84.4% of the participants. After

TABLE 2
General characteristics of the NQplus subcohort for the validation study of sugar and sweetener consumption[1]

	All[2]	No urine sample	3 urine samples	P-diff[3]
N	848	560	288	
N recalls	4 [3–5]	3 [3–4]	5 [5–6]	<0.001
Age, y	53.5 (11.5)	52.8 (12.1)	54.7 (9.9)	0.02
Women, n (%)	399 (47)	225 (40.2)	174 (60.4)	<0.001
Education, n (%)				0.23
low	6 (1)	4 (1)	2 (1)	
medium	367 (43)	254 (45)	113 (39)	
high	475 (56)	302 (54)	173 (60)	0.26
Smoking, n (%)				
never	398 (52)	255 (51)	143 (52)	
former	310 (40)	196 (39)	114 (42)	
current	65 (8)	48 (10)	17 (6)	
BMI, kg/m^2	26.0 (4.0)	26.2 (4.1)	25.6 (3.9)	0.06
BMI categories, n (%)				0.02
normal	377 (45)	230 (41)	147 (51)	
overweight	351 (41)	247 (44)	104 (36)	
obese	119 (14)	82 (15)	37 (13)	
Waist circumference, cm	91.6 (12.5)	92.5 (12.6)	90.0 (12.0)	0.01
Intense PA, MET-min/wk	350 [0–1474]	330 [0–1493]	420 [0–1418]	0.64
Moderate PA, MET-min/wk	837 [280–1740]	898 [359–1865]	648 [140–1470]	<0.001
Sedentary behavior, min/wk	1860 [1260–2700]	1800 [1200–2745]	1920 [1320–2640]	0.74
Energy intake FFQ, kcal/d	1991 [1692–2406]	2009 [1707–2439]	1975 [1652–2280]	0.045
Diet during past month, n (%)	47 (6.4)	35 (7)	12 (5)	0.31
History of diseases, n (%)				
Type 2 diabetes	28 (3)	17 (3)	11 (4)	0.69
CVD	26 (3)	15 (3)	11 (4)	0.48
Hypertension	202 (24)	141 (25)	61 (21)	0.23
Hypercholesterolemia	158 (19)	103 (18)	55 (19)	0.88

Abbreviations: BMI, body mass index; CVD, cardiovascular diseases; FFQ, food frequency questionnaire; MET, metabolic equivalent of task; NQplus, Nutritional Questionnaires plus; PA, physical activity; SD, standard deviation.

[1] Values are mean ± SD, median [25th–75th percentiles], or n (%).

[2] Missing values for smoking (n = 75), physical activity (n = 60), and diet during the past month (n = 109).

[3] P values for the difference between groups from t-test or nonparametric equivalent for continuous variables and chi-square tests for categorical variables.

TABLE 3
Mean, median intake, and %users of sugars, sweet foods, and beverages from one FFQ and multiple 24hRs in the NQplus validation study (n = 848)

Dietary variable (g/d)	FFQ			24hRs			Mean difference (FFQ – recall)	*P*-diff[1]
	Mean (SD)	Median [25th–75th percentile]	Users (%)	Mean (SD)	Median [25th–75th percentile]	Users (%)		
Mono- and disaccharides	97 (35)	94 [73–117]	848 (100)	101 (34)	97 [77–119]	848 (100)	−4 (32)	0.001
Sucrose	44 (22)	40 [28–55]	848 (100)	44 (21)	41 [29–54]	848 (100)	−0.2 (20)	0.75
Fructose	17 (8)	16 [11–21]	848 (100)	18 (9)	17 [12–22]	848 (100)	−1 (8)	0.002
Sugar intake[2]	61 (26)	57 [42–75]	848 (100)	62 (25)	58 [45–74]	848 (100)	−1 (24)	0.20
Free sugar	50 28)	45 [30–64]	848 (100)	54 (29)	41 [29–59]	848 (100)	−4 (25)	<0.001
Added sugar	45 (26)	38 [26–57]	848 (100)	47 (25)	50 [34–69]	848 (100)	−2 (23)	0.02
Sugary foods	75 (77)	55 [33–93]	846 (99)	69 (41)	63 [39–89]	843 (99)	6 (80)	0.02
SSBs	26 (84)	0 [0–13]	361 (43)	64 (134)	0 [0–73]	424 (50)	−38 (108)	<0.001
Fruit juice	63 (78)	27 [5–107]	680 (80)	78 (104)	46 [0–124]	548 (65)	−14 (93)	<0.001
LNCSBs	23 (74)	0 [0–7]	273 (32)	31 (102)	0 [0–0]	183 (22)	−8 (77)	0.09
LNCSFs	—	—	—	19 (50)	0 [0–4]	417 (49)	—	
LNCSBs + LNCSFs	—	—	—	50 (117)	1 [0–50]	488 (58)	—	

Abbreviations: 24hR, 24-h recall; FFQ, food frequency questionnaire; LNCSB, low/no-calorie sweetened beverage; LNCSF, low/no-calorie sweetened food; NQplus, Nutritional Questionnaires plus; SSB, sugar-sweetened beverage.
[1] *P* value for the difference between FFQ and 24hRs evaluated with Wilcoxon signed-rank test.
[2] Sugar intake = fructose + sucrose.

correcting for estimates of individual LNCS absorption, estimated LNCS consumption amounted to 4.2 [1.1–17.1] mg/d. Urinary excretions showed substantial day-to-day variation (ICC <0.50), albeit less for total LNCSs (ICC 0.56) than for the total of sucrose and fructose (ICC 0.28). Among specific LNCSs, steviol glucuronide had the highest day-to-day variation (ICC 0.26) and cyclamate the lowest (ICC 0.56).

FFQ compared with 24-h dietary recalls

Overall, Spearman correlation coefficients between the FFQ and 24hRs were acceptable for sugary foods, SSBs (r_s = 0.39) and LNCSBs (r_s =0.42), and good ($r_s \geq 0.50$) for fruit juice and dietary sugars (Table 5). All dietary intakes assessed with the 24hRs had an ICC <0.50, indicating a high day-to-day variation in the intakes. When comparing the FFQ to 24hRs using measurement error models, the intake-related bias (e.g., underreporting with higher intakes) varied greatly across dietary variables, highest for beverages/sugary foods (0.47–0.59), and lowest for sugars (0.68–0.81). Accounting for measurement error, the lowest VC was observed for fruit juice (0.38) followed by sugary foods (0.49) and SSBs (0.55), whereas the highest VC was observed for LNCSBs (0.74). Accordingly, the lowest AFs were observed for fruit juice (0.30), sugary foods (0.42), and SSBs (0.64), indicating a stronger attenuation of the diet–disease association when comparing the FFQ with multiple 24hRs when studying these foods, whereas no attenuation (AF close to 1.0) was observed for LNCSBs. Using energy-adjusted variables did not substantially change VC and AF, nor did additional adjustment for sex, age and BMI, whereas day-to-day variation and intake-related bias slightly increased (ICC and βx closer to zero) (Table 5). Finally, comparing FFQ and 24hR data showed acceptable ranking agreement between all dietary variables of interest, where the highest level of agreement was observed for energy-adjusted LNCSBs (67% in the same quartile, weighted κ 0.37) and the lowest levels of agreement for energy-adjusted sugary foods (35% in the same quartile, weighted κ 0.24).

FFQ and 24hRs compared with urinary excretions

Scatterplots visualizing the associations between self-reports and urinary excretions are shown in Figure 1 for sugars and Figure 2 for LNCSs. Correlations between the FFQ and urinary sugar excretions were moderate for dietary sugars, ranging from 0.21 to 0.24 (Table 6). Comparing 24hRs with urinary excretions showed slightly higher correlations, in the range 0.31–0.33. Correlations between LNCSB consumption and LNCS excretions were 0.32 for the FFQ and 0.29 for the 24hRs, whereas the correlation between LNCSBs + LNCSFs (only 24hRs) was higher (r_s = 0.46). Adjusting individual LNCS urinary excretion for average percentage of absorption did not affect these results. Estimated VCs comparing the FFQ sugar intakes and urinary sugar excretions were similar or slightly higher than the correlation coefficients, due to adjustment for ICC, but after adjustment for sex, age, and BMI, they were similar. Estimated crude and adjusted VCs for calibrated LNCS urinary excretions were 0.38 for LNCSBs with FFQ, 0.35 with 24hRs, and 0.45 for all LNCS foods with the 24hRs.

Except LNCSBs, all dietary variables as assessed by both FFQ and 24hRs showed acceptable ranking agreement with >50% of participants classified in the same or adjacent category of intakes or excretions (Table 6). Results for LNSCBs showed less agreement, with 18% (FFQ) and 21% (24hRs) classified in the opposite extreme category, but this proportion was below 10% with both LNCSBs + LNCSFs for the 24hRs (weighted κ 0.18).

TABLE 4
Descriptive statistics, comparison with ADI and ICC of urinary excretion of sugars and LNCS in the NQplus validation study ($n = 288$)

Urinary marker, mg/d	Urinary excretion			Estimated consumption[1]		ADI, mg/kg	%ADI[3] [25th–75th percentiles] (max)	ICC[4]
	Mean (SD)	Median [25th–75th percentile]	*n* (%)[2]	Mean (SD)	Median [25th–75th percentile]			
Fructose	36.9 (33.8)	29.2 [16.0–46.0]	260 (90.3)	—	—	—	—	0.34
Sucrose	32.4 (33.9)	24.5 [14.2–37.8]	288 (100.0)	—	—	—	—	0.26
Total urinary sugars[5]	69.3 (52.1)	56.1 [37.2–84.8]	288 (100.0)	—	—	—	—	0.28
Cyclamate	5.9 (19.5)	0.0 [0.0–2.0]	170 (59.0)	14.8 (48.6)	0.1 [0.0–5.1]	0–7	0.0 [0.0–1.0] (87.4)	0.56
Sucralose	0.1 (0.3)	0.0 [0.0–0.1]	163 (56.6)	5.2 (11.9)	0.1 [0.0–0.5]	0–15	0.0 [0.0–0.1] (3.0)	0.45
Acesulfame K	4.7 (10.7)	0.7 [0.0–4.4]	239 (83.0)	5.2 (11.9)	0.8 [0.0–4.9]	0–9	0.1 [0.0–0.7] (19.5)	0.47
Saccharin	2.2 (4.8)	0.4 [0.1–1.6]	282 (97.9)	2.5 (5.4)	0.4 [0.2–1.8]	0–5	0.1 [0.0–0.5] (8.6)	0.52
Steviol glucuronide	0.6 (3.3)	0.1 [0.0–0.2]	193 (67.0)	1.0 (5.4)	0.1 [0.0–0.3]	0–4	0.0 [0.0–0.1] (31.6)	0.26
Total urinary LNCS[6]	13.5 (28.0)	3.0 [0.7–10.3]	285 (99.0)	24.2 (57.6)	4.2 [1.1–17.1]	—	—	0.56
Total urinary LNCS without saccharin[7]	11.3 (24.3)	2.2 [0.4–9.4]	278 (96.5)	21.8 (53.3)	3.2 [0.6–16.1]	—	—	-
Excretion of at least 3 LNCS, %	—	—	243 (84.4)	—	—	—	—	

Abbreviations: ADI, acceptable daily intake; ICC, intraclass correlation coefficient; LNCS, low/no-calorie sweetener; NQplus, Nutritional Questionnaires plus.
Detection limits (ng/mL): fructose 76, sucrose 3.6, cyclamate 0.7, sucralose 1.8, acesulfame K 0.2, saccharin 0.3, steviol acyl glucuronide 2.3.
[1] Intake estimated with average % absorption from pharmacokinetic data provided in Logue et al., 2020 [29].
[2] *n* (%) represents the number of samples in which sugar or LNCS excretion was detected with ultrapressure liquid chromatography coupled to tandem mass spectrometry.
[3] %ADI calculated as (estimated intake/body weight [kg])/ADI × 100%.
[4] ICC calculated with a mixed model on log scale.
[5] Total urinary sugars = fructose + sucrose excretions.
[6] Total urinary LNCS = sum of all LNCS excreted in the urine.
[7] Saccharin excluded due to its presence in oral hygiene products.

Stratification by sex, age, and BMI

Detailed data on stratified analyses are included in the Supplemental Material. Overall, sugar intakes and excretions were higher in men than in women (Supplemental Tables 1 and 2). Although women reported higher LNCSB consumption than men, LNCS excretion did not differ. Overall, women reported slightly higher day-to-day variation, intake-related bias was higher, and VC and AF were lower in women than men, except for LNCSBs and fruit juice (Supplemental Table 3). In women, VCs comparing LNCSs with the self-report assessment methods against urinary excretions were higher than in men for the FFQ but not for 24hRs (Supplemental Table 4). Younger participants (<56 y) had higher reported sugar intakes and fructose excretions than older participants (Supplemental Tables 5 and 6). Although younger participants also reported higher LNCSB consumption, mean total urinary LNCS excretions did not differ between age groups, although LNCS was detected more often in the young. Urinary sugar excretions varied slightly more in older participants (lower ICC), whereas LNCS excretions varied more in younger ones. Overall, older participants tended to show better correlations than younger participants when comparing the FFQ to the 24hRs (Supplemental Table 7). However, when comparing both methods to urinary excretions, younger participants generally showed higher VCs for sugar intakes but lower VCs for LNCSs (Supplemental Table 8). Participants with normal weight (BMI <25 kg/m^2) had higher urinary fructose excretion and lower total LNCS excretions than participants with overweight, but, in contrast, self-reported intakes were similar (Supplemental Tables 9 and 10). Participants with overweight showed more day-to-day variation in both total urinary sugars and LNCSs than participants with normal weight. Most comparisons showed overall slightly better agreement in participants with lower BMI than higher BMI (Supplemental Tables 11 and 12).

Discussion

This study showed that the validity of the FFQ to assess sugars and LNCSBs ranged from moderate to good compared with multiple 24hRs. The comparison between self-reports and urinary excretions also showed moderate agreement. Notably, the urinary data indicated a substantial underestimation of the proportion of LNCS consumers. This was especially true when only LNCSBs were used to estimate LNCS intake, as with the FFQ.

Comparing the performance of the FFQ to multiple 24hRs showed good VCs (i.e., correlations adjusted for measurement errors, including day-to-day variation) for sugar intakes and LNCSBs but less so for the food groups fruit juice, sugary foods, and SSBs, and they were reduced after energy adjustment. Our results for dietary sugars are consistent with 2 other Dutch studies [35,47] reporting deattenuated correlations of 0.56 and 0.69 for total sugar intake (mono- and disaccharides) compared with 0.67 in the present study. Other studies have reported varying correlations for different types of sweetened beverages when comparing FFQs to dietary records or 24hRs. For example, correlations were 0.49 for soft drinks and syrup in a study with 24hRs [48], 0.84 for cola beverages, and 0.38 for noncarbonated beverages when comparing an FFQ to a 7-d dietary record in the Nurses' Health Study [49], and 0.66 for soft drinks with sugars and 0.48 without sugars when comparing an FFQ to 4-d records in a more recent Swiss study [50]. Social desirability bias may explain some of the differences in relative validity found between beverage types because it is generally higher in 24hRs than in FFQs [51,52]. For

TABLE 5
Spearman correlation coefficients, measurement error model estimates, and cross-classification comparing sugar intakes using 1 FFQ compared with multiple 24hRs in the NQplus validation study (n = 848)

Dietary variable	Spearman correlation coefficient[1]	Measurement error models[2]				Cross-classification[3,4]			
		ICC $^{24\text{-hR}}$	Intake-related bias (βx)	VC	AF	Same, %	Adjacent, %	Extreme, %	Weighted κ[1]
Crude									
Mono+disacch	0.57	0.46	0.81	0.67	0.55	41	43	2	0.38
Sucrose	0.56	0.43	0.73	0.66	0.60	44	38	2	0.39
Fructose	0.53	0.36	0.76	0.70	0.64	43	39	4	0.37
Sugar intake	0.56	0.45	0.75	0.66	0.58	44	38	2	0.39
Free sugars	0.60	0.44	0.73	0.69	0.64	46	38	2	0.42
Added sugars	0.59	0.45	0.68	0.67	0.66	46	39	3	0.42
Sugary foods	0.39	0.32	0.59	0.49	0.42	39	38	6	0.28
SSBs	0.39	0.22	0.47	0.55	0.64	48	29	7	0.31
LNCSBs	0.42	0.43	0.51	0.74	1.08	67	16	5	0.37
Fruit juice	0.53	0.26	0.48	0.38	0.30	42	39	4	0.37
Energy-adjusted[5]									
Mono+disacch	0.57	0.46	0.74	0.68	0.63	42	41	2	0.38
Sucrose	0.52	0.45	0.58	0.62	0.67	43	39	4	0.37
Fructose	0.56	0.40	0.69	0.68	0.67	45	38	3	0.39
Sugar intake	0.56	0.47	0.66	0.66	0.66	41	38	2	0.38
Free sugars	0.59	0.47	0.57	0.64	0.72	44	39	2	0.40
Added sugars	0.56	0.48	0.52	0.62	0.74	43	40	2	0.39
Sugary foods	0.36	0.37	0.46	0.45	0.43	35	41	6	0.24
SSBs	0.38	0.26	0.33	0.45	0.61	48	28	7	0.30
LNCSBs	0.42	0.46	0.59	0.79	1.07	67	17	5	0.37
Fruit juice	0.53	0.22	0.51	0.35	0.24	41	40	4	0.36

Abbreviations: 24hR, 24-h recall; AF, attenuation factor; BMI, body mass index; FFQ, food frequency questionnaire; ICC, intraclass correlation coefficient; LNCSB, low/no-calorie sweetened beverage; NQplus, Nutritional Questionnaires plus; SSB, sugar-sweetened beverage; VC, validity coefficient.

[1] All P values for Spearman correlation coefficients and weighted κ statistics were below 0.001.

[2] In measurement error models, variables were log-transformed to improve model fit, except for beverages. The VC and AF for beverages (SSBs, LNCSBs, and fruit juice) were estimated via a 2-part logistic model (probability of consumption × amount consumed) to take into account the large number of zeros (see online Supplemental Material for assumptions made in these models). With all variables, adjustments for age, BMI, and sex did not change the model estimates.

[3] For the cross-classification with beverages, 4 groups were created: 1 group for nonconsumers and 3 groups based on tertiles of intake among consumers.

[4] Same/adjacent % = percentage of nonconsumers correctly classified in the same or adjacent category of intake; extreme % = percentage of participants classified into the fourth category of intake, or vice versa.

[5] Energy adjusted using the residual method for nutrients and foods (log-transformed) and the density method (g/1000 kcal) for beverages.

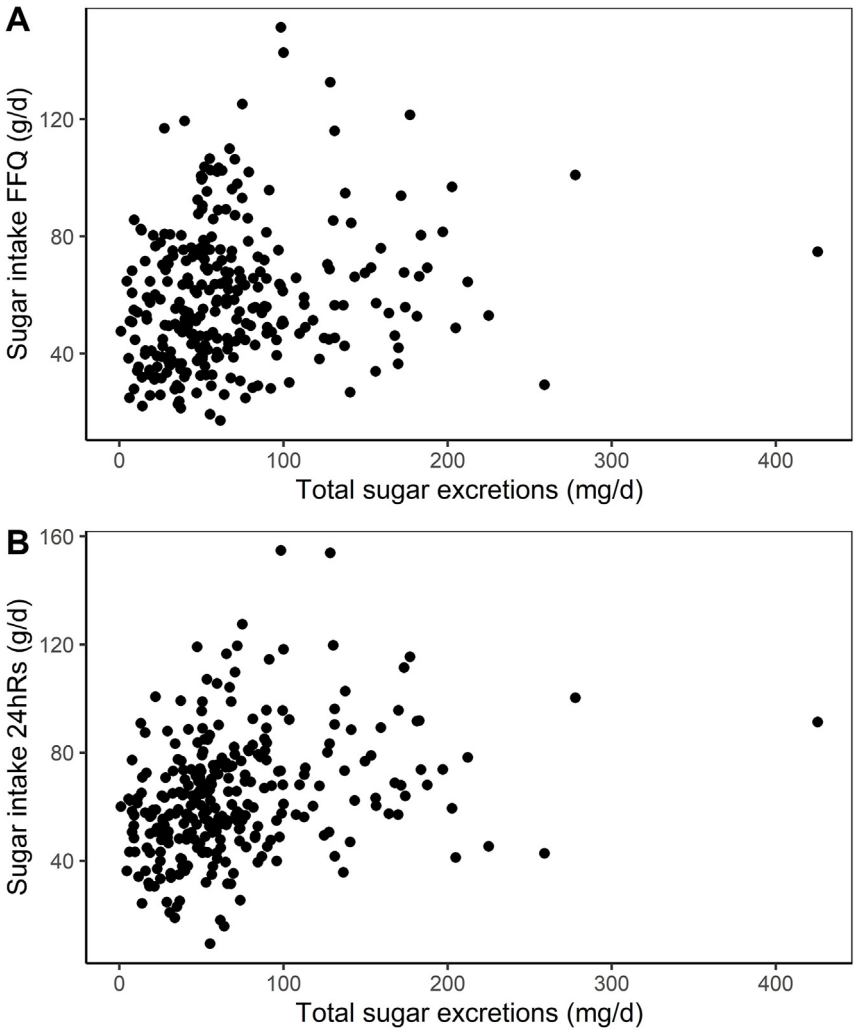

FIGURE 1. Scatterplot of self-reported reported sugar intakes with the FFQ (A) and with multiple 24hRs (B) against urinary sugar excretions. Sugar intake and excretions = sucrose + fructose.
24hR, 24-h recall; FFQ, food frequency questionnaire.

example, participants' perception of unhealthy compared with healthy foods may explain why SSBs and fruit juice showed a lower ranking agreement between the FFQ and 24hRs than LNCSBs [52]. Such differences in reporting may affect the validity of epidemiologic studies on associations between use of these beverages and health outcomes. In the full NQplus study, we observed, for example, an association between SSB (serving/day, FFQ) and annual body weight change of 0.08 kg/y [11], but with an energy-adjusted AF 0.61 as observed currently, this would translate to a "true" regression coefficient of 0.13 kg/y, substantially larger than the one observed for LNCSBs (0.09 kg/y per serving/d).

However, the comparison of self-reports to urinary sugars and excretion also highlighted important discrepancies between identified self-reported consumption and excretion. First, this shows that the 24hRs is a flawed reference method, as argued previously [53].

Although several human studies already investigated the potential of urinary sucrose and fructose as biomarkers for sugar intake [20–24, 42], only a few studies evaluated the association between self-reported dietary intake and urinary LNCS excretions [27–29]. Logue et al. [29] found LNCS excretions in 92% of participants compared with <10% of participants identified as LNCSB consumers in self-reports. This is in line with our findings as we identified at least 1 LNCS in 99% of the urine samples and at least 3 different LNCSs in 84% of the samples, compared with 30% of LNCSB consumers with the FFQ and 21% with the 24hRs. The better performance of the FFQ for LNCSBs might be due to its better performance for episodic foods because the 24hRs may have missed the days where the food item was consumed. However, accounting for the foods containing LNCSs in the 24hRs allowed for better estimation of overall low-calorie sweetener consumption (58%), which also matches the Dutch national survey consumption in which 59% of participants reported consuming LNCSs [54].

Nevertheless, the differences in identification of LNCS users between self-report using 24hRs and urine excretions remain large. One explanation may be misclassification when completing the 24hRs, as participants may not always be aware whether they used LNCSBs or LNCSFs instead of the sugar-sweetened alternatives. Moreover, LNCSs are present in nondietary products, such as oral hygiene products (e.g., toothpaste) or supplements [29], and these are likely not reported. This implies that epidemiologic studies evaluating associations between LNCSBs and health may underestimate actual LNCS exposure. This may also lead to underpowered studies, as the squared value of the VCs represent the loss in statistical power to test the significance of exposure–disease association [41]. Furthermore, underestimation of LNCS intake may also affect compliance measurements

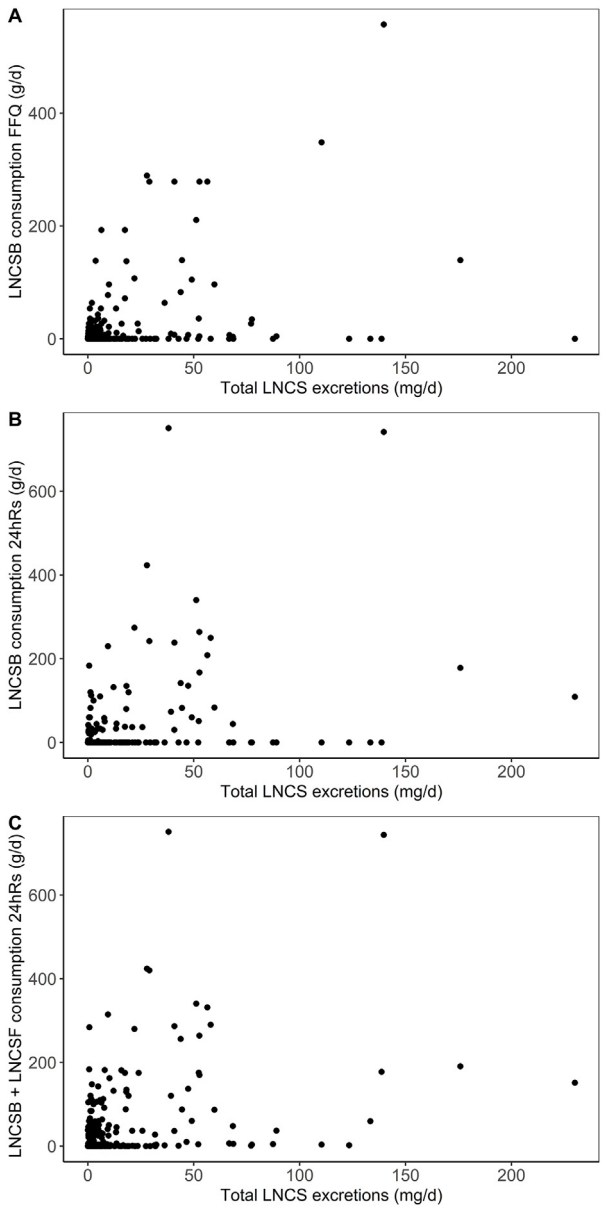

FIGURE 2. Scatterplot of self-reported LNCSB consumption with the FFQ (A), LNCSB with 24hRs, (B) and LNCSB + LNCSF consumption with 24hRs (C) against urinary LNCS excretions. 24hR, 24-h recall; FFQ, food frequency questionnaire; LNCS, low/no-calorie sweetener; LNCSB, low/no-calorie sweetened beverage; LNCSF, low/no-calorie sweetened food.

in experimental studies. For example, Sylvetsky et al. [28] studied urinary sucralose excretions in 18 participants who identified as non-LNCS consumers. They found that 8 participants had sucralose present in their urine, even after being instructed to avoid products containing LNCSs.

Despite underestimation of LNCS exposure, we observed moderate VCs (correlations adjusted for measurement errors) between reported LNCSB consumption and urinary LNCS excretions of 0.37–0.39 with the FFQ and 24hRs, compared with lower VCs (0.25–0.29) for sugar intakes. Urinary excretions of fructose and sucrose have been correlated with sugar intakes in several studies [22,42]. In the Observing Protein and Energy Nutrition study, estimated correlations for total sugar intake comparing 1 FFQ against urinary excretions were 0.16 in women and 0.43 in men and for 2 24hRs, 0.25 and 0.58, respectively [42]. Similarly, Abreu and colleagues [22] found VCs ranging from 0.30 to 0.59 with 2 24hRs. As the correlations with urine excretions in our study were higher for LNCSs than dietary sugars, this highlights the potential of LNCS biomarkers as possible predictive biomarkers of LNCS intake. Also note that for urinary LNCS, the day-to-day variation was less than for urinary sugars (ICC was higher, 0.56 compared with 0.28), indicating that fewer repeated samples are needed for accurate estimation.

Moreover, our urinary LNCS analysis also allowed identification of individual LNCSs, which is information that we could not estimate from the 24hRs due to lack of product brand reporting and lack of data in the national food composition database. The most common LNCS excreted was saccharin, followed by acesulfame K, both indeed most frequently used in processed foods [55]. Overall, all intakes were estimated to be below the ADI, similar to results reported by Logue et al. [29] and estimated for Europe in a recent report [56].

We also noted interesting differences in the comparisons of intake of sugars and LNCSs between methods depending on sex, age, and BMI categories. In general, correlations between self-reports and urinary data were better in men than women and in younger than older participants, except for LNCSs. Moreover, participants with lower BMI consistently showed better agreement across methods than those with higher BMI. These findings are consistent with previous reports [16,57,58]. For sex and BMI, the results are likely explained by social desirability, which may cause bias in reporting unhealthy foods [16]. On the other hand, the overall higher correlations for sugars observed among younger participants for self-reported data against urinary sugar excretions might be related to higher recall bias in older participants [57], although also the higher and possibly more frequent intake in younger participants may play a role.

Several limitations of the current study should be noted. First, the urinary excretions were not calibrated for individual characteristics. Although calibration equations have been validated for total sugars in populations in United Kingdom and United States and appeared to be similar [24], the intercepts differed, and prior validation in a Dutch population may be warranted. For LNCSs, we adjusted the urinary excretions to produce estimates of intake using average percentages of absorption from pharmacokinetic studies as reported by others [29]. However, this did not affect our results when comparing to those of the simple total of urinary LNCSs. Some of the measured LNCSs have larger individual differences in absorption rate, e.g., sucralose is excreted 10%–15% in urine with high interindividual variability [59], whereas acesulfame K has been shown to be almost completely excreted in human within 24 h [60]. Thus, total LNCSs, even calibrated for average absorption, may still be inaccurate, and further work is required to better understand the associations between consumption and excretion and to develop individual calibration equations to translate urinary excretion to estimated intake amounts for each LNCS. Furthermore, not all LNCSs are excreted in urine, and a specific urinary biomarker for aspartame, for example, is lacking, as it is metabolized into 3 common metabolites that are also produced upon consumption of other common foods [61]. Another limitation with the comparison to urinary biomarkers is that we did not have an objective measure of total energy to adjust the urinary excretion.

Second, both the FFQ used in this study and 24hRs were not specifically designed for individual LNCS estimation. Although this seems apparent for the FFQ, specific estimations might have been possible with the 24hRs, for example, using brand-level data combined with

TABLE 6
Spearman correlation coefficients, measurement error model estimates, and cross-classification comparing sugars and LNCS intake of 1 FFQ and multiple 24hRs against urinary excretions in the NQplus validation study ($n = 288$)

Dietary variable	Spearman correlation coefficient[1]	Measurement error model[2]		Cross-classification[4,5]			
		VC	VC_{adj}[3]	Same (%)	Adjacent (%)	Extreme (%)	Wt κ[1]
Comparison to urinary sugar excretion (sucrose + fructose)							
Mono+disacch							
FFQ	0.22	0.27	0.22	27	41	9	0.09
24hRs	0.31	0.35	0.32	35	38	7	0.21
Sucrose							
FFQ	0.22	0.27	0.21	30	36	7	0.12
24hRs	0.33	0.38	0.33	30	44	6	0.19
Sugar intake (sucrose + fructose)							
FFQ	0.21	0.25	0.21	32	35	7	0.14
24hRs	0.33	0.35	0.35	32	43	6	0.20
Added sugar							
FFQ	0.23	0.28	0.21	29	42	7	0.13
24hRs	0.31	0.31	0.28	31	41	5	0.18
Free sugars							
FFQ	0.24	0.29	0.23	29	42	7	0.14
24hRs	0.31	0.33	0.29	32	40	5	0.19
Comparison to urinary LNCS excretion (total urinary LNCS excretion) [f]							
LNCSB							
FFQ	0.32	0.39	0.39	16	39	19	0.11
24hRs	0.29	0.37	0.35	11	39	21	0.08
LNCSB + LNCSF							
24hRs	0.46	0.45	0.46	23	47	6	0.17
Comparison to total LNCS consumption (total LNCS calibrated excretions)[6,7]							
LNCSB							
FFQ	0.31	0.38	0.38	15	39	18	0.10
24hRs	0.28	0.35	0.35	11	37	21	0.07
LNCSB + LNCSF							
24hRs	0.47	0.45	0.45	25	46	7	0.18

Abbreviations: 24hR, 24-h recall; AF, attenuation factor; BMI, body mass index; FFQ, food frequency questionnaire; LNCS, low/no-calorie sweetener; LNCSB, low/no-calorie sweetened beverage; LNCSF, low/no-calorie sweetened food; NQplus, Nutritional Questionnaires plus; SSB, sugar-sweetened beverage; VC, validity coefficient.

[1] All P values for Spearman correlations were below 0.001; weighted κ statistics were <0.001.

[2] In all measurement error models, both amount consumed and urinary markers were log-transformed to improve the fit of the models (see online Supplemental Material for details).

[3] Validity coefficient adjusted for age, sex, and BMI.

[4] For the cross-quartile classification for LNCSB/urinary LNCS, 4 groups were created: 1 group for nonconsumers and 3 groups based on tertiles of intake among consumers.

[5] Same/adjacent % = percentage of nonconsumers correctly classified in the same or adjacent category of intake; extreme % = percentage of participants classified into the fourth category of intake, or vice versa.

[6] Validity coefficients estimated via a 2-part logistic model (probability of consumption × amount consumed) to take into account the large number of zeros (see online Supplemental Material).

[7] Calibrated with average % absorption based on pharmacokinetics data reported in Logue et al. [29], specifically: 90% for acesulfame K, 88% for saccharin, 40% for cyclamate, 14.5% for sucralose, and 60.0% for steviol.

maximum permitted levels [62]. However, information on product brands was lacking in our study, and we could not use this approach. Large variation in blends used between brands for a similar product can exist, for example, in sodas, and more detailed information is necessary to accurately assess specific LNCS intake. However, this limitation also holds for other studies investigating associations between LNCSs and disease risk using FFQs or unbranded recalls, highlighting the need for improvement of self-report methods and food composition databases for this purpose.

Third, our measurement error models required several assumptions, which may not be completely realistic and may have inflated our findings [40,63,64]. For example, we could not estimate the person-specific bias with the FFQ because we did not have a repeated FFQ. For the same reason, we could not account for the correlated errors between the FFQ and 24hRs, which may have inflated the observed correlations compared with the true correlation [40,42,53,64], as also suggested by our lower VCs obtained with urinary concentration markers than 24hRs.

Finally, our results may not be completely generalizable as our sample was not completely representative of the Dutch population. Participants tended to be higher educated [31], and this may have favorably affected our estimates.

In conclusion, this study showed a moderate to good relative validity of our FFQ compared to multiple 24hRs for the assessment of sugars and LNCSBs. Comparing FFQ or 24hRs and urine excretions showed moderate ranking agreement and highlighted an important

underestimation of identified LNCS consumers with the self-reports. Overall, our results suggest that self-reports are useful tools for the assessment of sugars and LNCSs, but results of observational studies with health outcomes should be interpreted with caution. Future epidemiologic studies would benefit from improvements, such as a specific FFQ for LNCS-containing foods and beverages or a combination of an FFQ and 24hRs with branded items. Additionally, this study underlines the utility of LNCS biomarkers to explore the accuracy of self-reported intakes and to rank participants according to specific LNCS intakes. Further validating and employing these objective measures may clarify inconsistencies in current literature on LNCS as sugar substitutes and their impact on health.

Author contributions

The authors' responsibilities were as follows – MECB, EJMF, EMBB: designed research; MECB: conducted research; MECB, HCB: analyzed data; MECB: wrote the manuscript; EJMF, EMBB: had primary responsibility for the final content; and all authors: read, contributed, and approved the final manuscript.

Conflict of interest

EJMF reports financial support from the Knowledge Center Sugar and Health (NL). JCGH reports financial support from the American Beverage Association, board membership with DuPont and Mars, and speaking and lecture fees from the International Sweeteners Association. AR reports speaking and lecture fees from Nestlé SA and the International Sweeteners Association; travel reimbursement from the International Sweeteners Association; and consulting or advisory fees from Unilever Plc. JAH reports financial support from the American Beverage Association. All other authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.11.019.

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