Dietary flavonoids and flavonoid-rich foods: validity and reproducibility of food frequency questionnaire-derived intake estimates

Yiyang Yue[1,2,*], **Joshua Petimar**[1,2,3,*], **Walter C. Willett**[1,2,4], **Stephanie A. Smith-Warner**[1,2], **Changzheng Yuan**[1,2,5], **Sinara Rosato**[1,6], **Laura Sampson**[1], **Bernard Rosner**[4,5], **Aedin Cassidy**[7], **Eric B. Rimm**[1,2,4,#], **Kerry L. Ivey**[1,8,9,#]

[1]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[3]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA [4]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [5]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA [6]Public Health post-graduation program, Universidade do Estado de Sao Paulo Jdlio Mesquita Filho, Botucatu, Brazil [7]Institute for Global Food Security, Queen's University Belfast, Belfast, Northern Ireland [8]South Australian Health and Medical Research Institute, Infection and Immunity Theme, South Australia, Australia [9]Department of Nutrition and Dietetics, College of Nursing and Health Sciences, Flinders University, Adelaide, Australia

Abstract

Objective: To evaluate the validity and reproducibility of a 152-item SFFQ for estimating flavonoid intakes.

Design: Over a one-year period, participants completed two SFFQs and two weighed 7-day dietary records (7DDR). Flavonoid intakes from the SFFQ were estimated separately using Harvard (SFFQ$_{Harvard}$) and Phenol-Explorer (SFFQ$_{PE}$) food composition databases. 7DDRs flavonoid intakes were derived using the Phenol-Explorer database (7DDR$_{PE}$). Validity was

Corresponding Author: Kerry L. Ivey, Department of Nutrition, Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Boston, MA, 02115, Telephone number: 617 599 3034, kivey@hsph.harvard.edu.
*Denotes co-first authorship
#Denotes co-last authorship

assessed using Spearman rank correlation coefficients deattenuated for random measurement error(r_s) and reproducibility was assessed using rank intraclass correlation coefficients.

Setting: This validation study included primarily participants from two large observational cohort studies.

Participants: 641 men and 724 women

Results: When compared to two $7DDR_{PE}$, the validity of total flavonoid intake assessed by $SFFQ_{PE}$ was high for both men and women (r_s=0.77 and r_s=0.74, respectively). The r_s for flavonoid subclasses ranged from 0.47 for flavones to 0.78 for anthocyanins in men, and from 0.46 for flavonols to 0.77 for anthocyanins in women. We observed similarly moderate (0.4 - 0.7) to high ($\geq$ 0.7) validity when using $SFFQ_{Harvard}$ estimates, except for $flavones_{Harvard}$ (r_s=0.25 for men and r_s=0.19 for women). The SFFQ demonstrated high reproducibility for total flavonoid and flavonoid subclass intake estimates when using either food composition database. The intraclass correlation coefficients ranged from 0.69 ($flavonols_{PE}$) to 0.80 ($proanthocyanidins_{PE}$) in men and from 0.67 ($flavonols_{PE}$) to 0.77 (flavan-3-ol $monomers_{Harvard}$) in women.

Conclusions: SFFQ-derived intakes of total flavonoids and flavonoid subclasses (except for flavones) are valid and reproducible for both men and women.

Keywords

Dietary assessment; flavonoids; food frequency questionnaire; diet record; validation study

INTRODUCTION

Flavonoids comprise a diverse group of biologically active plant-derived polyphenolic compounds [1] that have been associated with improved health outcomes[2; 3; 4] and reduced risk of all-cause mortality[5; 6; 7]. They are found in many foods such as red wine, blueberries and tea[8]. Over 4,000 flavonoid compounds have been identified and grouped into one of seven sub-classes: flavonols, flavan-3-ols monomers, proanthocyandins, flavanones, flavones, anthocyanins, and isoflavones[9]. These subclasses have demonstrated specific relationships with several health outcomes. For example, flavones and flavan-3-ols have been associated with lower cardiovascular mortality[10], while protective associations have been observed for intake of flavonols and flavones with risk of breast cancer[11].

In order to fully understand the subclass-specific relevance of flavonoids to health and the population-level impacts of a flavonoid-rich diet, it is essential to obtain valid and reproducible intake estimates of flavonoid subclasses and the foods from which they are derived from semi-quantitative food frequency questionnaires (SFFQ). This is because SFFQs are often the primary dietary assessment tool in nutritional epidemiology studies, owing to their generally valid measures of various macro- and micronutrients and the ease with which they can be administered and analyzed in large-scale cohort studies[12; 13]. The validity and reproducibility of SFFQs for measuring flavonoid intake are especially important because there are few appropriate biomarkers for intake due to the short half-life of flavonoids and their metabolites, as well as the complex and underdefined microbial and human metabolism of these compounds[14; 15]. However, few validation studies have

considered flavonoid intake, and those that have were generally small and used only a few days of diet records or 24-hour recalls to compare against SFFQs[16; 17; 18; 19; 20].

To address this gap, we used data from two large validation studies of men and women, including two weighed 7-day diet records (7DDR) to evaluate the validity and reproducibility of an SFFQ to estimate intakes of flavonoids, flavonoid subclasses, and flavonoid-rich foods.

METHODS

Study population.

The Men's Lifestyle Validation Study (MLVS) was conducted from 2011-2013 and consisted of 914 men aged 45 to 80 years randomly sampled from the Health Professionals Follow-up Study (HPFS), an ongoing, nationwide, prospective cohort of 51,529 U.S. male health professionals established in 1986[21]. To be eligible for participation in MLVS, participants had to have completed a 2006/2007 SFFQ administered in HPFS, have previously provided blood samples, currently have internet access, and never have been diagnosed with coronary heart disease, stroke, cancer, or major neurological disease. The Women's Lifestyle Validation Study (WLVS) was conducted in 2010-2012 and sampled 796 women from the Nurses' Health Study (NHS) and NHS-II, two prospective cohorts established in 1976 and 1989, respectively[22; 23]. The inclusion criteria for WLVS were identical to those of ML VS.

We excluded participants who did not complete both SFFQs and at least one 7DDR over the course of the study. We additionally excluded those who reported extreme energy intake (men: <800 or >4,200 kcal/day; women: <600 or >3,500 kcal/day) or if they left 70 or more SFFQ items blank, resulting in 641 men and 724 women included in the final analysis (Supplementary Figure 1).

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital. Written informed consent was obtained from all subjects/patients.

Semi-quantitative food frequency questionnaire.

In both the MLVS and WLVS, a 152-item SFFQ was administered at baseline[12], as well as at the end of the study one year later. Respondents were asked how often, on average, they consumed a specified amount of each food or beverage on the SFFQ during the past year with nine possible frequency categories ranging from "never/almost never" to "≥6 times per day." Open-ended questions were used to obtain information on usual brand and type of margarine, cooking oil, cold breakfast cereal, and multivitamins. Flavonoid intakes were calculated from the questionnaire by multiplying a weight proportional to the intake frequency by the flavonoid content for the portion size specified for each food item. Intakes were then summed across all foods to obtain overall intakes for total flavonoids and several flavonoid subclasses for every individual.

Weighed 7-day dietary records.

Each participant in MLVS and WLVS completed two weighed 7DDRs approximately six months apart in order to capture seasonal variability. Each participant therefore completed up to 14 days of weighed diet records. The 7DDRs were completed approximately six months apart in order to capture seasonal variability, and were completed in the time between repeated SFFQ assessments. Research dietitians provided participants with detailed instructions on keeping the 7DDRs (via telephone), an instructional video on DVD, a Primo Multifunction Kitchen Scale (Model P115NB; Escali Corporation, Burnsville, MN), and ruler (printed on the 7DDR booklet developed by Nutrition Coordinating Center, University of Minnesota). A computerized system was used to send reminders and encouragement emails to participants on days of diet recording. Participants measured and reported gram weights for foods before and after eating so that actual intake could be computed. They also provided recipes of all home-prepared foods, including the number of servings in the recipe and the portions of the recipes that they consumed, as well as labels of store-brand products.

Application of food composition databases to obtain flavonoid intake estimates.

We used the Phenol-Explorer database, which includes detailed information on polyphenol content in 452 foods and beverages using estimates from published literature[24], to derive flavonoid intake estimates for the 7DDRs (7DDR$_{PE}$). We also used Phenol-Explorer to estimate flavonoid intake as measured by the SFFQ (SFFQ$_{PE}$), but additionally estimated intake using a database maintained by Harvard dietitians (available for request at: https:// regepi.bwh.harvard.edu/health/nutrition.html) that is largely based on USDA data (SFFQ$_{Harvard}$). We took these two approaches because they allowed us to investigate different sources of error in SFFQ-derived flavonoid intake estimation. Using Phenol-Explorer to estimate flavonoid intake in both the SFFQ and 7DDR allowed us to isolate differences in intake estimation due to the measurement tool alone (i.e. not due to the food composition database)[9]. Conversely, using Phenol-Explorer for the 7DDR and the Harvard database for the SFFQ allowed us to compare estimates of flavonoid intake from the two assessment tools without introducing the same source of errors in calculating intakes, which can inflate validity[13]. Methods used to apply these databases to obtain intake estimates have been previously described[9; 25]. The two databases differ in terms of the composition of foods included and the analytic methods used to obtain the composition estimates. Briefly, the Phenol-Explorer database represented glycosides or aglycones in the form that they naturally occur in food, while in the Harvard database, the flavonoid compounds were expressed largely as aglycone. For details of the differences between databases, see Ivey et al.[26]

We considered seven flavonoid sub-classes: flavonols, flavan-3-ol monomers, proanthocyanidins (a class of flavan-3-ol polymers, limited to proanthocyanidin dimers and trimers to allow for comparison between Harvard and Phenol Explorer databases), flavanones, flavones, anthocyanins, and isoflavones. Chalcones, dihydrochalcones and dihydroflavonols were also not included in this analysis because they are typically considered precursors to many flavonoid compounds but are not flavonoids themselves.

Statistical analysis.

All analyses were conducted separately in men and women. We calculated means and standard deviations (SD) for absolute daily total flavonoid intakes and intakes for each subclass from the baseline SFFQ, the second SFFQ, and average of two 7DDRs.

In our primary analyses, we assessed the validity of SFFQ-derived flavonoid intake estimates by comparing intake from the second SFFQ, which assessed diet over the same period as the 7DDR collection, to intake as measured by the average of the two 7DDRs using Spearman correlation coefficients (r_s). For total flavonoids and each subclass, we calculated r_s and 2-sided 95% confidence intervals (CI) that were deattenuated for random measurement error in the 7DDRs using a method to account for the variable number of repeats of the 7DDR[27; 28; 29]. We adjusted r_s for total energy intake using the residual method[30] with a reference energy level of 1,600 kcal for women and 2,000 kcal for men. We additionally calculated r_s that were deattenuated but not adjusted for total energy intake. We determined reproducibility of the SFFQ by calculating rank intraclass correlation coefficients (ICC) comparing intakes from the first SFFQ to those from the second SFFQ. We calculated ICCs that were adjusted and not adjusted for total energy intake. To reduce the influence of extreme nutrient intakes, ICCs were based on the ranks of the log-transformed and energy-adjusted nutrient values[12; 27].

In secondary analyses, we determined the validity and reproducibility of the SFFQ for measuring intake of the top three food contributors to each flavonoid subclass according to the second SFFQ. For isoflavones, we considered only the top two contributors because subsequent contributors were composite group which included soy as a minor ingredient. We did this using the same analytic approach that we used for flavonoids in our primary analyses. We additionally explored whether the SFFQ adequately captured the absolute intake and variance of these top flavonoid contributors. We did this by calculating, in the 7DDR, the mean flavonoid intake and variance in intake that were captured by items listed on the SFFQ. We also summarized the mean intake and variance in the intake from foods not represented by the SFFQ that contributed to intake of each flavonoid subclass.

All analyses were conducted in SAS version 9.4.

RESULTS

Most study participants were white (men: 98%; women: 90%) and had overweight (men: 45%; women: 30%) or obesity (men: 13%; women: 22%). Only 1% of men and 2% of women were current smokers. At baseline, men had a mean (SD) age of 67 years (8) and women had a mean age of 62 years (10)

According to the 7DDR$_{PE}$ intake estimates, the mean (SD) total flavonoid intake was 356mg/day (241) for men and 328 (250) for women (Table 2). Total flavonoid intakes estimated from SFFQ$_{PE}$ were slightly higher in women, but not in men. Intakes of most flavonoid subclasses were generally similar between SFFQ$_{PE}$ and 7DDR$_{PE}$. However, estimated intakes of flavan-3-ol monomers were substantially higher when measured by the SFFQ$_{PE}$ (58% and 68% higher in SFFQ$_{PE}$ than 7DDR$_{PE}$ in men and women, respectfully),

and intakes of flavonols were substantially higher when measured by the $7DDR_{PE}$ (39% and 38% lower in $SFFQ_{PE}$ than $7DDR_{PE}$ in men and women, respectfully). For total flavonoids, flavonols, flavan-3-ol monomers, flavones, and isoflavones, $SFFQ_{Harvard}$ intakes were substantially lower than $SFFQ_{PE}$ intakes. SFFQ-estimated intake of proanthocyanidins, flavanones, and anthocyanins were generally similar when using either the Harvard or Phenol-Explorer database. For any given flavonoid subclass, the top whole food contributors to that subclass, as measured by the second SFFQ, were generally the same between men and women. However, the percent of intake accounted for by the top three food contributors varied by subclass. In men, this ranged from 45% (flavonols) to 91% (flavanones); in women, it ranged from 43% (flavones) to 90% (flavanones).

The second $SFFQ_{PE}$ generally demonstrated moderate (0.4-0.7) to high (≥0.7) validity as assessed by Spearman correlation coefficients for measuring intake of total flavonoids and flavonoid subclasses compared to the average of two $7DDR_{PE}$ (Table 3). The deattenuated, energy-adjusted rs for total flavonoid intake was 0.77 (95% CI: 0.72-0.82) for men and 0.74 (95% CI: 0.69-0.79) for women. The r_s for intake of flavonoid subclasses ranged from 0.47 for flavones to 0.78 for anthocyanins in men, and from 0.46 for flavonols to 0.77 for anthocyanins in women. Results for all were similar when not adjusting for total energy intake. Results were similar or slightly weaker when using $SFFQ_{Harvard}$. We observed the strongest difference between databases for measuring intake of flavones (r_s=0.25 in men and 0.19 in women).There was moderate to high agreement (r_s≥0.43) in the ranking of flavonoid subclass consumers between $SFFQ_{PE}$ and $SFFQ_{Harvard}$, with the exception of flavones (r_s≤0.12), despite differences in absolute intakes (Supplementary Table 1).

The SFFQ demonstrated high reproducibility when comparing total flavonoid intake estimates from two assessments one year apart in both men ($ICC_{Harvard}$=0.78, ICC_{PE}=0.80) and women ($ICC_{Harvard}$=0.71, ICC_{PE}=0.75) (Table 4). The ICCs for $SFFQ_{PE}$ flavonoid subclasses ranged from 0.69 (flavonols) to 0.80 (proanthocyanidins) in men and from 0.68 (anthocyanins) to 0.77 (flavan-3-ol monomers) in women. The ICC ranges were similar for the $SFFQ_{Harvard}$. As for 7DDR, the ICC was generally lower than SFFQ, ranging from 0.39 (isoflavones) to 0.67 (flavanones) in men and from 0.39 (flavones and isoflavones) to 0.62 (flavonols) in women (Supplementary Table 2). These results were similar when not adjusting for total energy intake.

When we identified items in the 7DDR that were assessed on the SFFQ and calculated their total flavonoid intake, we found that these items accounted for 95% and 96% of the total flavonoid intake in men and women, respectively (Supplementary Table 3). SFFQ foods captured the vast majority (≥92%) of 7DDR intake for all flavonoid subclasses except for anthocyanins, which accounted for only 75% of intake in men and 76% in women. In post hoc analyses, we found that this discrepancy was largely due to the absence of cherries from the SFFQ food list, which contributed 7.4 mg/d (13%) to 7DDR anthocyanin intake in men and 4.9 mg/d (13%) in women. Blackberries, raspberries and cranberries also contributed more than 1% of 7DDR anthocyanin intake in both men and women. For flavones, the SFFQ foods accounted for 94% of 7DDR intake in men and 92% in women. Artichokes, which were not listed on the SFFQ, accounted for 0.4 mg/d (4%) and 0.4 mg/d (5%) of the 7DDR flavone intake in men and women, respectively. We also found that the foods represented by

the SFFQ captured most of the variance in subclass intake, though anthocyanins and flavones similarly had the least amount of variance explained by SFFQ foods (Supplementary Tables 4).

Using 7DDR as the reference method, the SFFQ demonstrated moderate to high validity for ranking all major food contributors to flavonoid intake, with similar results for men (mean r_s=0.75) and women (mean r_s=0.68); Table 5. Among the major food contributors to flavonoid intake, the SFFQ demonstrated the strongest validity for red wine intake and orange juice in both men (r_s=0.88, 95% CI: 0.85–0.91 for red wine; r_s=0.88, 95% CI: 0.85–0.90 for orange juice) and women (r_s=0.83, 95% CI: 0.80–0.86 for red wine; r_s=0.82, 95% CI: 0.79–0.85 for orange juice). The SFFQ demonstrated the poorest validity for intake of onion in men (r_s=0.43, 95% CI: 0.34–0.51) and women (r_s=0.48, 95% CI: 0.37–0.56). The SFFQ estimated food intakes for all major flavonoid contributors were highly reproducible in both men and women, except for oranges (ICC=0.40 for men and ICC=0.37 for women) and orange juice (ICC=0.40 for men and ICC=0.38 for women). Men reported higher intakes of all major food contributors to flavonoid intake than women, but women consumed more tea in both the SFFQ and 7DDR (Supplementary Table 5). When compared to the 7DDR, the SFFQ tended to overestimate intakes of major food contributors to flavonoid intake, particularly apples, blueberries, onions, and tofu. However, tea intake was consistently lower for the SFFQ than the 7DDR.

DISCUSSION

The 152-item SFFQ used in this study generally demonstrated moderate to high validity for measuring intake of total flavonoids and major flavonoid subclasses when compared to intake from two weighed 7DDRs. This was true when using either the Phenol-Explorer or Harvard-based food composition databases, but not for flavones when estimated using the Harvard database. The SFFQ also showed high reproducibility for measuring intake of these compounds when comparing estimates from SFFQs one year apart. The SFFQ demonstrated moderate to high validity for measuring intake of all major food contributors to flavonoid subclass intakes except for onions. This study highlights that this SFFQ is appropriate for ranking individuals by flavonoid intake, which is often the primary goal of dietary assessment in nutritional epidemiology studies, even when absolute intakes differ from the gold standard. This SFFQ has previously demonstrated moderate to high validity for measuring other major nutrients in WLVS (mean r_s=0.64 among 44 nutrients)[12].

Few previous studies have evaluated the validity and reproducibility of SFFQs to measure flavonoid intake. Three studies conducted in China observed similar but slightly higher validity estimates than we did for flavonols and flavones[16; 17; 18]; however, these studies compared SFFQs to 24-hour recalls, whose errors are expected to be more highly correlated with SFFQs than diet records because both 24-hour recalls and SFFQs rely on participant memory[13]. Also, two of these studies were conducted in adolescents or young adults, making it difficult to compare results with the present study. Two other studies, which were conducted in Australia, evaluated the validity of an SFFQ specifically designed to capture flavonoid intake, whereas the present study evaluated an SFFQ designed to capture overall diet. Despite these differences, validity estimates for several flavonoid subclasses were

similar or higher for the SFFQ in the present study than for this specialized SFFQ[19; 20]. However, these two Australian studies only used 3- or 4-day diet records and had very small sample sizes (n=60 and n=42 participants, respectively). Compared to these previous studies, our study thus had a very large sample size and used two repeated implementations of 7DDRs, capturing a total of 14 days of dietary intake, which is well above the minimum number of days of weighed diet records needed for accurately capturing flavonoid intake[31].

The relatively high validity estimates we observed for most flavonoid subclasses is likely because most of their top food contributors were measured with good accuracy by the SFFQ compared to 7DDR (generally $r_s > 0.65$). The SFFQ demonstrated poorer ability to accurately measure intake of flavones and flavonols. This may be due to the fact that both of these subclasses are found in a variety of foods[8], some of which may not be measured accurately by the SFFQ. The lower r_s estimates for flavonols in particular is likely partially due to the SFFQ's poorer ability to measure onion intake, which is the top contributor to this flavonoid subclass. For flavones, we noted that artichokes and oregano, which contributed significantly to total intake and the variance in intake, were not assessed by the SFFQ. Future investigations that seek to identify the role of flavones in health should consider adding these foods to existing SFFQs. We also noted that the absence of cherries, blackberries, raspberries, and cranberries from the SFFQ food list could underestimate estimation of anthocyanin intake because these foods contributed substantially to total intake and variance in intake (except for cranberries) in the 7DDR. However, the SFFQ demonstrated good ability to measure anthocyanin intake despite the fact that these foods were not assessed.

With the exception of flavones, the estimated validity of the SFFQ to measure flavonoid intakes did not appear to be driven by the choice of which food composition database to apply to the SFFQ; we observed similar results when using both the Phenol-Explorer and Harvard databases. Using either database alone has the potential to introduce bias to validity estimates. Comparing SFFQ and 7DDR intake estimates using the same food composition database (i.e. $SFFQ_{PE}$ vs. $7DDR_{PE}$) might introduce the same source of errors in calculating intake and thereby overestimate true validity; conversely, comparing these assessment tools using different databases (i.e. $SFFQ_{Harvard}$ vs. $7DDR_{PE}$) incorporates error that is not solely due to differences in the tools' measurement ability, thereby underestimating true validity[13]. Indeed, when compared against $7DDR_{PE}$, nearly all r_s were slightly lower when estimating intake from $SFFQ_{Harvard}$ than from $SFFQ_{PE}$. However, this discrepancy was small for total flavonoid and flavonoid subclasses (other than flavones), highlighting the robustness of our findings. The larger differences we observed for flavone intake between the two databases may be because absolute flavone intake estimates from $SFFQ_{PE}$ were more than 4 times greater than from $SFFQ_{Harvard}$, which was a larger discrepancy than for any other flavonoid subclass. Perhaps more importantly, there was also poor agreement in ranking participants by intake of flavones between the two methods. We have previously shown[26] that application of the USDA and Phenol-Explorer databases to a different FFQ resulted in participants being ranked differently based on their flavone intake estimates. This lack of agreement was due to differences in the flavone concentration of foods between the two databases as well as analytic differences between the two databases. Primarily, the high proportion of C-glycosides making up this subclass are difficult to hydrolyze, and the data in the USDA database presents hydrolyzed values only. Thus, the flavone intake estimates from

the Harvard database, which is based upon the USDA database, are expected to be lower than estimates from Phenol-Explorer. It is worth noting that flavones were minor contributors to total flavonoid intake. Thus, even with these discrepancies in flavone estimates, our total flavonoid estimates were still valid.

To our knowledge, this is the largest validation study of an SFFQ for measuring flavonoid intakes compared to 7DDRs, but it has limitations. Participants in this study were all health professionals and the vast majority were White. Our results may therefore not be generalizable to other populations, such as those with large proportions of non-White individuals and individuals who are not in healthcare professions. Additionally, diet records have their own sources of errors, including the fact that participants may change their normal eating habits when completing the records[13]. If these errors were uncorrelated with errors in completing the SFFQ, the validity of the SFFQ could be underestimated. On the other hand, if the errors were correlated, which could occur due to use of the same food composition database, the validity of the SFFQ could be overestimated. However, we observed fairly high validity and reproducibility estimates for total flavonoids and most subclasses when using either of two different databases to derive SFFQ intake, increasing the robustness of our findings. Finally, isoflavone intake was relatively low and very skewed (Supplementary Figure 2) in our study population. Therefore, the validity of SFFQs for measuring isoflavones may not be generalizable to populations with high isoflavone intakes, such as Asian populations.

In conclusion, the 152-item SFFQ demonstrated reasonable validity and reproducibility for measuring intake of total flavonoids and most flavonoid subclasses compared with the mean of two 7DDR assessments, regardless of the food composition database used. Intake of flavonoid-rich foods was also measured with generally high validity and reproducibility. Future investigations that seek to determine the health effects of specific flavonoid subclasses (mainly flavonols and flavones) should consider supplementing questionnaires with additional food items that may be informative for ranking individuals' intake.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

7DDR	weighed 7-day dietary record
CI	confidence interval

ICC	rank intraclass correlation coefficient
MLVS	Men's Lifestyle Validation Study
PE	Phenol-Explorer
r_s	Spearman-ranked correlation coefficients
SD	standard deviation
SFFQ	semi-quantitative food frequency questionnaire
WLVS	Women's Lifestyle Validation Study

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Table 1.

Baseline characteristics and dietary intake of participants in the Men's Lifestyle Validation Study and Women's Lifestyle Validation Study

	Men (n=641)		Women (n=724)	
	Value*	SD	Value*	SD
Age (years)	67	8	62	10
Geographic region				
West	20%		20%	
Midwest	17%		24%	
South	20%		31%	
Northeast	43%		25%	
Body mass index (kg/m^2)	26	4	27	5
$18 \leqslant BMI < 25$	42%		47%	
$25 \leqslant BMI < 30$	45%		30%	
$BMI \geqslant 30$	13%		22%	
Dietary intake[†]				
Total energy (kcal/day)	2109	579	1867	523
Carbohydrate (g/day)	246	80	219	70
Protein (g/day)	85	25	81	24
Total fat (g/day)	79 ± 29		71	25
Saturated fat (g/day)	24 ± 10		22	9
Monounsaturated fat (g/day)	31	13	27	11
Polyunsaturated fat (g/day)	17	7	15	6
Alcohol (g/day)	17	17	9	13
Dietary fiber (g/day)	27	10	24	9

*
Values are presented as means (standard deviation) or percent where appropriate

[†]
Dietary intake from the second semi-quantitative food frequency questionnaire

Table 2.

Mean (SD) flavonoid intakes (mg/d) in MLVS and WLVS as estimated by two semiquantitative food frequency questionnaires and two 7-day dietary records

| | $SFFQ_{Harvard}$ | | | | $SFFQ_{PE}$ | | | | $7DDR_{PE}$[*] | | Major food contributors (%)[†] |
| | SFFQ1 | | SFFQ2 | | SFFQ1 | | SFFQ2 | | | | |
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Men											
Total flavonoids	237	132	234	132	362	234	352	225	356	241	Onion (23%), tea (13%), apple (9%)
Flavonols	27	15	26	15	86	57	84	53	137	163	Tea (41%), blueberry (17%), red wine (10%)
Flavan-3-ol monomers	62	62	61	62	97	134	93	131	59	85	Red wine (25%), apple (18%), tea (7%)
Proanthocyanidins[‡]	54	32	52	31	53	46	50	43	44	40	
Flavanones	38	34	38	35	46	60	44	59	42	56	Orange juice (53%), orange (30%), grapefruit (8%)
Flavones	4	3	3	3	15	10	15	10	11	8	Red wine (23%), orange juice (20%), orange (9%)
Anthocyanins	49	48	50	48	58	50	58	50	58	56	Blueberry (63%), Red wine (12%), strawberry (9%)
Isoflavones	4	6	3	6	7	15	7	15	4	16	Tofu (32%), Soymilk (18%)
Women											
Total flavonoids	216	125	207	132	374	246	358	249	328	250	Onion (27%), tea (19%), apple (9%)
Flavonols	27	16	26	16	91	59	91	61	146	172	Tea (58%), blueberry (12%), apple (6%)
Flavan-3-ol monomers	69	73	65	73	140	159	128	155	76	114	Apple (20%), red wine (15%), tea (13%)
Proanthocyanidins[‡]	48	27	46	28	51	40	48	40	35	38	
Flavanones	27	30	23	27	28	54	26	50	21	35	Orange juice (50%), orange (32%), grapefruit (8%)
Flavones	3	2	2	2	13	8	13	8	8	5	Orange juice (18%), red wine (17%), orange (8%)
Anthocyanins	39	36	41	40	45	38	47	42	39	40	Blueberry (62%), strawberry (12%) red wine (8%)
Isoflavones	3	6	3	6	6	12	6	11	3	8	Tofu (21%), Soymilk (18%)[§]

$7DDR_{PE}$, weighed 7-day diet record derived using Phenol-Explorer; MLVS, Men's Lifestyle Validation Study; SD, standard deviation; SFFQ1, first semiquantitative food frequency questionnaire; SFFQ2, second semiquantitative food frequency questionnaire; $SFFQ_{Harvard}$, semiquantitative food frequency questionnaire derived using the Harvard database; $SFFQ_{PE}$, semiquantitative food frequency questionnaire derived using the Phenol-Explorer database; WLVS, Women's Lifestyle Validation Study

* Values are for the average of two weeks of weighed diet records.

† Foods are as estimated from the second semiquantitative food frequency questionnaire using the Harvard food composition database. The number in parentheses is the percent that the food contributes to mean intake of that flavonoid subclass.

‡Includes proanthocyanidin dimers and trimers.

§other contributors were composite foods

Table 3.

Deattenuated Spearman correlation coefficients (95% CI) comparing flavonoid intake as measured by the second semiquantitative food frequency questionnaire with intake as measured by the average of two weeks of 7-day diet records in MLVS and WLVS

	SFFQ$_{Harvard}$ vs. 7DDR$_{PE}$		SFFQ$_{PE}$ vs. 7DDR$_{PE}$	
	Unadjusted	Energy-adjusted*	Unadjusted	Energy-adjusted*
Men				
Total flavonoids	0.65 (0.59-0.70)	0.65 (0.59-0.70)	0.75 (0.70-0.80)	0.77 (0.72-0.82)
Flavonols	0.49 (0.41-0.55)	0.52 (0.44-0.58)	0.49 (0.42-0.56)	0.53 (0.46-0.59)
Flavan-3-ol monomers	0.60 (0.53-0.66)	0.59 (0.52-0.65)	0.73 (0.67-0.79)	0.74 (0.68-0.79)
Proanthocyanidins[†]	0.66 (0.59-0.72)	0.69 (0.62-0.75)	0.73 (0.65-0.79)	0.74 (0.67-0.80)
Flavanones	0.73 (0.67-0.78)	0.67 (0.61-0.71)	0.80 (0.75-0.85)	0.74 (0.69-0.79)
Flavones	0.26 (0.17-0.35)	0.25 (0.15-0.34)	0.51 (0.43-0.58)	0.47 (0.38-0.54)
Anthocyanins	0.76 (0.69-0.82)	0.76 (0.68-0.82)	0.77 (0.70-0.82)	0.78 (0.71-0.84)
Isoflavones	0.51 (0.42-0.59)	0.51 (0.41-0.59)	0.51 (0.41-0.59)	0.48 (0.38-0.57)
Women				
Total flavonoids	0.63 (0.57-0.68)	0.63 (0.57-0.67)	0.73 (0.68-0.78)	0.74 (0.69-0.79)
Flavonols	0.48 (0.41-0.55)	0.48 (0.40-0.54)	0.47 (0.39-0.53)	0.46 (0.39-0.53)
Flavan-3-ol monomers	0.58 (0.51-0.64)	0.57 (0.50-0.63)	0.74 (0.68-0.79)	0.73 (0.67-0.79)
Proanthocyanidins[†]	0.50 (0.42-0.57)	0.51 (0.43-0.58)	0.62 (0.54-0.68)	0.61 (0.54-0.68)
Flavanones	0.60 (0.54-0.66)	0.56 (0.48-0.62)	0.68 (0.62-0.73)	0.65 (0.58-0.70)
Flavones	0.20 (0.11-0.29)	0.19 (0.10-0.28)	0.45 (0.37-0.53)	0.48 (0.38-0.55)
Anthocyanins	0.73 (0.65-0.80)	0.74 (0.66-0.81)	0.76 (0.68-0.82)	0.77 (0.69-0.84)
Isoflavones	0.48 (0.39-0.56)	0.46 (0.37-0.54)	0.54 (0.45-0.61)	0.49 (0.40-0.57)

7DDR$_{PE}$, weighed 7-day diet record derived using Phenol-Explorer; CI, confidence interval; MLVS, Men's Lifestyle Validation Study; SFFQ$_{Harvard}$, semiquantitative food frequency questionnaire derived using the Harvard database; SFFQ$_{PE}$, semiquantitative food frequency questionnaire derived using the Phenol-Explorer database; WLVS, Women's Lifestyle Validation Study

* Adjusted for total energy intake using the residual method.

[†] Includes proanthocyanidin dimers and trimers.

Table 4.

Rank intraclass correlation coefficients comparing flavonoid intake from the first and second semiquantitative food frequency questionnaires in MLVS and WLVS

	SFFQ_Harvard		SFFQ_PE	
	Unadjusted	**Energy-adjusted[1]**	**Unadjusted**	**Energy-adjusted[*]**
Men				
Total flavonoids	0.81	0.78	0.82	0.80
Flavonols	0.75	0.72	0.71	0.69
Flavan-3-ol monomers	0.79	0.74	0.79	0.77
Proanthocyanidins[2]	0.77	0.75	0.82	0.80
Flavanones	0.81	0.79	0.81	0.79
Flavones	0.79	0.78	0.74	0.72
Anthocyanins	0.78	0.75	0.77	0.75
Isoflavones	0.68	0.66	0.78	0.75
Women				
Total flavonoids	0.77	0.71	0.78	0.75
Flavonols	0.70	0.67	0.71	0.70
Flavan-3-ol monomers	0.75	0.72	0.78	0.77
Proanthocyanidins[†]	0.74	0.71	0.78	0.74
Flavanones	0.73	0.69	0.80	0.75
Flavones	0.77	0.70	0.69	0.69
Anthocyanins	0.72	0.70	0.71	0.68
Isoflavones	0.67	0.66	0.73	0.75

MLVS, Men's Lifestyle Validation Study; SFFQ_Harvard, semiquantitative food frequency questionnaire derived using the Harvard database; SFFQ_PE, semiquantitative food frequency questionnaire derived using the Phenol-Explorer database; WLVS, Women's Lifestyle Validation Study

[*] Adjusted for total energy intake using the residual method.

[†] Includes proanthocyanidin dimers and trimers.

Table 5.

Validity and reproducibility estimates by SFFQ for major food contributors to flavonoid intake in MLVS and WLVS (reference methods: 7DDR)

		r_s (95% CI)[*]	ICC[†]
Men			
	Apple	0.78 (0.70-0.83)	0.71
	Blueberry	0.77 (0.70-0.82)	0.72
	Grapefruit	0.79 (0.71-0.85)	0.71
	Onion	0.43 (0.34-0.51)	0.62
	Orange	0.81 (0.67-0.90)	0.39
	Orange juice	0.88 (0.85-0.90)	0.40
	Red wine	0.88 (0.85-0.91)	0.88
	Soymilk	0.89 (0.84-0.92)	0.74
	Strawberry	0.74 (0.62-0.83)	0.63
	Tea	0.71 (0.66-0.75)	0.77
	Tofu	0.54 (0.45-0.62)	0.62
Women			
	Apple	0.63 (0.54-0.70)	0.66
	Blueberry	0.67 (0.61-0.73)	0.70
	Grapefruit	0.77 (0.59-0.88)	0.67
	Onion	0.48 (0.37-0.56)	0.62
	Orange	0.44 (0.39-0.48)[‡]	0.37
	Orange juice	0.82 (0.79-0.85)	0.38
	Soymilk	0.83 (0.80-0.86)	0.66
	Red wine	0.83 (0.80-0.86)	0.86
	Strawberry	0.67 (0.52-0.79)	0.59
	Tea	0.72 (0.67-0.75)	0.75
	Tofu	0.59 (0.47-0.68)	0.67

ICC, rank intraclass correlation coefficient; MLVS, Men's Lifestyle Validation Study; r_S, Spearman rank correlation coefficient; WLVS, Women's Lifestyle Validation Study

[*] Values represent r_S comparing the second semiquantitative food frequency questionnaire to the average of two weeks of weighed 7-day diet records.

[†] Values represent the ICC comparing the first and second semiquantitative food frequency questionnaires.

[‡] Represents the r_S not deattenuated for random measurement error because of high within-person variation in intake (see Supplementary Table 6)