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Carotenoids and alkylresorcinols as objective biomarkers of diet quality when assessing the validity of a web-based food record tool and a food frequency questionnaire in a middle-aged population

Sanna Nybacka[1*], Anna Karin Lindroos[2], Elisabet Wirfält[3], Per Leanderson[4], Rikard Landberg[5,6], Ulrika Ericson[7], Ingrid Larsson[8], Eva Warensjö Lemming[2], Göran Bergström[9], Bo Hedblad[7], Marju Orho-Melander[7], Olle Melander[7], Anna Winkvist[1] and Heléne Bertéus Forslund[1]

Abstract

Background: Recently, two web-based dietary assessment tools were developed; a 4-day food record tool (the Riksmaten method), and a food frequency questionnaire (MiniMeal-Q). The aim of this study was to use objective biomarkers to examine the ability of the two methods to capture habitual dietary intake.

Methods: In total, 200 individuals from the pilot study of the Swedish CArdioPulmonary bioImage Study (SCAPIS) participated. Plasma concentration of carotenoids were determined with high-performance liquid chromatography (HPLC) and used as biomarkers of fruit and vegetable intake. A gas chromatography mass spectrometry (GC-MS) method was used to quantify alkylresorcinol homologues, which were used as biomarkers of whole grain wheat and rye intake.

Results: The correlations between energy-adjusted fruit and vegetable intakes and plasma carotenoid concentrations (except lycopene) were stronger amongst women than men ($r = 0.46$ and $r = 0.20$ for the Riksmaten method, and $r = 0.50$ and $r = 0.31$ for MiniMeal-Q, respectively). For whole grains, the correlations of energy-adjusted intakes and alkylresorcinols were higher using the Riksmaten method ($r = 0.30$ and $r = 0.29$ for women and men) than the MiniMeal-Q ($r = 0.25$ and $r = 0.20$, respectively). In regression analyses between plasma carotenoids (except lycopene) and reported intake of fruits and vegetables, the R^2 were 21.6 % and 5.1 % for women and men by the Riksmaten method, and correspondingly, 18.0 % and 6.6 % by the MiniMeal-Q. In the final full models, adjusted for smoking and BMI, all regression models remained statistically significant. The regression analyses of plasma alkylresorcinols and reported intake of whole grains showed an R^2 of 9.4 % and 9.7 % for women and men by the Riksmaten method, and correspondingly, 5.3 % and 8.4 % by the MiniMeal-Q. In the final full models, adjusted for smoking and age, all regression models remained statistically significant, except for women in MiniMeal-Q.

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* Correspondence: sanna.nybacka@gu.se
[1]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Box 459, 405 30, Gothenburg, Sweden
Full list of author information is available at the end of the article

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Conclusion: Both dietary assessment methods were able to capture dietary intake based on food groups with a similar precision. Agreements with objective biomarkers ranged from low to moderate, depending on sex and diet quality indicator. While the ability to capture whole grain intake was weak for both methods and sexes, the assessment of vegetable and fruit intake performed in a satisfactory manner for women in both methods.

Keywords: Dietary assessment, Web-based, Validation, Biomarkers, Carotenoids, Alkylresorcinols

Abbreviations: B, Biomarker; CI, Confidence intervals; CV, Coefficcient of variation; GC-MS, Gas chromatography mass spectrometry; HPLC, High-performance liquid chromatography; M, MiniMeal-Q; NFA, National food agency; QC, Quality control; R, The Riksmaten method; SCAPIS, Swedish CArdioPulmonary bioImage Study; SES, Socio-economic status; T, Theoretical true intake; ρ, Validity coefficients

Background

Assessing dietary intake with methods that are both precise and applicable to a heterogeneous population is a major challenge in nutrition research [1]. In westernized countries, the habitual diet of most individuals consist of a large variety of foods, and food selection varies during the day, between the days of the week, and by season [2, 3]. Although the various dietary assessment methodologies are designed to cater for some of these characteristics of dietary habits, there is still no method that can be considered to measure the true habitual intake without considerable limitations. In addition, there is still a high dependence on self-reported dietary intake data. These data have been associated with many cognitive pitfalls, for example failure to recall true habitual intakes, a tendency to alter food choices during the registration period to make it appear more "socially desirable" and the general under-estimation of portion sizes [4–8].

Validating newly developed dietary assessment methods is essential to gain a thorough understanding of the quality of the collected data. The process often involves comparisons with recovery biomarkers such as the doubly labeled water technique as a marker of energy intake [8, 9], urinary nitrogen of protein intake [10] and urinary sodium and potassium [11, 12]. Although these recovery biomarkers have the advantage of covering total intake they do not capture intake of specific foods or food groups [13].

There is convincing evidence that high intakes of fruit, vegetables and whole grains are associated with a lower risk of several chronic diseases [14–16]. Although the available recovery or prediction biomarkers do not capture total intake of these food groups on an absolute scale, it is possible to distinguish between high and low intakes of these food groups using concentration biomarkers. Plasma carotenoids are considered to reflect the intake of fruits and vegetables in a satisfactory manner [17, 18] and are amongst the most commonly used concentration biomarkers in dietary validation studies today. In a "western diet", approximately 80 to 90 % of the total carotenoid intake derives from fruit and vegetable consumption of which yellow-orange fruits and vegetables and dark green leafy vegetables are particularly rich in carotenoids [17]. Alkylresorcinols (AR), found in the outer parts of wheat and rye grain kernels but not in significant amounts in the refined flour or in other commonly consumed foods, have been suggested as a candidate biomarker of wholegrain wheat and rye intake [19–21]. Moreover, the ratio between the alkylresorcinol homologues C17:0/C21:0 is typically 1.0 in rye, 0.1 in common wheat, and 0.01 in durum wheat [22]. This ratio measured in plasma has been suggested as a way to differentiate a diet dominated by whole grain wheat from a diet dominated by whole grain rye. Alkylresorcinols and their metabolites have been used as biomarkers in several recent endpoint studies [23–25].

Recently, two innovative dietary assessment tools for use in large-scale studies were developed; the detailed 4-day food record tool called the Riksmaten method [26], and the more rapid food frequency questionnaire called MiniMeal-Q [27, 28]. The aim of this study was to use carotenoids as biomarkers of fruit and vegetable intake and alkylresorcinols as biomarkers of whole grain wheat and rye intake, when examining and comparing the ability of the two self-reported methods to capture habitual dietary intake. The validation on energy intake has previously been carried out [29]. Both methods are web-based and the validation process involves novel biomarkers, which makes this topic of interest for anyone involved in developing and evaluating new dietary assessment methods.

Methods

Study population

The Swedish CArdioPulmonary bioImage Study (SCAPIS) is a prospective, multicenter observational study. The study design has previously been described elsewhere [30]. The pilot study was conducted in Gothenburg during 2012, and the Diet sub-study was a part of the pilot study. The SCAPIS pilot study randomly recruited women and men aged 50–64 years from different socioeconomic status (SES) areas in the Gothenburg city region, and in

total 1111 individuals (50% women) carried out all examinations. The diet sub-study aimed for recruiting 100 women and 100 men among 575 eligible subjects, among those who had finished all examinations in SCAPIS pilot visit 1 and 2 and were feasible to be enrolled within five weeks from visit 1. After exclusions and drop-outs a total of 190 subjects were available for the carotenoid analyses and 185 subjects were evaluable for the alkylresorcinol analyses (Fig. 1).

Study protocol

At visit 1 of the SCAPIS Pilot study, all anthropometrical examinations were undertaken and blood samples were drawn (Fig. 2). After completing all examinations at SCAPIS Pilot visit 1 and 2, participants were invited to a one-hour group meeting with a dietitian. At this visit, the MiniMeal-Q questionnaire was completed and an introduction to the web-platform of the Riksmaten method was given. Participants were instructed to record all foods and drinks consumed for four consecutive days maintaining their "normal" diet during the registration period. For the current analyses, average daily energy and nutrient intakes were calculated. The food record was scheduled to begin either on the next coming Tuesday, Wednesday or Saturday to ensure a more equal distribution among weekdays. Participants were encouraged to enter the food intake continuously via the web, but participants who did not want to do so ($n = 15$) could report food intake by telephone to the study dietitian. All participants were contacted by a dietitian two days after the food record had started to enhance compliance and to provide an opportunity to ask questions.

The Riksmaten method

The Riksmaten method is a self-administered web-based 4-day food record, developed by the National Food Agency (NFA) in Sweden [26]. The food list in the web tool consisted of 1909 different food items and mixed dishes and is linked to the Swedish food composition database (Livsmedelsdatabasen, version Riksmaten adults 2010–11). The food record was accessed with a personalized login from a webpage. All foods and drinks in the food list were linked to individual portion size estimates, which were incorporated in the web-based food record. The usual food size references consisted of six different photos illustrating the portion sizes, but for some foods up to eight options were selectable. Dietary supplements taken during the recording days, as well as questions regarding physical activity level, were reported in a separate form on the website. All energy and nutrient intakes were calculated as the average intake of unit/per day.

MiniMeal-Q

The web-based food frequency questionnaire MiniMeal-Q used in the study is a short form of Meal-Q [27]. The Meal-Q was developed at Institute of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden. The questionnaire is semi-quantitative and five portion size options are included for (1) meat, chicken, fish and vegetarian substitutes (2) potatoes, rice and pasta and (3) vegetables (both raw and cooked). Other foods are calculated by standard portion sizes, and by portion sizes developed by the research group at Karolinska Institutet. The questionnaire covers a time-period of the past few months and includes follow-up questions only on food items and dishes

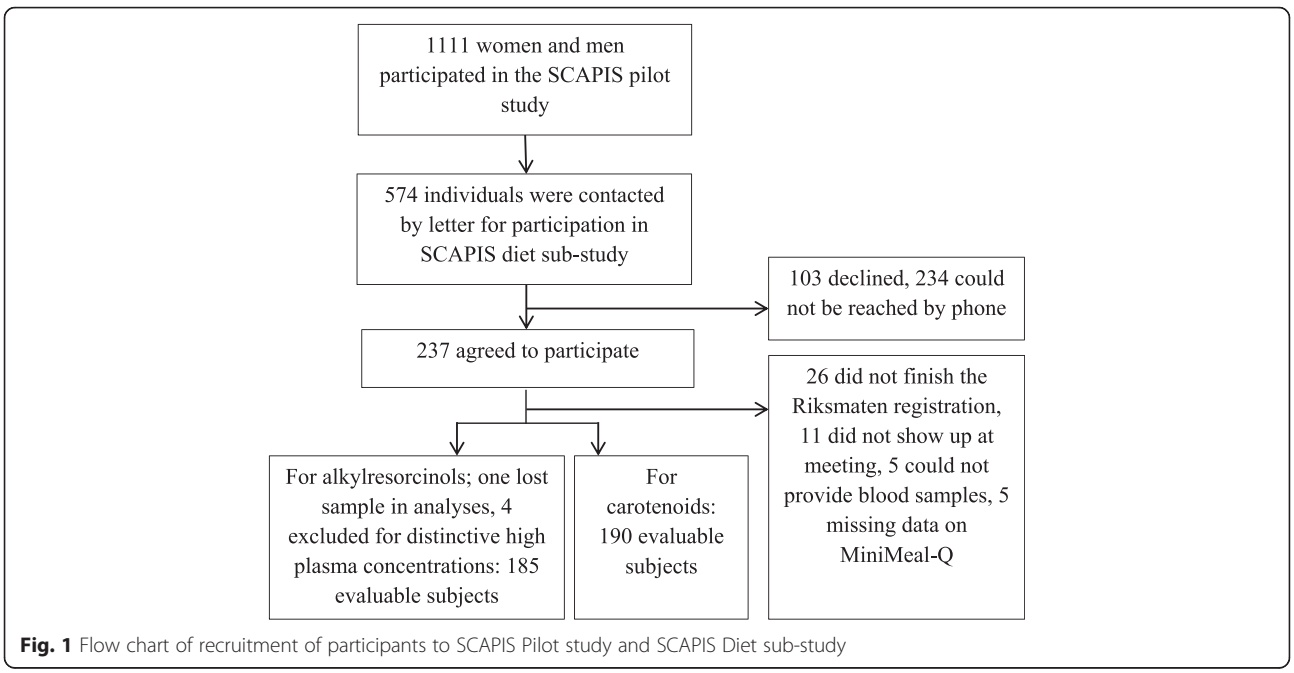

Fig. 1 Flow chart of recruitment of participants to SCAPIS Pilot study and SCAPIS Diet sub-study

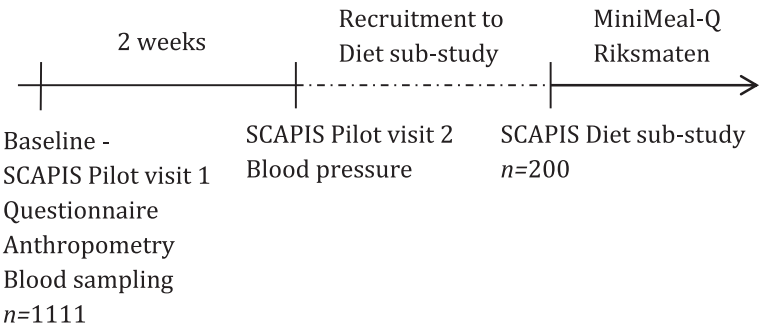

Fig. 2 Flow chart of data collection and visits in SCAPIS Pilot study and SCAPIS Diet sub-study

that were consumed at least once a month. Because of its dynamic structure, it includes between 75 to 126 food items. For most questions, frequencies are reported on a nine-grade scale from "five times a day" to "one-to-three times a month". All energy and nutrient intakes were calculated as the average intake of unit/per day. Energy and nutrient calculations were based on Swedish food composition database from NFA [31].

Food intake categories

In both methods, the food intakes are reported both as single food items and in mixed dishes. Thus, to be able to calculate the total amount of fruits and vegetables consumed, each mixed dish was split into its various ingredients. Thereafter the total intake of fruit and vegetables (fresh, frozen and canned) was calculated per day and subdivided into four different groups; (1) intake of vegetables: salad, spinach, tomatoes, green beans, green peas, peppers, corn, avocado, broccoli, cabbage, cucumber, leek, olives, aubergine, fennel, sugar pea, squash, asparagus, mushrooms, cauliflower, radish, sweet potatoes and carrots; (2) intake of fruits and berries: apple, orange, satsuma, apricot, grapes, peach, pear, pineapple, nectarine, mango, melons, papaya, banana, cherries, Sharon fruit, plums, pomegranate, rhubarb, blueberries, blackberries, lemon, kiwi, lingonberries, gooseberries, currants, raspberries, strawberries; (3) intake of juice: apple juice, orange juice, cranberry juice, grapefruit juice, lemon juice; and finally (4) intake of the sum of vegetables, fruits, berries and juice.

Carotenoids

The plasma concentrations of six carotenoids (i.e.; lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene and β-carotene) were used as biomarkers of fruit and vegetable intake [17, 18]. The plasma concentrations were determined with high-performance liquid chromatography (HPLC). Since lutein and its stereo isomer zeaxanthin are almost structurally identical this analysis does not discriminate between them and the sum of the carotenoids is presented as a single value. All chemicals were from Sigma-Aldrich (St. Louis, MO, USA) and the validity of the biochemical analysis method was ensured by including a reference sample that was calibrated against an external standard (SRM 968E) from the National Institute of Standard and Technology (NIST). Briefly, the frozen samples were thawed and 150 ml was mixed with 150 ml water, 300 ml 95% ethanol with 0.1 mg/ml butylated hydroxytoluene and 400 ml n-hexane. The mixture was vortexed vigorously for 5 min before centrifugation at 14 000 rpm for 2 min. The hexane phase (300 ml) was then transferred to new tubes and evaporated under a gentle stream of nitrogen. The residue was dissolved in 50 μl mobile phase consisting of acetonitril:methanol (80:20 v/v) and the mixture was then sonicated in an Ultrasonic bath for 5 min. The samples were centrifuged for another 2 min at 14 000 rpm prior to HPLC analysis. The HPLC analysis was performed with a PU-980 Pump and a UV-975 UV/vis detector both from Jasco Inc. (Japan Spectroscopic Company, Tokyo, Japan). The column was a Grace Smart 100 × 2.1 mm, RP18, 3 μm (Grace Davison Discovery Sciences Deerfield, IL, USA). The flow rate was set to 500 μl/min and 20 μl of the sample was injected. The carotenoids were detected at a wavelength of 450 nm and the concentrations were calculated from a standard curve of carotenoids in reference samples using the software Clarity v. 2.6.5 (DataApex, Prag, Czech Republic). The intra- and inter-assay coefficients of variation were 5.1 % and 7.0 %.

Alkylresorcinols

The plasma concentrations of five alkylresorcinol homologues (C:17:0-C:25:0) were used as biomarkers of whole grain (i.e. wholegrain from wheat and rye) intake [20, 25]. A gas chromatography mass spectrometry (GC-MS) method was used to quantify alkylresorcinol homologues C17:0-C25:0 in 0.2 ml plasma samples as described previously [32]. Samples were analyzed in seven batches together with four reference samples included in each batch to allow estimation of analytical variability. The within-batch coefficient of variation (CV) for total alkylresorcinol was <12 % in all seven batches estimated from $n = 4$ quality control-samples (QC) included in each

batch. The between batch CV of total alkylresorcinol was 13 %, based on results from five out of seven batches. Mean total alkylresorcinol concentration of QC-samples in two batches were higher than expected for unknown reason. Between-batch variation was adjusted for by dividing each observed alkylresorcinol concentration with a batch-specific correction factor for each alkylresorcinol homologue. The batch correction factor was defined as: Batch-correction factor = within-batch QC mean/grand QC mean (based on batch 1–5). Between-batch corrected data was used for statistical analysis.

Statistical analysis

Characteristics of the study population are presented as mean ± SD or as median (IQ range) for continuous data and as proportions of categorical data for women and men separately. The ranking ability was examined using Spearman's correlation analyses of biomarker plasma concentrations and energy-adjusted food variables (g/MJ). The associations of plasma carotenoid concentrations were analyzed both individually (all six carotenoids) and as the sum of total plasma carotenoids with each food group accordingly. Correlation analyses of dietary intake of whole grain and alkylresorcinols were conducted for individual alkylresorcinol homologues and as sum of all five homologues.

The method of triads [33] was applied to estimate the validity coefficients (ρ) between the theoretical true intake (T) and dietary intakes estimated with the Riksmaten method (R), MiniMeal-Q (M), and biomarkers (B). Equations for calculating ρ are as follows;

$$\rho_{RT} = \sqrt{((r_{RM} \times r_{RB})/r_{MB})},$$

$$\rho_{MT} = \sqrt{((r_{MR} \times r_{MB})/r_{RB})},$$

$$\rho_{BT} = \sqrt{((r_{MB} \times r_{RB})/r_{RM})},$$

where r is the correlation coefficient. The 95 % confidence intervals (CI) for the estimates of the ρ were obtained using the biased corrected and accelerated percentile CI bootstrap method with 1 000 000 bootstrap samples [34]. This method involves the repeated drawing of samples, with replacements, from the population that has been measured in order to provide an empirical distribution of the three validity coefficients. The method of triads is applicable only under the assumption that none of the measured exposures have correlated random errors. Some correlations between random errors cannot be ruled out and therefore the estimated validity coefficients might be overestimated and may thus be interpreted as the upper limit of the true validity coefficients [33].

Further, multiple linear regression analysis was used to evaluate the associations between food intake data (independent variable) and plasma concentrations of biomarkers (dependent variable). Because biomarker data were non-normally distributed, all biomarker variables were log-transformed to improve normality. Variables evaluated for potential confounding effect included current smoking, age, S-cholesterol, S-triglycerides, dietary fat intake, BMI [30] and use of any dietary supplements (derived from the Riksmaten registration). Based on the % change in the beta coefficient from each potential confounder, a final model was chosen; carotenoid analyses were adjusted for smoking status and BMI, and alkylresorcinol analyses were adjusted for smoking status and age. All statistical analyses were two-sided with a significance level at $\alpha < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp.), and the bootstrap was performed in R [35].

Results

Background characteristics of the study population including plasma concentrations of carotenoids and alkylresorcinol homologues are presented in Table 1. Mean age of the population was 57.7 years and approximately 50 % of women and 80 % of men were classified as overweight (BMI ≥ 25.0–29.9 kg/m^2) or obese (BMI ≥ 30.0 kg/m^2). Among women, β-carotene was the most abundant carotenoid in plasma (35 %) whereas lycopene was most abundant among men (37 %). The ratio of alkylresorcinol C17:0/C21:0 was 0.32 for women and 0.30 for men.

Absolute intakes of fruit, vegetables, β-carotene and whole grains are shown in Table 2. The total reported intake of fruits and vegetables was generally higher amongst women than men in both dietary assessment methods. Men reported a somewhat higher daily intake with the Riksmaten method compared to MiniMeal-Q, 340 g/day and 317 g/day respectively ($P = 0.009$), whereas no differences were seen for women.

For whole grains, women reported a slightly higher intake in MiniMeal-Q compared to the Riksmaten method, 25.6 g/day and 19.3 g/day, respectively ($P = 0.021$), whereas no differences between the methods were seen for men.

In general, stronger correlations were observed between energy-adjusted intakes of fruit and vegetables and plasma carotenoid concentrations amongst women than men, and the associations were stronger when excluding lycopene from the plasma carotenoid contents; $r = 0.46$ and $r = 0.20$ for the Riksmaten method, and $r = 0.50$ and $r = 0.31$ for MiniMeal-Q, respectively, Table 3. Reported intakes of β-carotene and plasma concentrations of β-carotene were significantly correlated among women by the Riksmaten method, but not among men ($r = 0.33$ and $r = 0.07$), and statistically significant for both women and men by MiniMeal-Q ($r = 0.35$ and $r = 0.29$, respectively).

Table 1 Characteristics of the study population in the SCAPIS Diet sub-study

	Women (*n* =102) *n* (%)	Men (*n* =98) *n* (%)
SES area		
low	42 (41)	36 (37)
high	60 (59)	62 (63)
Smoking: current smoker[a]	14 (14)	9 (9)
Education: university or college degree	43 (42)	37 (38)
BMI (kg/m^2)		
< 24.9	50 (49)	20 (21)
25–29.9	37 (36)	63 (64)
30+	15 (15)	15 (15)
	Mean ± SD	Mean ± SD
Age (y)	57.7 ± 4.5	57.7 ± 4.7
Weight [30]	72.1 ± 13.7	88.3 ± 10.5
BMI (kg/m^2)	26.4 ± 4.8	27.4 ± 2.9
Total cholesterol (mmol/L)	5.98 ± 0.94	5.69 ± 1.02
LDL-cholesterol (mmol/L)	3.95 ± 0.88	3.61 ± 0.97
HDL-cholesterol (mmol/L)	1.71 ± 0.52	1.85 ± 0.62
Triglycerides (mmol/L)	1.31 ± 0.79	1.29 ± 0.98
	Median ± IQR	Median ± IQR
Plasma carotenoids (μmol/L)		
α-carotene	0.21 ± 0.27	0.16 ± 0.16
β-carotene	0.77 ± 0.79	0.56 ± 0.43
β-cryptoxanthin	0.13 ± 0.14	0.11 ± 0.11
lycopene	0.73 ± 0.42	0.71 ± 0.48
lutein + zeaxanthin	0.42 ± 0.31	0.39 ± 0.24
Total carotenoids	2.40 ± 1.51	2.01 ± 1.14
Plasma alkylresorcinol homologues (nmol/L)		
C:17	2.3 ± 2.0	2.7 ± 3.1
C:19	6.6 ± 7.8	7.5 ± 11.2
C:21	8.7 ± 8.7	10.6 ± 16.0
C:23	4.1 ± 4.0	4.3 ± 5.5
C:25	4.4 ± 5.1	5.0 ± 6.3
Total AR homologues	21.4 ± 32.8	26.9 ± 28.4
Ratio C17:0/C21:0	0.32 ± 0.15	0.30 ± 0.16

Abbreviations: *AR* alkylresorcinol, *BMI* body mass index, *IQR* interquartile range, *SES* socio economic status
[a]Missing data; smoking (*n* =1)

The correlation coefficient between energy-adjusted intake of whole grain and alkylresorcinols was higher by the Riksmaten method ($r = 0.30$ and $r = 0.29$ for women and men) than by MiniMeal-Q ($r = 0.25$ and $r = 0.20$ for women and men), Table 4. All correlations were statistically significant except for men in MiniMeal-Q.

The correlation between the two dietary assessment methods and each of the diet biomarkers were used to calculate the validity coefficients using the method of triads. In Table 5, the validity coefficients and their 95 % CI are presented. For the CI bootstrapping, several calculations exceeded the limitations for correlation coefficients, which by definition can only extend between −1 and +1. When this occurred, the limits were set to either maximum −1 or +1. For capturing intake of fruits and vegetables, the Riksmaten method seemed to perform best for women and the MiniMeal-Q for men. The opposite was true for intake of whole grain, where the MiniMeal-Q performed best for women and the Riksmaten method for men.

A multiple linear regression model was used to study the relation between plasma carotenoid concentrations (sum of plasma carotenoids except lycopene) and reported dietary intake of vegetables, fruits, berries and juice, Table 6. In crude analyses, women had a higher degree of explained variance in carotenoid concentration than men by both methods; 21.6 % for women and 5.1 % for men by the Riksmaten method, and correspondingly, 18.0 % and 6.6 % by MiniMeal-Q. In the final full models, confounders adjusted for were smoking status and BMI. The major confounding factor was current smoking for women and BMI for men. In the fully adjusted models, all regressions remained statistically significant. Highest adjusted R^2 was found for women in the Riksmaten method, 29.3 %.

The results from the regression analyses of the relation between plasma alkylresorcinol homologues and reported intake of whole grain are shown in Table 7. In crude analyses, the concentration of alkylresorcinols was to a similar degree explained by the reported dietary intake of whole grains in both methods. In the Riksmaten method, the R^2 was 9.4 % and 9.7 % for women and men, and correspondingly, 5.3 % and 8.4 % in the MiniMeal-Q. In the final full models, data were adjusted for smoking status and age and here the adjusted R^2 was 8.0 % for women and 14.9 % for men in the Riksmaten method, and 5.7 % and 10.0 % in MiniMeal-Q. After adjusting for possible confounding factors, all regressions remained statistically significant except for women in MiniMeal-Q.

Discussion

The present study is one of the first validation studies using alkylresorcinols as objective biomarkers of whole grain wheat and rye intake to assess the validity of two web-based dietary assessment methods. In addition, carotenoids were used as markers of vegetable and fruit intake. The study also included a relative comparison of the reported intake of fruits, vegetables and whole grains between the two subjective methods. Both dietary

Table 2 Absolute food intake data (g/day) are presented with mean (SD) and median (25th and 75th percentiles) for women and men separately

	Riksmaten intakes (g/day)		MiniMeal-Q intakes (g/day)		
	Mean ± SD	Median (25th and 75th percentile)	Mean ± SD	Median (25th and 75th percentile)	*P*-value[a]
Women					
Fruits and vegetables[b]					
vegetables	175 ± 118	156 (96, 228)	155 ± 89	134 (86, 202)	0.105
fruit + berries	166 ± 150	144 (70, 218)	168 ± 140	130 (62, 250)	0.708
juice	44 ± 72	0 (0, 50)	68 ± 151	0 (13, 34)	0.046
total intake[c]	374 ± 249	346 (192, 480)	335 ± 205	264 (188, 446)	0.122
β-carotene (μg)	2314 ± 1778	1971 (1035, 3094)	3605 ± 2222	3102 (1825, 5157)	<0.001
Whole grains[d]					
wholegrain wheat	8.6 ± 8.3	6.8 (2.7, 11.7)	11.2 ± 9.2	9.4 (3.3, 16.0)	0.003
wholegrain rye	10.7 ± 10.5	7.6 (3.9, 16.2)	14.4 ± 19.3	9.6 (0.3, 21.1)	0.152
Total wheat + rye	19.3 ± 13.3	17.3 (9.6, 26.0)	25.6 ± 25.1	21.2 (6.6, 35.6)	0.025
Men					
Fruits and vegetables[e]					
vegetables	182 ± 106	164 (108, 225)	145 ± 79	130 (87, 195)	<0.001
fruit + berries	130 ± 111	100 (48, 191)	161 ± 185	104 (53, 226)	0.172
juice	56 ± 94	0 (0, 100)	71 ± 98	34 (13, 100)	0.004
total intake[c]	340 ± 176	303 (220, 419)	317 ± 223	262 (182, 410)	0.009
β-carotene (μg)	2431 ± 1844	1836 (1145, 3652)	3060 ± 1877	2654 (1595, 4300)	<0.001
Whole grains[f]					
wholegrain wheat	10.5 ± 10.7	7.3 (2.4, 16.3)	12.7 ± 11.1	9.0 (4.0, 18.2)	0.034
wholegrain rye	14.7 ± 13.2	13.3 (3.9, 20.7)	14.6 ± 17.4	8.9 (0.7, 21.7)	0.396
Total wheat + rye	25.1 ± 17.6	21.7 (13.4, 32.7)	27.5 ± 23.5	22.4 (6.2, 41.0)	0.919

[a]Related samples Wilcoxon signed rank test
[b]$n = 94$
[c]Total reported intake from carotenoid-containing plant derived foods e.g. vegetables, fruits, berries and juice
[d]$n = 92$; [e]$n = 96$
[f]$n = 93$

assessment methods have been compared to biomarkers among women as well as among men, and for two different diet quality indicators.

Methodological considerations

A major strength with this study is the large number of participants, as a sample size of at least 50 individuals is considered to be sufficient when using biomarkers in dietary validation studies [36]. As a result of the recruitment procedure, almost half of the study population came from areas classified as having a low SES, which is in contrast to many other studies. Given that the study was population-based, and had a low drop-out rate, findings of this study are likely to be applicable to the general population.

Another strength of the study is that fruits and vegetables from mixed dishes were included in the estimate of total intakes, and that we did not use a proxy of the intake frequency. This increases the quality of the data and the ability to study reported food intake in relation to plasma biomarkers. To assess the ability of the MiniMeal-Q to capture fruit intake, one must take into consideration that one answering frequency ("5–6 times a week") was missing for assessment of fruit intake, which might have led to inaccurate estimates for some individuals and thus made the associations of plasma carotenoids and reported dietary intake of fruit and vegetables weaker.

A limitation of the study could be that biomarkers and the dietary assessment methods to some extent reflect different time dimensions, and that blood samples used for biomarker analyses were sampled up to 5 weeks from collecting dietary intake data. The relatively short half-life of the biomarkers cause substantial within-person random variation in the biomarker concentrations measured, which will attenuate the observed association between true intake and the biomarker. Ideally, repeated measures of the biomarkers would have been preferable to provide some idea of the within-person variability, and also, a second sampling in conjunction with

Table 3 Spearman's correlation between energy adjusted intake (g/MJ) of vegetables, fruits + berries, juice, as sum of vegetables + fruits + berries + juice and β-carotene against plasma carotenoid concentrations

	Riksmaten					MiniMeal-Q				
	V	F + B	J	V + F + J	β-carotene	V	F + B	J	V + F + J	β-carotene
Women *n* = 94										
α-carotene	0.27*	0.31**	0.16	0.38**	0.36**	0.31**	0.41**	0.04	0.47**	0.50**
β-carotene	0.22*	0.35**	0.16	0.38**	0.33**	0.21*	0.38**	0.08	0.40**	0.35**
β-cryptoxanthin	0.24*	0.37**	0.16	0.42**	0.24**	0.21*	0.32**	0.16	0.45**	0.24*
lycopene	0.25*	0.21*	0.02	0.24*	0.14	0.16	0.25*	−0.07	0.24*	0.04
lutein + zeaxanthin	0.46**	0.29**	0.10	0.48**	0.13	0.34**	0.17	0.02	0.42**	0.08
Total carotenoids	0.32**	0.33**	0.14	0.42**	0.28**	0.30**	0.35**	0.04	0.46**	0.31**
Total carotenoids - lycopene	0.30**	0.38**	0.17	0.46**	0.32**	0.31**	0.39**	0.07	0.50**	0.35**
Men *n* = 96										
α-carotene	0.23*	−0.04	0.14	0.15	0.16	0.26*	0.11	0.16	0.21*	0.46**
β-carotene	0.11	−0.12	0.20	0.07	0.07	0.17	0.02	0.25*	0.16	0.29**
β-cryptoxanthin	0.24*	0.10	0.21*	0.31**	0.23*	0.27**	0.21*	0.25*	0.42**	0.25*
lycopene	0.09	−0.11	0.00	−0.04	0.05	0.28**	0.05	0.09	0.17	0.26*
lutein + zeaxanthin	0.19	−0.00	0.06	0.17	0.14	0.25*	0.21*	0.03	0.29**	0.20*
Total carotenoids	0.21*	−0.06	0.14	0.15	0.14	0.32**	0.12	0.18	0.28**	0.39**
Total carotenoids - lycopene	0.21*	−0.03	0.20	0.20	0.15	0.27**	0.15	0.22*	0.31**	0.38**

Abbreviations; V, vegetables (e.g. green leafy vegetables, tomatoes, green beans, peppers, green peas, corn, avocado, broccoli, mushrooms, cabbage, cucumber, leek, olives, aubergine, squash, asparagus, cauliflower and carrots); F + B, fruits and berries (both fresh and frozen); J, juice
*significant at $P < 0.05$
**significant at $P < 0.01$

Table 4 Spearman's correlation between energy-adjusted intake of whole grain wheat and rye (g/MJ) and plasma alkylresorcinol homologues for women and men separately

	Riksmaten	MiniMeal-Q
	Whole grain wheat and rye	Whole grain wheat and rye
Women *n* = 92		
C:17	0.36**	0.31**
C:19	0.30**	0.30**
C:21	0.20	0.14
C:23	0.23*	0.20
C:25	0.31**	0.23*
Total AR homologues	0.30**	0.25*
Men *n* = 93		
C:17	0.32**	0.31**
C:19	0.39**	0.30**
C:21	0.23*	0.17
C:23	0.21*	0.11
C:25	0.26*	0.13
Total AR homologues	0.29**	0.20

Abbreviations: *AR* alkylresorcinol homologues
*significant at $P < 0.05$
**significant at $P < 0.01$

finishing the food record would have been valuable in order to reflect that same time period. However, we do not expect that this time-period should affect the seasonal variations in consumptions of fruits, vegetables or whole grains, and if these two subjective methods are assumed to be able to measure the habitual dietary intake, the timing of the blood sampling should not play any major role in the outcome of the results.

We applied the triad analyses of associations to estimated validity coefficients. This method builds on the assumption of independent error structure among the three methods. This assumption has however been questioned for all subjective dietary assessment methods [37–39]. Still, the results of the validity coefficients were inconsistent; neither of the methods seemed to be superior over the other, but both self-reported methods displayed higher validity coefficients than the biomarkers. Since the Riksmaten method and MiniMeal-Q correlated well against each other on reported intakes based on food groups, this may partly explain why all biomarkers consistently displayed lower validity coefficients than the subjective methods did. Hence, our results from the triad analyses should be interpreted with caution.

Carotenoids

We decided not to include lycopene in the total plasma carotenoid content because studies have repeatedly

Table 5 Validity coefficients (95 % confidence intervals) for the Riksmaten method, MiniMeal-Q and total plasma carotenoids and total plasma alkylresorcinols for women and men

	Carotenoids			Alkylresorcinols		
ρ (95 % CI)	Women	Men	Women + men	Women	Men	Women + men
ρRT	0.78 (0.58, 0.97)	0.66 (−0.32, 1[a])	0.80 (0.63, 0,98)	0.66 (−1[a], 1[a])	0.73 (−1[a], 1[a])	0.69 (−1[a], 0.97)
ρMT	0.62 (0.40, 0.79)	0.94 (−1[a], 1[a])	0.69 (0.53, 0.72)	0.75 (−0.16, 1[a])	0.60 (−0.12, 1[a])	0.68 (0.29, 1[a])
ρBT	0.55 (0.29, 0.73)	0.24 (−0.01, 0.22)	0.44 (0.28, 0.58)	0.31 (−0.01, 0.38)	0.33 (−0.01, 0.39)	0.30 (0.03, 0.53)

Abbreviations: *ρ* validity coefficient, *ρRT* validity coefficient for the Riksmaten method, *ρMT* validity coefficient for MiniMeal-Q, *ρBT* validity coefficient for biomarker, *T* theoretical true intake
[a]The maximum limits were set to either −1 or +1

displayed poor results with lycopene as an indicator of fruit and vegetable intake [40–43]. This might be due to large individual variations in absorption, metabolism and excretion of lycopene [44, 45]. When evaluating the reported dietary intakes from the two subjective methods against the sum of plasma lutein, zeaxanthin, β-cryptoxanthin, α-carotene and β-carotene, women tended to report dietary intake that could explain a larger part of the variations in plasma biomarker content than did men. This applied for both methods, and the results were satisfying for women. For men, the results were overall poorer although the fruit and vegetable intake was somewhat better captured with the MiniMeal-Q.

The correlation coefficients were somewhat lower than in a validation study assessing fruit and vegetable intake with a food frequency questionnaire against plasma carotenoids (except for lycopene) with a $r = 0.59$ [40]. Otherwise, validation studies attempting to assess total fruit and vegetable intake with food frequency questionnaires normally range from $r = 0.18–0.35$ [41, 46, 47] and for repeated 24-h recalls at $r = 0.38–0.42$ [46, 47] using the sum of carotenoids (except for lycopene) as objective biomarkers.

Only 20 % of all women and 17 % of all men reported a consumption of more than 500 g of vegetables and fruits per day, which is the same amount as in the national food survey in adults, Riksmaten 2010–2011 [26]. We observed that men reported higher intakes of vegetables than women with the Riksmaten method, which is contrary to the Riksmaten survey 2010–11 [26]. It may also be that men have a more irregular intake of fruit and vegetables, and therefore a four-day period of recording might not be sufficient to cover the true habitual intake in males. Biomarkers determined in a single sample will reflect the true biomarker concentration with a higher precision if the habitual intake has low day-to-day variation. A more regular intake of fruit and vegetables among women might thus explain why rankings based on dietary intake versus biomarker data performed better for women than for men. Also, from the multiple regression models it appears that smoking status and BMI accounted for a large degree of the explained variance in plasma carotenoid concentration among men, but not in women. Adjusting for fat intake or cholesterol levels did surprisingly not improve the overall R^2 in our study. It is generally acknowledged that intake of fat together with intake of fruits and vegetables improves the absorption of the fat-soluble carotenoids and leads to higher plasma levels [48, 49]. In the blood, carotenoids are associated with lipoprotein particles that also contain cholesterol and subjects with high cholesterol

Table 6 Relation between dietary intake of vegetables, fruits, berries and juice and plasma carotenoid concentrations[a]

	Riksmaten				MiniMeal-Q			
	Beta coefficient for plasma carotenoids	SEM	*P* for beta coefficient	R^2	Beta coefficient for plasma carotenoids	SEM	*P* for beta coefficient	R^2
Women								
Crude model: carotenoid intake[a]	0.006	0.001	<0.001	0.216	0.006	0.001	<0.001	0.180
Full model[b]	0.005	0.001	<0.001	0.293[c]	0.004	0.001	0.001	0.248[c]
Men								
Crude model: carotenoid intake[a]	0.002	0.001	0.027	0.051	0.003	0.001	0.011	0.066
Full model[b]	0.003	0.001	0.008	0.231[c]	0.003	0.001	0.002	0.250[c]

[a]All plasma carotenoids except lycopene
[b]Adjusted for current smoking and BMI
[c]Adjusted R^2

Table 7 Relation between dietary intake of whole grains and plasma total alkylresorcinols

	Riksmaten				MiniMeal-Q			
	Beta coefficient for plasma AR	SEM	*P* for beta coefficient	R^2	Beta coefficient for plasma AR	SEM	*P* for beta coefficient	R^2
Women								
Crude model: whole grain wheat and rye intake[a]	0.276	0.091	0.003	0.094	0.133	0.060	0.028	0.053
Full model[b]	0.244	0.095	0.012	0.080[c]	0.108	0.063	0.089	0.057[c]
Men								
Crude model: whole grain wheat and rye intake[a]	0.298	0.095	0.002	0.097	0.183	0.063	0.005	0.084
Full model[b]	0.306	0.093	0.001	0.149[c]	0.152	0.065	0.021	0.100[c]

Abbreviations: AR, alkylresorcinol homologues
[a]Whole grain intake refers to intake of whole grain wheat and rye (energy-adjusted values of g/day)
[b]Adjusted for current smoking and age
[c]Adjusted R^2

levels might therefor have higher plasma carotenoids. However, in the present study we found no association with cholesterol and carotenoids.

Alkylresorcinols

The Spearman rank correlation coefficients between whole grain wheat and rye intake and total plasma alkylresorcinol homologues in this study were generally lower than those observed in most whole grain intervention studies [19, 25, 50, 51]. However, the correlations were similar to those previously reported by a Danish observational study including post-menopausal women, where the correlation coefficient of 0.25 was found between the plasma total alkylresorcinol concentration and rye bread intake assessed with a semi-quantitative food frequency questionnaire [51].

The slightly better ranking capacity of the Riksmaten method compared to the MiniMeal-Q could be explained by the larger variety of whole grain products in the food list of the Riksmaten method, which may have increased the precision, while the MiniMeal-Q lacks specific questions for foods with high whole grain content. The extended version of the same questionnaire, Meal-Q, is designed to better capture whole grain intake by more detailed questions regarding fiber and whole grain content on a selected number of carbohydrate sources [27]. Still, it is difficult for study participants to report their intakes of food products containing whole grains accurately because of the well-known difficulties in distinguishing whole grain from fiber, and to distinguish dark colored bread from whole grain bread.

In summary, both web-based assessment methods validated in this study managed to capture fruit and vegetable intake in a satisfactory manner, especially for women. The performance of wholegrain wheat and rye assessment was in contrast not quite adequate, and we suggest that wholegrain intakes measured with these both methods should be interpreted with caution if used as exposure variable. One should have in mind that we have only examined the validity of these methods to capture a few components of the diet, and there is a need for a greater variety of nutritional biomarkers to be able to reflect different aspects of dietary intakes. Although this validation study was carried out in a similar setting and group of people that these methods were intended to be used in, it is important to recall that the performance of the questionnaire can differ in other populations, particularly among less educated groups or among people of various ages. This limitation should always be taken into consideration while planning to use a validated dietary assessment method.

Conclusions

Both dietary assessment methods captured dietary intake based on food groups with similar precision. Agreements with objective biomarkers ranged from low to moderate, depending on sex and diet quality indicator. While the ability to capture whole grain intake was weak for both methods and sexes, the assessment of vegetable and fruit intake performed in a satisfactory manner for women in both methods. Choice of method should thus be guided by several considerations including research questions, simplicity and time requirement to perform the method and the overall costs for managing of the survey.

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Availability of data and material
The datasets generated during the current study are available from the corresponding author on reasonable request.

Authors' contributions
AW, EW, AKL, HBF, IL, designed the research; GB and BH provided essential databases; SN conducted research, analyzed data and wrote the manuscript; all authors have been involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Competing interests
The authors declares that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This study was approved by the Gothenburg Regional Ethics Committee (Dnr: 1061–11), and written informed consent was obtained from all study subjects.

Author details
[1]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Box 459, 405 30, Gothenburg, Sweden. [2]National Food Agency, Uppsala, Sweden. [3]Department of Clinical Sciences in Malmö, Research group in Nutritional Epidemiology, Lund University, Malmö, Sweden. [4]Occupational and Environmental Medicine Center and Department of Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden. [5]Department of Food Science, Uppsala BioCenter, Swedish University of Agricultural Sciences, Uppsala, Sweden. [6]Nutritional Epidemiology Unit, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [7]Department of Clinical Sciences in Malmö, Skåne University Hospital, Lund University, Malmö, Sweden. [8]Department of Gastroenterology and Hepatology, Sahlgrenska University Hospital, Gothenburg, Sweden. [9]Sahlgrenska Centre for Cardiovascular and Metabolic Research, Wallenberg Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden.

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