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Comparison of phytosterol intake from FFQ with repeated 24HDRs of the Adventist Health Study-2 calibration sub-study

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Abstract

We evaluated the performance of a food frequency questionnaire (FFQ) in estimating phytosterol intake against multiple 24 hr dietary recalls (24HDRs) using data from 1,011 participants of the calibration sub-study of the Adventist Health Study-2 (AHS-2) cohort. Dietary assessments of phytosterol intake included a self-administered FFQ and six 24HDRs and plasma sterols. Plasma sterols were determined using the gas-liquid chromatography (GLC) flame ionization method. Validation of energy-adjusted phytosterol intake from the FFQ with 24HDR was conducted by calculating crude, unadjusted, partial, and de-attenuated correlation coefficients (*r*) and cross-classification by race. On average, total phytosterol intake from the FFQ was 439.6 mg/day in blacks and 417.9 mg/day in whites. From the 24HDRs, these were 295.6 mg/day in blacks, and 351.4 mg/day in whites. Intake estimates of β-sitosterol, stigmasterol, other plant sterols and total phytosterol from the FFQ had moderate to strong correlations with estimates from 24HDR (r=0.41 to 0.73). Correlations were slightly higher in whites (r=0.42 to 0.73) than in blacks (r=0.41 to 0.67). FFQ estimates were poorly correlated with plasma sterols as well as 24HDR versus plasma sterols. We conclude that the AHS-2 FFQ provided reasonable estimates of phytosterol intake and may be used in future studies relating phytosterol intake and disease outcomes.

Keywords

validation; dietary assessment tools; correlation coefficient; phytosterol

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Introduction

Phytosterols are the phytochemicals which are found to have a structure comparable to cholesterol[1]. They are found in plant foods where they function as part of the plant cell membrane[2]. There are various types of phytosterol widely grouped into plant sterols and plant stanols. The most abundant phytosterols are β-sitosterol, stigmasterol, and campesterol[3]. The main sources of plant sterols are vegetable oils, nuts and seeds[4]. Plant stanols are a subgroup of phytosterols that are saturated[3]. Plant stanols are found in mixtures of extracted sterols, which is the mixture of free sterols and stanols and their esters. Enriched extracted sterols are found mostly in commercial products such as margarine, fermented milk drinks, salad dressing, spreads, milk, soy, yogurt, cheesy products, soy and fruit drinks, sausages and breads, ready-to-eat meals, snack bars and candies[5].

Dietary intake of plant sterols varies greatly in Western countries. The median phytosterol intake in the European Perspective Investigation into Cancer and Nutrition (EPIC) Spanish cohort is approximately 315 mg/day[6]. The average intake of phytosterol in the United Kingdom (UK) is 163 mg/day[7]. Phytosterol intake in the usual Spanish diet is approximately 276 mg/day[8].

The cholesterol lowering property of phytosterols is one of the well-established health benefits of plant sterols and plant stanols. For example, it has been shown that an intake of 2 grams per day of stanols or plant sterols lowers plasma LDL-cholesterol levels by approximately 10%[9]. Plant sterols and stanols also have anticancer properties[10].

Phytosterol intake is difficult to assess due to the lack of comprehensive updated plant sterol and stanol composition data, particularly related to plant stanols in fortified foods. Of the published reports on phytosterol intake to date, the most comprehensive and referenced article dates back to 1978[11]. To our knowledge, only one validation study on phytosterol consumption was conducted in 2013 by Northern Sweden group whom found the moderate to high association between FFQ and 24HDR[12].

We estimated phytosterol intake in the Adventist Health Study-2 (AHS-2) population, which is a prospective cohort of adult Adventists in North America, with a wide range of plant foods intake[13]. AHS-2 participants are 48.2% non-vegetarian, 5.5% semi-vegetarian, 9.8% pesco-vegetarian, 28.9% lacto-ovo vegetarian and 7.6% vegan[14]. The primary dietary assessment method in the AHS-2 is the food frequency questionnaire (FFQ), a widely used approach to assess habitual dietary intake of large study populations[15]. In order to further associate dietary intake (based on FFQs) with disease outcomes, it is crucial to first examine the performance of the FFQ in measuring *true* intake. In the AHS-2, a calibration sub-study was conducted for the purpose of validating food frequency data and to correct biases related to measurement errors[13].

The objective of this paper is to compare plant sterol and plant stanol intake assessed by the FFQ intake with multiple 24 hr dietary recalls (24HDR) as the reference, using data from the calibration sub-study of the AHS-2.

Methods

Study design

The AHS-2 is a prospective cohort of 95,873 adults. Baseline data collection was from 2002 through 2007. Participants of this cohort had to be 30 years or older and sufficiently fluent in English in order to complete a comprehensive lifestyle questionnaire which included the FFQ[13]. In order to validate the dietary information of the comprehensive lifestyle questionnaire, the investigators of AHS-2 conducted a calibration sub-study of 1,011 subjects from the AHS-2 cohort. Calibration sub-study subjects were randomly selected by church location, and then subjects within each church were selected by gender and age. Black participants were purposefully oversampled to ensure more similar proportions of black and white participants. Throughout the 9–12 month period of the calibration study, the data collection included the FFQ, six 24HDRs and collection of biological specimens (i.e., plasma, serum, urine, etc.).

We excluded subjects who did not complete the requisite number of recalls (n=96), or subjects with an incomplete FFQ (n=34), total energy intake (kcal) greater than 4500 or less than 500, and/or a body mass index (BMI) greater than 50 or less than 15 kg/m^2 (n=102). After these exclusions, the number of participants available for statistical analysis was 779. The analytic subjects and those who were excluded from the analysis were found to be similar in baseline characteristics.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the institutional review board of Loma Linda University; (IRB#48134). Written informed consent was obtained from all subjects.

Dietary assessments

Food frequency questionnaire—The AHS-2 FFQ is the largest portion of the comprehensive enrollment questionnaire which consists of 204 foods with 54 questions pertaining to food preparation and 46 open-ended questions[16]. Frequencies are categorized into never or rarely, 1–3 times per month, 1 time per week, 2–4 times per week, 5–6 times per week, 1 time per day, 2–3 times per day, and 4+ times per day and 6 + times per day, which were weighted 0, 0.067, 0.143, 0.429, 0.786, 1, 2.5, 4.5 and 6.5 in terms of times/day respectively. The amount of food consumption was categorized into one standard serving size, half or less, and one and a half or more of a standard serving size, and weighted 1, 0.5 and 1.5 respectively[16].

24-hour dietary recall—We used multiple 24HDRs as the reference method which were obtained over the telephone and without prior announcement[16]. Participants were sent a two-dimensional food portion visual to help estimate portion size. Each 24HDR was conducted by a trained research dietitian who asked specific details about food preparation and recipes. These 24HDRs were digitally recorded and entered into the Nutrition Data System for Research (NDS-R) version 4.06 or 5.0 (The Nutrition Coordinating Center, Minneapolis, MN, USA), and nutrient composition was calculated based on the NDS-R

2008 database. Quality control of the recalls was performed by a senior research dietitian who listened to randomly selected recorded interviews, verified and compared the audio data with the actual entries on the NDS-R database[16].

Two sets of 24HDRs were obtained approximately 6 months apart; each set included one Saturday, one Sunday and one weekday, with a total of six 24HDRs per participant. Using one set of the 24HDR, a synthetic week was created using the following formula: (Saturday intake + Sunday intake + 5 × weekday intake) divided by 7 days. Thus the two sets of 24HDRs provided two synthetic weeks of intake data. To estimate the average food intake of each participant in each of the 24HDRs, we averaged their phytosterol intake over these two approximated weeks[16].

Phytosterol database

The USDA National Nutrient Database for Standard Reference (USDA SR) is produced by the U.S. Department of Agriculture (USDA), which is the primary database source of food composition data in the United States[4]. For the current study, we used the USDA SR 27 (August 2014) as the primary source of standard phytosterol contents of over 500 food items.

Throughout this paper, “plant sterol” refers to β-sitosterol, campesterol, and stigmasterol; “other phytosterol” refers to Δ5+Δ7 avenasterols, avenasterol, brassicasterol, stanols, stigmastanol, sitostanol, campestanol, and other unknown sterols. “Total phytosterol” refers to plant sterols and other phytosterols combined.

For unavailable foods and ingredients (n=189) in the USDA SR 27, we used the phytosterol content which were quantified by gas chromatography method[5, 8, 11, 12, 17–25] or gas chromatography – mass spectrometer[26]. This particular method was used to quantify phytosterol content in the USDA SR 27[27].

Our compiled phytosterol database was comprised of plant sterols, other phytosterols and total phytosterol. Phytosterol content was quantified as mg/100g from each food item. Once we were able to identify phytosterol content in foods, we quantified phytosterol content based on the FFQ and 24HDRs by matching the food ID in the compiled phytosterol database with the food ID and food description in the FFQ and 24HDRs of the calibration sub-study.

We also grouped plant foods as sources of phytosterol as follows: nuts and seeds, legumes and soy, vegetables, grains, oils and added fats, olives and avocados, and fruits (Table 1).

Phytosterol intake

We determined the 24HDR plant sterol and other phytosterol intake of individual subjects by using the following formula: $\Sigma C_n \times P_n$ where C = the reported grams of $food_n$ consumed and P = milligrams of phytosterol content per 100 grams of $food_n$.

Phytosterol intake estimates (mg) from the FFQ were obtained by $\Sigma F_n \times S_n \times G_n \times P_n$, where F = the weighted frequency of $food\ intake_n$, S = weighted serving size of food

consumed$_n$, G = the standard serving size of food$_n$, P = milligrams of phytosterol content per 100 grams of food$_n$.

Laboratory methods

Blood was collected from participants during clinic visits between first and second 24HDR. Blood processing followed a standard protocol[28]. Plasma was derived from blood collected in heparin tubes. Collected blood was separated into layers by centrifuge, and then aliquots of plasma were separated into straws. These sealed plasma straws were put into containers and kept in liquid nitrogen tanks at the temperature of −182°C[13].

One of these plasma straws from each participant was used for the determination of plant sterol and cholesterol concentration. The concentrations of β-sitosterol, campesterol, cholesterol were measured using the gas-liquid chromatography (GLC) flame ionization detection method[29]. Plasma samples were sent to the Institute of Clinical Chemistry and Clinical Pharmacology, University Clinics of Bonn, Bonn, Germany for quantifying plasma sterol and cholesterol concentration.

Statistical analysis

Prior to analysis, we applied log(x+1) to variables with zero phytosterol intake (n=8 which represent less than 1% of the analytic sample). After transformation, the distribution of these phytosterol and other transformed variables was greatly improved and the four usual statistical assumptions (normality, homogeneity of variance, linearity and independence) were met.

All phytosterol intake levels from the FFQs and 24HDRs were energy-adjusted using the residual method [15], in order to obtain phytosterol intake without the undue influence of total energy intake. Due to the fact that some individuals had phytosterol intake and few did not, we applied a partitioning method [30]. This method allowed us to retain zero intakes and only energy adjusted the non-zero intakes. We then combined energy adjusted non-zero intake levels with the zero intakes, thus keeping all values on the same scale.

Previous reports on the calibration sub-study showed differences in nutrient and food intake by race and no distinct patterns by gender. Therefore, we stratified by race in the analysis of this paper.

Comparison of baseline characteristics by race was done using the independent t-test for continuous and chi-square for categorical variables. Untransformed phytosterol intake determined from the FFQ, 24HDR and plasma were presented as arithmetic means and standard deviations.

Unadjusted Pearson correlations of the transformed energy-adjusted plant sterols, other phytosterols and total phytosterol intake between FFQs and 24HDRs were first determined. De-attenuation correlation coefficient determination was then conducted to correct for within person variation of the 24HDRs prior to correlation with the FFQs.

Contingency tables (cross classification) between the FFQ and 24HDR data, stratified by race, were also produced to determine the agreement between the FFQ and 24HDR reporting methods. These provided the quantitative differences of the phytosterol intake of the two dietary measurements in a categorical manner[15].

Additionally, we calculated the contribution percentage of each food group to total phytosterol intake levels assessing by FFQs of the calibration sub-study participants. All analyses were done using SAS, Version 9.4 (SAS Institute, Inc., Cary, NC)

Results

Selected characteristics of the calibration sub-study participants by race are shown in Table 2. Age, gender, BMI and energy intakes were statistically significantly different between blacks and whites. Therefore, we further conducted analysis stratified by race. In general, intake of individual plant sterols and total phytosterol was higher when assessed by FFQ than 24HDR in both races. The mean estimated intake of energy-adjusted total phytosterol was 295.6 mg/day in blacks and 351.4 mg/day in whites from six 24HDRs. Using the FFQ, energy-adjusted total phytosterol was estimated to be 439.6 mg/day in blacks and 417.9 mg/day in whites.

Mean plasma concentrations of β-sitosterol, campesterol in blacks were higher than whites (Table 3). However, statistically significant differences by race were seen only for β-sitosterol and campesterol. The correlations between plasma sterol versus FFQ and 24HDR were 0.02 to 0.09 and not statistically significant (results not shown).

Unadjusted Pearson correlations between energy-adjusted phytosterol intake in FFQs and 24HDRs (Table 4) showed poor to moderate associations (r= 0.15 to 0.51 in blacks and 0.10 to 0.57 in whites). Overall, de-attenuation improved the correlations of all plant sterol groups in both blacks and whites; however, de-attenuated correlations remained poor for campesterol. All correlations between energy-adjusted phytosterol intake in the FFQs and 24HDRs were statistically significant ($P < 0.05$). Correlations between plant sterols in plasma and plant sterol intake in FFQ or 24HDR were generally poor (below 0.07).

Compared to blacks, whites had higher percentages of exact agreements in all types of named plant sterols but slightly lower in other phytosterol (Table 5). The proportion of exact agreements ranged from 27.4 – 38.6% in blacks and 30.8 – 42.3% in whites. Gross misclassification (GM) in blacks was higher than whites, which ranged from 4.2 – 9.7% in blacks and 1.6 – 11.3% in whites. Overall, total phytosterol had the highest percentage of exact agreement and the lowest GM in both blacks and whites.

The contribution to total phytosterol by food groups is shown in Figure 1. On assessment by FFQ, the legumes and soy food group also contributed the greatest proportion (32.61%), followed by fruits (18.59%) and fat (17.22%), and the olives and avocados food group also contributed the least (1.00%) to total phytosterol.

Discussion

Our assessment of the performance of the FFQ in estimating plant sterol intake showed moderate to high correlations when compared to 24HDRs for β-sitosterol, stigmasterol, other phytosterol and total phytosterol. The correlations that we found on phytosterol consumption are consistent with the previous validation study for a range of nutrients in our and other cohorts[16,31].

The average mean intake of phytosterol from the FFQ was higher than in the 24HDRs. It is possible that the FFQ overestimated intake because our FFQ asked about the consumption of over 200 food items which facilitated our study to capture more phytosterol-containing foods than actual intake by the 24HDRs. In general, correlations and agreement between the FFQ and 24HDRs were higher among whites than blacks.

To our knowledge, only one other group, from Northern Sweden, validated plant sterol intake from a FFQ (with 84 food items) with 24HDRs (ten recalls) as a reference[12]. In the Northern Sweden study, both crude and de-attenuated correlations were somewhat lower than what we found in AHS-2. In both the Northern Sweden and AHS-2 cohorts, correlations improved after de-attenuation. These findings suggest that both within-person error and energy-adjustment are important components to consider when estimating phytosterol intake.

We note that the definition of "total phytosterol" by Klingberg[12] is different from our study. For Klingberg[12], the total phytosterol was comprised of 5 different types of phytosterols whereas in the AHS-2 calibration sub-study the total included 11 types of phytosterols. The updated comprehensive phytosterol database we compiled in the AHS-2 partly explains the higher estimates observed in our study compared to the Northern Sweden cohort. The relatively higher intake of phytosterols in the AHS-2 also may be driven by the fact that 52% of the AHS-2 cohort are vegetarian (28.9% lacto-ovo vegetarian, 9.8% pesco vegetarian, 7.6% vegan and 5.5% semi vegetarian)[32]. Moreover, the wide range of phytosterol intake is a possible reason for the moderately higher correlations in our validation study, which will be beneficial for future disease related hypothesis testing.

We have previously demonstrated the AHS-2 FFQ's ability to discriminate intake of food among individual, particularly foods that contribute to total phytosterol consumption. These food groups included nuts and seeds, legumes and soy, vegetables, grains, oils and added fats, olives and avocado and fruits. Because of this, we examined if the phytosterol concentration in plasma would reflect the wide range of phytosterol intake in our population. We found as others have that correlations of plasma sterol levels with phytosterol intake from either the FFQ or the 24HDRs were poor and not significant. These results confirmed that plasma sterol is not an ideal biomarker of phytosterol intake[33]. Phytosterol absorption is less than 2%, whereas cholesterol absorption is up to 60%[34]. The poor absorption of phytosterol is due to its poor substrate for acetyl-CoA acetyltransferase 2 (ACAT2) which prevents plant sterol to be packaged into chylomicrons for further circulation throughout body[35]. Phytosterol is returned from the intestinal cells back to gut lumen via the ATP-binding cassette (ABC) transporters[36]. In a study that examine the metabolism of β-

sitosterol and cholesterol in men, Salen et al further report that cholesterol absorption is inversely correlated with fecal β-sitosterol[37]. Therefore, phytosterol levels in fecal samples could be explored as a possible biomarker of phytosterol intake.

The main contributing food group to total phytosterol intake in both the British diet (46.96%)[7] and the Spanish diet (39.3%)[8] was the oils food group, whereas in the AHS-2 it was the legumes and soy food group (32.61%). The proportion of the population following a British diet who consumed plant sterols from added fats (18.32%) was slightly higher when compared to those in the AHS-2 cohort sub-study (17.22 %).

Phytosterol intake from the fruit food group in the present study, particularly as measured by the FFQ (18.59%), was greater than in the British diet (12.7%)[7]. The AHS-2 cohort also had a greater proportion of phytosterol intake from the nuts and seeds food group (7.37%) when compared to the British diet (1.35%)[7] and the Spanish diet (2.4%)[8].

We recognize that our present study has limitations. Lower estimates of the plant sterol intake are greatly influenced by the quality of the database of plant sterol content in foods. We have minimized this effect by compiling the phytosterol content in foods from several sources. The first is the USDA SR 27, for phytosterol content in approximately 115 food items, and from other references[5, 8, 11, 12, 17–26] for phytosterol content in approximately 189 food items. In addition to deriving phytosterol content from multiple sources, we calculated de-attenuated correlation coefficients which removed the “noise” of within-person error from 24HDR, and also minimized the influence of total energy intake by using energy-adjusted intake.

Conclusion

The AHS-2 FFQ is a suitable measurement tool for estimating phytosterol intake in the AHS-2 cohort and may be used to relate intake levels to disease outcomes. Regression calibration will be a necessary step for future studies relating phytosterol intake with an outcome, to minimize measurement error in the exposure.

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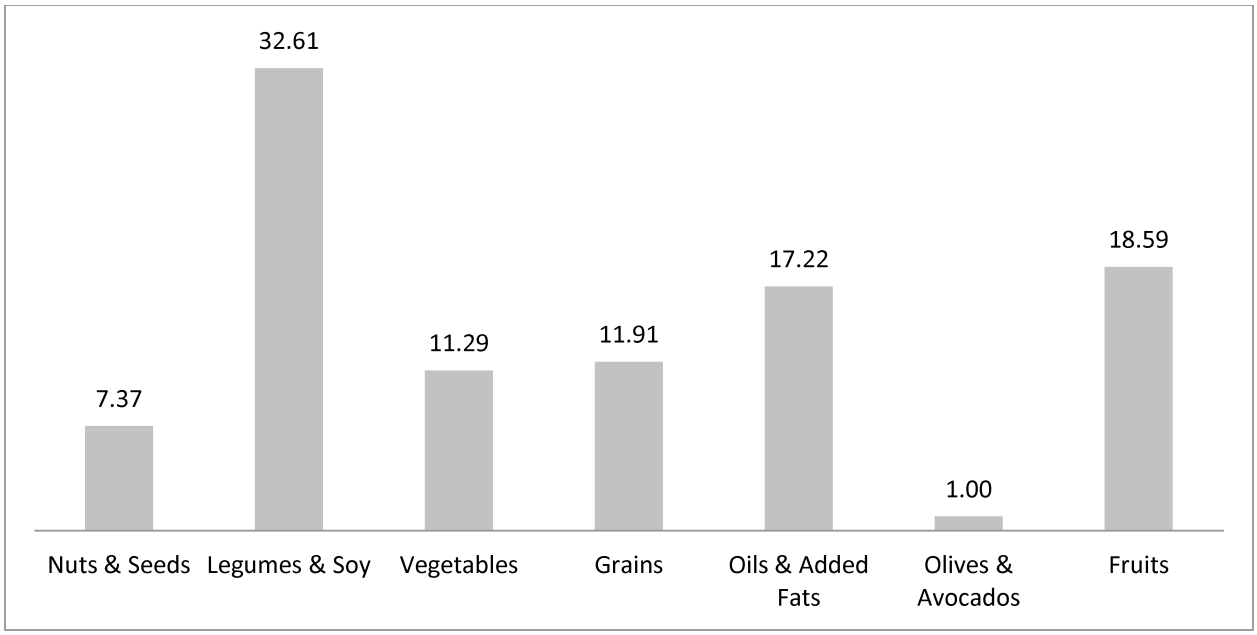

Figure 1.
Percentage contribution to total phytosterol intake by food group from FFQ in the Adventist Health Study-2 calibration sub-study

Table 1

Phytosterol food groups and their components

Phytosterol Food Groups	Components
Nuts and Seeds	almonds, cashews, flax seeds, nuts, seeds, walnuts, tree nuts, trail nuts
Legumes and Soy	legumes, peanuts butter, peanuts, soy beans, tofu
Vegetables	fried potatoes, leafy greens, onions, other vegetables, potatoes, vegetables, green beans
Grains	whole grains, refined grains, mixed grains, refined cereals, mixed cereals
Oils and Added Fats	added fats and liquid fats: margarine spread or stick with vegetable oil or soybean oil, almond oil, canola oil, cocoa butter oil, coconut oil, corn and canola oil, corn oil, cottonseed oil, flaxseed oil, grape seed oil, hazelnut oil, palm oil, peanut oil, nutmeg butter oil, poppy seed oil, rice bran oil, safflower oil, sesame oil, shea nut oil, soybean oil, sunflower oil, tea seed oil, tomato seed oil, vegetable oil, walnut oil, wheat germ oil, olive oil
Olives and avocados	olives and avocados
Fruits	berries, dried fruits, fruits, fruit juice

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Table 2

Subjects characteristics by race in the AHS-2 calibration sub-study (*n*=781)

Baseline Characteristics	Blacks (*n*=339)		Whites (*n*=442)	
	% or Mean	SD	% or Mean	SD
Age ***	58.56	12.80	62.37	13.69
Gender				
Females (%) ***	69.91		63.12	
Males (%)	30.09		36.88	
BMI(kg/m^2) ***	29.17	6.53	26.51	5.44
Energy Intake(Kcal) ***	1502.07	515.88	1737.10	493.20
β-sitosterol(mg)				
FFQ	289.30 *	160.40	273.40 **	132.70
24HDR ***	197.50	73.48	238.10	90.93
Campesterol(mg)				
FFQ	63.48 *	36.05	61.82	35.49
24HDR ***	49.72	21.52	59.64	26.69
Stigmasterol(mg)				
FFQ	59.41 *	41.81	54.62 **	37.41
24HDR ***	39.89	27.02	44.69	28.91
Other phytosterol(mg) †				
FFQ	27.49 *	18.24	28.05 **	13.78
24HDR ***	8.47	3.26	9.00	3.10
Total phytosterol(mg) ‡				
FFQ	439.60 *	242.20	417.90 **	208.90
24HDR ***	295.60	116.40	351.40	142.10

† Sum of Δ5+ Δ7 avenasterol, avenasterol, brassicasterol, stanols, stigmastanol, sitostanol, campestanol and unknown

‡ Sum of β-sitosterol, campesterol, stigmasterol, other phytosterol

§ Average intake of these phytosterol was significantly different in FFQ compared with 24HDR in blacks:

* $P<0.05$

// Average intake of these phytosterol was significantly different in FFQ compared with 24HDR in whites:

** $P<0.05$

¶ Statistical significantly different in blacks compared with whites:

*** $P<0.05$

Table 3

Average concentration of plasma sterol by race

Plasma Sterol	Blacks (mcg/ml)		Whites (mcg/ml)	
	Mean	SD	Mean	SD
Plasma Sitosterol †	3.75	1.87	3.06	1.43
Plasma Campesterol †	4.87	2.63	3.78	1.96

† Mean concentration of these plasma sterol were significantly different in blacks compared with whites:

* $P < 0.05$

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Table 4

Pearson correlations between energy-adjusted phytosterol intake in FFQ and 24HDR of the AHS-2 calibration sub-study by race

phytosterol	Unadjusted		De-Attenuated	
	Blacks	Whites	Blacks	Whites
β-Sitosterol	0.51**	0.56**	0.67**	0.70**
Campesterol	0.15*	0.10*	0.20*	0.14*
Stigmasterol	0.41**	0.55**	0.58**	0.73**
Other Phytosterol†	0.32**	0.42**	0.45**	0.56**
Total Phytosterol‡	0.50**	0.57**	0.65**	0.72**

†Sum of Δ5+ Δ7 avenasterol, avenasterol, brassicasterol, stanols, stigmastanol, sitostanol, campestanol, unknown

‡Sum of β-sitosterol, campesterol, stigmasterol and other phytosterol

§Correlations between FFQ and 24HDR were significantly difference:

*$P < 0.05$

**$P < 0.0001$

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Table 5

Agreement between the categorization of energy-adjusted phytosterol intake estimated from FFQ and 24HDR by race in the AHS -2 calibration sub-study participants

	Blacks (%)(*n*=338)				Whites (%)(*n*=441)			
Phytosterol	**Exact**	**± One quartile**	**±Two quartiles**	**GM‡**	**Exact**	**± One quartile**	**±Two quartiles**	**GM‡**
β-Sitosterol	38.60	38.60	18.30	4.20	42.30	40.70	14.30	2.70
Campesterol	27.40	41.00	21.80	9.70	30.80	34.80	23.10	11.30
Stigmasterol	38.10	37.80	19.20	5.00	38.50	43.40	16.50	1.60
Other Phytosterol *	36.60	37.20	17.70	8.60	35.80	44.30	14.70	5.20
Total Phytosterol †	40.10	38.10	18.30	3.50	42.50	41.40	14.50	1.60

*Sum of Δ5+ Δ7 avenasterol, avenasterol, brassicasterol, stanols, stigmastanol, sitostanol, campestanol, unknown

†Sum of β-sitosterol, campesterol, stigmasterol and other phytosterol

‡GM = Gross Misclassification: disagreement by three quartiles