Biomarkers of Dietary Intake Are Correlated with Corresponding Measures from Repeated Dietary Recalls and Food-Frequency Questionnaires in the Adventist Health Study-2^{1–3}

Gary E Fraser,^{4,5} Karen Jaceldo-Siegl,^{4,5*} Susanne M Henning,⁶ Jing Fan,⁴ Synnove F Knutsen,^{4,5} Ella H Haddad,⁵ Joan Sabaté,^{4,5} W Lawrence Beeson,^{4,5} and Hannelore Bennett⁴

⁴Adventist Health Study and ⁵Center for Nutrition, Healthy Lifestyle and Disease Prevention, Loma Linda University, Loma Linda, CA; and ⁶UCLA Center for Human Nutrition, School of Medicine, Los Angeles, CA

Abstract

Background: Accurate assessment of diet in study populations is still a challenge. Some statistical strategies that use biomarkers of dietary intake attempt to compensate for the biasing effects of reporting errors.

Objective: The objective was to correlate biomarkers of dietary intake with 2 direct measures of dietary intake.

Methods: Subjects provided repeated 24-h dietary recalls and 2 food-frequency questionnaires (FFQs) separated by ~3 y. Correlations between biomarkers and reported dietary intakes as measured by the recalls and FFQs were de-attenuated for within-person variability. The Adventist Health Study-2 (AHS-2) has a large database of biomarkers of dietary intake (blood, urine, adipose tissue) from a calibration study (909 analytic subjects) representing the cohort. Participants were black and non-black Adventists in the United States and Canada.

Results: Dietary items with higher-valued de-attenuated correlations (≥ 0.50) between biomarkers and recalls included some fatty acids (FAs), the non-fish meats, fruit (non-black subjects), some carotenoids, vitamin B-12 (non-black subjects), and vitamin E. Moderately valued correlations (0.30–0.49) were found for very long chain ω -3 (n-3) FAs, some carotenoids, folate, isoflavones, cruciferous vegetables, fruit (black subjects), and calcium. The highest correlation values in non-black and black subjects were 0.69 (urinary 1-methyl-histidine and meat consumption) and 0.72 (adipose and dietary 18:2 ω -6), respectively. Correlations comparing biomarkers with recalls were generally similar for black and non-black subjects, but correlations between biomarkers and the FFQ were slightly lower than corresponding recall correlations. Correlations between biomarkers and a single FFQ estimate (the usual cohort situation) were generally much lower.

Conclusions: Many biomarkers that have relatively high-valued correlations with dietary intake were identified and were usually of similar value in black and non-black subjects. These may be used to correct effects of dietary measurement errors in the AHS-2 cohort, and in some cases they also provide evidence supporting the validity of the dietary data. *J Nutr* 2016;146:586–94.

Keywords: biomarkers, validity, adipose fatty acids, carotenoids, Adventist, African Americans

Introduction

Usual measures of dietary intake, whether from an FFQ or a reference measure (such as repeated recalls or diaries), are

well-known to incorporate subjective errors related to memory and perception that can adversely affect the validity of descriptions of the diet and estimates of its effects on disease outcomes. Biomarkers of intake can be used to provide more objective information about the validity of dietary measures (1, 2), although they have their own scaling, offset, and apparently random errors.

Thus, most biomarkers fall short of a gold standard that measures true intake. Individual differences are found in absorption and rates of metabolism and excretion which may cause concentrations and absolute amounts of the biomarkers in biological fluids to differ even among subjects with the same

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³ Supplemental Tables 1–4 and Supplemental Materials are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online posting table of contents at <http://jn.nutrition.org>.

*To whom correspondence should be addressed. E-mail: kjaceldo@llu.edu.

dietary intakes. However, these errors in biomarkers are reasonably assumed to be independent of errors in dietary questionnaires (3). Because of this, 2 appropriately selected biomarkers can be used to provide approximately unbiased estimates of correlations between dietary estimators and true intakes (4).

A related but different motivation is calibration rather than validation. This uses biomarkers to calibrate parameters of a regression analysis in such a way that the effects of dietary measurement errors on regression estimates of disease risk are corrected or at least improved (5, 6) and builds on the correlation between dietary estimators and true intakes mentioned in the previous paragraph. However, if the correlations between the chosen biomarkers and true diet are weak, the corrected regression β coefficient (that for instance allows estimation of a relative risk) will have poor precision. This motivates a search for biomarkers that have higher correlations with dietary intake.

The biomarker-guided measurement error correction strategy alluded to is a form of regression calibration. In traditional regression calibration (7), a calibration study is used that includes both the usual questionnaire estimate (Q) from the whole cohort and a measure of the true diet (T) from a sample of the cohort. Then the regression of T on Q is used to provide the variable $E(T|Q)$ for the whole cohort that with certain assumptions can be used to produce unbiased estimates of the effect of T on risk of the disease of interest.

A central problem is that in dietary work T can rarely if ever be observed. If a more accurate, but still error-containing, "reference" method (R) is used as a surrogate for T, this unfortunately requires new assumptions that are unlikely to be met in most circumstances. Specifically, these are that errors in R and Q are uncorrelated and that errors in R follow the classic error model. A better option may be to perform biomarker-guided regression calibration, which uses 2 carefully selected dietary intake biomarkers of T and does not require R. With this approach the previously unmet assumptions that result from the use of R are replaced by assumptions about correlations between errors in the 2 biomarkers and between errors in biomarkers and the questionnaire. With care, including the use of long half-life biomarkers when possible, these new assumptions can approximately be met (3, 5).

The brief description of a previously published (5) simulated example that was based on observed variances and covariances may be helpful. When associating intake of saturated FAs with $\log(\text{BMI})$ (in kg/m^2) and adjusting for age, sex, and intake of vitamin E, the saturated FA estimate for the cohort was obtained from a FFQ (Q). Instead of using a reference dietary method (R) as a surrogate for T (true values of saturated FA intake), biomarker-guided regression calibration instead used adipose SFAs as the first biomarker (M) (long half-life), and minus of blood β -carotene (P) as the second. We have evidence that β -carotene is moderately (and negatively) correlated with true SFA intake (T). The uncorrected regression coefficient between saturated fats and $\log(\text{BMI})$ was 1.53 units, and, after biomarker-guided regression calibration with a moderate-sized calibration study, the equivalent result was 3.55 units, an important difference, whereas the best estimate of the true value was 3.62 (with the use of a large calibration study).

This report provides results from the Adventist Health Study-2 (AHS-2)⁷ cohort calibration substudy (8) and has the objective of identifying biomarkers that have higher-valued correlation

coefficients with dietary intake, because these are most likely to be useful in biomarker-guided regression calibration and, in some cases, will also provide evidence about the validity of the dietary data. Results are shown separately for black and non-black subjects because our previous work indicates that food choices (9) and the validity of questionnaire data as measured by correlations (10, 11) vary between these 2 groups of subjects.

Methods

The study was approved by the institutional review board of Loma Linda University, and all subjects gave written informed consent.

Calibration substudy design

The AHS-2 cohort (8) consists of adult member volunteers from Adventist churches, geographically spread throughout the United States and Canada. More than 25% of the 96,335 cohort members are black (largely African American and West Indian living in the United States or Canada); the remaining subjects are of other races, and >90% of these are white. All study subjects completed an FFQ at study baseline (8) between 2002 and 2007. A calibration subgroup was formed as a representative sample ($n = 1011$) of the AHS-2 cohort (8) between 2004 and 2006, the sample of a size to provide estimated correlation coefficients that have good precision. Participants were randomly selected from the parent cohort by church and then subject within church. Because of a special focus on black Adventists as a minority group in the cohort, the calibration study has an overweighting (45%) of black subjects. The duration of the calibration study was 9–12 mo for any 1 subject. To further assess diet, subjects in this substudy provided 2 sets of three 24-h dietary recalls and a further FFQ.

Fasting blood, adipose, and overnight urine samples were collected at field clinics (held in church halls) (12), the blood was collected in heparin and plain tubes. Adipose samples were collected with the use of the squeeze technique (13) from the upper outer quadrant of the buttock. The serum was separated from the cells in the plain tubes within 30 min, and all blood, urine, and adipose samples were shipped overnight on wet ice back to Loma Linda, CA, where aliquots were frozen in nitrogen vapor.

Dietary assessment

The 24-h dietary recalls were obtained by an unannounced telephone call, and the interviews were digitally recorded. An experienced research dietitian later reviewed a random 5% as a quality measure. In addition, an extensive search for outliers was undertaken, focusing both on foods and nutrients. Three recalls were obtained (1 Saturday, 1 Sunday, and 1 weekday) during the first 2 mo, and this was then duplicated ~6 mo later. The recalls within a set of 3 were typically separated by 7–10 d from each other. These data were finally used to constitute 2 synthetic weeks, $X_{\text{Saturday}} + X_{\text{Sunday}} + 5X_{\text{Weekday}}$, where X is the nutrient or food of interest (expressed in weight units) and the subscript is the day of the week that the recall pertained to.

During the 6-mo interval between recall sets, subjects also completed a self-administered FFQ that was identical to the study baseline FFQ and attended a study clinic at their local church. The AHS-2 FFQ is a quantitative and comprehensive 22-page instrument that contained 204 foods, 54 questions about food preparation, and 46 fields for open-ended questions. It was designed to include foods commonly eaten by US Adventists and later modified to accommodate foods specific to black Adventists of US and Caribbean origin (9). Frequency categories varied with food type. The lowest category for most foods and beverages was never or rarely, followed by 1–3/mo, then categories that indicated higher frequencies. The highest frequency category for vegetables, soups, cereals, pasta, dressing, meats, fish, vegetarian protein products, and soymilk was $\geq 2/\text{d}$; for nuts and seeds, $\geq 4/\text{d}$; for breads, eggs, dairy products, snacks, and beverages, $\geq 6/\text{d}$. Portion sizes included 3 values: a given standard, $\leq 50\%$ of standard, and $\geq 150\%$ of standard. Subjects were instructed to recall eating habits during the previous 1 y.

To reflect the marketplace throughout the study, dietary intake data were collected with the use of Nutrition Data System for Research

⁷ Abbreviations used: AHS-2, Adventist Health Study-2; NDS-R, Nutritional Data System for Research; PTH, parathyroid hormone; 25(OH)D, 25 hydroxyvitamin D.

(NDS-R) software versions 4.06 and 5.03 (Nutrition Coordinating Center, University of Minnesota). Final calculations were completed with the use of NDS-R version 2008. The NDS-R time-related database updates analytic data while maintaining nutrient profiles true to the version used for data collection (14). For foods and supplements not found in the NDS-R database we obtained nutrient composition data from the USDA Standard Reference Release 18 (15), manufacturers, and the Caribbean Food and Nutrition Institute Food Composition Tables (16). Recipes were created for home-cooked vegetarian dishes ($n > 500$), homemade and commercial soy and nut milks ($n > 180$), and commercial meat analogs ($n = 309$) frequently consumed by our study population. For the last we contacted manufacturers or worked with a senior food technologist who had experience in this industry. This FFQ was extensively validated by comparisons with the repeated 24-h recalls (10, 11).

Laboratory methods

The UCLA Center for Human Nutrition Biomarker laboratory (SMH) provided estimates of erythrocyte folate, plasma carotenoids, serum parathyroid hormone (PTH), and adipose FAs. All samples were analyzed in a blinded fashion. Further details of the laboratory methods are found in the **Supplemental Materials**.

Erythrocyte folate. Erythrocyte folate was measured with the use of the Immulite Chemiluminescence Immunoassay Analyzer (Siemens Healthcare Diagnostics). This assay is a competitive, ligand-labeled, protein-binding chemiluminescent assay with in situ immobilization and antiligand detection system.

Plasma carotenoids. Plasma carotenoids (canthaxanthin, α -carotene, β -carotene, β -cryptoxanthin, lycopene, and zeaxanthin) and α - and γ -tocopherol were analyzed with the use of HPLC (17, 18).

Adipose FAs. Adipose FAs were estimated with the use of gas chromatography. Adipose total FAs were extracted with hexane and converted to methyl esters according to the method by Bagga et al. (19).

Urinary biomarkers. Urinary 1-methyl-histidine was estimated by Dr. Stan Louie at University of Southern California with a modification of a previously described method (20). Urinary isothiocyanate and thiocarbamate (isothiocyanate equivalents) were estimated by EHH at the Department of Nutrition Laboratory, Loma Linda University, with the method described by Ye et al. (21) and Zhang et al. (22), using a reverse-phase HPLC system. Urinary isoflavonoid analyses were conducted at the University of Hawaii with the use of HPLC with photodiode array and mass spectrometry detection (23).

Serum biomarkers. Serum 25 hydroxyvitamin D [25(OH)D] was estimated by the Reproductive Endocrinology Research Laboratory, Keck School of Medicine, University of Southern California, with the use of the 2-step radioimmunoassay Diasorin procedure (Diasorin) (24). Serum holotranscobalamin (active serum vitamin B-12) was estimated by EHH at the School of Public Health Nutrition Laboratory, Loma Linda University, with the use of the holotranscobalamin enzyme immunoassay from Axis-Shield Diagnostics Limited (25). Serum intact PTH was determined with the use of the Siemens Immulite Chemiluminescence Immunoassay Analyzer (Siemens Healthcare Diagnostics).

Statistical methods

Analyses are run separately for black and non-black subjects because their diets have distinct characteristics (9, 26). Because values of Pearson correlation coefficients are adversely affected by large skewness on either of the variables being correlated, where the skew of either variable was >2 , a logarithmic transformation was used. Tests of differences between black and non-black subjects were conducted with the use of t tests for continuous and χ^2 tests for categorical variables. Statistical significance was indicated according to the criterion $\alpha = 0.05$.

Apparently valid zero values were relatively common among the intake values of our foods/food groups. The corresponding biomarkers were then often also near zero or below the laboratory limit of detection.

This was particularly relevant for soy or meat intake, for instance. When many data points were found below the level of detection (treated here as zero), the distribution was usually quite skewed. The transformation $X' = \log(X + 1)$ was used, which leaves an original zero unchanged and usually reduced the skew of the non-zero data.

Because the units of adipose FAs were percentages of total FAs in the adipose samples, the corresponding dietary FAs were also expressed as percentage of total dietary fat rather than an adjustment for total energy. Other nutrient and food variables (X') were adjusted for total energy with the use of the residual method and the equation $X' = a + b \cdot \text{Energy} + e$ was used to define the residual. The final energy-adjusted value on a logarithmic scale is $e + E(X' | \text{energy})$. For dietary data, ethnicity-specific calculations were made. The 2 sets of recall data each represent 1 synthetic week divided by 7 to estimate intake of 1 d.

The recalls and questionnaires contain random and systematic within-person errors, which generally bias correlations toward the null (27). Because the recall data contained 2 synthetic weeks, the repetition allowed an estimate of within-person variance and the correction of correlation coefficients for the attenuating effects of random errors in the recalls (27, 28). De-attenuation was performed only on the subgroup of subjects whereby at least 1 of their 6 recalls had a non-zero value, as we have described (11). If all recalls were zero, it was assumed that the true within-person error for that subject was zero or very small. Similarly, de-attenuation for effects of random errors in FFQ data when correlated with biomarkers was possible with the use of the 2 questionnaires (study baseline and calibration substudy), although there was the complication of a 1- to 4-y time lapse between them that varied by subject. The possibility that systematic time trend quantities may have increased the estimated within-person variances was evaluated, because this would artificially inflate the attenuation adjustment. We could find no evidence for any dietary variable of significant dependence of the within-person variance on time during the relatively short period that separated the FFQs.

Serum concentrations of α -tocopherol and carotenoids were also adjusted for serum total cholesterol with the use of the residual method. The 95% CIs for correlation coefficients were estimated by bootstrap re-sampling with the use of 2000 samples and bias-corrected and accelerated estimation (29). We were unable to adjust for any seasonal trends in biomarkers because collections were scattered throughout the year.

Results

Basic demographic and dietary pattern descriptors are shown in **Table 1**. These data were generally similar to those from the full cohort (also shown), confirming that the calibration substudy was a representative sample. The 909 analytic calibration substudy participants were those who provided bio-samples and either 6 dietary recalls or a second FFQ. This includes 90% of all calibration subjects.

Untransformed means ($\pm$ SDs) for biomarkers are shown in **Table 2**. Similar data for dietary variables were published and are also shown in **Supplemental Tables 1 and 2**. Several differences by race were evident. Relatively small but significant differences were seen for several FAs. Compared with non-black subjects, black subjects had higher adipose 22:6 ω -3 (0.22% compared with 0.17%; $P < 0.0001$) but lower 15:0 (0.34% compared with 0.40%; $P < 0.0001$). Black subjects had lower concentrations of serum α -tocopherol (33.0 compared with 40.0 nmol/L; $P < 0.0001$) and erythrocyte folate (0.95 compared with 1.28 $\mu\text{g/mL}$; $P < 0.0001$), much lower concentrations of 25(OH)D (17.9 compared with 29.1 $\mu\text{g/L}$; $P < 0.0001$) and isoflavones (108 compared with 181 pmol/mg creatinine; $P = 0.0002$) but much higher concentrations of urinary 1-methyl histidine (a meat metabolite; 55.8 compared with 21.5 nmol/mL; $P < 0.0001$).

Correlations between selected biomarkers and the dietary estimates between black and non-black subjects are shown in **Table 3** (repeated recall data) and **Table 4** (FFQ data). The uncorrected correlations with the questionnaire used data from

TABLE 1 Comparison of selected characteristics between the AHS-2 cohort and Calibration Study participants according to race, 2003–2008¹

Characteristic	AHS-2 cohort ² (n = 96,116)		Calibration study ³ (n = 909)	
	Non-black subjects	Black subjects	Non-black subjects	Black subjects
Sex, %				
Male	37.0	29.8	36.2	30.7
Female	63.0	70.2	63.8	69.3
Age, ⁴ %				
<50 y	28.2	43.8	25.1	34.5
50–59 y	23.0	25.3	23.4	28.7
60–69 y	21.3	17.1	24.2	22.3
70–79 y	17.9	10.2	19.4	12.5
≥80 y	9.6	3.6	7.9	2.0
Mean age, ⁴ y ± SD	60.2 ± 14.4	53.8 ± 13.7	60.7 ± 13.6	55.8 ± 12.7
Education, %				
≤High school	21.6	24.4	21.3	22.4
Some college	39.0	41.0	38.8	42.6
≥College graduation	39.4	34.6	39.9	35.0
Diet pattern, ⁵ %				
Vegan	8.1	5.6	10.0	6.8
Lacto-ovo	33.4	13.3	34.0	13.0
Pesco	8.9	13.8	9.8	15.7
Semi	6.3	3.7	5.7	2.5
Nonvegetarian	43.3	63.6	40.5	62.0
BMI, %				
<25 kg/m ²	44.8	29.7	46.6	30.1
25–29.9 kg/m ²	33.6	36.9	33.1	35.3
≥30 kg/m ²	21.6	33.4	20.3	34.6
Mean BMI, kg/m ² ± SD	26.6 ± 5.8	28.6 ± 6.3	26.5 ± 5.7	28.9 ± 6.8

¹ AHS-2, Adventist Health Study-2.

² Proportion of missing data: sex, 0.04%; age, 1.2%; education, 1.5%; BMI, 4.8%.

³ Proportion of missing data: age 0.0%; sex 0.0%; education, 2.0%; BMI, 4.8%.

⁴ Differences in the age distribution between the AHS-2 cohort and the Calibration Study participants were significant in black subjects ($P \leq 0.05$); otherwise, no significant differences were observed in the distribution of sex, age, education, vegetarian status, or BMI between the AHS-2 cohort and Calibration Study participants according to race.

⁵ Vegans eat no animal products; lacto-ovo vegetarians eat no meats but do eat dairy and/or eggs; pesco-vegetarians eat fish but no other meats; semi-vegetarians eat meats (aside from fish) but less often than weekly; nonvegetarians eat meats (not only fish) at least weekly.

the calibration study FFQ only to emulate the common situation of a single FFQ in a study. In addition, both available FFQs were used to provide de-attenuated correlations. Data in several of the lower cells of the tables describe associations where, for budgetary reasons, we could estimate biomarkers only in smaller randomly selected subsamples.

Across all dietary variables, the distributions of the de-attenuated correlations between biomarkers and recalls in black and non-black subjects are similar with means of 0.40 (range: 0.04–0.72) and 0.39 (range: 0.11–0.69), respectively. Average race-specific de-attenuated correlations between biomarkers and FFQ are also close at 0.37 (range: 0.09–0.65) and 0.39 (range: 0.05–0.77), respectively, but are lower at 0.30 and 0.32 on average when based on a single FFQ.

In the following sections selected correlations for black and non-black subjects, respectively, are reported in parentheses. Many biomarkers of intake showed relatively high correlations with the recalls compared with other published results. Certain dietary FAs were relatively highly correlated with their biomarkers, especially 14:0 (0.61, 0.58), 16:0 (0.66, 0.49), 18:2 ω -6 (0.72, 0.64), and 18:3 ω -3 (0.67, 0.66). Of the very long-chain ω -3 FAs, 22:6 ω -3 intake was most strongly correlated (0.54, 0.38) with adipose values.

The dietary carotenoids, α - and β -carotene, lutein, lycopene, β -cryptoxanthin, and total carotenoids (0.44, 0.52) were also

relatively highly correlated with corresponding plasma biomarkers (adjusted for serum cholesterol), as was vitamin E (0.64, 0.59). Erythrocyte and dietary folates were correlated moderately (0.42, 0.30). Dietary calcium was also moderately correlated with 25(OH)D (0.42, 0.30) as might have been expected from physiologic considerations. However, PTH showed rather low-valued negative correlations (–0.21, –0.16) with dietary calcium. Dietary vitamin B-12 was moderately correlated with serum vitamin B-12 (0.28, 0.50) in non-black subjects.

Intakes of animal protein (0.59, 0.61), red meat (0.44, 0.54), and poultry (0.58, 0.62), were highly correlated with urinary 1-methyl-histidine. Correlations with fish intake were lower (0.21, 0.30), however. Intakes of soy isoflavones (e.g., daidzein) (0.42, 0.43) and fruit (0.37, 0.50) were moderately correlated with urinary isoflavones and plasma β -cryptoxanthin, respectively.

De-attenuated correlations between biomarkers and repeated FFQs are on average ~5% lower than those between biomarkers and repeated dietary recalls. Thus, this provides some evidence that recalls have greater validity than FFQs, but the difference is modest. Correlations between biomarkers and a single FFQ (the usual cohort situation) are ~25% lower on average than correlations between biomarkers and repeated recalls. These, of course, are not de-attenuated. Exceptions to this trend were the correlations between 1-methyl histidine and fish (0.51, 0.65)

TABLE 2 Biomarkers in Calibration Sub-study participants of the AHS-2 cohort according to race, 2003–2008¹

Biomarker	Non-black subjects	Black subjects	P ²
Adipose tissue, % of total FAs			
12:0	0.46 (0.14, 0.93)	0.41 (0.12, 0.85)	<0.02
14:0	1.89 (1.28, 2.60)	1.72 (1.10, 2.44)	<0.0001
15:0	0.40 (0.21, 0.68)	0.34 (0.17, 0.58)	<0.0001
16:0	18.3 (15.1, 22.2)	19.9 (16.1, 24.0)	<0.0001
18:0	3.72 (2.49, 5.42)	4.79 (3.13, 6.88)	<0.0001
18:1 ω-9	46.6 (43.0, 50.4)	44.3 (40.8, 48.2)	<0.0001
18:2 ω-6	20.8 (16.7, 25.2)	21.8 (18.1, 26.6)	<0.0001
18:3 ω-3	1.32 (0.86, 2.01)	1.33 (0.90, 1.96)	0.79
20:4 ω-6	0.48 (0.29, 0.73)	0.47 (0.27, 0.67)	0.33
20:5 ω-3	0.05 (0.00, 0.12)	0.06 (0.00, 0.12)	0.003
22:5 ω-3	0.24 (0.15, 0.35)	0.26 (0.16, 0.39)	0.05
22:6 ω-3	0.17 (0.08, 0.30)	0.22 (0.09, 0.42)	<0.0001
Very long chain ω-3 FAs	0.45 (0.27, 0.71)	0.53 (0.29, 0.89)	<0.0001
All ω-3 FAs	1.78 (1.25, 2.55)	1.88 (1.31, 2.56)	0.01
Plasma biomarkers			
β-Carotene, mmol/L	0.67 (0.21, 1.44)	0.61 (0.19, 1.37)	0.08
α-Carotene, mmol/L	0.17 (0.04, 0.36)	0.16 (0.02, 0.37)	0.31
Lutein and zeaxanthin, mmol/L	0.41 (0.19, 0.69)	0.45 (0.24, 0.74)	0.04
Lycopene, mmol/L	0.55 (0.29, 0.87)	0.53 (0.26, 0.89)	0.26
β-Cryptoxanthin, mmol/L	0.25 (0.07, 0.50)	0.23 (0.07, 0.45)	0.21
Carotenoids, mmol/L	2.05 (1.07, 3.54)	1.99 (1.09, 3.29)	0.35
PTH, pg/mL	33.2 (18.9, 62.3)	39.2 (21.3, 76.9)	<0.01
Serum biomarkers			
Retinol, mmol/L	2.57 (1.67, 3.77)	2.34 (1.59, 3.35)	<0.0001
γ-Tocopherol, mmol/L	4.74 (2.67, 8.16)	5.09 (2.74, 9.27)	0.03
α-Tocopherol, mmol/L	40.0 (27.1, 61.7)	33.0 (24.0, 47.8)	<0.0001
Holotranscobalamin, pmol/L	87.3 (44.1, 169)	94.2 (49.3, 171)	<0.05
25(OH)D, µg/L	29.1 (18.0, 43.6)	17.9 (9.48, 35.6)	<0.0001
Erythrocyte folate, µg/mL	1.28 (0.798, 1.93)	0.948 (0.538, 1.51)	<0.0001
Urinary biomarkers			
Genistein, pmol/mg creatinine	87.1 (7.33, 1770)	56.9 (5.58, 832)	0.002
Daidzein, pmol/mg creatinine	237 (13.9, 4750)	137 (6.70, 2310)	0.0001
Total isoflavones, pmol/mg creatinine	411 (34.3, 6920)	247 (24.3, 3470)	0.0001
1-Methylhistidine, nmol/mL	21.5 (3.51, 232)	55.8 (4.35, 589)	<0.0001
Isothiocyanate equivalents, µmol/L	1.87 (0.16, 6.74)	1.54 (0.12, 7.03)	0.39

¹ Values are geometric means (10th, 90th percentiles). Please consult Tables 3 and 4 for numbers of subjects. Geometric means are calculated as $\exp(\text{mean}[\log(\text{biomarker} + 1)]) - 1$. AHS-2, Adventist Health Study-2; PTH, parathyroid hormone; 25(OH)D, 25 hydroxyvitamin D.

² P values test the null hypothesis of no difference between non-black and black subjects.

and adipose and dietary very long-chain ω-3 FAs (0.50, non-black subjects), which were higher in the FFQ data.

Geometric means and the 10th and 90th percentiles (stratified by race) for the dietary variables from this population are found in Supplemental Tables 1 and 2 and correlations between biomarkers and dietary estimators separately for men and women are found in Supplemental Tables 3 and 4. On average, the correlations are a little higher for the women.

Discussion

In a relatively large study population, we show variable but often moderate- to high-valued de-attenuated correlation coef-

ficients between putative biomarkers of dietary intake (blood, urine, adipose tissue) and repeated 24-h dietary recalls. Similar correlations between biomarkers and the average of 2 FFQs are a little lower and with a single FFQ are substantially lower. Values of corresponding correlation coefficients are generally remarkably similar between black and non-black subjects.

By comparison de-attenuated correlations between 2 dietary estimates (FFQ and repeated recalls) in these same subjects are on average ~25–30% higher, this being across 47 foods/food groups or 51 nutrients, vitamins, and minerals (10, 11). This may be because of positive correlations between errors in the dietary estimates (similar misperceptions of diet or incorrect memories) or the inability of many biomarkers to accurately represent intake because of differences in absorption, metabolism, and excretion between individuals.

Many other studies have provided broadly similar estimates of correlations between carotenoid intakes and questionnaire data (28, 30–36). Moderate-valued correlations between plasma lycopene and tomatoes, also between plasma α- and β-carotene and intakes of carrots and other vegetables (33, 34, 37), were reported. Some have found that correlations for carotenoids are lower among overweight subjects (30), and others found higher correlations among nonsmokers (34), a population similar in this respect to our Adventist population.

Reported correlations between dietary intake and blood folate measures were highly variable (28, 36, 38), and Jacques et al. (28) found that energy adjustment improved the correlations. The best laboratory analytic methods and whether to use serum or erythrocyte values in the form of whole blood are controversial (39, 40).

Reported correlations between serum tocopherols and vitamin E consumption have generally been relatively good (28, 31, 36), although lower in one report (36). For the carotenoids improvement after adjustment for serum cholesterol concentrations is often found.

Correlations between adipose and dietary FAs were reported by a number of studies (41–45), and Holmes et al. (41) have summarized others. Results in AHS-2 are similar to those from much of this other work. Possibly because of the high intakes of α-linolenic acid in the AHS-2 population, validity for this ω-3 FA is better than usual. However, our results for EPA are lower than some others, perhaps because of lower intakes. Results for DHA are considerably better, as often found by others.

Correlations between urinary isoflavones and soy intake (expressed as soy protein) were similar to or higher than others from Western countries (46, 47) but lower than some from Asia (48, 49) or Hawaii (50). The commonly eaten soy foods in the continental United States are often commercial unfermented products that are based on isoflavone-containing soy isolates. It is often challenging to accurately assign quantities of soy protein or dietary isoflavones, especially because large variability is often found within the same product (51). The bioavailability of the fermented soy products (more commonly used in Asia) may also be greater than that of processed soy products (52).

The best known biomarker of meat intake is 1-methylhistidine. Our new results are similar to those that we and others reported previously (53, 54), although more precise because of larger numbers. This marker does not clearly distinguish between red meat, poultry, and fish, although correlations tend to be lower with fish in our present and previous data.

Useful biomarkers of calcium and dairy intake are not well known. We do show low but possibly useful correlations between calcium intake, serum PTH, and 25(OH)D. Other proposed markers of dairy intake include the FAs 15:0 and 17:0, also alkyl

TABLE 3 De-attenuated correlations between selected biomarkers of dietary intake and dietary intakes estimated from repeated 24-h recalls of non-black and black subjects¹

Dietary variable	Biomarker	n	Non-black subjects	n	Black subjects
			De-attenuated correlation (95% CI)		De-attenuated correlation (95% CI)
12:0	Adipose 12:0	472	0.15 (−0.01, 0.30) ²	389	0.04 (−0.17, 0.28) ²
14:0	Adipose 14:0	472	0.58 (0.46, 0.69)	389	0.61 (0.48, 0.74)
16:0	Adipose 16:0	472	0.49 (0.39, 0.58)	389	0.66 (0.58, 0.73)
18:0	Adipose 18:0	472	0.24 (0.13, 0.35)	389	0.30 (0.16, 0.42)
18:1 ω-9	Adipose 18:1 ω-9	472	0.41 (0.28, 0.55)	389	0.49 (0.31, 0.64)
18:2 ω-6	Adipose 18:2 ω-6	472	0.64 (0.54, 0.73)	389	0.72 (0.60, 0.83) ²
18:3 ω-3	Adipose 18:3 ω-3	472	0.66 (0.55, 0.76) ²	389	0.67 (0.54, 0.78) ²
20:4 ω-6	Adipose 20:4 ω-6	472	0.17 (0.04, 0.28)	389	0.27 (0.16, 0.37) ²
20:5 ω-3	Adipose 20:5 ω-3	472	0.20 (0.10, 0.32) ²	389	0.28 (0.13, 0.41) ²
22:5 ω-3	Adipose 22:5 ω-3 ²	472	0.11 (0.03, 0.18) ²	389	0.30 (0.17, 0.42) ²
22:6 ω-3	Adipose 22:6 ω-3 ²	472	0.38 (0.24, 0.53) ²	389	0.54 (0.38, 0.68) ²
Very long chain ω-3 FAs	Adipose very long chain ω-3 FAs ²	472	0.30 (0.18, 0.41) ²	389	0.50 (0.36, 0.63) ²
All ω-3 FAs	All adipose ω-3 FAs	472	0.65 (0.54, 0.75) ²	389	0.62 (0.49, 0.74) ²
β-Carotene	Plasma β-carotene ²	423	0.52 (0.39, 0.63) ²	334	0.49 (0.33, 0.71)
α-Carotene	Plasma α-carotene ²	421	0.59 (0.42, 0.75) ²	341	0.62 (0.50, 0.75) ²
Lutein and zeaxanthin	Plasma lutein and zeaxanthin ²	424	0.40 (0.26, 0.53) ²	338	0.52 (0.34, 0.67) ²
Lycopene	Plasma lycopene	420	0.32 (0.09, 0.56)	343	0.27 (0.04, 0.47) ²
β-cryptoxanthin	Plasma β-cryptoxanthin ²	424	0.50 (0.33, 0.64) ²	343	0.41 (0.22, 0.55) ²
Total carotenoids	Plasma carotenoids	424	0.52 (0.40, 0.63) ²	343	0.44 (0.28, 0.62)
Retinol	Serum retinol	450	0.18 (0.08, 0.28) ²	361	0.13 (0.02, 0.27) ²
γ-Tocopherol	Serum γ-tocopherol	424	0.23 (0.03, 0.41)	343	0.35 (0.19, 0.49)
α-Tocopherol	Serum α-tocopherol	424	0.59 (0.49, 0.66) ²	343	0.64 (0.54, 0.74) ²
Vitamin E	Serum α-tocopherol	424	0.59 (0.50, 0.67) ²	343	0.64 (0.54, 0.74) ²
Vitamin B-12	Serum HoloTC	497	0.50 (0.39, 0.61) ²	391	0.28 (0.16, 0.40) ²
Folate	Erythrocyte folate	462	0.30 (0.20, 0.41)	373	0.42 (0.30, 0.52) ²
Calcium	Plasma PTH	200	−0.16 (−0.28, −0.02)	94	−0.21 (−0.42, 0.01)
Calcium	Serum 25(OH)D	258	0.30 (0.17, 0.44)	197	0.42 (0.26, 0.60)
Daidzein	Urinary daidzein ²	459	0.43 (0.33, 0.52) ²	374	0.42 (0.29, 0.54) ²
Genistein	Urinary genistein ²	459	0.39 (0.28, 0.49) ²	374	0.43 (0.30, 0.53) ²
Soy protein	Urinary genistein ²	459	0.40 (0.28, 0.51)	374	0.39 (0.24, 0.52) ²
Soy protein	Urinary daidzein ²	459	0.44 (0.33, 0.55)	374	0.37 (0.22, 0.50) ²
Soy protein	Urinary isoflavone ²	459	0.44 (0.33, 0.55)	374	0.38 (0.23, 0.51) ²
Animal protein	Urinary 1-methylhistidine ²	454	0.61 (0.54, 0.69)	367	0.59 (0.48, 0.67)
Dairy fat	Adipose 15:0 ²	472	0.27 (0.13, 0.40)	389	0.13 (−0.03, 0.28)
Cruciferous vegetables	Urinary isothiocyanate ²	97	0.28 (−0.21, 0.80)	58	0.29 (−0.18, 0.71) ²
Tomatoes	Plasma lycopene	418	0.26 (0.07, 0.47)	333	0.27 (0.10, 0.44)
All fruits	Plasma β-cryptoxanthin ²	417	0.50 (0.38, 0.63)	340	0.37 (0.25, 0.49)
Red meat	Urinary 1-methylhistidine ²	451	0.54 (0.46, 0.60) ²	357	0.44 (0.36, 0.52) ²
Poultry	Urinary 1-methylhistidine ²	447	0.62 (0.55, 0.70) ²	364	0.58 (0.48, 0.66)
Fish	Urinary 1-methylhistidine ²	447	0.30 (0.17, 0.39) ²	364	0.21 (0.11, 0.31) ²
Total meat	Urinary 1-methylhistidine ²	447	0.69 (0.61, 0.75) ²	364	0.63 (0.54, 0.70)
Average			0.391		0.399

¹ CIs were estimated with the use of the bias-corrected and accelerated resampling method. HoloTC, holotranscobalamin; PTH, parathyroid hormone; 25(OH)D, 25 hydroxyvitamin D.

² The biomarkers and/or the 24-h recalls (when superscript is on the correlation value) are log-transformed because the skew of either variable being correlated is >2. Plasma carotenoid, lutein and zeaxanthin, lycopene, β-cryptoxanthin, and serum γ-tocopherol and α-tocopherol are adjusted for blood cholesterol.

resorcinol (55) and phytanic acid (56). For unclear reasons, correlations in AHS-2 data between dairy fat intake and 15:0 were much lower than those from Scandinavia (57, 58), but similar in our non-black subjects to those reported from Costa Rica (44).

Analyses such as these are much less common among African American populations (36, 41, 59, 60). In the Jackson Heart Study (59) correlations for carotenoids were generally a little lower than our results for the black subjects. In the Southern

Community Cohort (36) for most variables measured, correlations for black subjects did not differ greatly from those in white subjects. Correlations in AHS-2 compared with the Southern Community Cohort black subjects were similar for carotenoids but considerably higher for folate and tocopherols.

In our data black subjects had higher adipose values of 22:6 ω-3 than non-black subjects, which may be because of higher fish consumption (61); lower adipose 15:0, perhaps because of much lower dairy consumption (26, 61); and higher isoflavone

TABLE 4 De-attenuated correlations between selected biomarkers of dietary intake and dietary intakes estimated from FFQs of non-black and black subjects¹

Dietary variable	Biomarker	Non-black subjects			Black subjects		
		<i>n</i>	Uncorrected correlation (95% CI)	De-attenuated correlation (95% CI)	<i>n</i>	Uncorrected correlation (95% CI)	De-attenuated correlation (95% CI)
12:0	Adipose 12:0	465	0.08 (0.00, 0.18)	0.10 (0.00, 0.22) ²	347	0.15 (0.05, 0.25)	0.21 (0.08, 0.36) ²
14:0	Adipose 14:0	465	0.55 (0.46, 0.62)	0.61 (0.51, 0.70)	347	0.44 (0.34, 0.52)	0.52 (0.40, 0.60)
16:0	Adipose 16:0	465	0.54 (0.48, 0.60)	0.60 (0.52, 0.66)	347	0.52 (0.43, 0.58)	0.59 (0.50, 0.67)
18:0	Adipose 18:0	465	0.24 (0.14, 0.32)	0.26 (0.16, 0.37)	347	0.21 (0.11, 0.31)	0.24 (0.13, 0.36)
18:1 ω-9	Adipose 18:1 ω-9	465	0.24 (0.16, 0.32)	0.30 (0.18, 0.39)	347	0.29 (0.19, 0.39)	0.35 (0.22, 0.47)
18:2 ω-6	Adipose 18:2 ω-6	465	0.54 (0.46, 0.60)	0.62 (0.53, 0.69)	347	0.55 (0.48, 0.61)	0.64 (0.55, 0.72)
18:3 ω-3	Adipose 18:3 ω-3	465	0.32 (0.22, 0.41)	0.41 (0.28, 0.53)	347	0.31 (0.23, 0.40)	0.43 (0.31, 0.56)
20:4 ω-6	Adipose 20:4 ω-6	465	0.16 (0.08, 0.25)	0.18 (0.08, 0.26) ²	347	0.14 (0.03, 0.25)	0.18 (0.02, 0.29)
20:5 ω-3	Adipose 20:5 ω-3	465	0.20 (0.12, 0.29)	0.32 (0.19, 0.44) ²	347	0.14 (0.03, 0.25)	0.22 (0.10, 0.37) ²
22:5 ω-3	Adipose 22:5 ω-3 ²	465	0.20 (0.11, 0.28)	0.37 (0.19, 0.51) ²	347	0.19 (0.08, 0.31)	0.33 (0.21, 0.46) ²
22:6 ω-3	Adipose 22:6 ω-3 ²	465	0.42 (0.32, 0.51)	0.55 (0.42, 0.66) ²	347	0.25 (0.15, 0.34)	0.43 (0.33, 0.53) ²
Very long chain ω-3 FAs	Adipose very long chain ω-3 FAs ²	465	0.37 (0.29, 0.45)	0.50 (0.40, 0.61) ²	347	0.36 (0.27, 0.45)	0.40 (0.29, 0.50) ²
All ω-3 FAs	All adipose ω-3 FAs	465	0.30 (0.21, 0.38)	0.39 (0.28, 0.51)	347	0.19 (0.09, 0.28)	0.24 (0.11, 0.36)
β-Carotene	Plasma β-carotene ²	420	0.39 (0.29, 0.50)	0.47 (0.34, 0.62) ²	302	0.35 (0.25, 0.44)	0.44 (0.31, 0.57) ²
α-Carotene	Plasma α-carotene ²	418	0.37 (0.26, 0.52)	0.52 (0.35, 0.70)	307	0.44 (0.36, 0.52)	0.54 (0.43, 0.63) ²
Lutein and zeaxanthin	Plasma lutein and zeaxanthin ²	421	0.22 (0.12, 0.30)	0.25 (0.13, 0.35) ²	305	0.32 (0.18, 0.55)	0.45 (0.26, 0.77)
Lycopene	Plasma lycopene	417	0.21 (0.11, 0.32)	0.28 (0.13, 0.45)	309	0.19 (0.10, 0.28)	0.23 (0.13, 0.34) ²
β-Cryptoxanthin	Plasma β-cryptoxanthin ²	432	0.42 (0.32, 0.49)	0.52 (0.40, 0.60) ²	328	0.37 (0.28, 0.45)	0.45 (0.34, 0.56) ²
Total carotenoids	Plasma carotenoids	421	0.35 (0.25, 0.47)	0.42 (0.30, 0.56) ²	309	0.30 (0.20, 0.41)	0.36 (0.25, 0.48) ²
Retinol	Serum retinol	459	0.14 (0.05, 0.21)	0.18 (0.08, 0.29)	345	0.06 (−0.04, 0.16)	0.09 (−0.04, 0.23)
γ-Tocopherol	Serum γ-tocopherol	432	0.06 (−0.03, 0.15)	0.09 (−0.03, 0.20)	328	0.35 (0.24, 0.45)	0.42 (0.28, 0.55)
α-Tocopherol	Serum α-tocopherol	432	0.52 (0.45, 0.60)	0.61 (0.52, 0.68)	328	0.41 (0.32, 0.50)	0.58 (0.45, 0.72)
Vitamin E	Serum α-tocopherol	421	0.54 (0.47, 0.61)	0.61 (0.53, 0.69)	309	0.39 (0.29, 0.47)	0.51 (0.40, 0.63)
Vitamin B-12	Serum HoloTC	541	0.33 (0.24, 0.41)	0.44 (0.32, 0.55) ²	425	0.31 (0.21, 0.39)	0.41 (0.29, 0.54) ²
Folate	Erythrocyte folate	470	0.17 (0.05, 0.27)	0.23 (0.05, 0.36) ²	359	0.22 (0.10, 0.31)	0.31 (0.14, 0.46)
Calcium	Plasma PTH	204	−0.10 (−0.21, 0.02)	−0.12 (−0.24, 0.05)	83	−0.08 (−0.27, 0.10)	−0.11 (−0.35, 0.12)
Calcium	Serum 25(OH)D	256	0.23 (0.11, 0.36)	0.28 (0.12, 0.42)	175	0.25 (0.11, 0.39)	0.32 (0.13, 0.49)
Daidzein	Urinary daidzein ²	465	0.38 (0.30, 0.46)	0.42 (0.33, 0.49) ²	358	0.26 (0.15, 0.37)	0.32 (0.17, 0.45)
Genistein	Urinary genistein ²	465	0.32 (0.24, 0.40)	0.36 (0.27, 0.45) ²	358	0.28 (0.17, 0.41)	0.34 (0.19, 0.48)
Soy protein	Urinary genistein ²	465	0.28 (0.19, 0.37)	0.31 (0.22, 0.40)	358	0.28 (0.15, 0.38)	0.35 (0.18, 0.47)
Soy protein	Urinary daidzein ²	465	0.34 (0.26, 0.43)	0.37 (0.28, 0.46)	358	0.25 (0.14, 0.34)	0.32 (0.16, 0.44)
Soy protein	Urinary isoflavone ²	465	0.34 (0.24, 0.41)	0.37 (0.27, 0.45)	358	0.26 (0.14, 0.36)	0.33 (0.18, 0.46)
Animal protein	Urinary 1-methylhistidine ²	459	0.52 (0.44, 0.58)	0.56 (0.48, 0.63)	348	0.50 (0.42, 0.56)	0.57 (0.47, 0.64)
Dairy fat	Adipose 15:0 ²	465	0.21 (0.11, 0.30)	0.23 (0.11, 0.34)	347	0.15 (0.05, 0.27)	0.18 (0.04, 0.30) ²
Cruciferous vegetables	Urinary isothiocyanate ²	94	0.04 (−0.15, 0.26)	0.05 (−0.18, 0.30)	56	0.31 (−0.03, 0.59)	0.46 (−0.02, 0.90)
Tomatoes	Plasma lycopene	448	0.17 (0.07, 0.27)	0.22 (0.11, 0.37)	330	0.15 (0.06, 0.24)	0.17 (0.06, 0.28) ²
All fruits	Plasma β-cryptoxanthin ²	430	0.32 (0.20, 0.46)	0.40 (0.26, 0.59)	312	0.28 (0.17, 0.37)	0.32 (0.19, 0.43) ²
Red meat	Urinary 1-methylhistidine ²	437	0.53 (0.45, 0.59)	0.62 (0.53, 0.70) ²	322	0.45 (0.34, 0.53)	0.54 (0.43, 0.64) ²
Poultry	Urinary 1-methylhistidine ²	437	0.68 (0.62, 0.73)	0.77 (0.70, 0.82) ²	322	0.49 (0.41, 0.57)	0.65 (0.53, 0.75)
Fish	Urinary 1-methylhistidine ²	437	0.56 (0.49, 0.62)	0.65 (0.56, 0.72) ²	322	0.44 (0.34, 0.52)	0.51 (0.40, 0.62)
Total meat	Urinary 1-methylhistidine ²	437	0.69 (0.63, 0.73)	0.73 (0.67, 0.78) ²	322	0.48 (0.36, 0.56)	0.59 (0.47, 0.69)
Average			0.317	0.386		0.292	0.368

¹ CIs were estimated with the use of the bias-corrected and accelerated resampling method. HoloTC, holotranscobalamin; PTH, parathyroid hormone; 25(OH)D, 25 hydroxyvitamin D.

² Biomarkers and/or FFQ variables (when superscript is on the correlation value) are log-transformed because the skew of either variable being correlated is >2. Plasma carotenoid, lutein and zeaxanthin, lycopene, β-cryptoxanthin, and serum γ-tocopherol and α-tocopherol are adjusted for blood cholesterol.

excretion to reflect higher intake of soy foods (26, 61) (possibly because of a higher prevalence of lactase deficiency); and also higher excretion of 1-methyl histidine probably related to the higher intake of meats among AHS-2 black subjects (61).

Our previous work (5) has suggested that correlations between dietary variables and a biomarker <0.30 may lead to wide CIs for β-coefficients when such markers are used in biomarker-guided regression calibration. Although it is correlations with the unobservable true dietary intake that should ideally be one criterion to guide the selection of biomarkers for calibration, we expect that correlations between biomarkers and good

reference measures (repeated recalls, diet diaries) will provide imperfect but useful bases for such choices.

A low-valued correlation could be because of lack of association between the biomarker and the true nutrient/food intake (because of low bioavailability or other metabolic homeostatic mechanisms), laboratory analytic error, lack of validity of the dietary measure, or high within-person variability of either of the variables involved. A short half-life biomarker has the problem that much of its variance relates to irregularities of recent intake rather than the longer term measures usually sought in epidemiologic studies (62, 63). A moderate or high-valued

correlation with the dietary estimates suggests that, despite these potential problems, the biomarker remains a good measure of long-term intake.

De-attenuation of correlation coefficients that result from random within-person errors in one or both of the variables being correlated allows estimates of correlations with the mean (s) of a large number of hypothetical repetitions by extracting the within-person variance(s). Duplicate collections of the biomarker at different time periods would have allowed de-attenuation of correlation coefficients because of random within-person errors in biomarker estimates, but such duplicates were not available to us.

The range of exposure for plant-based foods is unusually large in Adventists (about one-half are vegetarian), and this is a factor that generally increases correlational values. A limitation includes the restriction to a special population. We would have preferred 24-h (rather than overnight) urine samples for urinary biomarkers, but this was not practical in a large (often working) population. However, the overnight urinary biomarkers generally seemed to perform well.

In conclusion, we have evaluated, in a relatively large population, correlations between a collection of biomarkers of dietary intake and corresponding dietary data. These results are generally similar to those reported by others (often from smaller samples) and thus may approximately generalize to other populations with similar recall ability. The results also provide some support for our plan to use many of these biomarkers as another means of dealing with the biasing effects of measurement errors.

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GEF wrote most of the manuscript; KJ-S directed the acquisition of repeated recalls; SMH and EHH directed the analysis of the biomarkers; JF performed much of the statistical analysis; SFK organized the clinics at which the bio-specimens were collected; GEF, SFK, JS, WLB, and HB designed the study; EHH was manager of the bio-repository of serum, adipose, and urine samples; and HB helped organize the clinics and organized retrieval of the samples from around the United States. All authors read and approved the final manuscript.

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