ARIC Manuscript Proposal #2360

PC Reviewed: 5/13/14   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Change in 25-hydroxyvitamin D levels over 3-years and 10-years of follow-up: the ARIC study

   b. Abbreviated Title (Length 26 characters):
      Change in vitamin D levels

2.   Writing Group:

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(Note Myron Gross, UMN was invited, but did not reply after multiple emails).

I, the corresponding author, confirm that all the coauthors have given their approval for this manuscript proposal. _EM _ **[please confirm with your initials electronically or in writing]**

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3.   Timeline:

Preliminary analyses have begun, will continue to fine-tune and complete immediately pending approval of this proposal. Will target a manuscript by end of Spring 2014.

4. Rationale:

25-hydroxyvitamin D [25(OH)D] deficiency has been associated with increased risk of cardiovascular disease (CVD) and all-cause mortality.[1] Suboptimal vitamin D status is thought to influence CVD risk predominantly by acting on established CVD risk factors, namely hypertension, diabetes, and inflammation.[1]

Almost all of the observational data linking 25(OH)D to CVD outcomes were based on a single baseline measure of 25(OH)D. However within an individual it is well-documented that there is considerable variation in one's 25(OH)D level by season. Less is known about how well a single 25(OH)D measurement reflects vitamin D status long term.

While NHANES has reported on population-level temporal changes of serum 25(OH)D by measuring 25(OH)D in repeated cross-sections of the US population,[2] few studies have reported longitudinal measures within the same individual (in non-intervention studies). There have been only 2 observational studies (i.e. not treatment intervention studies), from Norway[3] and Canada[4], that have measured serial 25(OH)D levels in their cohorts. Both study populations reside at high latitudes, and were almost exclusively Caucasian. Marked seasonal variation is noted in both studies. Jorde and colleagues found that after accounting for season, the correlation coefficient for 25(OH)D levels from 1994-2008 ranged from 0.42-0.52.[3] The Canadian study found that over a 10-year period, 25(OH)D levels increased on average in association with increasing use of supplemental vitamin D.[4] However, black individuals are known to have a greater prevalence of vitamin D deficiency. Little is known about change in their vitamin D status over time.

Using data from the ARIC Brain Ancillary study, we will determine correlations of vitamin D status measured on average 3 years apart in 1573 white and black participants [*between ARIC visit 2 and ARIC visit 3*] and 10 years apart in 430 black participants [*ARIC visit 3 to ARIC 2004-2006 Brain study*]. We seek to evaluate questions such as: Do vitamin D deficient participants remain deficient and replete individuals remain replete?   Do changes in levels correspond to the increase utilization of vitamin D supplements between ARIC visit 2 and visit 3, and between ARIC visit 3 and the ARIC BRAIN exam? What other demographic and clinical factors are associated with change in vitamin D levels over time?

Strengths of this paper proposal: Having 25(OH)D levels measured at 3 time points among the same individuals will provide insight on long-term patterns of vitamin D status. Furthermore, this will be the <u>first time</u> longitudinal measures of 25(OH)D are obtained in a cohort of individuals of black race/ethnicity and from a US population (at generally southern latitude that is less influenced by seasonal variation). Temporal trends in the use of vitamin D supplements for this population, and their association with changes in 25(OH)D levels will be determined.

5. Main Hypothesis/Study Questions:

Hypotheses:
1. 25(OH)D levels will be moderately correlated across the study visits spanning ~3 years and ~10 years.

a. Measurements spanning 3 years will be better correlated than measurements taken 10 years apart.
   b. Most deficient people will stay deficient, and most replete individuals will stay replete.
2. Certain key demographics will be related to change in 25(OH)D over time.
   a. We anticipate that blacks, those with elevated BMI, and those with current smoking (as a proxy for less healthy lifestyle status) are more likely to stay deficient at ~3 years and ~10 years later than participants without these characteristics.
   b. Conversely, participants reporting taking vitamin D supplements or multivitamin supplements at visit 3 and those with increased physical activity levels would be less likely to remain or become deficient.
   c. Furthermore, while we generally think of low 25(OH)D as a potential causal factor for incident CVD risk factors (and not vice versa), we do anticipate to find that people in poorer health (such as with diabetes and hypertension) are more likely to remain vitamin D deficient.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Participants:

ARIC VISIT 2 PARTICIPANTS (1990-1992): Serum 25(OH)D was measured in samples collected at ARIC visit 2 (1990-1992), which was attended by 14,348 white and black participants. Thus, visit 2 is 'baseline' for the present analysis. Excluded from the analysis are participants self-identified as neither black nor white (n=42), blacks from the Minnesota and Maryland centers (n=49), or missing 25(OH)D data (n=1,178). Thus, visit 2 vitamin D data was available in 13,079 participants.

ARIC VISIT 3 PARTICIPANTS (1993-1994): The ARIC Brain MRI ancillary study contains a subset of ARIC participants age ≥55 years from the Forsyth County and Jackson sites that were invited for a cerebral MRI and cognitive testing during the first two years of ARIC visit 3 (1993-1994) (n=1949, 60% women and 50% blacks). Inclusion/exclusion criteria for that ancillary study have previously been published.[4] 25(OH)D was measured in serum samples from ARIC Brain MRI Ancillary Study participants who attended visit 3. Of the 1,934 participants with available MRI data included in the visit 3 Brain MRI Ancillary Study, we excluded those missing stored serum, insufficient serum for 25(OH)D measurement, or samples that did not pass internal quality control (n=169) for a total sample at visit 3 with measured 25(OH)D of 1769. However, there are 191 participants who had visit 3 measurements of vitamin D but not visit 2 measurements. This leaves a total sample of 1573 for assessing change in levels between visit 2 and visit 3.

ARIC BRAIN VISIT (2004-2006): 25(OH)D was also measured from a subset from the ARIC brain visit from 2004-2006. Although over 1100 individuals participated in the later ARIC Brain visit, stored plasma (related to an ancillary proposal) was only available for

550 participants. This stored plasma [drawn as part of an ancillary study] was almost exclusively from the Jackson site (black race) with only a very few samples from white participants from Forsythe County. This is because funding status for this blood work from this ancillary proposal ended before more whites from FC could be recruited.

After excluding those individuals with inadequate samples to run the 25(OH)D levels, there were 512 individuals who had vitamin D levels measured at the latter brain visit. After matching ARIC ID identifiers, 494 individuals had 25(OH)D levels at ARIC visit 3 and the 2004-2006 Brain visit (n=474 blacks, n=20 whites). Of these 474 blacks, only 430 blacks had vitamin D measurements at both visit 3 and the 2004-2006 Brain visit to assess for change at ~10 years time. Since there are only 20 whites from Forsythe County at the Brain visit, and this is not a representative sample of all whites from FC, these 20 white participants will be excluded from analyses using the latter Brain visit data.

ARIC Study Timeline			ARIC Brain		ARIC Brain	ARIC-NCS
Exam	1	2	3	4		5
Calendar year	1987-1989	1990-1992	1993-1995	1996-1999	2004-2006	2011-2013
Followup year	0	3	6	9	17	24
Number, N	15792	14348	12887	11656	1134	7229
Age range, y	45-64	48-67	51-70	54-73	62-82	70-89
Brain MRI, n			1949		1134	2000

25(OH)D
N=13,079

25(OH)D
N=1,769

25(OH)D
N=512

Statistical methods:

Seasonally adjusted vitamin D: 25(OH)D concentrations vary by season. Therefore we adjusted 25(OH)D [at visit 2, visit 3, and brain MRI visit] for seasonal variation by computing the residuals from a linear regression model with vitamin D as the dependent variable and month of blood draw as the independent variable. By definition, these residuals are uncorrelated with month of blood draw. The grand mean was then added to the vitamin D residuals obtained from this model. We performed this adjustment separately for whites and for blacks, as seasonal variation in 25(OH)D concentrations also vary by race. This new variable "vitamin D adjusted for month of blood draw" is an estimate of average annual 25(OH)D levels, and was used as the exposure variable in all analyses.

Adjusted 25(OH)D levels <20 ng/ml were considered deficient as level ≥20 ng/ml were considered adequate (or "replete") for health per Institute of Medicine recommendations.

Other covariates of interest: From visit 2: Age, sex, race, center, BMI, smoking status, diabetes (self-report, medication use, or fasting blood glucose ≥126 mg/dl), hypertension (BP >140/90 and/or use of antihypertensive medications). Education and income, as proxies for SES, was obtained at visit 1. Physical activity was measured at visit 1.

Information regarding use of vitamin D and/or multivariate supplements was obtained from visit 3.

<u>Analyses:</u>

The data for this analysis will be largely descriptive.

1. Determination of correlation of vitamin D status over time.

The pearson correlation (r) between 25(OH)D levels at visit 2 vs. visit 3 and visit 3 vs. the brain visit will be determined.

Preliminary scatterplots and correlations have been performed for the comparison between visit 2 and visit 3 for whites and blacks, and for visit 3 with the 2004-2006 brain visit 10 years later (black participants only). See supplementary figures attached at the end.

We will compared correlation coefficients of 25(OH)D levels at 3 and 10 years with other laboratory and risk factor variables such as blood pressure, cholesterol, and BMI, to see if 25(OH)D levels are more or less correlated over time compared to other key variables.

2. Prevalence of vitamin D deficient (<20 ng/ml) and vitamin D replete (>=20 ng/ml) status will be calculated at each time point, stratified by blacks and whites

See supplemental tables at the end.

3. Determination of factors associated with change in vitamin status

a. Vitamin D supplement and multivitamin supplement use at visit 3 and Brain visit will be determined. (Supplement use at Visit 2 was not characterized)

b. For whites and blacks separately, we will tabulate vitamin D status (deficient, replete) at each visit by other clinical factors such as age groups (>=60, <60), sex, BMI categories, presence of hypertension, presence of diabetes, physical activity status (active/inactive), smoking status, and markers of SES such as income and education (low/high).

c. To assess the longitudinal association between clinical factors and vitamin D trajectory, we will use linear mixed model with 2-level hierarchy for longitudinal data. At the first within-participant level, the change in Vitamin D level Y_{ti} from visit 2 (t = 0) to visit 3 (t = 1) or from visit 3 to the brain MRI visit (t=2) for participant i = 1,…, n was described through the linear relation

$$Y_{ti} = \alpha_{0i} + \alpha_{1i}X_{ti} + \varepsilon_{ti}$$

in which α_{0i} and α_{1i} were the expected 25(OH)D levels at baseline and the expected change in 25(OH)D levels associated with time-varying covariates, respectively, for that participant, and the within-participant errors ε_{ti} were assumed to be independent and normally distributed with mean 0 and constant variance σ^2.

The second level represented the variability in the parameters α_{0i} and α_{1i} across participants. The individual baseline 25(OH)D α_{0i} were allowed to vary by sex, center and other time-fixed variables (C_i). The individual changes of 25(OH)D (α_{1i}) were also allowed to differ across individuals. Specifically, the second-level (between-participant) model was

$$\alpha_{0i} = \beta_{00} + \beta_{01}*sex + \beta_{02}*center + \beta_{03}*C_i + b_{0i},$$
$$\alpha_{1i} = \beta_{10} + b_{1i}$$

in which the between-participant errors b_{0i} and b_{1i} were assumed to be independent and normally distributed with mean 0 and respective variances τ_0^2 and τ_1^2. Combining the 2 nested models, we obtained the linear mixed model

$$Y_{ti} = (\beta_{00} + b_{0i}) + \beta_{01}*sex + \beta_{02}*center + \beta_{03}*C_i + (\beta_{10} + b_{1i})X_{ti} + \varepsilon_{ti}$$

The longitudinal effects of lifestyle and clinical factors on changes in levels of 25(OH)D is estimated from coefficients β_{10}

d. Both continuous 25(OH)D and binary (deplete or replete status) will be used as outcomes. All results will be stratified by race.

e. We will also use multivariable linear regression model with the outcome of vitamin D change (3 year change for black and whites or 10 year change for blacks) as outcome.

   i. Exposures included in this analysis will be as follows: Model 1 will consider basic demographic factors age and sex. Subsequent models will include lifestyle (Model 2: Vitamin D supplement use, BMI, physical activity, smoking, alcohol consumption, education) and CVD factors (Model 3: HTN, DM, dyslipidemia).

f. We will use logistic regression models to determine which factors are associated with odds of becoming vitamin D deficient at each follow up visit (those with deficiency at baseline will be excluded). Exposures considered will be the same as outlined in e.1. See supplementary table at end for preliminary analysis.

g. We will also use logistic regression models to determine which factors are associated with a significant decrease in 25(OH)D levels >5 ng/ml.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes __X__ No

We are not studying CVD outcomes per se. But we are considered risk factors associated with CVD (such as BMI, DM, HTN) and how those factors are associated with changes in vitamin D levels over time.

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __ Yes __ No (This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _____ Yes _____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

No other proposal is comparing vitamin D levels across 3 time points in ARIC. Dr. Lutsey has several other papers using vitamin D data from visit 2 as part of her ancillary study, and she is included as a co-author on this paper.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X___ Yes _____ No

11.b. If yes, is the proposal
__X__ A. primarily the result of an ancillary study (list number* 1999.01, 2009.17, 2010.01)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.
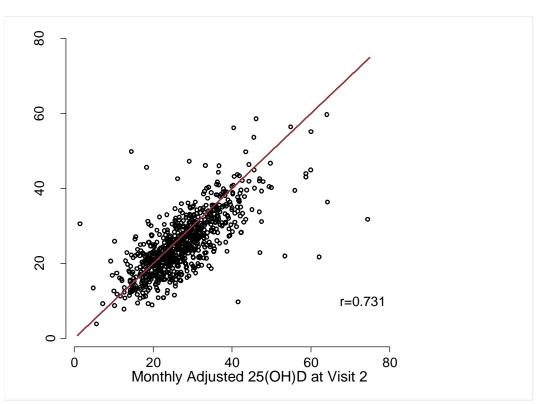
12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

Literature Cited:

1. Michos ED, Reis JP, Melamed ML. Vitamin D status and cardiovascular health: a 2009 update. Open Clinical Chemistry Journal, 2010;3:51-59. Published on-line. http://bentham.org/open/tocchemj/openaccess2.htm

2. Looker AC, Peiffer CM, Lacher DA, Scleicher RL, Picciano MF. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. Am J Clin Nutr 2008;99:1519-27.

3. Jorde R, Sneve M, Hutchinson M, Emaus N, Figenschau Y, Grimnes G. Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population based study and during 12 months in an intervention study. Am J Epidemiol 2010;171:903-908.

4. Berger C, Greene-Finestone LS, Langsetmo L, Kreiger N, Joseph L, Kovacs CS, Richards JB, Hidiroglou N, Sarafin K, Davison KS, Adachi JD, Brown J, Hanley DA, Prior JC, Goltzman D, and the CaMos Research Group. Temporal trends and determinants of longitudinal change in 25-hydroxyvitamin D and parathyroid hormone levels. J Bone Miner Res. 2012 Jun;27(6):1381-9.
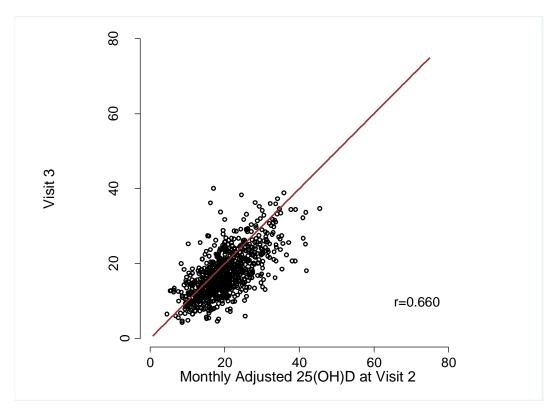
SUPPLEMENTAL FIGURES AND TABLES (PRELIM DATA)

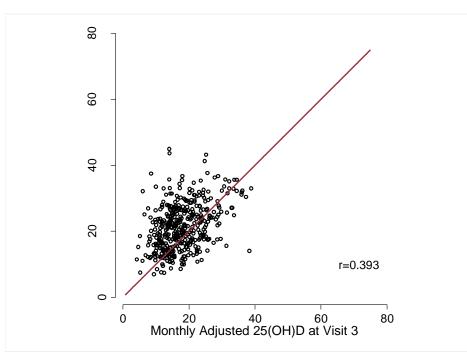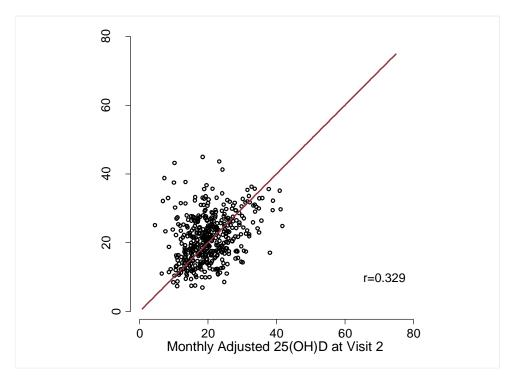1. Correlation of monthly adjusted 25(OH)D between visit 2 and visit 3

    a. Whites:

b. Blacks

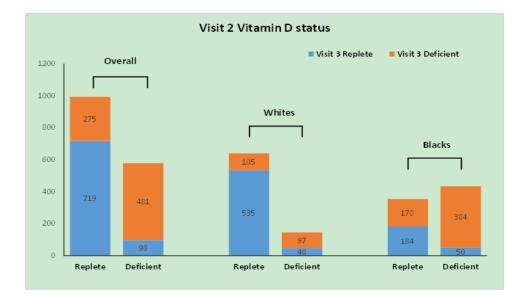2. Correlation of monthly adjusted 25(OH)D between visit 3 and brain MRI visit in Blacks

r=0.393

Monthly Adjusted 25(OH)D at Visit 3

3. 3. Correlation of monthly adjusted 25(OH)D between visit 2 and brain MRI visit in Blacks

r=0.329

Monthly Adjusted 25(OH)D at Visit 2

4. Vitamin D deficient/vitamin D replete status at each time point.

| | Visit 2 | | | | | |
| Visit 3 | Overall (n=1,573*) | | Whites (n=785) | | Blacks (n=788) | |
	Replete	Deficient	Replete	Deficient	Replete	Deficient
Replete	719 (72.3)	98 (16.9)	535 (83.6)	48 (33.1)	184 (52.0)	50 (11.5)
Deficient	275 (27.7)	481 (83.1)	105 (16.4)	97 (66.9)	170 (48.0)	384 (88.5)
Total	994 (100.0)	579 (100.0)	640 (100.0)	145 (100.0)	354 (100.0)	434 (100.0)

| | Visit 3 Blacks (n=430) | |
Brain MRI visit	Replete	Deficient
Replete	101 (71.1)	131 (45.5)
Deficient	41 (28.9)	157 (54.5)
Total	142 (100.0)	288 (100.0)

Table: Odds ratio for change of Vitamin D status from replete to deficient (participants with vitamin D deficiency at baseline excluded)*

| | Visit 2 to Visit 3 | | | | | | Visit 3 to Brain MRI visit | | |
| | Whites | | | Blacks | | | Blacks | | |
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
No. of cases/subjects	105/640	105/638	105/634	170/354	169/350	165/343	41/142	41/141	41/141
Age, 10 years	0.93 (0.58, 1.50)	0.94 (0.56, 1.58)	0.98 (0.58, 1.67)	0.75 (0.47, 1.20)	0.85 (0.52, 1.40)	0.83 (0.50, 1.37)	0.94 (0.37, 2.35)	1.29 (0.46, 3.60)	1.07 (0.37, 3.13)
Male	0.47 (0.30, 0.73)	0.48 (0.28, 0.82)	0.38 (0.20, 0.69)	0.40 (0.26, 0.62)	0.33 (0.20, 0.54)	0.33 (0.19, 0.57)	0.93 (0.45, 1.93)	1.13 (0.47, 2.73)	1.05 (0.38, 2.87)
Vitamin D Supplementation Use		0.33 (0.19, 0.58)	0.32 (0.18, 0.57)		0.42 (0.25, 0.71)	0.44 (0.26, 0.75)		0.92 (0.39, 2.13)	0.89 (0.37, 2.12)
Education									
<High School		Reference	Reference		Reference	Reference		Reference	Reference
High School		1.52 (0.74, 3.13)	1.64 (0.79, 3.44)		1.25 (0.71, 2.21)	1.36 (0.76, 2.42)		1.29 (0.42, 3.96)	1.53 (0.47, 5.06)
≥College		1.94 (0.92, 4.09)	2.32 (1.08, 4.98)		1.67 (0.95, 2.96)	1.78 (0.99, 3.20)		1.11 (0.43, 2.83)	1.29 (0.48, 3.47)
BMI, kg/m²		1.03 (0.98, 1.09)	1.02 (0.96, 1.08)		0.97 (0.92, 1.02)	0.98 (0.93, 1.03)		1.13 (1.03, 1.24)	1.10 (1.00, 1.22)
Smoking									
Never		Reference	Reference		Reference	Reference		Reference	Reference
Former		1.43 (0.82, 2.49)	1.45 (0.82, 2.56)		1.26 (0.73, 2.19)	1.27 (0.72, 2.23)		1.03 (0.41, 2.59)	1.10 (0.43, 2.82)
Current		2.38 (1.31, 4.34)	2.40 (1.30, 4.44)		1.05 (0.55, 2.00)	1.23 (0.62, 2.41)		1.84 (0.56, 6.01)	2.33 (0.67, 8.12)
Drinking									
Never		Reference	Reference		Reference	Reference		Reference	Reference
Former		0.37 (0.17, 0.83)	0.38 (0.17, 0.86)		0.93 (0.53, 1.64)	0.92 (0.51, 1.67)		1.64 (0.61, 4.42)	1.63 (0.60, 4.42)
Current		0.56 (0.33, 0.94)	0.59 (0.35, 1.01)		1.36 (0.73, 2.51)	1.37 (0.73, 2.58)		1.67 (0.60, 4.68)	1.66 (0.57, 4.86)
Physical activity		0.66 (0.49, 0.88)	0.67 (0.50, 0.90)		0.74 (0.52, 1.05)	0.73 (0.51, 1.04)		0.99 (0.57, 1.72)	1.03 (0.58, 1.81)
Hypertension			0.86 (0.50, 1.48)			0.90 (0.56, 1.45)			2.02 (0.82, 4.98)
Diabetes			2.36 (1.15, 4.82)			0.86 (0.48, 1.55)			1.72 (0.67, 4.42)
HDL Cholesterol, 10 mg/dl			0.91 (0.77, 1.06)			0.98 (0.84, 1.14)			0.92 (0.72, 1.19)
Total Cholesterol, 10 mg/dl			1.01 (0.95, 1.07)			1.04 (0.98, 1.09)			1.01 (0.91, 1.12)

* <u>Model 1</u> (demographic variables): age (years; continuous), sex (male; female)

Model 2 (demographic + behavioral variables): Model 1 + vitamin D supplementation use at visit 3 (yes; no), education (<High School; High School or Vocational School; College, Graduate, or Professional School), body mass index (kg/m^2; continuous), smoking status (never; former; current), alcohol drinking status (never; former; current), and physical activity (based on replies to the Baecke Physical Activity questionnaire; continuous).

Model 3 (demographic + behavioral + comorbidities): Model 2 + hypertension (yes; no, defined by self-report of physician diagnosis or medication use, or systolic blood pressure ≥ 90 mmHg, or diastolic blood pressure ≥ 140 mmHg) diabetes (yes; no, defined by self-report of physician diagnosis or medication use, or fasting glucose ≥126 mg/dl, or non-fasting glucose ≥200 mg/dl), HDL cholesterol (mg/dl; continuous) and total cholesterol (mg/dl; continuous).