Greater Adherence to Cancer Prevention Guidelines Is Associated with Higher Circulating Concentrations of Vitamin D Metabolites in a Cross-Sectional Analysis of Pooled Participants from 2 Chemoprevention Trials[1,2]

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Abstract

Background: Several lifestyle factors targeted by the American Cancer Society (ACS) Nutrition and Physical Activity Cancer Prevention Guidelines are also associated with circulating concentrations of vitamin D metabolites. This suggests that greater adherence to the ACS guidelines may be related to better vitamin D status.

Objective: We examined the relation between adherence to the ACS guidelines and circulating concentrations of 2 vitamin D metabolites, 25-hydroxycholecalciferol [25(OH)D] and 1α,25-dihydroxyvitamin D [1,25$(OH)_2$D].

Methods: We conducted cross-sectional analyses of pooled participants from the Wheat Bran Fiber (n = 503) and Ursodeoxycholic Acid (n = 854) trials. A cumulative adherence score was constructed with the use of baseline data on body size, diet, physical activity, and alcohol consumption. Continuous vitamin D metabolite concentrations and clinically relevant categories were evaluated with the use of multiple linear and logistic regression models, respectively.

Results: The most adherent participants were more likely to be older, white, and nonsmokers than were the least adherent. A statistically significant association was observed between guideline adherence and concentrations of circulating 25(OH)D (means ± SEs—high adherence: 32.0 ± 0.8 ng/mL; low adherence: 26.4 ± 0.7 ng/mL; P-trend < 0.001). For 1,25$(OH)_2$D concentrations, high adherence was again significantly related to greater metabolite concentrations, with mean ± SE concentrations of 36.3 ± 1.3 pg/mL and 31.9 ± 1.0 pg/mL for high- and low-adherers, respectively (P-trend = 0.008). Furthermore, the odds of attaining a sufficient 25(OH)D status were 4.37 times higher for those most adherent than for those least adherent (95% CI: 2.47, 7.71 times).

Conclusion: These findings demonstrate that greater adherence to the ACS guidelines is associated with higher circulating concentrations of both of 25(OH)D and 1,25$(OH)_2$D. *J Nutr* 2017;147:421–9.

Keywords: adherence, vitamin D, cancer prevention guidelines, diet, physical activity

Introduction

Obesity, advancing age, limited sun exposure, poor diet, and higher skin pigmentation are all risk factors for vitamin D deficiency (1–7). Vitamin D deficiency has been linked to several major causes of death, including cardiovascular disease, diabetes, and cancer (8). Although the definition of clinical vitamin D deficiency has been updated (9, 10), it remains debated (8, 11). Furthermore, the optimal amount of vitamin D intake required to meet definitions of vitamin D sufficiency also remains unclear (12–14). Vitamin D supplementation with cholecalciferol (vitamin D_3) is the primary clinical strategy used to increase circulating concentrations of 25-hydroxycholecalciferol

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[25(OH)D][9], the metabolite most often measured to determine vitamin D status in adults (15). However, studies of vitamin D supplementation and health outcomes have produced equivocal results (16, 17). In addition, there are emerging data that genetic background may influence response to vitamin D supplementation (18, 19). Humans can also produce 25(OH)D via exposure to UVB radiation (20), but this route is rarely promoted, because excessive sunlight exposure can cause sunburns and increase the risk of skin cancer (8). With regard to diet, naturally occurring vitamin D is found in only a limited number of foods, such as fatty fish, whereas vitamin D–fortified foods such as dairy products, ready-to-eat cereals, and orange juice are more common. Therefore, the optimal strategy for improving vitamin D status remains equivocal.

Several lifestyle factors targeted by the American Cancer Society (ACS) Nutrition and Physical Activity Cancer Prevention Guidelines, including body size, diet, and physical activity, have also been associated with circulating concentrations of vitamin D (12, 21, 22). Our group recently completed a systematic review that found strong and consistent evidence indicating that adherence to the ACS or similar World Cancer Research Fund/American Institute for Cancer Research guidelines was associated with significant reductions in cancer incidence and mortality (23). One study included in the review by Kabat et al. (24) reported a statistically significant association between higher adherence to the guidelines and increased melanoma incidence. One explanation for these findings is that adherence to the guidelines, particularly for physical activity, is related to increased sun exposure and potentially higher vitamin D concentrations. Thus, we hypothesized that greater adherence to the guidelines would be associated with higher concentrations of vitamin D metabolites. We used data from a pooled sample of 2 completed chemoprevention trials to construct an adherence score for the ACS nutrition and physical activity cancer prevention guidelines and assess the relation between adherence and concentrations of 25(OH)D (n = 1357) and 1α,25-dihydroxyvitamin D [1,25(OH)$_2$D] (n = 854).

Methods

Study population. Data were pooled from 2 randomized, controlled, double-blind, Phase III clinical trials conducted at the University of Arizona Cancer Center from 1990 to 1999. These studies evaluated the effect of either a wheat bran fiber (WBF) supplement (25, 26) or ursodeoxycholic acid (UDCA) (27) on the development of a new colorectal adenoma in patients with previously removed colorectal adenomas. The present analyses were conducted with the use of data for baseline diet, physical activity, and vitamin D biomarkers from the pooled population. The University of Arizona Human Subjects Protection Program approved both studies. Written informed consent was obtained from each participant before trial enrollment.

Recruitment and data collection. Phoenix and Tucson gastroenterology practices served as recruitment centers from 1990 to 1995 for the WBF supplement and 1995 to 1999 for the UDCA. Men (69.5%) and women (30.5%) with a mean age of 65.5 y (range: 40–80 y) who had ≥1 adenomas measuring ≥3 mm removed during a colonoscopy within a 6-mo period before study registration were included in the study. Mean ± SD BMI (in kg/m^2) was 28.3 ± 4.2 and 27.7 ± 5.5 for men and women, respectively. Participants in the WBF supplement trial were randomly assigned to a daily WBF supplement (13.5 g/d) or a low-fiber supplement (2.0 g/d) (25). Participants in the UDCA trial were randomly assigned to receive 8–10 mg UDCA/kg body weight or placebo daily (27). Primary findings from the trials were null; neither the WBF supplement nor the UDCA treatment prevented new colorectal adenomas (26, 27). For the present cross-sectional analysis, participants from the pooled sample (n = 3221) were excluded if they did not have serum 25(OH)D data (n = 1253), had missing BMI data (n = 16), were underweight (BMI <18.5) (n = 16), had unreliable dietary data (<600 kcal/d) (n = 14), had missing baseline physical activity data (n = 544), or were missing any other covariate included in the models (race, n = 16; education, n = 5). The analytic cohort for 25(OH)D was thus composed of 1357 participants, whereas 1,25(OH)$_2$D data were only available from the UDCA trial (n = 854).

Analysis of serum vitamin D metabolites. Baseline vitamin D metabolites were measured in a blinded fashion at Heartland Assays (Ames) with the use of an established RIA (28). Quality-assurance and -control measures, including pooled serum samples and duplicates in different batches, were performed. The CV was <7.0% for 25(OH)D and 11.5% for 1,25(OH)$_2$D. Serum 1,25(OH)$_2$D was assessed as a continuous variable and 25(OH)D was assessed as both a continuous and a categorical variable, in which clinically important categories were defined as deficient (<20 ng/mL), insufficient (≥20 to <30 ng/mL), or sufficient (≥30 ng/mL) (9, 10, 29–31).

Nutrition and physical activity cancer prevention guidelines score. An a priori score was constructed based upon previously published work by Thomson et al. (32) for adherence to the 2012 ACS cancer prevention guidelines for nutrition and physical activity (33) (**Table 1**). These guidelines focused on overall patterns of lifestyle behaviors that included body size, physical activity, diet, and alcohol consumption. Baseline diet and physical activity were collected with the use of frequency questionnaires. The Arizona FFQ is a semiquantitative 175-item validated questionnaire that asks respondents to report how often (per day, week, or month) and how much (small, medium, or large usual portion) participants consumed each food item over the previous 12-mo period (34). The Arizona Activity Frequency Questionnaire is a 59-item validated questionnaire that groups physical activity by leisure, recreational, household, and other activity categories (35). The provided output contains metabolic equivalent task (MET) units per day and per activity, kilojoules, number of hours per day per activity, and number of activities reported by respondents for each category, which were used to generate the physical activity score. Each ACS recommendation was equally weighted 0–2 points. Zero points were allocated for not meeting the recommendation at all, 1 point for partially meeting the recommendation, and 2 points for fully meeting the recommendation. The overall score, summed from individual recommendations, ranged from 0 for those participants who were not adherent at all to the recommendations to 8 for those participants who were fully adherent to all 4 lifestyle factor recommendations. Adherence categories were defined as low (0–2 points), moderate (3–5 points), and high (6–8 points). The recommendations for each lifestyle factor, how they were measured, how scores were assigned based upon the guidelines, and the proportion of the study population within each category are outlined in Table 1. Smoking status was not included in the ACS adherence scoring, but was included as a potential confounder in the current analyses.

The first recommendation to "maintain a healthy weight throughout life" was scored based upon calculated BMI from height and weight reported at baseline. The best score (2 points) was given to those with a BMI within normal range (18.5–25), 1 point was given those in the overweight range (25–30), and 0 points were given to those in the obese category (>30.0). Underweight participants (<18.5) were excluded from the present analysis.

The second recommendation to "adopt a physically active lifestyle" was evaluated by MET (36) scores from the Arizona FFQ recreational activities section. Any participant doing less than the minimum recommendation [30 min on 5 d (2.5 h/wk) of moderate activity (3.5 METs) was equal to 8.75 MET-h/wk] received a score of 0 points. One hour per day, 5 d/wk (5.0 h/wk), of moderate activity (3.5 METs) equaled 17.5 MET-h/wk. Therefore, 8.75–17.5 MET-h/wk earned a

[9] Abbreviations used: ACS, American Cancer Society; MET, metabolic equivalent task; UDCA, ursodeoxycholic acid; WBF, wheat bran fiber; 1,25(OH)$_2$D, 1α,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxycholecalciferol.

TABLE 1 Components of the adherence score and distribution in the study sample

Score	Description	Percentage of study sample		
		All	Men	Women
BMI, kg/m^2				
0	>30	29.9	30.1	29.7
1	>25 to ≤30	43.8	48.6	32.8
2	18.5 to ≤25	26.1	21.2	37.4
Physical activity, MET-h[1]/wk				
0	<8.75	40.4	35.8	50.9
1	8.75–17.5	25.1	25.5	24.1
2	>17.5	34.4	38.6	24.8
Diet[2]				
0		23.9	23.4	24.9
1		64.4	64.5	64.3
2		11.7	12.1	10.9
Fruits and vegetables, cups/d				
0	<2.5	51.9	52.0	51.7
1	≥2.5	48.1	48.0	48.3
Quality				
0	1st tertile of total carotenoids	32.3	33.0	30.7
1	2nd tertile of total carotenoids	33.8	33.4	34.8
2	3rd tertile of total carotenoids	33.9	33.6	34.5
Whole grains				
0	1st quartile of whole:refined ratio	63.1	62.3	64.9
1	2nd quartile of whole:refined ratio	0	0	0
2	3rd quartile of whole:refined ratio	11.6	12.4	9.7
3	4th quartile of whole:refined ratio	25.3	25.2	25.4
Red and processed meat				
0	4th quartile of red and processed meat intake	25.2	25.0	25.6
1	3rd quartile of red and processed meat intake	25.4	25.1	26.1
2	2nd quartile of red and processed meat intake	25.1	25.0	25.1
3	1st quartile of red and processed meat intake	24.3	24.8	23.2
Alcohol,[3] g/d				
0	Men ≥42, women ≥28	9.3	10.6	6.3
1	Men 14 to <42, women 14 to <28	53.8	57.7	44.9
2	Nondrinkers	36.9	31.7	48.8

[1] MET-h, metabolic equivalent task hours.
[2] Generated from the summation of the fruit and vegetable, quality, whole grains, and red and processed meat scores. Summed for ≤9 points and then collapsed into 3 categories (0–2, 3–6, and 7–9) for subsequent diet adherence values (0, 1, and 2).
[3] 1 drink/d = 14 g ethanol/d.

score of 1 point. Participants meeting preferable levels, >17.5 MET-h/wk, earned a score of 2 points.

The third recommendation to "consume a healthy diet with an emphasis on plant sources" was assessed with 3 separate diet scores that were constructed and summed to capture the recommended dietary pattern. The first diet score for the recommendation "eat 5 or more servings of a variety of vegetables and fruits each day" was assigned 1 point for meeting the recommended number of servings (≥2.5 cups), which were measured from the food group categories fruits, fruit juice, vegetables, and vegetable juice. An additional 1 or 2 points were assigned for diet quality based upon being in the second or third sex-specific tertile of total carotenoids, respectively, which included β-carotene, α-carotene, β-cryptoxanthin, lycopene, and lutein plus zeaxanthin combined. The second diet score for the recommendation "choose whole grains in preference to processed (refined) grains" was evaluated by the percentage of grains consumed as whole grains. Points were assigned by the sex-specific quartile distribution with the highest quartile receiving 3 points and lowest quartile receiving 0 points. The third diet score for the recommendation "limit consumption of processed and red meats" was measured similarly to the whole grains assessed by sex-specific quartile distribution. However, the lowest quartile received 3 points and the highest quartile received 0 points. The 3 diet scores were summed for a potential total of 9 points. Dietary pattern scores were further collapsed into 0 points (0–2 summed diet scores), 1 point (3–6 summed diet scores), and 2 points (7–9 summed diet scores).

The fourth recommendation used in this analysis was "if you drink alcohol, limit consumption to 1 drink/d for women or 2 drinks/d for men." Alcohol was captured in the Arizona FFQ in terms of total grams of alcohol per day. One drink was estimated as 14 g alcohol or approximately one 12-ounce regular beer, 5-ounce glass of wine, or 1.5-ounce shot of 80-proof distilled spirit (37). Nondrinkers were assigned 2 points, moderate drinkers who consumed the limit or less were assigned 1 point, and heavy drinkers who consumed more than the limit were assigned 0 points.

Statistical analysis. Descriptive statistics were generated for vitamin D metabolites, adherence scores, and demographic variables. Means and SEs were estimated for continuous variables and percentages were calculated for the categorical variables.

Multiple linear regression models were used to assess the relations between adherence score categories and circulating concentrations of 25(OH)D and 1,25$(OH)_2$D. Estimated mean concentrations of 25(OH)D and 1,25$(OH)_2$D for individuals in the reference categories were centered on mean age and energy intake of the strata with the use of linear combinations of variables. Reference categories were selected to represent the majority of the pooled sample (white, male, not a college graduate, and nonsmoker in the UDCA trial). Associations between adherence scores and clinically significant categories for serum 25(OH)D were evaluated with the use of multinomial logistic regression models to estimate ORs. Individual adherence score components were also examined for associations with adjusted mean concentrations of 25(OH)D and $1,25(OH)_2D$. Regression modeling was also used to calculate *P*-trend. Potential confounders included age, education, race, smoking status, supplement use, season of blood draw, and energy intake (21, 22, 38–40). A covariate was considered to be a confounder if it changed the measure of association by ≥10% when included in a regression model (41). To assess whether the associations between adherence score and vitamin D metabolites were modified by sex or study, likelihood ratio tests were used to determine whether there was a difference in the log-likelihoods from models with and without interaction terms. Statistical significance was determined at an α level of 0.05. Data from the trials were merged and managed with the use of Stata version 14.1.

Results

More women than men met the BMI recommendation of a healthy body size (18.5–25), whereas more men than women met preferable physical activity levels of >1 h/d, 5 d/wk (>5.0 h/wk) of moderate activity (3.5 METs), or >17.5 MET-h/wk total (Table 1). Men and women had similar adherence to diet recommendations overall; however, a greater percentage of women were nondrinkers at baseline than men. Baseline characteristics of men and women by category of adherence score are shown in **Table 2**. In general, participants in the most adherent overall category of adherence score (6–8 points) were more likely to be older, white, and nonsmokers than were participants in the least adherent category (0–2 points).

Adjusted mean circulating 25(OH)D and $1,25(OH)_2D$ concentrations for each adherence score category from multivariate linear regression models for individuals in reference categories (white, male, not a college graduate, nonsmoker in the UDCA trial) centered on mean age and energy intake are shown in **Table 3**. In the pooled sample, those in the highest adherence category to the ACS guidelines (6–8 points) had a mean ± SE 25(OH)D concentration of 32.0 ± 0.8 ng/mL and a mean ± SE $1,25(OH)_2D$ concentration of 36.3 ± 1.3 pg/mL, with significant dose-dependent trends for both metabolites (*P*-trend < 0.001 and *P*-trend < 0.008, respectively) (Table 3). For 25(OH)D, there were no statistically significant interactions for sex (*P*-interaction = 0.42) or study (*P*-interaction = 0.19). Study interaction was not evaluated for $1,25(OH)_2D$, because it was only available for the UDCA study. There was no statistically significant interaction between score and sex (*P*-interaction = 0.86) for $1,25(OH)_2D$.

The results of multinomial logistic regression models for the association between categories of adherence scores and clinically-defined categories of 25(OH)D are presented in **Table 4**. The odds of having an insufficient vitamin D status (≥20 ng/mL and <30 ng/mL) compared with a deficient status (<20 ng/mL) were 1.76 times greater (95% CI: 1.21, 2.57) for those who had moderate adherence to the guidelines and 2.29 times greater (95% CI: 1.35, 3.90) for individuals who had high

TABLE 2 Baseline characteristics of participants in the pooled sample by categories of adherence score to the ACS Nutrition and Physical Activity Cancer Prevention guidelines, stratified by sex[1]

	Adherence Score (points)					
	Men			Women		
	0–2	3–5	6–8	0–2	3–5	6–8
Subjects	151 (16.0)	638 (67.7)	154 (16.3)	64 (15.5)	271 (65.5)	79 (19.1)
Age, y	62.7 ± 8.1	65.8 ± 8.8	68.4 ± 7.6	64.1 ± 8.6	64.6 ± 8.7	67.1 ± 8.6
White	142 (94.0)	598 (93.7)	146 (94.8)	62 (96.8)	252 (93.0)	77 (97.5)
College graduate	54 (35.8)	279 (43.7)	57 (37.0)	12 (18.8)	61 (22.5)	14 (17.7)
BMI, kg/m^2	31.7 ± 4.3	28.4 ± 3.9	25.0 ± 2.4	33.5 ± 5.1	27.4 ± 5.1	24.0 ± 3.0
Physical activity, MET-h/wk	4.7 ± 4.7	18.8 ± 18.2	31.6 ± 18.1	3.7 ± 5.0	11.3 ± 15.3	28.2 ± 17.3
Diet						
Total energy, kcal/d	2300 ± 778	2120 ± 781	2140 ± 729	1650 ± 564	1550 ± 593	1610 ± 579
Fruits and vegetables, 2.5 cups/d	4.9 ± 3.3	5.4 ± 3.2	6.9 ± 3.9	4.8 ± 3.1	5.8 ± 4.3	7.0 ± 3.6
Total carotenoids, mg/d	13.5 ± 9.72	14.0 ± 8.41	15.7 ± 7.85	10.1 ± 5.03	12.4 ± 8.93	13.6 ± 7.56
Red and processed meat, servings/d	2.0 ± 0.9	1.5 ± 0.8	1.3 ± 0.8	1.4 ± 0.9	1.0 ± 0.6	0.9 ± 0.6
Whole grains, g/d	11.2 ± 36.1	21.8 ± 48.2	52.9 ± 79.3	6.5 ± 15.5	15.8 ± 31.1	39.2 ± 68.6
Dietary vitamin D intake	156 ± 121	162 ± 116	153 ± 108	143 ± 112	135 ± 104	148 ± 130
Vitamin D supplement, IU/d	187 ± 227	206 ± 259	225 ± 221	240 ± 266	224 ± 268	315 ± 272
Supplement use	85 (56.3)	412 (64.6)	120 (77.9)	49 (76.6)	191 (70.5)	69 (87.3)
Alcohol						
Nondrinker at baseline	21 (13.9)	193 (30.3)	85 (55.2)	15 (23.4)	132 (48.7)	55 (69.6)
Intake for drinkers,[2] drinks/d	1.7 ± 1.9	0.9 ± 1.1	0.7 ± 0.5	0.4 ± 0.4	0.4 ± 0.5	0.5 ± 0.4
Current smoker	20 (13.3)	76 (11.9)	18 (11.7)	10 (15.6)	40 (14.8)	10 (12.7)
Serum vitamin D biomarkers						
25(OH)D, ng/mL	26.4 ± 9.1	29.5 ± 9.9	31.1 ± 10.3	20.9 ± 7.5	23.6 ± 9.9	28.0 ± 11.4
$1,25(OH)_2D$,[3] pg/mL	32.3 ± 10.5	34.5 ± 10.8	35.8 ± 10.8	31.1 ± 12.3	32.8 ± 11.7	34.4 ± 12.2

[1] Values are means ± SDs or *n* (%), *n* = 1357. Some percentages do not add up to 100% because of missing data or rounding. ACS, American Cancer Society; MET-h, metabolic equivalent task hours; $1,25(OH)_2D$, 1α,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxycholecalciferol.

[2] 1 drink = 14 g ethanol/d.

[3] Only the Ursodeoxycholic Acid Trial measured $1,25(OH)_2D$ (*n* = 854).

TABLE 3 Mean circulating serum 25(OH)D and 1,25(OH)$_2$D concentrations and category of adherence score by study[1]

	Adherence score									
	25(OH)D, ng/mL					1,25(OH)$_2$D, pg/mL				
	n	0–2	3–5	6–8	*P*-trend	*n*	0–2	3–5	6–8	*P*-trend
Pooled sample	1357	26.4 ± 0.7	29.6 ± 0.5	32.0 ± 0.8	<0.001	854	31.9 ± 1.0	34.5 ± 0.7	36.3 ± 1.3	0.008
UDCA	854	25.8 ± 0.8	29.4 ± 0.6	32.2 ± 1.1	<0.001	854	31.7 ± 1.0	34.3 ± 0.7	36.2 ± 1.3	0.001
WBF[2]	503	29.1 ± 1.6	30.1 ± 0.8	32.6 ± 1.0	0.012	—	—	—	—	—

[1] Values are means ± SEs computed from linear regression for individuals in reference categories (white, male, not a college graduate, and nonsmoker in the UDCA trial) centered on mean age and energy intake. Adjusted for sex, study, mean age, race, education, smoking status, and mean energy intake. UDCA, ursodeoxycholic acid; WBF, wheat bran fiber; 1,25(OH)$_2$D, 1α,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxycholecalciferol.

[2] WBF supplement trial (low fiber compared with high fiber) did not measure 1,25(OH)$_2$D.

adherence compared with those with low adherence. The odds of having a sufficient vitamin D status (≥30 ng/mL) compared with a deficient status were 2.41 times greater (95% CI: 1.58, 3.68) for those achieving moderate adherence and 4.37 times greater (95% CI: 2.47, 7.71) for those who had high adherence compared with those within the lowest adherence category.

Adjusted mean concentrations of 25(OH)D and 1,25(OH)$_2$D for individuals in the reference categories (white male, not a college graduate, and a nonsmoker in the UDCA trial) by adherence score components are displayed in **Table 5**. An inverse relation between BMI categories and both 25(OH)D and 1,25(OH)$_2$D exhibited a dose-dependent trend (both comparisons, *P*-trend < 0.001). Similarly, a significant trend was seen for higher levels of physical activity and higher concentrations of both vitamin D metabolites (*P*-trend < 0.001). In contrast, any association or trend between diet component and either vitamin D metabolite was less clear. A diet score of 1 point was significantly associated with 25(OH)D with a significant overall trend (*P*-trend = 0.039). No significant association was observed between diet score and 1,25(OH)$_2$D. A significant trend was seen for increasing alcohol consumption and increasing concentrations of both 25(OH)D (*P*-trend = 0.009) and 1,25(OH)$_2$D (*P*-trend = 0.040).

Discussion

Greater adherence to nutrition and physical activity cancer prevention guidelines that have been developed by the ACS and other leading cancer organizations has been found to be associated with a reduced risk of overall cancer incidence and mortality, including some site-specific cancers (23). These guidelines are consistent with recommendations for the prevention of other major diseases as well, and, if followed, are associated with healthier lives overall (42–44). To our knowledge, no studies have assessed the relation between ACS guidelines for cancer prevention and circulating concentrations of vitamin D metabolites, which are biomarkers often linked to health outcomes (45). This current work offers evidence indicating that greater adherence to an overall lifestyle pattern as outlined by the ACS nutrition and physical activity cancer prevention guidelines is associated with higher concentrations of both 25(OH)D and 1,25(OH)$_2$D, based on a pooled sample of participants enrolled in one of 2 chemoprevention trials in Arizona. Furthermore, significant dose-dependent trends were seen for BMI, physical activity, and alcohol intake and both vitamin D metabolites. The lack of significant association between diet adherence scores and vitamin D was not unexpected, because the fruit, vegetable, grain, and red and processed meat variables included in the diet adherence score are not considered to be substantial dietary sources of vitamin D. The relation between alcohol intake and higher circulating concentrations of vitamin D has been reported previously, with suggestions of residual confounding or heavier consumers of alcohol having lifestyles favorable to higher concentrations of circulating vitamin D (46, 47). To our knowledge, there is no clear biological mechanism, and this warrants further investigation.

Concentrations of 25(OH)D can vary from many nonmodifiable factors, such as skin pigmentation, sex, genetic background, and season (30, 40). However, 25(OH)D also varies from modifiable factors, such as amount of sun exposure, dietary intake, and supplementation (20). Sun exposure increases vitamin D production, but also can cause skin damage or even skin cancer, the risk of which varies according to skin pigmentation and possibly body size (48, 49). Compared with normal-weight adults, obese adults have been found to have significantly lower concentrations of the vitamin D metabolite 25(OH)D, possibly because of lower dietary intake or

TABLE 4 Association between adherence score category and serum 25(OH)D status for pooled sample of Wheat Bran Fiber Supplement and Ursodeoxycholic Acid trial participants[1]

	Vitamin D status		
Adherence score category	Deficient (<20 ng/mL) (*n* = 296)	Insufficient (≥20 ng/mL and <30 ng/mL) (*n* = 575)	Sufficient (≥30 ng/mL) (*n* = 486)
Low (0–2)	1.00	1.00	1.00
Moderate (3–5)	1.00	1.76 (1.21, 2.57)	2.41 (1.58, 3.68)
High (6–8)	1.00	2.29 (1.35, 3.90)	4.37 (2.47, 7.71)

[1] Values are ORs (95% CIs) obtained from multinomial logistic regression adjusted for study, age, sex, race, education, and energy intake. 25(OH)D, 25-hydroxycholecalciferol.

TABLE 5 Mean serum concentrations of 25(OH)D and 1,25 $(OH)_2D$ by adherence score components for pooled sample of WBF and UDCA trial participants[1]

Score components	Overall population			
	n	25(OH)D, ng/mL	*n*	$1,25(OH)_2D$, pg/mL
Diet				
0	324	26.3 ± 1.1	315	32.5 ± 1.5
1	874	28.2 ± 1.1	538	33.9 ± 1.5
2	159	27.5 ± 1.3	1	50.0 ± 11.0[2]
P-trend		0.039		0.059
BMI, kg/m^2				
≥30	407	26.3 ± 1.1	267	32.5 ± 1.5
≥25 and <30	595	28.7 ± 1.1	367	34.4 ± 1.5
≥18.5 and <25	355	30.4 ± 1.2	220	36.7 ± 1.6
P-trend		<0.001		<0.001
Physical activity, MET-h/wk				
<8.75	549	26.3 ± 1.1	344	32.5 ± 1.5
≥8.75 and ≤17.5	341	26.8 ± 1.2	210	35.0 ± 1.6
>17.5	467	30.5 ± 1.2	300	36.0 ± 1.6
P-trend		<0.001		<0.001
Alcohol				
Heavy (mean 3.0 drinks/d)	126	26.3 ± 1.1	91	32.5 ± 1.5
Moderate (mean 0.5 drinks/d)	730	25.1 ± 0.8	458	29.8 ± 1.1
Never (0 drinks/d)	501	24.0 ± 0.8	305	29.3 ± 1.1
P-trend		0.009		0.040

[1] Values are means ± SEs computed from adjusted linear regression for individuals in reference categories (white male, not a college graduate, and nonsmoker in the UDCA trial) centered on mean age and energy intake. Adjusted for sex, age, race, education, smoking status, energy intake, and all other score components. $1,25(OH)_2D$ was not measured for the WBF supplement trial. MET-h, metabolic equivalent task hours; UDCA, ursodeoxycholic acid; WBF, wheat bran fiber; $1,25(OH)_2D$, 1α,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxycholecalciferol.
[2] Only 1 observation in the UDCA trial in which diet score = 2.

lesser exposure of skin to sunlight, volumetric dilution, or sequestration in adipose tissue (49–51). Healthy-weight adults with higher levels of physical activity are more likely to meet DRIs for vitamin D and other micronutrients than are overweight adults (52). Furthermore, several studies have suggested that obese adults may need higher doses of supplementation than normal do weight adults to achieve sufficient 25(OH)D status (12, 53).

A recent review of vitamin D supplementation trials estimates that 2990 IU/d is required to surpass deficient concentrations (20 ng/mL) of serum 25(OH)D in 97.5% of healthy individuals (13). The RDA for healthy adults aged 19–70 y is 600 IU, and it is 800 IU for those >70 y of age (1). However, it has been suggested that these recommendations have been miscalculated, are too low, and should be reconsidered (14). The means and SDs of 25(OH)D for selected large vitamin-D supplementation trials (54–60) presented in the review by Veugelers et al. (13), as well as a trial conducted by our group (57), are presented in **Table 6**. Three studies used dosages of 400 IU/d with follow-up times of 4, 48, and 108 wk, resulting in mean ± SD 25(OH)D concentrations of 28.3 ± 8.9 ng/mL in healthy men and women (57), and 36.9 ± 9.5 ng/mL (56) and 24.4 ± 12.2 ng/mL (60) in 2 separate studies of postmenopausal women. Dosages of 800 IU/d were used in 2 trials with a range of follow-up times from 13 to 156 wk, resulting in mean ± SD 25(OH)D concentrations of 28.39 ± 9.18 ng/mL and 29.91 ± 8.78 ng/mL in women (54, 58). In a study that evaluated the effect of a daily dose of 1000 IU in preventing new colorectal adenomas, healthy non-Hispanic white subjects aged 45–75 y had mean ± SD concentrations of 31.5 ± 8.9 ng/mL after 1 y (55). Comparably in our study, moderate and high adherence to the ACS guidelines demonstrated mean ± SD concentrations of 25(OH)D of 29.6 ± 0.5 ng/mL and 32.0 ± 0.8 ng/mL, respectively. Therefore, following the ACS guidelines could potentially increase 25(OH) D concentrations as much as or more than a supplement of 1000 IU/d. Improving vitamin D status through lifestyle modifications as opposed to supplementation allows for a strategy that would avoid any potential toxicity, such as renal calcifications (16), and is likely to incur other health benefits as well.

Less is known about lifestyle factors that may be associated with circulating concentrations of $1,25(OH)_2D$ (61). Few epidemiologic studies have evaluated the association between $1,25(OH)_2D$ and physical activity. One examined the effects of long-term aerobic exercise and ω-3 supplementation on bone health in postmenopausal women and found that $1,25(OH)_2D$ increased with the intervention (62). Similarly, in a study within the UDCA cohort included in the present study, moderate to vigorous physical activity was positively associated with 1,25 $(OH)_2D$, with women experiencing the greatest increase (21). Hibler et al. (21) suggested that the association between physical activity and vitamin D may be beyond sun exposure and driven

TABLE 6 Comparison of 25(OH)D concentrations in supplementation trials and adherence score category[1]

Study (reference)	Sample or population	Cholecalciferol dosage, IU/d	Follow-up, wk	Postsupplementation 25(OH)D,[2] ng/mL
Aloia et al., 2005 (54)	104 healthy postmenopausal African-American women, aged 50–75 y	800	13	28.39 ± 9.18
Baron et al., 2015 (55)	1755 healthy non-Hispanic white subjects, aged 45–75 y	1000 and/or 1200 mg Ca/d	52	31.5 ± 8.9
Dawson-Hughes et al., 1991 (56)	125 postmenopausal women	400 + 377 mg Ca/d	48	36.93 ± 9.46
Hibler, 2011 (57)	28 healthy adults	400	4	28.3 ± 8.9
Karkkainen et al., 2010 (58)	306 OSTPRE-FPS Finnish women, aged >65 y	800 + 1000 mg Ca/d	156	29.91 ± 8.78
Lappe et al., 2007 (59)	288 postmenopausal women in rural Nebraska	1100 + 1400–1500 mg Ca/d	288	38.50 ± 8.58
Schnatz et al., 2014 (60)	285 postmenopausal women, Women's Health Initiative	400 + 1000 mg Ca/d	104	24.38 ± 12.23
Current study	909 subjects moderately adherent to ACS guidelines	—	—	29.6 ± 0.5
Current study	233 subjects highly adherent to ACS guidelines	—	—	32.0 ± 0.8

[1] ACS, American Cancer Society; OSTPRE-FPS, Osteoporosis Risk Factor and Prevention Study–Fracture Prevention Study; 25(OH)D, 25-hydroxycholecalciferol.
[2] Values are means ± SDs.

by the role of 1,25$(OH)_2$D in bone health. It is also possible that increased physical activity exerts an effect on metabolism that itself results in higher production of vitamin D metabolites; however, any biological mechanism would be speculative at this time. BMI, the measure used to estimate body size in our study, has a well-known inverse relation with 25(OH)D, but evidence of its relation with 1,25$(OH)_2$D is limited. A statistically significant association between higher circulating concentrations of 1,25$(OH)_2$D and a lower risk of metabolic syndrome, which consists of waist circumference, TGs, blood pressure, glucose, and HDL cholesterol, was also reported in a sample population from the UDCA and WBF supplement cohorts (63).

The major strengths of the current study include the availability of data from a prospective cohort of >1300 participants with complete data on a wide range of available baseline nutrition, physical activity, and serum vitamin D metabolite data. However, even though the original trials were prospective cohorts, this secondary data analysis is cross-sectional in nature, with measurements coming from baseline assessments. Furthermore, only one measure of 25(OH)D was used for the assessment of vitamin D status, although previous findings suggest that single baseline 25(OH)D measurements provide reasonably representative measures of the biomarker (64). In addition, the “maintenance of a healthy weight throughout life” ACS guideline could not be precisely assessed because height and weight data were not available for earlier periods in life. Although the instruments used to collect lifestyle data asked for usual dietary consumption in the previous 12-mo period and the last 4 wk for physical activity, the reported behaviors may not be representative of the participants’ longer-term behaviors. Participants in this study had already had a colorectal adenoma removed, and may have changed their lifestyle habits after removal of their adenoma, which had to have occurred within the previous 6 mo before study enrollment, thus affecting the generalizability of the results. Although self-reports of physical activity and dietary and alcohol intake are susceptible to measurement error or misclassification bias, the frequency questionnaires used had been validated in the study sample. There is also the potential issue that the various healthy behaviors included in the ACS adherence score may cluster in individuals, making it difficult to separate the effect of the score components. Finally, circulating concentrations of vitamin D metabolites may merely be a biomarker of risk, or, in this case, an overall lifestyle pattern, and not necessarily a mechanism of action for disease risk (40). Nonetheless, these findings indicate the potential for increasing concentrations of vitamin D when the overall guidelines are more closely followed.

In summary, there remains a great deal of debate regarding vitamin D status and the strategy for best achieving sufficient concentrations, including the use and dosing of supplements. Our results suggest that following an overall pattern of healthy behaviors as recommended in the ACS Nutrition and Physical Activity Cancer Prevention guidelines may be associated with higher concentrations of both 25(OH)D and 1,25$(OH)_2$D. In addition, score components also demonstrated significant associations. Therefore, close adherence to the ACS nutrition and physical activity cancer prevention guidelines may be a viable public health strategy for increasing both 25(OH)D and 1,25 $(OH)_2$D concentrations.

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EAH designed, performed, and analyzed the supplement trial; LNK analyzed the secondary data; LNK and ETJ designed the secondary analysis and had primary responsibility for the final content; and all authors wrote the paper. All authors read and approved the final manuscript.

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