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Authors
Kositsawat, Jatupol
Kuchel, George A
Tooze, Janet A
et al.

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Vitamin D Insufficiency and Abnormal Hemoglobin A1c in Black and White Older Persons

Jatupol Kositsawat,[1] George A. Kuchel,[1] Janet A. Tooze,[2] Denise K. Houston,[3] Jane A. Cauley,[4] Stephen B. Kritchevsky,[3] Elsa S. Strotmeyer,[4] Alka M. Kanaya,[5] Tamara B. Harris,[6] Karen C. Johnson,[7] Lisa C. Barry[8]; for the Health ABC

[1]UCONN Center on Aging, Department of Medicine, University of Connecticut Health Center, Farmington.
[2]Department of Biostatistical Sciences, Division of Public Health Sciences and
[3]Section on Gerontology & Geriatric Medicine, Sticht Center on Aging, Wake Forest School of Medicine, Winston-Salem, North Carolina.
[4]Department of Epidemiology, Center for Aging and Population Health, Graduate School of Public Health, University of Pittsburgh, Pennsylvania.
[5]Division of General Internal Medicine, University of California, San Francisco.
[6]Intramural Research Program, Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, Maryland.
[7]Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis.
[8]UCONN Center on Aging, Department of Psychiatry, University of Connecticut Health Center, Farmington.

Address correspondence to Jatupol Kositsawat, MD, DMSc, MPH, UCONN Center on Aging, Department of Medicine, University of Connecticut Health Center, Farmington, CT 06030-6232. Email: kositsawat@uchc.edu

Background. Although vitamin D has been mechanistically linked to insulin secretion and sensitivity, it remains unclear whether low 25-hydroxyvitamin D levels confer an increased risk of impaired glucose metabolism. We evaluated the relationship between vitamin D insufficiency (25-hydroxyvitamin D < 20 ng/mL) and abnormal hemoglobin A1c (A1c) (≥6.5%) in community-dwelling older persons and examined whether this relationship differed according to race.

Methods. Participants were 2,193 persons of age 70–79 years at Year 1 (52% women; 37% black) in the Health, Aging, and Body Composition study who had clinic visits at Years 2 and 4. Logistic regression analyses, adjusted for potential confounders, were used to evaluate the association between vitamin D insufficiency and abnormal A1c 2 years later. Interaction of race and vitamin D insufficiency was tested.

Results. A total of 665 (30%) and 301 (14%) of the participants had vitamin D insufficiency at Year 2 and abnormal A1c at Year 4, respectively. After controlling for demographics, other potential confounders, and diabetes status at Year 4 (n = 477 diabetics), we found that vitamin D insufficiency was associated with an increased likelihood of having abnormal A1c (odds ratio = 1.56; 95% CI: 1.03–2.37). We also found that this relationship persisted among the 1,765 participants without diabetes in Year 2 (odds ratio = 2.33; 95% CI: 1.00–5.40). Findings did not differ by race.

Conclusions. Vitamin D insufficiency was associated with abnormal A1c levels among black and white older persons independent of diabetes status. Future studies are needed to establish the temporal relationship between vitamin D and A1c in diverse samples of older persons.

Key Words: Vitamin D—Hemoglobin A1c—Older persons.

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THE 2011 Institute of Medicine report indicated that current evidence regarding the association between vitamin D and diabetes remains inconsistent and inconclusive (1,2). However, additional studies have found that low 25-hydroxyvitamin D (25(OH)D) levels are associated with increased incidence of diabetes (3,4) and metabolic syndrome (5).

Hemoglobin A1c (A1c) is an important indicator of glycemic control and has recently been introduced to diagnose diabetes. Earlier cross-sectional studies have shown an inverse association between 25(OH)D levels and A1c (6,7). In addition, a case series examining the possible benefits of vitamin D3 supplementation showed improvement in A1c levels in patients with diabetes who had 25(OH)D levels < 15 ng/mL prior to supplementation (8). Moreover, although race is known to influence the association between vitamin D status and health (9–14), data relating vitamin D and A1c in the U.S. black and white older persons remain scarce. Such knowledge could help clinicians to target those individuals who are at greatest risk of both vitamin D insufficiency and diabetes and who may be most likely to benefit from vitamin D supplementation.

The objective of our study was to evaluate the association between vitamin D insufficiency (25(OH)D <20 ng/mL) (15) and abnormal A1c (≥6.5%) in a large cohort of

community-dwelling older persons in the United States, with an effort to determine whether this relationship is related to a diagnosis of diabetes or influenced by race.

Methods

Study Population

Participants were enrolled in the Health, Aging, and Body Composition Study (Heath ABC), a longitudinal study of 3,075 community dwelling persons age 70–79 years at Year 1. The cohort has been described elsewhere (16). In brief, a random sample of white Medicare-eligible residents (N = 1,794) and all black Medicare-eligible residents (N = 1,281) from Memphis, Tennessee, and Pittsburgh, Pennsylvania, were enrolled between April 1997 and June 1998. At Year 1, all participants reported no difficulty walking 0.25 miles, walking up 10 steps without resting, and performing basic activities of daily living.

Data Collection

Data for the present study were collected during face-to-face interviews in Year 2 (1998–1999) and clinic visits in Years 2 and 4 (2000–2001) of the Health ABC study. Demographic data, including age (years), sex, and race, were collected during the face-to-face interview. During this interview, participants were also asked total minutes of walking for exercise in the previous week, categorized as 0, 1–149, and ≥150 min/wk. Participants were considered as having diabetes if they reported a physician diagnosis of diabetes, and/or if they were taking insulin or an oral diabetes medication, and/or if their fasting plasma glucose was ≥126 mg/dl. Body mass index (kg/m^2) was calculated from measured weight and height collected during the Year 2 and Year 1 clinic assessments, respectively. Body mass index was then categorized as >30 kg/m^2 (obese), 25–30 kg/m^2 (overweight), and <25 kg/m^2 (normal). At the Year 2 clinic visit, data were collected on use of vitamin D supplements and multivitamins in the past 2 weeks, with use of each categorized as yes or no. Vitamin D containing supplements were defined as supplements that contained no more than three ingredients, one of which was vitamin D. If a supplement contained more than three vitamin or mineral ingredients, it was considered to be a multivitamin. To account for seasonal variation in serum 25(OH)D, we included a four-category variable indicating the season during which the blood sample was obtained: Spring (March–May), Summer (June–August), Fall (September–November), or Winter (December–February).

Blood samples collected during the Year 2 clinic visit were used to assess serum 25(OH)D and plasma intact parathyroid hormone (PTH) (17). Serum 25(OH)D, the independent variable in this study, was analyzed by a two-step radioimmunoassay kit (DIASORIN, 25-hydroxyvitamin D ^{125}I RIA kit, no. 68100, Stillwater, MN). The interassay coefficient of variation for 25(OH)D was 6.78% for log-transformed values. Plasma intact PTH was measured with a two-site immunoradiometric assay (DIASORIN, N-tact PTH SP kit, no. 26100, no. 68100, Stillwater, MN). The interassay coefficient of variation for PTH was 8.6%. The outcome variable, A1c level, was determined from blood samples collected during the Year 4 clinic visit and was assessed by the Tosoh 2.2 Plus automated analyzer that utilizes nonporous ion-exchange high performance liquid chromatography for separation of A1c (17). Separation was performed without interference from Schiff base (labile A1c), lipemia, or temperature fluctuations. Because vitamin D and A1c levels were highly skewed to the right, we operationalized them as binary variables, with vitamin D insufficiency defined as 25(OH)D levels <20 ng/mL (15) and abnormal A1c defined as A1c level ≥6.5%. Plasma PTH was operationalized as a continuous variable.

Statistical Analysis

Our sample consisted of the 2,322 Health ABC participants who had 25(OH)D data (n = 2,793) and A1c data (n = 2,388) from the clinic visits in Years 2 and 4, respectively. Of these, 129 participants were excluded due to missing data for the covariates (117 missing multivitamin use, 1 missing PTH, 6 missing multivitamin and vitamin D supplement use, and 5 missing walking category), resulting in an analytic sample of 2,193 participants (52% women; 37% black). We determined the characteristics of the sample at Year 2 using descriptive statistics. We then compared the characteristics between blacks and whites, using chi-square tests for categorical variables and t tests for continuous variables.

We determined the association between Year 2 vitamin D insufficiency and abnormal A1c at Year 4 using multivariable logistic regression. The first model was adjusted for sex, age, and field site, with subsequent models adjusted for other potential confounders. In addition to the aforementioned factors, the second model also adjusted for race, total minutes walking per week categories, body mass index categories, PTH, season of blood collection, vitamin D supplement use, and multivitamin use. Lastly, diabetes status at Year 4 was added to the third model. We used diabetes status at Year 4 instead of Year 2 to account for those participants who developed diabetes in 2 years between the Year 2 and Year 4 assessments. To formally test for an interaction between vitamin D insufficiency and race, we included a vitamin D insufficiency by race interaction term in separate logistic regression models. We also conducted the above analyses separately for the sample of participants without diabetes at Year 2 (n = 1,765). We reran sensitivity analyses using linear regression and substituting vitamin D and A1c as continuous variables. Furthermore, we tested for mediation by Year 4 diabetes status in the sample of participants without diabetes in Year 2 (18,19). All statistical analyses

were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

Results

Table 1 presents the Year 2 participant characteristics overall and according to race. A total of 665 (30.3%) and 428 (19.5%) of the participants had vitamin D insufficiency and diabetes, respectively. The majority of participants were white, with a slight female preponderance. Approximately 39% of the participants reported that they spend no time walking for exercise each week and more than half of the participants had a body mass index indicating overweight or obese. One-third of the participants reported multivitamin use and 11% used vitamin D supplements. Compared with blacks, fewer whites had vitamin D insufficiency and diabetes at Year 2 and had lower PTH levels (all p values <.001). Whites were more likely than blacks to use multivitamins and vitamin D supplements, spent more time walking, and were less likely to be obese (all p values <.001).

There was considerable overlap between those with abnormal A1c at Year 4 and diabetes in that same year. At Year 4, 301 (13.7%) participants had abnormal A1c. Of these, approximately 92.7% had diabetes. Of the 477 (21.8%) participants with diabetes, 58.5% had abnormal A1c, reflecting good glycemic control in nearly half of the diabetic participants.

Table 2 presents the independent associations between vitamin D insufficiency and abnormal A1c. After adjusting for sex, age, and field site, participants with vitamin D insufficiency were more likely to have abnormal A1c than participants without vitamin D insufficiency (odds ratio [OR] = 2.50; 95% CI: 1.94–3.21). This association persisted when race and other potential confounders, including diabetes status at Year 4, were included in the model (OR = 1.56; 95% CI: 1.03–2.37). Blacks were also more likely to have abnormal A1c compared with whites (OR = 2.55; 95% CI: 1.72–3.79). The interaction term of vitamin D insufficiency × race was not statistically significant in any model (all p values >.05). As shown in Table 3, after limiting the sample to the 1,765 participants who did not have diabetes in Year 2, vitamin D insufficiency was still associated with an increased likelihood of having abnormal A1c in Year 4 after adjusting for sex, age, and field site (OR = 2.59; 95% CI: 1.36–4.92). This association also persisted in the fully adjusted model (OR = 2.33; 95%CI: 1.00–5.40). Results from the linear regression models were consistent with the findings from the logistic models. Finally, diabetes in Year 4 did not emerge as a mediator of the association between vitamin D insufficiency and abnormal A1c (data available upon request).

Discussion

Using a large sample of well-functioning community-dwelling black and white older persons, we found that participants with serum 25(OH)D concentrations lower than 20 ng/mL were more likely to have abnormal A1c ≥6.5%

Table 1. Participant Characteristics from Year 2

Variables	Overall (N = 2,193)	Whites (n = 1,389)	Blacks (n = 804)	p Value
Age (y), mean (*SD*)	74.6 (2.9)	74.7 (2.9)	74.4 (2.9)	.03
Female sex, *n* (%)	1,147 (52.3)	669 (48.2)	478 (59.5)	<.001
Memphis site, *n* (%)	1,083 (49.4)	705 (50.8)	378 (47.0)	.09
Minutes walking/wk, *n* (%)				<.001
0 min	856 (39.0)	452 (32.5)	404 (50.3)	
1–149 min	713 (32.5)	473 (34.1)	240 (29.9)	
≥150 min	624 (28.5)	464 (33.4)	160 (19.9)	
BMI categories, *n* (%)				<.001
Obese (>30 kg/m^2)	545 (24.8)	249 (17.9)	296 (36.8)	
Overweight (25–30 kg/m^2)	938 (42.8)	635 (45.7)	303 (37.7)	
Normal (<25 kg/m^2)	710 (32.4)	505 (36.4)	205 (25.5)	
Vitamin D supplement use, *n* (%)	252 (11.5)	199 (14.3)	53 (6.6)	<.001
Multivitamin use, *n* (%)	849 (38.7)	636 (45.8)	213 (26.5)	<.001
Season, *n* (%)				.006
Spring (March–May)	666 (30.4)	412 (29.7)	254 (31.6)	
Summer (June–August)	396 (18.1)	248 (17.9)	148 (18.4)	
Fall (September–November)	562 (25.6)	335 (24.1)	227 (28.2)	
Winter (December–February)	569 (26.0)	394 (28.4)	175 (21.8)	
Parathyroid hormone (pg/mL), mean (*SD*)	37.7 (22.2)	34.5 (16.3)	45.1 (33.1)	<.001
Vitamin D insufficiency (<20 ng/mL), *n* (%)	665 (30.3)	245 (17.6)	420 (52.2)	<.001
Prevalence of diabetes at Year 2, *n* (%)	428 (19.5)	206 (14.8)	222 (27.6)	<.001
A1c* (%), mean (*SD*)	5.7 (1.0)	5.5 (0.8)	6.0 (1.2)	<.001
25(OH)D (ng/mL), mean (*SD*)	26.3 (11.5)	29.3 (11.0)	21.2 (10.7)	<.001

Notes: 25(OH)D = 25-hydroxyvitamin D; BMI = body mass index.
*Year 4.

Table 2. Logistic Regression Analyses Evaluating the Association Between Vitamin D Insufficiency (25-OH Vitamin D (25(OH)D) Levels <20 ng/mL) at Year 2 and Abnormal Hemoglobin A1c (A1c) Levels (≥6.5%) at Year 4

	Model 1*	Model 2†	Model 3‡
	Odds Ratio (95% CI)		
Overall (N = 2,193)			
25(OH)D < 20 ng/mL	2.50 (1.94, 3.21)	1.45 (1.08, 1.96)	1.56 (1.03, 2.37)
Female sex	0.61 (0.47, 0.78)	0.54 (0.41, 0.71)	0.74 (0.51, 1.08)
Age	0.96 (0.92, 1.00)	0.98 (0.93, 1.02)	0.95 (0.89, 0.86)
Memphis site	0.85 (0.66, 1.09)	0.89 (0.68, 1.15)	0.64 (0.42, 2.36)
BMI categories			
>30 kg/m^2		3.20 (2.19, 4.69)	1.38 (0.83, 2.29)
25–30 kg/m^2		2.14 (1.49, 3.07)	1.59 (0.98, 2.56)
<25 kg/m^2		1.00	1.00
Minutes walking/wk			
≥150		0.78 (0.56, 1.10)	0.73 (0.46, 1.17)
1–149		0.82 (0.61, 1.10)	0.88 (0.58, 1.34)
0		1.00	1.00
No vitamin D supplement use		1.93 (1.04, 3.58)	2.11 (1.00, 4.44)
No multivitamin use		1.00 (0.75, 1.35)	0.82 (0.55, 1.23)
Season			
Spring (March–May)		0.90 (0.64, 1.26)	1.00 (0.63, 1.59)
Summer (June–August)		0.93 (0.62, 1.38)	1.23 (0.71, 2.13)
Fall (September–November)		0.82 (0.57, 1.18)	1.02 (0.61, 1.71)
Winter (December–February)		1.00	1.00
PTH		1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
Black race		2.64 (1.98, 3.51)	2.55 (1.72, 3.79)
Diabetes status at Year 4			105.7 (65.5, 170.7)

Notes: BMI = body mass index; CI = confidence interval; PTH = parathyroid hormone.
*Adjusted for sex, age, and recruitment site.
†Adjusted for confounders in Model 1 and BMI categories, minutes walking/wk categories, vitamin D supplement use, multivitamin use, season, PTH, and race.
‡Adjusted for confounders in Model 2 and diabetes status at Year 4.

compared with participants who had higher serum 25(OH) D concentrations, independent of diabetes status. This finding remained and was somewhat stronger when we limited the sample to those without diabetes at Year 2.The relationship between vitamin D insufficiency and abnormal A1c did not differ according to race.

The association between vitamin D and glucose homeostasis has several plausible biological mechanisms. Pancreatic β-islet cells possess receptors for 1,25-$(OH)_2$ vitamin D, the physiologically active form of vitamin D (20). In addition, they also express 1α-hydroxylase that converts biologically inert 25(OH)D to active 1,25-$(OH)_2$ vitamin D. Thus, vitamin D deficiency can result in the reduction of islet β-cell calcium, inhibiting insulin secretion. Another potential mechanism involves insulin sensitivity which can be estimated using the homeostatic model assessment of insulin resistance (a reliable surrogate for insulin resistance), glucose intolerance, and presence of metabolic syndrome (5,12,21–23). All these measures have been reported to identify future diabetes. Proposed direct mechanistic links include the vitamin D response element found in the human insulin receptor gene promoter influencing insulin receptor expression (24). Moreover, the addition of 1,25-$(OH)_2$ vitamin D3 induces insulin receptor gene transcription and protein expression in vitro (25). Beyond such direct effects, vitamin D may also facilitate insulin-mediated responses through suppression of inflammation (a strong predictor of type 2 diabetes) (26).

The association between vitamin D insufficiency and abnormal A1c shown in this study provides evidence for the role of vitamin D in glucose homeostasis. Our findings were consistent with previous cross-sectional studies. In the National Health and Nutrition Examination Survey, an inverse relationship between 25(OH)D and A1c was reported among those aged 35–74 years and among those without a reported history of diabetes (7). Additionally, findings from the Health Survey for England found an association between low 25(OH)D levels and hyperglycemia (A1c ≥6.5%) among participants aged ≥65 years, regardless of diabetes status (6). Because A1c was not collected at Year 2, this precluded our ability to establish a temporal association between vitamin D insufficiency and abnormal A1c. However, we found that vitamin D insufficiency in Year 2 was associated with abnormal A1c 2 years later among those without diabetes, and therefore most likely had normal A1c, in Year 2. These results may indicate a beneficial effect of sufficient 25(OH)D levels on glycemic control in older black and white persons. However, additional research is needed to confirm this finding.

Despite prior research indicating that blacks have lower levels of 25(OH)D and higher levels of A1c than whites (17,27,28), we did not find that the relationship between

Table 3. Logistic Regression Analyses Evaluating the Association Between Vitamin D Insufficiency 25(OH)D Levels < 20 ng/mL) at Year 2 and Abnormal Hemoglobin A1c (A1c) Levels (≥6.5%) at Year 4 in Participants Without Diabetes at Year 2

	Model 1*	Model 2†	Model 3‡
	Odds Ratio (95% CI)		
Overall (N = 1,765)			
25(OH)D < 20 ng/mL	2.59 (1.36, 4.92)	1.94 (0.90, 4.18)	2.33 (1.00, 5.40)
Female	0.87 (0.46, 1.67)	0.87 (0.43, 1.73)	0.94 (0.44, 2.02)
Age	0.92 (0.82, 1.04)	0.95 (0.85, 1.07)	0.94 (0.83, 1.07)
Memphis site	0.83 (0.43, 1.57)	0.95 (0.49, 1.85)	0.84 (0.41, 1.75)
BMI categories			
>30 kg/m^2		5.51 (1.53, 19.9)	2.91 (0.74, 11.5)
25–30 kg/m^2		5.92 (1.75, 20.1)	4.96 (1.40, 17.6)
<25 kg/m^2		1.00	1.00
Minutes walking/wk			
≥150		0.89 (0.37, 2.17)	1.09 (0.42, 2.85)
1–149		1.10 (0.52, 2.31)	1.06 (0.47, 2.42)
0		1.00	1.00
No vitamin D supplement use		1.65 (0.37, 7.32)	1.58 (0.32, 7.80)
No multivitamin use		0.67 (0.32, 1.40)	0.70 (0.31, 1.55)
Season			
Spring (March–May)		1.27 (0.51, 3.16)	1.43 (0.52, 3.96)
Summer (June–August)		1.65 (0.61, 4.45)	2.36 (0.79, 7.08)
Fall (September–November)		1.04 (0.39, 2.81)	1.20 (0.40, 3.65)
Winter (December–February)		1.00	1.00
PTH		1.00 (0.99, 1.01)	1.00 (0.98, 1.00)
Black race		2.55 (1.22, 5.30)	2.51 (1.12, 5.59)
Diabetes status at Year 4			38.0 (16.8, 85.8)

Notes: 25(OH)D = 25-OH Vitamin D; BMI = body mass index; PTH = parathyroid hormone.
*Adjusted for sex, age, and recruitment site.
†Adjusted for confounders in Model 1 and BMI categories, minutes walking/wk categories, vitamin D supplement use, multivitamin use, season, PTH, and race.
‡Adjusted for confounders in Model 2 and diabetes status at Year 4.

vitamin D insufficiency and abnormal A1c differed according to race. In contrast to our findings, a differential effect of race on other health outcomes has been shown. Cross-sectional findings from the National Health and Nutrition Examination Survey data found an inverse association between 25(OH)D and diabetes (12) and an association between 25(OH)D and bone mineral density (10) in whites and but no significant associations in blacks. From the Women's Health Initiative study, whites with increasing levels of 25(OH)D had a lower risk of fracture, with the opposite finding among blacks (9). Higher incident coronary heart disease events were found in white but not in black participants with low 25(OH)D (11). In addition, race-related differences in 25(OH)D levels explained only about half of the increased hypertension prevalence in blacks compared with whites (13), thereby suggesting that there is a differential effect of race on association of 25(OH)D and hypertension prevalence.

Differences in population, methodology, and definitions may account for our negative racial findings compared with other studies evaluating the impact of race on health benefits of vitamin D on both diabetes and other health outcomes. For example, the question of whether cutoffs for abnormal A1c, our primary outcome measure, should differ between blacks and whites remains the subject of an ongoing debate. Although A1c has been used to diagnose diabetes with the same diagnostic threshold of 6.5% in all races (28), A1c in blacks was higher than whites in any given glycemic level and thus a higher cut-off may be needed (29). Although reasons for race differences in A1c remain unconfirmed, factors other than glucose levels, such as red blood cell survival and hemoglobinopathies, have also been proposed (30). In a counterpoint to this argument, the prevalence of retinopathy begins to increase at a lower A1c level in blacks than in whites, thus not supporting the argument for increasing the diagnostic threshold for abnormal A1c in blacks (31). In addition, recent research indicates lower levels of vitamin D binding protein in blacks compared with whites. This difference, which occurs through a genetic polymorphism that leads to comparable levels of bioavailable vitamin D in blacks and whites, may also help to explain blacks' lower total levels of vitamin D without clinical manifestations of vitamin D deficiency (32).

Our study has several limitations that should be noted. Because A1c was not collected at Year 2, we could not confirm if participants already had abnormal A1c when 25(OH)D was measured. Consequently, we could not determine a temporal relationship between vitamin D insufficiency and abnormal A1c. However, to mitigate this challenge, we included a sensitivity analysis of participants without diabetes at Year 2 and showed an association with abnormal A1c 2 years later. Second, because the cohort included only

well-functioning participants at enrollment, the results may not be applicable to the general older population. Third, although we adjusted for seasonal variation, 25(OH)D levels were derived from only a single measurement. Similarly, within-person variation in circulating 25(OH)D levels also may vary. However, recent evidence indicates that a single, baseline 25(OH)D measurement provides a reasonably representative measure of 25(OH)D for both white and black adults (33). Lastly, there may be some concerns regarding the overlap of diabetes and abnormal A1c in the outcome and that this may cause the model to be unstable. However, to include both diabetes and abnormal A1c at Year 4 as one outcome would not be justifiable due to the fact that only 59% of participants with diabetes had abnormal A1c. In addition, the analysis removing diabetes from the model also showed significance of the association. Despite these limitations, the large and racially diverse Health ABC cohort provided a unique opportunity to rigorously evaluate our research questions while controlling for a range of important potential confounders, many of which were unable to be included in prior studies (6,7).

In conclusion, our findings confirm that vitamin D insufficiency is associated with abnormal A1c. These results highlight the potential role of low vitamin D levels in poor glycemic control and provide support for future studies to evaluate the longitudinal effect of vitamin D on glycemic control. Furthermore, our findings encourage the development of clinical trials to determine if vitamin D supplementation improves glycemic control through improved A1c levels.

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References

1. Institute of Medicine. *Dietary reference intakes for calcium and vitamin D*. http://books.nap.edu/openbook.php?record_id=13050. Accessed February 20, 2013.
2. Shapses SA, Manson JE. Vitamin D and prevention of cardiovascular disease and diabetes: why the evidence falls short. *JAMA*. 2011;305:2565–2566. doi:10.1001/jama.2011.881
3. Munger KL, Levin LI, Massa J, Horst R, Orban T, Ascherio A. Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel. *Am J Epidemiol*. 2013;177:411–419. doi:10.1093/aje/kws243
4. Pittas AG, Nelson J, Mitri J, et al.; Diabetes Prevention Program Research Group. Plasma 25-hydroxyvitamin D and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program. *Diabetes Care*. 2012;35:565–573. doi:10.2337/dc11-1795
5. Gagnon C, Lu ZX, Magliano DJ, et al. Low serum 25-hydroxyvitamin D is associated with increased risk of the development of the metabolic syndrome at five years: results from a national, population-based prospective study (The Australian Diabetes, Obesity and Lifestyle Study: AusDiab). *J Clin Endocrinol. Metabol*. 2012;97:1953–1961. doi:10.1210/jc.2011-3187
6. Hirani V. Relationship between vitamin D and hyperglycemia in older people from a nationally representative population survey. *J Am Geriatr Soc*. 2011;59:1786–1792. doi:10.1111/j.1532-5415.2011.03590.x
7. Kositsawat J, Freeman VL, Gerber BS, Geraci S. Association of A1C levels with vitamin D status in U.S. adults: data from the National Health and Nutrition Examination Survey. *Diabetes Care*. 2010;33:1236–1238. doi:10.2337/dc09-2150
8. Schwalfenberg G. Vitamin D and diabetes: improvement of glycemic control with vitamin D3 repletion. *Can Fam Physician*. 2008;54:864–866.
9. Cauley JA, Danielson ME, Boudreau R, et al. Serum 25-hydroxyvitamin D and clinical fracture risk in a multiethnic cohort of women: the Women's Health Initiative (WHI). *J Bone Miner Res*. 2011;26:2378–2388. doi:10.1002/jbmr.449
10. Gutiérrez OM, Farwell WR, Kermah D, Taylor EN. Racial differences in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey. *Osteoporos Int*. 2011;22:1745–1753. doi:10.1007/s00198-010-1383-2
11. Robinson-Cohen C, Hoofnagle AN, Ix JH, et al. Racial differences in the association of serum 25-hydroxyvitamin D concentration with coronary heart disease events. *JAMA*. 2013;310:179–188. doi:10.1001/jama.2013.7228
12. Scragg R, Sowers M, Bell C; Third National Health and Nutrition Examination Survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care*. 2004;27:2813–2818.
13. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens*. 2007;20:713–719. doi:10.1016/j.amjhyper.2007.01.01
14. Kritchevsky SB, Tooze JA, Neiberg RH, et al.; Health ABC Study. 25-Hydroxyvitamin D, parathyroid hormone, and mortality in black and white older adults: the health ABC study. *J Clin Endocrinol Metab*. 2012;97:4156–4165. doi:10.1210/jc.2012-1551
15. Looker AC, Johnson CL, Lacher DA, et al. *Vitamin D status: United States, 2001–2006*.http://www.cdc.gov/nchs/data/databriefs/db59.htm Accessed August 6, 2013.
16. Newman AB, Haggerty CL, Kritchevsky SB, Nevitt MC, Simonsick EM; Health ABC Collaborative Research Group. Walking performance and cardiovascular response: associations with age and morbidity–the Health, Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci*. 2003;58:715–720.
17. Shea MK, Houston DK, Tooze JA, et al.; Health, Aging and Body Composition Study. Correlates and prevalence of insufficient 25-hydroxyvitamin D status in black and white older adults: the health, aging and body composition study. *J Am Geriatr Soc*. 2011;59:1165–1174. doi:10.1111/j.1532-5415.2011.03476.x
18. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Meth*. 2013;18:137–150. doi:10.1037/a0031034
19. VanderWeele TJ. Marginal structural models for the estimation of direct and indirect effects. *Epidemiology*. 2009;20:18–26. doi:10.1097/EDE.0b013e31818f69ce
20. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. *Science*. 1980;209:823–825.
21. Forouhi NG, Luan J, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin D is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990–2000. *Diabetes*. 2008;57:2619–2625. doi:10.2337/db08-0593

22. Holick MF. Diabetes and the vitamin d connection. *Curr Diab Rep*. 2008;8:393–398.
23. Hyppönen E, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes*. 2008;57:298–305. doi:10.2337/db07-1122
24. Maestro B, Davila N, Carranza MC, Calle C. Identification of a vitamin D response element in the human insulin receptor gene promoter. *J Steroid Biochem Mol Biol*. 2003;84:223–230.
25. Maestro B, Campion J, Davila N, Calle C. Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. *Endocr J*. 2000;47:383–391.
26. Neyestani TR, Nikooyeh B, Alavi-Majd H, et al. Improvement of vitamin D status via daily intake of fortified yogurt drink either with or without extra calcium ameliorates systemic inflammatory biomarkers, including adipokines, in the subjects with type 2 diabetes. *J Clin Endocrinol Metab*. 2012;97:2005–2011. doi:10.1210/jc.2011-3465
27. Lipska KJ, De Rekeneire N, Van Ness PH, et al. Identifying dysglycemic states in older adults: implications of the emerging use of hemoglobin A1c. *J Clin Endocrinol Metab*. 2010;95:5289–5295. doi:10.1210/jc.2010-1171
28. Nathan DM, Balkau B, Bonora E, et al. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care*. 2009;32:1327–1334. doi:10.2337/dc09-9033
29. Sacks DB. A1C versus glucose testing: a comparison. *Diabetes Care*. 2011;34:518–523. doi:10.2337/dc10-1546
30. Herman WH, Cohen RM. Racial and ethnic differences in the relationship between HbA1c and blood glucose: implications for the diagnosis of diabetes. *J Clin Endocrinol Metab*. 2012;97:1067–1072. doi:10.1210/jc.2011-1894
31. Tsugawa Y, Mukamal KJ, Davis RB, Taylor WC, Wee CC. Should the hemoglobin A1c diagnostic cutoff differ between blacks and whites? A cross-sectional study. *Ann Intern Med*. 2012;157:153–159. doi:10.7326/0003-4819-157-3-201208070-00004
32. Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med*. 2013;369:1991–2000. doi:10.1056/NEJMoa1306357
33. Sonderman JS, Munro HM, Blot WJ, Signorello LB. Reproducibility of serum 25-hydroxyvitamin d and vitamin D-binding protein levels over time in a prospective cohort study of black and white adults. *Am J Epidemiol*. 2012;176:615–621. doi:10.1093/aje/kws141