ABSTRACT
African Americans have higher rates of type 2 diabetes (T2D) and some forms of cardiovascular disease (CVD) than do European Americans. African Americans also have much higher rates of vitamin D deficiency. There is emerging evidence that vitamin D deficiency may be a risk factor for hypertension, T2D, and CVD, but the extent to which racial disparities in disease rates are explained by racial differences in vitamin D status is uncertain. Despite a large number of observational studies and a limited number of clinical trials that examined 25-hydroxyvitamin D [25(OH)D] concentrations as a potential determinant of CVD and T2D or its precursors, it remains uncertain whether improving vitamin D status would reduce risk of these conditions in the general US population or in African Americans specifically. However, if the associations reported from the observational studies are of the estimated magnitudes and causal, vitamin D supplementation could potentially have a strong preventive effect on some of these conditions and could reduce race-related disparities in their prevalence. Because of the low 25(OH)D concentrations of many, if not most, African Americans, and the low risk associated with vitamin D supplementation, it is important to obtain more definitive answers to these questions. *Am J Clin Nutr* doi: 10.3945/ajcn.110.003491.

INTRODUCTION
Hypertension, stroke, and diabetes are more prevalent (*Table 1*), and deaths from major cardiovascular diseases (CVDs) and diabetes are substantially higher (*Table 2*), in African Americans than in European Americans. Reasons for this disparity are unclear. Some of these differences may be explained by a higher prevalence of obesity in African American women (*Table 1*). Another potential explanation is the much higher rate of vitamin D deficiency in African Americans, in both men and women. Emerging evidence suggested that vitamin D deficiency may be an important risk factor for CVD and type 2 diabetes (T2D). The purpose of this article was to use current evidence to discuss the possibility that low vitamin D concentrations in African Americans increase risk of these conditions and 2) contribute to the race-related disparities in their prevalence.

VITAMIN D ACQUISITION AND METABOLISM
Vitamin D is produced in the body when the skin is exposed to ultraviolet B light. It enters the circulation and is converted in the liver to 25-hydroxyvitamin D [25(OH)D], which is the metabolite that best reflects the acquisition of vitamin D over preceding weeks. 25(OH)D is converted in the kidney to the most biologically active metabolite, 1,25-dihydroxyvitamin D, which is a secosteroid hormone that influences many physiologic processes including, but not limited to, calcium absorption and skeletal mineralization. 25(OH)D is also converted to 1,25-dihydroxyvitamin in many norennal cells where it exerts local effects that appear to include antinflammatory and immune-regulatory actions. Sunlight exposure is the main source of vitamin D for most people, but the vitamin can also be obtained in small amounts from a limited number of natural and fortified foods and in greater amounts from vitamin supplements. Substantial evidence shows that, compared with European Americans, African Americans have lower blood concentrations of 25(OH)D, which are the accepted clinical indicator of vitamin D status (3). This likely results from multiple factors including genetics [eg, variants of the vitamin D binding protein gene (4)], higher rates of obesity (5), modestly lower vitamin D intake (6), and skin pigmentation. Obesity is an important contributor to vitamin D deficiency because it reduces the increase in 25(OH)D concentrations that occurs with the oral consumption of vitamin D (7) and perhaps also because vitamin D acquired from the sun and diet may be sequestered in fat tissue and, thus, made unavailable to the circulation (8). Skin pigmentation affects vitamin D status because melanin, which is the predominant pigment, is an effective sunscreen that protects the skin from sun damage but, like exogenous sunscreens, also reduces vitamin D production in the skin. Thus, although European Americans and African Americans show seasonal changes in 25(OH)D concentrations that are commensurate with reduced and less-effective ultraviolet B exposure in the winter, the summer-related increases in 25(OH)D concentrations of African Americans, especially African Americans in the northern states, are substantially lower than

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ASSOCIATIONS OF VITAMIN D STATUS WITH CHRONIC HEALTH CONDITIONS

There is some controversy as to the optimal blood concentration for 25(OH)D for the prevention of chronic health conditions, but most estimates, based largely on studies in older, predominantly white populations, range between 50 and 80 nmol/L. The Third National Health and Nutrition Examination Survey (NHANES III) showed that >60% of non-Hispanic blacks compared with <30% of non-Hispanic whites in the United States have 25(OH)D concentrations below this range (3). However, there is little direct evidence that low vitamin D concentrations have had negative consequences with respect to disease risk in African Americans. A recent clinical trial in 280 postmenopausal African American women tested vitamin D supplementation to prevent bone loss (11). Baseline 25(OH)D concentrations of the study participants averaged 43 and 48 nmol/L in the supplemented and placebo groups, respectively, and the authors observed no benefit of supplementation (20–50 μg vitamin D3/d) on changes in bone mineral density over 3 y. Some evidence suggested that African Americans may have a relative resistance to the resorptive skeletal effects of parathyroid hormone (12), and thus, decreases in parathyroid hormone concentrations that occur with vitamin D supplementation may fail to provide a benefit in this group as it appears to do in others. However, because mechanisms relating vitamin D status to nonskeletal conditions, including CVD and T2D, may differ from those affecting bone, this study did not address potential benefits of improved vitamin D status on these conditions in African Americans.

Evidence that vitamin D deficiency might increase CVD and T2D risk in the US population comes largely from animal studies and observational studies in humans. A recent systematic review and meta-analysis of observational studies that involved 99,745 study participants examined the association of 25(OH)D concentrations with peripheral arterial disease (PAD), which is a consequence of atherosclerosis and a contributor to CVD mortality, in NHANES 2001–2004. In this study, ~8.5% of non-Hispanic black participants were shown by a physical exam to have PAD compared with only 5.3 of non-Hispanic whites. The authors calculated that almost 31% of the race difference in PAD prevalence was attributed to lower 25(OH)D concentrations of blacks accounted for about one-half of the increased prevalence of hypertension compared with whites. Reis et al (15) examined the association of 25(OH)D concentrations with systolic blood pressure in non-Hispanic blacks and non-Hispanic whites, such that each 10 nmol/L increase in 25(OH)D concentrations was associated with a decrease in systolic blood pressure of ~0.2 mm Hg. They further estimated that the much lower 25(OH)D concentrations of blacks accounted for about a 43% reduction in cardiometabolic disorders compared with the lowest concentrations, and reductions of 51% and 55% were seen for metabolic syndrome and T2D, respectively (13). If these associations are actually of this magnitude and causal, they would indicate that improving vitamin D status could substantially reduce morbidity and mortality from CVD and T2D. Even a much smaller benefit would be extremely important from a public health standpoint because appropriate vitamin D supplementation is inexpensive and safe, especially relative to the pharmaceutical and surgical methods currently used to prevent and treat these conditions.

Most of the observational studies that have examined associations of 25(OH)D concentrations with CVD- or T2D-related outcomes did not include enough African American participants to conduct analyses stratified by race. An important exception is NHANES, which is the largest US population-based study that includes a large number of African American participants and blood measurements of 25(OH)D concentrations. Scragg et al (14) examined the association of 25(OH)D concentrations with blood pressure and hypertension in NHANES III. They reported similar inverse associations of 25(OH)D concentrations with systolic blood pressure in non-Hispanic blacks and non-Hispanic whites, such that each 10 nmol/L increase in 25(OH)D concentrations was associated with a decrease in systolic blood pressure of ~0.2 mm Hg. They further estimated that the much lower 25(OH)D concentrations of blacks accounted for about one-half of the increased prevalence of hypertension compared with whites. Reis et al (15) examined the association of 25(OH)D concentrations with peripheral arterial disease (PAD), which is a consequence of atherosclerosis and a contributor to CVD mortality, in NHANES 2001–2004. In this study, ~8.5% of non-Hispanic black participants were shown by a physical exam to have PAD compared with only 5.3 of non-Hispanic whites. The authors calculated that almost 31% of the race difference in PAD prevalence was attributed to lower 25(OH)D concentrations of the non-Hispanic black participants. If the associations between 25(OH)D concentrations and hypertension and PAD in the preceding studies were causal, they suggested both a potentially substantial benefit of improving vitamin D status in African Americans and supported the possibility that their lower vitamin D status contributes to health disparities in some components of CVD.

Some articles from NHANES have suggested that the association of 25(OH)D concentrations with certain outcomes may differ by race. For example, Reis et al (15) reported that lower 25(OH)D concentrations were associated with a higher prevalence of CVD in non-Hispanic whites but not in non-Hispanic blacks. In the simplest statistical model, which was only adjusted for age

### TABLE 1

Age-adjusted prevalence (SE) of selected conditions in non-Hispanic Americans aged ≥18 y in 2008

<table>
<thead>
<tr>
<th>Condition</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>Obesity</td>
<td>28.6 (1.5)</td>
<td>26.3 (0.8)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>9.7 (1.0)</td>
<td>14.0 (0.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28.6 (1.3)</td>
<td>24.1 (0.6)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.6 (0.4)</td>
<td>2.7 (0.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.7 (1.0)</td>
<td>7.6 (0.4)</td>
</tr>
</tbody>
</table>

1 Data are from reference 1.
and sex, the odds ratios suggested a protective effect of 25(OH)D concentrations ≥49.2 nmol/L in whites and ≥24.6 in blacks, although a statistical significance for these associations was only shown in the much larger white subset. When numerous additional factors were adjusted for, including income and education, the apparent protective effect remained for whites but was eliminated for blacks. In an article from NHANES III, Scragg et al (16) observed that 25(OH)D concentrations were inversely associated with prevalent diabetes in non-Hispanic whites and Mexican Americans but not in non-Hispanic blacks. In non-Hispanic whites and Mexican Americans, there was a decrease of more than two-thirds in estimated diabetes risk of participants with 25(OH)D concentrations ≥44.0 nmol/L, but there was no evidence of any similar benefit in non-Hispanic blacks. In contrast, Zhao et al (17) examined the association of 25(OH)D concentrations with markers of insulin resistance in NHANES 2003–2006 and observed an inverse association that did not differ across race/ethnic groups before or after adjustment for multiple confounders. NHANES had numerous limitations, including its cross-sectional design and the small number of non-Hispanic blacks in the highest 25(OH)D quartile. Also, apparent race effects can be difficult to untangle from socioeconomic effects. Nevertheless, potential race differences in the association of 25(OH)D concentrations with CVD outcomes and T2D merit further examination.

Another observational study worth nothing here is the African American Diabetes Heart Study. Investigators of this study examined the cross-sectional association of 25(OH)D concentrations with CVD-related outcomes, including calcified atherosclerotic plaque, in 340 African American adults with diabetes (18). Calcified atherosclerotic plaque, which is an indicator of atherosclerosis, is a predictor of future cardiovascular events. Although prior studies in European Americans showed an inverse association between 25(OH)D concentrations and calcified atherosclerotic plaque, a positive association was shown for calcified atherosclerotic plaque of the aorta and carotid artery in the African American Heart Study cohort. However, it was apparent from the plotted values for aortic calcified plaque by 25(OH)D concentrations that the estimated increased risk occurred at 25 (OH)D concentrations >75 nmol/L. Thus, this study, although it suggested that improving vitamin D status may not reduce risk of calcified aortic plaque in African Americans, should not be interpreted as providing evidence of harm from increasing 25 (OH)D concentrations to 75 nmol/L, which is a commonly recommended concentration that is well within the physiologic range for blacks as well as whites.

LIMITATIONS OF OBSERVATIONAL STUDIES

The well-known axiom that observational studies can describe associations but cannot establish causality is particularly important to remember when it comes to vitamin D research. This is because many of the same factors that determine 25(OH)D concentrations (eg, the use of multivitamins and other supplements, body size and adiposity, and outdoor physical activity) are also strong determinants of many chronic health conditions. Although NHANES and other important studies collect extensive data related to these and other relevant covariates, the potential for residual confounding is always present. Furthermore, it is not always easy to distinguish confounding variables, which should be adjusted for, from those in the causal pathway, which should not be adjusted for. For example, body mass index (BMI) is a potential confounder of the association of 25(OH)D concentrations with CVD because an elevated BMI is a cause of vitamin D deficiency and a risk factor for CVD. However, one can also argue that 25(OH)D is in the causal pathway between BMI and CVD, and therefore, adjustment for BMI would dilute a true 25 (OH)D effect. This may explain the findings of Schmitz et al (19) who observed an inverse association of 25(OH)D concentration with blood pressure in African Americans before but not after adjustment for BMI. For these and other reasons, including timing (ie, 25(OH)D concentrations reflect vitamin D status over a short period relative to that over which chronic diseases develop) and small numbers of African Americans, especially those with purportedly optimal 25(OH)D concentrations, observational studies should be complemented by well-designed intervention studies.

INTERVENTION STUDIES OF VITAMIN D AND CVD OR T2D

As yet, there are few published results from large randomized trials of vitamin D supplementation to prevent CVD outcomes or T2D in any population, and no such trials in African Americans specifically. The Women’s Health Initiative showed no effect of calcium plus low-dose (10 µg/d) vitamin D supplementation on coronary or cerebrovascular risk in 36,282 postmenopausal women followed for 7 y, but benefits were seen in some subgroups including subjects with higher BMI, higher cholesterol, or on statin medications (20). Although results were not reported separately for the African American subset, the authors noted that there were no interactions of treatment with ethnicity. Another report from the Women’s Health Initiative showed no effect of the same treatment on incident diabetes (21). The findings from this study are limited by the low vitamin D dose given and the fairly high baseline 25(OH)D concentrations of participants (an estimated 75% of participants had concentrations ≥80 nmol/L). Similarly, in a study of 158 overweight Norwegian adults, Jorde et al (22) observed no significant effect of supplementation with 1000 µg vitamin D3 or placebo/wk for 1 y on thrombosis risk. The mean baseline 25(OH)D concentration in this group was 62 nmol/L. Zitterman et al (23) also studied overweight subjects, but their group of 200 German subjects was more vitamin D deficient (30 nmol vitamin D/L at baseline), and the authors observed a significant improvement in several CVD risk markers after supplementation for 1 y with 83 µg vitamin D3/d. In New Zealand, von Hurst et al (24) conducted a small, randomized, placebo-controlled trial of 100 µg vitamin D/d to improve insulin sensitivity in insulin-resistant women of South Asian origin who had very low starting 25(OH)D concentrations (20 nmol/L), presumably because of, in part, dark skin color. Supplementation in this study led to a 9.7% increase in insulin sensitivity in the 42 supplemented women compared with a 9.0% decrease in the 39 women on the placebo over a 6-mo period. Our group conducted a secondary analysis of the effect of calcium plus vitamin D supplementation (17.5 µg/d) on measures of glucose homeostasis in 445 older adults and only observed a benefit of supplementation in subjects who had impaired glucose tolerance at baseline (25). These diverse findings were consistent with the principle that increasing the intake of
a nutrient is most likely to benefit those who 1) are not already getting enough of it and 2) are at elevated risk of the condition under study.

CONCLUSIONS

Despite a large number of observational studies and a limited number of clinical trials that have examined 25(OH)D as a potential determinant of CVD and T2D or its precursors, it remains uncertain whether improving vitamin D status would reduce risk of these conditions in the general US population or in African Americans specifically. However, if the associations reported from the observational studies are of the estimated magnitudes and causal, vitamin D supplementation could potentially have a strong preventive effect on some of these conditions and could reduce race-related disparities in their prevalence. Because of the low 25(OH)D concentrations of many, if not most, African Americans and the low risk associated with vitamin D supplementation, it is important to obtain more definitive answers to these questions. This will require clinical trials in African Americans studied alone or in comparison with other groups. In the meantime, it seems prudent for African Americans, like others, to aim for 25(OH)D concentrations of 50–80 nmol/L, which are substantially higher than current median values in the United States. Although this may not provide a benefit with respect to CVD and T2D, it is unlikely to cause harm and may reduce risk of these and other serious chronic conditions.

The author had no conflicts of interest to declare.

REFERENCES