

Letters

RESEARCH LETTER

Trends in Use of High-Dose Vitamin D Supplements Exceeding 1000 or 4000 International Units Daily, 1999-2014

Since 2000, there has been an increase in research on possible health benefits of vitamin D. However, a 2011 Institute of Medicine (IOM; now the National Academy of Medicine) report concluded that vitamin D was beneficial for bone health but evidence was insufficient for extraskeletal health.¹ Several large-scale trials are ongoing to evaluate the effect of vitamin D supplementation on extraskeletal outcomes.² The IOM report noted possible harm (eg, hypercalcemia, soft tissue or vascular calcification) for intakes above the tolerable upper limit, which is the highest level of intake likely to pose no risk of adverse effects for most adults.¹

The recommended dietary allowance for vitamin D is 600 IU/d for adults 70 years or younger and 800 IU/d for those older than 70 years. The tolerable upper limit is 4000 IU/d; beyond this level risk of toxic effects increases.¹ Multivita-

mins typically contain about 400 IU/d; consumption of 1000 IU or more daily likely indicates intentionally seeking supplemental vitamin D.

We assessed trends in daily supplemental vitamin D intake of 1000 IU or more and 4000 IU or more from 1999 through 2014.

Methods | Repeat cross-sectional data from the nationally representative National Health and Nutrition Examination Survey (NHANES) were used. NHANES, which includes survey and examination components, samples noninstitutionalized US residents through a complex, stratified, multistage probability sampling design with certain populations overrepresented (overall response, 74%).³ Informed consent was obtained from participants of the NHANES study. This analysis was based on anonymized data freely available to the public and, therefore, was exempt from ethics review.

For this analysis, participants who were younger than 20 years, pregnant, or had inadequate supplement information were excluded. Participants self-reported their daily supple-

Table 1. Prevalence of Daily Vitamin D Supplement Use of 1000 IU or More in the United States, 1999-2014^a

	Daily Vitamin D Supplement Use ≥1000 IU, % (95% CI)								P Trend ^{b,c}
	1999-2000 (n = 4580)	2001-2002 (n = 5080)	2003-2004 (n = 4796)	2005-2006 (n = 4636)	2007-2008 (n = 5043)	2009-2010 (n = 5401)	2011-2012 (n = 4794)	2013-2014 (n = 4913)	
Overall	0.3 (0.1-0.5)	0.2 (0.1-0.4)	0.4 (0.3-0.8)	0.7 (0.5-1.2)	4.4 (3.7-5.1)	9.4 (8.2-10.8)	15.8 (13.5-18.4)	18.2 (16.0-20.7)	<.001
Sex									
Women	0.4 (0.2-1.0)	0.3 (0.1-0.6)	0.7 (0.4-1.2)	1.1 (0.6-1.9)	6.7 (5.7-7.9)	12.9 (11.1-15.1)	20.9 (17.6-24.6)	25.9 (22.8-29.3)	<.001
Men	0.1 (0.0-0.5)	0.1 (0.0-0.2)	0.2 (0.1-0.4)	0.4 (0.2-0.8)	2.0 (1.5-2.7)	5.7 (4.6-7.0)	10.3 (8.5-12.5)	10.3 (8.7-12.3)	<.001
Race/ethnicity ^d									
Non-Hispanic white	0.3 (0.2-0.7)	0.2 (0.1-0.5)	0.6 (0.3-1.1)	0.9 (0.5-1.5)	5.9 (4.9-7.0)	11.9 (10.7-13.3)	19.3 (16.1-23.0)	21.8 (19.3-24.6)	<.001
Non-Hispanic black	0.2 (0.0-1.1)	0.1 (0.0-0.8)	0.2 (0.0-0.8)	0.4 (0.1-0.8)	1.4 (0.8-2.4)	5.8 (4.2-8.1)	9.5 (7.0-12.7)	11.7 (9.5-14.4)	<.001
Hispanic	0	0	0	0	1.2 (0.7-1.9)	4.4 (3.1-6.4)	7.8 (5.7-10.5)	10.0 (6.7-14.8)	NA
Mexican American	0.1 (0.0-0.3)	0.4 (0.1-1.2)	0.1 (0.1-0.3)	0.0 (0.0-0.2)	0.4 (0.2-0.7)	2.2 (1.5-3.2)	4.2 (2.8-6.4)	8.1 (6.0-10.9)	<.001
Asian American ^e	NA	NA	NA	NA	NA	NA	11.4 (9.1-14.3)	16.8 (13.5-20.7)	NA
Age, y									
20-39	0	0.0 (0.0-0.2)	0	0.2 (0.1-0.6)	1.2 (0.7-2.2)	3.1 (2.2-4.3)	7.2 (5.4-9.5)	8.0 (6.8-9.4)	NA
40-59	0.2 (0.1-1.1)	0.2 (0.1-0.8)	0.3 (0.1-1.3)	0.9 (0.5-1.8)	4.3 (3.5-5.1)	9.3 (7.3-11.8)	14.2 (11.2-17.7)	16.8 (14.0-20.0)	<.001
60-69	1.2 (0.4-3.2)	0.0 (0.0-0.2)	1.6 (1.1-2.3)	1.3 (0.6-2.7)	11.3 (8.5-14.8)	17.8 (14.0-22.2)	27.8 (20.9-35.9)	30.9 (24.8-37.7)	<.001
≥70	0.4 (0.1-2.2)	0.6 (0.2-1.6)	1.1 (0.5-2.5)	1.5 (1.1-2.0)	8.6 (5.6-13.1)	21.2 (18.3-24.4)	32.8 (26.7-39.7)	38.5 (31.8-45.7)	<.001

Abbreviation: NA, not applicable.

^a Repeat cross-sectional data from the nationally representative National Health and Nutrition Examination Survey were used. Estimates were weighted to be nationally representative. Cells containing a 0 value indicate no use was reported during that survey period; 0.0 indicates a proportion less than 0.01.

^b Linear trend tested via linear regression by modeling survey period as a continuous variable. Trend tests were NA when intake was 0 in any survey period.

^c Trends significantly different (*P* for interaction, <.001) by race/ethnicity, sex, and age categories.

^d Individuals self-identified their race and whether they were of Hispanic ethnicity. Those who reported other race—including multiracial—are reported in the overall population but not separately.

^e NA indicates that oversampling and inclusion of the race/ethnicity group response "Non-Hispanic Asian" did not begin until the 2011-2012 cycle.

Table 2. Prevalence of Daily Vitamin D Supplement Use of 4000 IU or More in the United States, 2007-2014^a

	Daily Vitamin D Supplement Use \geq 4000 IU, % (95% CI)				P Trend ^b
	2007-2008 (n = 5043)	2009-2010 (n = 5401)	2011-2012 (n = 4794)	2013-2014 (n = 4913)	
Overall	0.2 (0.1-0.4)	0.8 (0.5-1.2)	1.8 (1.1-3.0)	3.2 (2.5-4.0)	<.001
Sex					
Women	0.2 (0.1-0.7)	0.9 (0.5-1.4)	2.2 (1.2-4.0)	4.2 (3.0-5.7)	<.001
Men	0.1 (0.0-0.6)	0.6 (0.3-1.4)	1.4 (0.9-2.2)	2.2 (1.6-3.0)	<.001
Race/ethnicity ^c					
Non-Hispanic white	0.2 (0.1-0.6)	1.1 (0.7-1.6)	2.3 (1.3-4.1)	3.9 (3.0-5.1)	<.001
Non-Hispanic black	0.3 (0.1-0.9)	0.4 (0.1-1.2)	0.8 (0.4-1.4)	2.0 (1.4-2.9)	<.001
Hispanic	0	0.1 (0.0-0.6)	1.0 (0.4-2.6)	1.8 (0.8-3.8)	NA
Mexican American	0	0.0 (0.0-0.3)	0.3 (0.1-1.5)	0.5 (0.2-1.5)	NA
Asian American ^d	NA	NA	1.8 (1.1-3.1)	3.3 (2.3-4.8)	NA
Age, y					
20-39	0	0.2 (0.0-1.0)	0.9 (0.5-1.7)	1.6 (1.0-2.5)	NA
40-59	0.3 (0.1-0.9)	0.9 (0.4-1.9)	2.1 (0.8-5.6)	2.2 (1.9-2.7)	<.001
60-69	0.6 (0.1-2.7)	1.6 (0.9-2.9)	1.9 (1.0-3.9)	6.6 (4.8-9.1)	<.001
\geq 70	0	1.3 (0.6-2.7)	3.5 (1.9-6.4)	6.6 (4.2-10.2)	NA

Abbreviation: NA, not applicable.

^a Repeat cross-sectional data from the nationally representative National Health and Nutrition Examination Survey were used. Estimates weighted to be nationally representative. Cells containing a 0 value indicate no use was reported during that survey period; 0.0 indicates a proportion less than 0.01. Survey periods between 1999-2006 had proportion less than 0.1 overall and across all demographic groups.

^b Linear trend tested via linear regression by modeling survey period as a

continuous variable. Trend tests were NA when intake was 0 in any survey period. Trends significantly different by race (eg, black vs white; *P* for interaction, .01) and age categories (*P* for interaction, <.001).

^c Individuals self-identified their race and whether they were of Hispanic ethnicity. Those who reported other race—including multiracial—are reported in the overall population but not separately.

^d NA indicates that oversampling and inclusion of the race/ethnicity group response "Non-Hispanic Asian" did not begin until the 2011-2012 cycle.

mental vitamin D intake for the past 30 days; they were asked to bring supplement bottles to aid in reporting.³

STATA (StataCorp), version 14.1, was used. Sample weights were applied. The prevalence of daily vitamin D supplementation of 1000 IU or more and 4000 IU or more was calculated for each survey period overall and by sex, age, and race/ethnicity. Linear trends were tested via linear regression, and a 2-sided *P* value of less than .05 was considered statistically significant.

Results | Of 39 243 participants, the mean age was 46.6 years (SD, 16.8), 51.1% were women, and 69.7% self-reported as non-Hispanic white in weighted analyses. The prevalence of daily supplemental vitamin D use of 1000 IU or more in 2013-2014 was 18.2% (95% CI, 16.0%-20.7%), which was higher than in 1999-2000 (0.3% [95% CI, 0.1%-0.5%]; *P* for trend <.001) (Table 1).

In 2013-2014, prevalence of daily supplemental intake of 4000 IU or more was 3.2% (95% CI, 2.5%-4.0%) (Table 2). Prior to 2005-2006, prevalence of daily intake of 4000 IU or more was less than 0.1% (*P* for trend from 2007-2014: <.001).

Trends of increasing supplemental vitamin D use were found for most age groups, race/ethnicities, and both sexes; though there were interactions (Table 1 and Table 2). In 2013-2014, intake of 4000 IU or more daily was highest among women (4.2% [95% CI, 3.0%-5.7%]), non-Hispanic white individuals (3.9% [95% CI, 3.0%-5.1%]), and those 70 years or older (6.6% [95% CI, 4.2%-10.2%]).

Discussion | From 1999 through 2014 the number of US adults taking daily vitamin D supplements of 1000 IU or more and 4000 IU or more increased. Overall, 3% of the population exceeded the tolerable upper limit of 4000 IU daily, and may be at risk of adverse effects as a consequence, and 18% exceeded 1000 IU daily, likely indicating intentionally seeking supplemental vitamin D. These findings extend a prior NHANES report documenting an increase in daily vitamin D supplement intake of 600 IU or more, particularly among women, non-Hispanic white populations, and older persons from 1988 through 2010.⁴ Concentrations of 25-hydroxyvitamin D (25[OH]D) have also modestly increased over this time frame.⁴ One limitation of the study is that data were self-reported; however, participants were asked to bring supplement bottles to aid in reporting. Also, the design was serial cross-sectional rather than longitudinal, and clinical outcomes were not available.

Although research has emphasized possible benefits of vitamin D, high dosages pose potential risks.¹ A randomized clinical trial with high-dose vitamin D supplementation found increased risk of fractures and falls,⁵ and an increased risk of kidney stones has been found with vitamin D taken in combination with calcium.⁶ Some epidemiologic investigations have reported adverse associations of high 25(OH)D levels with prostate cancer, pancreatic cancer, and all-cause mortality.¹

Characterizing trends in vitamin D supplementation, particularly at doses above the tolerable upper limit, has important and complex public health and clinical implications.

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Accepted for Publication: March 27, 2017.

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Obtained funding: Lutsey.

Administrative, technical, or material support: Lutsey.

Supervision: Ogilvie, Lutsey.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Michos reports receiving personal fees from Siemens Healthcare Diagnostics. No other disclosures were reported.

Funding/Support: This research was supported by grants R01 HL103706 and T32-HL-007779 from the National Institutes of Health National Heart, Lung, and Blood Institute and grant R01 HL103706-S1 from the Office of Dietary Supplements.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institutes of Health or the US Department of Health and Human Services.

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COMMENT & RESPONSE

Changes in Coronary Artery Plaque With Testosterone Therapy

To the Editor Dr Budoff and colleagues demonstrated that testosterone therapy compared with placebo in elderly men

for 1 year increased noncalcified plaque volume in coronary arteries as measured by computed tomographic angiography.¹ An analysis of the individual components revealed that the increase was confined to the fibrous component of the plaque, which provides for plaque stability.² Fatty and necrotic portions, characterized by low attenuation and indicative of a vulnerable plaque,² as well as calcified plaque volume did not alter. Thus, testosterone therapy may have resulted in stabilization of coronary plaques. This finding is consistent with retrospective reports of decreased major adverse cardiovascular events after testosterone therapy.³ The placebo group had greater calcified and noncalcified plaque volume at baseline. The adjusted mean change in fibrous plaque volume in the testosterone group was numerically higher than the change in median volumes between the 2 groups. Were the results driven by large changes in a few men who drove the mean but not the median? It would be informative if the authors could provide the number of participants who had an increase or a decrease in plaque volume.

It cannot be assumed that an increase in plaque volume would always result in a limitation of the vascular lumen. Expansive vascular remodeling may maintain luminal volume.⁴ The data could be reanalyzed including plaque volume as a percentage of vessel volume because after therapy the median plaque volume in the testosterone group was still less than the baseline plaque volume in the placebo group.

A longer-term trial to evaluate cardiovascular events after testosterone therapy should be undertaken. A change in surrogate markers, including an increase in the volume of the atherosclerotic plaque, would not obviate the need for such a trial.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Dhindsa reported receiving speaker's honoraria and research support from AbbVie. Dr Dandona reported receiving grants and personal fees from AbbVie, Novo Nordisk, GlaxoSmithKline, Merck, Novartis, and Takeda; personal fees from Eli Lilly and Co and Sanofi; and a grant from Solvay Pharmaceuticals. No other disclosures were reported.

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