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Associations between concentrations of uric acid with concentrations of vitamin A and beta-carotene among adults in the United States☆

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Abstract

Our objective was to examine the cross-sectional associations between concentrations of vitamin A and beta-carotene, a major source of vitamin A, with concentrations of uric acid in a nationally representative sample of adults from the United States. We conducted a cross-sectional study using data from up to 10893 participants aged ≥20 years of National Health and Nutrition Examination Survey from 2001 to 2006. Concentrations of uric acid adjusted for numerous covariates increased from 305.8 μmol/L in the lowest quintile of vitamin A to 335.3 μmol/L in the highest quintile (p for linear trend <0.001). The prevalence ratio for hyperuricemia also increased progressively across quintiles of serum vitamin A reaching 1.82 (95% confidence interval [CI]: 1.52, 2.16; p for linear trend <0.001) in the top quintile in the maximally adjusted model. Adjusted mean concentrations of uric acid decreased progressively from quintile 1 (333.8 μmol/L) through quintile 4 of concentrations of beta-carotene and were similar for quintiles 4 (313.5 μmol/L) and 5 (313.8 μmol/L). Concentrations of beta-carotene were inversely associated with hyperuricemia (adjusted prevalence ratio comparing highest with lowest quintile = 0.61; 95% CI: 0.52, 0.72; p for linear trend <0.001). Concentrations of uric acid were significantly and positively associated with concentrations of vitamin A and inversely with concentrations of beta-carotene. These cross-sectional findings require confirmation with experimental studies of vitamin A and beta-carotene supplementation.

Keywords

Beta-carotene; Health surveys; Nutrition surveys; Uric acid Vitamin A

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1. Introduction

Gout is a common complication of hyperuricemia, an end product of the metabolism of purine nucleotides. In 1992, Mawson and Onor proposed a role for hypervitaminosis A in the etiology of gout and suggested that xanthine oxidase which converts xanthines to uric acid and retinol to retinoic acid could provide the underlying mechanism for their hypothesis [1]. However, little subsequent investigation has tested their hypothesis. Almost a decade earlier, the Food and Drug Administration had received reports of patients with acne who developed hyperuricemia and gout after using isotretinoin, a synthetic derivative of vitamin A [2]. A later report linked the use of acitretin, another derivative of vitamin A, to gouty tophi [3]. Furthermore, in at least one cross-sectional study, concentrations of uric acid were significantly and positively associated with concentrations of vitamin A and significantly and inversely associated with concentrations of beta-carotene [4]. More recently, an analysis of data from a large population-based survey showed that concentrations of vitamin A were directly and concentrations of beta-carotene were inversely associated with concentrations of uric acid [5].

Given the range of adverse health outcomes associated with high concentrations of uric acid [6–10], a thorough understanding of the impact of dietary and other factors on concentrations of uric acid may help in the development of approaches to minimize potential adverse effects among those who are at risk for complications attributable to hyperuricemia. Despite the recent publication of the results of a large cross-sectional study that examined the relationships between concentrations of vitamin A, beta-carotene and uric acid [5], a paucity of information on this topic still remains and additional investigations in this area are needed. Therefore, our objective was to examine the cross-sectional association between concentrations of vitamin A and uric acid in a large national sample of adults in the United States. Because beta-carotene is a provitamin A carotenoid that constitutes a valuable source of vitamin A, we also explored the association between circulating concentrations of this carotenoid and uric acid.

2. Methods and materials

2.1. Study population

The present analyses were conducted using data from three 2-year cycles (2001–2006) of the National Health and Nutrition Examination Survey (NHANES). A multistage, stratified sampling design was used to generate a sample of participants who were representative of the noninstitutionalized civilian US population. After an interview at home, participants were invited to complete additional questionnaires, undergo a set of tests, and provide blood and other biological specimens in the mobile examination center. Methodological details about the NHANES have been published [11]. The National Center for Health Statistics Research Ethics Review Board granted approval for the conduct of NHANES, and, participation in the study was contingent on signing an informed consent form. Because we analyzed public-use data from these surveys, which reside in the public domain, our study did not require human subjects review.

2.2. Study variables

The principal study variables comprised concentrations of uric acid, vitamin A, and beta-carotene. In addition, we included the following covariates: age, gender, race or ethnicity (white, African American, Mexican American, and other), educational attainment (<high school, high school graduate or equivalent, >high school), cotinine concentration, leisure-time physical activity, alcohol use, energy intake, hypertension, body mass index, estimated glomerular filtration rate, and concentrations of high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and C-reactive protein. Participants were asked about engaging in moderate and vigorous physical activities and, for those who did, the time spent being physically active was calculated from their responses to the frequency and duration of the activities. The intakes of total energy intake and alcohol were obtained from information provided during a single 24-hour dietary recall. Body mass index (kg/m^2) was calculated from measured weight and height. Up to four attempts were made to measure blood pressure. The average of the last two measurements of blood pressure for participants who had three measurements, the last measurement for participants with only two measurements, and the only measurement for participants who had one measurement were used. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the current use of antihypertensive medications by self-report.

2.3. Blood analyses

Serum concentrations of uric acid were measured on a Hitachi Model 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN) or a Beckman Synchron LX20 (Beckman Coulter, Inc., Brea, CA) after oxidation of uric acid by uricase to form allantoin and H_2O_2. Concentrations of uric acid were dichotomized as follows: 1) >416 μmol/L for men and >339 μmol/L for women, 2) >357 μmol/L regardless of gender, and 3) >416 μmol/ L regardless of gender [12–14]. Serum concentrations of vitamin A and serum concentrations of beta-carotene were measured by using high performance liquid chromatography (HPLC) with photodiode array detection on a Waters HPLC system (Waters Chromatography Division, Milford, MA) for cycles 1 and 3 and on a ThermoSeparation HPLC System (ThermoSeparation Products, CA) for cycle 2.

Concentrations of cotinine were determined by using isotope dilution - high performance liquid chromatography / atmospheric pressure chemical ionization tandem mass spectrometry. Serum creatinine was measured by using a Jaffé rate reaction on a Beckman Synchron CX3 clinical analyzer (Beckman Instruments, Inc., Brea, CA). Estimated glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [15]. Concentrations of total cholesterol and high-density lipoprotein cholesterol (measured after precipitation of other lipoproteins with a polyanion-divalent cation mixture or measured directly) were measured enzymatically on Hitachi 704, 717, or 912 Analyzers (Roche Diagnostics (formerly Boehringer-Mannheim Diagnostics) (Hitachi Global Storage Technologies, San Jose, CA). Non-high-density lipoprotein cholesterol was calculated by subtracting the concentration of high-density lipoprotein cholesterol from that of total cholesterol. Concentrations of C-reactive protein were measured by using latex-enhanced nephelometry on a Dade Behring Nephelometer II Analyzer System (BNII) (Dade Behring Diagnostics Inc., Somerville, NJ).

2.4. Statistical analyses

The analyses were limited to participants who were aged ≥20 years and nonpregnant women. Chi-square tests and t-test were used to examine differences in percentages and means, respectively. Tests for trends of age-adjusted percentages or means were conducted by using orthogonal linear contrasts. Age-adjustment was performed using the direct method with the projected year 2000 U.S. population. Tests for differences in percentages or means after adjustment for study covariates were conducted by using linear regression analysis for continuous dependent variables and with log-linear regression analysis for dichotomous dependent variables. Tests for trends in percentages or means after adjustment for study covariates across quintiles of concentrations of vitamin A and beta-carotene were conducted by using linear regression analysis for continuous dependent variables and with log-linear regression analysis for dichotomous dependent variables using the median concentrations of vitamin A and beta-carotene of the quintiles. Least-square adjusted mean concentrations of uric acid were calculated by analysis of covariance. Prevalence ratios using dichotomized uric acid as the dependent variable were estimated by using log-linear analysis. Tests for trend for the prevalence ratios were conducted by using the median concentrations of vitamin A and beta-carotene of the quintiles. The statistical software SUDAAN (Research Triangle Institute, Research Triangle Park, NC) was used to generate the estimates.

3. Results

3.1. Analytical sample size

During the 6-year study period, 14542 participants attended the mobile examination center. After excluding pregnant women (n = 867), 12390 participants had data for both serum concentrations of vitamin A, beta-carotene, and uric acid. Additional exclusions for participants using medications to treat gout (n = 162) and participants who had missing data for covariates reduced the final sample size to 10893.

3.2. Characteristics of sample

The median age was 45 years, 49% were men, 73% were white, 10% were African American, 7% were Mexican American, 9% were of another race or ethnicity, and 57% had at least a high school diploma or its equivalent. The mean and median concentrations of uric acid were 320.5 and 315.2 μmol/L, respectively. The unadjusted prevalence of hyperuricemia was present in 20.6% (men: 23.2%, women: 18.1%) of participants using the gender-specific cut points, in 30.5% (men: 48.1%, women: 13.6%) of participants with a concentration of uric acid >357 μmol/L, and in 16.6% (men: 27.8%, women: 5.9%) of participants with a concentration of uric acid >416 μmol/L. The mean and median concentrations of vitamin A were 2.1 and 2.1 μmol/L, respectively, and of beta-carotene 0.36 μmol /L and 0.23 μmol /L, respectively.

3.3. Study variables in relation to uric acid status

Compared to participants without hyperuricemia, those with hyperuricemia, defined using gender-specific cutpoints, were older (Table 1). In age-adjusted analyses, participants with hyperuricemia were more likely to be men and more likely to have hypertension, had a higher mean intake of alcohol, a higher mean body mass index, a lower mean concentration

of high-density lipoprotein cholesterol and higher mean concentration non-high-density lipoprotein cholesterol, a higher mean concentration of C-reactive protein, a lower mean estimated glomerular filtration rate, and a higher mean concentration of vitamin A. Most of these differences persisted in analyses that adjusted for covariates.

3.4. Study variables in relation to quintiles of concentrations of Vitamin A

Table 2 shows trends in age-adjusted means or percentages of covariates across quintiles of vitamin A. Except for concentrations of cotinine and high-density lipoprotein cholesterol, all other covariates displayed significant negative or positive trends. After adjustment for covariates, p-values lost statistical significance for several variables including physical activity, energy intake, body mass index, C-reactive protein, and beta-carotene.

After multiple adjustments, mean concentrations of uric acid increased steadily from 305.8 μmol/L in the lowest quintile of vitamin A to 335.3 in the highest quintile (p for linear trend <0.001) (Fig.). The prevalence ratio for hyperuricemia also increased progressively across quintiles of serum vitamin A reaching 1.82 (95% confidence interval: 1.52, 2.16) in the top quintile in the maximally adjusted model (Table 3).

3.5. Study variables in relation to quintiles of concentrations of beta-carotene

Numerous significant linear trends were present for study covariates across quintiles of beta-carotene concentrations (Table 4). Only the trends in the percentages of whites and mean estimated glomerular filtration rate were not significant.

After multiple adjustments, mean concentrations of uric acid decreased progressively from quintile 1 (333.8 μmol/L) through quintile 4 (313.5 μmol/L) of concentrations of beta-carotene and were similar for quintiles 4 and 5 (Fig. 1). Concentrations of beta-carotene were inversely associated with hyperuricemia (Table 5).

4. Discussion

In this large cross-sectional study of a representative sample of U.S. adults, concentrations of uric acid and the likelihood of hyperuricemia were significantly and positively associated with vitamin A. Furthermore, the association demonstrated a dose–response relationship across quintiles of serum concentrations of vitamin A. In contrast, concentrations of uric acid were significantly and inversely associated with concentrations of beta-carotene.

Because of its role in various pathologies, identifying factors that contribute to elevations of concentrations of uric acid can yield new insights into therapeutic options to optimize concentrations of uric acid. Known lifestyle predictors of concentrations of uric acid include dietary factors (meat, seafood, dairy intake, fructose-rich foods and beverages), excess weight, and alcohol use [16]. Our results now suggest that vitamin A may also affect circulating concentrations of uric acid.

Good sources of dietary vitamin A are found in liver, carrots, broccoli, sweet potato, kale, spinach, pumpkins, and collard greens. Furthermore, a large percentage of adults take dietary supplements many of which contain vitamin A. During 2003–2006, 53% of

participants in NHANES reported using dietary supplements (54% of adults), and 33% reported using multivitamin/multimineral supplements [17]. For example, a leading multivitamin/multimineral supplement contains 3500 IU of vitamin A. Current recommended dietary allowances for vitamin A are 3000 IU (900 mcg) for men and 2310 IU (700 mcg) for women with additional allowances for pregnant and lactating women [18]. Although vitamin A deficiency is a major concern in many poor countries, intake of vitamin A may be high in developed countries due to the fortification of many foods and the use of supplements and may exceed the recommended daily allowance [19]. In the United States, however, 44% of the population had inadequate dietary intake of vitamin A during 2001–2002 but the intake from supplementary sources was not specified [20]. If future clinical trials generate corroborating evidence about the effects of vitamin A intake on concentrations of uric acid, persons who suffer from gout or are prone to this condition may wish to consider moderating their intake of vitamin A [1].

Xanthine oxidase, which converts retinol to retinoic acid and xanthines to uric acid, provides a mechanistic explanation for why changes in concentrations of vitamin A may impact concentrations of uric acid.

The results from the present study are very consistent with those of a cross-sectional study that was recently published [5]. In an analysis of data from 14349 adults of a national survey conducted from 1988 to 1994 in the United States, concentrations of vitamin A were inversely associated with concentrations of uric acid. Compared to the lowest quintile of serum retinol, adjusted concentrations of uric acid were 42 μmol/L higher in the highest quintile of serum retinol. In comparison, the difference in adjusted concentrations of uric acid between the top and bottom quintile of serum retinol in the present study was about 29 μmol/L. The differences in the estimates of the two studies that included two completely different representative samples of US adults may be due to sampling variation, to differences in adjustment factors, or to unobserved trends in factors that may influence concentrations of the study variables of interest.

Because of the cross-sectional design of the present study, the directionality of the association cannot be conclusively established. Based on a previous premise, we hypothesized that the arrow points from vitamin A to uric acid. Alternatively, uric acid concentrations may determine concentrations of vitamin A, or a common factor to both may provide the link between the two. Consequently, our findings need to be tested in experimental studies to establish whether the administration of vitamin A changes circulating concentrations of uric acid.

Beta-carotene is typically, but not exclusively, found in orange and yellow colored vegetables, and rich sources include sweet potatoes, carrots, kale, spinach, turnip greens, winter squash, collard greens, and some herbs such as cilantro and fresh thyme. When cleaved, beta-carotene yields vitamin A, and the inverse association between concentrations of beta-carotene and uric acid that we described may seem contrary to the direct association between concentrations of vitamin A and uric acid [21]. Other carotenoids with provitamin A activity include alpha-carotene and beta-cryptoxanthin but not lutein, zeaxanthin, and lycopene. Compared with retinol, however, beta-carotene in foods exhibits only a fraction of

the vitamin A activity [21]. It is conceivable that concentrations of beta-carotene represent markers for other constituents of fruits and vegetables that may be inversely related to concentrations of uric acid. Deserving of mention is that observational studies of beta-carotene and adverse health outcomes have produced false signals in some instances as shown by the generally favorable associations between concentrations of beta-carotene and major causes of morbidity and mortality such as cancer and cardiovascular disease. Subsequent clinical trials failed to show a beneficial effect of the administration of beta-carotene on cardiovascular disease and cancer [22,23].

Limited information about the associations between concentrations of beta-carotene and uric acid exists in the literature. At least three supplementation studies of beta-carotene have reported data about changes in concentrations of uric acid. Among 12 Dutch adults aged 18–24 years, supplementation with microcrystalline beta-carotene suspension at 40 g/kg for three weeks did not significantly affect concentrations of uric acid (from 253 mmol/L to 244 mmol/L) [24]. Concentrations of beta-carotene increased from 0.253 to 2.608 μmol/L. In a European multicenter trial, no significant change in concentration of uric acid among 35 participants (mean age 34 years) who were supplemented with 15 mg/day of beta-carotene was reported after 12 weeks (343 μmol/L at week 0 and 360 μmol/L at week 12) [25]. Concentrations of beta-carotene increased from 0.39 to 1.66 μmol/L. However, another study that included 42 participants age 20–30 years who were supplemented with 5 mg, 10 mg, 20 mg, and 40 mg of beta-carotene for five weeks did observe significant reductions in concentrations of uric acid [26]. Concentrations of beta-carotene increased from 0.36 to 0.83 μmol/L, 0.24 to 1.43 μmol/L, 0.36 to 2.72 μmol/L, and 0.20 to 4.38 μmol/L in the four supplementation groups, respectively. These three supplementation studies provide inconsistent results about the possible effect of supplementation with beta-carotene on concentrations of uric acid, and only one of the studies is consistent with the findings of our analyses. Consequently, additional supplementation studies with larger sample sizes should prove useful shedding light on the nature of the relationship between beta-carotene and uric acid. Concentrations of beta-carotene achieved after supplementation were higher than the median concentration of 0.734 μmol/L in the highest quartile in our study.

A limited number of observational studies provide supportive evidence for the associations between concentrations of vitamin A, beta-carotene, and uric acid that we noted. In a study of 415 Australian adults aged 60–64 years, concentrations of uric acid were positively correlated with concentrations of vitamin A ($r = 0.216$, $P < .001$) and negatively correlated with concentrations of beta-carotene ($r = -0.24$, $P < .001$) [4]. Recently, concentrations of beta-carotene were found to be inversely associated with concentrations of uric acid among 14,349 participants aged ≥20 years in the Third National Health and Nutrition Examination Survey conducted from 1988 to 1994 [5]. Thus, the results of that completely separate population-based study based on data from a survey that was conducted more than a decade earlier were very consistent with the results of the present study. Nevertheless, additional research is needed to shed light on the relationships between beta-carotene and concentrations of uric acid and the mechanisms underlying such a relationship, if a relationship is confirmed.

The principal limitation of our study is its cross-sectional design. In addition, study variables may have been imperfectly measured and we may not have included all relevant confounders. Consequently, the results are subject to the possibility of residual confounding.

In conclusion, concentrations of vitamin A were positively and concentrations of beta-carotene were inversely associated with concentrations of uric acid. These results, if confirmed by experimental studies, possibly point to approaches to preventing elevated concentrations of uric acid.

Abbreviation

NHANES National Health and Nutrition Examination Survey

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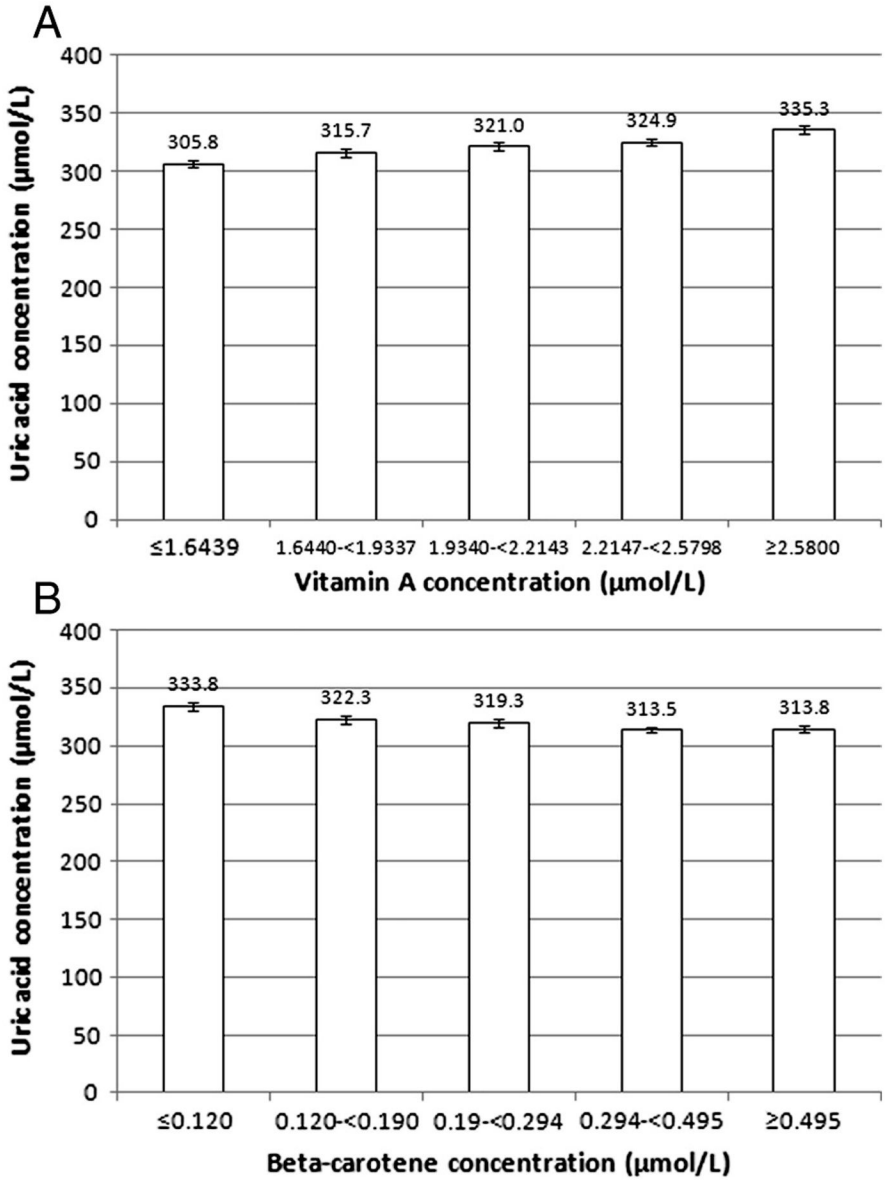

Fig.

Adjusted mean concentrations (95 % confidence interval) of serum uric acid among adults aged ≥ 20 years, by quintiles of concentrations of serum, vitamin A (panel A) and beta-carotene (panel B). National Health and Nutrition Examination Survey. Results are adjusted for age, gender, race or ethnicity, education, cotinine concentraion, leisure-time physical activity, alcohol intake, energy intake, hypertension, body mass index, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, estimated glomerular filtration rate, C-reactive protein, and beta-carotene (panel A) or serum vitamin A (panel B).

Table 1

Selected age-adjusted baseline characteristics among U.S. adults aged ≥20 years, by hyperuricemia status, National Health and Nutrition Examination Survey 2001–2006

Characteristics	Hyperuricemia [a]	No hyperuricemia	P	P [b]
	Mean or % (95% CI)	Mean or % (95% CI)		
N, unweighted	2346	8547	–	–
Age (years)	49.9 (48.8, 51)	45.1 (44.4, 45.7)	< .001	< .001
Men, %	58.0 (55.7, 60.2)	47.3 (46.3, 48.3)	< .001	.220
Whites, %	73.4 (69.1, 77.2)	73.7 (70.5, 76.6)	.756	< .001
>High school, %	54.3 (50.9, 57.7)	57.0 (54.8, 59.1)	.141	.174
Cotinine (ng/ml)	63.2 (55.1, 71.3)	65.7 (60.4, 7.0)	.514	.148
Alcohol intake (g/d)	17.8 (15.2, 20.4)	11.5 (10.4, 12.6)	< .001	< .001
Leisure-time physical activity (MET-h/month)	84.2 (72.3, 96.1)	77.7 (72.5, 83.0)	.285	.050
Energy intake (kcals/d)	2255 (2202, 2308)	2245 (2219, 2272)	.736	< .001
Hypertension, %	43.6 (40.8, 46.3)	26.3 (25.2, 27.4)	< .001	< .001
Body mass index (kg/m^2)	31.2 (30.7, 31.7)	27.3 (27.1, 27.5)	< .001	< .001
High-density lipoprotein cholesterol (mmol/L)	1.26 (1.24, 1.28)	1.41 (1.4, 1.42)	< .001	< .001
Non-high-density lipoprotein cholesterol (mmol/L)	4.12 (4.06, 4.18)	3.74 (3.71, 3.77)	< .001	.005
C-reactive protein (mg/L)	5.2 (4.7, 5.6)	3.8 (3.6, 3.9)	< .001	.004
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	87.9 (87.0, 88.9)	95.1 (94.4, 95.8)	< .001	< .001
Serum vitamin A (μmol/L)	2.3 (2.3, 2.3)	2.1 (2.1, 2.1)	< .001	< .001
Beta-carotene (μmol/L)	0.3 (0.3, 0.3)	0.4 (0.4, 0.4)	< .001	< .001
Uric acid (μmol/L)	431 (429, 434)	292 (291, 294)	< .001	< .001

[a] Hyperuricemia is defined as >416 μmol/L in men and >339 μmol/L in women.

[b] P-values for differences adjusted for all other covariates in table.

Table 2

Selected age-adjusted baseline characteristics among U.S. adults aged ≥20 years, by quintiles of serum vitamin A concentration, National Health and Nutrition Examination Survey 2001–2006

Characteristics	Vitamin A quintiles (μmol/L)						
	≤1.6439	1.6440–1.9337	1.9340–2.2143	2.2147–2.5798	≥2.5800	*P* for trend	*P* for trend
	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)		
N, unweighted	2461	2179	2133	2073	2047	–	–
Age (years)	40.8 (40.0, 41.7)	43.7 (42.6, 44.7)	45.9 (44.9, 47.0)	48.3 (47.2, 49.3)	51.6 (50.6, 52.5)	< .001	.001
Men, %	29.7 (27.6, 31.9)	43.5 (40.7, 46.3)	52.8 (50.6, 55.1)	59.1 (56.4, 61.7)	62.4 (60.0, 64.8)	< .001	< .001
Whites, %	59.5 (54.1, 64.8)	71.0 (66.6, 75.0)	74.6 (70.7, 78.0)	79.4 (75.3, 82.9)	84.8 (82.3, 87.0)	< .001	< .001
>High school, %	49.8 (47.3, 52.2)	55.6 (52.8, 58.4)	57.1 (53.9, 60.2)	57.0 (54.5, 59.4)	62.3 (59.1, 65.5)	< .001	.021
Cotinine (ng/ml)	69.1 (60.9, 77.2)	67.1 (60.7, 73.4)	66.8 (58.4, 75.3)	63.1 (55.1, 71.0)	65.6 (56.5, 74.7)	.340	.111
Alcohol intake (g/d)	5.8 (5.1, 6.6)	9.0 (7.5, 10.5)	12.5 (10.6, 14.4)	16.1 (13.9, 18.3)	22.6 (19.8, 25.4)	< .001	.001
Leisure-time physical activity (MET-h/month)	59.7 (53.0, 66.5)	71.0 (64.1, 77.8)	76.4 (68.5, 84.3)	88.9 (79.6, 98.2)	95.3 (82.2, 108.3)	< .001	.264
Energy intake (kcals/d)	2009 (1957, 2062)	2174 (2116, 2233)	2308 (2259, 2358)	2350 (2288, 2413)	2416 (2346, 2486)	.001	.589
Hypertension, %	26.0 (23.7, 28.4)	27.7 (25.8, 29.6)	28.8 (26.6, 31.0)	30.8 (28.5, 33.2)	35.2 (33.4, 37.1)	< .001	.001
Body mass index (kg/m^2)	28.7 (28.3, 29.1)	28.3 (27.9, 28.6)	28.1 (27.8, 28.5)	27.9 (27.6, 28.3)	27.3 (27.0, 27.6)	< .001	.831
High-density lipoprotein cholesterol (mmol/L)	1.39 (1.37, 1.41)	1.38 (1.35, 1.40)	1.37 (1.35, 1.39)	1.38 (1.36, 1.40)	1.40 (1.37, 1.42)	.478	.230
Non-high-density lipoprotein cholesterol (mmol/L)	3.47 (3.42, 3.52)	3.70 (3.64, 3.76)	3.87 (3.81, 3.92)	3.94 (3.89, 4.00)	4.10 (4.00, 4.20)	< .001	.032
C-reactive protein (mg/L)	6.8 (6.2, 7.5)	4.3 (3.8, 4.7)	3.3 (3.1, 3.5)	3.3 (3.0, 3.5)	3.0 (2.8, 3.2)	< .001	.208
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	99.9 (99.2, 100.6)	95.8 (94.8, 96.7)	93.6 (92.7, 94.5)	91.6 (90.7, 92.4)	86.7 (85.5, 87.9)	< .001	< .001
Beta-carotene (μmol/L)	0.3 (0.3, 0.3)	0.4 (0.3, 0.4)	0.4 (0.3, 0.4)	0.4 (0.4, 0.4)	0.4 (0.3, 0.4)	.016	.072
Uric acid (μmol/L)	286 (282, 290)	309 (305, 313)	323 (318, 327)	334 (330, 338)	352 (348, 356)	< .001	< .001

*P-values for differences adjusted for all other covariates in table.

Table 3

Associations between hyperuricemia and concentrations of vitamin A among U.S. adults aged ≥20 years, National Health and Nutrition Examination Survey 2001–2006

	Vitamin A quintiles (μmol/L)					
	≤1.6439	1.6440– < 1.9337	1.9340– < 2.2143	2.2147– < 2.5798	≥2.5800	*P* for trend
	Reference	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	
Uric acid 1 [a]						
Model 1	1.00	1.38 (1.19, 1.59)	1.53 (1.28, 1.83)	1.76 (1.51, 2.05)	2.34 (2.04, 2.69)	< .001
Model 2	1.00	1.38 (1.19, 1.59)	1.53 (1.27, 1.84)	1.74 (1.47, 2.07)	2.31 (1.97, 2.72)	< .001
Model 3	1.00	1.37 (1.19, 1.59)	1.52 (1.26, 1.84)	1.71 (1.43, 2.04)	2.23 (1.89, 2.64)	< .001
Model 4	1.00	1.34 (1.16, 1.55)	1.46 (1.22, 1.74)	1.57 (1.31, 1.89)	1.82 (1.52, 2.16)	< .001
Uric acid 2 [b]						
Model 1	1.00	1.64 (1.46, 1.85)	1.97 (1.73, 2.25)	2.29 (2.03, 2.58)	2.99 (2.66, 3.36)	< .001
Model 2	1.00	1.38 (1.23, 1.54)	1.49 (1.31, 1.70)	1.64 (1.45, 1.85)	2.06 (1.81, 2.34)	< .001
Model 3	1.00	1.37 (1.22, 1.53)	1.48 (1.29, 1.69)	1.60 (1.42, 1.80)	1.98 (1.75, 2.25)	< .001
Model 4	1.00	1.36 (1.20, 1.54)	1.46 (1.26, 1.68)	1.54 (1.35, 1.75)	1.79 (1.56, 2.05)	< .001
Uric acid 3 [c]						
Model 1	1.00	1.46 (1.25, 1.70)	2.02 (1.64, 2.49)	2.45 (1.97, 3.05)	3.56 (2.97, 4.27)	< .001
Model 2	1.00	1.19 (1.02, 1.38)	1.46 (1.17, 1.82)	1.66 (1.31, 2.10)	2.30 (1.86, 2.86)	< .001
Model 3	1.00	1.18 (1.01, 1.38)	1.45 (1.16, 1.81)	1.62 (1.27, 2.05)	2.21 (1.78, 2.75)	< .001
Model 4	1.00	1.16 (0.98, 1.38)	1.42 (1.13, 1.78)	1.51 (1.16, 1.96)	1.81 (1.42, 2.30)	< .001

Model 1 is adjusted for age.

Model 2 is adjusted for age plus gender, race or ethnicity, and education.

Model 3 is adjusted for variables in model 2 plus cotinine concentration, leisure-time physical activity, alcohol intake, and energy intake.

Model 4 is adjusted for variables in model 3 plus hypertension, body mass index, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, estimated glomerular filtration rate, and C-reactive protein.

[a] Hyperuricemia is defined as >416 μmol/L in men and >339 μmol/L in women.

[b] Hyperuricemia is defined as >357 μmol/L for both men and women.

[c] Hyperuricemia is defined as >416 μmol/L for both men and women.

Table 4

Selected age-adjusted baseline characteristics among adults aged ≥20 years, by quintiles of serum beta-carotene concentration, National Health and Nutrition Examination Survey 2001–2006

Characteristics	Beta-carotene quintiles (μmol/L)						
	<0.120	0.120– < 0.190	0.190– < 0.294	0.294– < 0.495	≥0.495	*P* for trend	*P* for trend
	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)		
N, unweighted	2057	2074	2179	2306	2277	–	
Age (years)	41.0 (40.1, 41.9)	43.0 (42.1, 43.9)	45.9 (45.1, 46.7)	48.2 (47.2, 49.1)	52.2 (51.1, 53.4)	< .001	< .001
Men, %	59.8 (57.0, 62.7)	54.3 (51.9, 56.8)	50.9 (49.0, 52.8)	44.6 (42.6, 46.7)	35.4 (33.1, 37.9)	< .001	< .001
Whites, %	73.4 (68.2, 78.1)	74.4 (70.5, 77.9)	73.4 (69.3, 77.1)	71.4 (68.3, 74.2)	73.7 (69.4, 77.5)	.677	.005
>High school, %	45.9 (42.1, 49.7)	50.0 (47.5, 52.5)	54.7 (52.2, 57.3)	62.0 (58.7, 65.1)	69.9 (66.7, 72.8)	< .001	< .001
Cotinine (ng/ml)	114.4 (105.9, 122.9)	89.5 (80.8, 98.2)	60.6 (52.4, 68.8)	37.7 (33.2, 42.1)	19.6 (16.0, 23.2)	< .001	< .001
Alcohol intake (g/d)	20.2 (17.2, 23.1)	11.7 (9.9, 13.4)	12.8 (11.1, 14.6)	10.1 (8.7, 11.4)	7.7 (6.2, 9.1)	< .001	< .001
Leisure-time physical activity/m(MET-h)	60.2 (52.3, 68.1)	67.2 (59.2, 75.2)	87.3 (75.5, 99.1)	81.6 (73.8, 89.5)	92.9 (83.8, 102.0)	< .001	.009
Energy intake (kcals/d)	2334 (2274, 2393)	2285 (2226, 2343)	2254 (2199, 2308)	2161 (2118, 2203)	2144 (2090, 2198)	< .001	.015
Hypertension, %	38.2 (35.9, 40.6)	32.6 (30.6, 34.7)	30.4 (28.5, 32.3)	28.2 (26.4, 30.0)	21.3 (19.8, 22.8)	< .001	< .001
Body mass index (kg/m^2)	30.0 (29.6, 30.4)	29.2 (28.9, 29.6)	28.1 (27.7, 28.5)	27.4 (27.1, 27.7)	25.6 (25.3, 25.8)	< .001	< .001
High-density lipoprotein cholesterol (mmol/L)	1.3 (1.2, 1.3)	1.3 (1.3, 1.3)	1.4 (1.3, 1.4)	1.4 (1.4, 1.4)	1.6 (1.5, 1.6)	< .001	< .001
Non-high-density lipoprotein cholesterol (mmol/L)	3.6 (3.6, 3.7)	3.8 (3.8, 3.9)	3.8 (3.8, 3.9)	3.9 (3.9, 4.0)	3.7 (3.7, 3.8)	.006	< .001
C-reactive protein (mg/L)	6.1 (5.6, 6.7)	4.9 (4.5, 5.4)	3.7 (3.5, 4.0)	3.2 (2.9, 3.4)	2.5 (2.1, 2.8)	< .001	< .001
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	94.5 (93.5, 95.5)	93.5 (92.4, 94.6)	92.8 (91.6, 94.0)	93.3 (92.5, 94.2)	93.2 (92.1, 94.4)	.142	.020
Serum vitamin A (μmol/L)	2.07 (2.03, 2.11)	2.12 (2.08, 2.15)	2.14 (2.11, 2.16)	2.16 (2.12, 2.20)	2.13 (2.09, 2.17)	.002	.107
Uric acid (μmol/L)	347 (342, 352)	331 (326, 335)	322 (319, 326)	309 (305, 313)	293 (288, 297)	< .001	< .001

*P-values for differences adjusted for all other covariates in table.

Table 5

Associations between hyperuricemia and concentrations of beta-carotene among U.S. adults aged ≥20 years, National Health and Nutrition Examination Survey 2001–2006

	Beta-carotene quintiles (μmol/L)					
	<0.120	**0.120– < 0.190**	**0.190- < 0.294**	**0.294- < 0.495**	**≥0.495**	***P* for trend**
	Reference	**Prevalence ratio (95% CI)**	**Prevalence ratio (95% CI)**	**Prevalence ratio (95% CI)**	**Prevalence ratio (95% CI)**	
Uric acid 1 [a]						
Model 1	1.00	0.69 (0.60, 0.79)	0.62 (0.55, 0.70)	0.50 (0.43, 0.58)	0.41 (0.35, 0.48)	< .001
Model 2	1.00	0.70 (0.61, 0.80)	0.64 (0.57, 0.72)	0.52 (0.45, 0.60)	0.43 (0.37, 0.50)	< .001
Model 3	1.00	0.70 (0.61, 0.80)	0.62 (0.55, 0.70)	0.50 (0.43, 0.58)	0.41 (0.35, 0.48)	< .001
Model 4	1.00	0.74 (0.65, 0.83)	0.71 (0.62, 0.81)	0.61 (0.53, 0.71)	0.61 (0.52, 0.72)	< .001
Uric acid 2 [b]						
Model 1	1.00	0.79 (0.71, 0.87)	0.69 (0.63, 0.76)	0.57 (0.51, 0.64)	0.43 (0.38, 0.48)	< .001
Model 2	1.00	0.83 (0.76, 0.91)	0.75 (0.70, 0.82)	0.67 (0.61, 0.74)	0.56 (0.51, 0.63)	< .001
Model 3	1.00	0.84 (0.77, 0.91)	0.74 (0.68, 0.80)	0.66 (0.59, 0.72)	0.55 (0.49, 0.61)	< .001
Model 4	1.00	0.87 (0.79, 0.94)	0.81 (0.74, 0.88)	0.75 (0.67, 0.82)	0.71 (0.64, 0.79)	< .001
Uric acid 3 [c]						
Model 1	1.00	0.65 (0.56, 0.77)	0.59 (0.52, 0.68)	0.44 (0.37, 0.54)	0.32 (0.27, 0.40)	< .001
Model 2	1.00	0.70 (0.60, 0.82)	0.66 (0.59, 0.75)	0.55 (0.46, 0.65)	0.46 (0.38, 0.56)	< .001
Model 3	1.00	0.70 (0.60, 0.82)	0.64 (0.56, 0.73)	0.52 (0.43, 0.63)	0.44 (0.36, 0.53)	< .001
Model 4	1.00	0.73 (0.64, 0.83)	0.71 (0.62, 0.81)	0.61 (0.51, 0.73)	0.59 (0.48, 0.74)	< .001

Model 1 is adjusted for age.

Model 2 is adjusted for age plus gender, race or ethnicity, and education.

Model 3 is adjusted for variables I model 2 plus cotinine concentration, leisure-time physical activity, alcohol intake, and energy intake.

Model 4 is adjusted for variables in model 3 plus hypertension, body mass index, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, estimated glomerular filtration rate, serum vitamin A, and C-reactive protein.

[a] Hyperuricemia is defined as >416 μmol/L in men and >339 μmol/L in women.

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