Title: **The Independent Association of Serum Retinol and β-Carotene Levels with Hyperuricemia – A National Population Study**

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ABSTRACT

Objective. Use of synthetic vitamin A derivatives (e.g. isotretinoin used for severe acne) and high doses of preformed vitamin A have been implicated in the pathogenesis of hyperuricemia and gout, whereas a trial reported that β-carotene may lower serum uric acid (SUA) levels. We evaluated the potential population impact of these factors on SUA in a nationally representative sample of US adults.

Methods. Using data from 14,349 participants aged 20 years and older in the Third National Health and Nutrition Examination Survey (1988-1994), we examined the relation between serum retinol, β-carotene, and uric acid levels using weighted linear regression. Additionally, we examined the relation with hyperuricemia using weighted logistic regression.

Results. SUA levels increased linearly with increasing serum retinol levels, whereas SUA levels decreased with increasing serum β-carotene levels. After adjusting for age, sex, dietary factors, and other potential confounders, the SUA level differences from the bottom (referent) to top quintiles of serum retinol levels were 0, 0.16, 0.31, 0.43, 0.71mg/dL (P for trend < 0.001) and for β-carotene were 0, -0.15, -0.29, -0.27, -0.40 mg/dL (P for trend < 0.001). Similarly, the multivariate odds ratios of hyperuricemia from the bottom (referent) to top quintiles of serum retinol levels were 1.00, 1.30, 1.83, 2.09, and 3.22 (P for trend <0.001) and for β-carotene were 1.00, 0.85, 0.68, 0.73, and 0.54 (P for trend <0.001). The graded associations persisted across subgroups according to cross-classification by both serum retinol and β-carotene levels.

Conclusions. These nationally representative data raise concerns that vitamin A supplementation and food fortification may contribute to the high frequency of hyperuricemia in the US population, whereas β-carotene intake may be beneficial against hyperuricemia. The use of β-carotene as a novel preventive treatment for gout deserves further investigation.

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SIGNIFICANCE AND INNOVATIONS

- In this nationally representative population study of US men and women, we found that serum uric acid levels and the frequency of hyperuricemia increased with increasing serum retinol levels in a graded manner.

- These findings provide the first evidence that supports a substantial link between vitamin A levels and serum uric acid at the national population level, and raise concerns that vitamin A supplementation and food fortification may contribute to the high frequency of hyperuricemia in the US.

- In contrast, there was an inverse association between serum β-carotene and uric acid levels, suggesting that β-carotene intake may be beneficial against hyperuricemia.

INTRODUCTION

Hyperuricemia is the precursor of gout, an excruciatingly painful inflammatory arthritis with a growing disease burden (1). Use of synthetic vitamin A derivatives and high doses of preformed vitamin A (i.e. retinyl esters, the retinol precursor) have been implicated in the pathogenesis of hyperuricemia and gout (2-4). For example, the FDA has reported cases of hyperuricemia and gout developing after the use of isotretinoin, a synthetic derivative of vitamin A, for severe acne (5). Furthermore, acitretin use, a synthetic retinoid, has also been associated with development of severe hyperuricemia (17mg/dL) and tophaceous gout (4), The conversion step from retinol to its more toxic metabolite, retinoic acid, by xanthine oxidase has been hypothesized to potentiate uric acid production when the retinol level is increased (3). Furthermore, several shared factors that may link hypervitaminosis A to hyperuricemia and gout have also been proposed, including alcohol use, renal insufficiency, and common food sources (2,3).

Vitamin A represents a family of compounds that play essential roles in human health, but its acute and chronic effects of toxicity are also well-documented in the literature (2,3,6). Vitamin A is fortified in various foods in developed countries where regular dietary supplements are also commonly used, especially among older people. Because fortified foods, pharmaceutical supplements, and animal foods provide retinol levels that often exceed the recommended dietary allowances (RDA) for adults (6), subtoxicity without obvious clinical signs is a growing concern in developed countries (7,8). For example, prospective observational studies found that serum and dietary retinol levels that are readily attainable in many Western countries have been associated with an increased risk of osteoporosis and hip fracture (6-8). As these subtoxicity concerns call for reassessment of the current levels of vitamin A

supplementation and food fortification in Western countries (7,9), vitamin A levels attained in these countries may also have a significant urate-raising influence through the mechanisms discussed above. To evaluate this potential population impact in the US, we examined the relation between serum retinol and uric acid levels in a nationally representative sample of men and women (the Third US National Health and Nutritional Examination Survey, NHANES III) (11). We also examined the relation between serum β-carotene and uric acid levels, because despite β-carotene being a precursor of vitamin A (i.e. provitamin A), it is known to be largely free of vitamin A toxicity (6). Its cleavage to retinal is highly regulated, unlike preformed vitamin A (retinol) (6). Because long-term supplementation with β-carotene did not significantly contribute to retinol levels (12,13) and a metabolic trial reported that β-carotene supplementation actually lowered serum uric acid levels (14), we hypothesized that β-carotene may have a beneficial population impact on serum uric acid levels.

METHODS

Study population

Conducted between 1988 and 1994, the NHANES III included a representative sample of the noninstitutionalized civilian US population, which was selected by using a multistage, stratified sampling design . After a home interview, participants were invited to attend examination sessions where blood and urine specimens were obtained. For participants unable to attend the examination for health reasons, a blood sample was obtained during the home interview. We limited our analysis to participants 20 years or older who attended the medical examination and included the 14,349 participants (6,698 men and 7,651 women) with complete information in our analyses. We repeated our analyses among 13,915 participants after

excluding participants who self-reported gout or were taking allopurinol or uricosuric agents (n=434).

Measurements

Serum retinol and β-carotene levels were measured with use of an isocratic, reversed phase HPLC (Waters Chromatography Division, Milford, MA). Analytic protocols for other serum analytes and laboratory quality-assurance procedures were described elsewhere (11,15). Values are reported in micrograms per deciliter; to convert to micromoles per liter, multiply by 0.03491 for retinol and by 0.01863 for β-carotene.

Serum uric acid was measured by oxidization with the specific enzyme uricase to form allantoin and H_2O_2 (Hitachi Model 737 Multichannel Analyzer, Boehringer Mannheim Diagnostics, Indianapolis, IN). Details about quality-control procedures have been published elsewhere (11). Values are reported in milligrams per deciliter; to convert to micromoles per liter, multiply by 59.48.

Assessment of Covariates

The average daily intakes of total meat, seafood, dairy foods, sugar-sweetened soft drinks, coffee, and alcohol were derived from responses to a food frequency questionnaire (16). Food frequency questionnaire assessment of dietary intake has been shown to be a valid and reliable method for assessing average dietary consumption (17,18). The NHANES III collected information on body measurements (including height and weight), medication use (including diuretics, anti-hypertensives, allopurinol, and uricosuric agents), medical conditions (including self-reported hypertension and gout), and serum creatinine. Glomerular filtration rate (GFR) was estimated by using the simplified Modification of Diet in Renal Disease study equation: GFR

$(mL/min\ per\ 1.73\ m^2) = 186\ x\ (serum\ creatinine\ level\ [mg/dL])^{-1.154}\ x\ (age)^{-0.203}\ x\ [0.742,\ if\ female]\ x\ [1.212,\ if\ black]$ (19-21). Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters.

Statistical analysis

All statistical analyses were computed using survey commands of STATA (e.g SVYMEAN and SVYREG) to incorporate sample weights and adjust for clusters and strata of the complex sample design (STATA Corporation, College Station, Texas).

We used linear regression modeling to evaluate the relation between serum retinol, β-carotene, and uric acid levels. For these analyses, serum retinol and β-carotene levels were categorized into quintiles and each quintile was compared with the lowest quintile. Multivariate models were adjusted for age (continuous), sex (men, women), smoking status (current, past, never), BMI (continuous), use (yes or no) of diuretics, β-blockers, allopurinol and uricosuric agents, self-reported hypertension (yes or no), GFR (continuous), serum vitamin C levels (quintiles), and intake (quintiles) of alcohol, total energy, meats, seafood, dairy foods, coffee, and sugar-sweetened soft drinks, and mutually for serum retinol and β-carotene levels (quintiles). Trends in serum uric acid levels across categories of intake were assessed in linear regression models by using the median values of each category to minimize the influence of outliers. We also performed logistic regression with a dichotomous outcome of hyperuricemia (i.e. serum uric acid ≥ 7.0 mg/dL among men and serum uric acid ≥ 5.7 mg/dL among women (11)), adjusting for the same covariates. We examined the potential impact of alternative definitions of hyperuricemia (serum uric acid level ≥ 6.0 mg/dL and ≥ 7.0 mg/dL, both regardless of sex) in these regression models.

We examined whether the observed associations persisted within the subgroups stratified by major risk factors for gout, including sex, age group (20-39 years, 40-59 years, and $\geq$ 60 years), BMI (< 25 kg/m^2 vs ≥ 25 kg/m^2), and alcohol use (abstainer vs drinker). We determined the statistical significance of potential subgroup effects by testing the significance of interaction terms added to our final multivariate models. We also explored the relations within subgroups according to cross-classification by tertiles of serum retinol and β-carotene levels. For all difference estimates and odds ratios, we calculated 95% confidence intervals (CI). All P values are two-sided.

RESULTS

The population's mean age was 45 years. The mean serum uric acid level was 5.32 mg/dL (6.06 mg/dL among men and 4.65 mg/dL among women) and 18% were hyperuricemic (19% among men and 17% among women). The characteristics of the study population according to serum retinol and β-carotene levels are shown in **Table 1**. With higher serum retinol levels, age, the proportion of males, the frequency of hypertension, use of diuretics, β-blockers, allopurinol and uricosuric agents, intake of alcohol, total energy and dairy foods, and serum vitamin C levels tended to be higher, but GFR and intake of sugar-sweetened beverages tended to be lower. With higher β-carotene levels, age, diuretic use, and serum vitamin C levels tended to be higher, but the proportion of males and current smokers, BMI, and intake of alcohol, total energy, meat, and sugar-sweetened beverages tended to be lower.

Higher serum uric acid levels were linearly associated with higher serum retinol levels (**Figure 1**). After adjusting for age and sex, serum uric acid levels in individuals in the highest quintile of serum retinol levels were higher than in the lowest quintile by 0.94 mg/dL (95% CI,

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0.85 to 1.04; P for trend < 0.001). After adjusting for other covariates, the difference was

attenuated to 0.71mg/dL (95% CI, 0.58 to 0.84) but remained significant (P for trend < 0.001)

(**Table 2**). After adjusting for age and sex, serum uric acid levels in the highest quintile of serum

β-carotene were lower than in the lowest quintile by 0.62 mg/dL (95% CI, 0.51 to 0.72; P for

trend, < 0.001). After adjusting for other covariates, the difference was attenuated to 0.40 mg/dL

(95% CI, 0.31 to 0.48) but remained significant (P for trend, < 0.001) (**Table 2**). When we

repeated our analyses after excluding participants who self-reported gout or were taking

allopurinol or uricosuric agents (n=434), the results did not materially change. Furthermore,

when we adjusted additionally for vitamin D levels, our results did not change materially.

When hyperuricemia was examined as a dichotomous outcome, the relations were similar.

For example, the multivariate odds ratios (ORs) for hyperuricemia according to increasing

quintiles of serum retinol level were 1.00, 1.30 (95% CI, 0.91 to 1.87), 1.83 (1.32 to 2.54), 2.09

(1.49 to 2.91), and 3.22 (2.30 to 4.49; P for trend <0.001) and the corresponding ORs for β-

carotene were 1.00, 0.85 (95% CI, 0.70 to 1.04), 0.68 (0.57 to 0.82), 0.73 (0.59 to 0.93), and 0.54

(0.44 to 0.66; P for trend <0.001). Alternative definitions of hyperuricemia (serum uric acid

levels ≥ 6.0mg/dL and ≥ 7.0mg/dL, both regardless of sex) did not materially alter these results

(all P values for trend <0.001).

When we stratified our multivariate analysis by subgroups, the association with serum

retinol levels persisted in all subgroups (all P values for trend <0.05) (**Figures 1& 2**). The

association did not vary significantly by subgroups of sex, BMI, and alcohol intake (**Figure 2**),

whereas the association tended to be larger in older age groups (P for interaction = 0.07). The

association with serum β-carotene levels also persisted in all subgroups except for the youngest

age group (20-39 years). The association with serum β-carotene was larger in males and those

who did not drink alcohol (P for interaction ≤ 0.004), but did not vary significantly by age or

BMI subgroups (P for interaction ≥ 0.15) (**Figure 2**). The graded associations persisted across

subgroups according to cross-classification by tertiles of serum retinol and β-carotene levels (P

for interaction = 0.07) (**Figure 3**). After adjusting for age and sex, the difference in serum uric

acid levels between extreme categories was 0.95 mg/dL (95% CI, 0.80 to 1.10; P for trend, <

0.001). After adjusting for other covariates, the difference was attenuated to 0.77 mg/dL (95%

CI, 0.62 to 0.93) but remained significant (P for trend, < 0.001) (**Figure 3**).

DISCUSSION

In this nationally representative population study of US men and women, we found that

serum uric acid levels and the frequency of hyperuricemia increased with increasing serum

retinol levels in a graded manner. In contrast, there was an inverse association between serum β-

carotene and uric acid levels. The graded associations persisted across subgroups according to

cross-classification by both serum retinol and β-carotene levels. These associations were

independent of other risk factors for hyperuricemia such as age, sex, BMI, dietary risk factors,

alcohol intake, renal function, hypertension, and diuretic use. The associations persisted across

subgroups stratified by sex, BMI, and alcohol use and tended to get stronger with age. These

findings provide the first evidence that supports a substantial link between vitamin A levels and

serum uric acid at the national population level, and raise concerns that vitamin A

supplementation and food fortification may contribute to the high frequency of hyperuricemia in

the US (1), whereas β-carotene intake may be beneficial against hyperuricemia.

The differences in serum acid levels between the extreme quintiles of serum retinol and

β-carotene levels were 0.71mg/dL and 0.40 mg/dL, respectively. This magnitude of a population

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mean difference in serum uric acid levels (22,23) can be translated into a clinically relevant

difference in the risk for incident gout, as demonstrated in our previous studies (24,25). For

example, one daily serving increase in beer intake was associated with a mean serum uric acid

level increase of 0.40 mg/dL in a cross-sectional analysis of NHANES III (24), which translated

to a 50% increased risk of incident gout in our prospective analysis of the Health Professionals

Follow-up Study (22). This potentially significant impact on the eventual risk of gout is also

supported by our results using various definitions of hyperuricemia as a dichotomous outcome.

These results provide population evidence that supports the purported link between

retinol, hyperuricemia, and gout (2-4). Earlier FDA reports described cases of hyperuricemia

and gout after the use of isotretinoin, a synthetic derivative of vitamin A, for severe acne (5). In

the nine cases reported to FDA, hyperuricemia was detected after 16 to 109 days of treatment

with 40 to 80 mg isotretinoin daily (5). Two of the nine developed podagra. Another case

reported that acitretin use, a synthetic retinoid, was associated with marked increase in serum

uric acid (7 mg/dL to 17 mg/dL) and development of tophaceous gout (4). Apart from these

dramatic cases related to pharmaceutical use of vitamin A derivatives, vitamin A subtoxicity at

the population level, derived from fortified foods, supplements, and animal foods has become a

growing concern in many Western countries (7,8), as these sources provide retinol levels that

often exceed the recommended dietary allowances (RDA) for adults (6). For example, serum

and dietary retinol levels that are readily attainable in many Western countries have been

associated with an increased risk of osteoporosis and hip fracture (6-8).   This usual intake is

associated with a highly regulated level of serum retinol ranging from 20.1 to 80.2 µg per

deciliter (7), which vastly overlaps our data distribution. Furthermore, previous studies have

shown serum retinol is positively associated with both dietary and supplemental vitamin A intake

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(7,26-29). The urate-raising influence of retinol at the population level observed in our study could add to this potential subtoxicity from vitamin A supplementation and food fortification in the US (6-8). As an expert panel has not been able to establish a safe upper limit for vitamin A because of toxicity overlap within reasonable dietary intakes (6), further research is needed in this area.

A biologic mechanism underlying the link between retinol and hyperuricemia is hypothesized to be through the action of xanthine oxidase shared by the uric acid production step and retinol oxidation step to its more toxic metabolite, retinoic acid (3). This hypothesis postulates that the shared role of xanthine oxidase could result in hyperuricemia and hypervitaminosis A toxicity when retinol or xanthine levels are increased, due to increased production or decreased renal excretion of these factors (3). Other factors associated with both hypervitaminosis toxicity and gout, such as alcohol use, renal insufficiency, and food source (e.g. purine-rich foods of animal origin), were also speculated to be involved in the link between the two conditions (2,3). Nonetheless, our multivariate results adjusted for these factors suggest that the strong association between the two conditions is independent of these factors.

The mechanism underlying the inverse association between serum β-carotene and uric acid levels is unknown. A previous metabolic trial randomly assigned 42 participants to β-carotene supplementation at 5 mg, 10 mg, 20 mg or 40 mg daily for five weeks and found that uric acid levels significantly decreased in all intervention groups (14). The cleavage of provitamin A carotenoids to retinol is a highly regulated step, and vitamin A toxicity from provitamin A sources such as β-carotene is largely impossible (6). Further, long-term supplementation with β-carotene has failed to increase retinol concentrations (12,13). For example, supplementation with β-carotene 50 mg daily led to a persistent 9- to 10-fold increase

in plasma β-carotene concentrations, but did not affect retinol levels for up to five years (13).

Interestingly, serum and dietary β-carotene levels were not associated with an increased risk of

osteoporosis and hip fracture in the aforementioned prospective studies that showed retinol

subtoxicity on these outcomes (6-8). These data, together with our findings, suggest that the

biologic effect of β-carotene on serum uric acid levels is different from that of retinol. β-

carotene could be preferred to meet the need for vitamin A and to help lower uric acid levels,

particularly among individuals with hyperuricemia or gout, as similarly advocated by some for

bone health(6-8) .

Strengths and limitations of our study deserve comment. This study was performed in a

nationally representative sample of US men and women; thus, the findings are likely to be

generalizable to the US general population. Although the aforementioned dramatic case reports

(2-5), clinical trial data (14), and biological plausibility (2,3) suggest that retinol and β-carotene

would affect the risk of hyperuricemia, a cross-sectional study design tends to leave uncertainty

regarding the temporal sequence of exposure-outcome relations. Thus, confirming the relation

with prospective longitudinal data (e.g. the relation between prior retinol and β-carotene levels

and incident hyperuricemia or gout) would be valuable. Furthermore, as our interaction analysis

results were exploratory without clear pre-existing biological hypotheses, these data also require

confirmation by future studies. Further investigation of the potentially modifiable impact of

retinol and β-carotene intake would also be warranted, including clinical trials.

In conclusion, these nationally representative data indicate that serum retinol levels are

strongly associated with serum uric acid levels and the frequency of hyperuricemia at the

population level, whereas serum β-carotene levels are inversely associated. Vitamin A

supplementation and food fortification may have contributed to the high frequency of

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hyperuricemia in the US (1) and β-carotene could be a preferred source for vitamin A among

those with hyperuricemia or gout. The use of β-carotene as a novel preventive treatment for gout

deserves further investigation.

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Table 1. Characteristics According to Quintiles of Serum Retinol and β-Carotene Levels in NHANES III[*]

Quintiles of	N	Age (yr)	Men (%)	Current Smoker (%)	Body Mass Index (kg/m²)	Diuretic Use (%)	Beta-blocker Use (%)	Uric Acid Drug Use[†] (%)	History of Hypertension (%)	GFR (mL/min per 1.73 m²)	Alcohol (servings/d)	Total Energy (Kcal/d)	Total Meat (servings/d)	Seafood (servings/d)	Dairy Foods (servings/d)	Coffee (servings/d)	Sugar-Sweetened Beverages (servings/d)	Serum Vitamin C Levels (mg/dL)
	2,857	39	22	31	26	3	3	0	16	111.9	0.2	1995	1.1	0.2	1.3	1.0	0.6	0.69
	3,196	42	40	31	26	4	3	0	18	104.5	0.2	2164	1.1	0.2	1.4	1.2	0.6	0.71
	2,553	45	51	27	27	5	4	1	22	99.3	0.3	2216	1.0	0.2	1.5	1.2	0.5	0.76
	2,892	46	58	29	27	6	6	1	26	95.6	0.3	2301	1.0	0.2	1.5	1.3	0.5	0.76
	2,851	50	61	23	27	13	9	2	35	86.9	0.4	2252	1.0	0.2	1.5	1.2	0.4	0.83
	3,589	38	61	46	28	4	4	1	24	105.8	0.4	2411	1.2	0.2	1.4	1.2	0.9	0.52
	2,510	42	52	36	27	6	5	1	24	100.8	0.3	2261	1.1	0.2	1.5	1.2	0.6	0.65
	2,522	44	47	26	27	7	4	1	23	98.7	0.2	2199	1.1	0.2	1.4	1.3	0.4	0.75
	2,878	48	42	19	26	8	6	1	23	95.4	0.2	2103	1.0	0.2	1.5	1.3	0.3	0.85
	2,850	52	33	11	25	9	6	1	25	92.7	0.2	1980	0.9	0.2	1.5	1.0	0.2	1.03
Participants	14,349	45	48	28	27	7	5	1	24	98.8	0.3	2196	1.0	0.2	1.5	1.2	0.5	0.75

* Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.

† Allopurinol and uricosuric agents

Table 2. Differences in Serum Uric Acid Levels (mg/dL) According to Quintiles of Serum Retinol and β-Carotene Levels in NHANES III[*]
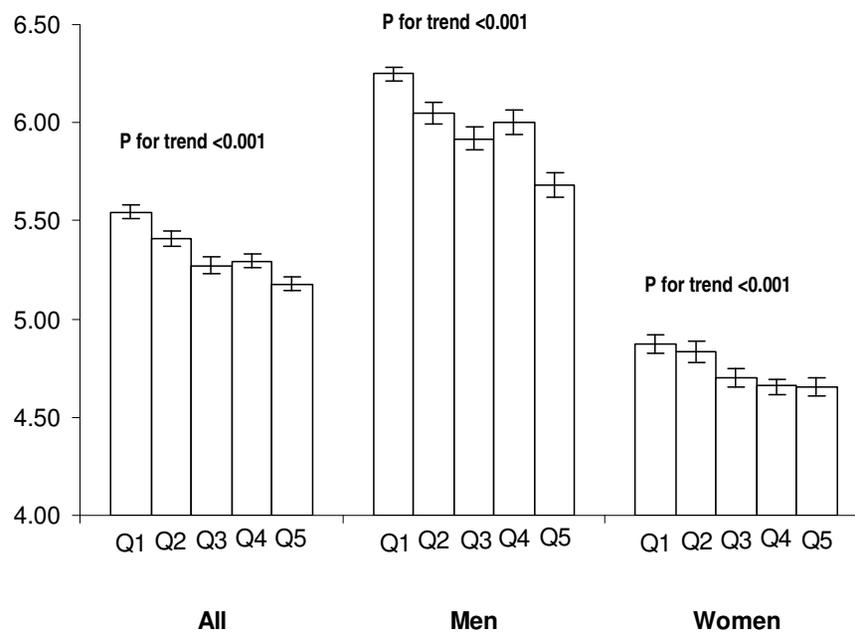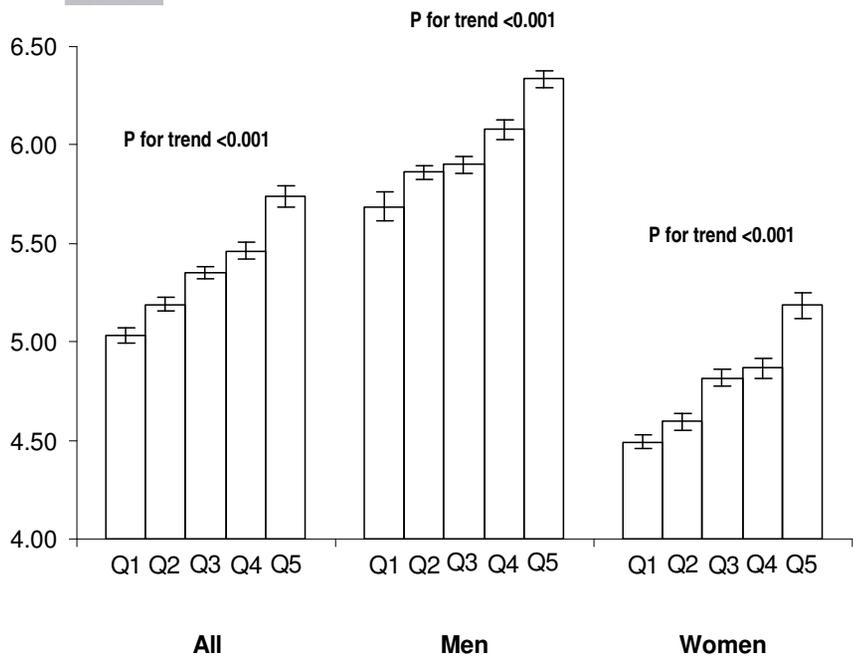
Serum Retinol Levels (µg/dL)	Quintile 1 2-43	Quintile 2 44-52	Quintile 3 53-59	Quintile 4 60-69	Quintile 5 70-259	P value for trend
Age- and sex-adjusted difference (95% CI)	0 (referent)	0.22 (0.10, 0.35)	0.41 (0.31, 0.52)	0.56 (0.47, 0.66)	0.94 (0.85, 1.04)	<0.001
Multivariate difference[†] (95% CI)	0 (referent)	0.14 (0.02, 0.25)	0.28 (0.17, 0.39)	0.39 (0.28, 0.51)	0.67 (0.55, 0.80)	<0.001
Multivariate difference[‡] (95% CI)	0 (referent)	0.16 (0.05, 0.27)	0.32 (0.22, 0.42)	0.43 (0.31, 0.55)	0.71 (0.58, 0.84)	<0.001
Serum β-carotene Levels (µg/dL)	Quintile 1 0-8	Quintile 2 9-12	Quintile 3 13-17	Quintile 4 18-27	Quintile 5 28-674	
Age- and sex-adjusted difference (95% CI)	0 (referent)	-0.20 (-0.32, -0.07)	-0.37 (-0.48, -0.25)	-0.40 (-0.53, -0.27)	-0.62 (-0.72, -0.51)	<0.001
Multivariate difference[†] (95% CI)	0 (referent)	-0.16 (-0.28, -0.05)	-0.30 (-0.41, -0.19)	-0.27 (-0.39, -0.16)	-0.41 (-0.50, -0.32)	<0.001
Multivariate difference[‡] (95% CI)	0 (referent)	-0.15 (-0.26, -0.04)	-0.29 (-0.40, -0.18)	-0.27 (-0.39, -0.16)	-0.40 (-0.48, -0.31)	<0.001

[*]Uric acid levels are reported in milligrams per deciliter; to convert to µmoles per liter, multiply by 59.48. Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.

CI denotes confidence interval.

[†]Adjusted for age, sex, smoking status, body mass index, use of diuretics, beta-blockers, allopurinol and uricosuric agents, hypertension, and glomerular filtration rate.

[‡]Additionally adjusted for intake of alcohol, total energy, total meats, seafood, dairy foods, coffee, sugar-sweetened soft drinks, serum vitamin C levels, and mutually for serum retinol β-carotene levels.

Quintiles of Serum Retinol Levels

Quintiles of Serum β-Carotene Levels

Figure 1. **Multivariate Adjusted Serum Uric Acid Levels According to Quintiles of Serum Retinol and β-Carotene Levels**. The median values according to increasing quintiles of serum retinol and β-Carotene levels (among all participants) were 38, 48, 56, 64, 78 µg/dL and 6, 10, 15, 22, 39 µg/dL, respectively. Error bars indicate standard errors. Serum uric acid levels are adjusted for the same covariates in Table 2 except for sex in sex-specific levels. Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.
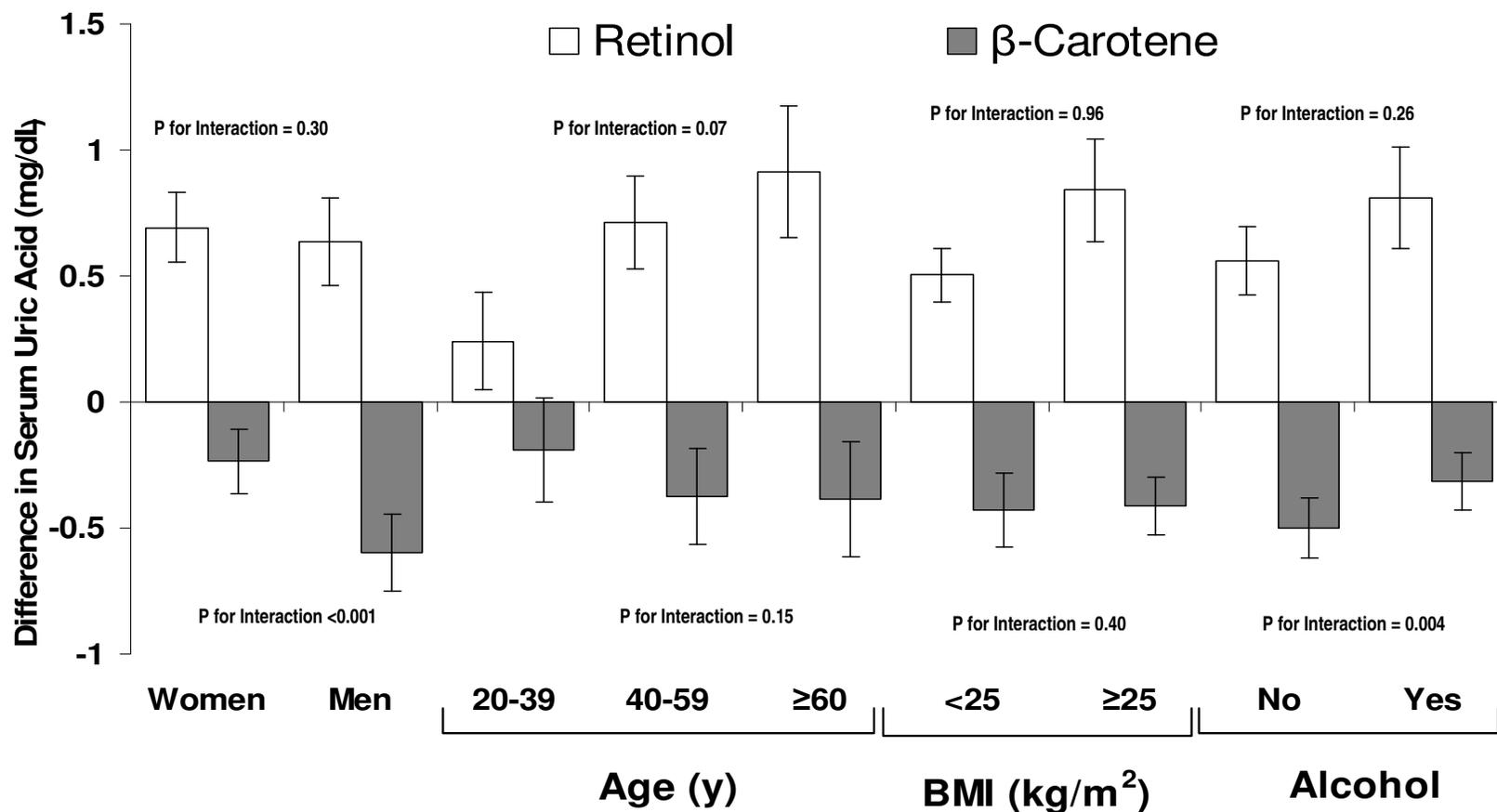
Figure 2. **Multivariate Adjusted Differences in Serum Uric Acid Levels (mg/dL) between Quintile 1 and Quintile 5 of Serum Levels**. Error bars indicate 95% confidence intervals. The P values for interaction in the upper panel are for serum retinol levels and those in the lower pannel are for serum β-carotene levels. Multivariate differences are adjusted for the same covariates in Table 2 except for the sub-grouping variables themselves. Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.
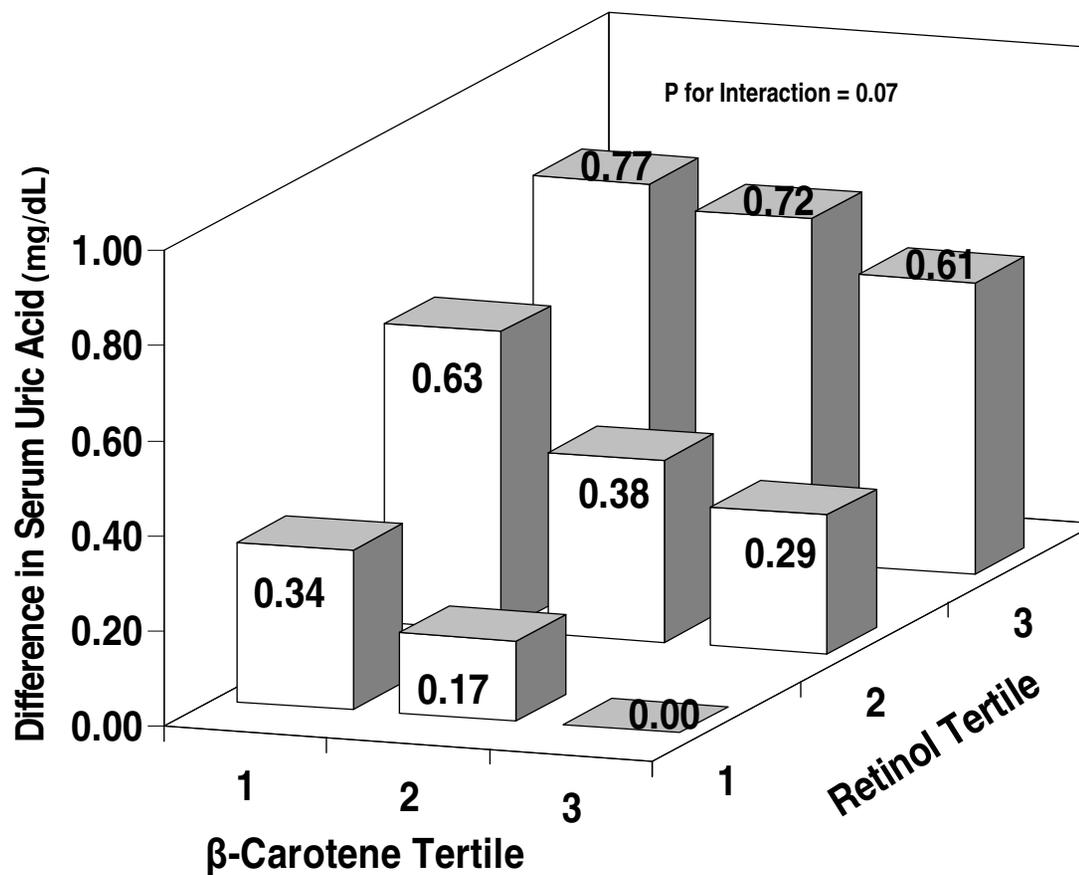
Figure 3. **Multivariate Adjusted Differences in Serum Uric Acid Levels (mg/dL) According to Cross-Classification by Tertiles of Serum Retinol and β-Carotene Levels**. Multivariate differences are adjusted for the same covariates in Table 2. The reference group was participants in the top tertile of β-carotene level and bottom tertile of serum retinol level. Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.