

Dietary vitamin A intakes of Filipino elders with adequate or low liver vitamin A concentrations as assessed by the deuterated-retinol-dilution method: implications for dietary requirements^{1–3}

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ABSTRACT

Background: The vitamin A requirements of elderly humans have not been studied.

Objective: In a cross-sectional study of 60–88-y-old men ($n = 31$) and women ($n = 31$) in rural Philippines, we assessed the dietary intakes of elders with adequate ($\geq 0.07 \mu\text{mol/g}$) or low ($< 0.07 \mu\text{mol/g}$) liver vitamin A concentrations to estimate vitamin A requirements for this age group.

Design: Total-body vitamin A was assessed by the deuterated-retinol-dilution technique; liver vitamin A concentrations were assessed by assuming that liver weight is 2.4% of body weight and that, in this marginally nourished population, 70% of total-body vitamin A is in the liver; serum retinol was measured by HPLC; and dietary intakes were assessed with 3 nonconsecutive 24-h dietary recalls. The mean vitamin A intake + 2 SDs of subjects with adequate liver vitamin A concentrations was used to estimate an acceptable or sufficient vitamin A intake value for elders.

Results: The mean (\pm SD) vitamin A intakes of the men and women with adequate vitamin A in liver were 135 ± 86 and $134 \pm 104 \mu\text{g}$ retinol activity equivalents (RAE)/d, respectively; intakes of the men and women with low vitamin A in liver were 75 ± 53 and $60 \pm 27 \mu\text{g}$ RAE/d, respectively. Total-body vitamin A or liver vitamin A but not serum retinol correlated with dietary RAE, preformed vitamin A, β -carotene, fat, and protein. An estimated acceptable or sufficient dietary vitamin A intake associated with adequate liver vitamin A concentrations in elders is $6.45 \mu\text{g}$ RAE/kg body wt; for a reference 76-kg man and a 61-kg woman, these values are ≈ 500 and $400 \mu\text{g}$ RAE/d, respectively.

Conclusion: The dietary vitamin A intakes of elders with adequate or low liver vitamin A concentrations as estimated by use of the deuterated-retinol-dilution technique are useful for assessing vitamin A requirements. *Am J Clin Nutr* 2004;79:633–41.

KEY WORDS Vitamin A, retinol, deuterated retinol dilution, stable-isotope dilution, carotenoids, β -carotene, retinol activity equivalent, vitamin A requirements, elderly humans

INTRODUCTION

The vitamin A requirements of elderly humans have not been studied. The current US recommended dietary allowances (RDAs) for vitamin A of 900 and 700 μg retinol activity equivalents (RAE)/d for men and women, respectively, have been set to be the same for all adults aged ≥ 19 y (1). The 1989 Philippine

RDAs for men and women aged ≥ 16 y are 525 and 450 μg retinol equivalents (RE)/d, respectively (2). The 2002 FAO/WHO “recommended safe intake” of vitamin A for men and women aged 19–65 y are 600 and 500 μg RE/d; that for all subjects aged > 65 y is 600 μg RE/d (3). However, because no data on the vitamin A needs of elderly persons are available, it is unknown whether the vitamin A requirements of the elderly are similar to or different from those of younger adults.

The liver is the main storage organ for vitamin A (4); thus, liver concentrations of vitamin A are a good indicator of vitamin A status. With the use of the deuterated-retinol-dilution (DRD) technique (5), quantitative estimates of total-body vitamin A and of liver vitamin A concentrations can be obtained without directly measuring liver samples.

In this cross-sectional study, we aimed to assess the vitamin A status of men and women aged ≥ 60 y and to estimate their vitamin A requirements. Specifically, we aimed to determine the habitual dietary vitamin A intakes of elders with adequate or low liver vitamin A concentrations by using a value of $\geq 0.07 \mu\text{mol}$ vitamin A/g liver ($20 \mu\text{g/g}$) as being indicative of an adequate liver reserve. According to Olson (6–8), this concentration of vitamin A in liver will meet all physiologic needs for the vitamin and will maintain a reserve for 3–4 mo when intakes are low or during periods of increased need resulting from infections and other stresses. Another aim of our study was to correlate dietary intakes of vitamin A, provitamin A carotenoids, and other nutri-

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ents (fat, protein, and carbohydrates) with total-body vitamin A, liver vitamin A concentrations, and serum retinol concentrations.

SUBJECTS AND METHODS

Subjects

The study participants were men and women aged ≥ 60 y who resided in the adjacent rural villages of Malabanan and Palsara in the municipality of Balete, Batangas province, ≈ 80 km south of Manila. These villages were selected as study sites because of their relatively large elderly populations and the good probability of finding some elders with low liver vitamin A stores. These communities have low socioeconomic status and a high prevalence of malnutrition among schoolchildren; a 1998 survey conducted by the Nutrition Center of the Philippines (NCP) among schoolchildren in the area showed that vitamin A intake was low (47% of the Philippine RDA) and the prevalence of anemia was high (55%) (9). A list of elderly residents in the villages was verified by house-to-house visits made by NCP personnel with the help of local health workers. Written informed consent was obtained from the elders, and approval to conduct the study was obtained from the Ethical Review Board of the Philippine Council for Health Research and Development and the Tufts University–New England Medical Center Human Investigation Review Committee.

The present study was conducted between March and May 2000. Elders ($n = 179$) were initially interviewed to determine their medical history and dietary habits. Volunteers ($n = 98$) with no history of major illnesses, who did not take medications or nutritional supplements, and who were ambulatory were given a physical examination, a chest X-ray, and an electrocardiogram. Trained nutritionists and nurses performed anthropometric measurements. Fasting blood was drawn for blood tests, which included a complete blood count and measurement of fasting blood sugar, cholesterol, and other biochemical variables (hemoglobin, hematocrit, C-reactive protein, albumin, prealbumin, serum retinol, and carotenoids). The DRD procedure (5) for measurement of total-body and liver vitamin A was conducted on 78 generally healthy subjects; however, 9 of these subjects had incomplete dietary or biochemical data.

Fat absorption test

For the fat absorption test, a 3-d high-fat (≈ 80 g fat/d) menu was prepared by NCP dietitians for the subjects to consume as morning and afternoon snacks for 3 consecutive days in their homes. Stool samples were collected on the fourth day and were transported under ice to a laboratory in Manila for fecal fat analysis with the use of Sudan III dye (Sigma-Aldrich, St Louis) (10, 11). The criteria established by Drumme et al (11) for the microscopic evaluation of split fat in stools were used: a normal (+) stool may contain a fairly large number of fat globules, but the globules are tiny ($< 4 \mu\text{m}$ in diameter); increased fat (++) in stool is characterized by the presence of up to 100 fat globules per high-power field, the diameter of the fat globules being 4–8 μm ; and markedly increased fat (+++) in stool is characterized by the presence of fat globules that are 6–75 μm in diameter and increased in number (> 100 fat droplets per high-power field).

Helminthic infections

Fecal samples were examined for helminths (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm) by using the Kato-

Katz procedure (12). The thresholds proposed for use by a World Health Organization Expert Committee (13) for the classes of intensity of infection (light, moderate, and heavy) for each helminth are as follows: for *A. lumbricoides*, 1–4999 eggs/g feces (epg) (light), 5000–49 999 epg (moderate); and $\geq 50 000$ epg (heavy); for *T. trichiura*, 1–999 epg (light), 1000–9999 epg (moderate), and $\geq 10 000$ epg (heavy); and for hookworm, 1–1999 epg (light), 2000–3999 epg (moderate), and ≥ 4000 epg (heavy). The fecal analyses were done by parasitologists from the Department of Parasitology, University of the Philippines.

Blood handling and tests

Blood hemoglobin and hematocrit measurements were done in the field immediately after blood drawing. Hemoglobin was assayed by using the HemoCue B-Hemoglobin System (Angelholm, Sweden). A centrifuge and refrigerator-freezer were transported from Manila to the study sites to prepare and store the serum samples. To prevent photodegradation of retinoids and carotenoids, venous blood was drawn into aluminum-wrapped evacuated tubes, allowed to clot, and centrifuged at $2800 \times g$ for 10 min in a darkened room at room temperature. Serum (0.5–1 mL aliquots) was transferred into cryovials that were immediately stored at -20°C . At the end of each day, the specimens were transported under dry ice to Manila and stored at -70°C until hand-carried under dry ice to the Human Nutrition Research Center at Tufts University in Boston, where they were kept at -70°C until analyzed.

Serum retinol and carotenoids were analyzed under red light by gradient reversed-phase HPLC with the use of a C_{30} column (14) and retinyl acetate and echinenone as internal standards. Serum albumin was assayed by using the Roche reagent for albumin (Roche Diagnostic Systems, Inc, Somerville, NJ). Serum prealbumin and C-reactive protein were assayed by immunoprecipitation analysis with use of the SPQ Antibody Reagent Set II (Atlantic Antibodies, Stillwater, MN).

Deuterated-retinol-dilution procedure

The DRD procedure was used to assess total-body stores of vitamin A (5). Tetradeuterated retinyl acetate (*all-trans*-retinyl-10,19,19,19- $[\text{}^2\text{H}_4]$ acetate) was synthesized by Cambridge Isotope Laboratories (Andover, MA). We prepared capsules containing 0.015 mmol $[\text{}^2\text{H}_4]$ retinyl acetate in corn oil by dissolving a known amount of isotope in absolute ethanol, adding a predetermined amount of corn oil, and allowing the ethanol to evaporate under nitrogen, as previously described (15).

DRD involves the administration of an oral dose of deuterated retinyl acetate, determination of the ratio of deuterated retinol to nondeuterated retinol (D:H) in serum after the administered isotope has equilibrated with the body's vitamin A pool, and application of a mathematical formula to calculate total-body vitamin A (5). We reported previously that, in elders, an oral dose of deuterated vitamin A will equilibrate (reach a plateau in serum) by 20 d postdosing (15). The DRD technique has been used to assess total-body and liver vitamin A in US (5, 16), Bangladeshi (16–18), and Guatemalan (15) adults. The technique has been validated by Furr et al (5) in generally healthy adult American surgical patients and by Haskell et al (17) in adult Bangladeshi surgical patients with low-to-adequate vitamin A status. In these 2 studies, good agreement was found between the calculated values and values obtained by direct measurement of liver biop-

sies; Pearson product-moment correlation coefficients (r) were 0.88 and 0.75, respectively (5, 17), and the Spearman rank-order correlation coefficient (ρ) in the US study was 0.95 (5).

In the present study, a capsule containing [$^2\text{H}_4$]retinyl acetate was ingested by volunteers with a high-fat meal (consisting of fried rice and fried chicken), and after 20 d, fasting blood was drawn for measurements of serum D:H by gas chromatography–mass spectrometry (19). Values of vitamin A reserves were expressed as total-body vitamin A (mmol retinol or μmol retinol/kg body wt) and as liver vitamin A concentrations (μmol retinol/g liver). The vitamin A concentration in liver was estimated by assuming that liver weight is 2.4% of body weight in adults (6) and that, in this study cohort of marginally nourished individuals, 70% of total-body vitamin A is found in the liver. In well-nourished persons, the liver contains > 90% of total-body vitamin A (4, 6). In poorly or marginally nourished individuals, liver vitamin A concentrations are lower than in well-nourished persons, although vitamin A in other tissues remains relatively constant (4); thus, the percentage of total-body vitamin A in extrahepatic tissues is raised from < 10% to \approx 10–50% and that in liver becomes lowered from > 90% to \approx 50–90% (4, 6).

Dietary assessment

Three nonconsecutive 24-h dietary recalls were obtained from study participants by NCP dietitians. Food models and household measuring tools were used by dietitians to aid the subjects in estimating their food intakes. Dietary intakes of vitamin A, β -carotene, fat, protein, and carbohydrate were assessed by using Philippine food tables (20), and because these food tables do not currently provide information on food carotenoid content other than for β -carotene, intakes of other provitamin A carotenoids (ie, β -cryptoxanthin and α -carotene) were assessed by using the *USDA-NCC Carotenoid Database for US Foods* (21). Note, however, that many Philippine foods are not listed in the USDA-NCC database; thus, intakes of β -cryptoxanthin and α -carotene may have been underestimated. The results from the 3 dietary recalls were averaged. Vitamin A intake was expressed as retinol activity equivalents (RAE), a dietary index that is more conservative than the RE. One RAE is equal to 1 μg retinol or 12 μg β -carotene or 24 μg of other provitamin A carotenoids, whereas 1 RE is equal to 1 μg retinol or 6 μg β -carotene or 12 μg of other provitamin A carotenoids (1).

Statistical analyses

For total-body vitamin A, diet, and serum retinol and provitamin A carotenoid concentrations, a two-factor analysis of variance (ANOVA) was used to study the main effects of sex and liver vitamin A status and their interaction. Variables that were not normally distributed were log transformed. When the sex \times liver vitamin A status interaction was not significant ($P > 0.05$), no further subgroup analysis was performed and only the main effects of sex and of vitamin A status are described and discussed. When appropriate, comparisons between men and women, between subjects with adequate and those with low liver vitamin A concentrations, between subjects with and those without helminthic infections, and between subjects with normal and those with abnormal fat absorption test results were done by using Student's unpaired t test or the Mann-Whitney U test for normal or non-normal distributions, respectively. Additionally, data that could be normalized by log transformation were analyzed by use of

Student's unpaired t tests. To study correlations between variables, Spearman rank-order correlations or Pearson product-moment correlations were done. All statistical analyses were performed by using STATVIEW SE + GRAPHICS software (Abacus Concepts, Inc, Berkeley, CA). For all tests, $P < 0.05$ was considered statistically significant.

RESULTS

Measures of dietary intakes and vitamin A status were obtained from 69 generally healthy elderly volunteers. However, data from 7 women with abnormal fat absorption test results were not included in the final analyses because the total-body vitamin A values of these women were significantly lower than those of the women who absorbed fat normally (median: 0.098 compared with 0.171 mmol retinol; $P = 0.04$). Among the women who malabsorbed fat, total-body vitamin A in those with markedly increased fat (+++) in stool ($n = 4$) was not significantly different from that in those with increased fat (++) in stool ($n = 3$) (median: 0.098 compared with 0.107 mmol retinol, respectively; $P > 0.05$).

Only one subject (a male) had an abnormal C-reactive protein value of 25 mg/L. C-reactive protein concentrations ≥ 10 mg/L are indicative of an acute phase response to infection, during which serum retinol may decrease transiently (22). Because this subject's serum retinol concentration was normal (2.76 $\mu\text{mol/L}$), however, his data were included in the final analyses.

The characteristics of the study participants are presented in **Table 1**. There were no significant differences between the men ($n = 31$) and the women ($n = 31$) in age, body mass index, and serum albumin. However, body weight, height, serum prealbumin, blood hemoglobin, and hematocrit were significantly higher in the men than in the women. The percentage of subjects who were underweight [body mass index (in kg/m^2) < 18.0] was 25.8% (16.1% of the men and 35.5% of the women); the percentage who were overweight (body mass index: 28–30) was 4.8% (6.5% of the men and 3.2% of the women). All subjects had normal serum albumin concentrations (3.6–5.2 g/dL). Three subjects (1 man and 2 women) were anemic on the basis of the World Health Organization hemoglobin cutoff values for anemia of < 13 g/dL for men and < 12 g/dL for women (23); one subject (a woman) had a low hematocrit value on the basis of the World Health Organization criteria for normal hematocrit of 37–43% for women (23).

The loads of *A. lumbricoides* and *T. trichiura* were not significantly different in the men and the women; however, the men tended to have more hookworm than did the women ($P = 0.06$). The intensities of these helminthic infections were mild to moderate and were unrelated to total-body vitamin A, liver vitamin A concentrations, or serum retinol concentrations (data not shown).

The vitamin A status of the study participants is shown in **Table 2**. Total-body vitamin A values tended to be higher in the men than in the women ($P = 0.098$), but not when expressed per kg body wt. Total-body vitamin A was correlated with body weight ($r = 0.48$, $P = 0.0001$). Liver vitamin A concentrations were not significantly different between the men and the women.

Nine subjects (14.5%) had low liver vitamin A concentrations (< 0.07 $\mu\text{mol/g}$); and 25 subjects (40.3%) had liver values that were marginally adequate (0.07–0.14 $\mu\text{mol/g}$). However, none of the subjects had serum retinol values that were low (< 0.7

TABLE 1

Characteristics of the elderly study participants

	Men (n = 31)	Women (n = 31)
Age (y)	66.8 ± 7.0 (60–86) ¹	67.8 ± 8.1 (60–88)
Weight (kg)	53.3 ± 9.7 (40.0–75.1)	45.9 ± 10.1 (30.0–74.8) ²
Height (cm)	159 ± 5 (149–170)	150 ± 5 (144–161) ²
BMI (kg/m ²)	21.0 ± 3.5 (16.8–29.6)	20.2 ± 4.1 (14.5–30.0)
Serum albumin (g/dL)	4.3 ± 0.3 (3.7–4.8)	4.4 ± 0.2 (4.0–4.7)
Serum prealbumin (mg/L)	309 ± 50 (198–394)	259 ± 56 (150–381) ²
Blood hemoglobin (g/dL)	17.2 ± 1.6 (12.4–19.8)	15.2 ± 2.3 (7.2–18.4) ²
Blood hematocrit (%)	45.1 ± 3.3 (40–50)	41.6 ± 2.9 (35–48) ²
<i>Ascaris lumbricoides</i>		
Prevalence (%)	21.4	13.3
Intensity (eggs/g feces)	670 ± 2232 (0–10896)	438 ± 2320 (0–12720)
<i>Trichuris trichiura</i>		
Prevalence (%)	14.3	10.0
Intensity (eggs/g feces)	20 ± 70 (0–360)	20 ± 74 (0–336)
Hookworm		
Prevalence (%)	57.1	30.0
Intensity (eggs/g feces)	419 ± 913 (0–3792)	275 ± 779 (0–3744)

¹ $\bar{x} \pm$ SD; minimum and maximum values in parentheses (all such values).² Significantly different from men, $P \leq 0.002$.

$\mu\text{mol/L}$), and only 2 had serum values that were marginal (0.7–1.05 $\mu\text{mol/L}$). Nevertheless, a significant correlation was found between liver vitamin A concentrations and serum retinol concentrations in this marginally nourished population ($\rho = 0.31$, $P = 0.02$).

The total-body vitamin A values that corresponded to adequate ($\geq 0.07 \mu\text{mol/g}$) or low ($< 0.07 \mu\text{mol/g}$) liver vitamin A concentrations in men and women are shown in **Figure 1**. ANOVA results were as follows: $P = 0.33$ for sex, $P = 0.0001$ for liver vitamin A status, and $P = 0.71$ for sex \times liver vitamin A status interaction. In all subjects (both sexes) with adequate or low liver vitamin A, the total-body vitamin A values were 0.269 ± 0.131 and 0.064 ± 0.025 mmol retinol, respectively ($P = 0.0001$).

We calculated the value of total-body vitamin A/kg body wt that was equivalent to a minimally adequate liver vitamin A concentration of $0.07 \mu\text{mol/g}$ and found this to be $2.40 \mu\text{mol/kg}$. This value was obtained by proportion by using the individual values for liver vitamin A concentration (assuming that 70% of the body's vitamin A reserves are in the liver) and total-body vitamin A/kg body wt.

Selected dietary intakes of the men and women whose liver vitamin A concentrations were either adequate or low are shown in **Table 3**. ANOVA showed no significant sex \times liver vitamin A status interaction related to any of the dietary variables ($P \geq 0.24$).

In all subjects (both sexes), RAE intake was significantly higher among those with adequate than among those with low liver vitamin A concentrations ($P = 0.01$). All subjects with adequate liver vitamin A also had significantly greater intakes of preformed vitamin A ($P = 0.04$), β -carotene ($P = 0.05$), and α -carotene ($P = 0.03$) than did subjects with low liver vitamin A (Table 3).

Between the men and the women, there were no significant differences in mean intakes of RAE (127 and 122 $\mu\text{g/d}$), preformed vitamin A (99 and 103 $\mu\text{g/d}$), β -cryptoxanthin (55 and 47 $\mu\text{g/d}$), α -carotene (26 and 11 $\mu\text{g/d}$), fat (14.4 and 14.1 g/d), carbohydrate (242 and 215 g/d), and total energy (5.2 and 4.7 MJ/d), but the men had significantly higher protein intakes than did the women (36 and 29 g/d; $P = 0.03$) and tended to have higher intakes of β -carotene (294 and 208 $\mu\text{g/d}$; $P = 0.06$). The percentages of total energy obtained from fat, protein, and carbohydrates were 10.4%, 11.7%, and 77.9% for the men and 11.5%, 10.6%, and 77.9% for the women.

All of the elderly male study participants had energy intakes that were below the Philippine RDAs of 2090 kcal (8.7 MJ) for men aged 60–69 y and 1880 kcal (7.9 MJ) for men aged ≥ 70 y (22); their energy intakes were 63% of the Philippine RDA. Among the women, 87% had energy intakes that were below the Philippine RDAs of 1540 kcal (6.4 MJ) for women aged 60–69 y and 1390 kcal (5.8 MJ) for women aged ≥ 70 y (22); their energy intakes were 71% of the RDA.

TABLE 2Vitamin A status of the elderly study participants¹

	Men (n = 31)	Women (n = 31)
Total-body vitamin A (mmol retinol) ²	0.263 ± 0.144 (0.038–0.664)	0.215 ± 0.137 (0.020–0.590)
Total-body vitamin A/kg body wt ($\mu\text{mol retinol/kg}$)	4.8 ± 2.0 (0.9–8.9)	4.8 ± 3.2 (0.6–15.0)
Liver vitamin A ($\mu\text{mol retinol/g}$) ³	0.139 ± 0.058 (0.026–0.260)	0.140 ± 0.095 (0.019–0.438)

¹ All values are $\bar{x} \pm$ SD; minimum and maximum values in parentheses.² Assessed by use of the deuterated-retinol-dilution procedure (5).³ Estimated by assuming that liver weight is 2.4% of body weight and that, in this marginally nourished population, 70% of total-body vitamin A is in the liver.

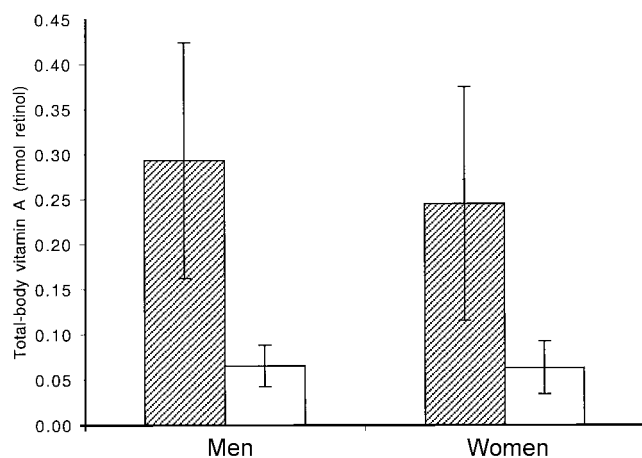


FIGURE 1. Mean (\pm SD) total-body vitamin A values corresponding to adequate (▨; $\geq 0.07 \mu\text{mol/g}$) and low (□; $< 0.07 \mu\text{mol/g}$) liver vitamin A concentrations in elderly men ($n = 27$ with adequate vitamin A concentrations and 4 with low concentrations) and women ($n = 26$ with adequate vitamin A concentrations and 5 with low concentrations). Total-body vitamin A was estimated by the deuterated-retinol-dilution procedure (5); liver vitamin A was estimated by assuming that liver weight is 2.4% of body weight and that, in this marginally nourished population, 70% of total-body vitamin A is in the liver. ANOVA: $P = 0.33$ for sex, $P = 0.0001$ for vitamin A status, and $P = 0.71$ for sex \times vitamin A status interaction.

Among the men, 94% had protein intakes that were below the Philippine RDA of 60 g for adult males (22); their protein intakes were 61% of the RDA. Among the women, 94% had protein intakes that were below the Philippine RDA of 52 g for adult females (22); their protein intakes were 56% of the RDA.

The Spearman rank-order correlation coefficients (ρ) or Pearson product-moment correlation coefficients (r) between selected dietary intakes and vitamin A status measures in elders are shown in **Table 4**. Dietary RAE, preformed vitamin A, β -carotene, fat, and protein were significantly correlated with total-body vitamin A. Dietary RAE and preformed vitamin A were also significantly correlated with liver vitamin A concentrations, and dietary β -carotene and fat tended to be correlated with liver vitamin A concentrations ($P = 0.09$ and $P = 0.06$, respectively). In contrast, none of the dietary intakes mentioned were correlated with serum retinol concentrations. Intakes of carbohydrate were unrelated to total-body vitamin A, liver vitamin A concentrations, and serum retinol concentrations.

The serum concentrations of retinol and provitamin A carotenoids in the men and women with adequate or low liver vitamin A concentrations are shown in **Table 5**. ANOVA showed no significant sex \times liver vitamin A status interaction related to any of the variables in serum ($P \geq 0.50$), but a sex effect on serum retinol was noted ($P = 0.047$).

Serum retinol was significantly higher in the men than in the women (2.06 and 1.78 $\mu\text{mol/L}$; $P = 0.02$), but there were no significant differences in serum concentrations of *trans*- β -carotene, β -cryptoxanthin, α -carotene, and 13-*cis*- β -carotene between the sexes. Among all subjects (both sexes), serum retinol tended to be higher in those with adequate than in those with low liver vitamin A concentrations (1.96 and 1.64 $\mu\text{mol/L}$; $P = 0.06$). However, serum carotenoid values (*trans*- β -carotene, β -cryptoxanthin, α -carotene, and 13-*cis*- β -carotene) between these 2 groups were not significantly different.

We calculated an acceptable or sufficient dietary vitamin A intake value (in $\mu\text{g RAE/kg body wt}$) associated with adequate liver vitamin A concentrations ($\geq 0.07 \mu\text{mol/g}$) in persons ≥ 60 y of age by taking the mean RAE + 2 SDs [$135 + 2(95) = 325 \mu\text{g RAE}$] consumed by all subjects whose liver vitamin A concentrations were adequate ($n = 53$) and dividing this value by their mean body wt (50.40 kg). Adding 2 SDs to the mean RAE in the calculation gives a margin of safety to cover the needs of most healthy elders. We had chosen a midpoint value of 70% as the percentage of total-body vitamin A present in livers of marginally nourished individuals; however, these percentages may range from $\approx 50\%$ to 90% (4, 6). We calculated that for most relatively healthy elders, an acceptable or sufficient daily dietary vitamin A intake associated with adequate liver vitamin A reserves is 6.45 $\mu\text{g RAE/kg body wt}$. For a reference 76-kg man and a 61-kg woman who are ≥ 60 y old, acceptable vitamin A intakes are 490 and 393 $\mu\text{g RAE/d}$, respectively. These numbers may be rounded to 500 and 400 $\mu\text{g RAE/d}$, respectively.

We also calculated, for comparison, what the acceptable vitamin A intake would be if 50% or 90% of total-body vitamin A was assumed to be in the liver. Assuming a 50% liver storage value, 44 subjects had adequate liver vitamin A concentrations ($\geq 0.07 \mu\text{mol/g}$), and an acceptable daily vitamin A intake was calculated to be 6.78 $\mu\text{g RAE/kg body wt}$ (515 and 414 $\mu\text{g RAE}$ for a reference man and women, respectively). Assuming a 90% liver storage value, 55 subjects had adequate liver vitamin A concentrations, and an acceptable daily vitamin A intake was calculated to be 6.39 $\mu\text{g RAE/kg body wt}$ (486 and 390 $\mu\text{g RAE}$ for a reference man and women, respectively).

DISCUSSION

The mean total amount of vitamin A in the body of rural Filipino elders (0.24 mmol retinol) is 3 times lower than what we reported for rural Guatemalan elders (0.78 mmol retinol) (15) by using the same DRD procedure (5). The better vitamin A status of the Guatemalan elders is most likely due to the national Guatemalan program of fortifying domestic sugar with vitamin A and not to socioeconomic differences between the rural populations. The calculated mean liver vitamin A concentration of the Filipino elders (0.14 $\mu\text{mol/g liver}$) is also lower than values obtained by direct measurement of liver vitamin A in autopsies of subjects who were ≥ 60 y old at the time of death (values in $\mu\text{mol/g liver}$): 0.34 in Illinois (24), 0.44 in Canada (25), 0.57 in 5 US areas (Missouri, Iowa, Ohio, California, and Texas) (4), 0.57 in London (26), 0.93 in New Zealand (27), and 1.22 in Washington, DC (28).

An adequate liver vitamin A concentration is considered to be $\geq 0.07 \mu\text{mol/g liver}$ (20 $\mu\text{g/g}$) (6–8). We determined that the corresponding value expressed as total-body vitamin A is 2.4 $\mu\text{mol/kg body wt}$. We investigated the dietary vitamin A intakes of men and women aged ≥ 60 y whose liver vitamin A concentrations were \geq or $< 0.07 \mu\text{mol/g}$ (or whose total-body stores of vitamin A were \geq or $< 2.4 \mu\text{mol/kg body wt}$), with the goal of obtaining insights regarding the vitamin A requirements of this age group. This approach is appropriate because the data indicate that dietary vitamin A intakes are correlated with total-body vitamin A or liver vitamin A. A similar approach cannot be done by using serum retinol concentrations because this measure is subject to homeostatic control (29). The present study and other studies (30–32) found that vitamin A intakes are unrelated or

TABLE 3

Selected dietary intakes of the elderly men and women with adequate ($\geq 0.07 \mu\text{mol/g}$) or low ($< 0.07 \mu\text{mol/g}$) liver vitamin A concentrations¹

	Men		Women		All subjects	
	Adequate (n = 27)	Low (n = 4)	Adequate (n = 26)	Low (n = 5)	Adequate (n = 53)	Low (n = 9)
RAE ($\mu\text{g/d}$) ²						
$\bar{x} \pm \text{SD}$	135 \pm 86	75 \pm 53	134 \pm 104	60 \pm 27	135 \pm 95	67 \pm 38 ³
Minimum–maximum	31–422	17–141	27–513	30–85	27–513	17–141
Preformed vitamin A ($\mu\text{g/d}$)						
$\bar{x} \pm \text{SD}$	104 \pm 76	64 \pm 47	113 \pm 102	50 \pm 22	108 \pm 89	56 \pm 34 ³
Minimum–maximum	2–321	12–124	10–510	28–76	2–510	12–124
β -Carotene ($\mu\text{g/d}$)						
$\bar{x} \pm \text{SD}$	319 \pm 255	125 \pm 75	229 \pm 249	100 \pm 71	275 \pm 254	112 \pm 69 ³
Minimum–maximum	8–1199	52–198	7–1152	18–195	7–1199	18–198
β -Cryptoxanthin ($\mu\text{g/d}$)						
$\bar{x} \pm \text{SD}$	63 \pm 173	0	49 \pm 85	35 \pm 68	56 \pm 136	19 \pm 51
Minimum–maximum	0–858	0	0–309	0–155	0–858	0–155
α -Carotene ($\mu\text{g/d}$)						
$\bar{x} \pm \text{SD}$	30 \pm 84	0	13 \pm 29	0	22 \pm 63	0 ³
Minimum–maximum	0–359	0	0–136	0	0–359	0
Energy (MJ/d)						
$\bar{x} \pm \text{SD}$	5.2 \pm 1.7	5.4 \pm 1.3	4.8 \pm 2.0	3.9 \pm 1.0	5.0 \pm 1.8	4.6 \pm 1.3
Minimum–maximum	2.2–8.6	4.1–7.2	1.7–9.3	2.6–5.2	1.7–9.3	2.6–7.2
Fat (g/d)						
$\bar{x} \pm \text{SD}$	15.3 \pm 10.7	8.3 \pm 5.0	14.1 \pm 8.2	14.4 \pm 11.8	14.7 \pm 9.5	11.7 \pm 9.4
Minimum–maximum	2.8–43.4	3.8–14.7	3.1–37.9	5.1–33.3	2.8–43.4	3.8–33.3
Protein (g/d) ⁴						
$\bar{x} \pm \text{SD}$	36.5 \pm 14.6	35.7 \pm 9.9	29.5 \pm 12.8	26.2 \pm 7.0	33.1 \pm 14.0	30.4 \pm 9.3
Minimum–maximum	11.1–71.1	25.3–48.2	11.7–62.9	20.0–37.8	11.1–71.1	20.0–48.2
Carbohydrate (g/d)						
$\bar{x} \pm \text{SD}$	238 \pm 80	267 \pm 73	223 \pm 99	177 \pm 55	231 \pm 89	217 \pm 76
Minimum–maximum	104–418	208–361	81–444	116–254	81–444	116–361

¹ Philippine food tables (20) were used to assess intakes of preformed vitamin A, β -carotene, fat, protein, and carbohydrate, and the *USDA-NCC Carotenoid Database for US Foods* (21) was used to assess intakes of α -carotene and β -cryptoxanthin. Liver vitamin A concentrations were estimated by assuming that liver weight is 2.4% of body weight and that, in this marginally nourished population, 70% of total-body vitamin A is in the liver. Total-body vitamin A was assessed by use of the deuterated-retinol-dilution procedure (5). ANOVA showed no significant sex \times liver vitamin A status interaction related to any of the dietary variables.

² Total dietary vitamin A intake expressed in μg retinol activity equivalents (RAE). 1 RAE = 1 μg dietary preformed vitamin A or 12 μg β -carotene or 24 μg β -cryptoxanthin or α -carotene (1).

³ Significantly different from all subjects with adequate liver vitamin A concentrations, $P < 0.05$ (main effect of vitamin A status).

⁴ Significant main effect of sex ($P < 0.05$).

only weakly related (33) to serum retinol concentrations, because serum retinol values remain in the normal range unless liver reserves are severely depleted.

We included data from elders found to have mild-to-moderate helminthic infections because we found these to be unrelated to vitamin A status. Among 3–6-y-old Indonesian children with parasitic loads that were 10 times greater than what we observed among these elders, it was reported that serum retinol concentrations were improved by anthelmintic treatment plus provision of additional dietary fat and β -carotene sources (34).

Elderly men tended to have greater amounts of total-body vitamin A than did elderly women. However, when expressed per kg body wt or per g liver, vitamin A values in men and women were similar. The lack of a sex difference in the vitamin A content of livers obtained at autopsies has been reported (4, 25). The male study participants, however, had higher serum retinol concentrations than did the women, as was found in the third National Health and Nutrition Examination Survey (35) and other studies (30, 33, 36).

The 3 nonconsecutive 24-h dietary recalls provided a reasonable average estimate of usual vitamin A intakes because signif-

icant correlations were found between RAE and total-body or liver vitamin A. However, the study was done during a relatively short time period (March to May), and we did not test whether seasonality might affect estimates of dietary vitamin A intake and vitamin A status in the population. There were no significant differences between men and women in RAE intakes. Assuming that 70% of total-body vitamin A was in the liver of these study participants, 15% had liver vitamin A concentrations that are considered to be low ($< 0.07 \mu\text{mol/g}$). The mean total vitamin A intake (RAE) of subjects with low liver vitamin A reserves was only about one-half of that of subjects with adequate liver reserves.

The term *estimated average requirement* (EAR) was introduced by a US scientific panel who evaluated the dietary reference intakes of US and Canadian populations (1). The EAR is defined as “the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and sex group,” and the RDA—which is defined as “the average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97–98%) healthy individuals in a particular life stage and sex group”—was set to be equal

TABLE 4Correlations of selected dietary intakes with vitamin A status in Filipino elders¹

	ρ or r	P
RAE vs total-body vitamin A	0.43	0.0004
RAE vs liver vitamin A concentration	0.36	0.004
RAE vs serum retinol concentration	0.12	0.35
Preformed vitamin A vs total-body vitamin A	0.35	0.01
Preformed vitamin A vs liver vitamin A concentration	0.27	0.03
Preformed vitamin A vs serum retinol concentration	0.08	0.52
β -Carotene vs total-body vitamin A	0.30	0.02
β -Carotene vs liver vitamin A concentration	0.22	0.09
β -Carotene vs serum retinol concentration	0.16	0.22
β -Cryptoxanthin vs total-body vitamin A	0.12	0.58
β -Cryptoxanthin vs liver vitamin A concentration	0.03	0.90
β -Cryptoxanthin vs serum retinol concentration	-0.09	0.50
α -Carotene vs total-body vitamin A	0.14	0.30
α -Carotene vs liver vitamin A concentration	0.16	0.22
α -Carotene vs serum retinol concentration	0.07	0.59
Fat vs total-body vitamin A	0.35	0.01
Fat vs liver vitamin A concentration	0.24	0.06
Fat vs serum retinol concentration	0.05	0.72
Protein vs total-body vitamin A	0.27	0.03
Protein vs liver vitamin A concentration	0.12	0.37
Protein vs serum retinol concentration	0.16	0.20
Carbohydrate vs total-body vitamin A	0.09	0.49
Carbohydrate vs liver vitamin A concentration	0.01	0.93
Carbohydrate vs serum retinol concentration	0.17	0.19

¹ Spearman rank-order correlation coefficient (ρ) or Pearson product-moment correlation coefficient (r) for 62 elders. One retinol activity equivalent (RAE) = 1 μg dietary preformed vitamin A or 12 μg β -carotene or 24 μg β -cryptoxanthin or α -carotene (1). Total-body vitamin A was assessed by use of the deuterated-retinol-dilution procedure (5). Liver vitamin A concentrations were estimated by assuming that liver weight is 2.4% of body weight and that, in this marginally nourished population, 70% of total-body vitamin A is in the liver.

to the EAR + 2 SDs (1). In the present study, the small number of subjects with low liver vitamin A concentrations (< 0.07 $\mu\text{mol/g}$) did not allow us to determine an accurate EAR. How-

ever, the habitual RAE intakes of elderly subjects whose liver vitamin A amounts are adequate ($\geq 0.07 \mu\text{mol/g}$) can provide information regarding the vitamin A requirements of elderly

TABLE 5Serum concentrations of retinol and provitamin A carotenoids in the elderly men and women with adequate ($\geq 0.07 \mu\text{mol/g}$) or low (< 0.07 $\mu\text{mol/g}$) liver vitamin A concentrations¹

	Men		Women	
	Adequate ($n = 27$)	Low ($n = 4$)	Adequate ($n = 26$)	Low ($n = 5$)
	$\mu\text{mol/L}$		$\mu\text{mol/L}$	
Retinol ²				
$\bar{x} \pm \text{SD}$	2.08 \pm 0.48	1.89 \pm 0.62	1.84 \pm 0.61	1.44 \pm 0.34
Minimum-maximum	1.47-3.32	1.32-2.74	0.97-3.53	1.01-1.88
Total provitamin A carotenoids				
$\bar{x} \pm \text{SD}$	0.40 \pm 0.33	0.34 \pm 0.18	0.42 \pm 0.26	0.26 \pm 0.11
Minimum-maximum	0.03-1.43	0.08-0.48	0.11-1.23	0.17-0.39
<i>trans</i> - β -Carotene				
$\bar{x} \pm \text{SD}$	0.22 \pm 0.20	0.19 \pm 0.11	0.23 \pm 0.14	0.16 \pm 0.07
Minimum-maximum	0.01-0.79	0.04-0.30	0.05-0.70	0.11-0.25
β -Cryptoxanthin				
$\bar{x} \pm \text{SD}$	0.11 \pm 0.17	0.09 \pm 0.09	0.12 \pm 0.12	0.05 \pm 0.02
Minimum-maximum	0.01-0.78	0.02-0.21	0.01-0.51	0.03-0.08
α -Carotene				
$\bar{x} \pm \text{SD}$	0.06 \pm 0.04	0.05 \pm 0.04	0.06 \pm 0.02	0.04 \pm 0.03
Minimum-maximum	0.01-0.18	0.02-0.10	0.02-0.12	0.02-0.07
13- <i>cis</i> - β -Carotene				
$\bar{x} \pm \text{SD}$	0.01 \pm 0.01	0.01 \pm 0.01	0.02 \pm 0.01	0.01 \pm 0.01
Minimum-maximum	0-0.05	0-0.03	0-0.05	0.01-0.02

¹ Liver vitamin A concentrations were estimated by assuming that liver weight is 2.4% of body weight and that, in this marginally nourished population, 70% of total-body vitamin A is in the liver. Total-body vitamin A was assessed by use of the deuterated-retinol-dilution procedure (5).


² ANOVA showed no significant sex \times vitamin A status interaction, but a sex effect on serum retinol was noted ($P = 0.047$).

people. We defined an acceptable or sufficient dietary vitamin A intake associated with adequate liver vitamin A reserves in nearly all relatively healthy men and women aged ≥ 60 y by taking the mean RAE + 2 SDs of elders with adequate liver vitamin A and adjusting for differences in body weights. There was no advantage to having separate calculations for men and women because their total-body vitamin A when expressed per kg body wt was identical. The acceptable or sufficient amount of vitamin A intake by elders is 6.45 μg RAE/kg body wt, or 500 and 400 μg RAE/d for a reference 76-kg man and a reference 61-kg woman, respectively. On the basis of the results of the present study, the Philippine (2) and FAO/WHO (3) recommendations for elderly persons appear adequate, whereas the US recommendations for the elderly (1) seem high.

Olson (6) calculated that the recommended dietary intake for adult men and women is 9.3 μg retinol/kg body wt, or 707 and 567 μg for a reference man and a reference woman, respectively. Thus, he suggested that the US dietary vitamin A recommendations should be lowered to 700 and 600 μg retinol, respectively, for adult men and women of all ages (6). Our study was done on ≥ 60 -y-old subjects only and did not test whether the vitamin A requirements of young and older adults differ. However, age-related changes in vitamin A status and metabolism have been reported. Data from the third National Health and Nutrition Examination Survey showed an increase in serum retinol in older compared with younger adults (35). Absorption of β -carotene and its conversion into retinyl esters have been reported to be enhanced in older humans (37). In rats, the intestinal absorption of vitamin A was found to be increased with age (38, 39), possibly as the result of decreased thickness of the unstirred water layer in the small intestine of older animals (40). Another study in rats, however, did not show any effect of age on vitamin A absorption (41). Furthermore, decreased clearance of vitamin A from the circulation by hepatic uptake has been reported in elderly humans (42) and in aged mice (43).

Use of the DRD technique for assessing the body's vitamin A reserves shows associations that are not discernible with the use of serum retinol, which is subject to homeostatic control. Our finding of a significant correlation of dietary β -carotene with total-body vitamin A, but not serum retinol, has important implications for the effectiveness of plant carotenoids as a vitamin A source. de Pee et al (44) reported no improvement in serum or breastmilk retinol in breastfeeding Indonesian women after they consumed dark-green leafy vegetables and carrots; thus, the authors questioned whether increasing vegetable intakes can combat vitamin A deficiency. However, this question can best be answered by using stable-isotope-dilution procedures for assessment of vitamin A reserves, and not by serum retinol measurements.

We found a significant correlation of fat intake with total-body vitamin A but not with serum retinol concentrations. Studies in ferrets (45) and Mongolian gerbils (46) fed β -carotene showed that increasing dietary fat results in higher hepatic vitamin A but has no effect on serum or plasma retinol. Furthermore, our study showed a significant correlation of protein intake with total-body vitamin A, although the correlation was weaker than that observed between dietary fat and total-body vitamin A; dietary protein was unrelated to serum retinol concentrations. In ferrets fed β -carotene, increased dietary protein resulted in increased vitamin A concentrations in liver but not plasma (45).

In summary, we assessed the total-body and liver vitamin A reserves of men and women aged ≥ 60 y by use of the DRD technique and determined the subjects' total dietary vitamin A intakes (RAE). Elders with low liver reserves ($< 0.07 \mu\text{mol/g}$) had intakes that were about one-half the intakes of those with adequate liver reserves ($\geq 0.07 \mu\text{mol/g}$). We estimated that an acceptable or sufficient dietary vitamin A intake associated with adequate vitamin A reserves in liver is 6.45 μg RAE/kg body wt; for a reference 76-kg man and a reference 61-kg woman aged ≥ 60 y, these intakes are 500 and 400 μg RAE/d, respectively. 

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JDR-M was responsible for study design, HPLC and gas chromatography–mass spectrometry analyses of serum, data analysis and interpretation, and writing of the manuscript; FSS was responsible for study design and the fieldwork and procedures in the Philippines; LSF was responsible for fieldwork and dietary assessments; CSP was responsible for subject screening and medical procedures; JAAS was responsible for assessment of helminthic loads; GGD was responsible for gas chromatography–mass spectrometry procedures; and RMR was responsible for study design and data interpretation. The authors had no conflicts of interest with the sponsoring organization.

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