Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women

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Article abstract—*Background:* Antioxidant nutrients may reduce the risk of MS. In a recent case-control study, vitamin C intake was significantly inversely associated with MS risk among women. However, no prospective data are available. *Objective:* To examine prospectively the associations of intakes of carotenoids, vitamin C, and vitamin E with the risk of MS among women. *Methods:* The authors documented the occurrence of definite and probable MS within two large cohorts of women who completed detailed and validated semiquantitative food frequency questionnaires. One cohort (Nurses' Health Study) comprised 81,683 women aged 38 to 63 years in 1984, who were followed for 12 years; the other (Nurses' Health Study II) comprised 95,056 women aged 27 to 44 years in 1991, who were followed for 6 years. *Results:* The authors documented a total of 214 cases of MS. After adjustments for age, latitude of birthplace, pack-years of smoking, and total energy intake, the pooled multivariate relative risks (95% CIs) comparing women in the highest quintile with those in the lowest quintile were 1.1 (0.7 to 1.7) for α-carotene, 1.1 (0.7 to 1.6) for β-carotene, 1.4 (0.8 to 2.2) for β-cryptoxanthin, 1.0 (0.6 to 1.5) for lycopene, 1.0 (0.7 to 1.6) for lutein/zeaxanthin, 1.4 (0.9 to 2.1) for total vitamin C, 1.3 (0.9 to 2.0) for dietary vitamin C, 0.8 (0.6 to 1.3) for total vitamin E, and 0.9 (0.6 to 1.4) for dietary vitamin E. The authors found no associations between intakes of fruits and vegetables and risk of MS. Use of vitamin C, vitamin E, and multivitamin supplements was also unrelated to risk of MS. *Conclusions:* These findings do not support hypotheses relating higher intakes of dietary carotenoids, vitamin C, and vitamin E to reduced risk of MS in women.

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White matter has a low concentration of antioxidant enzymatic activities and is therefore particularly vulnerable to damage from exposure to reactive oxygen species.[1] Lipid peroxidation caused by reactive oxygen species has been hypothesized to damage white matter of the brain in MS.[1] This hypothesis was supported by the findings that individuals with MS have increased concentrations of lipid peroxidation products in the CSF,[2,3] lower blood concentrations of vitamin E[4] and selenium,[5,6] and reduced glutathione peroxidase activities in major types of blood cells[5-10] and CSF[3] compared with healthy control subjects. Decreased concentrations of glutathione and α-tocopherol and increased concentrations of uric acid were also found in plaques compared with surrounding white matter.[11] However, no significant difference was observed in the mean concentrations of vitamin E in CSF in patients with MS compared with control subjects, although MS patients had lower concentrations of serum vitamin E.[12] The etiologic significance of these findings is uncertain, as they could be a consequence of the disease itself. Because of their antioxidant properties, dietary carotenoids, vitamin C, and vitamin E can neutralize reactive oxygen species[13] and thus are hypothesized to reduce the risk of MS. Epidemiologic data relating intakes of dietary carotenoids, vitamin C, and vitamin E to risk of MS are sparse. A case-control investigation reported a lower risk with vitamin C intake and observed no associations with dietary intakes of carotene and vitamin E.[14] Intakes of fruits and vegetables, which are rich in carotenoids, vitamin C, and vitamin E, were also not associated with risk of MS in several case-control studies.[14–18] Because no prospective data are available, we examined the associations between intakes of dietary carotenoids, vitamin C, and vitamin E and risk of MS in two large cohorts of women, the Nurses' Health Study (NHS) and NHS II.

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Methods. *Study population.* The NHS cohort was established in 1976, when 121,700 female registered nurses

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aged 30 to 55 years living in 11 states completed a mailed questionnaire about their medical history and health-related behaviors. Every 2 years, questionnaires have been sent to women to update information on potential risk factors and to ascertain newly diagnosed diseases. In 1980, a 61-food item semiquantitative food frequency questionnaire was included to obtain dietary information. In 1984, the food frequency questionnaire was expanded to 116 food items. Similar questionnaires were used to update dietary intakes in 1986, 1990, and 1994. Because the expanded questionnaires contained more food items that are major contributors to certain specific dietary carotenoids in this cohort, we followed the cohort who returned the 1984 food frequency questionnaire in this study. Through May 31, 1996, the follow-up was 98% complete as a percentage of potential person-years. After more than four mailings, 81,757 women returned the 1984 food frequency questionnaire. For the analyses presented here, women were excluded from the 1984 baseline population if they completed a 1984 dietary questionnaire with implausible total energy intake (i.e., <2,761 kJ/day [660 kcal/day] or >14,644 kJ/day [3,500 kcal/day]) or if they left more than 10 food items blank. These exclusions left a total of 81,683 women for the analyses. The study was approved by the Human Research Committee at the Brigham and Women's Hospital.

The NHS II cohort was established in 1989 when 116,671 female registered nurses aged 25 to 42 who were living in 14 states responded to a mailed questionnaire on their life style and other health-related information. Follow-up questionnaires were sent to cohort members every 2 years. The response rate was 90% through May 31, 1997. In 1991, a 133-food item semiquantitative food frequency questionnaire was included to obtain dietary information. A similar questionnaire was used to update dietary information in 1995. For the analyses presented here, women were excluded from the 1991 baseline population if they completed a 1991 dietary questionnaire with implausible total energy intake (i.e., <3,347 kJ/day [800 kcal/day] or >17,573 kJ/day [4,200 kcal/day]) or if they left more than 70 food items blank. These exclusions left a total of 95,056 women for the analyses. The study was approved by the Human Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

Dietary assessment. The validity and reliability of the food frequency questionnaires used in the NHS and NHS II have been described elsewhere.[19-22] For each food, a commonly used unit or portion size (i.e., one orange or one-half cup of broccoli) was specified, and women were asked how often on average over the previous year they had consumed that amount of each food. There were nine possible responses, ranging from "never" to "six or more times per day." Nutrient intakes were computed by multiplying the frequency response by the nutrient content of the specified portion sizes. Values for nutrients were derived from the US Department of Agriculture (USDA) sources[23] and supplemented with information from manufacturers. Food composition data for specific types of carotenoids were based on the USDA-National Cancer Institute carotenoid database.[24,25] Values for lutein and zeaxanthin were reported as combined. The carotenoid content of tomato-based food products was recently updated with values from the USDA.[26]

We first asked questions on the use of specific vitamins and brand and type of multivitamins as well as dose and duration of use in 1980 in the NHS. In the NHS II, similar questions were asked in 1991 for vitamin A, C, and E supplements and in 1989 for multivitamins. Information on the use of specific vitamin supplements and multivitamins was updated every 2 years in these two cohorts.

Nutrient intakes calculated from the 1986 food frequency questionnaire in the NHS were reasonably correlated with those recorded by 191 participants who kept diet diaries for two 1-week periods over 1 year.[22] The Pearson correlation coefficient was 0.76 for vitamin C between energy-adjusted nutrient estimate from the 1986 food frequency questionnaire and from the two 1-week dietary records.[22] Vitamin E intake calculated by the food frequency questionnaires used in the NHS and NHS II was positively correlated with its plasma concentrations in three studies ($r = 0.34$[27]; $r = 0.51$[28]; $r = 0.41$[29]). The estimates of specific dietary carotenoids from the 1986 food frequency questionnaire in the NHS were significantly correlated with their respective plasma concentrations; among non-smoking women, the Pearson correlation coefficients were 0.48 for α-carotene, 0.27 for β-carotene and lutein/zeaxanthin, 0.32 for β-cryptoxanthin, and 0.21 for lycopene.[30]

Ascertainment of MS cases. Newly diagnosed cases of MS were identified by self-report on each biennial questionnaire from 1986 to 1996 in the NHS and from 1993 to 1997 in the NHS II. Deaths in the cohorts were identified by reports from family members, the postal service, and a search of the National Death Index; we estimated that 98% of all deaths were identified.[31] We asked women who reported MS for permission to obtain medical records. We then sent a questionnaire to the treating neurologists and asked about the certainty of their diagnosis (definite, probable, possible, not MS), the clinical history, and the results of laboratory tests. We sent the questionnaire to the participant's internist if the neurologist did not respond to us or a neurologist was not involved. For the analyses presented here, we included the cases that were definite and probable according to the treating physicians. As previously described, the validity of these diagnoses was confirmed by applying the Poser criteria[32] to the clinical and laboratory data provided by the treating physicians and by review of a sample of medical records.[33] We documented 97 new cases of MS during 12 years of follow-up in the NHS and 117 new cases of MS during 6 years of follow-up in the NHS II.

Statistical analysis. Person-years of observation for each participant were calculated from the date of returning the dietary questionnaire to the date of diagnosis of MS, death, or end of follow-up, whichever came first. The end of follow-up was May 31, 1996, for the NHS and May 31, 1997, for the NHS II. For nutrient analyses, women were categorized by quintiles of the baseline intakes of dietary carotenoids, vitamin C, and vitamin E. We had limited power to detect a weak effect (power = 45% for relative risk [RR] = 0.7 in the highest quintile, assuming $\alpha = 0.05$) because of the relatively small number of MS cases documented in these two cohorts.

For each category of nutrient intake, we calculated the incidence rate by dividing the number of MS cases by the number of person-years of follow-up. RRs were calculated by dividing the incidence rate in an exposure category by

Table 1 *Multivariate relative risks (RR) of MS and 95% CI according to intakes of dietary carotenoids, vitamin C, and vitamin E (quintile 5 vs quintile 1) in different models*

Nutrient	Nurses' Health Study, RR* (95% CI)				Nurses' Health Study II, RR* (95% CI)			
	Baseline 1984 diet follow-up: 1984–1996, 97 cases	Baseline 1984 diet follow-up: 1986–1996, 83 cases	Cumulative average diet follow-up: 1984–1996, 97 cases	Most recent diet follow-up: 1984–1996, 97 cases	Baseline 1991 diet follow-up: 1991–1997, 117 cases	Baseline 1991 diet follow-up: 1993–1997, 83 cases	Cumulative average diet follow-up: 1991–1997, 117 cases	Most recent diet follow-up: 1991–1997, 117 cases
α-Carotene, μg/d	1.0 (0.6–2.0)	1.1 (0.6–2.2)	1.1 (0.6–2.1)	0.7 (0.3–1.6)	1.1 (0.6–2.0)	1.1 (0.6–2.1)	1.2 (0.7–2.0)	1.1 (0.6–2.0)
β-Carotene, μg/d	1.1 (0.6–2.2)	1.1 (0.5–2.2)	1.1 (0.5–2.4)	1.3 (0.6–2.5)	1.0 (0.6–1.7)	1.1 (0.5–2.1)	1.0 (0.6–1.8)	0.8 (0.5–1.4)
β-Cryptoxanthin, μg/d	2.3 (1.1–4.4)	2.1 (1.0–4.3)	1.4 (0.7–2.9)	1.0 (0.5–2.0)	0.8 (0.4–1.6)	0.9 (0.4–1.8)	1.0 (0.6–1.9)	1.2 (0.6–2.1)
Lycopene, μg/d	0.8 (0.4–1.5)	0.9 (0.5–1.7)	0.9 (0.5–1.6)	1.5 (0.8–3.0)	1.1 (0.6–1.9)	0.9 (0.4–1.7)	1.2 (0.7–2.0)	0.9 (0.5–1.6)
Lutein/zeaxanthin, μg/d	0.8 (0.4–1.5)	0.6 (0.3–1.3)	1.0 (0.5–2.0)	1.1 (0.6–2.3)	1.3 (0.7–2.4)	1.0 (0.5–2.0)	1.2 (0.7–2.2)	1.2 (0.7–2.2)
Total vitamin C, mg/d	1.3 (0.7–2.5)	1.2 (0.6–2.5)	2.0 (1.0–4.2)	1.2 (0.7–2.2)	1.4 (0.8–2.5)	1.5 (0.7–2.9)	1.3 (0.7–2.3)	1.3 (0.7–2.3)
Dietary vitamin C, mg/d	1.4 (0.8–2.6)	1.4 (0.7–2.6)	1.5 (0.7–2.9)	1.3 (0.7–2.4)	1.2 (0.6–2.2)	1.1 (0.5–2.3)	1.0 (0.5–1.9)	1.0 (0.5–1.9)
Total vitamin E, IU/d	1.1 (0.6–2.0)	1.1 (0.6–2.1)	1.1 (0.6–2.1)	1.4 (0.7–2.7)	0.7 (0.4–1.2)	0.7 (0.4–1.5)	0.7 (0.4–1.3)	0.6 (0.3–1.1)
Dietary vitamin E, IU/d	0.6 (0.3–1.2)	0.6 (0.3–1.2)	0.6 (0.3–1.2)	0.8 (0.4–1.6)	1.2 (0.6–2.2)	1.1 (0.6–2.2)	0.9 (0.5–1.7)	0.9 (0.5–1.7)

* Adjusted for age (5-year categories), time period (2-year intervals), latitude of birthplace (north, middle, or south), pack-years of smoking (never, >0 to <10, ≥10 to <25, ≥25 to <45, or ≥45), and total energy (quintiles).

the corresponding rate in the reference category. Age-adjusted RRs were calculated with the use of 5-year age categories by the Mantel–Haenszel method.[34] In multivariate analysis using pooled logistic regression with 2-year time increments,[35,36] we simultaneously adjusted for age (5-year categories), latitude of birthplace (North, Middle, or South), pack-years of smoking (never, >0 to <10, ≥10 to <25, ≥25 to <45, or ≥ 45), length of follow-up, and total energy intake (quintiles). Age and latitude of birthplace are risk factors for MS,[33,37] and smoking was associated with an increased risk of MS in these two cohorts.[38] We controlled for total energy to control for confounding and to reduce measurement errors due to general over- or under-reporting of food items.[22] Log RRs from the two studies were pooled by the inverse of their variances. Tests for trend were conducted by using the median values for quintiles of nutrient intake as a continuous variable for nutrient analyses or by using the frequency responses in servings per day as a continuous variable for food analyses.

In separate analyses that incorporated repeated dietary measurements, the incidence of MS was related to the cumulative updated average intake from all available dietary questionnaires up to the start of each 2-year follow-up interval or to the most recent intake at the start of each 2-year follow-up interval.[39] Indicator variables were used to denote any time period for which a questionnaire was not available. For all RRs, we calculated 95% CIs. All *p* values were two tailed.

Results. Intakes of α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin, total vitamin C, dietary vitamin C, total vitamin E, and dietary vitamin E were not significantly associated with risk of MS. After adjustments for age, latitude of birthplace, pack-years of smoking, and total energy intake, the pooled multivariate RRs (95% CIs) comparing women in the highest quintile with those in the lowest quintile were 1.1 (0.7 to 1.7) for α-carotene, 1.1 (0.7 to 1.6) for β-carotene, 1.4 (0.8 to 2.2) for β-cryptoxanthin, 1.0 (0.6 to 1.5) for lycopene, 1.0 (0.7 to 1.6) for lutein/zeaxanthin, 1.4 (0.9 to 2.1) for total vitamin C, 1.3 (0.9 to 2.0) for dietary vitamin C, 0.8 (0.6 to 1.3) for total vitamin E, and 0.9 (0.6 to 1.4) for dietary vitamin E. The tests for heterogeneity between the two studies were not significant for comparisons of RRs in the highest quintile except for β-cryptoxanthin, suggesting that the pooled RRs are an appropriate summary of the data for the nutrients except for β-cryptoxanthin. Intake of β-cryptoxanthin had a significantly positive association with risk of MS in the NHS but not in the NHS II (table 1). In the pooled multivariate analyses controlling for age and other potential risk factors, none of the tests for trend across quintiles approached statistical significance (additional material related to this article can be found on the *Neurology* Web site; go to www.neurology.org and scroll down the Table of Contents to find the title link for this article). The median intake of dietary vitamin C among women in the lowest quintile was 67 mg/day in both cohorts, which was close to the value of 60 mg/day of the Recommended Dietary Allowance (RDA).[40] The median intakes of dietary vitamin E among women in the lowest quintile were 6 IU/day (9 mg/day) in the NHS and 7 IU/day (10 mg/day) in the NHS II, which were also similar to the level of 8 mg/day of the RDA.[41]

To address the possibility that women might have changed their diet because of clinical symptoms of MS before they were diagnosed, we examined RRs after excluding new cases of MS occurring during the first 2 years of follow-up for the NHS (14 cases) and the NHS II (34 cases); the estimates were virtually unchanged (see table 1). We conducted an additional analysis using date of first symptom rather than date of diagnosis in the NHS (41 cases); the results were similar. However, we had too few MS cases (14 cases) to conduct a meaningful analysis using date of first symptom in the NHS II. The multiple measures of diet in the NHS and NHS II provided an opportu-

Table 2 *Multivariate relative risks (RR) of MS and 95% CI according to supplement use of vitamin C, vitamin E, and multivitamins: Nurses' Health Study, 1980–1996, and Nurses' Health Study II, 1991–1997*

	Nurses' Health Study		Nurses' Health Study II		Pooled analysis	
Nutrient	Cases, n	Multivariate RR* (95% CI)	Cases, n	Multivariate RR* (95% CI)	Multivariate RR* (95% CI)	*p* Value for heterogeneity
Vitamin C						
Never users	95	1.0 (Referent)	83	1.0 (Referent)	1.0 (Referent)	
Past users	10	0.9 (0.5–1.8)	3	0.8 (0.2–2.5)	0.9 (0.5–1.6)	0.84
Current users, y						
≤4	15	1.0 (0.6–1.8)	14	1.3 (0.7–2.3)	1.1 (0.8–1.7)	0.53
5–9	14	1.5 (0.8–2.6)	8	1.3 (0.7–2.8)	1.4 (0.9–2.2)	0.86
≥10	7	0.7 (0.3–1.6)	6	1.2 (0.5–2.9)	0.9 (0.5–1.6)	0.35
Vitamin E						
Never	103	1.0 (Referent)	100	1.0 (Referent)	1.0 (Referent)	
Users	38	1.1 (0.7–1.5)	14	1.1 (0.6–2.0)	1.1 (0.8–1.5)	0.87
Multivitamins						
Never users	55	1.0 (Referent)	45	1.0 (Referent)	1.0 (Referent)	
Past users	30	1.1 (0.7–1.7)	26	0.9 (0.5–1.5)	1.0 (0.7–1.4)	0.57
Current users, y						
≤4	19	1.3 (0.8–2.3)	10	0.9 (0.4–1.8)	1.2 (0.8–1.7)	0.33
5–9	18	1.2 (0.7–2.1)	19	0.8 (0.5–1.3)	1.0 (0.7–1.4)	0.26
≥10	19	1.0 (0.6–1.8)	14	0.8 (0.5–1.5)	0.9 (0.6–1.4)	0.59

* Adjusted for age (5-year categories), time period (2-year intervals), latitude of birthplace (north, middle, or south), pack-years of smoking (never, >0 to <10, ≥10 to <25, ≥25 to <45, or ≥45), and total energy (quintiles).

nity to examine various temporal relationships between diet and risk of MS.[39] Neither the cumulative updated average intakes nor the most recent intakes of dietary carotenoids, vitamin C, and vitamin E were significantly associated with the risk of MS, except for total vitamin C, which was positively associated with risk of MS in the cumulative updated average analysis in the NHS (see table 1).

In these two cohorts, the major contributors to dietary intakes were carrots for intake of α-carotene, carrots and cantaloupe for intake of β-carotene, oranges, orange juice, and peaches for intake of β-cryptoxanthin, tomatoes, tomato sauce, and tomato juice for intake of lycopene, raw and cooked spinach, romaine or leaf lettuce, iceberg or head lettuce, and broccoli for intake of lutein/zeaxanthin, orange juice and oranges for dietary vitamin C, and mayonnaise or other creamy salad dressing and cold breakfast cereal for intake of dietary vitamin E. We examined the associations of these foods with risk of MS and observed no significant associations except for a positive association with orange juice in the NHS (RR = 1.9; 95% CI = 1.0 to 3.7) but not in the NHS II (RR = 0.9; 95% CI = 0.5 to 1.6). We also saw no significant associations between intakes of fruits, vegetables, citrus fruits, cruciferous vegetables, yellow vegetables, and green leafy vegetables and risk of MS (additional material can be found on the *Neurology* Web site; go to www.neurology.org). Use of vitamins C and E supplements and multivitamins was not significantly associated with risk of MS even among those who used these supplements for ≥10 years (table 2).

Discussion. In these two large cohorts of women, we found no evidence that higher intakes of specific dietary carotenoids, vitamin C, vitamin E, and fruits and vegetables were associated with reduced risk of MS. Use of vitamins C and E supplements and multivitamins was also unrelated to risk of MS.

Because of the prospective design, recall or selection biases are unlikely in this study, and the high follow-up rates minimize the concern that differential follow-up rates have affected our results. Moreover, the estimates of dietary carotenoids, vitamin C, and vitamin E derived from the dietary questionnaires used in this study reasonably reflect long-term intakes of study subjects,[22,27-30] suggesting that if strong associations existed between intakes of dietary carotenoids, vitamin C, and vitamin E and risk of MS within the NHS and NHS II population, they would have been apparent. However, with the number of MS cases available for analysis, we cannot exclude the possibility of small to modest effects.

One potential source of bias in this study is that women may increase their intakes of vitamins because of clinical symptoms of MS before they are diagnosed with MS. However, the results after excluding incident cases of MS diagnosed during the first 2 years of follow-up and using date of first symptom in the NHS did not support this explanation. Although confounding by unknown variables

cannot be excluded, it seems unlikely as adjustments for potential risk factors for MS, including age, latitude of birthplace, and smoking, had minimal effects on the RRs.

To our knowledge, no previous data are available to examine the associations between intakes of specific dietary carotenoids and risk of MS. In a Canadian case-control study, significant inverse associations were observed among women for intakes of vitamin C and fruit juices, but intakes of carotene, vitamin E, fruits, and vegetables were unrelated to risk of MS.[14] Findings from other case-control studies that have examined intakes of fruits and vegetables and foods contributing to specific dietary carotenoids, vitamin C, and vitamin E and risk of MS suggested null associations.[15,16,18] Also, a hospital case-control study conducted in Moscow found no association between consumption of fruits and vegetables during childhood and risk of MS.[17] The weaknesses are accentuated in studies including individuals who have had MS for several years as their ability to recall their diet before the onset of neurologic symptoms may be limited and probably affected by their current diet. It is therefore important to confirm these findings in prospective investigations.

Of note, this study was conducted to examine the association between dietary antioxidants and risk of MS, and whether or not antioxidants may benefit women with MS cannot be assessed from these data.

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Testosterone supplementation improves spatial and verbal memory in healthy older men

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Article abstract—*Objective:* To determine the relationship between exogenous testosterone administration and cognitive abilities in a population of healthy older men. *Background:* Serum levels of total and bioavailable testosterone gradually decrease with age in men and are associated with reductions in muscle mass, osteoporosis, decreased sexual activity, and changes in cognition. *Methods:* Twenty-five healthy, community-dwelling volunteers, aged 50 to 80 years, completed a randomized, double-blind, placebo-controlled study. Participants received weekly intramuscular injections of either 100 mg testosterone enanthate or placebo (saline) for 6 weeks. Cognitive evaluations were conducted at baseline, week 3, and week 6 of treatment by use of a battery of neuropsychologic tests. *Results:* Circulating total testosterone was raised an average of 130% from baseline at week 3 and 116% at week 6 in the treatment group. Because of aromatization of testosterone, estradiol increased an average of 77% at week 3 and 73% at week 6 in the treatment group. Significant improvements in cognition were observed for spatial memory (recall of a walking route), spatial ability (block construction), and verbal memory (recall of a short story) in older men treated with testosterone compared with baseline and the placebo group, although improvements were not evident for all measures. *Conclusions:* The results suggest that short-term testosterone administration enhances cognitive function in healthy older men. However, it remains unclear whether these improvements in cognition are attributable to increased testosterone or estradiol levels, or both. The potential role of testosterone vs its metabolites on cognition requires further research.

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Serum levels of total testosterone, bioavailable testosterone (testosterone that is not bound to sex hormone–binding globulin), and free testosterone decrease with age in men.[1,2] This gradual decrease is associated with decreased muscle mass and strength, osteoporosis, reduced sexual activity, and changes in cognition.[3] Testosterone replacement therapy in normal older men has shown benefits on body composition, bone mass, muscle strength, and sexual functioning.[4] In addition to peripheral physiologic effects, age-related declines in testosterone levels appear to affect spatial memory. Aging mice show a progressive impairment of spatial learning and memory related to decreases in plasma testosterone, which can be reversed with testosterone administration.[5] In healthy older men, declines in endogenous testosterone levels have been found to correlate significantly with declines in both visual and verbal

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