In the Literature: New and Noteworthy Nutrition Research

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SLEEP DEPRIVATION, HUNGER AND SATIETY HORMONES, AND OBESITY

In the past few decades, Americans have been eating more and sleeping less, and some researchers now suspect that there may be a connection. A number of cross-sectional and longitudinal cohort studies have suggested that chronic sleep deprivation is associated with an increased risk of obesity.[1-4] It is thought that sleep deprivation may promote weight gain by altering sympathetic nervous system activity or by affecting serum levels of hormones involved in energy metabolism, such as insulin and cortisol. Leptin, an anti-obesity hormone secreted primarily by adipocytes, and ghrelin, a hunger-inducing peptide produced by gastric cells, may also be affected by sleep deprivation. In one cohort study involving over 1000 individuals, sleep duration was positively associated with serum leptin concentration and negatively associated with serum ghrelin concentration.[4] In keeping with this epidemiologic evidence, one small clinical trial involving healthy volunteers suggested that total sleep deprivation leads to a marked diminution of the diurnal amplitude of leptin.[5]

A recent study by Spiegel et al.[6] explored the complex and intriguing relationship among sleep deprivation, hormones, and appetite. Using a randomized crossover design, the investigators studied 12 young, healthy, normal-weight men under two different experimental conditions: sleep restriction and sleep extension. Subjects completed the two phases of the study in randomized order with a wash-out period of at least 6 weeks between the two phases. During the sleep restriction phase of the study, subjects were allowed to sleep for only 4 hours each night on two consecutive nights. Subjects spent the remainder of each night awake, resting quietly in a bed or chair. Daytime naps were not permitted. During the sleep extension phase of the study, the men were allowed to sleep for up to 10 hours each night on two successive nights. On the third day of each phase, blood samples were taken at regular intervals between 8:00 am and 9:00 pm for analysis of serum leptin and ghrelin concentration. In addition, at hourly intervals, subjects were asked to rate their hunger and appetite for certain foods. In order to minimize the effects of food intake on hormone concentration, hunger, and appetite, subjects were not allowed to eat during the third day of the study; instead, calories were provided as a constant intravenous infusion of glucose (5 g/kg body weight/d).

During the sleep restriction phase, subjects' mean leptin levels were 18% lower and mean ghrelin levels were 28% higher than they were during the sleep extension phase. In addition, mean hunger ratings were 24% higher after sleep deprivation than after extended sleep. Appetite ratings were also significantly higher after sleep restriction, especially for high-carbohydrate, energy-dense foods such as sweets, bread, pasta, and potatoes.

These findings lend support to the hypothesis that chronic sleep deprivation may promote weight gain

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and increase the risk of obesity. However, this was a small study of short duration, so further research is clearly necessary. Longer-term studies should be undertaken to assess whether the observed effects persist during prolonged periods of sleep restriction and whether the observed changes lead to weight gain when subjects are allowed to eat ad libitum. In addition, the results of this study should be confirmed in different populations, including women and overweight individuals.

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HIGH-DOSE VITAMIN E SUPPLEMENTATION AND MORTALITY

A meta-analysis published in the *Annals of Internal Medicine* earlier this year by Miller et al.[1] suggests that high-dose vitamin E supplementation may increase all-cause mortality. The release of this report generated a flurry of sensational newspaper headlines, elicited passionate letters to the editor, and called into question Americans' faith in antioxidant supplements.

Researchers and patients have long been hopeful that antioxidants such as vitamin E would be able to reduce the burden of chronic diseases such as cardiovascular disease, cancer, and Alzheimer's disease. However, most of the trials conducted to date have failed to demonstrate the dramatic health benefits that antioxidant enthusiasts have been hoping to see. Despite this fact, millions of individuals continue to take antioxidant supplements. In an editorial accompanying the *Annals* meta-analysis, Dr. E. Robert Greenberg notes that in recent years, vitamin E has become the most widely used nutritional supplement, taken by 22% of Americans over the age of 55.[2] He rightly suggests that many people, including physicians, take vitamin E supplements out of an optimistic belief that they "won't hurt and might help." However, the results of the meta-analysis by Miller et al.[1] suggest that this belief is naive and possibly dangerous.

Miller et al.[1] searched MEDLINE and the Cochrane database to identify all randomized trials of vitamin E supplementation conducted between 1966 and August 2004. Studies lasting less than one year were excluded. In addition, the authors excluded 12 studies in which there were less than 10 reported deaths, three trials for which no mortality data were available, and two trials in which mortality could not be separated from other end points.

Nineteen randomized trials were included in the meta-analysis, of which 17 were placebo-controlled. In all, over 135,000 middle-aged and older adults were studied. In 14 of the trials, participants had or were at high risk of developing a chronic disease such as cardiovascular disease or cancer. In nine of the interventions, vitamin E was given by itself; in the other 10 studies, vitamin E was given in combination with other dietary supplements such as beta-carotene or vitamin C. The dosage of vitamin E administered in these 19 trials ranged from 16.5 to 2000 IU daily, with a median dosage of 400 IU. The duration of follow-up ranged from 1.4 to 8.2 years, during which time 12,504 deaths were reported.

In a pooled analysis of all 19 trials, vitamin E supplementation was not associated with either increased or decreased risk of death (risk ratio 1.01; 95% CI 0.98, 1.04; $p > 0.2$). Miller et al.[1] then sorted the trials into two groups based on vitamin E dosage: low-dose (defined by the authors as dosages < 400 IU) and high-dose (dosages ≥ 400 IU). In most of the individual low-dose trials, there was a nonsignificant trend towards decreased mortality with vitamin E supplementation. In many of the individual high-dose trials, on the other hand, there was a nonsignificant trend towards increased mortality with vitamin E supplementation.

In the pooled low-dose analysis by Miller et al.,[1] vitamin E supplementation was not found to be associated with either increased or decreased risk of mortality (risk ratio 0.98; 95% CI 0.96, 1.01; $p > 0.2$). However, in the pooled high-dose analysis, vitamin E supplementation was associated with a slightly increased risk of mortality (risk ratio 1.04; 95% CI 1.01, 1.07; $p = 0.035$). This suggests that vitamin E may increase the risk of mortality if it is taken in daily doses that exceed 400 IU, an amount almost 18 times the Recommended Daily Allowance (15 mg alpha-tocopherol equivalents or 22.5 IU) but not as much as the current Tolerable Upper Intake Level (1000 mg or 1500 IU) specified by the Institute of Medicine.[3] However, the authors then used a controversial dose-response model to suggest that the risk of mortality may actually increase with vitamin E dosages greater than 150 IU daily. The authors report that higher doses of vitamin E may have pro-oxidant or anticoagulant activity, which might explain the slightly increased risk of mortality suggested by their analyses. Figure 1 summarizes the data of Miller et al.[1]

The publication of this meta-analysis sparked a heated debate, as evidenced by the many electronic

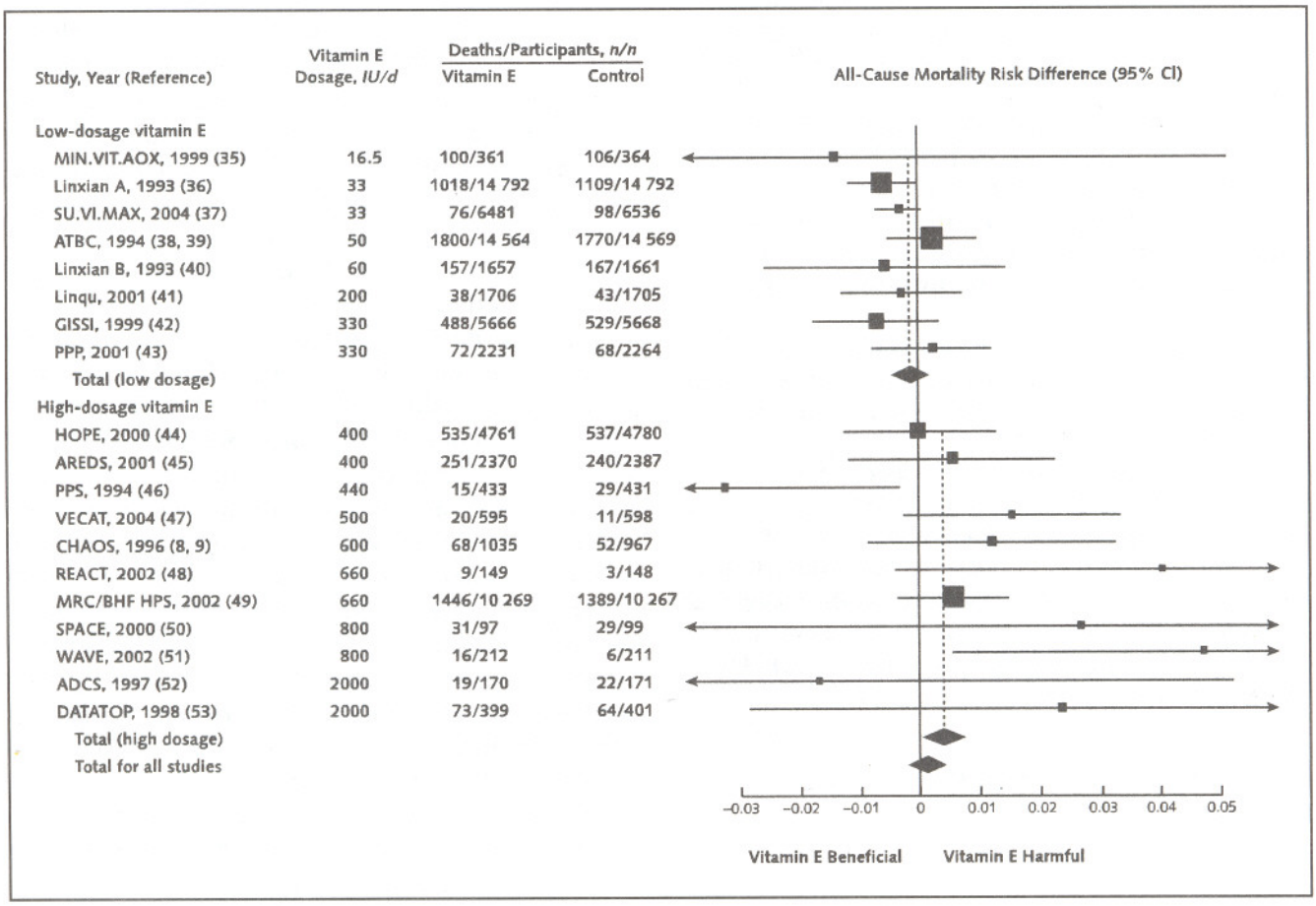

Figure 1. Risk difference in all-cause mortality for randomized, controlled trials of vitamin E supplementation and pooled results for low-dosage (<400 IU/d) and high-dosage (≥400 IU/d) vitamin E trials. Area of each square is proportional to inverse of study variance in the analysis. Horizontal lines represent 95% CIs. ADCS = Alzheimer's Disease Cooperative Study; AREDS = Age-Related Eye Diseases Study; ATBC = Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group; CHAOS = Cambridge Heart Antioxidant Study; DATATOP = Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; GISSI-Prevenzione = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardio Prevenzione; HOPE = Heart Outcomes Prevention Evaluation; MIN.VIT.AOX = The Geriatrie/MINéraux, VITamines, et AntiOXydants Network; MRC/BHF HPS = Medical Research Council/British Heart Foundation Heart Protection Study; PPP = Primary Prevention Project; PPS = Polyp Prevention Study; REACT = Roche European American Cataract Trial; SPACE = Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease; SU.VI.MAX = SUpplementation en VItamines et Minéraux AntioXydants; VECAT = Vitamin E, Cataracts, and Age-Related Maculopathy; WAVE = Women's Angiographic Vitamin and Estrogen. Used with permission.[1]

letters submitted to the *Annals* editors. Some writers suggested that the meta-analysis was flawed due to the exclusion of trials in which less than 10 deaths were reported.[4,5] Others suggested that the meta-analysis should not have included trials in which vitamin E was given along with other dietary supplements.[6] These authors point out that in a number of trials, participants received beta-carotene, which has been shown to be harmful at high doses in some populations. One writer reported that two of the high-dose trials were intrinsically biased against finding a benefit for vitamin E, and if these trials had been excluded from the meta-analysis, high-dose vitamin E would not have been associated with an increased risk of mortality.[7] Many authors questioned the use of particular statistical models in the meta-analysis, and suggested that if other valid and widely used statistical methods had been utilized with the data set, vitamin E supplementation would not have been associated with a higher risk of mortality.[8-10]

In light of this conflicting information, clinicians may find it difficult to decide how to approach the topic of vitamin E supplementation with their patients. Clearly, patients should be informed that most of the available data do not support the widely held belief that vitamin E supplementation (particularly at high doses) reduces mortality from chronic diseases. It also seems prudent to caution patients that vitamin E may actually increase the risk of mortality if it is taken daily in doses of 400 IU or more. It is this author's belief that unless additional evidence of benefit becomes available, higher-dose vitamin E supplementation (particularly with dosages many times higher than the RDA) should not be widely recommended.

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