

## Dietary Supplement Guide

### Vitamin E

#### Function

Vitamin E is a fat-soluble vitamin with the main function as a fat-soluble antioxidant.

Vitamin E is important for:

- Protecting cell membranes and fats in LDL particles from oxidation as a non-specific fat-soluble antioxidant
- Cell membrane integrity, function, signaling and adhesion, including cell-mediated immune functions
- Inhibition of platelet aggregation and enhancement of vasodilation

#### Mechanism of Action

Vitamin E refers to a family of 8 related antioxidant molecules: 4 tocopherols ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ) and 4 tocotrienols ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ). Alpha-tocopherol is preferentially absorbed and maintained in the human body and is the only vitamin E molecule capable of reversing symptoms of deficiency. Because of this, Dietary Reference Intake (DRI) values refer only to  $\alpha$ -tocopherol.

In humans,  $\alpha$ -tocopherol functions mainly as a fat-soluble chain-breaking antioxidant, which, after neutralization of a free radical, can be regenerated by vitamin C. Tocotrienols have shown in vitro activity against malignant cell lines, but due to poor bioavailability and lack of clinical studies, their significance is unclear. Other tocopherols (specifically gamma and delta) show potent anti-oxidant activity in vitro and have been studied clinically, though data is sparse and their potential as therapeutic agents remains to be elucidated.

Vitamin E is stored in the liver, and serum levels are regulated via active transport. Thus, measurement of serum vitamin E is not a reliable way to assess for nutritional status in the absence of frank deficiency or toxicity.<sup>1,2</sup>

Tocopherols and tocotrienols are chiral molecules. Only d- $\alpha$ -tocopherol is biologically active and available from natural sources.

#### Dietary Sources and Nutritional Status

Good sources of vitamin E include fortified cereals, vegetable oils (sunflower, almond), seeds (sunflower), nuts (almonds), avocados, asparagus, broccoli, and



## Vitamin E

green leafy vegetables. Sunflower seeds are an excellent source of vitamin E, providing about 12 mg or 80% of the Dietary Reference Intake (DRI) in  $\frac{1}{4}$  C (See Table 1).

Therefore, a Mediterranean diet is likely to provide ample amounts, whereas people consuming a Standard American Diet (SAD) are likely to have marginal vitamin E status, even in the absence of frank deficiency.

Mean dietary intake in the USA is estimated to be 6-8mg/day of  $\alpha$ -tocopherol, which is well below the **current Recommended Daily Allowance (RDA) of 15mg/day** (or 22.5 IU/day) and it is estimated that 93% of American adults do not meet the estimated average requirement of 12 mg/day.<sup>3</sup> It is unclear what the chronic effects of marginal vitamin E status are, but diets rich in Vitamin E (and by extension rich in other nutrients) are well established to protect against CVD, diabetes, cancer, and other chronic diseases.

Severe deficiency (rare in the absence of substantial malnutrition or genetic mutations affecting lipid metabolism) manifests primarily with neurologic signs and symptoms: ataxia & peripheral neuropathy, as well as myopathy and damage to the retina (retinitis pigmentosa).

Table 1 Vitamin E Content of Common Foods

Food	Serving Size	Amount (mg (ATE))	DRI (%)
Wheat Germ Oil	1 Tbl	20.3	135
Sunflower Seeds	0.25 C	12.3	82
Spinach	1 C	3.74	25
Swiss Chard	1 C	3.3	22
Asparagus	1 C	2.7	18
Beet Greens	1 C	2.6	17
Almonds	0.25 C	6.0	40
Broccoli	1 C	2.3	15
Kale	1 C	1.1	7
Avocado	1 C	3.1	21
Peanuts	0.25 C	3.0	20
Olive Oil	1 Tbs	1.9	13

### What About Supplementation for Treatment and Prevention?

*Trial and study results on Vitamin E supplementation have been complex and inconsistent.*

**While some trials have shown that certain populations may gain specific benefits from vitamin E supplementation, systematic reviews have not always confirmed these benefits. Furthermore, evidence suggests that supplementation with vitamin E may be harmful for certain populations.**



## Vitamin E

---

### The Good

- The often referenced  $\alpha$ -Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, an RCT of ~30,000 Finnish male smokers, found a decreased risk of **prostate cancer** in those taking 50 mg (75 IU) daily of vitamin E supplementation and no increase in mortality.<sup>4</sup>
- A Cochrane review determined that supplementation with antioxidants, including vitamin E may slow the progression of **age-related macular degeneration**, though does not appear to prevent this condition in asymptomatic patients.<sup>5</sup>
- A 2017 meta-analysis concluded that vitamin E is effective at reducing the incidence of **chemotherapy-induced neurotoxicity**.<sup>6</sup>

### The Neutral

- A 2017 Cochrane database systematic review of 4 studies and a total of 820 patients conclude from the limited evidence that no harms or benefits for **Alzheimer's disease or mild cognitive impairment** were identified from vitamin E supplementation. One of the trials within the review found that people with dementia due to AD who took vitamin E were better at managing their daily activities than people who took placebo.<sup>7</sup>
- A USPSTF systematic review found mixed results of studies on Vitamin E supplementation for primary prevention of CVD, with **overall no effect on mortality, CVD, or cancer**.<sup>8</sup>
- An RCT of over 39,000 women as part of the Women's Health Study found that vitamin E supplementation (600 IU (403 mg) every other day) decreased CVD mortality by 24%, but had **no effect on the incidence of CVD, MI, or stroke**.<sup>9</sup>
- An RCT of 7000 men did not find benefit for vitamin E supplementation (400 IU/day (268 mg)) in the primary prevention of **dementia**.<sup>10</sup>
- **Cataracts**: while some observational studies have suggested a protective effect for vitamin E, in several prospective controlled trials and a large systematic review, vitamin E supplementation has not been found to decrease the risk for developing age related cataracts.<sup>11</sup>
- A small RCT did not find vitamin E supplementation (300 mg (447 IU) BID) to reduce incidence of **peripheral neuropathy** in patients receiving neurotoxic chemotherapy.<sup>12</sup>

### The Bad



---

## Vitamin E

- Contrary to hopes that vitamin E supplementation could increase longevity, a meta-analysis of 46 trials with low-risk of bias revealed a small *increased* risk for **all-cause mortality** (RR 1.03) amongst those supplementing with vitamin E above the RDA of 15 mg/day. Though when trials at risk for bias were included, this association was not apparent. Data was more sparse for doses below the RDA, but did not seem to indicate an effect on mortality.<sup>13</sup>
- A large RCT of vitamin E and selenium (either alone or in combination) was halted after about 5 years, due to a statistically non-significant increased risk of **prostate cancer** in those taking vitamin E (400 IU/day or 268 mg/d).<sup>14</sup> Additional person-years of follow-up indicated a significant increase in risk of prostate cancer in healthy men with this dose of vitamin E.<sup>15</sup>
- A prospective cohort study found a small increased risk for development of **lung cancer** (NSCLC) amongst current smokers (no increased risk for former smokers) supplementing with vitamin E at doses >215 mg/day (320 IU).<sup>16</sup>

### Opportunities for Further Research

- Essentially all the studies referenced above have used  $\alpha$ -tocopherol in isolation. This has raised the concern that by supplementing with  $\alpha$ -tocopherol alone, serum levels of other tocopherols may fall to sub-nutritional levels, with resultant harm. Furthermore, some argue that other vitamin E molecules may be more therapeutic at supra-nutritional levels and should be the focus of future trials.<sup>17</sup>
- Targeting supplementation to patients with higher levels of oxidative stress or specific gene polymorphisms is another interesting area of relatively unexplored research which could reveal benefit to supplementation for specific populations.<sup>18</sup>

### Dosing

- The RDA is 15 mg for d- $\alpha$ -tocopherol (equivalent to 22.4 IU daily)
- 1 mg of d- $\alpha$ -tocopherol = 1.49 IU of the natural form vitamin E or 2.22 IU of synthetic alpha-tocopherol.
- The Tolerable Upper Intake Level (UL) is 1000mg daily (1490 IU). Beyond this dose, there may be risk for hemorrhage due to platelet inhibition.
- If decision is made to supplement due to poor dietary intake, we recommend supplementing with 30 IU (~20 mg) daily.

\*Currently, the vitamin E content of food and dietary supplement is listed on labels in international units (IUs), which is a measure of biological activity rather than quantity. New FDA labelling regulations that will take effect by January 1, 2020 will require that vitamin E be listed in mg and not IUs. In the future, the use of IUs will be discontinued.



## Vitamin E

---

### Interactions

- Due to blood thinning effects, vitamin E should be used with caution in patients taking **anti-coagulant medications**.
- Stop vitamin E supplementation 2 weeks prior to **surgery**.
- Stop vitamin E and other antioxidant supplements during active **chemotherapy** due to potential for reduction of efficacy.

### Clinical Bottom Line

- Dietary intake of vitamin E is suboptimal in an estimated 90% of the US population.<sup>19</sup> We recommend addressing this via dietary modification. When this is not practical, daily nutrient supplementation that includes vitamin E 30 IU daily may be considered.
- Consider higher dose vitamin E supplementation (200-300 IU daily) for patients with Alzheimer's dementia or age related macular degeneration, provided they do not smoke and are not at increased risk for prostate cancer. We recommend avoiding doses greater than 400 IU daily given the potential for increased risk of all-cause mortality.
- Despite substantial study, there is no established benefit for enhancing immunity or reducing infections. Nor is there evidence to support supplementation beyond RDA for prevention of CVD or cancer. However, a diet rich in sources of vitamin E will achieve these benefits.
- More study is needed to elucidate whether use of other tocopherols and/or tocotrienols will yield consistent clinical results. For now, if supplementing with vitamin E, we suggest inclusion of mixed tocopherols as opposed to isolated  $\alpha$ -tocopherol.

*Brought to you by the UW Department of Family Medicine and Community Health, Integrative Health Program.*

*Date created: October 2018*

### References

1. Higdon J. *An evidence-based approach to vitamins and minerals : health implications and intake recommendations*. New York: Thieme; 2003.
2. Traber MG. Vitamin E inadequacy in humans: causes and consequences. *Advances in nutrition (Bethesda, Md)*. 2014;5(5):503-514.
3. Fulgoni VL, 3rd, Keast DR, Bailey RL, Dwyer J. Foods, fortificants, and supplements: Where do Americans get their nutrients? *The Journal of nutrition*. 2011;141(10):1847-1854.



## Vitamin E

4. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *The New England journal of medicine*. 1994;330(15):1029-1035.
5. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *The Cochrane database of systematic reviews*. 2017;7:Cd000254.
6. Fu X, Wu H, Li J, et al. Efficacy of Drug Interventions for Chemotherapy-Induced Chronic Peripheral Neurotoxicity: A Network Meta-analysis. *Frontiers in neurology*. 2017;8:223.
7. Farina N, Llewellyn D, Isaac M, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. *The Cochrane database of systematic reviews*. 2017;4:Cd002854.
8. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. Preventive Services Task Force. *Annals of internal medicine*. 2013;159(12):824-834.
9. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *Jama*. 2005;294(1):56-65.
10. Kryscio RJ, Abner EL, Caban-Holt A, et al. Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADVISE). *JAMA neurology*. 2017;74(5):567-573.
11. Mathew MC, Ervin AM, Tao J, Davis RM. Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract. *The Cochrane database of systematic reviews*. 2012(6):Cd004567.
12. Kottschade LA, Sloan JA, Mazurczak MA, et al. The use of vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: results of a randomized phase III clinical trial. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2011;19(11):1769-1777.
13. Bjelakovic G, Nikolova D, Gluud C. Meta-regression analyses, meta-analyses, and trial sequential analyses of the effects of supplementation with beta-carotene, vitamin A, and vitamin E singly or in different combinations on all-cause mortality: do we have evidence for lack of harm? *PloS one*. 2013;8(9):e74558.
14. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Jama*. 2009;301(1):39-51.
15. Klein EA, Thompson IM, Jr., Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Jama*. 2011;306(14):1549-1556.
16. Slatore CG, Littman AJ, Au DH, Satia JA, White E. Long-term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer. *American journal of respiratory and critical care medicine*. 2008;177(5):524-530.
17. Yang CS, Suh N, Kong AN. Does vitamin E prevent or promote cancer? *Cancer prevention research (Philadelphia, Pa)*. 2012;5(5):701-705.



---

## Vitamin E

18. Mocchegiani E, Costarelli L, Giacconi R, et al. Vitamin E-gene interactions in aging and inflammatory age-related diseases: implications for treatment. A systematic review. *Ageing research reviews*. 2014;14:81-101.
19. Committee DGA. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*. United States Departments of Agriculture and Health and Human Services; 2015.