Lead Article

Effects of dietary *RRR* α-tocopherol vs all-*racemic* α-tocopherol on health outcomes

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Of the 8 vitamin E analogues, RRR α-tocopherol likely has the greatest effect on health outcomes. Two sources of α-tocopherol, naturally sourced RRR α-tocopherol and synthetic all-racemic α-tocopherol, are commonly consumed from foods and dietary supplements in the United States. A 2016 US Food and Drug Administration ruling substantially changed the RRR to all-racemic α-tocopherol ratio of biopotency from 1.36:1 to 2:1 for food-labeling purposes, but the correct ratio is still under debate in the literature. Few studies have directly compared the 2 α-tocopherol sources, and existing studies do not compare the efficacy of either source for preventing or treating disease in humans. To help close this gap, this review evaluates studies that investigated the effects of either RRR α-tocopherol or all-racemic α-tocopherol on health outcomes, and compares the overall findings. α-Tocopherol has been used to prevent and/or treat cancer and diseases of the central nervous system, the immune system, and the cardiovascular system, so these diseases are the focus of the review. No firm conclusions about the relative effects of the α-tocopherol sources on health outcomes can be made. Changes to α-tocopherol–relevant policies have proceeded without adequate scientific support. Additional research is needed to assemble the pieces of the α-tocopherol puzzle and to determine the RRR to all-racemic α-tocopherol ratio of biopotency for health outcomes.

INTRODUCTION

Vitamin E, which was discovered by Katherine S. Bishop and Herbert M. Evans in the 1920s, is a lipid-soluble antioxidant that plays a crucial role in human and animal reproduction. Although the name "vitamin E" appears to refer to a single compound, there are actually 8 vitamin E analogues: 4 tocopherols (α, β, γ, and δ) and 4 tocotrienols (α, β, γ, and δ) (Figure 1). However, only α-tocopherol was used to set the recommended dietary allowance (RDA) of vitamin E for Americans.[1] Humans consume 2 sources of α-tocopherol: naturally sourced α-tocopherol, which is commonly found in seed oils, and synthetic α-tocopherol, which is used to fortify food products such as ready-to-eat cereals.

CHEMICAL STRUCTURE OF α-TOCOPHEROL

Synthetic (all-*racemic*, or all-*rac*) α-tocopherol is an equimolar mix of its stereoisomers. The 3 chiral carbons of α-tocopherol (at positions 2, 4′, and 8′) can be in either an *R* or an *S* orientation, yielding 8 stereoisomers. One of the stereoisomers in all-*rac* α-tocopherol is 2*R*, 4′*R*, 8′*R* (or *RRR*), which is the sole stereoisomer found in nature. The other 7 stereoisomers consist of 3 *2R* stereoisomers (*RSS*, *RSR*, *RRS*) and 4 2*S* stereoisomers

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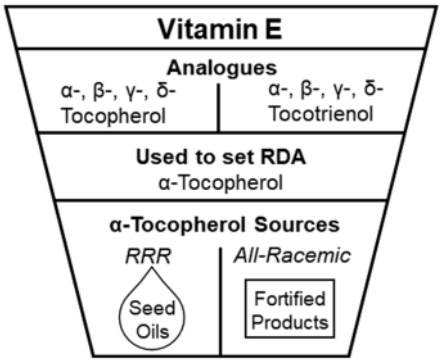

Figure 1 **Forms of vitamin E**. *Abbreviation:* RDA, recommended dietary allowance.

(*SSS*, *SRR*, *SRS*, *SSR*). The orientation (*R* or *S*) of the carbon at the 2-position is significant: the main α-tocopherol–binding protein in the liver, α-tocopherol transfer protein (α-TTP), has a higher affinity for *RRR* and the other 2*R* stereoisomers than for the 4 2*S* stereoisomers.[2,3] This hepatic discrimination means that 2*R* stereoisomers will be preferentially packaged into very low-density lipoproteins for transport in the circulation and, consequently, will accumulate in peripheral tissues.

INTAKE LEVELS OF α-TOCOPHEROL

The RDA for adults is 15 mg of *RRR* α-tocopherol,[1] but more than 88% of Americans do not meet this recommendation.[4] To establish the RDA, erythrocyte hemolysis by hydrogen peroxide was used as a biomarker of vitamin E depletion and repletion.[1] The use of this biomarker has been questioned,[5] and there may be grounds for basing future recommendations for vitamin E intake on endpoints related to chronic disease instead.[6] α-Tocopherol bioavailability is lower in cigarette smokers[7,8] and individuals with metabolic syndrome,[9] so certain populations may need more α-tocopherol than healthy individuals.

Vitamin E deficiency is very rare, but vitamin E insufficiency may be common, given the dietary intakes reported for Americans.[10] It is unknown whether marginal vitamin E deficiency leads to adverse health outcomes or to chronic disease.[11] Some research suggests that the RDA is actually too high for healthy adults.[12]

BIOAVAILABILITY AND BIOPOTENCY OF α-TOCOPHEROL

Determining the bioavailability and biopotency of synthetic and naturally sourced α-tocopherol is important for evaluating the roles of these vitamin E sources in health and disease. In the 1940s, experiments with rats showed that a dose of all-*rac* α-tocopheryl acetate 1.36 times the mass of a dose of naturally sourced α-tocopheryl acetate was required to prevent fetal resorption.[13] Based on these studies, all-*rac* α-tocopheryl acetate was assigned a value of 1 IU/mg, and 1.36:1 became the accepted *RRR* to all-*rac* ratio of biopotency. International units have long been used to denote vitamin E content on food labels, but this will soon change. More recent research does not support the 1.36:1 ratio of biopotency in humans.[5] Some animal and human bioavailability studies suggest a new ratio of *RRR* to all-*rac* biopotency of 2:1, as plasma and tissues accumulate about twice the amount of deuterated *RRR* α-tocopherol as all-*rac* α-tocopherol after simultaneous consumption.[14–16] The preferential binding of hepatic α-TTP to the 4 2*R* stereoisomers over the 4 *2S* stereoisomers also supports the 2:1 ratio. Therefore, it has been assumed that, at doses of an equivalent mass, all-*rac* α-tocopherol has one-half the biopotency of *RRR* α-tocopherol.

However, determining the *RRR* to all-*rac* α-tocopherol ratio of biopotency requires the measurement of a biological response, such as fetal resorption. The new 2:1 ratio relies solely on bioavailability data (α-tocopherol tissue concentrations) and does not reflect data on biopotency. Though there are only limited measurable clinical endpoints to study α-tocopherol biopotency,[5,13] data from α-tocopherol–deficient animal models can provide insight. Future studies should explore the effects of different dose ratios of *RRR* to all-*rac* α-tocopherol on tissue accumulation and functional parameters. To eliminate competition between these 2 sources of vitamin E in the liver, a nonsimultaneous dosing regimen may be most appropriate.

Still, some researchers hypothesize that there is no single ratio of biopotency for the 2 α-tocopherol sources. They assert that the bioavailability and biopotency of each source differs depending on the dosage, the type of tissue, and the duration of dosing.[5,17,18] For example, *RRR*:*SRR* ratios in the brain consistently increased the longer rats were fed a diet containing mass-equivalent doses of deuterated *RRR* and *SRR* α-tocopherol (from a ratio of 1.5:1 after 4 days up to 5.3:1 after 154 days).[18] The *RRR*:*SRR* ratios in other tissues changed much less than the ratios in the brain, but each tissue differed in its discrimination for *RRR* over time.[18] These differences in availability across tissues and over time obfuscate efforts to determine the biopotency of individual α-tocopherol stereoisomers, since doing so would require the use of a precise dosing regimen and a specific tissue type.

As already noted, the current unit of measurement of vitamin E on food labels (international units) will soon be replaced. Based on a May 2016 ruling, the US Food and Drug Administration (FDA) is modifying the labeling regulations for conventional foods and dietary supplements.[19] Food manufacturers will be required to

indicate vitamin E content in milligrams instead of international units. Furthermore, it will be assumed that 2 mg of all-*rac* α-tocopherol equals 1 mg of *RRR* α-tocopherol. This is a drastic change in the regulations, given the ongoing uncertainty over the ratio of biopotency.

BIOLOGICAL BASIS FOR DIFFERENTIAL EFFECTS

There is a solid biological basis for differential effects of *RRR* α-tocopherol and all-*rac* α-tocopherol on health outcomes. The body differentially distributes, metabolizes, and excretes α-tocopherol stereoisomers. As noted earlier, hepatic α-TTP has a clear preference for *RRR* α-tocopherol and the other 2*R* stereoisomers, and thus *RRR* α-tocopherol is preferentially taken up into tissues over *SRR* α-tocopherol.[2,3,18,20,21] For example, the only study that quantified all 8 stereoisomers in rat brain tissue found that the 4 *2R* stereoisomers accumulated equally; this further demonstrates the importance of the 2-position chiral carbon for α-tocopherol availability in tissues.[22]

The preference of hepatic α-TTP for 2*R* stereoisomers suggests that 2*R* stereoisomers are able to perform their functions better than 2*S* stereoisomers. Interestingly, the 2*S* stereoisomers do accumulate to varying degrees in milk[23] and other tissues such as the brain,[18,21,22,24] presumably via chylomicron delivery. This raises 2 questions about the role of 2*S* stereoisomers once they reach extrahepatic tissues. First, is there competition between *2R* and *2S* stereoisomers within cells? And second, do *2R* and 2*S* stereoisomers result in the same biological response?

Evidence in humans, though very limited, shows preferential incorporation of *RRR* α-tocopherol (over all 7 other stereoisomers) into tissues of the human infant brain.[24] The biological rationale for—and significance of—this is not clear, though discriminatory mechanisms in extrahepatic tissues have been proposed. For example, the blood–brain barrier may regulate the entry of α-tocopherol into the brain.[18] Additionally, the α-tocopherol–binding protein α-TTP has been detected in the brains of humans[25] and rats.[26] Tocopherol-associated protein, which has the same lipid-binding motif as α-TTP, has also been suggested as a potential binding protein for α-tocopherol.[27] Tocopherol-associated protein was detected in multiple human tissues (eg, brain, heart, lung)[28] and may be a transcriptional activator.[29] However, despite promising results with tocopherol-associated protein, the primary role of this protein (typically known as supernatant protein factor) is in cholesterol biosynthesis,[30] which likely has little physiological relevance to α-tocopherol metabolism.[31]

As for excretion of vitamin E, simultaneous consumption of deuterium-labeled *RRR* α-tocopherol and all-*rac* α-tocopherol led to the preferential excretion of all-*rac* (as α-CEHC) over *RRR* in urine at a remarkably high ratio of approximately 3:1.[32] This suggests that *RRR* is preserved over all-*rac* and provides evidence of the differential impact of the 2 sources of α-tocopherol.

The scientific community's understanding of vitamin E has evolved since its discovery nearly a century ago, but some aspects of vitamin E warrant further investigation. The existing research does not wholly support the FDA's changes to the US food labeling regulations with regard to vitamin E. A change in the unit of measurement used on food labels (international units to milligrams) is appropriate, since the conversion factors for international units have not been confirmed. However, the assertion of a 2:1 ratio of biopotency between naturally sourced and synthetic α-tocopherol has not been confirmed, either. Because very few studies directly compare the effectiveness of different α-tocopherol sources for health outcomes, this review evaluates and compares studies that investigated one source or the other. It focuses on 4 areas of human health that are often associated with the effects of α-tocopherol: the central nervous system (CNS), the immune system, the cardiovascular system, and cancer. The potential mechanisms responsible for the benefits of α-tocopherol in these 4 areas are also explored briefly. Many of the reviewed studies did not use vitamin E-depleted animals—those that did are specifically noted.

NEUROLOGICAL DISEASES

Role of α-tocopherol in the CNS

Animal studies show that α-tocopherol promotes brain health and reverses neurodegeneration by preventing oxidative stress to cell components (eg, lipids and mitochondria).[33,34] Studies using the α-TTP gene knockout ($Ttpa^{-/-}$) model have produced some of the most valuable findings. With age, these animals develop structural abnormalities in the cerebellum[35] and spinal cord[36] as well as behavioral deficits[36] caused by severe α-tocopherol deficiency. The $Ttpa^{-/-}$ model is particularly useful because neurological tissues retain α-tocopherol, even during dietary restriction.[36] This model is also relevant to humans who have ataxia with vitamin E deficiency. Individuals with this disorder have loss-of-function mutations in the α-TTP gene and experience severe neurological dysfunction.[37] Management of ataxia with vitamin E deficiency includes lifelong supplemental doses of α-tocopherol, which helps normalize plasma α-tocopherol levels and may partially reverse neurological symptoms.[38] Knowledge gained about the consequences of deficiency has led to increased understanding of the metabolic fate of α-tocopherol.

There is conflicting evidence about the role of α-tocopherol in other neurological outcomes, such as Alzheimer's disease (AD) and cognitive function in older adults. In epidemiological studies, high tocopherol intake is associated with decreased incidence of AD.[39] Moreover, patients with AD tend to have low plasma α-tocopherol concentrations,[40] and plasma α-tocopherol has been inversely associated with severity of dementia and positively associated with both abstract reasoning and retention in the Fuld Object-Memory Evaluation.[41] In contrast, α-tocopherol brain concentrations were not associated with AD neuropathology in deceased humans.[33] In other studies, there were no associations between plasma α-tocopherol and measures of cognitive function[42] or risk of cognitive impairment[43] in elderly participants. A 2017 Cochrane review concluded there is no evidence supporting the use of α-tocopherol for treatment of mild cognitive impairment, but the results of 1 trial indicate that α-tocopherol may slow the progression of AD.[44]

It is α-tocopherol's antioxidant properties that are most commonly associated with neurological health and disease. Oxidative stress is a factor in many brain disorders, including AD, and thus α-tocopherol status could be a critical factor.[45] Nonetheless, some research suggests that α-tocopherol has both antioxidant and nonantioxidant functions in the CNS.[46] For example, α-tocopherol may regulate gene expression. Two studies showed substantial changes in the expression of genes related to myelination, synaptic function, and oxidative stress in the cortices of adult *Ttpa*$^{-/-}$ mice.[47,48] Another study concluded that α-tocopherol regulates hippocampal genes involved in Parkinson disease and AD.[49]

Histological or behavioral indicators of neurodegeneration have not been observed in young *Ttpa*$^{-/-}$ rodents; histological markers were seen from 17 to 20 months of age,[35,36] and behavioral markers were seen at 18 months of age.[36] However, alterations in gene expression have been observed in younger mice. Molecular changes may therefore precede more advanced manifestations of neurodegeneration.[48]

Though only a handful of studies have compared the sources of α-tocopherol for their effects on neurological outcomes, work in equines has shown that *RRR* α-tocopherol more effectively increases serum and cerebrospinal fluid α-tocopherol concentrations than equivalent doses (international units) of all-*rac* α-tocopherol (Table 1).[50–55]

Neurological studies investigating *RRR* α-tocopherol

Most CNS-related studies with *RRR* α-tocopherol have used rodent models. For example, a daily dose of *RRR* α-tocopherol delayed the neurological symptoms of ataxia with vitamin E deficiency and decreased lipid peroxidation in *Ttpa*$^{-/-}$ mice.[36] An *RRR* α-tocopherol–supplemented diet also attenuated development of the tau pathology (a key component of Parkinson disease) in a transgenic mouse model that overexpresses a human tau isoform.[56]

Studies have also used *RRR* α-tocopherol to treat induced seizures[57] and permanent cerebral brain injuries[58] in otherwise healthy, vitamin E–sufficient rats. In both cases, *RRR* α-tocopherol reduced unfavorable hippocampal microglia activation.[57,58] Treatment also significantly decreased markers related to oxidative stress[57] and prevented pyramidal cell death.[58]

Using a mouse model of AD and vitamin E deficiency (*Ttpa*$^{-/-}$ + APP*sw*), *RRR* α-tocopherol supplementation reduced plasma amyloid β levels[59] and amyloid plaque areas in the cortex and hippocampus.[60] Supplementation normalized performance in the Morris water maze but did not improve performance in other behavioral tasks, such as a contextual fear conditioning test.[60]

Some animal research does not support a benefit of *RRR* α-tocopherol for CNS function.[61] Additionally, very few CNS-related trials in humans have studied the effect of *RRR* α-tocopherol. In a long-term trial of *RRR* α-tocopherol supplementation in healthy older women, no significant cognitive benefits after multiple assessments were observed.[62]

Neurological studies investigating all-*rac* α-tocopherol

Rats fed an α-tocopherol–deficient diet for 38 weeks followed by an all-*rac* α-tocopherol repletion diet for 20 weeks had less functional neural deterioration than rats fed an α-tocopherol–deficient diet throughout the study.[63] Their electrophysiological parameters were also more similar to those of controls.[63] The diet of the control group contained low levels of *RRR* α-tocopherol, indicating that repletion with all-*rac* α-tocopherol may be sufficient to restore the normal neural function observed in animals fed *RRR* α-tocopherol.

A second rodent study investigated long-term potentiation in the dentate gyrus (hippocampus) of aged and young rats fed a diet supplemented with all-*rac* α-tocopherol.[64] Long-term potentiation is the long-lasting strengthening of synapses, and it is one cellular mechanism used to explain learning and memory.[64] While aged control mice (consuming a diet containing standard α-tocopherol levels) exhibited reduced long-term potentiation and increased lipid peroxidation, aged rats fed all-*rac* α-tocopherol–supplemented diets showed sustained long-term potentiation and reduced lipid peroxidation, similar to findings in young rats.[64]

Table 1 **Central nervous system, immune system, and cardiovascular health outcomes in studies that compared *RRR* and all-*rac* α-tocopherol treatments**

Reference	Body system	Study group[a]	Treatment doses	Sample size (per group)	Dosing regimen	Dosing duration (days)	Outcomes	Overall effect of *RRR* vs all-*rac*
Pusterla et al. (2010)[50]	CNS	Horses	*RRR* α-toc: 10 000 IU (6711 mg)	4	Daily, mixed into 250 g of sweet feed	14	*RRR* α-toc: ↑ $[\alpha\text{-toc}]_{serum}$; 2.2- to 4.2-fold ↑ $[\alpha\text{-toc}]_{CSF}$ by day 14	*RRR* α-toc, but not all-*rac*, increased serum and CSF α-toc levels
			All-*rac* α-TA: 10 000 IU (10 000 mg)	5			All-*rac* α-TA: no differences in $[\alpha\text{-toc}]_{serum}$ or $[\alpha\text{-toc}]_{CSF}$ from day 0 to day 14	
Han et al. (2010)[51]	Immune system	Mice	*RRR* α-TA: 30 mg/kg diet or 500 mg/kg diet	4	Ad libitum, added to diet	28	*RRR* α-TA: *dose comparison—high:* ↑ gene expression of signaling lymphocyte activation molecule, TNF, and others; *low:* ↑ gene expression of IL-3 and others. *α-toc source comparison—RRR:* ↑ gene expression of lymphocyte activation molecule, TNFSF9, and others	Differences in spleen T lymphocyte gene transcription between α-toc doses and α-toc sources following ex vivo stimulation
			All-*rac* α-TA: 30 mg/kg diet or 500mg/kg diet	4			All-*rac* α-TA: *dose comparison—high*: ↑ gene expression of IL-2 and others; *low*: ↑ gene expression of IGF-1 and others	
Horn et al. (2010)[52]	Immune system	Cattle	*RRR* α-TA: 1000 IU (735 mg)	50	Daily, corn-based supplement	–[b]	*RRR* α-TA: ↑ $[\alpha\text{-toc}]_{serum}$; no differences in calf $[IgG]_{serum}$ or leukocyte CD14 and CD18 protein expressions compared with control. *Source comparison*—no overall difference in response to OVA challenge	No differences in immune response in suckling calves between α-toc sources
			All-*rac* α-TA: 1000 IU (1000 mg)	50			All-*rac* α-TA: ↑ $[\alpha\text{-toc}]_{serum}$; no differences in calf $[IgG]_{serum}$ or leukocyte CD14 and CD18 protein expressions compared with control	
Amazan et al. (2014)[53]	Immune system	Pigs	*RRR* α-TA: 150 mg or 50 mg	12	Daily, in water	[c]	*RRR* α-TA: *dose comparison—high:* ↑ $[\alpha\text{-toc}]_{serum}$ and ↑ $[IgA]_{serum}$	Higher α-toc serum levels in piglets from sows fed *RRR* α-toc compared with piglets from sows fed all-*rac* α-toc; no differences in immunoglobulin levels
			All-*rac* α-TA: 150 mg	12	Daily, in feed		*Source comparison—RRR:* ↑ $[\alpha\text{-toc}]_{serum}$; no differences in $[IgA]_{serum}$, $[IgG]_{serum}$, or $[IgM]_{serum}$	
Reaven & Witztum (1993)[54]	CV system	Humans	*RRR* α-TA: 800 mg	7	Twice daily, α-TA capsules	56	*RRR* α-TA: ↑ $[\alpha\text{-toc}]_{LDL}$; ≈ 30% ↑ lag time of LDL oxidation after 28 and 56 days of supplementation; ↓ TBARS; ↓ macrophage degradation of LDL	No differences in LDL α-toc levels, susceptibility to lipid peroxidation of LDL, or other outcomes between α-toc sources
			All-*rac* α-TA: 800 mg	8			All-*rac* α-TA: ↑ $[\alpha\text{-toc}]_{LDL}$; ≈ 30% ↑ lag time of LDL oxidation after 28 and 56 days of supplementation; ↓ TBARS; ↓ macrophage degradation of LDL	

(continued)

Table 1 **Continued**

Reference	Body system	Study group[a]	Treatment doses	Sample size (per group)	Dosing regimen	Dosing duration (days)	Outcomes	Overall effect of *RRR* vs all-*rac*
Devaraj et al. (1997)[55]	CV system	Humans	*RRR* α-TA: 100 IU (73.5 mg); 200 IU (147 mg); 400 IU (294 mg); or 800 IU (588 mg)	9–10	Daily, α-TA or placebo (soybean oil) capsules	56	*RRR* α-TA: *dose comparison*—↑ $[\alpha\text{-toc}]_{plasma}$ and ↑ $[\alpha\text{-toc}]_{LDL}$ with increasing dose; no differences in plasma lipid, lipoprotein, or fatty acid levels across doses or over time; prolongation of lag phase of oxidation with doses ≥ 400 IU	No differences in oxidative susceptibility of LDL or plasma α-toc concentrations between α-toc sources at any dose
			All-*rac* α-TA: 100 IU (100 mg); 200 IU (200 mg); 400 IU (400 mg); or 800 IU (800 mg)	9–10			All-*rac* α-TA: *dose comparison*—↑ $[\alpha\text{-toc}]_{plasma}$ and ↑ $[\alpha\text{-toc}]_{LDL}$ with increasing dose; no differences in plasma lipid, lipoprotein, or fatty acid levels across doses or over time; prolongation of lag phase of oxidation with doses ≥ 400 IU	

Abbreviations and symbols: α-TA, α-tocopheryl acetate; α-toc, α-tocopherol; CSF, cerebrospinal fluid; CV, cardiovascular; IgA, immunoglobulin A; IgG, immunoglobulin G; IGF-1, insulin-like growth factor 1; IgM, immunoglobulin M; IL-2, mouse interleukin 2; IL-3, mouse interleukin 3; LDL, low-density lipoprotein; OVA, ovalbumin; TBARS, thiobarbituric acid-reactive substances; TNF, mouse tumor necrosis factor; TNFSF9, mouse tumor necrosis factor (ligand) superfamily, member 9; ↑, increased; ↓, decreased.

[a]Animal groups were not vitamin E depleted prior to the study.

[b]Dams were supplemented at ≈ 6 weeks prepartum until the beginning of breeding season; outcomes were measured in their suckling calves.

[c]Sows were fed either all-*rac* α-TA or one of two *RRR* α-TA doses beginning 84 days prepartum and through lactation; after weaning, piglets were fed 3.33 mg of all-*rac* α-TA per day until 42 days of age.

This suggests that all-*rac* α-tocopherol helped prevent age-related oxidative stress in the hippocampus.

In a third animal study, transgenic mice were used to investigate apoE4, an apolipoprotein E isoform involved in CNS lipoprotein metabolism and implicated as an independent risk factor for AD. All-*rac* α-tocopherol supplementation did not affect most of the AD-related endpoints.[65]

In 2 randomized, placebo-controlled human trials, daily supplementation with high-doses synthetic α-tocopherol delayed AD progression in individuals with mild to moderately severe AD.[66,67]

RRR α-tocopherol vs all-*rac* α-tocopherol: conclusions for neurological outcomes

Some studies (both animal and human) did not specify whether *RRR* or all-*rac* α-tocopherol was used, which severely limits the comparability of results across studies. Despite the known consequences of low α-tocopherol status, the relative effect of *RRR* vs all-*rac* α-tocopherol in CNS health is not clear; none of the CNS studies aimed to show the ratio of biopotency between the 2 sources. Most research in animals showed some benefits from both *RRR* and all-*rac* α-tocopherol for the doses used. In 2 studies conducted in AD patients, all-*rac* α-tocopherol supplementation resulted in positive outcomes. Several human trials have used poorly defined vitamin E supplements that contain multiple tocopherol analogues; these studies were not included in this review.

IMMUNE RESPONSE

Role of α-tocopherol in the immune system

The role of α-tocopherol in the immune system has been studied through the lens of allergic airway disease and lung function. Following ovalbumin sensitization, *Ttpa*$^{-/-}$ mice displayed a reduced immune response in the lung, demonstrating a need for α-tocopherol.[68] Furthermore, higher serum α-tocopherol is related to favorable spirometric markers in young adults,[69] and α-tocopherol may improve or reverse the functional decline of T cells that occurs with aging.[70]

The best-known function of α-tocopherol (ie, antioxidant) may be linked to immune-related outcomes. Some studies suggest that antioxidant intake is inversely associated with asthma prevalence.[71] A second relevant function of α-tocopherol in the immune system involves signal transduction pathways. In endothelial cells, α-tocopherol inhibits protein kinase C α, thereby inhibiting the recruitment of leukocytes[72,73] and altering the inflammatory immune response. It may also

regulate the expression of immune-related genes in the heart[74] as well as a group of genes related to inflammation.[75]

A few immunological studies have explicitly compared all-*rac* α-tocopherol with *RRR* α-tocopherol (Table 1).[51–53] One ex vivo study used T lymphocytes from spleens of aged adult wild-type mice. The animals were fed diets with high or low levels of either *RRR* or all-*rac* α-tocopherol. After 4 weeks of treatment, it was shown that both the dose and the source of α-tocopherol influenced gene transcription.[51] Distinct gene expression profiles were observed, even when the high dose of all-*rac* α-tocopherol (500 mg per kilogram of diet) was compared with the low dose of *RRR* α-tocopherol (30 mg per kilogram of diet).[51] This suggests that the 2 α-tocopherol sources interact differently with their cellular targets and are not equivalent, even when all-*rac* α-tocopherol doses are well above the hypothesized 2:1 ratio of biopotency.

In another study, calves suckling cows whose diets were supplemented with either *RRR* α-tocopherol or all-*rac* α-tocopherol had higher serum α-tocopherol levels than controls, but there were no differences in immune function in calves after an ovalbumin challenge.[52] A third study found that piglets of sows fed *RRR* α-tocopherol had higher serum α-tocopherol levels than piglets of sows fed all-*rac* α-tocopherol.[53] However, serum immunoglobulin levels in the piglets did not differ between groups.[53]

Immune-response studies investigating *RRR* α-tocopherol

Some studies have assessed the effect of *RRR* α-tocopherol and age on immune outcomes. Linker for Activation of T cells is necessary for T-cell activation, and changes in phosphorylation signifies an altered response.[76] Phosphorylation of Linker for Activation of T cells was significantly reduced in spleen $CD4^+$ T cells of aged control mice, but *RRR* α-tocopherol treatment normalized phosphorylation.[76]

RRR α-tocopherol may reduce allergic responses and lung inflammation. Rodent dams were fed an *RRR* α-tocopherol–supplemented diet, and then their pups were sensitized with ovalbumin to induce an immune response. The pups had significantly lower eosinophil recruitment and inflammation in their lung tissue compared with the pups of dams fed a standard diet.[77] In the lungs of pups in the treatment group, there were also significant decreases in the expression of genes encoding allergen-induced proteins (eg, interleukin [IL]-4 and IL-33).[77] In contrast, a different rodent study showed that short-term (10-day) pretreatment with *RRR* α-tocopherol was ineffective in preventing the effects of an antigen challenge.[78]

Only a few human studies have examined the effects of *RRR* α-tocopherol supplementation on immune system outcomes. Research in asthmatics has yielded conflicting results: Supplemental doses of *RRR* α-tocopherol significantly decreased airway oxidative stress in 1 study[79] but had no measurable impact on asthma control in another.[80] However, the former study was small and was not randomized or placebo controlled.

Immune-response studies investigating all-*rac* α-tocopherol

T-cell function becomes impaired with age, but this was partially remedied by α-tocopherol in rodent studies. Feeding aged mice a diet containing high-dose all-*rac* α-tocopherol triggered changes in the transcription of genes important for the immune response: α-tocopherol led to induced expression of IL-2 and repressed expression of IL-4 in the animals' splenic T cells.[81] In another study examining T-helper 1 cytokine production, old influenza-infected mice were fed a diet containing high-dose all-*rac* α-tocopherol.[82] Splenocytes from these mice had higher production of some cytokines, eg, IL-2 and interferon-γ, but not of others, eg, IL-6 and IL-1β.[82] Production of prostaglandin E_2 (PGE_2) was also significantly reduced in macrophages of these mice.[82] Since PGE_2 levels increase with age and may reduce the normal T-helper 1 response, α-tocopherol may enhance T-helper 1 cell function by decreasing PGE_2.[82]

Numerous gene transcripts in lung tissue were either up- or downregulated in male and female mice fed diets supplemented with low-dose or high-dose all-*rac* α-tocopherol.[83] Despite similar levels of α-tocopherol in lung between sexes fed the high all-*rac* diet, substantially more genes were affected by α-tocopherol treatment in females than in males (≈ 500 vs ≈ 80).[83] Of particular interest was a cluster of 13 functionally related cytoskeleton genes that were all induced by an α-tocopherol–supplemented diet.[83] Though these findings lack statistical power, this research provides a starting point for future studies assessing the impact of sex and α-tocopherol on gene expression in lung tissue.

In a trial with healthy older adults, daily supplementation with all-*rac* α-tocopherol improved multiple measures; in particular, participants had significantly decreased plasma lipid peroxide concentrations and enhanced cell-mediated immunity.[84] De la Fuente et al.,[85] Meydani et al.,[86] and Lee et al.[87] also found that supplemental doses of all-*rac* α-tocopherol positively affected immune outcomes in older adults.

Effects on airway disease have been studied as well. Participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study who received daily synthetic 2-*ambo* α-tocopherol (which is 50% *RRR* and 50% *SRR*) supplements showed no differences in the development of chronic obstructive pulmonary disease symptoms, such as chronic bronchitis and dyspnea.[88]

RRR α-tocopherol vs all-*rac* α-tocopherol: conclusions for immune response outcomes

In human and animal studies, *RRR* α-tocopherol and all-*rac* α-tocopherol have resulted in both positive and null effects on immune-related outcomes. The human studies often provided very high daily doses of all-*rac* α-tocopherol, so it is possible that supplements provided sufficient amounts of *RRR* or other *2R* stereoisomers to produce beneficial effects. Using biomarkers of immune function to establish recommendations for α-tocopherol intake could be a worthwhile approach. Older adults may benefit most from the effect of α-tocopherol on immune function and inflammation.

CARDIOVASCULAR DISEASES

Role of α-tocopherol in the cardiovascular system

The development of cardiovascular diseases (CVDs), such as atherosclerosis, is intricately linked to the oxidation of low-density lipoprotein (LDL) particles and its consequences.[89,90] Hence, vitamin E, which can inhibit this oxidation, has been used to prevent and treat negative CVD outcomes. Epidemiological studies have supported an inverse relationship between vitamin E intake and risk of coronary heart disease in both women[91] and men.[92] An inverse association between plasma α-tocopherol levels and mortality due to ischemic heart disease in men from 16 European study populations was also reported.[93] In animal models, atherosclerosis-prone, vitamin E–deficient mice ($Ttpa^{-/-}$ $Apoe^{-/-}$) had significantly larger aortic lesions (in the arch and thorax) than atherosclerosis-prone mice without a genetic predisposition for vitamin E deficiency ($Ttpa^{+/+}$ $Apoe^{-/-}$).[94] The double knockout mice also showed increased lipid peroxidation in the proximal aorta.[94] This compelling study showed that adequate vitamin E status may prevent oxidative damage and formation of atherosclerotic lesions.

Gene regulation by α-tocopherol has been demonstrated in the heart, which could be an additional mechanism by which α-tocopherol prevents unfavorable cardiovascular outcomes. Genes related to proper immune response, lipid metabolism, and inflammation were dysregulated in hearts of $Ttpa^{-/-}$ mice.[74] Other nonantioxidant roles are possible for α-tocopherol in the CV system, as α-tocopherol has been shown to inhibit vascular smooth muscle cell proliferation through a protein kinase C–dependent mechanism,[95,96] to inhibit platelet aggregation,[97–99] and to modulate the inflammatory response via changes in monocyte function.[100]

Results from human studies evaluating the effect of α-tocopherol on the cardiovascular system are inconsistent. One meta-analysis found that vitamin E supplementation positively affected flow-mediated vasodilation (which serves as a marker of endothelial function and CVD risk).[101] In contrast, a separate meta-analysis concluded that α-tocopherol supplementation did not help prevent strokes.[102] Both meta-analyses included studies that used *RRR* or all-*rac* α-tocopherol, and neither distinguished between the α-tocopherol sources in their analyses. This highlights the challenge of evaluating the health effects of individual sources of α-tocopherol.

Very few studies have directly compared the effect of different α-tocopherol sources on cardiovascular health, and the 2 described below were conducted decades ago (Table 1).[54,55] In 1, participants received very high daily doses (1600 mg/d) of either *RRR* α-tocopherol or all-*rac* α-tocopherol for 8 weeks; afterward, their lipid levels and the susceptibility of isolated lipoproteins to oxidation were measured.[54] Although lag time for oxidation increased by approximately 30% in both treatment groups compared with controls, there were no differences between the 2 α-tocopherol sources for the outcomes measured.[54]

Devaraj et al.[55] provided participants with 100 IU, 200 IU, 400 IU, or 800 IU of either *RRR* α-tocopherol or all-*rac* α-tocopherol for 8 weeks (8 treatment groups). As dose increased, total plasma α-tocopherol concentrations also increased (measured at week 8); this was true for both α-tocopherol sources.[55] There were no significant differences in total plasma α-tocopherol levels between the *RRR* and all-*rac* α-tocopherol groups at any dose. This is not surprising, since even the lowest dose (100 IU) is high relative to the typical dietary intake. This study did not quantify individual α-tocopherol stereoisomers in the plasma, but future studies that compare *RRR* and all-*rac* α-tocopherol should consider doing so. Devaraj et al.[55] also measured the susceptibility of isolated lipoproteins to oxidation. Only at doses $\geq$400 IU was there a prolonged lag phase of oxidation, and there were no differences between the 2 α-tocopherol sources.[55] Lipoprotein oxidation may be a useful functional measurement, given its role in atherosclerosis. To investigate the ratio of biopotency of *RRR* to all-*rac* α-tocopherol, lower doses of α-tocopherol (closer to amounts normally consumed in the diet) are likely needed. Both studies included only healthy participants,

so it is unclear whether similar results would be seen in populations with CVD.

Cardiovascular studies investigating *RRR* α-tocopherol

In adult *Apoe*$^{-/-}$ mice fed a high-fat diet, an *RRR* α-tocopherol intervention significantly decreased lesion size in the aortic root but did not affect a marker of oxidative stress or improve the resistance of plasma lipids to oxidation when exposed to peroxyl radicals.[103]

RRR α-tocopherol improved CVD-related endpoints in several human studies. In an ex vivo experiment, *RRR* α-tocopherol supplements drastically inhibited platelet adhesion in study participants,[104] and researchers later showed that cosupplementation with *RRR* α-tocopherol and aspirin (a platelet antiaggregating agent) may help prevent ischemic events in patients with ischemic cerebrovascular disease.[105] *RRR* α-tocopherol significantly reduced the risk of nonfatal myocardial infarction and cardiovascular events in patients with atherosclerosis[106] and significantly reduced the risk of combined cardiovascular outcomes in hemodialysis patients.[107] However, it had no effect on any cardiovascular outcomes measured in a high-risk population.[108] In healthy women, *RRR* α-tocopherol significantly decreased cardiovascular-related deaths but did not reduce the risk of heart failure,[109] myocardial infarction,[110] or stroke.[110] These trials indicate that α-tocopherol may be of benefit to only some populations.

Cardiovascular studies investigating all-*rac* α-tocopherol

In an atherosclerosis-prone murine model (LDL receptor–deficient mice, ie, *Ldlr*$^{-/-}$), mice fed a low-fat, low-cholesterol diet combined with long-term all-*rac* α-tocopherol supplementation initiated at an early age showed a significantly reduced area of lesion on the descending aorta and a higher survival rate when compared with mice not given all-*rac* α-tocopherol.[111]

Several studies have investigated synthetic α-tocopherol to treat or prevent cardiovascular disease in human populations with varying health statuses (eg, smokers, patients with CVD or diabetes, patients with a history of other conditions), but most have reported null results.[112–116] In fact, α-tocopherol significantly *increased* the risk of hemorrhagic stroke in 1 study.[116] Fewer studies have been conducted in healthy populations, but 1 study reported that all-*rac* α-tocopherol reduced LDL levels and lowered LDL susceptibility to oxidation.[117]

RRR α-tocopherol vs all-*rac* α-tocopherol: conclusions for cardiovascular outcomes

Epidemiological studies have shown that the consumption of α-tocopherol from foods may provide some benefit to the cardiovascular system. The effectiveness of an α-tocopherol intervention may depend on the cardiovascular health status at the time the intervention is initiated. *RRR* α-tocopherol intake may improve cardiovascular outcomes in atherosclerosis-susceptible animal models and in humans with preexisting conditions, but not in healthy individuals or those at high risk for cardiovascular events. All-*rac* α-tocopherol has been beneficial in some animal studies, but most human research suggests no benefit to the cardiovascular system. Some potentially valuable research did not identify which α-tocopherol source was used. This was the case for 2 animal studies in which supplementary α-tocopherol reduced lesion areas in aortas of atherosclerosis-susceptible mice.[118,119] The contradictory results reported in the literature for the 2 different α-tocopherol sources may stem from the wide-ranging dosing regimens used: every study used a different amount, frequency, and duration of dosing.

CANCER

Role of α-tocopherol in cancer

To categorize the complex underpinnings of neoplastic diseases, Hanahan and Weinberg[120] identified 8 hallmarks and 2 enabling characteristics of cancer. One enabling characteristic (genome instability and mutation) may be relevant to the functions of α-tocopherol. In other words, the ability of α-tocopherol to quench free radicals could prevent damage to DNA and reduce the risk of cancer development. Oxidative stress may indeed be linked to carcinogenesis, since it damages cell components.[121] However, α-tocopherol has not been shown to prevent DNA damage via antioxidant action in humans, and it is unclear whether an antioxidant mechanism could result in clinically relevant health benefits.[122–124] In vitro, α-tocopherol inhibits vascular endothelial growth factor released from human breast cancer cells,[125] so α-tocopherol could theoretically influence another cancer hallmark, ie, angiogenesis.[120] Nevertheless, the existing literature does not support this relationship. In preclinical studies, α-tocopherol and α-tocopherol derivatives have been ineffective in preventing tumor formation in the colon, and results have been inconsistent in lung, prostate, and mammary gland studies.[126]

Studies assessing α-tocopherol intake from food sources or supplements and cancer risk have not shown

an unequivocal benefit from increased consumption, though there may be some benefit for particular types of cancer and specific patient populations.[127–129] High vitamin E intake significantly decreased pancreatic cancer risk,[130] colon cancer risk,[131] and bladder cancer mortality.[132] A significant inverse association between serum α-tocopherol and advanced and aggressive prostate cancer risk has also been reported.[133] On the contrary, vitamin E supplementation was not associated with colorectal cancer risk,[134] colon cancer mortality,[135] or stomach cancer mortality.[136]

On the whole, the literature does not support a beneficial role for α-tocopherol in the treatment or prevention of cancer. Nevertheless, because of the proposed link between antioxidants and cancer, and because α-tocopherol has been administered in relevant human trials, the results of interventions with *RRR* α-tocopherol and all-*rac* α-tocopherol will be briefly summarized.

Cancer studies investigating *RRR* α-tocopherol

In a large, long-term trial, supplementation with *RRR* α-tocopherol had no significant effect on the incidence of total cancer, breast cancer, lung cancer, colon cancer, or cancer deaths,[110] nor did it significantly reduce the incidence of total cancer, organ-specific cancer, or cancer deaths in a second trial with high-risk volunteers.[137] Daily antioxidant supplements, which included *RRR* α-tocopherol, also did not reduce adenoma incidence in patients with previously removed adenomas.[138]

Cancer studies investigating all-*rac* α-tocopherol

Debatably the most optimistic findings for cancer outcomes came from a trial in smokers, in which supplementation with synthetic α-tocopherol reduced colorectal cancer incidence,[139] prostate cancer incidence,[139] and prostate cancer mortality.[140] Conversely, there was no effect of all-*rac* α-tocopherol on incidence of prostate cancer, total cancer, cancer at other sites or on cancer mortality in other randomized, placebo-controlled studies.[141,142] In 1 of these studies, all-*rac* α-tocopherol supplementation actually nonsignificantly *increased* prostate cancer incidence.[141]

*RRR*α-tocopherol vs all-*rac* α-tocopherol: conclusions for cancer outcomes

Cancer-related benefits from α-tocopherol consumption have been observed in some epidemiological studies, but the majority of clinical trials of α-tocopherol supplementation do not confirm these findings. It is conceivable that diets containing antioxidant-rich foods, eg, fruits and vegetables, could be beneficial but that supplements are not. Despite a plausible basis for cancer-related benefits, it seems that neither α-tocopherol source affects cancer outcomes.

CONCLUSION

The effects of α-tocopherol on nonalcoholic steatohepatitis,[143,144] eye disorders,[145,146] and other health conditions have been studied previously, but this review focused on 4 of the more well-known areas of disease associated with vitamin E. Comparing studies that investigated the sources of α-tocopherol revealed many limitations, such as differences in population characteristics (vitamin E status, sex, age, health status), dose and dosing frequency of α-tocopherol, study size and duration, and the wide array of different endpoints considered. There is stronger evidence for a beneficial role of α-tocopherol in some health outcomes (eg, neurological function) than in others (eg, cancer), but unfortunately, a number of studies neglected to disclose which α-tocopherol source was investigated.

In 2000, Hoppe and Krennrich[5] called on researchers to discover novel in vivo biomarkers for α-tocopherol status and new methods for assessing the ratio of *RRR* to all-*rac* biopotency.[5] Almost 2 decades later, their optimistic call for action is still unrealized. Language used in the recent FDA ruling presumes a scientific consensus on the relative bioavailability and biopotency of the different α-tocopherol sources, and yet it is not possible to ascertain this essential information from the existing research. Studies have also failed to compare the effectiveness of *RRR* vs all-*rac* α-tocopherol for the selected health outcomes. In general, animal research has shown that both sources of α-tocopherol produce beneficial effects, while human trials have been less conclusive.

Significant questions remain unanswered. These require more targeted research that directly compares relevant dose levels of *RRR* and all-*rac* α-tocopherol in relation to human diseases. Key questions include the following: (1) What factors beyond hepatic α-TTP determine the accumulation of particular stereoisomers in tissues, and how does the preferential accumulation of stereoisomers affect human health? (2) What is the appropriate *RRR* to all-*rac* ratio of biopotency? (3) What human-relevant biochemical markers could be established for measuring α-tocopherol sufficiency? (4) How do age and health status affect the metabolism of *RRR* and all-*rac* α-tocopherol? (5) What are the implications for the food and supplement industries? These questions and others must be addressed to develop optimal policies and set α-tocopherol intake recommendations.

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