Chapter

Vitamin E: Recommended Intake

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Abstract

Data of vitamin E intake and status are controversial. Vitamin E is an essential micronutrient for humans and achieving an optimal status is assumed to produce beneficial health outcomes. Dietary intake recommendations for vitamin E vary considerably by different countries and organizations. It appears to be still a challenge to define these despite the wealth of data published. Vitamin E requirements have been proposed to depend on other nutritional factors, such as the intake of polyunsaturated fatty acids (PUFA). Although several foods contain naturally occurring sources of vitamin E, it is frequently the case that the intake recommendations are not achieved. Several other dietary factors affect the need for vitamin E. In this regard, significant challenges to be considered include the efficiency of other tocopherol variants and their properties that could affect the revision of the nutritional recommendations for vitamin E. Particularly, an ever-increasing evidence indicates that other vitamin E homologs may potentially present with a higher biological activity. Low dietary consumption of vitamin E, coupled with compelling evidence that increased intake of vitamin E above current recommendations for the general population may benefit older individuals.

Keywords: vitamin E recommendations, tocopherols, tocotrienols, nutrition, requirement, dietary intake, food source

1. Introduction

Vitamin E was first described in 1922 by Evans and Bishop as a dietary factor essential to prevent fetal reabsorption in rats [1], vitamin E was soon after identified as an antioxidant of polyunsaturated lipids [2]. Evans and Bishop (1922) reported the discovery of a molecule that was lacking in rats on a diet based on lard, and which resulted in an impaired fertility [3]. This deficiency was reversed by the administration of lipid extract prepared from cereals, which was defined as the "antisterility factor" [4]. Finally, vitamin E was officially recognized as the 5th vitamin in 1925. Subsequently, the name "tocopherol" originating from the Greek words "toc" (child) and "phero" (to bring forth) was conceived to characterize the roles of vitamin E as an essential dietary compound for a normal fetal development and childhood.

Vitamin E is a fat-soluble compound. The name represents a collective title for 4 tocopherols (α-, β-, γ-, and δ-tocopherol) and 4 tocotrienols (α-, β-, γ-, and δ-tocotrienols) that are present in food and exhibit antioxidant properties, however which cannot be interconverted, and only α-tocopherol meets the requirements for the daily intake of vitamin E in humans [5].

As an antioxidant vitamin E protects cell membranes from oxidation and destruction [4]. Oxidative processes are normal cellular events, but uncontrolled oxidation, particularly of membrane lipids and lipoproteins, has been implicated in a variety of degenerative conditions, including cancer, rheumatoid arthritis, drug-associated toxicity, coronary heart disease, diabetes, and acute clinical conditions, such as ischemia–reperfusion injury [6–9]. According to the widespread consensus, vitamin E is a powerful antioxidant molecule, which may be found in lipid compartments such as cell membranes because of its hydrophobic chemistry. Its primary function lies in the prevention of lipid peroxidation [10], leading to the preservation of the membrane stability. Vitamin E is also essential in the stabilization of erythrocytes and in the nerve conductivity of the central as well as peripheral nervous system [11, 12]. The molecule prevents hemolytic anemia and neurological dysfunction associated with its deficiency, such as ataxia, neuro-, myo- or retinopathy. The vitamin is also highly efficient in the prevention or stabilization of a variety of health complications because of its antioxidant, anti-inflammatory, antiaggregant and immune-enhancing properties [13]. However, the beneficial effects of vitamin E in human health may also be due to the ability of its phosphorylated metabolite to modulate signal transduction and gene expression in numerous conditions, including inflammation and immune system disorders [14]. This chapter aims to provide a brief overview of the current strategies that are employed to define the intake recommendation for vitamin E. Furthermore, we wish to evaluate the available evidence on the fundamental biological roles of vitamin E in the human body to in order to establish intake requirements for vitamin E to exhibit its antioxidant properties by protecting the polyunsaturated fatty acids (PUFAs) from being oxidized in human tissues. The question which will be addressed in this chapter is how the current vitamin E status (as measured by vitamin E intakes and serum levels) of populations in various countries differs. Special attention is also given to the vitamin E food sources.

2. Vitamin E intake recommendations

Vitamin E is defined as an essential micronutrient for humans, and its beneficial health outcomes are dependent upon reaching its optimal nutritional status. A variety of dietary intake recommendations for vitamin E have been established around the world, all of which point out to its ability to act as a chain-breaking antioxidant and thus to protect the stability of the cell membrane [1].

2.1 Determination vitamin E intake recommendations

In Europe, the **European Food Safety Authority (EFSA)** recently concluded that the recommended daily allowance (RDA), average requirements (ARs) and population reference intakes (PRIs) for vitamin E (in the form of α-tocopherol) cannot be established for adults, children and infants equally. As such, EFSA determined adequate intakes (AIs), which are based on intakes that had been observed in a supposedly healthy population that presents with no apparent α-tocopherol insufficiency in the EU [15].

The EFSA Panel on Dietetic Products, Nutrition and Allergies proposed RDA to replaced by a newly defined adequate intake (AI), depending on age, as follows: men, 13 mg/d; women, 11 mg/d (**Table 1**); and infants/children, 5–13 mg/d [15].

The US **Institute of Medicine (IOM)** define vitamin E recommendations for generally healthy population as intake level of 12 mg/d and above (**Table 1**).

		Age (years)	Men (mg/d)	Women (mg/d)
EFSA	(2015)[(a)]	≥18	13	11
IOM	(2000)[(b)(c)]	≥19–50	15	15
D-A-CH	(2013)[(a)]	≥19	13-15	12
WHO/FAO	(2004)[(d)]	≥19	10	7.5
AFSSA	(2001)	20–74	12	12
NCM	(2014)[(a)(b)]	≥18	10	8
SCF	(1993)[(e)(f)]	≥18	0.4	0.4
NL	(1992)[(c)(f)]	≥18	0.67	0.67
DH	(1999)[(g)]	>18	>4	>3

DRVs in α-tocopherol equivalents is defined by the biological activity of 1 mg natural α-tocopherol in the resorption-gestation test.
EFSA European Food Safety Authority; IOM US Institute of Medicine of the National Academy of Science; D-A-CH Deutschland (Germany)-Austria-Confoederatio Helvetica (Switzerland); WHO/FAO World Health Organization/ Food and Agriculture Organization of the United Nations; AFSSA Agence Française de Sécurité Sanitaire des Aliments; NCM Nordic Council of Ministers; SCF Scientific Committee on Food, NL Netherlands Food and Nutrition Council; DH UK Department of Health.
[(a)]Adequate Intake.
[(b)]Applicable to RRR-, RSR-, RRS- and RSS-isomers of α-tocopherol only.
[(c)]PRI – Population Reference Intake.
[(d)]Data were insufficient to set PRIs; the indicated figures represent the 'best estimates of requirements' (WHO/FAO, 2004)
[(e)]'vitamin E requirement'.
[(f)]mg α-TE/g PUFA.
[(g)]'Safe' intakes.

Table 1.
Vitamin E dietary reference values (DRVs) for adults - overview [15].

This value has been characterized as the Estimated Average Requirement (EAR) and is defined as the amount needed to meet the requirements of 50% healthy people, and it became the foundation to determine RDA, which is predicted to meet the dietary demands of 97.5% healthy individuals. In the case of the USA, the RDA for vitamin E is established to be 15 mg/d α-tocopherol for men as well as women older than 14 years of age [16].

The current intake recommendations for vitamin E vary between 3 and 15 mg/d in different countries and depending on the age and gender of the person.

The current adult Dietary Reference Values (DRVs) for vitamin E in UK is determined >3 mg/d, in German-speaking countries 15 mg/d for adult. The French Food Safety Agency (AFSSA) derived a separate reference value of 20–50 mg/d for adults aged 75 years and over [17].

The IOM [16, 18] recommends Vitamin E dietary reference doses based on a previous extensive research. The IOM recommendations are based on a premise that there is no scientific basis to assume variations in the demand for vitamin E between men and women, or that aging could impair its absorption or secretion. As such, the IOM recommendations do not discriminate between sex or age in adults.

On the other hand, DACH reference values [18, 19] for Germany, Austria and Switzerland published in the same year and based on a similar methodology, does distinguish between age and/or sex.

In the meantime, IOM and DACH applied two different methodological approaches to estimate the recommendations for dietary vitamin E intake. On one hand, IOM is based on the prevention of deficiency symptoms, particularly the sensitivity of erythrocytes to hemolysis. Available human data reveal that subjects with plasma concentrations of at least 12 μmol/L α-tocopherol present with a low degree of haemolysis.

On the other hand, the DACH recommendations, supported by EFSA, regard dietary intake of PUFA to estimate the demands for vitamin E. The basic vitamin E demand of 4 mg/d and a ratio of 0.4 mg α-tocopherol/g of dietary linoleic acid were used to compute vitamin E requirements [18]. Dietary vitamin E demands were estimated at levels of 12 and 15 mg/d based on a general dietary PUFA consumption, which differs between women and men due to the differences in energy intake.

It is nevertheless intriguing to observe, that despite two different methods, both approaches will result in reference values ranging between 10 and 30 mg/d.

It is recommended that a baseline α-tocopherol requirement should be estimated to which extra vitamin E compensating for the dietary PUFA intake can be added to finally obtain an appropriate balance of dietary fatty acids with vitamin E. Nevertheless, the optimum demand for vitamin E is also directly correlated to the amount and degree of dietary PUFA unsaturation. In order to assess the precise vitamin E prerequisites in infants, children, adolescent, adult men and women, an extended observation is imperative to deplete the body's vitamin E storage in order to describe anypotential long-term adverse or harmful consequences that are often complicated to be diagnosed at an early stage. Currently however it is not possible to carry out any long-term follow-up or depletion studies due to ethical reasons [18, 20].

2.2 Vitamin E – other nutritional factors

It has been suggested that vitamin E requirements depend on a variety of other nutritional factors, primarily on the ingestion of polyunsaturated fatty acids (PUFAs). Based on this factor, an increased demand for vitamin E should be regarded for RDA calculation, which has been estimated to oscillate between 15 and 25 mg/d or more [18, 19].

Various reports revealed that the nutritional demand for vitamin E requirement is associated with the dietary intake of PUFAs, which is why in order to calculate the actual vitamin E requirement, a basal vitamin E demand as well as an additional requirement for dietary PUFAs may be taken into consideration. Preclinical as well as human data point out to the fact that a minimal basal need for 4–5 mg/d of RRR-α-tocopherol is necessary even if the diet is lacking PUFAs [20]. Nevertheless, no consensus exists on the precise vitamin E/PUFA ratio in order to establish the vitamin requirement since a strictly pre-determined vitamin E/PUFA proportion may not be relevant to all diets or health conditions. On the other hand, the demand for vitamin E increases proportionally to the PUFA consumption and to the level of the PUFA unsaturation in the diet. As such, currently available human data hypothesize that the additional dietary need for vitamin E fluctuates between 0.4 and 0.6 mg RRR-α-tocopherol/g of PUFA, particularly in the case of a diet containing an average amount of PUFAs with linoleic acid being the predominant dietary PUFA [18]. What is more, animal experiments reveal that in case of fatty acids presenting with a higher degree of unsaturation, the demand for vitamin E increases almost in a linear fashion correspondingly to the extent of PUFA unsaturation in the relative proportions of 0.3, 2, 3, 4, 5, and 6 for, or alternatively, mono-, di-, tri-, tetra-, penta-, and hexaenoic fatty acids. Summarizing evidence from human as well as animal studies, it may be suggested that in the case of a standard ingestion of PUFAs, the estimated dietary need for vitamin E oscillates between 12 and 20 mg/d [20].

Generaly, the recommended intake of vitamin E should correlate with the amount of polyunsaturated fatty acids (PUFA) in food: 1 g of diene fatty acid or rather diene equivalent requires an intake of 0.5 mg RRR-α-TOH.

An optimal daily intake of vitamin E may be broken down into two categories: a required daily intake that provides enough vitamin E for the molecule to exhibit its basic biological effects, as well as a second one, which is determined by a higher

ingestion range that promotes its additional beneficial properties that may assist in the disease prevention. The most favorable intake of vitamin E in healthy subjects, defined as the actual dose that is associated with its major positive attributes in the absence of possible adverse effects, remains to be determined in appropriately designed and executed trials, which represents a considerable hurdle to be overcome in the definition process of appropriate nutritional vitamin E recommendations [1].

As the data come from different countries, it is important to take into account the differences in dietary behaviors in a comprehensive assessment of vitamin E intake. Nevertheless, a substantial number of countries are still not represented. Furthermore, the studies applied various scientific strategies to assess the intake of dietary vitamin E. If just one single 24-hour dietary anamnesis was performed per person, this might not necessarily reflect on an everyday nutrient ingestion, based on a day-to-day fluctuation. Other reports were based on 3-day food records, providing a better notion of the dietary routine [21]. Other research strategies may include food frequency questionnaires or a dietary history.

2.3 Vitamin E – dietary intake

Diet, nutritional status, lifestyle and environmental factors are among the most complicated issues to be investigated with respect to chronic diseases [22]. Large multicentre nutritional studies are accompanied by additional challenges to assess, correlate, and understand dietary exposure in a comparable way across countries, as well as to conclude evidence and recommendations.

Generally speaking, the intake of vitamin E is low and very similar across regions all around the world. According to a recent systematic review, dietary ingestion of α-tocopherol and other vitamin E derivates is well below the RDA for the majority of the population, or even lower than the EAR of 12 mg/d, which is applicable equally for developing as well as industrialized countries [23]. The biggest investigation focused on the vitamin E intake is the pan-European EPIC study involving 36 000 participants recruited across 10 European countries and followed-up for as long as 15 years. Details on the dietary patterns, lifestyle characteristics, anthropometric measurements, and medical history were collected in the EPIC study at recruitment (1992–1999). While the overall mean consumption of vitamin E was 11.9 mg/d, an intriguing regional difference was observed: the intake was higher in the southern countries in comparison to the northern ones [24]. This revelation may be explained by the differences in the food preferences, particularly in the case of vegetable oils, which are more popular in the south.

The NHANES study showed a mean intake of α-tocopherol of 7.2, 6.8, 6.1, 6.0 mg/d in men aged 19–50 years, >50 years, women aged 19–50 years, and > 50 years, respectively [25]. Vitamin E RDA (15 mg/d) was recorded only in 4% women and 5% men, while EAR (12 mg/d) was observed in 7–8% women and 10–11% men.

The prevalence of inadequate vitamin E intake was reported to be 92.5% in the total Brasil adolescent population, 91.6% in boys, and 93.5% in girls ($p = 0.358$). Brasil adolescents aged 10 to 13 years showed a less inadequate ingestion ($p < 0.001$) when compared to those aged 14 to 19 years: 87.7% and 95.1%, respectively [26] (**Table 2**). Jordão et al. [26] identified a high prevalence of vitamin E inadequacy, verified by a low intake of the nutrient, and the observation that ultra-processed foods, such as cookies, packaged snacks, and margarine, provided for almost 33% of the vitamin E content ingested by adolescents in Campinas. Furthermore, healthy foods considered as critical dietary sources of vitamin E did not contribute significantly when extrapolated to the total nutrient intake.

State/city/years/ [Ref.]	Subjects (n: M/F)	Intake of vitamin E (estimation methods)	Plasma/serum concentration
Europe pan-European EPIC study recruitment participants in (1992–1999) Jenab et al. [24]	n = 36000	11.9 mg α-TE/day	
West Europe ZENITH study (2002–2005) Polito et al. [27]	older European adults aged 55-70y and 70-85y (n = 387; 195 M/192F) Clermont-Ferrand (France) n = 95 Grenoble (France) n = 106 Coleraine (Northem Ireland) n = 95 Roma (Italy) n = 96	4-day recall-record method (2 week and 2 weekend days) mean ± SD; (dietary adequacy as % of RDA); [% of subjects at dietary risk] middle-aged (55-70y): C-Ferrand (France) M: 11.3 ± 6.3 mg/d; (141 ± 79%); [8%] F: 9.5 ± 4.6 mg/d; (118 ± 57%); [15%] older aged (70-85y) Grenoble (France) M: 7.1 ± 3.0 mg/d; (89 ± 37%); [26%] F: 7.1 ± 4.8 mg/d; (91 ± 59%); [33%] Roma (Italy) M: 13.7 ± 3.3 mg/d; (172 ± 41%); [0%] F: 12.3 ± 2.6 mg/d; (154 ± 32%); [0%]	α-TOH (HPLC) mean ± SD middle-aged (55-70y): C-Ferrand (France) M: 28.2 ± 5.2 μmol/L F: 28.8 ± 5.4 μmol/L Coleraine (N. Ireland) M: 28.4 ± 6.0 μmol/L F: 29.0 ± 4.9 μmol/L older aged (70-85y) Grenoble (France) M: 29.7 ± 5.4 μmol/L F: 32.5 ± 5.5 μmol/L Roma (Italy) M: 29.3 ± 5.8 μmol/L F: 29.4 ± 6.2 μmol/L
Ireland/Europe (2008–2010) The National Adult Nutrition Survey (NANS) Zhao et al. [28]	healthy Irish adult population aged 18 years and above; mean 40.3 ± 15.9 years BMI 25.9 ± 3.9 kg/m^2 (n = 601; 305 M/296F)	(record over four consecutive survey days) (dietary + supplemental vitE) α-tocopherol equivalent (α-TE) vitamin E intake quartiles: Q1: 6.0 ± 1.1 mg/d Q2: 9.0 ± 0.7 mg/d Q3: 11.9 ± 1.0 mg/d Q1: 20.5 ± 8.5 mg/d	plasma α-TOH (HPLC) vitamin E intake quartiles: Q1: 24.0[b] ± 5.9 μmol/L Q2: 25.8[a] ± 7.4 μmol/L Q3: 25.4[a] ± 6.3 μmol/L Q1: 25.7[a] ± 7.1 μmol/L
US/North America (NHANES) (2001–2002) Gao et al. [25]	US population aged >18 years M: 19-50y n = 1141 >50y n = 997 F: 19-50y n = 1196 >50y n = 1017	(dietary + supplemental vitE) α-tocopherol equivalent (α-TE) M: 19-50y 7.2 ± 0.1 mg/d M: >50y 6.8 ± 0.2 mg/d F: 19-50y 6.1 ± 0.1 mg/d F: >50y 6.0 ± 0.2 mg/d	

State/city/years/ [Ref.]	Subjects (n: M/F)	Intake of vitamin E (estimation methods)	Plasma/serum concentration
Brazil/South America/ city Campinas ISACamp (2014–2015) ISACamp-Nutri (2015–2016) Jordão et al. [26]	Brazilian adolescents aged 10–19 years (n = 891; 463 M/428F) M: 10-13y n = 169 14-19y n = 294 F: 10-13y n = 143 14-19y n = 285	food consumption assessment questionnaire that contained the 24-hour recall mean (95%CI) M: 10-13y 2.8 mg/d (2.5–3.1) 14-19y 3.4 mg/d (3.0–3.7) F: 10-13y 3.5 mg/d (2.8–4.2) 14-19y 3.6 mg/d (2.8–4.4)	
South Africa/ Sharpeville - periphery of city Johannesburg Oldewage-Theron et al. [29]	(n = 235; 39 M/196F) mean age 73.4 ± 7.0y (60-93y) BMI M: 25.7 ± 4.6 kg/ m^2 (64.1% normal BMI) F: 29.9 ± 6.4 kg/ m^2 (20.9% normal BMI; 31.1% overweight and 47.4% obese)	two 24-h recall (DRI 12 mg/d) M: (n = 26) 5.4 ± 5.2 mg/d 88%DRI F: (n = 113) 4.0 ± 0.5 mg/d 96% DRI total: (n = 139) 4.3 ± 5.8 mg/d 95% DRI	by HPLC mean ± SD (95%CI) deficient <1.2 mg/L) marginal 1.2–1.6 mg/L M: n = 39 2.01 ± 1.11 mg/L (1.65–2-37) deficient 8 (20.5%) marginal 9 (23.1%) F: n = 196 2.07 ± 1.12 mg/L (1.92–2.23) deficient 41 (20.9%) marginal 29 (14.8%) total: n = 235 2.07 ± 1.11 mg/L (1.92–2.21) deficient 49 (20.9%) marginal 38 (16.2%)
Korea/Soul (2009–2010) Kim & Cho [30]	20-59y old health adults (n = 106; 33 M/73F)	(3 consecutive 24-h food recalls) dietary α-TE/day: 17.68 ± 14.34 and total α-TE/day: 19.55 ± 15.78 mg (dietary + supplemental vitE) α-tocopherol equivalent (α-TE) daily α-TOH 3.07 ± 2.27 mg daily γ-TOH 5.98 ± 3.74 mg • 12.3% consumed vitamin E less than the AIs for vitamin E	plasma α-TOH M: 15.45 ± 10.16 μmol/L F: 15.00 ± 4.54 μmol/L • 23% < 12 μmol/L indicating a biochemical deficiency of vitE • 89.6% < 20 μmol/L

Table 2.
Selection of surveys/studies regarding intake vitamin E and serum (α-tocopherol) concentrations.

In Germany infants and children up to age twelve commonly do not reach the recommended levels of vitamin E intake [31], as shown in a number of studies including the VELS investigation and the EsKiMo study, a follow-up of the KiGGS study.

Although the recommended amount of vitamin E is higher for men than for women, Dutch women consume less vitamin E more often compared to Dutch men [32].

Numerous research groups analyzing compliance to the vitamin E intake recommendations in Americans have found that a significant number of individuals consume insufficient amount [33, 34]. Data by Traber [35] suggest that more than 90% of United States Americans consume insufficient amounts of vitamin E from natural sources. Bjelakovic et al. [36] claims that when combined with the dietary ingestion, the total intake of vitamin E of antioxidant supplement users in the United States exceeds 700% of the estimated average requirement.

A systematic review (2000–2012) by Péter et al. [37] focused on vitamin E intake levels and serum concentrations in order to obtain a global overview of α-tocopherol status. The authors state that only 17 studies (12.9%) included both intake data as well as vitamin E status measured in blood. Most of the studies (132) were conducted in Europe (47.7%), followed by North America (24.2%), and the Western Pacific region (14.8%). Worldwide, 82% of the population had a vitamin E intake below 15 mg/d, 91% in North and South America, 80% in Europe and 79% in the Asian-Pacific region.

Nutrient intake in children and adolescents in Slovakia was studied in 1991–1994 and 1995–1999. Apart from these surveys, no nationally representative data were found for Slovakia, which would be carried out since 2000, which is why a comprehensive information on vitamin E intake and status in all age groups of the population are missing. The Slovak surveys were not indeed nationally representative but were nationwide and designed to "recruit a diverse sample of entities of different ages and socio-economic backgrounds" [38].

The situation is similar in other countries, particularly in the case of Central and Eastern Europe, Africa, Asia (India), and South America [37].

Evidence in the literature that vitamin E intake does not correlate with plasma levels of α-tocopherol is inconclusive [28, 35]. Previous studies have shown that total α-tocopherol intake was positively associated with the plasma α-tocopherol levels [28], while the main indicator of plasma α-tocopherol concentration was the intake of vitamin E supplements [28]. However, other studies have shown that plasma concentrations of α-tocopherol correlated weakly with dietary vitamin E ingestion [16]. The reasons for the lack of a conclusive correlation may lie in the variations of the activity of the α-tocopherol transfer protein [35], genes involved in lipid metabolism [28, 39] and micronutrients with a synergistic effect, such as vitamin C [28, 40]. Niki et al. [41] revealed that lipid peroxidation and oxidative damage may lead to decline in the levels of plasma and tissue α-tocopherol, which may be another plausible argument for different relationships observed between the vitamin E intake and plasma α-tocopherol levels.

Many scientists believe that it is difficult for an individual to consume more than 15 mg/d α-tocopherol form food (RRR-α-tocopherol) alone, without increasing fat intake above recommended levels [42].

3. Vitamin E status

Unlike vitamins A and D, vitamin E does not have a specific carrier protein in the plasma. Instead, it is rapidly transferred from chylomicra to plasma lipoproteins, to which it binds nonspecifically. The metabolism of circulating chylomicra can result in tocopherols being transferred directly to tissues by partitioning into their plasma membranes, or indirectly by transfer to and between circulating lipoproteins [43]. 90% of the tocopherol is transported by the lymph, the rest by the

portal circulation. It is stored 65% in LDL-c, 8% in VLDL and about 24% in HDL-c. There is a close correlation between tocopherol concentration and total plasma lipid content [44]. These transport processes can be disrupted under dyslipidemic conditions. Patients with hypercholesterolemia and/or hypertriglyceridemia show reduced plasma uptake of newly absorbed vitamin E [43]. Vitamin E is present in all tissues where it has a universal protective effect (**Table 3**).

All tocopherols and tocotrienols belonging to the vitamin E family are absorbed from the intestine to a comparable extent and are subsequently transported via chylomicrons and HDL-c to the liver. Within liver, α-tocopherol is sorted out and is distributed to the bloodstream via VLDL and HDL-c [45]. Consequently, among all vitamin E varieties α-tocopherol is present at the highest proportion in the body, followed by γ-tocopherol. Inversely, tocotrienols are usually not found in tissues [46]. That postprandial levels of tocopherols exceed those of tocotrienols reflects the more rapid metabolic degradation of the latter [43]. In the meantime, only minimal concentrations of β- and δ-tocopherols are found in the blood plasma. An advantageous distribution of α-tocopherol in comparison to other vitamin E forms comes from a faster metabolic rate of the other tocopherols as well as from the α-tocopherol transfer protein (α-TTP). Because of this affinity, α-tocopherol is largely excreted through the urine, while most of the absorbed β-, γ- and δ-tocopherol will be secreted into the bile and subsequently excreted in the feces [13]. Nevertheless, as each class of lipoproteins derives its tocopherols ultimately from chylomicra, α-tocopherol transport by the latter is the major source of interindividual variation in response to ingested vitamin E [43].

Until today and nearly a century after the discovery of vitamin E [1], the molecular mechanisms controlling cellular sorting and preferential retention of one of the eight vitamin E congeners, α-tocopherol, are still incompletely understood.

As with other serum nutrients, vitamin E concentrations are affected primarily by age and a variety of lifestyle factors (obesity, smoking, alcohol consumption, etc.) [47].

Differences in the serum and tissue levels of vitamin E have been studied on different occasions. According to Campbell et al. [48] vitamin E decreased in

Tissue	**α-tocopherol**	
	μg/g Tissue	**μg/g Lipid**
Adipose	150	0.2
Adrenal	132	0.7
Hypophysis	40	1.2
Testis	40	1.0
Platelets	30	1.3
Heart	20	0.7
Muscle	19	0.4
Liver	13	0.3
Ovary	11	0.6
Plasma	9.5	1.4
Uterus	9	0.7
Kidney	7	0.3
Erythrocytes	2.3	0.5

Table 3.
Concentration of α-tocopherol in human tisseues [43].

participants aged over 80 years, which may be associated with a generally reduced food intake in elderly people. Inversely, hepatic levels of vitamin E have been reported to be unaffected by age [49]. According to other reports, increased serum concentrations of vitamin E were found in people older than 60 years [47, 50, 51], which may be explained by an age-dependent rise in the levels of serum cholesterol and lipoproteins [50]. Arguabely, this phenomenon may exhibit protective effects against extensive lipid peroxidation occuring as a side effect of aging [49, 52]. In the meantime, Succari et al. [51] hypothesize that lifestyle and age-associated changes independent of serum cholesterol/lipoprotein levels could be responsible for an increased vitamin E level observed in elderly French women [53].

With respect to smoking as an important factor contributing to the fluctuations of vitamin E, Al-Azemi et al. [54] and Shah et al. [55] reported that smokers presented with lower serum concetrations of α-tocopherol in comparison to non-smokers (**Table 4**).

The presence of 5-nitro-gamma-tocopherol in the blood plasma of smokers indicates that vitamin E can be nitrated by reactive nitrogen species heavely overproduced during smoking, coupled with inflammatory processes frequently observed in smokers. This process will then enhance the turnover of tocopherols and lead to a reduction of carboxyethyl-chromanyl metabolites in smokers [56].

Alcoholism could also contribute to decreased serum levels of α-tocopherol, partially due to malnutrition [57]. *In vivo* studies have also revealed that chronic consumption of alcohol is associated with lower hepatic levels of α-tocopherol, which may be caused by decreased amounts of α-tocopherol in the hepatic mitochondria [57–59].

3.1 Assessment of vitamin E status

Vitamin E status is often assessed by determining the concentration of α-tocopherol in blood plasma or serum [60].

Human studies published in the 1950s and 1960s aimed to address vitamin E levels that could prevent peroxide-induced hemolysis as well as a reduction in the cell survival in subjects on a vitamin E-deprived diet over a period of six years [1]. It was found that ingestion of 12 mg α-tocopherol/day was sufficient to reach a threshold level of 12 μmol/L serum α-tocopherol exhibiting protective effects on the organism. This conclusion was then extrapolated to the definition of the Estimated Average Requirement (EAR) which became the theoretical ground for RDA calculated. Even though this approach has been heavely criticized, currently there is no alternative for the RDA calculation that has been agreed upon. Accordingly, the American Institute of Medicine (IOM) defined the levels of serum α-tocopherol as deficient, if these are to be found below 12 μmol/L [16].

Metabolite	Non-smokers (n = 19)	Smokers (n = 15)
α-tocopherol (μmol/L)	16.0 ± 4.0	15.9 ± 5.0
γ-tocopherol (μmol/L)	1.76 ± 0.98	1.70 ± 0.69
5-nitro-γ-tocopherol (nmol/L)	4.03 ± 3.10*	8.02 ± 8.33

*Note: *P < 0.05.*

Table 4.
Plasma α- and γ-tocopherol in smokers and non-smokers [56].

To evaluate tocopherol levels in the human body, the serum concentration is commonly analyzed after 12–24 h of fasting.

Tocopherol exchanges rapidly between the lipoproteins mediated by the phospholipid transfer protein [43], and between lipoproteins and erythrocyte (about one-quarter of total erythrocyte vitamin E turns over every hour); thus, the level of vitamin E and the concentration of erythrocytes are strongly correlated (as red blood cells carry 15–25% of total vitamin E found in the blood) [43]. As vitamin E is a membrane-protective molecule, tocopherol levels found in the plasma are inversely correlated to the sensitivity toward oxidative hemolysis. This association makes the plasma levels of alpha-tocopherol a suitable indicator of vitamin E status. In the healthy population concentrations above 0.5 mg/dL (12 μmol/L) are associated with hemolysis prevention and are accepted as indicators of nutritional adequacy [43].

For adults, an amount of 0.5–2 mg tocopherols/100 mL plasma (12–46 μmol/L) is recommended according to D-A-CH association [61].

As noted by Traber [35], circulating α-TOH concetrations are not necessarily a reliable marker for an adequate vitamin status in humans.

Serum concentrations of vitamin E are significantly affected by the levels of lipids, which is why they do not reflect its tissue levels in a consistent manner [62]. Thus, more accurate vitamin E levels may be assessed as follows:

$$\text{effective serum vitamin E level} = \alpha - \text{tocopherol} / \left(\text{cholesterol} + \text{triglycerides}\right)$$

Based on the equation, a ratio above 0.8 mg α-tocopherol/g total lipids is considered to be normal. In the case of individuals with normal levels of serum lipids, the concentration of serum α-tocopherol levels serve as an adequate estimate of vitamin E sufficiency. Any cocentration of alpha-tocopherol lower than 0.5 mg/dL or 5 μg/mL, or 11.5 μmol/L is considered deficient [4].

Supplementation of α-TOH, for example increased amount of α-CEHC in urine. Hence, α-CEHC in urine can be used as a marker for α-TOH status in healthy humans [63] or at a minimum as a marker for an adequate level of α-TOH [64].

Péter et al. [37] determined ranges of α-tocopherol concentrations based on a systematic review of the global state of alpha-tocopherol as the concentration in functional deficiency range (≤12 μmol/L), concentration between functional deficiency and desirable threshold (13–29 μmol/L), and finally concentration in desirable range (≥30 μmol/L). Alpha-tocopherol levels less than 20 μmol/L, is yet a more conservative cut-off marker, because of the apparent increased risk for cardiovascular diseases below this limit [24].

More attention should be given to further explore of measuring vitamin E serum levels as they may be a much more useful marker to assess vitamin E status rather than relying on dietary intake reports. Determining the right analytical parameters for evaluating vitamin E status is critically important; however it is also crucial that new analytical parameters and procedures be validated, optimized and standardized for ensuring optimal diagnosis and comparability [59].

3.2 Vitamin E status in the population

Plasma α-tocopherol concentrations in humans range from 11 to 37 μmol/L, whereas γ-tocopherol concentrations are roughly 2–5 μmol/L, and tocotrienol concentrations are less than 1 μmol/L in non-supplemented humans [65].

In an US national survey, the 5th percentile for vitamin E serum levels was 0.62 mg/dL or 14.3 μmol/L, and the 25th percentile was 0.79 mg/dL or 18.5 μmol/L [4].

Results on vitamin status presented in a review from Valtuena et al. [66] and Böhm et al. [60] were published between 2001 and 2011. Besides data from the United States and India, several studies were conducted in Europe (Austria, France, Germany, Greece, Slovakia - only children and adolescents, and Sweden). Intake surveys as well as the assessment of vitamin E concentrations in the blood plasma/serum of children and teenagers were performed in a number of countries. While the intake oscillated between 2.1 and 12.2 mg/dL, the plasma or serum levels of vitamin E ranged between 16.9 and 29.2 μmol/L.

In the case of rural Nepal, about 33% of pregnant females were affected by a severe vitamin E deficiency (less than 10 μmol α-tocopherol/L serum) [67]. Vitamin E status was found to be even worse in Bangladesh, where almost 65% of women in early pregnancy presented with a more severe vitamin E deficiency (< 9.3 μmol α-tocopherol/L serum). On the other hand, a recent study has reported that more than 65% of South Korean adults presented with suboptimal blood vitamin E levels (12–30 μmol α-tocopherol/L serum; lower than the threshold set at 30 μmol/L, as per recommendations by the German Federal Ministry of Health Consensus Statement [68]), while 25% of the participants were vitamin E deficient (less than 12 μmol α-tocopherol/L serum) [46]. Zhao et al. [28] have demonstrated a positive relationship between vitamin E intake and plasma α-tocopherol concentration and plasma n-3 PUFA profile (**Table 2**).

Malik et al. [69] collated for the purpose of review limited available data from 31 studies on vitamin E status in healthy people from Asia, the most populated continent.

Despite a substantial quantity of reports focused on the evaluation of the vitamin E status, data on the extent of vitamin E deficiency from Asian countries, such as India, are lacking. In this sense, information on validated biomarkers for vitamin E status are missing, and no consensus exists on cut off values to define a possible vitamin E deficiency. As such, a possible interpretation of the collected data is complicated.

With respect to a threshold concentration of 20 μmol/L as recommended by various nutritionists [35], data collected from previous studies reveal that 27% Americans, 80% Middle Eastern/Africans, 62% Asians, and 19% Europeans presented with serum levels below this value. Average blood serum concentrations of 20 μmol/L α-tocopherol can be acheived in normal adults on a balanced diet, which includes nuts, seeds and whole grains. Inversely, only 21% of the total data revised in global review [17] indicated a desirable serum concentration of α-tocopherol equal to or above 30 μmol/L. Furthermore, 66% of all subentries ranged between 12 and 30 μmol/L.

Several prospective observational studies (**Table 5**) suggested that a serum α-tocopherol concentration of 30 μmol/L or above has beneficial effects on human health, with alleged applications including prevention of cardiovascular disease and different types of cancer, higher baseline serum concentrations of α-tocopherol were associated with lower total and cause-specific mortality; the lowest total mortality was observed at 30 μmol/L serum α-tocopherol concentrations.

On the other hand, results from the large SELECT trial reveal that vitamin E supplements (400 IU/day [180 mg/d] as *dl*-alpha-tocopheryl acetate) may harm adult men in the general population by increasing their risk for prostate cancer [76]. Follow-up studies are assessing whether the cancer risk was associated with baseline blood amounts of vitamin E and selenium prior to the consumption of supplements as well as whether changes in one or more genes might increase a man's risk to develop prostate cancer while consuming supplemental vitamin E.

3.3 Deficiency of vitamin E (hypovitaminosis)

There exists a subtle difference in definitions describing levels of vitamin intake [59]. Whereas vitamin deficiency is caused by diseases, metabolic disorders [31], or

Source	Aim of the study	Treatment	Results and conclusion of the study
Mangialasche et al. [70]	To examined the relation of all plasma vitamin E forms and markers of vitamin E damage to mild cognitive impairment (MCI) and Alzheimer's disease (AD)	plasma tocopherols, tocotrienols, α-tocopherylquinone, and 5-nitro-γ-tocopherol were assessed in 168 AD cases, 166 MCI, and 187 cognitively normal (CN) people	• Low plasma tocopherols and tocotrienols levels are associated with increased odds of MCI and AD.
Wright et al. [71]	To examine whether baseline serum α-tocopherol concentrations are associated with total and cause-specific mortality	A prospective cohort study Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study 29 092 Finnish male smokers aged 50–69 y who participated in the study Fasting serum α-TOH was measured at baseline by using HPLC	• Higher circulating concentrations of α-tocopherol within the normal range are associated with significantly lower total and cause-specific mortality in older male smokers
Meydani et al. [72] Meydani et al. [73]	The effect of vitamin E supplementation and in vivo immune response in healthy elderly subjects	Elderly (n = 88); age ≥ 65 60, 200, 800 mg/d for 235 days	• ⇑DTH and antibody titer to hepatitis B and tetanus • with 200 and 800 mg • Subjects in the upper tertile of serum α-TOH concentration (>48.4 μmol/L [2.08 mg/dL]) after supplementation • dose of 200 IU vitamin E was shown to be most effective in improving T cell–mediated functions, compared with 60- or 800-IU/d doses
Pallast et al. [74]	The effect of 50- and 100-mg vitamin E supplements on cellular immune function in noninstitutionalized elderly persons	Elderly (n = 161); age 65–80 50, 100 mg/d for 6 months baseline plasma α-TOH 29.4 ± 6.9 μmol/L	• ⇑Number of positive DTH response with 100 mg • ⇑Diameter of induration of DTH response in a • ⇔ IL-2 production • significant trend toward increased postintervention plasma α-TOH • 50 mg supll: ⇑ by 10.1 ± 5.0 μmol/L • 100 mg supll: ⇑ by 15.8 ± 7.4 μmol/L

Source	Aim of the study	Treatment	Results and conclusion of the study
Ohrvall et al. [75]	To determine the tocopherol concentrations in serum after two diets with identical nutrient content but with different fat quality	20 moderately hyperlipidemic, healthy subjects (6 females and 14 males) double-blind cross-over study two isoenergetic diets in a randomized order during two 3-week periods, wash-out period of 3–4 weeks	• ⇑lipid-corrected serum concentrations of α- and γ-TOH during the diet rich in rapeseed oil (by 7 and 23%, respectively, $P < 0.001$) compared with on the baseline diet, while these concentrations ⇓ (by 5 and 37%, respectively, $P < 0.01$) during the diet rich in saturated fat • ⇓ ratio between α- and γ-TOH significantly during the rapeseed oil diet (−23%, $P < 0.01$) and ⇑ (+46%, $P < 0.001$) during the butter diet

Table 5.
Selection of prospective observational studies regarding serum α-tocopherol concentrations.

impaired absorption of the vitamin. Vitamin undersupply is characterized as an intake issue and they can result from insufficient dietary intake, which does not achieve reference values [31]. Because of an abundance of tocopherols in the human diet, its deficiency is rare except in individuals with pancreatic insufficiency or other conditions causing substantial fat malabsorption, or protein-energy malnutrition and may be caused by rare genetic defects affecting vitamin E metabolism or transport [4].

Vitamin E can be mobilized from adipose tissue for a relatively long time [77], so that the symptoms of slightly vitamin E deficiency may manifest following many years, even decades [59].

Nevertheless, a severe vitamin E deficiency may reveal itself almost immediately in acute symptoms such as neuro- and myopathy, as vitamin E is essential for an optimal development and condition of the central nervous system [78]. Insufficient vitamin E saturation can occur in intestinal resection, in severe liver disease (e.g., biliary cirrhosis) and in cystic fibrosis (less frequently). In the absence of vitamin E, the accumulation of radicals with lipoperoxidation in humans leads to various defects in membrane function, muscle metabolism and the nervous system [1]. These reactions should be considered if vitamin E is not absorbed or cannot be used.

Next to dietary habits, hereditary disorders are known to cause primary and secondary vitamin E deficiencies or inadequate vitamin E bioavailability [59].

Although several foods contain naturally occurring sources of vitamin E, it is frequently the case that the intake recommendations are not achieved. Several other dietary factors affect the need for vitamin E. Two are most important in this regard: selenium and PUFAs.

Selenium spares the need for vitamin E. In contrast, the dietary intake of PUFAs directly affects the need for vitamin E. Previous studies have established values neccessary for the incremental impact of dietary PUFAs on the nutritional demand for vitamin E in the range of 0.18–0.60 mg α-tocopherol/g PUFA. Even though the upper limit of the established range is often noted as a guideline to estimate the needs for vitamin E, it must be said that there is no consensus with respect to the quantitation of this certainly critical relationship [43].

3.4 Excess intake of vitamin E (hypervitaminosis)

Vitamin E has been viewed as one of the least toxic of the vitamins. No syndrome of acute vitamin E toxicity has been described. Both animals and humans appear to be able to tolerate rather high levels [43].

When obtained from food sources alone, vitamin E has no documented evidence of toxicity. However, evidence of pro-oxidant damage has been found to be associated with supplements, but usulally only at very high doses (for example at >1000 mg/d) [13, 79]. In the case of humans, daily doses as high as 400 IU are recognized to be nontoxic, while high oral dosages reaching up to 3200 IU, have not been revealed to have any persistent adverse effects [43].

These opinions were questioned a few years ago by a meta-analysis comprising 19 trials, and hypothesizing that supplemental vitamin E (≥400 IU/day) could contribute to an all-cause mortality [43]. Nevertheless, a recently published meta-analysis which comprised even a larger set (57) of trial data, suggested that vitamin E supplements do not have an impact on the all-cause mortality even at doses up to 5500 IU/day [80]. In premature infants, high-dose vitamin E treatment was associated with increased risk for sepsis. Chronic intake of supplements in excess of 400 IU daily has been associated with increased risk of hemorrhage and all-cause mortality [4].

Factors, they could influence the interpretation of data from studies focused on intake of vitamin E, are several: e.g., the NHANES study [25] reported the most data on serum concentrations, differentiated by gender, age group, and race; the EPIC study [81] focused on intake levels, differentiated by country, gender, and age categories, whereas race was not differentiated. No distinction has been made between representative and nonrepresentative studies. No consideration could be given to the quality of the dietary assessment data or to the standardization of blood assays in different studies, and supplement use was not always sufficiently reported [17].

Higher vitamin E doses than the RDA seem to significantly increase the general mortality. In a meta-analysis by Bjelakovic et al. [36] vitamin E at a dose above the RDA (> 15 mg) significantly increased the mortality of the subjects (RR 1.03, 95% CI 1.00 to 1.05, I2 = 0%). The effects of vitamin E on the mortality seemed neutral when administered in doses within the RDAs, however the available data are sparse.

In observational studies, high α-tocopherol intake was reported to be associated with a lower risk of cardiovascular disease, type 2 diabetes, hypertension, cancer, loss of cognitive function, and Alzheimer's disease [82]. Nevertheless, randomized, placebo-controlled intervention trials did not support these observations [25]. Recent studies speculate about possible adverse effects of high dose vitamin E supplements [25]. To avoid risks associated with high-dose nutritional supplements, emphasis on an optimal food intake of vitamin E within the range of the DRI is crucial.

4. Conclusions

Dietary intake recommendations for vitamin E are set in many countrie, however there is an ongoing need to review, establish, and harmonize dietary vitamin E requirements and daily allowance across populations. It has become clear that despite a major scientific progress, new understanding on a molecular level, as well as a broad variety of animal and human studies generating valuable data, the challenge to agree upon general and uniform dietary intake recommendations for vitamin E remains persistent. The key element in defining the recommended dietary recommendations for essential vitamin E is, of course, the biomarker chosen, and all agencies and science authorithis are trying to agree on a suitable biomarker. In future, more dietary intake data as well as status data are needed for specific

subgroups to adjust recommendations for vitamin E intake. However, well-founded recommendations are a reflection of current nutritional science and certainly not a definitive opinion. We are aware that research in the field of nutrition will bring new knowledge and conclusions, and that the nutritional recommendations for vitamin E within the European area will also have their dynamism and development. At present, only expertly based and transparently compiled recommendations can succeed and be applied in practical life. We believe that this emerging knowledge is worth of consideration to improve nutritional recommendations and the criteria to design the next generation of prevention trials on age-related and chronic diseases. More research is needed to understand the molecular action of metabolites and/or their targets in order to further develop therapeutic strategies and improve nutritional recommendations on vitamin E.

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Conflict of interest

The autors declare no conflict of interest.

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