Review

A Systematic Review of Global Alpha-Tocopherol Status as Assessed by Nutritional Intake Levels and Blood Serum Concentrations

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Abstract: The purpose of this study is to systematically review the published literature reporting vitamin E intake levels and serum concentrations in order to obtain a global overview of α-tocopherol status. Articles published between 2000 and 2012 were considered; 176 articles referring to 132 single studies were included. Applying an RDA (recommended daily allowance) of 15 mg/day and EAR (estimated average requirement) of 12 mg/day to all populations with a minimum age of 14 years, 82 and 61 % of mean and median data points were below the RDA and the EAR, respectively. Regarding serum concentrations, globally 13 % of the included data points were below the functional deficiency threshold concentration of 12 μmol/L, mostly for newborns and children. Several prospective observational studies suggest that a serum α-tocopherol concentration of ≥30 μmol/L has beneficial effects on human health. Of the reported study populations and subpopulations, only 21 % reached this threshold globally. This systematic review suggests that the α-tocopherol status is inadequate in a substantial part of the studied populations.

Keywords: alpha-tocopherol, vitamin E, intake, serum, global, status

Introduction

The term vitamin E covers eight compounds found in nature (α-, β-, γ-, δ-tocopherol, and α-, β-, γ-, δ-tocotrienol). Of the eight naturally occurring forms of vitamin E, α-tocopherol is the main form retained in human plasma [1, 2]. Vitamin E is a powerful, chain-breaking antioxidant, which is localized due to its lipophilic nature in lipid compartments such as cell membranes. There it prevents the peroxidation of lipids [3] and thus preserves cellular membrane integrity. Vitamin E also plays a crucial role in the stability of erythrocytes and the conductivity of central and peripheral nerves [4, 5]. It prevents hemolytic anemia and neurological symptoms of vitamin E deficiency (e. g., ataxia, peripheral neuropathy, myopathy, pigmented retinopathy). This essential role of vitamin E as an antioxidant in the human body has recently been underscored by the approval of a 13.1 European Food Safety Authority (EFSA) health claim [6].

Dietary intake recommendations for vitamin E are established in many countries. In the US, the Recommended Daily Allowance (RDA) is 15 mg α-tocopherol in adults for both men and women. This value is derived from the amount needed to prevent peroxide-induced hemolysis in vitamin E-deficient subjects, which was determined from a limited number of studies performed and published in the 1950 s and 1960 s to occur at 12 μmol/L serum α-tocopherol [7–9]. In subjects fed with a vitamin E-deficient diet for over 6 years, an intake of 12 mg α-tocopherol per day was sufficient to achieve this serum α-tocopherol concentration, which was then defined as the estimated average requirement (EAR) and became the basis to calculate the RDA. A daily intake of 12 mg α-tocopherol was also considered sufficient to protect polyunsaturated fatty acids (PUFAs) [1]. Dietary intake surveys in the US report mean daily α-tocopherol intakes of only 6.9 mg, suggesting that the majority of people in the US do not achieve the recommended daily intake [10]. However, inaccuracy of such studies must also be taken into consideration when interpreting the results. A recent review reported that in the UK and the US more than 75 % of the population do not meet the recommended daily intake [11]. Although dietary intake surveys are widely used to assess the nutrient status of populations, they have limitations because of possible underreporting, quality of food composition database used, etc. [12].

Measuring α-tocopherol serum concentrations is another approach to assess its status. At serum α-tocopherol concentrations below 8 μmol/L, manifest clinical symptoms of vitamin deficiency are reported, such as peripheral neuropathy, spinocerebellar ataxia, and skeletal myopathy [1]. Low plasma α-tocopherol concentrations are also associated with increased odds of mild cognitive impairment and Alzheimer's disease [13]. There is limited evidence on α-tocopherol serum concentrations needed to avoid manifest (about 8 μmol/L) or functional (12 μmol/L) deficiencies in the human body. However, an increasing number of studies report α-tocopherol serum concentrations at which beneficial effects may occur. Findings from the National Health and Nutrition Examination Survey (NHANES) cohort report α-tocopherol serum concentrations below 20 μmol/L in 32 % of the participants. This threshold concentration is preferred by some experts [14]. Results from a number of observational prospective studies have suggested additional benefits of α-tocopherol at or above 30 μmol/L serum concentration, with proposed applications including prevention of cardiovascular disease and different types of cancer [15–20]. This α-tocopherol serum concentration of ≥30 μmol/L as a desirable target for health benefits is further supported by the fact that urine excretion of α-carboxyethyl hydroxychroman (α-CEHC), a metabolite and status marker of α-tocopherol [21], increases when under healthy conditions an α-tocopherol serum threshold of 30 μmol/L is exceeded [1]. In addition, pentane concentration in the exhaled air (a marker of oxidative stress) is inversely related to vitamin E intakes and is very low at α-tocopherol serum concentrations of 30 μmol/L [22]. The beneficial effects associated with these serum concentrations have been acknowledged by the common recommendations of the German-speaking countries Germany, Austria, and Switzerland, which have set the desired α-tocopherol serum concentrations at or above 30 μmol/L [23].

However, insights from earlier reviews on vitamin E status are limited due to reporting only on, for example, specific geographic regions, age groups, or risk groups. Thus, in order to better understand the current α-tocopherol provision worldwide, we systematically review in this study existing and reported data on vitamin E intakes and serum concentrations in the general population globally, focusing on age groups and sex in different countries.

Methods

Literature search

We searched the Pubmed/Medline database for original articles on vitamin E status in the general population using Medical Subject Headings (MeSH) terms and free text. Keywords were chosen from the MeSH thesaurus. Free-text terms were searched in all fields (title, abstract, and other fields in PubMed). The following search strategy was applied: ("vitamin E"[MeSH terms] OR "vitamin E"[all fields] OR "alpha-tocopherol"[all fields] OR "beta-tocopherol"[all fields] OR "gamma- tocopherol"[all fields] OR

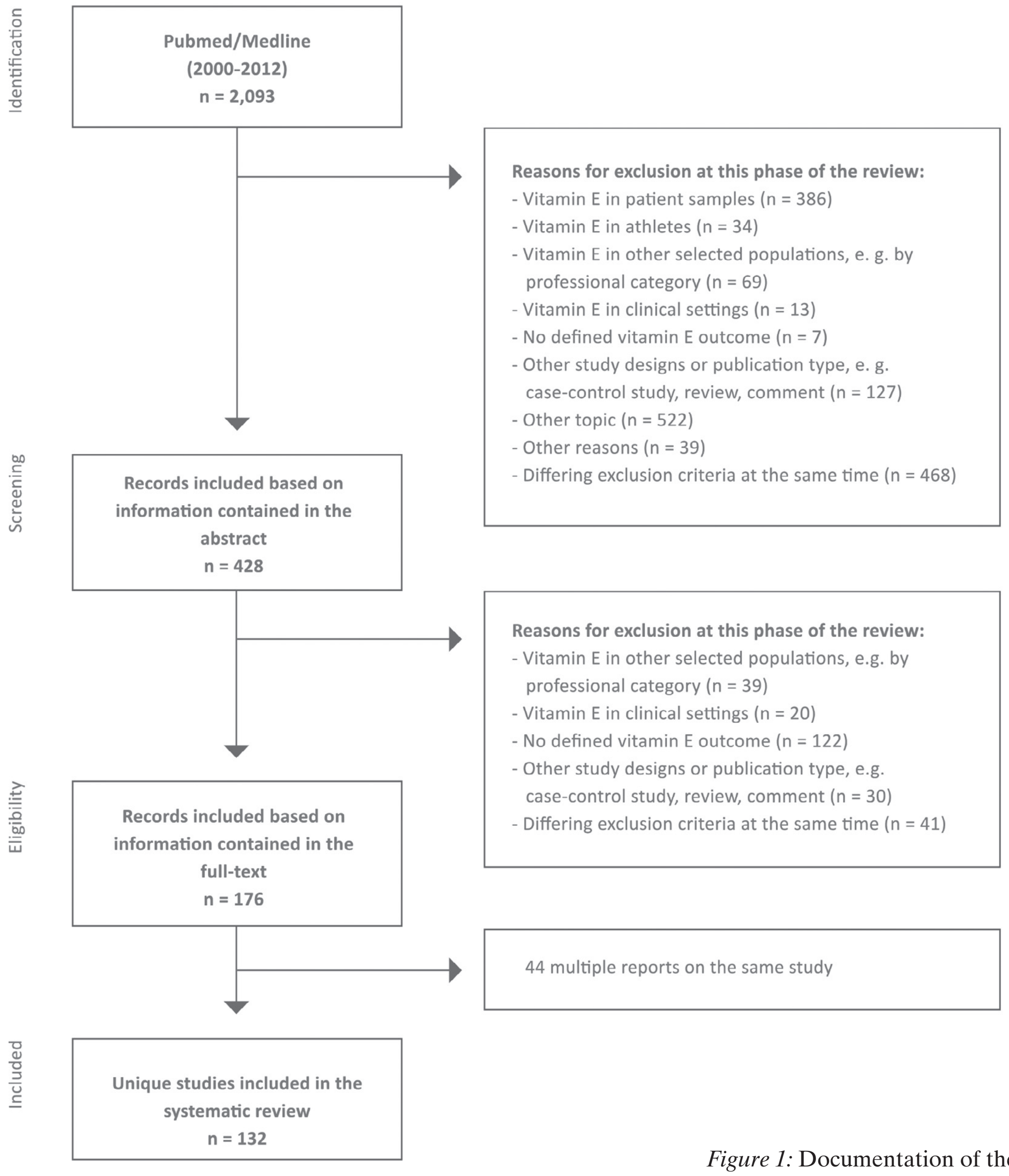

Figure 1: Documentation of the selection process.

"tocotrienol"[all fields]) AND ("blood"[subheading] OR "nutrition assessment"[MeSH terms] OR "nutritional status"[MeSH terms] OR "epidemiologic studies"[MeSH terms] OR "population-based"[all fields] OR "population"[all fields] OR "survey"[all fields] OR "representative"[all fields] OR "cross-sectional"[all fields] OR "observational"[all fields]) NOT ("case reports"[publication type] OR "case-control studies"[MeSH terms] OR "clinical trial"[publication type] OR "review"[publication type]) AND "humans"[MeSH terms] AND English[lang] AND ("2000/01/01"[PDAT] : "2012/06/30"[PDAT]). Articles published between 01. 01. 2000 and 30. 07. 2012 were considered. We excluded articles published before 2000 because of a probable general change in eating habits, particularly in low- and middle-income countries [24]. This exclusion might also have caused a shift in mean-population vitamin E intake levels and serum concentrations. The final screen on 30. 07. 2012 produced 2,093 hits. Wherever possible, the methods used in this review follow the Preferred Reporting Items For Systematic Reviews And Meta-Analyses (PRISMA) Statement [25].

Study selection

The outcome of interest was the vitamin E status assessed by nutritional intake level and/or by plasma or serum concentration of all vitamin E forms, with particular focus on α-tocopherol. Eligible studies included samples of randomly selected persons from the healthy general population all over the world. We considered subgroups of the population by age, sex, and geographic region, as well as by ethnicity, diet type, smoking, and physical activity status. However, studies on patients and thus clinical settings and athletes were excluded from this review because of presumably different demands on vitamin E intake not representing the healthy general population. To be included, studies had to have a cross-sectional design or provide baseline data of a population-based cohort. Study types such as clinical trials, case-control studies, case reports, case series, or reviews were excluded. The selection of records was performed independently by two scientists. Inter-rater agreement was good, and disagreements were discussed and resolved by consensus in all cases (abstract selection: kappa = 0.683; full-text selection: kappa = 0.630). After completion of both selection procedures, 176 records were included based on information contained in the full-text articles. The flow chart on records that were identified, included, or excluded in this review is provided in Figure 1.

Data extraction, calculations, and statistical analysis

We used a standardized extraction form to retrieve data from a wide range of variables, such as study characteristics, details on study population and recruitment strategies, and vitamin E values assessed by nutritional intake levels and/or by plasma or serum concentrations. We also retrieved data from study quality, such as response rate, information about selection bias, and validity of the instrument used to assess nutritional intake. Data from most studies were represented in the data set by a single entry for the total study population. However, since several studies did not publish a single consensus value, we also considered subentries (values for subgroups reported within a study). We included multiple subentries for a single study if data were presented by subgroups of interest such as age or sex.

We refer to the term "vitamin E" as reported in the selected publications, which often do not differentiate between the different isoforms (e. g. α-tocopherol and γ-tocopherol) but rather use vitamin E as a general term instead, including all eight isomers. For consistency and comparability, we converted intake measurements to mg/day and blood measurements of status to μmol/L. Since the Dietary Reference Intakes of the Institute of Medicine (IOM) from the US are well established, generally accepted, and globally referenced among scientists, we have chosen to apply these values (RDA = 15 mg/day and EAR = 12 mg/day) to evaluate the vitamin E intake in this systematic review [1]. The EAR is the amount of a nutrient that meets the requirement of adequacy for half of the individuals in different subgroups of the population (e. g., of a given age, sex, or physiological condition). This is a median value since the amount of the nutrient needed to achieve adequacy varies between individuals. A person whose nutrient intake is below the EAR has a 50–100 % risk of inadequacy. The RDA is the average daily nutrient intake level that meets the requirements of nearly all healthy persons of a certain population subgroup. If an individual has an intake less than the RDA but more than the EAR, his or her risk of inadequacy falls between 2–3 and 50 % [1]. Considering this, in the present review we have applied both reference values with a focus on the RDA. For serum concentrations needed to avoid functional deficiency [7–9] and at which beneficial effects possibly occur [15–20], we applied serum α-tocopherol concentrations of < 12 μmol/L and ≥ 30 μmol/L. Since α-tocopherol is the main form retained in human plasma, and γ-tocopherol degrades rapidly [1] and has low serum concentrations, we reported descriptive information on γ-tocopherol. We did not, however, pursue further analyses of γ-tocopherol. In humans, plasma α-tocopherol concentrations are generally 4–10 times higher than those of γ-tocopherol [26]. Furthermore, it is well described that plasma γ-tocopherol is suppressed by α-tocopherol supplementation [27, 28]. However, serum concentrations of γ-tocopherol that are lower than α-tocopherol do not necessarily reflect lower potency of γ-tocopherol on possible functional outcomes.

The focus of this review is on descriptive analyses. Thus, we calculated descriptive statistics and presented the distribution of categorical data using frequencies and percentages. Where applicable, overall means and proportions were weighted by taking the individual sample sizes into account. Statistical analyses and visualizations were performed in SAS 9.2 (SAS Institute Inc., Cary, NC, USA, 2002–2008) and in the R statistics software version 2.15.2 [29].

Results

Description of studies

Altogether 176 articles [30–205] referring to 132 single studies were included in this review, with a total of 249,637 participants from 46 countries. Subgroups by age, sex, geographic region, ethnicity, diet type, smoking, and physical activity status were considered. The 176 articles reported 1,419 discrete values on vitamin E intake levels or serum concentrations. They ranged from overall values for the total study population to values for specific subgroups, which we define as subentries. Thus it is possible that a value of a single individual contributes to multiple subentries. In case of an elderly female, for example, she contributes to the mean value of the total population, of the subgroup of females, and of her age group. The sample size of individual studies ranged from 10 to 48,776 participants, with a median of n = 374. While the majority of studies included data on males and females, 5 studies (3.8 %) restricted their focus to males and 13 studies (9.9 %) contained data on females only. The overall proportion of males and females was 36.0 % and 64.0 %, respectively. On average, participants had a mean age of 49.8 years, ranging from 0 (newborns) to 106 years. The age group of older adults (aged 50+ years) was considered in 27.3 % of the studies, followed by middle-aged adults (aged 35–49 years; 20.7 %) and adults in general, including younger adults (aged 18+ years; 15.7 %). Most of the studies were conducted in Europe (47.7 %), followed by North America (24.2 %), and the Western Pacific region (14.8 %) (Table I). The highest number of publications derived from the periodically repeated NHANES (n = 13). Of the 132 studies, about one fourth included participants taking vitamin supplements that could potentially influence the reported serum concentrations. However, supplement use was not sufficiently reported in half of the studies.

Description of vitamin E measurements

56 studies (42.4 %) provided nutritional intake data, with 81.3 % of the corresponding subentries referring to vitamin E as such. Food frequency questionnaires were used in 36.1 % of these studies, followed by 24-h recalls (31.9 %) and dietary records (20.8 %). A method used to a lesser extent was dietary history (6.9 %). In 63.4 % of intake values no adjustment had been performed, 27.1 % of intake values were energy-adjusted, 8.0 % represented a tocopherol-energy ratio, and 0.6 % a tocopherol-PUFA ratio. 59 studies (44.7 %) provided data on vitamin E status measured in blood, with most of them reporting α-tocopherol concentrations (58.2 % of the corresponding subentries). In 97.3 % of these studies, HPLC was used for the measurements. In 60.4 % of blood values no adjustment for blood lipids had been performed; 29.0 % of blood values represented a tocopherol-lipid ratio and 10.6 % of blood values had been adjusted for lipids. 17 studies (12.9 %) included both intake data and status measured in blood.

Global status

A descriptive analysis of intakes and blood concentrations of different isoforms of vitamin E is presented in Table II. Nutritional intake was analyzed for unadjusted α- and γ-tocopherol and all eight isomers together. The median intake was 6.2 mg/day for α-tocopherol, and 1 mg/day for γ-tocopherol. For intake of all eight isomers together the median was 10.2 mg/day. For circulating α- and γ-tocopherol concentrations, the unadjusted medians were 22.1 μmol/L and 2.2 μmol/L, respectively, and the lipid-adjusted medians were 27.4 μmol/L and 4.9 μmol/L, respectively. For all eight isomers together, the unadjusted median was 22.1 μmol/L and the lipid-adjusted median was 22.6 μmol/L (no significant difference, p = 0.63 after correction for age group).

Table I: Number of studies (sorted by descending frequency) on vitamin E status by world region, as assessed by intake levels and serum concentrations. N = 128 studies; 4 studies were excluded from the regional data set because it was not clear where the study population had been recruited [40, 81, 115, 202].

World region	n (studies)	% (studies)
Europe (including Russia, Turkey, and Israel)	61	47.7
North America	31	24.2
Western Pacific Region	19	14.8
Africa	6	4.7
Eastern Mediterranean Region	6	4.7
Latin America (including Mexico)	3	2.3
South East Asia Region	2	1.6

Table II: Descriptive analysis for vitamin E values estimated from nutritional intake (mg/day) and measured in blood (μmol/L) globally (n = 132 studies).

Vitamin E form	Nutritional intake		Serum concentrations			
	Unadjusted		Unadjusted		Lipid adjusted	
α-tocopherol	n (subentries)	Median [Min; Max] mg/day	n (subentries)	Median [Min; Max] μmol/L	n (subentries)	Median [Min; Max] μmol/L
All	88	6.2 [1.7; 76.1]	199	22.1 [5.3; 42.2]	29	27.4 [19.9; 34.2]
Male	24	6.6 [4.0; 76.1]	46	20.1 [6.2; 33.9]	5	24.4 [19.9; 27.8]
Female	30	5.0 [1.7; 66.7]	56	22.6 [6.4; 42.2]	5	25.4 [23.3; 28.3]
Mixed	34	6.6 [4.1; 20.8]	97	24.2 [5.3; 40.3]	19	29.9 [20.6; 34.2]
γ-tocopherol						
All	9	1.0 [0.7; 9.3]	63	2.2 [0.2; 8.1]	17	4.9 [3.8; 5.8]
Male	1	9.3 [n/a]	9	4.1 [1.2; 5.4]	4	4.9 [4.6; 5.1]
Female	0	n/a	18	1.8 [0.8; 5.5]	4	5.1 [4.5; 5.8]
Mixed	8	1.0 [0.7; 1.9]	36	2.4 [0.2; 8.1]	9	4.9 [3.8; 5.5]
All eight isomers together						
All	408	10.2 [1.1; 134.2]	54	22.1 [4.3; 49.0]	10	22.6 [17.1; 39.1]
Male	155	12.4 [4.7; 48.2]	6	23.7 [18.2; 32.3]	4	22.0 [17.7; 39.1]
Female	178	9.9 [4.6; 134.2]	11	26.0 [11.0; 49.0]	4	23.3 [17.1; 38.7]
Mixed	75	8.8 [1.1; 63.1]	37	18.0 [4.3; 41.3]	2	20.5 [17.4; 23.5]

Intake by region and country

The majority of reported mean or median intakes of α-tocopherol and all eight isomers together were below recommended intake values in all the countries and regions included in this global review (Figure 2). Applying an RDA of 15 mg/day and an EAR of 12 mg/day globally to all populations with a minimum age of 14 years [1], 82 and 61 % of all subentries are below the RDA and the EAR, respectively. In the Americas, 91 % of all subentries are below the RDA and 89 % below the EAR. We find 80 and 55 % of the subentries in Europe below the RDA and the EAR, respectively. The corresponding proportions in Asia Pacific are 79 % below the RDA and 68 % below the EAR. Even using the more conservative approach proposed by the WHO (10 mg/day intake), we find 83 % of the subentries in the Americas, 35 % of the subentries in Europe, and 60 % of the subentries in Asia Pacific below this intake level. However, the reported low intake levels in different countries do not necessarily reflect the serum concentrations in these countries.

Serum concentrations by region and country

Figure 3 depicts serum concentrations of α-tocopherol and all eight isomers together (subentries; mean or median) plotted by region and country. Globally 13 % of the reported values do not reach the functional deficiency threshold concentration of 12 μmol/L, mostly newborns and children up to the age of 12 years. In the Americas, 11 % of the reported subentries are in the functional deficiency range. The highest proportion of data points in the deficiency range is found in populations in the Middle East and Africa (27 %), but values are also relatively high in Asia Pacific (16 %) and Europe (8 %). Considering a threshold concentration of 20 μmol/L recommended by some experts [14], 27 % of the American, 80 % of the Middle East/African, 62 % of the Asian, and 19 % of the European study data points are below this serum value. The average serum α-tocopherol concentration of 20 μmol/L can be reached in normal healthy adults who consume a variety of foods, including whole grains, seeds, and nuts. On the other hand only 21 % of the total data points included in this global review reach a desirable mean serum concentration of 30 μmol/L or higher.

Serum concentrations by age group

In Figure 4 the serum concentrations of α-tocopherol and all eight isomers together are shown by age group. Concentrations below the deficiency threshold of 12 µmol/L (as defined by the IOM for healthy adults [1] and confirmed by other authors for children [14]) were found predominantly in newborns and children up to the age of 12 years. Globally, 13 % of the subentries were below 12 µmol/L (functional deficiency), 66 % between 12 and 30 µmol/L, and 21 % above 30 µmol/L (desirable mean serum concentration). Within the NHANES study, a significant association was found between age and serum concentrations [80]. This trend is also reflected in the rest of the data set.

Discussion

Intake

Since only a small proportion of the studies provided both nutritional intake data and data on status measured in blood, a correlation between the two data sets was beyond the scope of this review. Moreover, possible limitations of dietary intake surveys because of e. g. underreporting should also be considered when interpreting the results [12]. The intake of α-tocopherol and other isomers was generally low compared to the RDA recommended by the IOM and very similar across all the regions worldwide. Globally, 82 % of the subentries were below 15 mg/day intake; this value was 91 % in North and South America, 79 % in the Asia-Pacific region, and 80 % in Europe. The biggest study on intakes in the data set was the pan-European EPIC

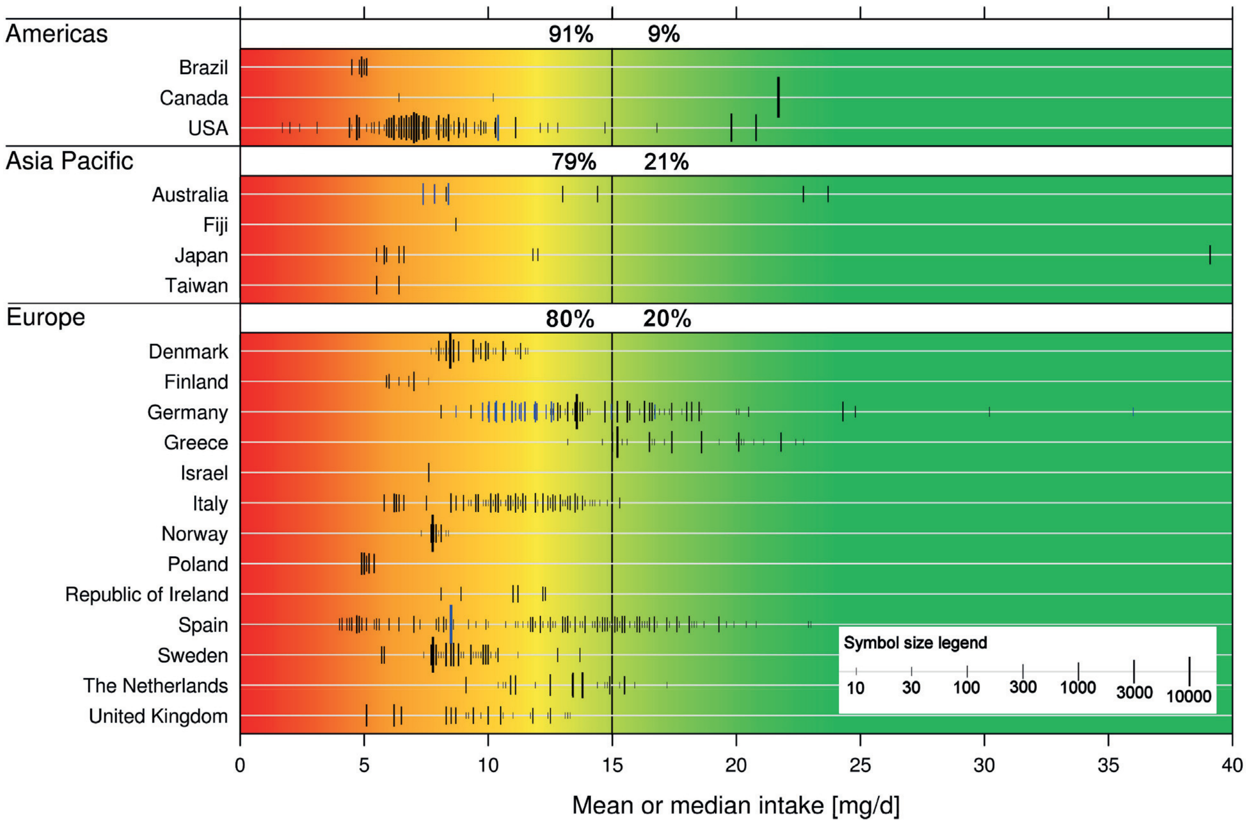

Figure 2: Vitamin E (alpha-tocopherol and all eight isomers together) intake values (in total 652 subentries; mean /black/ or median /blue/) by region and country for populations with a minimum age of 14 years. The figure shows all subentries as reported in the publications, with each symbol corresponding to one subentry. The symbol size was set to $0.3 \times N^{0.2}$ for intake values, where N refers to the subgroup size. The vertical line indicates the RDA of 15 mg/day recommended by IOM. Globally, 82 % of the subentries were below 15 mg/day while 18 % were above. For 284 subentries the subgroup size was not available, mostly for age subgroups in Jenab et al., 2009, who reported on the large pan-European EPIC study [107]. Wherever the subgroup size was not available, it was assumed to be N = 5 to obtain a small but visible symbol. Four values are not visible in the figure because they are higher than 40 mg/day. Red: low intake (≤5 mg/day), yellow: moderate intake (6–14 mg/day), green: recommended intake or above (≥15 mg/day). n = 128 studies.

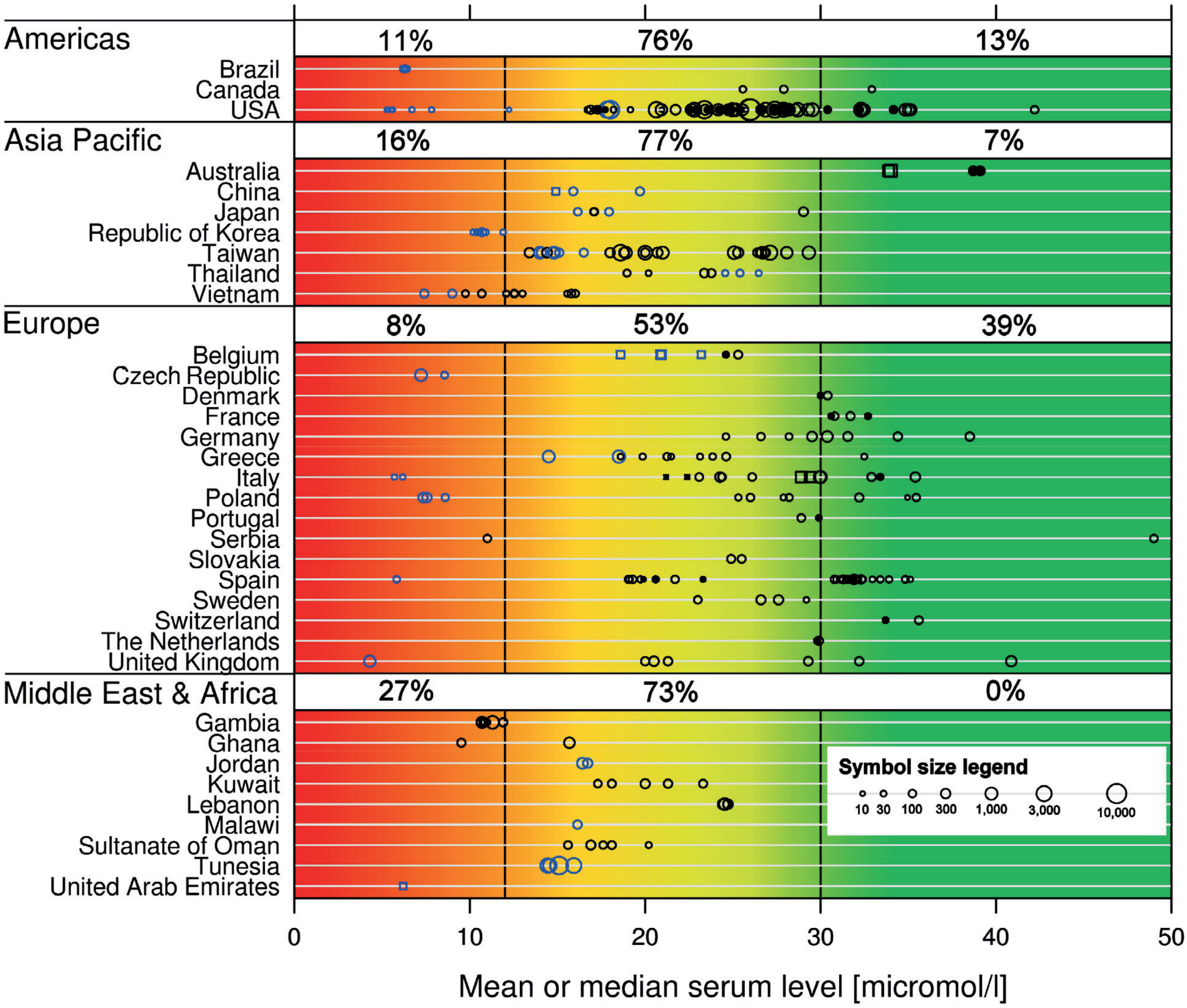

Figure 3: Vitamin E (alpha-tocopherol and all eight isomers together) serum concentrations (in total 278 subentries; mean or median) by region and country. The figure shows all subentries as reported in the publications, with each symbol corresponding to one subentry. The symbol size was set to $0.2{\times}N^{0.2}$ for serum values, where N refers to the subgroup size; o = unadjusted; = lipid adjusted; black = mean; □= median; blue: 0–12 years; black: >12 years. The graph includes 3 data points with unclear population size (assumed to be N = 5), located in the US, from the Diet, Supplement, and Health Study [197, 198]. Red: concentration in functional deficiency range (≤12 μmol/L), yellow: concentration between functional deficiency and desirable threshold (13–29 μmol/L), green: concentration in desirable range (≥30 μmol/L). n = 128 studies.

study with 36,000 participants. The overall mean intake was 11.9 mg/day. It showed an interesting regional difference: higher in the southern countries, lower in the northern ones. This may be related to the food sources, particularly vegetable oils, which are popular in the south [107]. The explanations of our findings regarding the generally low intake may be manifold. For methodological reasons, vitamin E might be underestimated and thus underreported in most of the intake assessments (e. g., misreporting food intake in the past, difficulty of portion size estimation, variability between interviewers) [12]. On the other hand, recent studies about vitamin E stability in vegetable oils suggest that the actual intakes might be even lower than estimated. Commercial vegetable oils, which contain vitamin E, are commonly stored in the supermarket or kitchen in transparent polyethylene terephthalate (PET) bottles. Light, temperature, and oxygen availability have been shown to promote rancidity in these vegetable oils. Recent studies demonstrated that storing soybean oil in transparent bottles under household conditions might pose an increased risk for accelerated lipid oxidation [206]. Therefore, the oxidative stability of vitamin E in edible oils is limited and vegetable

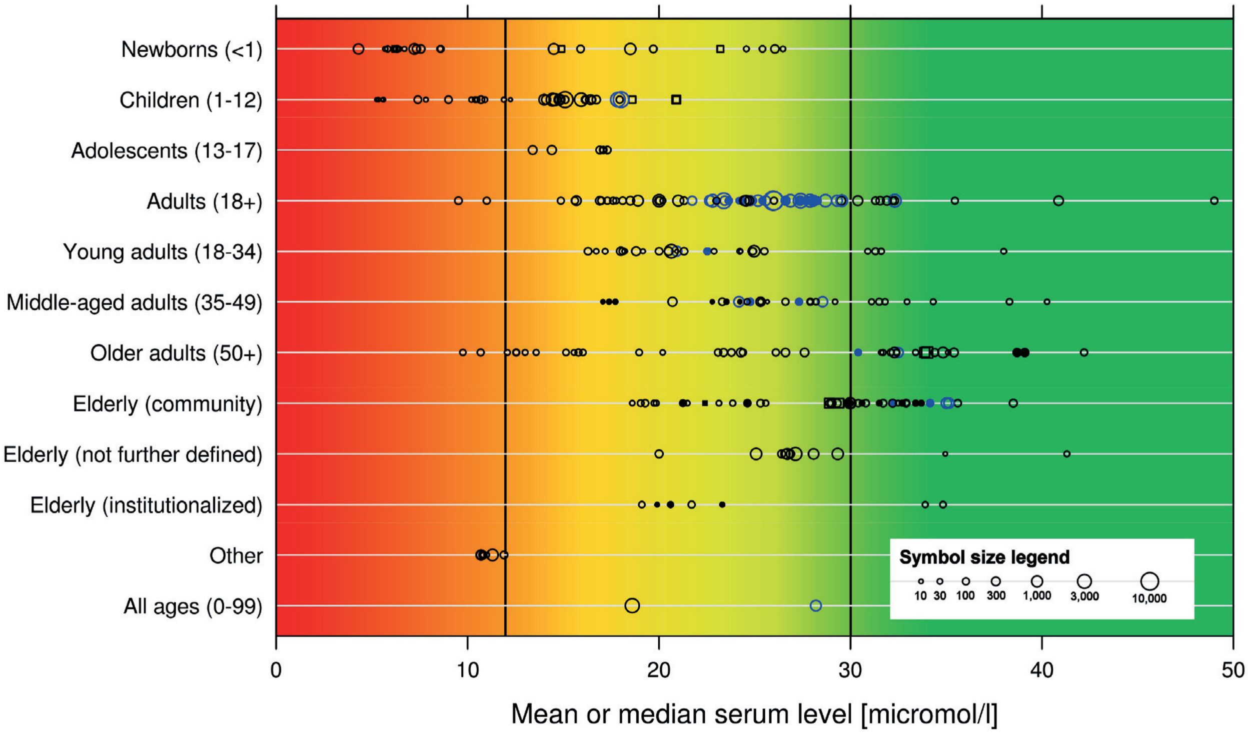

Figure 4: Vitamin E (alpha-tocopherol and all eight isomers together) serum concentrations (subentries; mean or median) by age group. The figure shows all subentries as reported in the publications, with each symbol corresponding to one subentry. The symbol size was set to $0.2 \times N^{0.2}$ for serum values, where N refers to the subgroup size; o = unadjusted; = lipid-adjusted; black = mean; □ = median; blue = NHANES data; other = not specified. Red: concentration in functional deficiency range (≤12 µmol/L), yellow: concentration between functional deficiency and desirable threshold (13–29 µmol/L), green: concentration in desirable range (≥30 µmol/L). n = 132 studies.

oils might contribute less to vitamin E intake than has been thought so far.

Serum concentrations

The few existing reviews on this topic report substantial variations in the prevalence of vitamin E deficiency across countries worldwide, with estimates ranging from 0.7 to 89.0 % depending on cut-off value and study population [207, 208]. By using a systematic approach, this review is the first to provide a detailed description of the existing data on vitamin E status worldwide, including developed and developing countries.

In our evaluation, 13 % of the subentries in the global data set were below the deficiency threshold of 12 µmol/L defined by the IOM [1]. The most affected age groups were newborns and children, who frequently had serum concentrations below 12 µmol/L. We also observed a steady and age-dependent increase of the serum concentrations, which can be explained by the higher circulating lipid concentrations in the older age groups.

The largest study on serum concentrations in the data set is the NHANES, which is also the study with the most publications (n = 13) in our data set. Ford et al. [2006] provided details about the statistically significant age gradient within the NHANES (p <0.001), which is in agreement with our global data set. The older the subjects, the higher the α-tocopherol concentration, even if adjusted for cholesterol [80]. In our review, globally 66 % of all subentries range between 12 and 30 µmol/L. Only 21 % of them meet the proposed desirable concentration of ≥30 µmol/L, at which beneficial health effects may occur.

However, interpretation of the measured α-tocopherol values is challenging due to the positive correlation with different blood lipids. Various methods to control the confounding effect of blood lipids have been suggested in the literature, but they are not completely effective [209]. The data are very heterogeneous; even within one country we observed values ranging from about 5 to 35 µmol/L. In the total data set we observed a significant difference between the adjusted and unadjusted serum concentrations. However, the difference between the adjusted and unadjusted serum concentrations disappeared in our data set once age group was included as a covariate ($p = 0.63$; data not shown). The previous difference was again mainly driven by newborns and children, who tend to have lower serum concentrations than adults [210]. Nevertheless, more research is needed to clarify and verify the biological relevance of the α-tocopherol serum range between 12 and 30 μmol/L in both adults and children. More accurate understanding of the relationship of vitamin E dosage to the level of protection is required. Biomarkers are needed to be used in the assessment of vitamin E intake and status. Large-scale studies in children have to be conducted using such validated biomarkers to assess their vitamin E requirements. More information is needed also on the other isoforms of vitamin E. By establishing the recommended α-tocopherol intake levels and reference serum concentrations, the functions and concentrations of the other tocopherol forms that can have antagonistic effects to that of α-tocopherol were not considered. Thus, much needs to be done to study what minimal concentrations are beneficial in the presence of other competing isoforms of tocopherols.

Strengths and limitations

To our knowledge, this systematic review, which was conducted in accordance with the PRISMA statement [25], is the first to focus on the worldwide published scientific literature reporting vitamin E dietary intake levels and serum concentrations. We purposefully identified studies with randomly selected persons from the general population living in both developing and developed countries. Special population groups (e. g., patients, subjects of clinical trials) were excluded.

It is important to consider the findings of this review in the context of potential limitations. All subentries were considered as reported in the publications (median, mean, or geometric mean), which provides a comprehensive picture and captures heterogeneity among subgroups but may also lead to under- or overrepresentation of some studies. Many studies report results according to several predictors. In Ford et al., 2006, for example, the serum concentrations of NHANES are differentiated by gender, age group, and race [80]. In contrast, the EPIC study focused on intake levels instead of serum concentrations. These intake levels are differentiated by country, gender, and age categories that differ from those of NHANES, whereas race is not differentiated [107]. We accepted this redundancy and the differences in reporting among studies for the sake of completeness. An alternative might have been to condense each study into a single value. However, this would have introduced a selection bias and provided an artificial sense of uniformity because it would have masked the considerable differences among population subgroups within a study, notably among age groups. Also, for the sake of completeness, no distinction has been made between representative and non-representative studies. Furthermore, no consideration could be given to the quality of the dietary assessment data, or to the standardization of blood assays in different studies.

Because only a small proportion of the obtained serum concentration data was lipid-adjusted, we conducted no statistical evaluations on this subset. Another factor that could influence the interpretation of data is that supplement use was not sufficiently reported in half of the studies. Furthermore, we limited ourselves to mostly descriptive data analysis due to the considerable heterogeneity of the data.

Conclusions

This comprehensive review of vitamin E dietary intake levels and serum concentrations demonstrates that the majority of reported intake values worldwide are below the recommended level. Similarly, it shows that a considerable proportion of the data points of the global population do not reach the functional deficiency threshold serum concentration for α-tocopherol, particularly in newborns and children. Probably due to language bias, we observe a geographical knowledge gap for Latin America, the Middle East and Africa, and Asia Pacific. While there is still no consensus among scientists regarding desirable α-tocopherol serum concentrations, our results based on the reported dietary intake levels and serum concentrations suggest that the vitamin E status of the included population groups can be improved. Possible measures include encouragement of consumption of vitamin E-rich food sources (e. g. vegetables, dairy products, eggs), adequate fortification of food products (e. g. vegetable oils), and supplementation. This systematic review could be a useful stepping stone for researchers to combine existing data, fill in data gaps, and to understand more about the complex field of vitamin E and its impact on human health.

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SP, AF, FR, AW, ME, KH, and PW designed the project; SP coordinated the project; AF reviewed the literature; FR analyzed and visualized data; SP, AF, FR, AW, ME, KH, and PW wrote the paper; KH and PW had primary responsibility for the final contents. All authors read and approved the final manuscript. The authors thank Tatiana Görig from the Mannheim Institute of Public Health for reviewing the literature and Susan Sills for language editing. The Mannheim Institute of Public Health, Social and Preventive Medicine received an unrestricted educational grant from DSM Nutritional Products Ltd.

Conflicts of interest

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