Vitamin E and cardiovascular diseases: an interest to public health?

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Abstract

Cardiovascular diseases (CVD) are the leading cause of death worldwide. From this perspective, the role of vitamin E and its metabolites in preventing CVD has been studied, being supported by the findings that low vitamin E concentrations are associated with an increased risk of cardiovascular events. Despite this, no studies have analysed the co-existence of vitamin E deficiency (VED) and CVD on the basis of population studies. Facing that, this study summarises information on the relationship between vitamin E status and CVD, providing a basis for understanding the determining and protective factors for its development. VED may be a public health problem since it has been observed to vary from 0·6% to 55·5% worldwide, with higher percentages in Asia and Europe, where CVD mortality rates stand out. Intervention studies with α-tocopherol supplementation do not confirm cardioprotective action of vitamin E, which may reflect that α-tocopherol alone does not provide cardiovascular protection to individuals, but the consumption of all isomers found in food. Considering that low concentrations of α-tocopherol can lead to a higher susceptibility to diseases involving oxidative stress in the population, in addition to the high and growing prevalence of CVD and VED, it is essential to investigate or reinterpret the mechanisms of action of vitamin E and its metabolites in the cardiovascular process to better understand the co-existence of CVD and VED. It is also important to implement public health policies and programmes aimed at promoting the consumption of natural food sources of vitamin E and healthy fats.

Introduction

Cardiovascular diseases (CVD) have gained prominence for constituting the main cause of death in the world. Its occurrence represents 16% of all deaths involving chronic non-communicable diseases (NCDs), with an increase in deaths of more than 7 million in the period from 2000 to 2019[1].

The CVD group includes diseases related to the heart and blood vessels such as atherosclerosis, coronary heart disease, peripheral arterial disease and heart disease, among others[2]. The risk factors commonly involved in developing these diseases are unhealthy eating patterns, physical inactivity, overweight, obesity, alcohol consumption, smoking and heredity[3]. These factors cause an increase in the generation of free radicals, which enhance the oxidation of low-density lipoprotein (LDL) cholesterol and the release of inflammatory cytokines[4], which are the main aspects presented by individuals with CVD.

Thus, implementing healthy eating habits can be part of a strategy for preventing and combating this public health problem. From this perspective, evidence indicates that a diet rich in sources of vitamins and minerals, such as fruits, vegetables and whole grains prevents CVD[5–7] and reduces the probability of myocardial infarction occurrence[8].

Vitamin E is among the most relevant micronutrients in preventing and fighting CVD. It protects cells from oxidative stress, reducing the formation of atheromatous plaques and decreasing platelet aggregation[9–11], which are fundamental aspects due to the pathophysiology of the disease. The anti-inflammatory potential of vitamin E metabolites has also been studied. Studies have observed that the metabolite 13'-carboxychromanol (13'-COOH) suppressed the expression of the gene that plays a role in the progression of CVD[12], in addition to an association between lipid metabolites, which have anti-inflammatory effects in CVD, and the serum concentration of vitamin E[13].

Low α-tocopherol (vitamin E) concentrations have been linked to an increased incidence of CVD, and increased intake of vitamin E appears to offer protection against CVD[14]. However, the data are conflicting, as although observational studies show an association between higher intake and vitamin E concentration with a lower risk of cardiovascular events[15,16], population-based clinical trials have not shown a beneficial effect of vitamin E supplementation against CVD[17–21]. In addition, meta-analyses suggest that vitamin E supplementation may increase all-cause mortality, including mortality from CVD[22–24]. Although some reviews have shown the relationship between vitamin E and CVD[25–27], the distribution of VED and CVD has not been analysed through population studies, mainly in primary risk groups for CVD, such as the adult and elderly

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population, and this deficiency is little explored as a public health problem.

Given the above, this narrative review aims to systematise information in the light of scientific evidence on the relationship of vitamin E status with cardiovascular diseases in population studies to provide support for understanding the determining and protective factors for developing chronic diseases.

Cardiovascular diseases: epidemiological aspects and risk factors

Cardiovascular diseases (CVD) have remained the leading cause of death in the world in the past 20 years, representing 16% of all deaths from chronic non-communicable diseases[1], with progressive prevalence in developed and developing countries[28]. The number of deaths from heart disease has increased from more than 2 million since the year 2000 to nearly 9 million in 2019, with the highest prevalence in the Western Pacific region[1].

The highest mortality rates attributable to CVD in 2020 occurred in Eastern Europe and Central Asia, with higher levels also seen in Oceania, North Africa and the Middle East. In regions with higher-income populations, such as Asia-Pacific, North America, Latin America and Western Europe, CVD mortality rates were lower[29].

Congenital heart disease, coronary heart disease, peripheral arterial disease, cerebrovascular disease, deep vein thrombosis, pulmonary embolism and rheumatic heart disease are examples of CVD[2]. The classic risk factors for developing CVD are dyslipidaemia, arterial hypertension, diabetes mellitus, family history, obesity, sedentary lifestyle and smoking[30]. With respect to attributable deaths, tobacco use causes an estimated 9% of CVD-related deaths, followed by high blood glucose (6%), sedentary lifestyle (6%) and obesity (5%)[31].

Other factors, such as dietary, cultural, behavioural, sociodemographic and ethnic issues, may also explain differences in CVD prevalence among populations and their trends over time. Encouraging healthy lifestyle habits associated with CVD prevention and treatment measures are essential public health policies for the control of these diseases[30].

An individual's eating habits are directly related and influence cardiovascular risk, mainly through risk factors such as body weight, hypertension, diabetes mellitus and dyslipidaemia[32]. The consumption of a healthy and balanced diet is important to prevent and combat the increased incidence of CVD in populations. Observational studies have indicated a strong association between the consumption of fruits, vegetables and grains, as well as diets high in vitamins and minerals, with low cardiovascular mortality[8] and lower risk for myocardial infarction[33].

Vitamin E stands out among micronutrients in preventing CVD due to its antioxidant capacity and protecting against LDL cholesterol oxidation, which contributes to heart disease through the inducing of endothelial dysfunction, the expression of adhesion molecules, the migration and proliferation of smooth muscle cells, and foam cell formation, leading to atherosclerosis[34]. Thus, there is a growing interest in the cardioprotective role of vitamin E based on studies which have observed a beneficial effect of vitamin E in reducing cardiovascular risk[15,16,35,36].

Vitamin E: from its functional aspects to its deficiency in the world

Function and metabolic aspects

The designation of vitamin E corresponds to a set of eight isomers produced by plants which perform antioxidant activity, but only the α-tocopherol (α-TOH) form protects against the destruction of peripheral nerves caused by oxidative damage from the action of free radicals, thus avoiding ataxia disorder[37]. Furthermore, the α-TOH isomer is the most bioactive form, as the hepatic α-tocopherol transfer protein (α-TTP) promotes selective incorporation of the α-TOH molecule into circulating lipoproteins to distribute the fractions of vitamin to non-hepatic tissues, while the other isomers are preferentially metabolised, and later excreted[38].

As a fat-soluble vitamin, α-TOH is absorbed along with fats, as they are responsible for promoting the uptake of this vitamin by enterocytes and facilitating its secretion by chylomicrons, among other functions[39]. Another point is that, although the absorption of vitamin E is not limited to the ingested fat, when this macronutrient is obtained through food, it enhances the output of α-TOH from the intestine towards the other organs[40]. Thus, the interest in studies which relate the consumption of fats and the lipid profile of adults with vitamin E has been growing in order to understand the influence of food consumption and situations which cause changes in the lipid profile in this relationship[41].

The relationship between fat and α-TOH circulation mainly occurs through its post-hepatic transport, which in turn occurs through very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL)[42,43], which justifies its dependence on fat intake[40,44], on the circulating lipid profile[45] and on diseases that increase fat deposition in the liver, such as obesity and steatosis[46–48].

In addition, it is important to report that vitamin E acts to prevent oxidative damage in cells, preventing the peroxidation of long-chain polyunsaturated fatty acids (PUFAs), including arachidonic acid (ARA; 20:4 ω-6) and docosahexaenoic acid (DHA; 22:6 ω-3) which are present in cell membranes and lipoproteins[9]. Due to this action, studies have investigated the role of vitamin E in reducing complications in some diseases that have membrane involvement, such as cancer, Alzheimer's, atherosclerosis and CVD[49–52]. Other functions are assigned to α-tocopherol, such as regulating genes at the transcriptional and post-translational levels, which can prevent the appearance of atheromatous plaques, decrease platelet aggregation and help modulate the vascular system's extracellular matrix structure[10,11].

Due to this inhibitory action on the formation of atherosclerosis, the relationship between vitamin E and stroke has also been studied, as atherosclerosis in the main intracranial arteries is responsible for the high prevalence of stroke in populations[53]. A systematic review with meta-analysis shows that there

is still a lack of statistically significant evidence of the effects of vitamin E in reducing the risk of stroke, especially haemorrhagic stroke. However, vitamin E may offer some benefits in preventing ischaemic stroke, possibly because it is associated with vascular obstruction[54].

Over the past 20 years, vitamin E metabolism has become better understood, with promising results from in vitro and animal studies demonstrating the strong anti-inflammatory potential of vitamin E metabolites. The first metabolites formed in vitamin E metabolism, the long-chain metabolites (LCMs 13'-hydroxychromanol (13'-OH) and 13'-carboxychromanol (13'-COOH)), stand out for their potential role as endogenous anti-inflammatory metabolites, which suggests that vitamin E may gain biological activity even after its degradation[55–57]. On the basis of these findings, methods for analysing vitamin E metabolites in human serum, plasma and urine were developed and validated[58–60].

Wallert et al. (2014) and Ciffolilli et al. (2015) were the first researchers to measure 13'-OH and 13'-COOH in human serum from healthy volunteers. They observed that the bioactivity of these metabolites and their serum concentrations are at low nanomolar levels compared with α-TOH, in addition to having different mechanisms of action from its precursor. Upon initiation and increasing dosage of RRR-α-TOH supplementation, concentrations of MCLs are steadily increased[61,62]. In another study carried out in seventeen healthy individuals, it was observed that after supplementation of 800 IU of RRR-α-TOH per day for one week, the concentrations and activities of the metabolites were affected by inter-individual variability and independently of the concentrations of its α-precursor TOH[63]. Thus, the concentrations of the metabolites in the serum and their activities depend on and can be altered by the dosages of supplementation, age and gender of the individual, as well as their level of physical activity, obesity, smoking, quality of sleep and alcohol consumption[64].

In investigating the anti-inflammatory mechanism of α-13'-COOH, it was observed that this metabolite suppressed the expression of the C–C motif chemokine ligand 2 (Ccl2) gene[12], which plays a role in the progression of CVD[65–67]. In addition, a spin-off Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study identified 252 metabolites in various chemical classes that were associated with serum α-tocopherol concentration, primarily represented by lipid and amino acid metabolites. The metabolites of diacylglycerol, sphingolipids and ceramides were those that had the strongest association with circulating α-tocopherol[13]. The metabolism of these metabolites plays a significant role in the regulation of inflammatory signalling pathways, suggesting that these dietary substances have anti-inflammatory effects, potentially inhibiting chronic diseases associated with inflammation[68,69]. However, studies are still needed to assess the impact of these metabolites on the genesis and prognosis of CVD.

All these aspects support the relevance of monitoring VED, especially considering the increasing occurrence of CVD. However, despite the functional and molecular knowledge on vitamin E, the biological activity of that vitamin in humans has not yet been fully clarified, as well as its role in chronic diseases' prevention and care[70].

Vitamin E deficiency: biomarker and results of population studies

Despite vitamin E importance in preventing oxidative damage and heart disease, in addition to the growing and exponential increase in the prevalence and mortality related to CVD in the world, VED is still little explored as a public health problem.

This is due to the rarity of clinical symptoms of VED in adults, mainly characterised by neuromuscular deficiencies, haemolytic anaemia, retinopathy, reduced immunity and increased inflammation. VED can be caused by genetic abnormalities in α-TTP or lipoprotein synthesis, or it can occur as a result of fat malabsorption syndromes[41].

Considering the estimated average requirement (EAR) of 12 mg/d, it was observed that 89% of the studied group in the Americas was below the EAR, 55% in Europe and 68% in Asia and the Pacific[71]. Despite the high prevalence of low vitamin E intake, clinical symptoms are not observed in these individuals, even if the variation in consumption found in population studies is from 1·7 to 76·1 mg/d[71,72].

An intake of 12 mg of vitamin E per day was sufficient to reach a minimum concentration of 12 µmol/l of serum α-tocopherol[73], which constitutes a concentration that prevents peroxide-induced haemolysis in VED[74] and protects the PUFAs[73]. Vegetable oils, seeds, fish oil, nuts, eggs, liver, dairy products and green vegetables are the primary dietary sources of vitamin E[9].

The European Prospective Investigation on Cancer and Nutrition (EPIC) study was carried out in twenty-seven centres in ten European countries. Data were collected between 1995 and 2000, with a total of 36 034 subjects (age range 35–74 years), and it was observed that the mean vitamin E intake ranged from 7·7 mg/d to 20·1 mg/d, with an average of 14·5 mg/d for men and 11·1 mg/d for women. The study also showed that the main food group contributing to vitamin E consumption was added fat[75].

The New Zealand Adult Nutrition Survey – conducted from 2008 to 2009 with the participation of 4721 adults over 15 years of age – showed that the mean usual vitamin E daily intake was 11·5 mg for men and 9·1 mg for women, with the butter and margarine group being the single largest contributor of vitamin E to the diet (13%), followed by vegetables (11%), fruits (7%), bread and potato dishes[76].

The National Health and Nutrition Examination Survey (NHANES), carried out in the United States from 1999 to 2002 with 8809 individuals over 19 years of age, showed that the average daily intake of vitamin E was 7·1 mg/d. The main food sources for dietary vitamin E intake were grains, fat, oil, sauces, meat, poultry and fish[77].

Therefore, since vitamin E intake is below the recommended level in most countries and regions of the world, it is expected that it may result in reduced blood vitamin E concentrations, with a high prevalence of VED in these populations.

Vitamin E status can be assessed in serum or plasma by measuring α-TOH[78], the biomarker most used one in population-based studies[71]. The cut-off point for VED in a healthy adult defined by the Institute of Medicine is 12 µmol/l, regardless of the individual's age or gender[73]. From prospective observational studies, it is suggested that a serum concentration

of α-tocopherol ≥30 μmol/l has beneficial effects on human health, such as reducing the risk of coronary heart disease[71].

Due to the relationship between vitamin E and the lipid profile, circulating α-TOH concentrations can be high in individuals with hyperlipidaemia, which makes it important to assess circulating lipids or cholesterol (α-TOH:lipid) in these situations. This assessment helps to identify possible confounding factors derived from pathological and physiological variations in lipid status[38,79]. Data from the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) indicate that, when compared with α-tocopherol alone, the α-tocopherol:total cholesterol ratio is a stronger indicator of vitamin E status in healthy people[80].

However, research carried out in a smaller number of participants demonstrates that urinary α-carboxyethyl hydroxychroman (α-CEHC), a catabolic product of α-TOH, may be a better measure of α-TOH status[70]. Michels *et al.* observed that, after an (unsupplemented) dietary intervention, urinary α-CEHC excretion increases with relatively small increases in α-TOH. Therefore, the authors concluded that α-CEHC is a more sensitive biomarker than plasma α-TOH:lipid ratios[81].

Population-based observational studies have assessed the status of α-TOH in the serum or plasma of adults and older adults, determining the prevalence of VED in such populations (Table 1).

Overall mean α-tocopherol levels ranged from 20 to 30·2 μmol/l in Asia, from 25·3 to 31·5 μmol/l in Europe and from 27·39 to 29·6 μmol/l on the American continent. Thus, the proportion of adults and older adults with indicative levels of VED reached 55·5%, 33% and 0·6% in Asia, Europe and America, respectively. Despite different cut-off points, it is possible to observe a high prevalence of VED in these regions. It is also important to highlight the lack of representative studies and data from other countries, as information on the prevalence of VED in other regions seems to be inexistent or limited.

In a systematic review carried out with data from the general population around the world focusing on age and gender groups in different countries, it was observed that VED (cut-off point <12 μmol/l) was found in studies in the Middle East and in Africa (27%) and some Asian countries (16%), followed by America (11%) and Europe (8%)[71]. However, when a serum concentration threshold of 20 μmol/l was used, the prevalence of VED was 80% of Middle Easterns/Africans, 62% of Asians, 27% of Americans and 19% of Europeans[71]. Thus, the percentage of people vulnerable to non-protective concentrations against health issues increases in many regions of the world when a superior cut-off point is considered.

Studies support the use a cut-off point of ≥30 μmol/l in studies that assess the relationship between the concentration of α-TOH and the risk or prevalence of CVD due to this value being linked with decreased odds of NCDs[82] and increased urine excretion of α-CEHC, a metabolite and status marker of α-tocopherol[83].

From the analysed studies, we observed that the prevalence of VED is quite high in most regions. As vitamin E is an antioxidant nutrient, low serum concentrations in populations may not lead to apparent clinical signs but may make this population more susceptible to diseases that involve oxidative

stress, such as CVD cancer and Alzheimer's[84]. Therefore, assessing vitamin E status in populations to monitor this situation is essential, mainly due to the growing increase in these diseases in the world.

Vitamin E and cardiovascular diseases: evidence and provisions

Although α-TOH is the most studied vitamin E isomer worldwide, both it and other forms of the vitamin are recognised as regulators of gene and protein expression, enzyme activators, lipoprotein pickups and inflammation, in addition to presenting important properties that enhance the control of events associated with atherosclerosis and CVD, such as reduced proliferation of smooth muscle cells, endothelial dysfunction, lipid peroxidation and platelet aggregation, as well as increased availability of nitric oxide[85–87].

As the role of oxidative stress in CVD became evident, population-based studies were conducted to assess the relationship between vitamin E status and the occurrence of CVD, as well as mortality from these diseases. These studies mainly reflected the dietary vitamin E intake of the individuals evaluated who did not use supplementation[15,16,35,36].

Evidence in the 1990s showed protective effects of vitamin E, where the higher the intake and/or circulating concentrations of the vitamin, the lower the risk of developing CVD[86–90].

A cross-section of the ATBC study – the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, which is a recent prospective cohort of 29 092 male smokers aged 50 to 69 – also found similar results. The study found that higher circulating α-tocopherol concentrations within the normal range at baseline were significantly associated with lower CVD mortality rates. As such, the ATBC study supports long-term health benefits in individuals who have higher serum α-TOH levels[15].

When the baseline serum α- and γ-TOH of the Japan Collaborative Cohort (JACC) study was evaluated in 39 242 participants (age range 40–79 years), it was observed that serum α-TOH was associated with lower total and haemorrhagic stroke mortality in women. However, in men or women, no association was found between α-tocopherol and coronary heart disease mortality[16].

Other studies performed with a smaller number of participants compared with the studies described above found no benefit from high blood concentrations of vitamin E[35,36].

The SENECA study (Survey in Europe on Nutrition and the Elderly, a Concerted Action) evaluated α-TOH status in 1168 older adults and found that plasma α-tocopherol concentrations were not associated with all-cause mortality or CVD mortality[35].

Hak *et al.* evaluated the association between α- and γ-TOH concentrations and myocardial infarction in 1062 men (531 cases and 531 controls), and found no significant results with α-TOH status, but noted that individuals who had higher γ-tocopherol plasma levels tended to have an increased risk of myocardial infarction[36].

After observational studies described an association between vitamin E intake/higher vitamin E concentrations and lower risk of cardiovascular events, population-based clinical trials were

Table 1. Prevalence of vitamin E deficiency in adults and older adults based on population studies.

Author, year	Continent	Country	N (individuals)	Objective	Age	Definition of deficiency (µmol/l)	Deficiency (%)	Mean α-tocopherol (µmol/l)
Kang et al., 2004[98]	Asia	Taiwan	1841	Assess vitamin E status in Taiwan using biochemical indicators and examine the influences of dietary factors.	>19 years	<11·6	1·02%	20
Cheng et al., 2005[99]	Asia	Taiwan	2373	Assess the plasma retinol and α-tocopherol concentration.	>65 years	Adequate ≥16·28 Marginal 16·28–11·63 Deficiency ≤11·6	10·61% marginal 2·91% deficient	27·12
Obeid et al., 2006[100]	Asia	Beirut, Lebanon	857	Determine plasma vitamin A and E concentrations and correlate with risk factors for cardiovascular disease.	25–64 years	Deficient: <5·8 Low: 5·8–11·6	Deficient: 0·7% Low: 3·7%	24·54
Al-Saleh et al., 2007[101]	Asia	Al Kharj, Saudi Arabia	737	Determine the status of selenium, dl-α-tocopherol and all-trans-retinol and analyse the association between these parameters and the aetiology of endemic diseases in the same area.	16–71 years	<11·6	2·3%	24·46
Assantachai and Lekhakula, 2007[102]	Asia	Thailand	2336	Examine the prevalence and risk factors for vitamin A, β-carotene, folic acid, vitamin B12, vitamin C, vitamin E and vitamin B1 deficiency.	>60 years	<14·0	55·5%	–
Hong et al., 2020[103]	Asia	South Korea (KNHANES 2016–2018)	3540	Investigate the correlation between serum retinol, α-tocopherol and serum inflammatory markers.	≥20 years	<11·6	0%	30·2
Polito et al., 2005[104]	Europe	France, North Ireland and Italy (ZENITH study)	387	Provide descriptive information on vitamin A, vitamin E and folate intake and status, and describe the correlation of vitamin status with zinc.	55–87 years	<11·6	0%	28·2–32·5
Cherubini et al., 2005[105]	Europe	Italy (InCHIANTI)	1033	To investigate the relationship between plasma vitamin E levels and cognitive impairment and dementia levels.	≥65 years	Lower tertile: <26	33%	Women: 30·9 Men: 28·7
Buijsse et al., 2005[35]	Europa	SENECA study	1168	To study the association of plasma carotene (α- and β-carotene) and α-tocopherol with all-cause and cause-specific mortality.	70–75 years	Lower tertile: 21·8	31·8%	25·3–35·6
Bartali et al., 2008[106]	Europe	Italy (InCHIANTI)	698	To determine whether a low serum micronutrient concentration (α-tocopherol, vitamin B12, B6, folate, D and iron) is associated with subsequent decline in physical function.	>65 years	<24·9	24·93%	30·6
Waniek et al., 2018[107]	Europe	Germany	641	To evaluate the distribution of α- and γ-tocopherol levels to investigate their clinical and biochemical correlates and to study the association of circulating α- and γ-tocopherol levels with a priori and a posteriori derived dietary patterns.	Mean 61 years	<12	0% 30 µmol/l: 42·4% 7·5% took vitamin E supplement	31·54
Zhu et al., 2020[108]	Europe	The Netherlands	1605	To compare vitamin status between low and high socioeconomic status (SES) in older adults, including folic acid and vitamins K, B12, B6, E, A and D, as well as to investigate whether diet mediates the association between SES and vitamin status.	60–75 years	<30	29%	33·4

Table 1. (Continued)

Author, year	Continent	Country	N (individuals)	Objective	Age	Definition of deficiency (µmol/l)	Deficiency (%)	Mean α-tocopherol (µmol/l)
Ford et al., 2006[109]	North America	United States (NHANES 1999 and 2000)	4087	Describe the distribution of serum concentrations of α-tocopherol and γ-tocopherol.	≥20 years	<11·6	0·5%	27·39
McBurney et al., 2015[110]	North America	United States (NHANES 2003–2006)	7922	To determine the prevalence of clinical vitamin E deficiency and non-compliance with a vitamin E adequacy criterion, serum α-tocopherol concentration of 30 µmol/l based on the estimated average requirement (EAR) and lowest mortality rate in the study of Alpha-Tocopherol Beta-Carotene (ATBC).	>20 years	<12	0·6%	29·6

For comparison purposes, the α-TOH concentration was converted to µmol/l, where 1 µmol/l = 43.07 µg/dl = 0.4307 µg/ml = 0.4307 mg/l. Bartali et al.[106] report that the value to convert vitamin E from µg/ml to µmol/l must be multiplied by 23.22.

conducted with long-term supplementation of this vitamin evaluating clinical outcomes and mortality. However, most studies carried out in large populations have not shown a beneficial effect of vitamin E supplementation on CVD[17–19].

Glynn et al. evaluated data from 39 876 women aged 45 years and older participating in the Women's Health Study. Women were randomly allocated to take a regular vitamin E dose (600 IU α-TOH) or a placebo every other day for a 10-year period. According to the findings, women who took vitamin E supplements had a 21% lower risk of developing venous thromboembolism. The study authors cautioned that regular vitamin E doses may reduce the risk of venous thromboembolism in women, but more research is needed to confirm the relationship between increased vitamin E consumption and prevention of venous thromboembolism[17].

Other results from the Women's Health Study showed that the difference between the supplemented and placebo groups were not statistically significant, despite the reduction in cardiovascular events in the vitamin E group. Mortality from CVD was lower in the vitamin E group; however, all-cause mortality was very low and did not differ between groups[18].

The Heart Outcomes Prevention Evaluation (HOPE) study is a 10-year randomised clinical trial which evaluated the effects of α-TOH supplementation (400 IU/d) versus placebo in 9541 patients at high risk for cardiovascular events. According to its findings, long-term vitamin E supplementation does not prevent major cardiovascular events and may increase the risk of heart failure. A regression analysis revealed that vitamin E is an independent predictor of heart failure and that it lowers left ventricular ejection fraction[19].

Other studies have evaluated vitamin E supplementation along with other vitamins and antioxidants and have also found no significant cardiovascular benefit[91–93].

The Physicians' Health II (PHS II) study used individual supplements of 400 IU α-TOH every other day and 500 mg vitamin C daily for 10 years in 14 641 US male physicians aged ≥50 years, including 754 (5·1%) men with CVD. In the outcome, it was observed that vitamin E and vitamin C supplementation did not reduce the risk of major cardiovascular events[91].

The Women's Antioxidant Cardiovascular Study (WACS) evaluated the effects of vitamin C (500 mg/d), α-TOH (600 IU every other day) and β-carotene (50 mg every other day) among 8171 female healthcare professionals aged 40 years or older, with a previous history of CVD or three or more risk factors for CVD, being followed for an average of 9·4 years. There were no overall effects of vitamin C, vitamin E or β-carotene on cardiovascular events in women at high risk for CVD, according to the study[92].

Furthermore, the *Supplementation en Vitamines et Minéraux Antioxydants* (SU.VI.MAX) study used a single daily capsule of a combination of 120 mg ascorbic acid, 30 mg vitamin E, 6 mg β-carotene, 100 µg selenium and 20 mg zinc or a placebo for a total of 13 017 French adults (7876 women aged 35–60 years and 5141 men aged 45–60 years) at a mean follow-up time of 7·5 years. No differences were observed after the analysed period in the incidence of ischaemic CVD between the supplemented and placebo groups[93].

Despite the role of oxidative stress in atherosclerosis, these clinical trials do not support the use of vitamin E supplementation in CVD prevention. These diseases are multifactorial and complex, as is vitamin E metabolism[43,94]. Furthermore, the type of supplement offered can also influence the results of the studies, as the natural RRR-α-tocopherol supplement is known to be more bioactive than the synthetic α-tocopherol (all-rac-α-tocopherol)[95].

It is interesting to note the findings of the Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS), which showed that consuming food sources of vitamins E, A and C was associated with a lower risk of adverse outcomes of cardiovascular events[96]. Therefore, showing that there are important differences between long-term intake of a nutrient in the food matrix and relatively short-term intervention with unique supplementation. In addition, it is important to note that most vitamin E supplements contain a chemically synthesised racemic mixture (all-rac-α-tocopherol), while vitamin E in foods comes in different forms.

Linked to this, the European Society of Cardiology, American College of Cardiology and Brazilian Society of Cardiology report that supplementation vitamin E is not recommended for CVD prevention because it has been demonstrated that getting it through diet is more effective and safe[30,32,97].

Importantly, VED in these population studies of vitamin E supplementation was not evaluated in the participants, and most studies only evaluated the serum α-TOH, but not the other isomers, the α-tocopherol corrected by blood cholesterol or urinary α-CEHC, which may demonstrate an under- or overestimation of vitamin E levels. Study results may also be affected by cohort selection, study design, comorbidities, age, genetic variations and the gender of participants.

Thus, public health interventions aimed at improving the nutritional status of this vitamin are encouraged to ensure the adequacy of vitamin E in population groups with a high risk or elevated prevalence of deficiency.

Intervention policies or programmes can be effective in improving vitamin E status. Public health programmes can focus on nutritional guidance for increasing consumption of source foods, food fortification or supplementation. Public health policies must guarantee the population access to healthy and adequate food, reducing the prevalence of food insecurity. Thus, policies and programmes can be directed at improving the status of antioxidant nutrients (such as vitamin E) depending on the population's needs and resources, which can reduce the prevalence of chronic noncommunicable diseases such as CVD.

Conclusion and future perspectives

Despite a growing prevalence of CVD and the importance of vitamin E in its antioxidant role, VED is poorly investigated and population studies reveal a high prevalence in Asia, Europe and America, with higher deficiency percentages in Asian countries and Europeans, regions that also stand out for their high CVD mortality rates, suggesting that VED is a public health problem which needs to be further investigated. However, there is still a lack of studies and data in several countries around the world,

making it difficult to track the prevalence of VED in these regions, which consequently reduces public health strategies targeted at improving vitamin E nutritional status. If an individual has low serum concentrations of vitamin E, the protective antioxidant effect that this nutrient confers against diseases that involve oxidative stress, such as CVD, cancer and Alzheimer's, may be partially reduced or ceased.

Several observational studies have reported that high overall vitamin E intake and/or high blood vitamin E concentrations are associated with a decreased risk of CVD and overall mortality. However, most clinical trials have not shown the benefit of vitamin E supplementation to prevent cardiovascular events.

The contrast between the negative results of α-tocopherol intervention studies in CVD and the positive results of observational studies with dietary vitamin E consumption may reflect the possibility that α-tocopherol alone does not confer cardiovascular protection to individuals, but the consumption of all isomers found in food. This reinforces that promoting healthy food consumption with the presence of natural sources of vitamin E and healthy fats provides individuals with protection against CVD.

It is also important to note that such α-tocopherol supplementation clinical trials do not indicate that vitamin E status was used as a criterion for inclusion in the study. Thus, it is unclear whether participants in these studies were vitamin E deficient and could benefit from additional α-tocopherol regarding CVD metabolism. Therefore, we support the relevance of developing population-based studies comparing the relationship of the effectiveness of vitamin E supplementation in the prevention of CVD considering the initial vitamin E concentrations and the characterisation of the disease, cardiovascular or cerebrovascular.

Also considering the emerging view of the active regulatory metabolites of vitamin E, clinical studies with larger numbers of individuals are needed to fully understand the mode of action of these metabolites, as their discovery may explain the inconsistent effects of α-TOH on diseases caused by inflammation, such as CVD. Future studies will show whether any vitamin E metabolites will be useful in nutritional or clinical therapies in the prevention or treatment of CVD.

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