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SCIENTIFIC OPINION

Scientific opinion on the tolerable upper intake level for vitamin E

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Abstract

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver a scientific opinion on the revision of the tolerable upper intake level (UL) for vitamin E. As *α*-tocopherol is recognised as the only essential form of vitamin E, the Panel restricted its evaluation to *α*-tocopherol. Systematic reviews of the literature were conducted to assess evidence on priority adverse health effects of excess intake of vitamin E, namely risk of impaired coagulation and bleeding, cardiovascular disease and prostate cancer. The effect on blood clotting and associated increased risk of bleeding is considered as the critical effect to establish an UL for vitamin E. No new evidence has been published that could improve the characterisation of a dose–response. The ULs for vitamin E from all dietary sources, which were previously established by the Scientific Committee on Food, are retained for all population groups, i.e. 300 mg/day for adults, including pregnant and lactating women, 100 mg/day for children aged 1–3 years, 120 mg/day for 4–6 years, 160 mg/day for 7–10 years, 220 mg/day for 11–14 years and 260 mg/day for 15–17 years. A UL of 50 mg/day is established for infants aged 4–6 months and a UL of 60 mg/day for infants aged 7–11 months. ULs apply to all stereoisomeric forms of *α*-tocopherol. ULs do not apply to individuals receiving anticoagulant or antiplatelet medications (e.g. aspirin), to patients on secondary prevention for CVD or to patients with vitamin K malabsorption syndromes. It is unlikely that the ULs for vitamin E are exceeded in European populations, except for regular users of food supplements containing high doses of vitamin E.

KEYWORDS

tolerable upper intake level, vitamin E, *α*-tocopherol

CONTENTS

1 | INTRODUCTION

1.1 | Background as provided by the European Commission

Article 6 of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods and Article 5 of Directive 2002/46/EC on the approximation of the laws of the Member States relating to food supplements provide that maximum amount of vitamins and minerals added to foods and to food supplements, respectively, shall be set.

The above-mentioned provisions lay down the criteria to be taken into account when establishing these maximum amounts that include the upper safe levels (ULs) of vitamins and minerals established by scientific risk assessment based on *'generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different groups of consumers.'*

To set maximum amounts of vitamins and minerals in fortified foods and food supplements, the Commission would like to ask the European Food Safety Authority (EFSA) to review the previous opinions of the Scientific Committee on Food (SCF) or the NDA Panel on the ULs for vitamin A,[1] folic acid/folate[1], vitamin D[1], vitamin E[1], Vitamin B_6[1], iron[1], manganese[1] and β-carotene[1] to take into account recent scientific developments and evidence.

In this context, EFSA should first review the guidelines of the SCF[1] for the development of tolerable upper intake levels for vitamins and minerals (adopted on 19 October 2000).

Tolerable Upper Intake Levels should be presented separately for the age group from 4/6 months onwards until 3 years of age and the general population group from 3 years onwards, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups. As foods intended for the general population are also consumed by young children, young children should be considered as a potentially sensitive consumer group.

1.2 | Terms of Reference as provided by the European Commission

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002,[2] the European Commission requests the European Food Safety Authority to:

1. Update the guidelines of the SCF for the development of Tolerable Upper Intake Levels for vitamins and minerals in the light of available recent scientific and methodological developments.
2. Review existing scientific evidence and provide advice on tolerable upper intake levels for the following vitamins and minerals including their currently authorised forms for the addition to fortified foods and food supplements for the general population and, as appropriate, for vulnerable subgroups of the population:

- vitamin A
- folic acid/folate
- vitamin D
- vitamin E
- iron
- manganese
- β-carotene
- vitamin B6

For nutrients for which there are no, or insufficient, data on which to base the establishment of an UL, an indication should be given on the highest level of intake where there is reasonable confidence in data on the absence of adverse effects.

1.3 | Interpretation of the Terms of Reference

According to the mandate, EFSA has first reviewed the guidelines of the SCF for the development of tolerable upper intake levels (ULs) for vitamins and minerals (SCF, 2000). A draft guidance has been endorsed by the Nutrition, Novel Foods and Food Allergens (NDA) Panel and published for a 1-year pilot phase EFSA NDA Panel (2022), after which it will be revised and complemented as necessary, following a public consultation. The Panel interprets that the UL for vitamin E should be revised according to the principles laid down in that guidance, following a protocol developed for that purpose (Annex A).

In the past, the term vitamin E was used as the generic term for four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ), collectively known as tocochromanols. However, in its opinion on Dietary Reference Values (DRVs) for vitamin E from

[1]SCF (2000). Scientific Committee on Food. Guidelines of the Scientific Committee on Food for the Development of Tolerable Upper Intake Levels for Vitamins and Minerals. in: Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies (2006). Tolerable Upper Intake Levels for Vitamins and Minerals.
[2]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

2015, the Panel concluded that, based on the available evidence and in line with other authoritative bodies, *α*-tocopherol was the only physiologically active vitamer (EFSA NDA Panel, 2015). Consistently, the Panel assesses the UL for vitamin E as *α*-tocopherol. All sources of *α*-tocopherol authorised for addition to foods and food supplements in the EU are covered by the assessment.

In the rest of this opinion, the expression 'vitamin E' is used when citing reports or articles which referred to the old definition (i.e. including *α*-tocopherol and other tocochromanols) or which did not specify the forms included. Vitamin E (without quotation marks) refers to *α*-tocopherol only.

1.4 | Context of the assessment

Previous safety assessments by the SCF and EFSA

The SCF evaluated the UL for 'vitamin E' in 2003 (SCF, 2003). The Committee considered the effect of 'vitamin E' on blood clotting as the critical effect and identified the study by Meydani et al. (1998) as the best basis to identify a reference point. The no observed adverse effect level (NOAEL) established in this study was 800 IU/day (540 mg/day). The Committee concluded that 'an uncertainty factor (UF) of 2 would adequately cover interindividual differences in sensitivity. A larger UF was not considered necessary because data from a number of other older but less well controlled studies showed no adverse effects at considerably higher intakes.' A UL of 300 mg/day was established for adults. The same UL was applied to pregnant and lactating women. ULs for children and adolescents were extrapolated from the UL for adults based on body surface area$^{0.75}$ (allometric scaling). No UL was established for infants (< 1-year old).

The safety and bioavailability of different preparations of 'vitamin E' as nutrient sources were previously assessed by EFSA (EFSA AFC Panel, 2005, 2008):

- *Assessment of D-α-tocopheryl acid succinate (TAS) for particular nutritional purposes, foods intended for the general population and food supplements*: the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) derived a NOAEL of 265 mg TAS/kg body weight (bw) per day from a 90-day oral toxicity study in rats. Considering a high-level 'vitamin E' intake from supplements of 336 mg/day in adults [equivalent to 5.6 mg/kg bw per day], and assuming that the bioavailability in humans and rats is similar, a margin of safety of 47.3 was calculated, which was considered acceptable. The Panel concluded that TAS, as a source of 'vitamin E', in foods for particular nutritional purposes, foods intended for the general population and food supplements was not of concern from the safety point of view (EFSA AFC Panel, 2005).
- *Assessment of 'mixed tocopherols', 'tocotrienol tocopherol' and 'tocotrienols' for use in food supplements*: regarding tocopherols, the AFC Panel considered the UL of 300 mg per day for adults set by the SCF and the acceptable daily intake (ADI) of 0.15–2 mg/kg bw per day calculated as α-tocopherol set by JECFA. Regarding tocotrienols, the Panel derived a NOAEL of 120 mg tocotrienol extract/kg bw per day for male rats and 130 mg tocotrienol extract/kg bw per day for female rats based on a 90-day study conducted with a tocotrienol-rich palm oil extract (70% tocotrienols). Considering the products specifications and proposed conditions of use, the AFC Panel considered the use of 'mixed tocopherols' and 'tocotrienol tocopherol' as sources of 'vitamin E' in food supplements for the general population not to be of safety concern. However, the available safety data were deemed insufficient to conclude on the safety of the preparation containing mainly tocotrienols at the proposed use levels (up to 1000 mg/day) (EFSA AFC Panel, 2008).

In 2015, the Panel on Food Additives and Nutrient Sources added to Food (ANS) re-evaluated the safety of tocopherol-rich extract (E 306), *α*-tocopherol (E 307), *γ*-tocopherol (E 308) and *δ*-tocopherol (E 309) as food additives (EFSA ANS Panel, 2015). There was no concern that tocopherols were genotoxic or carcinogenic. Data were considered insufficient to address the reproductive and developmental toxicity. The Panel considered prolonged coagulation time as the critical adverse effect. The Panel considered that the available data were too limited to establish an ADI for the tocopherols. However, given that 'vitamin E' is widely consumed from natural sources, it is an essential nutrient and that the ULs established by the SCF were not exceeded in any population group, except in children in one survey, *α*-tocopherol (E 307) was not considered to be of safety concern at the reported uses and use levels as a food additive. The Panel noted that lower concentrations and fewer uses for *γ*- and *δ*-tocopherol are reported in food than for *α*-tocopherol and concluded that other tocopherols (E 306, E 308, E 309) were not of safety concern at the levels used in food.

The safety and efficacy of vitamin E (*all rac-α*-tocopheryl acetate, *RRR-α*-tocopheryl acetate and *RRR-α*-tocopherol) as a feed additive for all animal species has been assessed by the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). The Panel identified no safety concerns for the consumer and concluded that there was no need to propose a maximum content for vitamin E in feed under this aspect (EFSA FEEDAP Panel, 2010). In 2012, the Panel extended its conclusions to synthetic *all rac-α*-tocopherol (EFSA FEEDAP Panel, 2012).

Adequate Intakes for vitamin E

In 2015, the Panel on Dietetic Products, Nutrition, Allergies (NDA) evaluated DRVs for vitamin E (EFSA NDA Panel, 2015). Data showed that *α*-tocopherol was the only physiologically active vitamer, as blood *α*-tocopherol concentrations are maintained by the preferential binding of *α*-tocopherol (compared to other tocopherols or tocotrienols) by the *α*-tocopherol

transfer protein (α-TTP). Thus, based on the available evidence and in line with other authoritative bodies, the Panel considered vitamin E as being α-tocopherol only. Also, among chemically synthesised α-tocopherol forms, only 2R-α-tocopherol stereoisomers (i.e. RRR-, RRS-, RSR-, RSS-) were found to meet human requirements for the vitamin, because the 2S-stereoisomers (i.e. SSS-, SSR-, SRS-, SRR-) possess low affinity for α-TTP and are rapidly metabolised in the liver.[3]

The Panel considered that average requirements (ARs) and population reference intakes (PRIs) for vitamin E, as α-tocopherol, could not be derived due to insufficient data. Therefore, the Panel established an adequate intake (AI) for adults of 13 mg/day for males and 11 mg/day for females, based on observed dietary intakes in healthy populations with no apparent α-tocopherol deficiency. The same approach was applied to defined AIs for children and adolescents: 6 mg/day for children aged 1–3 years, 9 mg/day for children aged 3–10 years, 13 mg/day for children and adolescent males aged 10–18 years and 11 mg/day for children and adolescent females aged 10–18 years. For infants aged 7–11 months, an AI for α-tocopherol of 5 mg/day was extrapolated upwards from the estimated α-tocopherol intake in exclusively breast-fed infants aged 0–6 months, using allometric scaling.

1.5 | Previous assessments by other bodies

Like the SCF (**Section 1.4**), previous safety assessments of vitamin E intake by other bodies considered the effect on blood coagulation/increased tendency to haemorrhage as the critical effect of excess vitamin E intake (EVM, 2003; IOM, 2001; NHMRC, 2006).

The Institute of Medicine (IOM) used the lowest observed adverse effect level (LOAEL) of 500 mg/kg bw per day derived from a 2-year toxicity study in rats (Wheldon et al., 1983), as a reference point. This LOAEL was found to be consistent with the results of two additional toxicity study in rats, i.e. a shorter term feeding study (Takahashi et al., 1990) and a gavage study (Abdo et al., 1986). A UF of 36 was applied to account for the extrapolation of the LOAEL to a NOAEL (UF = 2), from subchronic to chronic intake (UF = 2) and from experimental animals to humans (UF = 3), and to cover for interindividual variation in sensitivity (UF = 3). A UL of 1000 mg/day was established for adults, which applied to all eight stereoisomers of α-tocopherol. The same value was set for pregnant and lactating women. For children and adolescents, the values were extrapolated from the UL established for adults based on relative body weight (Table 1). For infants, the UL was judged not determinable because of insufficient data on adverse effects in this age group and concern about the infant's ability to handle excess amounts. The IOM recommended that the only source of intake for infants should be from food and formula (IOM, 2001).

The UK Expert Group on Vitamins and Minerals (EVM) established a NOAEL of 800–1600 IU/day (540–970 mg *RRR*-α-tocopherol equivalents/day) based on three trials (Gillilan et al., 1977; Meydani et al., 1998; Stephens et al., 1996) which did not indicate adverse effects at these supplemental doses. The Committee considered that no uncertainty factor was necessary and established a safe upper level of 540 mg RRR-α-tocopherol equivalents/day for supplemental 'vitamin E' (Table 1) (EVM, 2003).

In line with the approach followed by the SCF, the National Health and Medical Research Council (NHMRC) established a UL of 300 mg/day of for adults, applicable also to pregnant and lactating women (NHMRC, 2006) (Table 1). The ULs for children and adolescents were derived by applying isometric scaling. No UL for infants was set but the committee considered that the source of intake should be breast milk, formula and food only.

TABLE 1 Overview of existing tolerable upper intake levels (ULs) for 'vitamin E', in mg/day.

Population groups	SCF (2003)[a]	EVM (2003)[b]	IOM (2001)[c]	NHMRC (2006)[d]
Infants				
0–6 months	nd	nd	nd[e]	nd[e]
7–12 months	nd	nd	nd[e]	nd[e]
Children and adolescents				
1–3 year	100	nd	200	70
4–6 year	120	nd	–	
4–8 year	–	–	300	100
7–10 year	160	nd	–	
9–13 year	–	–	600	180
11–14 year	220	nd	–	
14–18 year	–	–	800	250
15–17 year	260	nd	–	–

[3]For this reason, the IOM redefined the human vitamin E requirement in milligrams of 2*R*-α-tocopherol and provided conversion factors, such that 1 mg *all rac*-α-tocopherol has the same biologic activity as 0.5 mg *RRR*-α-tocopherol (IOM, 2001).

TABLE 1 (Continued)

Population groups	SCF (2003)[a]	EVM (2003)[b]	IOM (2001)[c]	NHMRC (2006)[d]
Adults				
≥ 18 year	300[f]	540	–	–
≥ 19 year	–	–	1000[f]	300[f]

Abbreviations: EVM, Expert Group on Vitamins and Minerals; IOM, Institute of Medicine; nd, not defined; NHMRC, National Health and Medical Research Council; SCF, Scientific Committee on Food.

[a]In mg 'vitamin E' (i.e. all tocochromanols).

[b]In mg *RRR*-α-tocopherol equivalents/day; the value applies to supplemental 'vitamin E' (i.e. all tocochromanols).

[c]In mg α-tocopherol/day; the values apply to any form of supplementary α-tocopherol.

[d]In mg α-tocopherol equivalents/day; the value applies to supplemental 'vitamin E' (i.e. all tocochromanols).

[e]Source of intake should be breast milk, formula and food only.

[f]Including pregnant and lactating women.

2 | DATA AND METHODOLOGIES

2.1 | Problem formulation

In accordance with the draft NDA Panel guidance on establishing and applying ULs for vitamins and essential minerals (EFSA NDA Panel, 2022), the assessment questions underlying the UL evaluation are formulated as follows:

- What is the maximum level of total chronic daily intake of α-tocopherol (from all sources) which is not expected to pose a risk of adverse health effects to humans? *(Hazard identification and characterisation)*.
- What is the daily intake of α-tocopherol from all dietary sources in EU populations? *(Intake assessment)*.
- What is the risk of adverse effects related to the intake of α-tocopherol in EU populations, including attendant uncertainties? *(Risk characterisation)*.

The hazard identification and hazard characterisation relate to the identification of adverse health effects of a given nutrient and the qualitative and quantitative evaluation of the adverse health effects associated with the nutrient, including dose–response assessment and derivation of a UL, if possible.

Adverse (health) effects are defined as 'a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity to compensate for additional stress or an increase in susceptibility to other influences' (EFSA Scientific Committee, 2017a). 'The observable effects of high nutrient intake within the causal pathway of an adverse health effect can range from biochemical changes without functional significance (e.g., certain changes in enzyme activity) to irreversible clinical outcomes. Notably, some changes that occur before clinical manifestations could be used as surrogate or predictive markers of subsequent adverse health effects, i.e. biomarkers of effect' (EFSA NDA Panel, 2022).

Available risk assessments on dietary 'vitamin E' intakes from authoritative bodies (WHO/FAO, 2004) and systematic review identified in the literature (Loh et al., 2022; O'Connor et al., 2022; Schürks et al., 2010) were used to identify adverse health effects that have been associated with excess intakes in humans. As a result, the following priority adverse health effects, i.e. those that are expected to play a critical role for establishing a UL, were identified: impaired blood coagulation and risk of bleeding, cardiovascular disease risk and cardiovascular mortality and risk of prostate cancer and prostate cancer mortality. The rationale for the prioritisation is detailed in the protocol (Annex A).

Regarding the target population for this assessment, the Panel notes that, in its previous opinion, the SCF noted that oral intakes of high amounts of 'vitamin E' can increase blood coagulation defects in subjects with vitamin K deficiency caused by malabsorption or due to therapy with anticoagulants (SCF, 2003). Therefore, the UL was not considered to apply to patients receiving anticoagulant drugs or to patients with malabsorption syndromes, nor to other conditions where the synthesis of vitamin K by the gut microbiota might be impaired. In addition, the SCF noted some evidence that 'vitamin E' can increase the risk of haemorrhage in individuals taking aspirin. The Panel notes that the restrictions identified by the SCF still hold and that these groups are under specific medical management. Thus, patients receiving anticoagulant or antiplatelet drugs and patients with vitamin K malabsorption syndromes are excluded from the target population for this assessment.

As a result of the problem formulation, the overarching risk assessment questions were further specified into assessment subquestions (sQs) and the methods to address each sQ was selected as outlined in Table 2. The assessment should cover α-tocopherol from all dietary sources, including all α-tocopherol forms authorised for addition to foods and food supplements in the EU.

TABLE 2 Assessment subquestions and methods to address them.

	Subquestion	Method
sQ1	**Absorption, distribution, metabolism and excretion (ADME) of *α*-tocopherol**	
	1a. What is the ADME of *α*-tocopherol in humans?	Narrative review
	1b. Are there differences related to age or other individual factors, e.g. genetic polymorphisms of *α*-tocopherol metabolism?	Narrative review
sQ2	**Impaired blood coagulation and risk of bleeding**	
	2a. What is the dose–response relationship between *α*-tocopherol intake and impaired blood coagulation and risk of bleeding in humans?	Systematic review
	2b. What are the potential mechanisms/mode(s) of action underlying the relationship between *α*-tocopherol intake and these endpoints?	Narrative review
sQ3	**Risk of cardiovascular disease and cardiovascular risk mortality**	
	3a. What is the relationship between 'high' *α*-tocopherol intake and the risk of cardiovascular-related outcomes, including mortality? Could a dose–response be characterised?	Systematic review
	3b. What are the potential mechanisms/mode(s) of action underlying the relationship between *α*-tocopherol intake and these endpoints?	Narrative review
sQ4	**Risk of prostate cancer and prostate cancer mortality**	
	4a. What is the relationship between 'high' *α*-tocopherol intake and the risk of prostate cancer, including mortality? Could a dose–response be characterised?	Systematic review
	4b. What are the potential mechanisms/mode(s) of action underlying the relationship between *α*-tocopherol intake and this endpoint?	Narrative review
sQ5	**Other adverse health effects**	
	What other adverse health effects have been reported to be associated with 'high' intake of *α*-tocopherol?	Narrative review
sQ6	***α*-tocopherol intake**	
	6a. What are the levels of *α*-tocopherol in foods, beverages and food supplements in the EU?	Food composition and food consumption data in the EU
	7b. What is the distribution of daily *α*-tocopherol intake from all dietary sources in EU populations and subgroups thereof?	

2.2 | Hazard identification and characterisation

2.2.1 | Data

For this scientific assessment, a protocol (Annex A) has been developed in line with EFSA's existing methodology. The processes applied for evidence retrieval, study selection and data extraction are summarised below.

2.2.1.1 | *Priority adverse health effects*

To address sQ2a, sQ3a and sQ4a, relevant human studies on the selected adverse health effects were identified through systematic searches of the literature in MEDLINE (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials for articles published in English. The search strategies were created by information specialists of ESFA (Annex B). The searches were performed from October to December 2023. Grey literature was not searched.

Retrieved articles were screened in duplicate in Distiller SR® at title and abstract level, also with the use of the artificial intelligence tool of Distiller SR® as second reviewer. Full-text screening for inclusion/exclusion was performed in duplicate by human reviewers according to the criteria defined in the protocol (Annex A). Relevant systematic reviews were handsearched for additional pertinent studies. Reviews, expert opinions, editorials, letters to the editors, abstracts, posters and theses were excluded.

Eligible designs:

- For sQ2a, eligible study designs were limited to human intervention studies (randomised or non-randomised, controlled and uncontrolled).
- For sQ3a and sQ4a, eligible study designs were human controlled trials (randomised or non-randomised) and prospective observational studies (prospective cohort studies (PCs), nested case–control studies (NCCs) and case-cohort studies (CCs))

Eligible study populations:

- For sQ2a, studies were eligible if they involved individuals of any age (except premature infants). Studies in people with health conditions were not excluded a priori (their relevance for the general population will be assessed on a case-by-case basis), except for diseases affecting liver, pancreatic or gastrointestinal function, vitamin K malabsorption syndromes, medical conditions that could affect blood coagulation independently of *α*-tocopherol supplementation. Also, studies among individuals receiving anticoagulant or antiplatelet drugs were excluded.
- For sQ3a and sQ4a, eligible studies were restricted to adults. Studies in people with health conditions are not excluded a priori and their relevance for the general population was assessed on a case-by-case basis.

Eligible exposure measurements: Human intervention studies were eligible if they investigated oral *α*-tocopherol supplementation versus placebo/no treatment/lower doses. Observational studies were eligible if they measured total 'vitamin E' or total *α*-tocopherol intake (i.e. from diet and supplements) or supplemental 'vitamin E' or *α*-tocopherol by dietary assessment methods.

In relation to sQ2a, 7857 references were identified (flow chart in **Appendix A.1**). The title and abstract screening left 551 relevant articles that underwent a full-text review. Two articles were identified via references. Thirteen articles were included.

In relation to sQ3a, 4734 references were identified (flow chart in **Appendix A.2**). The title and abstract screening left 105 relevant articles that underwent a full-text review. One article was identified via references. Thirty-two articles were included.

In relation to sQ4a, 152 references were identified (flow chart in **Appendix A.3**). The title and abstract screening left two relevant articles. Additional relevant 36 articles were reported in the systematic review by Loh et al. (2022) that served as the main source of data of this sQ. Thirty-eight articles underwent a full-text review. Seventeen articles were included.

When the form and/or dose of oral *α*-tocopherol supplementation was not clearly stated in the eligible publications, study authors were contacted by EFSA. A response was not received in all cases, and thus, the exact form was not available for all studies.

Data were extracted by EFSA into Microsoft Excel®, for the purpose of data plotting and analysis, and in Microsoft Word® for the preparation of evidence tables.

2.2.1.2 | *Other background information*

The evidence used to inform sQ1, sQ2b, sQ3b, sQ4b, sQ5 was retrieved from textbooks, authoritative reviews and research papers through non-systematic searches in bibliographic databases and was synthesised as narrative reviews. In addition, for sQ5, studies reporting on the other adverse health outcomes identified in the protocol (i.e. all-cause mortality, cataract, pregnancy-related outcome, respiratory infection) were also identified through the full-text review of the articles retrieved for sQ2a (see above). As a result, 22 relevant publications were retrieved, which are discussed in **Section 3.4.4**.

2.2.2 | Methodologies

The methodology for this assessment follows the guidance for establishing ULs developed by the NDA Panel (EFSA NDA Panel, 2022). Other guidance documents from EFSA were also considered, including those addressing the application of the systematic review methodology in food and feed safety assessments (EFSA, 2010), the principles and processes for dealing with data and evidence in scientific assessments (EFSA, 2015), the statistical significance and biological relevance (EFSA Scientific Committee, 2011), the biological relevance of data (EFSA Scientific Committee, 2017a), the use of the weight of evidence approach (EFSA Scientific Committee, 2017b), the appraisal and integration of evidence from epidemiological studies (EFSA Scientific Committee, 2020) and the analysis of uncertainty in scientific assessments (EFSA Scientific Committee, 2018).

2.2.2.1 | *Evidence synthesis*

All authorised forms of *α*-tocopherol (i.e. either free or as esters, natural and synthetic) were eligible for the assessment. For harmonisation purposes, the opinion applies the current nomenclature, i.e. natural forms (historically called *d-α*-tocopherol) are named *RRR-α*-tocopherol and esters, and synthetic forms (historically called *dl-α*-tocopherol) are named *all rac-(racemic) α*-tocopherol and esters (see **Section 3.1**).

Depending on papers, study doses were reported in International Units (IU)[4] of 'vitamin E' or in mg of 'free' *α*-tocopherol or its esters. To allow study comparisons, doses were standardised into mg of 'free' *α*-tocopherol by applying the conversion factors reported in Table 3. For instance, 400 IU *all rac-α*-tocopheryl acetate corresponds to 400 mg *all rac-α*-tocopheryl

[4]The United States Pharmacopeia (USP) defined the IU for vitamin E relative to the synthetic form, racemic *all rac-α*-tocopheryl acetate, i.e. 1 IU = 1 mg of *all rac-α*-tocopheryl acetate (USP, 1979, 1999).

acetate and 364 mg 'free' α-tocopherol. For critical studies, authors were contacted when the chemical form was not reported in the article. When no information could be obtained, the opinion provides the dose as reported in the article.

When the supplemental dose was given an alternate days, it was converted into a daily dose by dividing the amount by two.

For sQ3a and sQ4a, relevant results from eligible studies were plotted in descriptive forest plots.

TABLE 3 Factors applied to standardise doses of α-tocopherol esters to mg 'free' α-tocopherol.

	mg/IU[a]	mg 'free' α-tocopherol/mg[b]
Natural forms[c]		
***RRR*-α-tocopherol**	0.67	1.00
***RRR*-α-tocopheryl acetate**	0.74	0.91
***RRR*-α-tocopheryl succinate**	0.83	0.81
Synthetic forms[d]		
***All rac*-α- tocopherol**	0.91	1.00
***All rac*-α-tocopheryl acetate**	1.00	0.91
***All rac*-α- tocopheryl succinate**	1.12	0.81

[a]1 International Unit (IU) = 1 mg of *all rac-α-tocopheryl* acetate = 0.67 mg *RRR*-α-tocopherol = 0.74 mg *RRR*-α-tocopheryl acetate (USP, 1979, 1999).

[b]Molecular weights: α-tocopherol 430.71 g/mol; α-tocopheryl acetate 472.74 g/mol; α-tocopheryl succinate 530.8 g/mol.

[c]Historically called *d*-α-tocopherol or *d*-α-tocopheryl esters.

[d]Historically called *dl*-α-tocopherol or *dl*-α-tocopheryl esters.

2.2.2.2 | *Evidence integration and uncertainty analysis*

Hazard identification

Regarding sQ2a, a causal relationship between 'high' α-tocopherol intake and changes in coagulation parameters and/or blinding is well established, and the assessment focussed on the characterisation of a dose–response and whether new evidence could lead to a revision of the previously established NOAEL based on this endpoint.

Regarding sQ3a and sQ4a, the hazard identification step consisted of assessing the evidence for a causal positive relationship between intake of α-tocopherol and the health effects identified. Conclusions on each health effect are reached by study design (human interventions separately from observational studies), through considering the uncertainties in the body of evidence (BoE) and in the methods. EFSA applies a stepwise approach for the formulation of hazard identification conclusions (**Figure 1**). It includes a prioritisation step to identify health effects for which the available BoE suggests a positive relationship between the dietary intake of nutrient and risk of disease/impaired function. This is based on a preliminary uncertainty analysis (UA). The Panel considers that health effects for which the available BoE (i) does not suggest a positive relationship (i.e. the relationship appears to be negative or null) or (ii) is insufficient to conclude on a relationship, cannot be used to inform the setting of a UL. Data gaps and research needs are identified, where appropriate. When the available BoE indicates a positive association between the intake of the nutrient and the risk of a disease/impaired function, a comprehensive UA is performed to inform the formulation of the hazard identification conclusions, i.e. judgement on the level of certainty for a causal relationship. In this assessment, the evaluation of the evidence for sQ3a and sQ4a stopped at the prioritisation step, i.e. the Panel concludes that the available BoEs could not be used to derive ULs for α-tocopherol. No comprehensive uncertainty analysis was conducted.

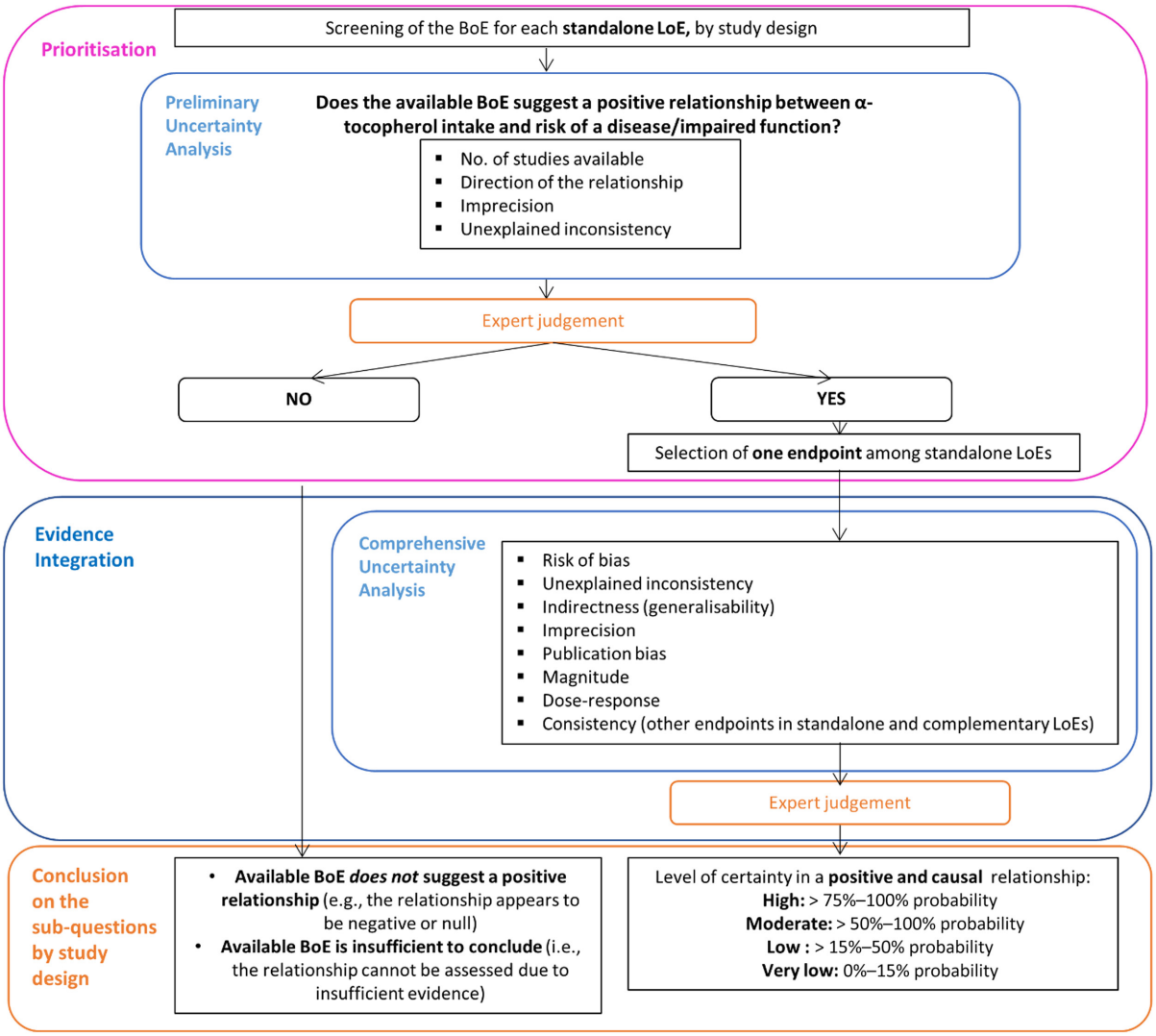

FIGURE 1 Stepwise approach for evidence integration and uncertainty analysis. BoE, body of evidence; LoE, line of evidence.

Hazard characterisation

At this step, evidence is integrated to select the critical effect(s) and identify a reference point (RP) for establishing the UL (EFSA NDA Panel, 2022). ULs are established to protect all members of the general population, including sensitive individuals, throughout their lifetime. However, the UL may exclude subpopulations with distinct vulnerabilities to adverse effects of nutrient 'excess' due to specific genetic predisposition or other factors (e.g. specific (chronic) medical conditions or use of certain medications). Including those subpopulations would result in ULs which are significantly lower than needed to protect most people against adverse effects of high nutrient intakes. Subpopulations needing special protection are better served through public health screening, healthcare providers, product labelling or other individualised strategies. The exclusion of such subpopulations must be considered on a nutrient-by-nutrient basis and is an area of scientific judgement and of risk management. In practice, the exclusion of a sub-population from a UL should take into consideration whether individuals from that group can be identified (e.g. through screening, diagnosis).

2.3 | Dietary intake assessment

The assessment follows the approach outlined in the protocol for the intake assessments performed in the context of the revision of ULs for selected nutrients (EFSA, 2022).

Briefly, the EFSA food composition database (FCDB)[5] and the EFSA Comprehensive European Food Consumption Database (hereinafter referred as Comprehensive Database)[6] were used to obtain harmonised estimates of the intake *α*-tocopherol from the background diet in EU populations. Other data sources were used to gather non-harmonised

[5]https://www.efsa.europa.eu/it/data-report/food-consumption-data.
[6]https://www.efsa.europa.eu/it/data-report/food-composition-data.

estimates of the intake of *α*-tocopherol from the background diet, fortified foods and food supplements, either alone or in combination, in European countries (i.e. intake estimates from nationally representative food consumption surveys), and data on the amounts of *α*-tocopherol used for food fortification and in food supplements (i.e. Mintel Global New Product Database (GNPD)).

2.3.1 | Data

Previously, the term vitamin E was used as the generic term for tocochromanols, which include four tocopherols (*α*, *β*, *γ*, *δ*) and four tocotrienols (*α*, *β*, *γ*, *δ*). Various factors have been used to convert food contents of tocopherols and tocotrienols to *α*-tocopherol equivalents (*α*-TE) (EFSA NDA Panel, 2015).

Due to the evolution of the definition of 'vitamin E', food composition data are not harmonised and sometimes ambiguous as to whether the 'vitamin E' content reported refers to *α*-tocopherol only or include all tocochromanols. Food composition data are still commonly expressed in *α*-TE. Regarding product labelling, the generic term 'vitamin E' is used for nutrition declarations, with reference to a nutrient reference value (NRV) of 12 mg/day 'vitamin E' (Regulation (EU) No 1169/2011[7]). These are sources of uncertainty when collecting data on the *α*-tocopherol content of food. Some assumptions had to be applied, which are described below.

2.3.1.1 | *Intake data calculated by EFSA in 2015*

Intakes of *α*-tocopherol for all population groups (excluding food supplements) were previously estimated in the context of the scientific opinion on DRVs for vitamin E as *α*-tocopherol (EFSA NDA Panel, 2015). Food intake data from the Comprehensive Database and data on content in foods from the FCDB were used (Roe et al., 2013). Given that the EFSA FCDB has not been updated since the 2015 EFSA assessment, and the number of national surveys that were newly integrated in the Comprehensive Database is limited, the intake estimates published in 2015 are still considered adequate for the purpose of the present assessment and were not updated.

In 2015, the Panel aimed at estimating intakes of *α*-tocopherol. However, only two national databases (Finland and Sweden) contained data on *α*-tocopherol only. Most food composition databases in EU countries contained values for 'vitamin E' expressed as *α*-TEs, i.e. included other tocopherols and tocotrienols. A definition of *α*-TE or the conversion factors applied to the other tocochromanols were not reported. Because of the limited data available on the *α*-tocopherol content of food, EFSA estimated intakes of both *α*-tocopherol and *α*-TEs (**Section 3.3.2**).

Regarding the use of *α*-tocopherol containing supplements, data in the Comprehensive Database have important limitations, in particular due to partial reporting in the database of the nutrient(s) contained in food supplements. In view of the uncertainties associated with these data, the Panel relied on information available from national dietary surveys to perform its assessment (see **Section 2.3.1.2** on other data sources).

2.3.1.2 | *Other data sources*

Food consumption data

Between September and November 2021, 64 competent authorities in 37 European countries have been contacted through the EFSA Focal Points[8] and the EFSA Food Consumption Network[9] to obtain 'vitamin E' intake estimates from natural sources, fortified foods and food supplements from nationally representative food consumption surveys (no date limits applied). Data from fortified foods and food supplements were of particular relevance as these estimates were absent from the 2015 EFSA's assessment. An additional search in sources of bibliographic information (Google Scholar, PubMed) was performed to collect reports of national surveys included in the Comprehensive Database that had not been obtained through the competent authorities. Between August and October 2022, EFSA contacted all EU Member States and Norway through the European Commission WG on Food supplements and Fortified foods[10] and collected data specifically on the intake of 'vitamin E' from food supplements.

The majority of the national food consumption surveys covered by this data collection relied on 24-h recalls, sometimes in combination with food frequency questionnaires (FFQs), food propensity questionnaires (FPQ) or food records to assess dietary intake. Intakes were reported in mg of *α*-tocopherol or mg of *α*-TEs[11] (see **Section 3.3.3** and Annex D).

[7]Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. OJ L 304, 22.11.2011, p. 18–63.

[8]https://www.efsa.europa.eu/en/people/fpmembers.

[9]https://www.efsa.europa.eu/sites/default/files/dcmfoodconsnetworklist.pdf.

[10]Working Group consisting of representatives of 27 EU Member States and Norway.

[11]Results from one survey which reported intakes in mg of 'total vitamin E' not further specified were excluded.

Food composition data

The Mintel GNPD was used as a data source to identify the type and content of food supplements and fortified foods containing added *α*-tocopherol, available on the EU market. The search was conducted in December 2022, and was limited to the 5 years before, i.e. between December 2017 and December 2022 (**Section 3.3.1**). The Panel notes that this search allows to capture the products that were newly introduced on the market and the products for which the packaging was changed during that period. Therefore, the information collected is indicative and does not represent a comprehensive overview of the products available on the market.

The following search strategy was applied:

- *Food supplements*: products belonging to Mintel category 'vitamins and dietary supplements', which reported 'vitamin E' on their nutrition declaration and reported an authorised form of *α*-tocopherol (**Table 4**) in their ingredient list, were selected. Food supplements that contained mixtures of tocochromanols were excluded as the *α*-tocopherol content could not be identified (ca. one-third of the products identified through the search).
- *Fortified foods*: a search for foods and beverages with 'vitamin E' in both the nutrition declaration and the ingredient list was performed, under the assumption that these were products fortified with α-tocopherol. Products for which the source of 'vitamin E' was identified to be seed or vegetable oil from the ingredient list were excluded as these are natural sources of mixed tocopherols and the proportion of α-tocopherol is unknown.
- Products retrieved through these searches, which contained tocopherols used as additives (labelled as E306, E307, E308, E309, 'antioxidants'), were excluded from the data sets.

Regulation (EC) No 1925/2006[12] on addition of nutrients to foods requires food manufacturers to label vitamin E content in mg 'vitamin E'. As *α*-tocopherol (free and esters) is the only tocochromanol authorised for addition to food (**Table 4**), *α*-tocopherol was assumed to be the predominant form in the fortified foods identified through the search and the doses reported were assumed to refer to mg *α*-tocopherol.

Directive 2002/46/EC[13] on addition of nutrients to food supplements requires to label vitamin E content in mg *α*-tocopherol equivalents (mg *α*-TE). As described above, food supplements that contained mixtures of tocochromanols were excluded. Thus, doses that were expressed in mg *α*-TE on the label of the products retrieved through the search were assumed to correspond to mg *α*-tocopherol.

2.3.2 | Methodologies

2.3.2.1 | *Intake data calculated by EFSA in 2015*

EFSA's intake estimates were calculated by matching the food intake data from the Comprehensive Database and the food composition data from the FCDB as available in 2015 (EFSA NDA Panel, 2015) (**Section 3.3.2**).

Food composition data from Finland, France, Germany, Italy, the Netherlands and Sweden were used for the estimations. 'Vitamin E' content in food was reported as mg *α*-tocopherol in the national composition databases of Finland and Sweden, while the national databases of France, Germany, Ireland, Italy, Latvia and the Netherlands reported contents as mg *α*-TEs.[14] For nutrient intake estimates of Ireland and Latvia, food composition data from the UK and Germany, respectively, were used, because no specific composition data from these countries were available. The percentage of borrowed values in the *α*-TE data sets of the FCDB varied between 12% and 92%, 35%–56% of these values being from Germany. The average values of the food contents in the Finnish and Swedish databases were used to calculate *α*-tocopherol intake in France, Germany, Italy and the Netherlands. To determine *α*-TEs intake in Finland and Sweden, the average values of the food contents in France, Germany, Italy and the Netherlands were used.

Data on intake estimates for infants (≥ 4 to < 12 months), which were not in the remit of the DRV Opinion from 2015, have been added to the present assessment. The methodology applied to estimated intakes in this population group is the same as for the other age groups.

2.3.2.2 | *Other data sources*

Data on *α*-tocopherol intakes from recent national food consumption surveys, including specific estimates of *α*-tocopherol intake from food supplements and/or fortified foods (as described in **Section 2.3.1.2**), were extracted (**Section 3.3.3**).

Information on food products fortified with *α*-tocopherol and *α*-tocopherol-containing supplements available on the EU market, and their *α*-tocopherol content as reported on the label was extracted from the Mintel GNPD (**Section 3.3.1**).

[12]Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26–38.

[13]Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51–57.

[14]The factors applied to convert the tocopherols and tocotrienols contents into *α*-TEs in these databases were not available.

These data were used qualitatively to describe the types of fortified foods and food supplements available and to gain insight into their potential contribution to total *α*-tocopherol intake.

2.4 | Public consultation

In line with EFSA's policy on openness and transparency, and for EFSA to receive comments from the scientific community and stakeholders, the draft Scientific Opinion was released for public consultation from 13 May to 9 June 2024. The outcome of the public consultation was described in a technical report published as Annex to the Scientific Opinion.

3 | ASSESSMENT

3.1 | Chemical forms

The term tocochromanols encompasses the four tocopherols and four tocotrienols synthesised by plants. These molecules have similar ring structures: trimethyl (*α*-), dimethyl (*β*- or *γ*-) and monomethyl (*δ*-) chromanols. Tocopherols have a phytyl side chain, while tocotrienols have an unsaturated side chain. The hydroxyl group on the chromanol ring is necessary for the antioxidant function (Burton & Ingold, 1981).

The human dietary requirement for vitamin E is met only by *α*-tocopherol, not other tocochromanols (EFSA NDA Panel, 2015; IOM, 2001).

The chemical synthesis of *α*-tocopherol results in an equimolar mixture of all eight stereoisomers (**Figure 2**). Half of the stereoisomers of *all racemic* (*all rac)*-*α*-tocopherol are in the 2*R*-conformation (*RRR*-, *RSR*-, *RRS*- and *RSS*-), while half are in the 2S-conformation (*SRR*-, *SSR*-, *SRS*- and *SSS*-) (Weiser & Vecchi, 1981). All the stereoisomers have equivalent antioxidant activities, are equally well absorbed in the intestine, but only the 2*R*-forms have vitamin E biologic activity (**Section 1.4**).

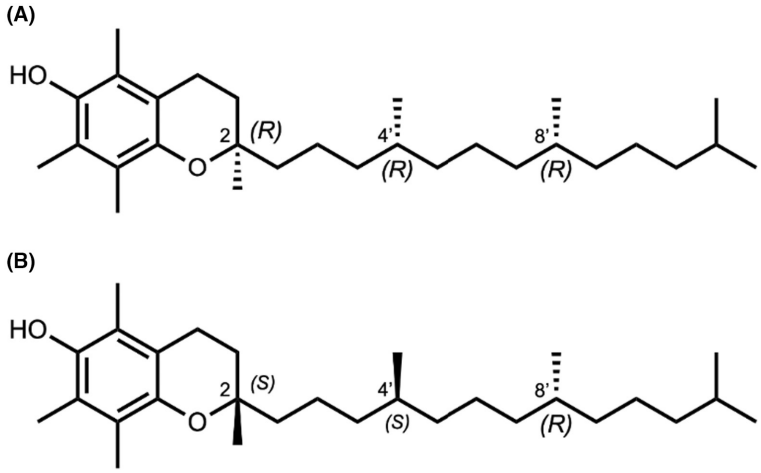

FIGURE 2 Chemical structure of different *α*-tocopherol forms.
Note: A: Natural α-tocopherol (i.e. RRR-α-tocopherol). RRR refers to R-conformation at the 2, 4 and 8 positions; B: Synthetic α-tocopherol (e.g. SSR-α-tocopherol). SSR refers to S-conformation at the 2, 4 and R- conformation at the 8 positions. Synthetic (all rac-) α-tocopherol include half of the stereoisomers in the 2R-conformation (RRR-, RSR-, RRS- and RSS-), and half in the 2S-conformation (SRR-, SSR-, SRS- and SSS-).

With regard to nomenclature, '*d*' stands for dextrorotatory and '*l*' stands for levorotatory; which means that the plane of polarised light rotates clockwise or anticlockwise, respectively, when it passes through a pure solution of the compound of interest. Originally, *RRR*-*α*-tocopherol isolated from plant oil was labelled '*d*'. The initial chemical *α*-tocopherol synthesis used phytol of plant origin and a chemically synthesised chromanol group, such that the tail bonded to the ring with half of the molecules in the 2*R*-conformation (*RRR*-) and half in the 2S-conformation (*SRR*-)- this compound was called '2-ambo' and labelled for commerce as '*dl*' because it no longer rotated light. Subsequently, chemically synthesised phytol was used for chemical *α*-tocopherol synthesis. The product was an equimolar racemic mixture of all eight possible stereoisomers and was called *all rac*-*α*-tocopherol but was labelled for commerce as '*dl*' because the biological effects of *all rac*- and ambo-*α*-tocopherols were indistinguishable (Weiser & Vecchi, 1981).

In the EU, *RRR-α*-tocopherol, *all rac-α*-tocopherol, *RRR-α*-tocopheryl acetate, *all rac-α*-tocopheryl acetate and *RRR-α*-tocopheryl acid succinate may be added to foods and food supplements, whereas 'mixed tocopherols'[15] and 'tocotrienol tocopherol'[16] may be added to food supplements only (Table 4).

TABLE 4 Forms of vitamin E authorised as nutrient sources in the EU.

Forms[a]	Addition to foods *regulation (EC) 1925/2006*[17]	Food supplements *directive 2002/46/EC*[18]
D-alpha-tocopherol	X	X
DL-alpha-tocopherol	X	X
D-alpha-tocopheryl acetate	X	X
DL-alpha-tocopheryl acetate	X	X
D-alpha-tocopheryl acid succinate	X	X
Mixed tocopherols	–	X
Tocotrienol tocopherol	–	X

[a]D-corresponds to the natural (*RRR-*) form; DL- corresponds to the synthetic (*all rac-*) form.

3.2 | Absorption, distribution, metabolism and excretion (ADME)

3.2.1 | Absorption

The absorption of *α*-tocopherol and other tocochromanols, like for other lipid compounds, involves non-specific transporters in the small intestine. Dietary tocochromanols, along with bile acids and products of fat digestion, are incorporated into mixed micelles, and the contents are taken up by intestinal enterocytes. *α*-Tocopheryl esters must be hydrolysed by pancreatic esterases to release *α*-tocopherol for incorporation into micelles. The *α*-tocopherol absorption rates, when administered either as free *α*-tocopherol or the ester forms, are similar (Cheeseman et al., 1995).

Tocochromanol uptake into intestinal enterocytes is facilitated by several transporters including Niemann-Pick C1 like 1 (NPC1L1), scavenger receptor class B type I (SR BI), cluster of differentiation 36 (CD36) and ATP-binding cassette A1 (ABCA1). Upon entry into enterocytes, tocochromanols and other fat-soluble compounds accumulate in lipid droplets. Tocochromanols in lipid droplets coalesce with nascent chylomicrons through the apolipoprotein B48 pathway. Chylomicrons are then secreted into the lymph for subsequent delivery to the circulation. Tocochromanols take a prolonged time (9–12 h) from being consumed for maximal concentrations to enter the circulation, a process that is promoted by a subsequent meal (Traber et al., 2019). This multistep process over time allows additional triacylglycerides and various fat-soluble compounds, including tocochromanols, to be incorporated into chylomicrons.

Based on a review of available data, the Panel previously considered that the average *α*-tocopherol absorption from a usual diet would be about 75% (EFSA NDA Panel, 2015). This was based on the means observed in two balance studies (75% and 69%) (Kelleher & Losowsky, 1968; MacMahon & Neale, 1970) and in a kinetic study using radioactive *α*-tocopherol and multi-compartmental modelling (81%) (Novotny et al., 2012). A more recent study using a dual-isotope method in healthy women estimated an average absorption of 55% of the oral dose (Traber et al., 2019). The unabsorbed oral *α*-tocopherol dose was excreted in the faeces.

3.2.2 | Distribution

3.2.2.1 | *Hepatic α-tocopherol secretion and lipoprotein transport*

Although all dietary tocochromanols are absorbed and delivered to the liver via chylomicrons remnants, only 2*R-α*-tocopherol is preferentially secreted from the liver. The hepatic *α*-TTP participates in a multistep process that results in plasma lipoprotein enrichment in *α*-tocopherol (Arai & Kono, 2021). *α*-TTP binds 2*R-α*-tocopherol with the highest affinity compared to other tocochromanols (Hosomi et al., 1997). It is responsible for the preferential incorporation of 2R-*α*-tocopherol into nascent lipoproteins (Traber et al., 1990). Specifically, 2*R-α*-tocopherol is transferred by *α*-TTP to the plasma membrane and by ABCA1 to an external lipoprotein acceptor, such as circulating nascent high-density or very

[15]Defined in Annex II of Directive 2002/46/EC as: alpha-tocopherol < 20%, beta-tocopherol < 10%, gamma-tocopherol 50%–70% and delta-tocopherol 10%–30%.

[16]Defined in Annex II of Directive 2002/46/EC as: typical levels of individual tocopherols and tocotrienols: 115 mg/g alpha-tocopherol (101 mg/g minimum), 5 mg/g beta-tocopherol (< 1 mg/g minimum), 45 mg/g gamma-tocopherol (25 mg/g minimum), 12 mg/g delta-tocopherol (3 mg/g minimum), 67 mg/g alpha-tocotrienol (30 mg/g minimum), < 1 mg/g beta-tocotrienol (< 1 mg/g minimum), 82 mg/g gamma-tocotrienol (45 mg/g minimum), 5 mg/g delta-tocotrienol (< 1 mg/g minimum).

[17]Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. *OJ L 404, 30.12.2006, p. 26–38*.

[18]Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. *OJ L 183, 12.7.2002, p. 51–57*.

low-density lipoproteins (HDL or VLDL). Defective or absent *α*-TTP causes rapid *α*-tocopherol excretion from the body (Traber et al., 1994), which results in vitamin E deficiency in both humans and animals (**Section 3.2.4.3**).

Plasma lipoproteins can contain tocochromanols released during the lipolysis of intestinally derived triacylglycerol-rich chylomicrons. Thus, during the post-prandial period, the plasma lipoproteins can contain a variety of tocochromanols. However, the liver-secreted, nascent triacylglycerol-rich VLDL preferentially contain 2*R*-*α*-tocopherol (Burton et al., 1998; Traber et al., 1990). These VLDL can also undergo lipolysis in the circulation, causing *α*-tocopherol to be distributed to circulating low-density lipoproteins (LDL) and HDL, respectively (Traber et al., 2019). This VLDL-enrichment process is repeated multiple times and enriches the plasma lipoproteins with 2*R*-*α*-tocopherol for delivery to tissues. Moreover, the entire plasma *α*-tocopherol pool is replaced daily because of the continued re-secretion from the liver of VLDL containing *α*-tocopherol (Traber et al., 1994).

3.2.2.2 | *Distribution to tissues*

The processes for tissue *α*-tocopherol acquisition include: (1) direct transfer to tissue membranes mediated by lipoprotein lipase during lipolysis of triacylglyceride-rich lipoproteins (chylomicrons and VLDL); (2) receptor-mediated uptake of LDL by the LDL receptor (or other receptors that recognise apoB or apoE); (3) receptor-mediated uptake of HDL by the SR-B1 or CD36 receptors; and (4) tocochromanols transfer from tocochromanol-rich lipoproteins to tocochromanol-poor membranes.

There are currently no data to suggest that any tissue serves as a storage site for *α*-tocopherol for its release on demand. Thus, tissues acquire *α*-tocopherol by non-specific lipid- or lipoprotein-dependent mechanisms that also deliver peroxidisable fats, but it is not known how the tissues release or secrete *α*-tocopherol. To study tissue concentrations relative to dosing, a 1:1 ratio of *RRR*- and *all rac*-*α*-tocopheryl acetates, labelled with different amounts of deuterium, were consumed by humans and the tissue concentrations and the labelled ratios measured (Burton et al., 1998). The ratio of *RRR*-:*rac*- measured in human tissues was 2:1, supporting that only 2*R*-*α*-tocopherols are retained by the body (Burton et al., 1998).

Adipose tissue contains most of the total body pool of *α*-tocopherol (Novotny et al., 2012; Traber & Kayden, 1987). Changes in adipose tissue *α*-tocopherol concentrations take years. In adults, Handelman et al. (1994) found that adipose tissue *α*-tocopherol concentration increased (10%–60% according to subjects) with 800 mg/day *all rac*-*α*-tocopherol supplementation for 1 year compared with before supplementation, but that it did not decrease after 1 year of discontinuation of the supplement. Adipose tissue *α*-tocopherol concentrations are depleted during vitamin E deficiency (Kayden et al., 1983) or during oxidative damage (burn injury) (Traber et al., 2010), and reflect depletion of peripheral nerve *α*-tocopherol concentrations (Traber et al., 1987).

3.2.3 | Catabolism and excretion

Tocochromanols undergo catabolism in the liver to water-soluble catabolites, which are excreted in the urine and bile. More than 90% of *α*-tocopherol catabolism to urinary *α*-carboxyethyl hydroxychroman (*α*-CEHC) in humans takes place in the liver (Traber et al., 2019). This catabolic process is initiated by cytochrome P450-4F2 (CYP4F2), which catalyses the ω-hydroxylation of the terminal methyl group of the tocochromanol side chain to 13′-hydroxychromanol. In murine models, this oxidation has been found to be the rate-limiting step in tocochromanol catabolism and excretion (Bardowell et al., 2012).

Truncation of the side chain then occurs by conversion of the 13′ hydroxychromanol to the 13′-carboxychromanol (COOH), followed by *β*-oxidation, ultimately yielding carboxyethyl hydroxychroman (CEHC) (Schubert et al., 2018). The shorter chain carboxychromanols generated by the *β*-oxidation process are largely conjugated with sulfate or glucuronic acid by the action of UDP-glucuronosyltransferase and are excreted in urine. Advances in analytical techniques have allowed detection of several conjugated forms, including *α*-CEHC-glucuronides, sulfates, glycine and taurine (Johnson et al., 2012).

α-Tocopherol is a relatively poor substrate for the CYP4F2-initiated ω-oxidation pathway compared to other dietary tocochromanols. Thus, tocochromanol catabolism by CYP4F2 complements *α*-TTP function in promoting preferential *α*-tocopherol retention and excretion and catabolism of other tocochromanols. Also, the *RRR*- compared with the *all rac*-*α*-tocopherol configuration is partially protected from degradation. In humans ($n = 6$) supplemented with 150 mg each d_3-*RRR*- and d_6-*all rac*-*α*-tocopheryl acetates, at 24 h post-dose the plasma d_3-*RRR*-*α*-tocopherol (4.1 ± 1.1 μmol/L) was double the d_6-*α*-tocopherol concentration (1.8 ± 0.5 μmol/L). By contrast, the total *α*-CEHC excreted over 9 days was greater from the d_6-*all rac*-*α*-tocopheryl acetates: d_6-*α*-CEHC (1.68 ± 0.03 μmol) compared with d_3-*α*-CEHC (0.65 ± 0.12 μmol) (Traber et al., 1998). Notably, the amount excreted was small relative to the administered dose. More recent studies showed similar results, when an oral 30 mg deuterated *α*-tocopheryl acetate dose was used to estimate catabolism and urinary excretion ($n = 10$). The excretion was estimated to be 0.7% (0.4%–0.9% median, range) of the oral dose, while the daily unlabelled *α*-CEHC excreted was 1.2 ± 0.3 μmol/g creatinine. Over 72 h only ~2% of the oral dose was found to be excreted in urine and ~5% in faeces (Traber et al., 2021). Similar quantitative excretion values had been found in a previous study (Lebold et al., 2012).

The Panel notes that although some *α*-tocopherol catabolism takes place in the intestine or the kidney, most catabolism takes place in the liver, where *α*-tocopherol is catabolised to long-chain carboxy-catabolites and, ultimately, *α*-CEHC. Notably, a relatively small fraction (< 3%) of supplemental *α*-tocopherol has been found to be excreted as *α*-CEHC in urine and faeces (**Figure 3**).

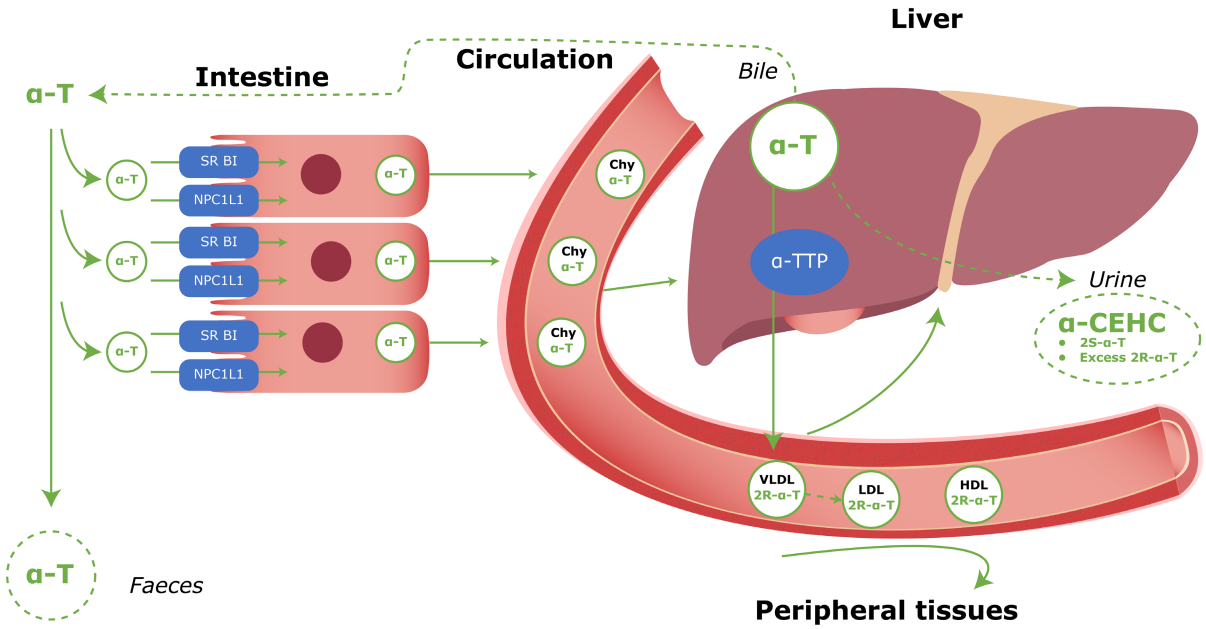

FIGURE 3 Pathways of *α*-tocopherol absorption, distribution, metabolism and excretion. *α*-T, *α*-tocopheroxyl radical; *α*-TTP, *α*-tocopherol transfer protein; CEHC, Carboxyethyl-hydroxychroman; CM, Chylomicron; HDL, high-density lipoproteins; LDL, low density lipoproteins; VLDL, very low-density lipoproteins.
Figure Legend: *α*-tocopherol in the presence of products from lipid digestion by biliary and pancreatic secretions is incorporated into mixed micelles. A portion is absorbed into enterocytes and the remainder excreted in the faeces. Enterocytes secrete *α*-tocopherol-containing chylomicrons (Chy) into the lymphatics, and following transit in the circulation, acquisition of apolipoprotein E and partial lipolysis, the chylomicron remnants are taken up by the liver. Hepatic *α*-tocopherol (*α*-T) has several possible fates: (i) *α*-TTP can facilitate its transfer to lipoproteins (e.g. VLDL, HDL) that transport *α*-T to and from the periphery; (ii) *α*-T can be excreted in bile; (iii) *α*-T can be catabolised to *α*-CEHC, which can be excreted in bile for faecal excretion, or secreted into plasma, transported to the kidney and excreted in urine; (iv) *α*-T can be oxidised by a peroxyl radical, but this is likely rapidly reduced to *α*-T by other antioxidants, such as ascorbate (v) *α*-T may remain in the liver in triacylglyceride droplets.

3.2.4 | Factors affecting the ADME of vitamin E

3.2.4.1 | *Age*

Infants

The newborn infant has low circulating *α*-tocopherol concentrations compared to older infants or adults (Bolisetty et al., 2002; Kelly et al., 1990; Ostrea Jr. et al., 1986). These concentrations are at or below 11 μmol/L in cord blood from infants compared with mothers' serum at 33 μmol/L (Didenco et al., 2011). The low cord total lipids (cholesterol plus triacylglcerides) in the infants (2 ± 0.5 mmol/L) compared with the mothers (8 ± 1 mmol/L) likely accounts for the low cord *α*-tocopherol concentrations (Didenco et al., 2011). Similar findings were reported using deuterated *α*-tocopherols given to pregnant women and measured in cord blood (Acuff et al., 1998).

In term neonates, plasma *α*-tocopherol concentrations increase rapidly during the first few weeks of feeding (González-Corbella et al., 1998; Ostrea Jr. et al., 1986; Phelps & Dietz, 1981). Irrespective of whether the infants were fed breast milk or infant formula, mean plasma concentrations increased from 13 μmol/L at 1 week to 27 μmol/L within 1 month (González-Corbella et al., 1998). Furthermore, studies in pigs fed deuterated *α*-tocopherol showed that the transfer from the sows to the piglets was undetectable at birth, as were fetal tissue concentrations of labelled *α*-tocopherol concentrations. Tissue deuterated *α*-tocopherol concentration increased substantially after 1 week of consuming labelled mother's milk (Lauridsen et al., 2002).

Stone et al. (2003) investigated the bioavailability of natural versus synthetic vitamin E among infants. Within 8 days after birth, term infants were randomly assigned to consume a formula containing 20 IU natural vitamin E (14.5 mg/L *RRR*-*α*-tocopheryl acetate)/L (HNF group; *n* = 26), 10 IU natural vitamin E (7.3 mg/L *RRR*-*α*-tocopheryl acetate)/L (LNF group; *n* = 25) or 13.5 IU synthetic vitamin E (13.5 mg/L *all rac*-*α*-tocopheryl acetate)/L (SF group; *n* = 26). At 1 month of age, mean plasma *α*-tocopherol concentrations in the respective groups were 29 μmol/L, 25 μmol/L and 25 μmol/L. In a reference group of 29 breastfed infants, the mean plasma *α*-tocopherol concentration was 18 μmol/L. Thus, natural (*RRR*-) *α*-tocopherol administered at 7.3 mg/L (LNF group) resulted in a plasma *α*-tocopherol concentration comparable to that obtained with twice the concentration of synthetic (*all rac*-) *α*-tocopherol (13.5 mg/L, SF group), indicating higher bioavailability of *RRR*-*α*-tocopherol. The amounts of 2*R*-tocopherol isomers delivered by the formula were similar (LNF group: 6.7 mg/L; SF group:

6.1 mg/L). When expressed as mg 2*R*-tocopherol isomers consumed/d, *α*-tocopherol intakes correlated with plasma *α*-tocopherol in this study population.

Data in animals and humans suggest that the ability of the infant to discriminate between *α*-tocopherol stereoisomers is present before birth (Acuff et al., 1998), with evidence for higher bioavailability of *RRR*-*α*-tocopherol than *all rac*-*α*-tocopherol in early life (Dersjant-Li & Peisker, 2010; Stone et al., 2003). These outcomes are consistent with findings in rats, which showed that the expression of hepatic *α*-TTP was very low in the rat pups immediately after birth but increased steadily during the first weeks of life and reached adult liver levels by 4 weeks (Kim et al., 1996; Tamai et al., 1998). During the same period, a gradual increase in the plasma ratio of *α*- to *γ*-tocopherol was observed, which seemed to correlate with the increase in the hepatic expression of *α*-TTP.

Children

Reference ranges of *α*-tocopherol in plasma, red blood cells and adipose tissue were reported to be relatively constant between 0 and 18 years of age. Reference ranges were 11.9–30 μmol/L in plasma, 2.0–7.8 μmol/L in red blood cells (RBC) and 60–573 nmol/g in adipose tissue (Cuerq et al., 2016). The HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) study, a cross-sectional evaluation of 3528 (1845 females) adolescents from 9 European countries aged 12.5–17.5 years reported plasma *α*-tocopherol average concentrations of 9.9 ± 2.1 μg/mL (equivalent to 23.0 ± 4.9 μmol/L). Deficient plasma *α*-tocopherol concentrations (< 12 μmol/L) were identified in only 5% of the population (Moreno et al., 2014).

Older adults

To evaluate *α*-tocopherol pharmacokinetics in younger (mean ± SD age: 32 ± 7 year; $n = 12$ women and 9 men) and older (aged 67 ± 8 year; $n = 8$ women and 12 men) adults, participants consumed deuterium-labelled collard greens (Zhu et al., 2022). Baseline plasma *α*-tocopherol concentrations were higher in older [28.3 ± 11.7 μmol/L (women), 24.8 ± 8.6 (men)] than younger [18.7 ± 4.8 μmol/L (women), 21.6 ± 5.7 (men)]) participants, as were total cholesterol concentrations. However, there were no differences in time of maximum plasma-labelled *α*-tocopherol concentrations, half-lives or estimated absorption between genders, or between ages. A similar lack of effect of age on pharmacokinetic parameters were also reported in 10 men (aged 20–75 years), using 30 mg each d_6-*RRR*- *α*- and d_2-g-tocopheryl acetates (Brigelius-Flohé et al., 2004).

In the Lifelines-MINUTHE study, urine and plasma samples were collected from 1519 participants (60–75 years, males: 50%) for the assessments of urinary *α*- and *γ*-CEHC/creatinine ratios and 24 h urinary excretions of *α*- and *γ*-CEHC, plasma *α*- and *γ*-tocopherols, along with dietary 'vitamin E' assessment. Plasma *α*-tocopherol was positively correlated with 24-h urinary excretion of *α*-CEHC. Dietary 'vitamin E' intake (expressed as *α*-TE) was positively correlated with the sum of 24-h urinary *α*- and *γ*-CEHC excretions (Zhu et al., 2022).

The panel notes that data on the maturation of the mechanisms involved in *α*-tocopherol absorption, metabolism and excretion during infancy are limited. Collectively, available data in humans and animals suggest that these mechanisms develop quickly after birth and are fully developed within the first months of life. The panel also notes that available data do not indicate an effect of age on *α*-tocopherol pharmacokinetics. Little information is available concerning vitamin E catabolism during aging.

3.2.4.2 | *Interactions with vitamin K*

Studies in animals have shown that high dietary *α*-tocopherol can lead to impaired coagulation (Frank et al., 1997). Specifically, fatal haemorrhaging was associated with excess dietary vitamin E (Takahashi et al., 1990) and was prevented with vitamin K supplementation (Frank et al., 1997). In rat experiments, a reduction of phylloquinone and menaquinone-4 (MK-4) concentrations in extra-hepatic tissues was found in animals administered excess *α*-tocopherol via diets or subcutaneous injection, compared to controls (Tovar et al., 2006). In healthy humans, high-dose *α*-tocopherol supplements (1000 mg/day *RRR*-*α*-tocopherol) for 12 weeks increased concentrations of Proteins Induced by Vitamin K Absence (PIVKA-II, the inactive under-*γ*-carboxylated forms of prothrombin) to concentrations indicative of poor vitamin K status (Booth et al., 2004).

Both *α*-tocopherol and phylloquinone (vitamin K1) are fat-soluble vitamins and share similar side chains. The two vitamins undergo some common processes at the level of intestinal absorption, transport, catabolism and excretion. Specifically, data suggest that the intestinal cholesterol transporter NPC1L1, which is involved in *α*-tocopherol absorption (**Section 3.3.1**), also mediates the absorption of vitamin K (Takada et al., 2015). Both vitamins are delivered to the liver in chylomicrons, where *α*-TTP mediates the secretion of *α*-tocopherol into the plasma (triglyceride-rich fractions) for distribution to tissues. No similar proteins facilitate hepatic vitamin K secretion (Hagstrom et al., 1995). Hepatic catabolism of the vitamins involves similar xenobiotic processes including: (1) phase I enzymes, or cytochrome P450s (CYP 4F2), responsible for their omega-oxidation; (2) phase II enzymes responsible for their conjugation to enhance water solubility; and (3) phase III transporters responsible for their movement into and out of tissues and their excretion in the bile or urine. Further, the first step in the catabolism of both vitamins involves their ω-hydroxylation by the phase I enzyme human CYP4F2 (McDonald et al., 2009; Sontag & Parker, 2002), then they are catabolised to tail-shortened, carboxy-compounds (Birringer et al., 2002; Harrington et al., 2005).

Low vitamin K status is prevalent in Western populations. In a nationally representative sample of 1154 British individuals aged 19–64 years from the 2000–1 National Diet and Nutrition Survey (Thane et al., 2006), plasma phylloquinone concentration ranged from ≤ 0.04 to 18.61 nmol/L, with a lower maximum of 13.25 nmol/L in men. 'Sub-optimal' plasma phylloquinone concentrations, defined as < 0.33 nmol/L, were found in 13% of participants, with a higher prevalence among women

than men (17% vs. 8%) and 2% of the participants had concentrations below the lower limit of quantification (0.02 nmol/L). In the Multiethnic Study of Atherosclerosis in the US, 25% participants had nearly undetectable serum phylloquinone concentrations (< 0.1 nmol/L) (Shea et al., 2013).

The Panel notes that excess intake of *α*-tocopherol (and other tocochromanols) may affect vitamin K status.

3.2.4.3 | *Genetics*

Mutations in the *TTPA* gene, which codes for *α*-TTP, cause a rare familial disorder known as ataxia with isolated vitamin E deficiency (AVED) (EFSA NDA Panel, 2015). Absorption and vascular transport of *α*-tocopherol are normal in these patients, whereas its release from the liver into circulation is defective, resulting in low plasma *α*-tocopherol concentrations and inadequate distribution of the vitamin to peripheral tissues. Concerns regarding this condition relate to vitamin E insufficiency rather than excess. Genetic variations in TTPA in persons among participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial only modestly affected serum *α*-tocopherol (Wright et al., 2009).

Other *α*-tocopherol binding proteins have been identified in humans. These include the tocopherol associated protein (TAPs), namely TAP1/SEC14-like 2 protein (SEC14L2; synonymously, supernatant protein factor, SPF), TAP2/SEC14L3 and TAP3/SEC14L4. However, current knowledge on the role of these proteins and their physiological relevance is limited. In silico search for single nucleotide polymorphisms found few polymorphisms in genes coding for these proteins, suggesting that they are unlikely to be critical factors of heterogeneity in the effects of *α*-tocopherol (Döring et al., 2004). The CRAL-TRIO motif is common to several lipid-binding proteins including cellular retinaldehyde binding protein (CRALBP), *α*-TTP, yeast phosphatidylinositol transfer protein (Sec14p) and SPF; however, based on ligand affinity constant, only *α*-TTP is likely to serve as the physiological mediator of the biological activity of *α*-tocopherol (Panagabko et al., 2003). Proteins involved in drug/lipid metabolism (e.g. members of the cytochrome P450 family, lipoprotein lipase) are more likely to influence inter-individual variation in responses to *α*-tocopherol intake. Polymorphisms in the CYP4F2 gene have also been reported (Caldwell et al., 2008; Chen et al., 2016; McDonald et al., 2009). Genome-wide association studies (GWAS) have identified genetic polymorphisms associated with differential responses to vitamin E supplementation (Major et al., 2011; Major et al., 2012; Major et al., 2014; Xu et al., 2022). However, at present, data are lacking on whether specific polymorphisms may be important determinants for the adverse effects of excess vitamin E intake.

There are also reported differences in the catabolism of tocochromanols between males and females (Frank et al., 2008; Kalsotra et al., 2002; Traber et al., 2017; Zhu et al., 2022). However, their relevance in terms of the health effects of the vitamin requires further investigation.

Mechanistic studies show that NPC1L1 is involved in tocopherol absorption **(Section 3.2.2)**. NPC1 defects cause a neurodegenerative disease, including ataxia. However, humans with NPC1 defects did not have altered plasma tocopherol or cholesterol levels, but elevated lysosomal storage of both was observed (Lee & Hong, 2023; Ulatowski et al., 2011).

The Panel considers that further research is needed regarding polymorphisms in genes involved in *α*-tocopherol absorption, distribution, metabolism and functions and their impacts on health and adverse effects of excess vitamin E intake.

3.2.4.4 | *Specific conditions causing vitamin E deficiency*

Some disorders such as AVED (**Section 3.2.4.3**) (Traber & Head, 2021), genetic defects in lipoprotein metabolism (Bredefeld et al., 2022; Zamel et al., 2008), cholestatic liver disease (Sokol et al., 1983; Veraldi et al., 2020) and cystic fibrosis (Farrell et al., 1977) can result in vitamin E deficiency. Large *α*-tocopherol supplements (grams per day) are required for the treatment of these diseases. These patients are outside the target population of the UL for vitamin E (*α*-tocopherol).

3.2.5 | Biomarkers of intake

Weak correlations have been reported between dietary *α*-tocopherol intake and plasma/serum *α*-tocopherol concentrations (EFSA NDA Panel, 2015), but these are stronger when participants consume vitamin E supplements (Ascherio et al., 1992). Plasma/serum *α*-tocopherol concentrations appear to reach a plateau (~ 3–4 times unsupplemented concentrations) when humans consume supplements (*RRR*- or *all rac*-*α*-tocopherol) containing ≥ 200 mg (465 μmol)/day (IOM, 2001). There are no established reference ranges or cut-offs of plasma/serum *α*-tocopherol concentrations associated with adverse effects. However, elevated serum *α*-tocopherol levels were reported in some patients with intracerebral haemorrhages that were suspected to be caused by the consumption of *α*-tocopherol supplements (Le et al., 2020).

As circulating *α*-tocopherol is associated with lipoproteins (**Section 3.2.3**), plasma/serum *α*-tocopherol concentrations are influenced by factors affecting plasma lipid concentrations (especially cholesterol), such as age, sex and lipid-lowering drugs. In adults, blood *α*-tocopherol concentrations have been found to increase with age (Ford et al., 2006), similar to the increase in blood cholesterol concentration (Downer et al., 2014). Reduced plasma *α*-tocopherol concentrations are reported in subjects taking cholesterol lowering drugs (statins) (Schmölz et al., 2016) and plant sterols and stanols (Baumgartner et al., 2017), but concentrations are similar between treated and untreated subjects once standardised for total cholesterol concentration. In a study on the fate of deuterium-labelled *α*-tocopherol from collard greens in younger and older adults, *α*-tocopherol half-lives were correlated with serum lipids (Traber et al., 2015). Serum lipids were 15% higher in the older group than in the younger group, while plasma *α*-tocopherol concentrations were 25% higher. These data suggest that plasma

α-tocopherol concentrations are more dependent on mechanisms that control lipoprotein metabolism and emphasise that vitamin E status cannot be assessed by using plasma α-tocopherol concentrations only. Other factors such as smoking and disease states associated with changes in α-tocopherol status can also affect plasma α-tocopherol concentrations.

Serum and urinary α-CEHC concentrations are sensitive to α-tocopherol supplementation (Huang et al., 2020; Mondul et al., 2016). Supplementation with 800 IU *RRR*-α-tocopherol (400 IU twice a day with meals) resulted in a 20-fold increase in α-CEHC, while serum α-tocopherol increased by 2.5-fold (Bartolini et al., 2021). In an experiment involving healthy, male Japanese college students (aged 18–25 years), the excretory percentage as α-CEHC was 3.7 ± 1.3, 2.3 ± 0.7, 2.3 ± 1.1 and 2.3 ± 0.6% for α-tocopherol intakes of 20, 41, 83 and 146 μmol/day, respectively (Imai et al., 2011). Overall, limited quantitative information is available on the relationship between urinary α-CEHC excretion and α-tocopherol intake and body pools, and its use has been limited to date.

3.3 | Intake assessment

3.3.1 | Source of dietary α-tocopherol

Natural sources

The highest contents of α-tocopherol are found in vegetable oils. Among other plant products, nuts and seeds are the richest sources, while smaller amounts are found in fruits and vegetables (Kornsteiner et al., 2006). Among animal products, some fatty fishes and eggs are the richest sources of α-tocopherol (Afonso et al., 2016). Meat and dairy products typically contain low amounts of α-tocopherol (Leonhardt et al., 1997).

National surveys indicate that mean α-tocopherol intakes in adults are higher in European countries (Amcoff et al., 2012; Helldan et al., 2013) than those observed in the USA (Mahabir et al., 2008; Signorello et al., 2010; Yang, Wang, Davis, Lee, Fernandez, Koo, Cho, & Chun, 2014; Yang, Wang, Davis, Lee, Fernandez, Koo, Cho, Song, & Chun, 2014), where γ-tocopherol is the most abundant tocopherol in the diet.

Food additives

Synthetic *(all rac-)* α-tocopherol is an authorised antioxidant, included in Group I of the Union list of food additives and labelled E 307.[19] Tocopherol-rich extract of natural origin (E 306), synthetic γ-tocopherol (E 308) and synthetic δ-tocopherol (E 309) are also authorised additives. Tocopherols (E 306-E 309) can be added *quantum satis*[20] to 68 food categories. Maximum levels (MLs) have been established for 'refined olive oils, including olive pomace oil' (ML = 200 mg/L), and for 'food for infants and young children', at an amount of 10 or 100 mg/kg, depending on the specific category. In the EU, α-tocopherol is the predominant tocopherol used by the food industry (EFSA ANS Panel, 2015).

Fortified foods and food supplements

The Mintel GNPD was used to extract information about fortified food and food supplements on the EU market. Forms of vitamin E authorised for addition to foods and food supplements in the EU are presented in **Table 4**. When labels did not allow to ascertain that the 'vitamin E' content reported referred to α-tocopherol only, or the actual amount was unclear, products were excluded (**Section 3.3.1**).

Fortified foods

Currently, there are no mandatory fortification policies for vitamin E (α-tocopherol) in the EU. The vitamin may be voluntarily added to foods (i.e. at the discretion of the manufacturer). EU legislation sets minimum and maximum content of α-tocopherol in infant and follow-on formulae (0.6–5 mg/100 kcal),[21] and in baby foods and processed cereal-based foods for infants and children (maximum limit = 3 mg α-TE/100 kcal).[22]

In the Mintel GNPD, a total of 1737 packaged food products available in 24 EU Member States and Norway were identified as containing added α-tocopherol. The majority of the products belonged to the Mintel categories 'juice drinks' (43%), 'dairy' (15%, includes dairy alternatives), 'nutritional drinks and other beverages' (9%), 'sugar, gum and chocolate confectionery & sugar and sweeteners (9 %), 'snacks' (8 %) and 'sports & energy drinks' (7%).

[19]Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16 and Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 083, 22.3.2012, p. 1.

[20]*'quantum satis'* shall mean that no maximum numerical level is specified and substances shall be used in accordance with good manufacturing practice, at a level not higher than is necessary to achieve the intended purpose and provided the consumer is not misled.

[21]Commission Delegated Regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding. OJ L 25, 22.2016, p. 1–29.

[22]Commission Directive 2006/125/EC of 5 December 2006 on processed cereal-based foods and baby foods for infants and young children, OJ L 339, 6.12.2006, p. 16–35.

Data on content per serving (as suggested by the manufacturer) were only available for 29% ($n = 508$) of the products. For the products of which content was reported in mg/serving, the median content of 'juice drinks' was 6 mg/serving ($n = 223$), of 'dairy' was 3.8 mg/serving ($n = 45$), of 'nutritional drinks and other beverages' was 3.95 mg/serving ($n = 30$), of 'sugar, gum and chocolate confectionery & sugar and sweeteners' was 2.1 mg/serving ($n = 42$), of 'snacks' was 4.9 mg/serving ($n = 36$) and of 'sports & energy drinks' was 5.7 mg/serving ($n = 28$). The highest α-tocopherol content declared on the label was found in some juices (13–20 mg/serving) and one protein bar (13 mg/serving).

Food supplements

In the Mintel GNPD, a total of 1159 food supplements available in 24 EU Member States and Norway were identified as containing α-tocopherol. The median dose declared on labels was 12 mg/serving.[23] About 95% of supplements contained doses ≤ 30 mg per serving, and about 2% ($n = 18$) had doses > 100 mg per serving, with a maximum of 294 mg per serving (**Figure 4**).

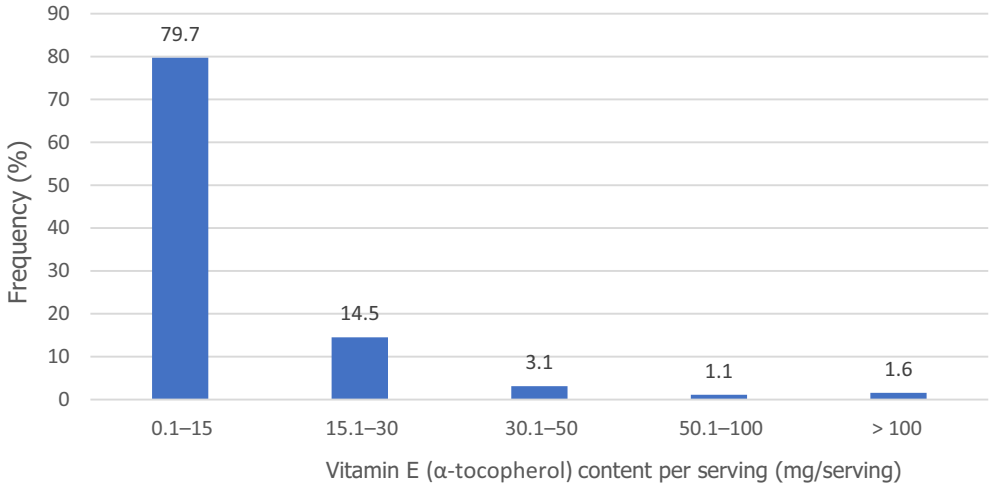

FIGURE 4 Distribution of vitamin E (α-tocopherol) content in food supplements as displayed on labels in EU Member States and Norway. *Source*: Mintel GNPD. Search for vitamin E-containing supplements available in the EU market in the last 5 years (from December 2017 to December 2022). A total of 1159 products available in 24 EU Member States and Norway were identified with complete data on dose per serving. Products which contained tocochromanols other than *A*-tocopherol or mixtures of tocochromanols were excluded. Thus, doses per serving expressed in mg *A*-TE on product labels were assumed to correspond to mg *A*-tocopherol.

3.3.2 | EFSA's intake assessment

The intakes of α-tocopherol from food sources (excluding food supplements) in European populations were calculated in the context of the scientific opinion on DRVs for Vitamin E as α-tocopherol (EFSA NDA Panel, 2015). Estimates were based on the data from the EFSA Comprehensive Database and the EFSA FCDB (**Section 2.3**).

The intake assessment did not distinguish between α-tocopherol 'naturally present' or 'added' to foods by manufacturers. No cleaning strategy was applied to exclude the contribution of fortified foods or food additives. Given the scarcity of data on the consumption of foods fortified with α-tocopherol available in the Comprehensive Database[24] and on the concentration of α-tocopherol in fortified foods available in the FCDB, the contribution of fortified foods to the intake estimates is expected to be low. In contrast, α-tocopherol is widely used as an additive (EFSA ANS Panel, 2015). As the analytical methods used to compile the FCDB cannot differentiate between α-tocopherol used as a food additive and the natural content in foods, the Panel notes that the EFSA's estimates can be considered to reflect the combined intake of α-tocopherol naturally present in foods and used as food additive across EU countries. However, the relative contribution of additives to the total estimates cannot be calculated based on available data, and there are uncertainties with respect to the representativeness of the composition data regarding the actual use of α-tocopherol as a food additive, which likely results in an underestimation of the actual exposure (see **Section 3.3.2.3**).

α-tocopherol intake is the major contributor to α-TEs intake in EU countries (EFSA NDA Panel, 2015). Given the scarcity of data regarding α-tocopherol only and related uncertainties (see below), estimates expressed in mg α-TEs/day are reported as well.

[23]The Mintel GNPD provides data on the content of supplements per serving which may not always reflect the daily dose recommended by the manufacturer.

[24]Indicatively, 2.4% of the overall eating occasions reported a fortification descriptor (e.g. 'F09.Fortification agent') in the latest version of the Comprehensive Database (updated in December 2022), of which 0.8% report a vitamin E/α-tocopherol-related fortification descriptor, for foods such as multivitamin juices and soft drinks, margarines and other vegetable fats and oils and biscuits.

3.3.2.1 | *Estimated intakes across countries and age groups*

The period of data collection covered by the surveys was from 2000 to 2012. Further information on the characteristics and methods used for the data collection in the respective surveys are provided in Annex C.

α-Tocopherol and *α*-TEs intakes estimated by EFSA are presented below by age group, sex and country of origin (Figures 5 and 6). A summary overview providing the ranges of means and 95th percentiles (P95) across EU surveys is given in Table 5 and 6.

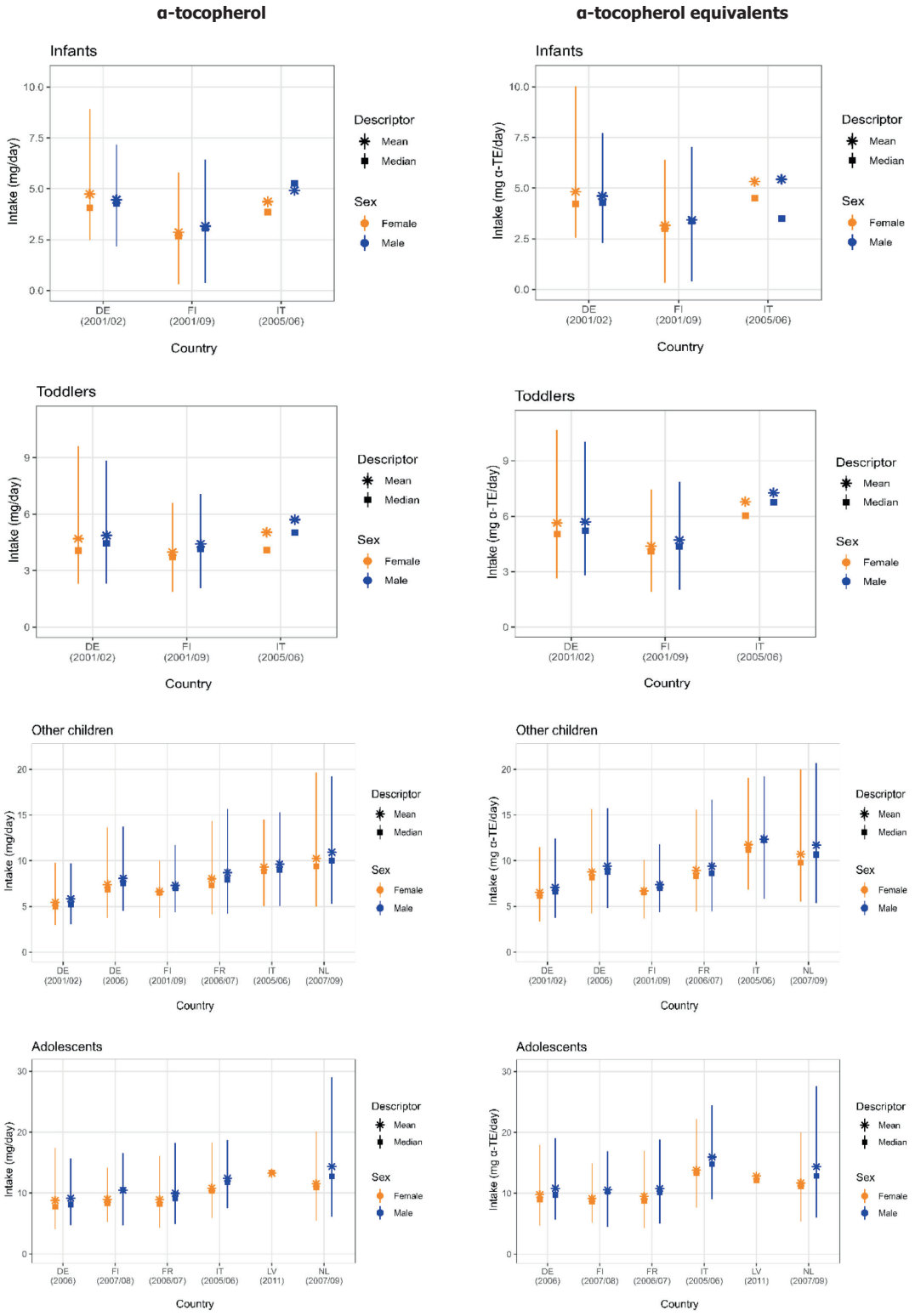

FIGURE 5 Mean, median, 5th and 95th percentiles of *α*-tocopherol and *α*-TEs intakes in infants (≥ 4 to < 12 months old), toddlers (≥ 1 year to < 3 years old), other children (≥ 3 years to < 10 years old) and adolescents (≥ 10 years to < 18 years old), by sex and country. DE, Germany; FI, Finland; FR, France; IT, Italy; LV, Latvia; NL, The Netherlands.
Note: Estimates for females in orange and for males in blue. Squares correspond to medians and stars to means. Lines represent the range between the 5th and 95th percentiles. Estimated intakes from 5th and 95th percentiles are not presented when sample size is below 60 participants.
Source: EFSA NDA Panel (2015) except for infants.

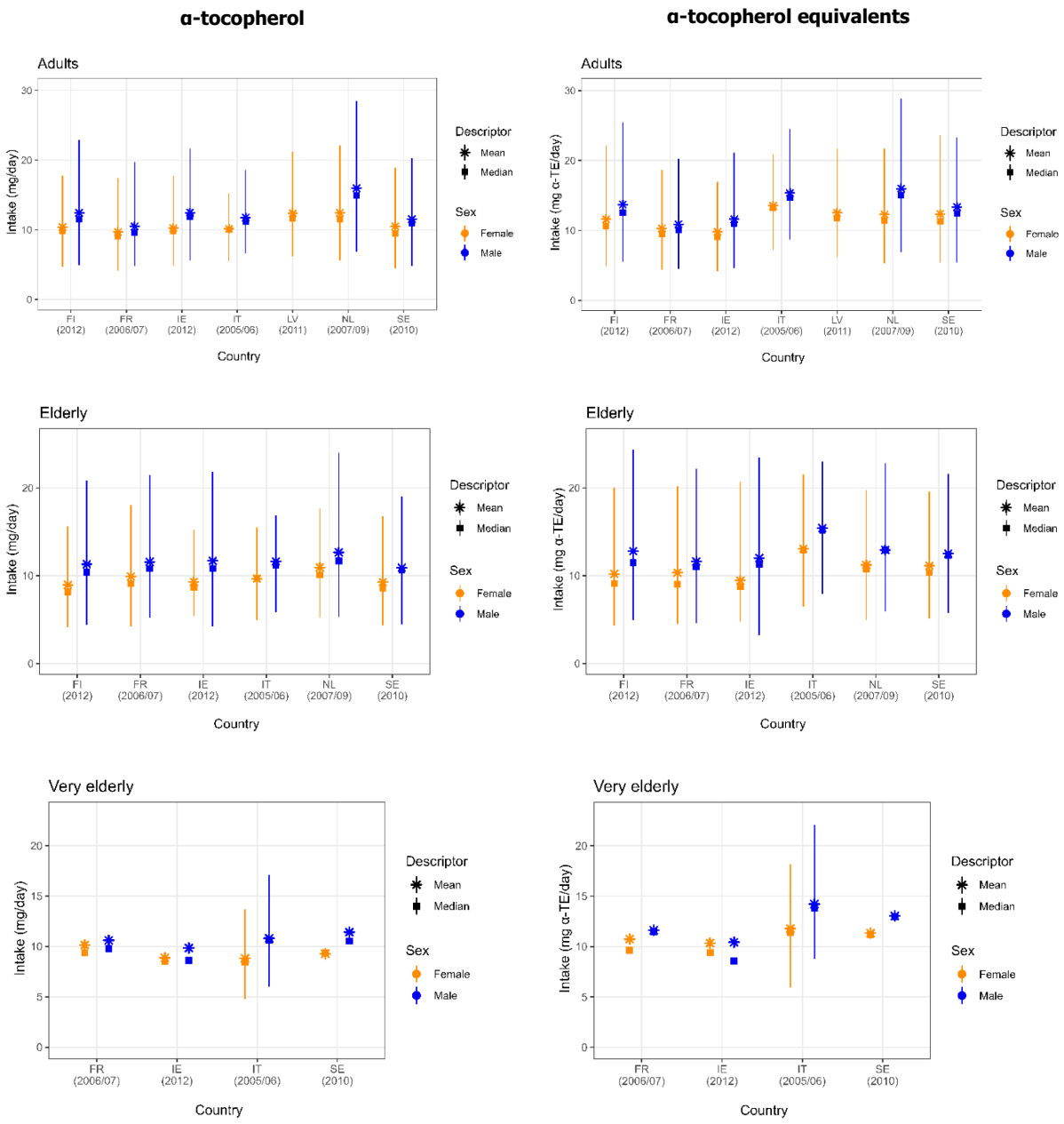

FIGURE 6 Mean, median, 5th and 95th percentiles of *α*-tocopherol and *α*-TEs intakes in adults (≥ 18 years to < 65 years), elderly (≥ 65 to < 75 years old) and very elderly (≥ 75 years old), by sex and country. FI, Finland; FR, France; IE, Ireland; IT, Italy; LV, Latvia; NL, The Netherlands; SE, Sweden.
Note: Estimates for females in orange and for males in blue. Squares correspond to medians and stars to means. Lines represent the range between the 5th and 95th percentiles. Estimated intakes from 5th and 95th percentiles are not presented when sample size is below 60 participants.
Source: EFSA NDA Panel (2015).

TABLE 5 Daily intake of *α*-tocopherol (mg/day) from food sources (supplements and fortified foods excluded) across European dietary surveys by population group.

		(mg/day)							
		Males				Females			
		Mean		P95[a]		Mean		P95[a]	
Population group, age range	N of surveys	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥ 4 to < 12 months	3	3.2	4.9	6.4	7.2	2.9	4.7	5.8	8.9
Toddlers, ≥ 1 to < 3 years	3	4.4	5.7	7.1	8.8	4.0	4.7	6.6	9.6
Other children, ≥ 3 to < 10 years	6	5.8	10.9	9.7	19.2	5.4	10.3	9.8	19.6
Adolescents, ≥ 10 to < 18 years	5	9.2	14.3	15.7	29.0	8.8	11.5	14.2	20.2
Adults, ≥ 18 to < 65 years	6	10.5	16.0	18.6	28.5	9.7	12.5	15.3	22.1
Elderly, ≥ 65 to < 75 years	6	10.9	12.7	16.9	24.0	9.0	10.9	15.2	18.1

TABLE 5 (Continued)

		(mg/day)							
		Males				Females			
		Mean		P95[a]		Mean		P95[a]	
Population group, age range	N of surveys	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Very elderly, ≥ 75 years	4	9.8	11.4	17.1[c]	17.1[c]	8.8	10.1	13.7[c]	13.7[c]
Pregnant women	1					12.4	13.2	21.2[c]	21.2[c]

Abbreviations: *N*, number; P, percentile.

Source: EFSA NDA Panel (2015) except for infants.

[a]The 95th percentile estimates obtained from dietary surveys and population groups with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently are not considered in this table.

[b]Minimum and maximum mean and 95th percentile estimates across European surveys, for each population group.

[c]Calculated only from one survey.

TABLE 6 Daily intake of *α*-TEs (mg/day) from food sources (supplements and fortified foods excluded) across European dietary surveys by population group.

		(mg *α*-TEs/day)							
		Males				Females			
		Mean		P95[a]		Mean		P95[a]	
Population group, age range	No. of surveys	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥ 4 to < 12 months	3	3.4	5.4	7.0	7.7	3.2	5.3	6.4	10.0
Toddlers, ≥ 1 to < 3 years	3	4.7	7.3	7.9	10	4.4	6.8	7.5	10.7
Other children, ≥ 3 to < 10 years	6	7.1	12.4	11.8	20.7	6.5	11.8	10.1	20.0
Adolescents, ≥ 10 to <18 years	5	10.5	15.9	16.9	27.6	9.1	13.8	14.9	22.2
Adults, ≥ 18 to <65 years	6	10.9	16.0	20.2	28.9	9.8	13.5	16.9	23.7
Elderly, ≥ 65 to <75 years	6	11.6	15.4	21.6	24.3	9.4	13.1	19.6	21.5
Very elderly, ≥ 75 years	4	10.4	14.2	22.1[c]	22.1[c]	10.3	11.8	18.1[c]	18.1[c]
Pregnant women	1					12.5	12.8	21.7[c]	21.7[c]

Abbreviations: *N*, number; P, percentile.

Source: EFSA NDA Panel (2015), except for infants.

[a]The 95th percentile estimates obtained from dietary surveys and population groups with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently are not considered in this table.

[b]Minimum and maximum mean and 95th percentile estimates across European surveys, for each population group.

[c]Calculated from one survey only.

3.3.2.2 | *Main food contributors*

The main food groups contributing to background *α*-tocopherol intake are fats and oils, grains and grain-based products and the sum of fruits and vegetables and derived products in all sex and age groups. In addition, human milk was an important source of these nutrients among infants, along with 'food products for young population'[25] for both infants and toddlers (Annex C). Minor differences could be identified between sexes in the main contributors to overall intakes.

3.3.2.3 | *Sources of uncertainty*

Sources of uncertainty specific to this intake assessment derived from the lack of harmonisation in the ways 'vitamin E' content is expressed across national composition databases (**Section 2.3.1.1**). Among countries which provided data to compile the EFSA FCDB, only two provided data on *α*-tocopherol content in foods, while the others provided data on *α*-TE, i.e. included other tocopherols and tocotrienols. The definition of *α*-TE and the conversion factors applied to the other tocochromanols were not reported. In addition, when compiler countries had data gaps, i.e. missing content values for certain foods, they substantially borrowed *α*-tocopherol and *α*-TE values from the food composition databases of other countries (**Section 2.3.1.1**). This may have resulted in an overestimation of *α*-tocopherol intake and an underestimation of *α*-TE. Overall, the estimates indicate that *α*-tocopherol is the largest contributor to *α*-TEs. This is consistent with evidence from the literature indicating that *α*-tocopherol is the most abundant form of tocochromanols present in foods consumed in Europe (**Section 3.3.1**).

[25]Infant and follow-on formulae, cereal-based- and ready-to-eat food for infants and young children.

Concerning the inclusion of *α*-tocopherol used as food additive in the intake estimates, the Panel notes that the composition data used, which dated 2012 or earlier, might not reflect the latest trends in additive uses (i.e. some analytical data may relate to products which are not anymore representative of current market). In addition, content values of certain foods estimated through recipe calculations do not necessarily reflect food additive uses. Thus, the contribution of *α*-tocopherol used as food additive is likely to be underestimated. In 2015, the ANS Panel re-evaluated the safety of tocopherols as food additives (E 306-E 309) (EFSA ANS Panel, 2015). As *α*-tocopherol is the predominant tocopherol used by the EU food industry, it was the only form considered for the exposure assessment. The standard approach for additives exposure assessment was applied. Different scenarios were performed, based on maximum regulatory levels, or use levels provided by manufacturers and occurrence data provided by Member States. Applying the refined non-brand-loyal exposure scenario (including loss factors), the resulting P95 estimates of the exposure to *α*-tocopherol as a food additive (E 307) were 1.1–3.5 mg/kg bw per day in infants, 3.5–5.9 mg/day in toddlers, 2.8–5.2 mg/kg bw day in children, 0.9–3.4 mg/kg bw per day in adolescents, 1.0–2.6 mg/kg bw day in adults and 1.0–1.7 mg/kg bw per day in the elderly. Meat products were the most important contributor to the estimates. The ANS Panel noted that several conservative assumptions were applied for these calculations and that these estimates were likely to overestimate the actual exposure to *α*-tocopherol from its use as a food additive (E 307).

3.3.3 | Complementary information

The following paragraphs summarise key information on intake from natural food sources, fortified foods and food supplements, available in national survey reports or other scientific publications collected from national competent authorities, as described in **Section 2.3.1**.

Data on 'vitamin E' intake were collected from 32 nationally representative consumption surveys (22 countries) (**Section 2.3.1.2**). Data collected were heterogeneous in terms of how 'vitamin E' intake was expressed in the different national reports.

Additional information on the survey characteristics, the equations used to express intake as *α*-TE in the different national surveys, and the mean and P95 intake estimates, are presented in Annex D.

3.3.3.1 | *Data on intake excluding food supplements*

Intake estimates from national food consumption surveys

From the 32 surveys providing data on the intake of *α*-tocopherol or *α*-TE, one has not reported the intake from natural sources, while 23 have also included fortified foods (Annex D). However, most of the survey reports did not distinguish between these two sources. For surveys that did not clearly indicate whether fortified foods were included/excluded in the estimates, or for which no clarification has been provided when requested, it is assumed that they were not excluded.

Data on *α*-tocopherol intake only were reported in 17 surveys (Austria, Denmark, Finland, Greece, Hungary, Iceland, Latvia, Lithuania, Norway, Portugal and Sweden), while 15 have reported intakes expressed in *α*-TE (Austria, Belgium, Bulgaria, Estonia, Germany, Ireland, Netherlands, Poland, Serbia, Slovenia and Spain). For those providing data expressed in *α*-TE, there was some heterogeneity across countries/surveys regarding the conversion factors applied to each tocochromanol (Annex D).

The highest P95 intake estimates from foods excluding food supplements were reported for infants (< 1 years) in Spain (males, 14.2 mg/day), for toddlers (≥ 1 to < 3 years) in Bulgaria (males and females, 18.4 mg/day), for children (≥ 3 to < 10 years) in Bulgaria (males and females, 24.1 mg/day), for adolescents (≥ 10 to < 18 years) in Germany (males, 32.7 mg/day), for adults (≥ 18 to < 65 years) in Austria (males, 32.7 mg/day) and for older adults (≥ 65 years) in Sweden (females, 38.4 mg/day). With the exception of Sweden, estimated intakes for females were generally lower than for males in all surveys and age groups.

Contribution of fortified foods to α-tocopherol intake

Data on the contribution of fortified foods to the total 'vitamin E' intake in EU countries are scarce. Estimates were available from two national surveys conducted in Belgium and the Netherlands.

Moyersoen et al. (2017) reported that, in Belgium, voluntary fortification with 'vitamin E' is most commonly used in milk (1.8–2.4 mg/100 g), 'growing-up milk' (0.83–1.1 mg/100 g), milk substitutes (1.4–1.85 mg/100 g), margarines and spreadable fats (9.1–34 mg/100 g), cereals (10 mg/100 g), biscuits (3.6–7.2 mg/100 g), fruit juices and lemonades (0.9–6 mg/100 g), cacao powder (12–15.8 mg/100 g) and weight-loss products (3.3–19 mg/100 g). According to Moyersoen et al. (2017), the contribution to total 'vitamin E' intake from fortified foods was highest in children 3–6 years of age (15.2% in boys and 11.8% in girls), and generally decreasing with increasing age. Data from the Dutch National Food Consumption Survey (DNFCS) 2012–2016 ($n = 4313$, 1–79 years) indicate that foods fortified with 'vitamin E' are frequently consumed in the Netherlands (39% of the recall days) (de Jong et al., 2022). Among consumers, the median contribution (P5-P95) of fortified foods to total intake of 'vitamin E' was 20.8% (1.2%–70.2%). For the population < 18 years old, estimated intake (median (P5-P95)) were 11.2 (5.5–19.8) mg/day for boys, and 9.4 (5.2–15.1) mg/day for girls among consumers of 'vitamin E' fortified foods, and 8.0 (3.8–14.1) mg/day for boys and 8.7 (4.0–16.6) mg/day for girls among non-consumers. Among adults (≥ 18 years old), estimated intakes (median (P5-P95)) among consumers were 14.9

(8.9–24.0) mg/day for men and 10.9 (6.7–17.3) mg/day for women; among non-consumers, estimates were 12.6 (7.0–22.2) mg/day for men and 9.9 (5.5–16.6) mg/day for women.[26]

3.3.3.2 | *Data on intake including food supplements*

A total of 17 dietary surveys conducted in 11 countries (Belgium, Denmark, Estonia, Finland, Germany, Ireland, the Netherlands, Norway, Poland, Portugal and Sweden) reported information on 'vitamin E' supplementation in whole survey populations or in a cohort of supplement users only, of which 12 surveys presented intake data resulting from food supplements only. Vitamin E forms used in food supplements were not reported in any of the data sources. Survey characteristics and intake estimates are presented in Annex D.

Data from national surveys among 'vitamin E' supplement users were available for seven countries and are presented in Tables 7 and 8.

Among users between 1 and < 18 years of age, absolute 'vitamin E' intakes from food supplements in high consumers (P95) have been calculated in three countries, and ranged from 8 mg/day in toddlers in Norway (2 years old, sex-aggregated results) to 22 mg/day in male adolescents in Norway (13 years old) (Table 7). The highest median contribution of food supplements to total 'vitamin E' intake (59%) was reported among Danish adolescent females (11–17 years).

Among adult supplements users, the highest absolute 'vitamin E' intake (P95) from food supplements was reported in Germany (133.2 in men and 221.3 in women mg/day), where total 'vitamin E' intakes in high consumers (P95) in the same survey (whole survey population) ranged between 183.9 mg/day in men and 234.1 mg/day in women (Table 8). Percent contribution of supplements to total 'vitamin E' intake was provided only by three countries (Belgium, Denmark and Ireland). The highest contribution intake was reported for the Danish adult population, ranging from 57% among males with 18–50 years of age to 70% among females aged 51–75 years (P95 intakes of total 'vitamin E': 43–53 mg/day).

TABLE 7 Percent 'vitamin E' supplement users in EU surveys and *α*-tocopherol intake from food supplements among users (toddlers, children and adolescents).

Country, reference, survey name	Dietary method (N of days)	Sex	Age range	N subjects	% supplement users in total survey sample/among supplements users	Absolute intake from supplements, P95 (mg/day)	% contribution of supplements to total intake
Belgium (Moyersoen et al., 2017)							
BFCS 2014	Food diaries (2 days) + FFQ	m	3–6 years	NR	NR	NR	2.2
		f	3–6 years				5.9
	FFQ + 24-h dietary recalls (2 days)	m	7–10 years				3.6
		f	7–10 years				4.0
		m	11–14 years				2.4
		f	11–14 years				2.8
		m	15–17 years				2.3
		f	15–17 years				2.8
Denmark (Hindborg, 2015, Unpublished)							
DANSDA 2011–2013	Dietary records (7 days)	mf	4–10 years	499	61[a]/NR	NR	42
		m	11–17 years	215	49/NR		58
		f	11–17 years	214	46/NR		59
Germany (Perlitz et al., 2019)							
EsKiMo II 2015–2017	Short questionnaire + weighing logs	mf	12–17 year	1356	3.6/22.3	NR	NR
Ireland (Kehoe & Walton, 2022)							
NPNS 2011–2012	Weighted food diary (4 days)	mf	1–4 year	500	14.0/65.4	14.0	34.9
NCFS II 2017–2018			5–12 year	600	16.6/76.0	12.0	37.4
NTFS II 2019–2020			13–18 year	428	5.6/39.8	19.9	18.2
Norway (VKM, 2017)							
Småbarnskost 2007	FFQ + food diary +24-h dietary interviews	mf	2 year	1674	55/NR	18	NR
Ungkost 3 2016			4 year	399	58/NR	11	
Ungkost 3 2015			9 year	636	47/NR	16	
Ungkost 3 2015			13 year	687	38/NR	20	

Abbreviations: BFCS, the Belgian Food Consumption Survey; DANSDA, The Danish National Survey of Diet and Physical Activity; EsKiMo, Eating study as a KiGGS Module; f, females; FFQ, food frequency questionnaire; m, males; *N*, number; NCFS, National Children's Food Survey; NPNS, National Pre-School Nutrition Survey; NR, not reported in the publication, NTFS, National Teen's Food Consumption Survey; VKM, Vitenskapskomiteen for mat og miljø [Norwegian Scientific Committee for Food and Environment].

[a]% users of multivitamin/mineral supplements. By default, multivitamin/mineral supplements were considered to contain retinol based on Danish households' purchases data.

[26]Data was extracted from de Jong et al., 2022 using WebPlotDigitizer 4.7, https://apps.automeris.io/wpd/.

TABLE 8 Percent 'vitamin E' supplement users in EU surveys and α-tocopherol intake from food supplements among users (≥ 18 years: Adults, elderly and very elderly).

Country, reference, survey name	Dietary method (N of days)	Sex	Age range	N subjects	% supplement users in total survey sample/among supplements users[a]	Absolute intake from supplements, P95 (mg/day)	% contribution of supplements to total intake
Belgium (Moyersoen et al., 2017)							
BFCS 2014	FFQ + 24-h dietary recalls (2 days)	m f m f	18–39 years 18–39 years 40–64 years 40–64 years	NR	NR	NR	3.5 10.3 4.5 14.4
Denmark (Hindborg, 2015, Unpublished)							
DANSDA 2011–2013	Dietary records (7 days)	m f m f	18–50 years 18–50 years 51–75 years 51–75 years	788 853 672 695	45/NR 53/NR 47/NR 61/NR	NR	57 63 68 70
Finland (Valsta et al., 2018)							
FinDiet 2017	FPQ	m f	18–74 years 18–74 years	1655	25/NR 31/NR	Mean 14 12	NR
Germany (Heuer et al., 2012)							
NVS II 2005–2007	24-h recall (2 days)	m f	15–80 years 15–80 years	6160 7593	8.3/NR 11.2/NR	168.0 221.3	NR NR
Ireland (Kehoe & Walton, 2022)							
NANS 2008–2010	Weighted food diary (4 days)	mf	18–64 years 65–90 years	1274 226	17.3/58.0 23.0/61.2	42.9 61.3	25.1 24.3
Norway (VKM, 2017)							
Norkost 32015	FFQ + food diary +24-h dietary interview	m f	18–70 years	862 925	39/NR 45/NR	41 31	NR
Poland (Stos et al., 2021) *Mean ± SD(range)							
National Dietary Survey 2019–2020	FPQ	m f	≥ 18 years	913 918	NR/NR	18.1 ± 22.0 (5–100) 11.7 ± 4.9 (3.6–30)	NR

Abbreviations: BFCS, the Belgian Food Consumption Survey; DANSDA, The Danish National Survey of Diet and Physical Activity; EsKiMo, Eating study as a KiGGS Module; f, females; FFQ, food frequency questionnaire; FinDiet, The Finnish National Dietary Survey in Adults and Elderly; FPQ, food propensity questionnaire; m, males; *N*, number; NANS, National Adult Nutrition Survey; NR, not reported in the publication; NVS II, German National Nutrition Survey II; VKM, Vitenskapskomiteen for mat og miljø [Norwegian Scientific Committee for Food and Environment].

[a]% users of multivitamin/mineral supplements. By default, multivitamin/mineral supplements were considered to contain α-tocopherol based on Danish households' purchases data.

3.3.4 | Overall conclusions on intake data

Due to the evolution of the definition of 'vitamin E', the Panel notes that food composition data are not harmonised and sometimes ambiguous as to whether the 'vitamin E' content reported refers to α-tocopherol only or include all tocochromanols. The lack of harmonisation regarding product labelling introduces further uncertainties. This could lead to an overestimation of the actual α-tocopherol content of food and resulting intake estimates. In contrast, intake estimate of α-TE is likely to be underestimated. Thus, both intake estimates of α-tocopherol and α-TE were presented in this Section.

The Panel notes that the P95 estimated dietary intake of α-tocopherol (excluding food supplements) across surveys included in EFSA's intake assessment were higher among females < 10 years with intakes up to 8.9 mg/day in infants (≥ 4 to < 12 months), up to 9.6 mg/day in toddlers (≥ 1 to < 3 years) and up to 19.6 mg/day in children (≥ 3 to < 10 years). Among adolescents (≥ 10 to < 18 years), the highest values were found among males, up to an intake of 29.0 mg/day in adolescents. Estimates in adults were up to 28.5 mg/day among males. The maximum P95 for pregnant women was 21.2 mg/day (Table 5) (Annex C). The highest contributors to the total α-tocopherol intake were vegetable fats and oils, grains and grain-based products and the sum of fruits, vegetables and derived products. The Panel notes that a fraction of the intake estimates comes from the use of α-tocopherol as food additive. However, available data do not allow to distinguish between the natural α-tocopherol content of food and its use as food additive and the contribution of food additives is likely to be underestimated.

α-Tocopherol may be voluntarily added to foods as a fortifying agent. A total of 1737 packaged food products with added *α*-tocopherol, which were available in 24 EU Member States and Norway, were identified from the Mintel GNPD. The majority of these products belong to the categories 'juice drinks', 'dairy', including dairy alternatives, 'nutritional drinks and other beverages', 'sugar, gum and chocolate confectionery & sugar and sweeteners, 'snacks' and 'sports & energy drinks'. The median amount varied from 2.1 mg/serving in 'sugar, gum and chocolate confectionery & sugar and sweeteners' to 6 mg/serving in 'juice drinks'. The highest contents of *α*-tocopherol declared on the label were found in some juices (13–20 mg/serving) and one protein bar under the category 'snacks' (13 mg/serving).

Regarding food supplements containing added *α*-tocopherol, a total of 1159 products available in 24 EU Member States and Norway were identified from the Mintel GNP database. The majority of supplements contained up to 15 mg per serving, and about 2% had doses > 100 mg per serving, with a maximum of 294 mg per serving.

Data on *α*-tocopherol intake from fortified foods and food supplements in EU populations are scarce. Available data from Belgium and the Netherlands indicate that fortified foods represented 15%–20% (average) and up to 70% (P95) of total *α*-tocopherol intake among consumers of those products. Among users of food supplements, the mean contribution of food supplements to total *α*-tocopherol intake ranged between about 3.5% and 70% in adults (data from 3 countries) and between about 2.2% and 59% in children and adolescents (data from 3 countries). The Panel notes that in regular consumers of *α*-tocopherol containing fortified foods and food supplements, the contribution of these foods to total *α*-tocopherol intake can be substantial.

3.4 | Hazard identification

3.4.1 | Impaired blood coagulation and risk of bleeding

3.4.1.1 | *Introduction and mechanisms of toxicity*

It is well established that high doses of *α*-tocopherol increase the risk of bleeding, as observed in animal studies (Abdo et al., 1986; EFSA ANS Panel, 2015; Frank et al., 1997; Helson, 1984; March et al., 1973; Takahashi et al., 1990; Wheldon et al., 1983; Woolley, 1945). An increased risk of haemorrhage and prolonged prothrombin times (PT) and activated partial thromboplastin times (aPTT) have been observed upon oral administration of high doses *α*-tocopherol to chicks, rodents and mini-pigs (EFSA ANS Panel, 2015; IOM, 2001). In vitro, ex vivo and in vivo data suggest that the mechanisms by which *α*-tocopherol could impair blood clotting could be similar in animals and humans.

Briefly, blood clot formation to stop bleeding (haemostasis) from an injured blood vessel arises from a complex series of cellular and biochemical events, which, when dysregulated, predispose to an increased risk of thrombosis or bleeding. Endothelial cells in the vascular wall, circulating platelets and coagulation factors are involved (O'Donnell et al., 2019). Platelet adhesion, secretion and aggregation are essential in primary homeostasis. Antiplatelet medications (e.g. aspirin, clopidogel) target one or more of these, are prescribed in prothrombotic states and increase the risk of bleeding. Most coagulation factors circulate in an inactive form and are synthesised by the liver (Palta et al., 2014). Factors II, VII, IX and X undergo a post-translational, vitamin K-dependent *γ*-carboxylation of glutamic acid residues that enables them to participate in the clotting cascade (EFSA NDA Panel, 2017). Vitamin K deficiency and vitamin K antagonist anticoagulants (e.g. warfarin) also increase the risk of bleeding (Palta et al., 2014).

Different mechanisms have been proposed by which high *α*-tocopherol intakes could increase the risk of bleeding in humans. First, *α*-tocopherol appears to impair vitamin K absorption, hepatic metabolism and status (**Section 3.2.4**). In animals, fatal haemorrhages associated with excess dietary *α*-tocopherol were prevented with vitamin K supplementation (Frank et al., 1997; Helson, 1984; Wheldon et al., 1983). In rat experiments, a reduction of phylloquinone and MK-4 concentrations in extra-hepatic tissues was found in animals administered excess *α*-tocopherol via diet or subcutaneous injection, compared to controls (Tovar et al., 2006). In healthy humans, high-dose *α*-tocopherol supplements (1000 mg/day *RRR*-*α*-tocopherol) for 12 weeks increased concentrations of the inactive under-*γ*-carboxylated forms of prothrombin (PIVKA-II) to levels indicative of poor vitamin K status (Booth et al., 2004). Second, *α*-tocopherol has been found to inhibit platelet aggregation in vitro (Kakishita et al., 1990; Srivastava, 1986) and reduced platelet adhesion has been observed in individuals taking *α*-tocopherol supplements (Jandak et al., 1989; Steiner, 1983). The exact mechanism for the effect is unknown but is thought to be mediated by the inhibition of protein kinase C (PKC), a major regulator of platelet granule secretion, integrin activation and platelet aggregation (Freedman et al., 1996; Steiner, 1999). Finally, *α*-tocopherol at high doses could potentiate the effect of antiplatelet and anticoagulant medications through different mechanisms (Podszun & Frank, 2014).

In this context, the SCF considered the effect of *α*-tocopherol on blood clotting as the critical endpoint to derive a UL for vitamin E (SCF, 2003). The value was based on the RCT by Meydani et al. (1998), where no adverse effects and no change in bleeding time (as surrogate measure for blood clotting) were observed in individuals supplemented with a daily dose of 800 IU *all rac*-*α*-tocopherol acetate for 4 months.

The aim of the current systematic review was to evaluate whether new evidence from human intervention studies allows a characterisation of the dose–response relationship between *α*-tocopherol intake and impaired blood coagulation in humans. Eligible endpoints were bleeding events, bleeding time and blood coagulation parameters. A common systematic search was performed for all endpoints because the inclusion/exclusion criteria were identical for all endpoints and some studies could report on more than one endpoint. Studies among individuals receiving anticoagulant or antiplatelet drugs, and studies which selected patients with medical conditions or on treatments that affect blood coagulation or with

vitamin K malabsorption syndromes, were not eligible (Annex A). These individuals are outside of the target population of the UL for vitamin E (*α*-tocopherol) (**Section 1.3**).

The Panel notes that all the intervention studies retrieved through the systematic search which reported on the effect of *α*-tocopherol supplementation on bleeding events (e.g. epistaxis, gastrointestinal bleeding, haematuria, gingival bleeding, bruising) involved participants on aspirin (either a proportion or all study participants) or exposed to other agents which could increase the risk of epistaxis (i.e. the medicine isotretinoin; high air pollution). No stratified analyses were provided in the papers which could allow assessing an independent effect of *α*-tocopherol on the risk of bleeding. The complete list of publications and the reasons for exclusion are in Annex E. One case report of 'vitamin E toxicity-related coagulopathy' was also identified, in which the patient reported sporadic use of ibuprofen (400 mg) for back pain (Abrol et al., 2023). The Panel considers that no conclusions can be drawn from these publications to derive a UL for vitamin E (*α*-tocopherol).

Among the 13 intervention studies that met the inclusion criteria, three report on bleeding time, five on PT, four on aPTT, two on platelet adhesion and 10 on platelet aggregation. Four studies report on two or more of these endpoints. The evidence table can be found in **Appendix B.1**.

3.4.1.2 | *Bleeding time*

Three human intervention studies investigated the effect of *α*-tocopherol supplementation on measures of bleeding time. Two were RCTs (Meydani et al., 1998; Stampfer et al., 1988) and one was an uncontrolled before–after study (Dereska et al., 2006).

The RCT by Meydani et al. (1998), previously assessed by the SCF, investigated the effect of *α*-tocopherol supplementation for 4 months on bleeding time. Participants were 88 men and women aged ≥ 65 years, non-smokers, with no known medical illnesses and were not taking prescription medications or dietary supplements. Participants were randomised to placebo ($n = 22$) or 60 ($n = 22$), 200 ($n = 25$) or 800 ($n = 19$) IU/day of *all rac-α*-tocopherol (55, 182, 728 mg/day *α*-tocopherol). Post-intervention plasma *α*-tocopherol concentrations (mean ± SD) were 23.3 ± 2.2 μmol/L in the placebo group; 38.4 ± 5.3, 51.0 ± 13.6, 71.5 ± 26.5 μmol/L in the respective supplement groups. Bleeding time was assessed using Simplate II. A total of 10 subjects (2, 3, 5 and none in the placebo, low-, medium- and high-dose *α*-tocopherol groups, respectively) dropped from the study for personal reasons, sickness unrelated to the study or non-compliance (Meydani et al., 1997). Among completers, bleeding time was available for 15–19 participants per group at all time points (exact number per group not given). Bleeding times were similar in all groups pre- (mean ± SD; placebo: 302 ± 97 s, 60 IU: 310 ± 78 s, 200 IU: 331 ± 68 s, 800 IU: 310 ± 89 s) and post-supplementation (placebo: 263 ± 77 s, 60 IU: 345 ± 94 s, 200 IU: 293 ± 64 s, 800 IU: 288 ± 72 s). The authors report that the vitamin K status was 'normal' (indices not reported).

The RCT by Stampfer et al. (1988) investigated the effect of *α*-tocopherol supplementation for 5 weeks on bleeding time in 10 men and 10 women (age not reported). Subjects were eligible if they did not use aspirin or other platelet active agents for 2 weeks before inclusion and throughout the study and were randomly assigned to 800 IU/day *all rac-α*-tocopherol[27] (728 mg/day *α*-tocopherol) or matching placebo. Compared to baseline values, supplementation resulted in a threefold increase in plasma *α*-tocopherol (mean, range; post-supplementation: 70, 28–114 μmol/mL), while no change was observed in the placebo group (post-supplementation: 26, 12–42 μmol/mL). Bleeding time was assessed twice using Simplate II (once per forearm) at each time point. There was no difference between groups in the change in bleeding time (mean ± SD; post-supplementation vs. pre-supplementation: 6.43 ± 1.86 min vs. 6.73 ± 1.30 min in the supplemented group; 6.58 ± 1.49 min vs. 6.28 ± 1.29 min in the control group).

Dereska et al. (2006) assessed the effect of *α*-tocopherol supplementation for 14 days on bleeding time in 20 men and 20 women (mean age 30.9 years). Subjects were eligible if they did not use aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) for at least 2 weeks before inclusion in the study. Subjects were eligible if they were free from any history of bleeding diathesis, recent liver disease or collagen vascular disease, hypertension, history of an abnormal bleeding time, abnormally elevated or low platelet count, current pregnancy, history of vitamin E intake, anticoagulant drugs or antibiotics within 2 weeks of initial participation in the study, history of chronic antibiotic ingestion or known vitamin K deficiency. Bleeding time was assessed pre- and post-supplementation with 800 IU/day *all rac-α*-tocopheryl acetate (728 mg/day *α*-tocopherol) supplementation for 14 days, using the Dade Behring PFA-100 instrument. Mean bleeding time post *α*-tocopherol supplementation (96.25 ± 23.40 seconds, range 65–168 seconds) did not differ from that of baseline (105.72 ± 31.78 seconds, range 70–179 seconds).

The Panel notes that no effect on bleeding time was found in three human intervention studies in which *α*-tocopherol was administered at doses of up to 728 mg/day for periods ranging from 2 weeks up to 4 months. Participants in these studies were adult men and women who were described as 'healthy'. Their vitamin K status was reported to be adequate/not deficient in two studies, but biochemical indices were not reported.

3.4.1.3 | *Coagulation parameters*

Several studies have investigated the effect of a-tocopherol supplementation on coagulation parameters such as PT, aPTT, measures of platelet adhesion or measures of platelet aggregation, primarily to explore the potential mechanisms by which a-tocopherol may affect blood coagulation processes (**Section 3.4.1.1**). These data are considered supportive evidence for the main endpoints, i.e. bleeding events and bleeding times.

[27]Based on the conversion reported in the paper, the Panel assumes that the form of supplementation was *all rac-α*-tocopherol.

Five human interventions, three RCTs (Kitagawa & Mino, 1989; Stampfer et al., 1988; Tsai et al., 1978), one CT (Morinobu et al., 2002) and one uncontrolled before-after study (Dereska et al., 2006), investigated the effect of *α*-tocopherol supplementation on PT in adults. Four of them also measured aPTT (Dereska et al., 2006; Kitagawa & Mino, 1989; Morinobu et al., 2002; Stampfer et al., 1988). The number of participants in a treatment group ranged between 10 and 104. They were mostly young adults and were described to be 'healthy'. Regarding vitamin K status, Kitagawa and Mino (1989) reported no detectable levels of PIVKA-II (< 0.5 μg/mL) among study participants, Dereska et al. (2006) excluded individuals with 'known vitamin K deficiency', while no information is available for the other studies. Supplementation doses ranged from 546 to 804 mg/day *α*-tocopherol, administered as natural or synthetic 'free' a-tocopherol (3 studies) or synthetic *α*-tocopheryl acetate (2 studies), and lasted from 2 to 12 weeks. No effect of *α*-tocopherol supplementation on PT or aPTT was observed in any of the studies.

Two studies by the same research group investigated the effect of *α*-tocopherol supplementation on measures of platelet adhesion in adults aged between 18 and 57 years (Jandak et al., 1989; Steiner, 1983). Participants were reported to be 'healthy' and abstained from medications during the study. In the first study, Steiner (1983), 47 participants (20 men and 27 women) were divided into four groups for a 6-week intervention. Participants received either placebo ($n = 11$), or an intervention ($n = 12$ each group) consisting of *α*-tocopherol at increasing doses of 400, 800, 1200 IU/day *all rac-α*-tocopheryl acetate (364, 728 and 1091 mg/day *α*-tocopherol) for 2 weeks each, aspirin (300 mg every other day), or both *α*-tocopherol and aspirin at the above-mentioned doses. Ex vivo platelet adhesion to collagen was assessed weekly for the 6 weeks of the intervention. Supplementation with *α*-tocopherol significantly reduced platelet adhesion in a dose-dependent manner as compared to placebo, whereas aspirin alone had no effect. Platelet adhesion to collagen in the *α*-tocopherol plus aspirin group did not differ significantly from the *α*-tocopherol group in the first 3 weeks but was significantly higher thereafter. In the second study, Jandak et al. (1989), a single group of six non-smoking men and women received 200 IU/day *RRR-α*-tocopheryl acetate (135 mg/day *α*-tocopherol) for 2 weeks and 400 IU/day (270 mg/day *α*-tocopherol) for the subsequent 2 weeks. Ex vivo platelet adhesion to four different adhesive surfaces (glass, collagen, fibronectin and fibrinogen) was assessed at baseline and after each supplementation period. The highest decrease in platelet adhesion (all surfaces) compared to baseline was observed after the first dose (by 75% on average), with a modest further reduction after the second dose (by 82% on average). Differences from baseline for the 135 and 270 mg/day doses were statistically significant for all adhesive surfaces. These studies suggest a cumulative dose–response effect of *α*-tocopherol on platelet adhesion at daily doses between 135 and 1091 mg/day.

Two studies by the same research group investigated the effect of *α*-tocopherol supplementation on measures of platelet ATP secretion in apparently healthy subjects. Individuals on aspirin and other drugs interfering with platelet function were explicitly excluded (Calzada et al., 1997; Mabile et al., 1999). The first study Calzada et al. (1997) was an RCT in which 40 healthy volunteers (age 20–50 years) were supplemented daily with either 300 mg *all rac-α*-tocopheryl acetate (273 mg *α*-tocopherol), vitamin C (250 mg), *β*-carotene (15 mg) or placebo for 8 weeks ($n = 10$ per group). Secretion of ATP from dense granules by platelets stimulated with a maximal dose of adenosine diphosphate (ADP) and to a lesser extent plasma concentration of *β*-thromboglobulin significantly decreased in the *α*-tocopherol (by 56% and 20% from baseline, respectively) as compared to placebo, whereas no significant changes were observed in the other supplementation groups. The second study, Mabile et al. (1999), was conducted to investigate whether lower doses of *α*-tocopherol could exert similar effects. A single group of 22 participants consumed placebo, 75 IU, 200 IU, 400 IU *RRR-α*-tocopherol[28] (50, 134 and 268 mg of *α*-tocopherol) daily for 2 weeks each in this order, for a total of 8 weeks. Secretion of ATP from dense granules by platelets stimulated with a fixed concentration of ADP (including 100% aggregation prior to supplementation) was gradually decreased over the 6 weeks of supplementation, with significant changes from the second period of intake with 134 mg/day of *α*-tocopherol and up to 1.7-fold decrease at the end of the study.

Nine studies investigated the effect of *α*-tocopherol supplementation on measures of platelet aggregation (Calzada et al., 1997; Dereska et al., 2006; Liu et al., 2003; Mabile et al., 1999; Morinobu et al., 2002; Silbert et al., 1990; Stampfer et al., 1988; Steiner, 1983; Szczeklik et al., 1985). Findings among the group of individuals with hyperlipoproteinaemia in the study of Szczeklik et al. (1985) are not considered, as most had a history of cardiovascular disease (CVD) and no information was provided on the use of medications which could have affected platelet function. Among the remaining studies, three were RCTs (Calzada et al., 1997; Liu et al., 2003; Stampfer et al., 1988), one was a CT (Morinobu et al., 2002), one compared within group changes from baseline in the intervention versus the control group (Steiner, 1983) and four were before–after studies reporting within-group comparisons, of which two compared post-treatment values with those obtained after a period on placebo (Silbert et al., 1990; Szczeklik et al., 1985), and two compared post-treatment values with baseline values (Dereska et al., 2006; Mabile et al., 1999). Eligible studies reported recruiting 'healthy' individuals. Five studies explicitly excluded individuals taking aspirin and other drugs that interfere with platelet function (Calzada et al., 1997; Dereska et al., 2006; Liu et al., 2003; Mabile et al., 1999; Stampfer et al., 1988), two studies reported that no subject was on taking any medication (Silbert et al., 1990; Steiner, 1983), one of which reported on the effect of *α*-tocopherol and aspirin alone and in combination, one study reported that the participants abstained from anti-inflammatory drugs (Szczeklik et al., 1985); group of healthy subjects) and one study did not provide information (Morinobu et al., 2002). Supplementation doses ranged from 50 mg/day to 1091 mg/day *α*-tocopherol, administered as natural or synthetic 'free' *α*-tocopherol (5 studies), synthetic *α*-tocopheryl acetate (3 studies) or an unspecified 'natural' form (1 study). The intervention lasted for 2–8 weeks.

[28]Based on the conversion reported in the paper, the Panel assumes that the form of supplementation was *RRR-α*-tocopherol.

Platelet aggregation was measured ex vivo, in response to collagen, ADP and/or arachidonic acid; one study also used epinephrine. Two studies also assessed the inhibition by PGE1 on platelet aggregation in response to a fixed concentration of ADP (Calzada et al., 1997; Mabile et al., 1999).

Out of the nine studies identified, three reported a decrease in measures of platelet aggregation, two of which also reported an increased platelet sensitivity to PGE_1 (Calzada et al., 1997; Mabile et al., 1999). All three have been described in detail above in relation to platelet adhesion (Steiner, 1983) or platelet secretion (Calzada et al., 1997; Mabile et al., 1999). In the study by Steiner (1983), *α*-tocopherol at increasing doses of 400, 800, 1200 IU/day *all rac-α*-tocopheryl acetate (364, 728 and 1091 mg/day *α*-tocopherol) for 2 weeks each induced a modest but significant decrease in collagen-induced maximal aggregation in women, but not in men, who had significantly lower values at baseline. No effect was observed when epinephrine or ADP was used as aggregating agents. Conversely, a potent antiaggregant effect was observed with aspirin alone or in combination with *α*-tocopherol with all three aggregating agents tested, with no differences between the groups. In the study by Calzada et al. (1997), the aggregation curve with increasing doses of ADP shifted to the right with 300 mg/day *all rac-α*-tocopheryl acetate (273 mg/day *α*-tocopherol) for 8 weeks (i.e. significantly lower platelet aggregation at each dose of ADP as compared to no supplementation), whereas no changes were observed for vitamin C or *β*-carotene. Similar results were obtained by Mabile et al. (1999), where the maximum shift in the aggregation curve was already observed after 2 weeks of supplementation with the lowest dose of 75 IU *RRR-α*-tocopherol (50 mg/day *α*-tocopherol). No effect of *α*-tocopherol alone at similar or higher daily doses on measures of platelet aggregation was observed in the remaining studies (Dereska et al., 2006; Liu et al., 2003; Morinobu et al., 2002; Silbert et al., 1990; Stampfer et al., 1988; Szczeklik et al., 1985). The aggregating agents used, the doses tested and the methods used varied widely among the studies.

The Panel notes that, among individuals not taking anticoagulant or antiplatelet medications, there are no indications of effects of *α*-tocopherol supplementation on PT and aPTT based on six studies, which tested doses between 546 mg/day and 804 mg/day *α*-tocopherol for up to 12 weeks. Based on two studies each, the Panel notes some evidence for reduced platelet adhesion upon supplementation with *α*-tocopherol at doses between 135 mg/day and 1091 mg/day for 2 weeks, and on platelet ATP secretion at doses between 50 mg and 273 mg, while the evidence for an effect on platelet aggregation is inconsistent, based on nine studies which tested doses up to 1091 mg day for up to 8 weeks.

3.4.1.4 | *Conclusions on impaired coagulation and risk of bleeding*

The Panel notes that no relevant data were retrieved regarding the risk of bleeding events with *α*-tocopherol supplementation in human intervention studies. The Panel notes that PT and aPTT were not affected by *α*-tocopherol supplementation (546–804 mg/day *α*-tocopherol for 2–12 weeks), and that the effects observed on platelet function (mainly reduction of platelet adhesion and ATP secretion) were not translated into changes in bleeding time in three studies using doses of *α*-tocopherol up to 728 mg/day for up to 4 months. All the studies used to reach these conclusions were conducted in populations not taking anticoagulant or antiplatelet drugs.

3.4.2 | Cardiovascular disease

Owing to its antioxidant properties and based on observations from prospective cohort studies associating higher vitamin E dietary intake with lower risk of cardiovascular events, several RCTs have been conducted in humans aiming to investigate the benefit of *α*-tocopherol supplementation, either alone or in combination with other antioxidants, in the primary and secondary prevention of atherosclerosis-related CVD morbidity and mortality given the involvement of oxidative stress mechanisms in their pathogenesis, among others (Vardi et al., 2013). Atherosclerosis-related CVDs mainly comprise coronary heart disease (CHD), including myocardial infarction and angina, ischaemic cerebrovascular disease, including transient ischaemic attack (TIA) and ischaemic stroke, peripheral artery disease and aortic sclerosis.

Through the scoping searches conducted in preparation of the protocol (Annex A), the Panel noted a higher risk of congestive heart failure (CHF) and a higher risk of haemorrhagic stroke had been reported in some *α*-tocopherol supplementation trials.

The Panel decided to systematically review the available evidence for the relationship between *α*-tocopherol intake and the main cardiovascular endpoints investigated in *α*-tocopherol supplementation trials. These include morbidity and mortality related to myocardial infarction and angina, ischaemic and haemorrhagic stroke, CHF and composite endpoints thereof. Any potential beneficial effects of *α*-tocopherol on CVD will not be discussed in this opinion.

Both prospective human observational and intervention studies were eligible. According to the protocol (Annex A), studies among subjects with pre-existing conditions, taking aspirin or anticoagulant medications, which may act as modifiers of any effect of *α*-tocopherol on CVD risk, were not excluded a priori. The results have been assessed and the generalisability of the findings to other groups of the general population are discussed below.

The systematic review identified 32 eligible articles, reporting the results of 25 studies (15 intervention studies and 10 observational prospective studies). The flow chart is provided in **Appendix A.2**. Data from these studies was systematically collected and extracted in evidence tables (**Appendix B.2**). Included studies reported on one or more of the cardiovascular endpoints described below.

3.4.2.1 | *CVD (composite endpoint)*

A total of 12 RCTs assessed the effect of *α*-tocopherol supplementation on the incidence of CVD as a composite endpoint.

Preliminary UA

The number of participants ranged from 196 to 39,876 participants and the duration of the follow-up from approximately 1.5 to 10 years. The dose of *α*-tocopherol supplementation varied from 50 mg *α*-tocopheryl acetate (45 mg *α*-tocopherol) to 1200 IU (804 mg *α*-tocopherol) per day and was compared to placebo in most studies. Five trials used synthetic (*all rac-*) *α*-tocopherol (ATBC, SELECT, GISSI- Prevenzione, PPP; PHS II) and seven used natural (*RRR-*) *α*-tocopherol (HOPE/HOPE-TOO; WHS; WACS; SPACE; CHAOS; (Devaraj et al., 2007; Milman et al., 2008)). The definition of CVD was heterogeneous across studies in relation to the endpoints included, but all studies included CVD mortality in the composite endpoint.

None of the included RCTs reported an increased risk of CVD (morbidity and/or mortality) in the *α*-tocopherol group compared placebo or no *α*-tocopherol (i.e. the relationship was null or negative in all the studies (Boaz et al., 2000; Cook et al., 2007; de Gaetano, 2001; Devaraj et al., 2007; GISSI – Prevenzione Investigators, 1999; Lee et al., 2005; Lippman et al., 2009; Lonn et al., 2005; Milman et al., 2008; Sesso et al., 2008; Stephens et al., 1996; Törnwall, Virtamo, Korhonen, Virtanen, Taylor, et al., 2004)).

In addition, five prospective observational studies were identified reporting on the relationship between *α*-tocopherol intake and CVD (morbidity and/or mortality) (Buijsse et al., 2008; Muntwyler et al., 2002; Pocobelli et al., 2009; Sheng et al., 2022; Stampfer et al., 1993). Similar to what was reported in the RCTs, *α*-tocopherol intake was not associated with an increased risk in any of the studies (i.e. the relationship was either null or negative).

The Panel considers that the available BoE does not suggest a positive relationship between the intake of *α*-tocopherol and an increased risk of CVD (composite endpoint). No comprehensive UA is performed.

3.4.2.2 | *Coronary heart disease*

Twelve RCTs investigated the effect of *α*-tocopherol supplementation on the incidence of myocardial infarction, angina and/or CHD (i.e. composite endpoint combining myocardial infarction and angina).

Preliminary UA

The number of participants ranged from 161 to 39,876 participants and duration follow-up from approximately 1.5 to 10 years. The dose of *α*-tocopherol supplementation varied from 50 mg *α*-tocopheryl acetate (45 mg *α*-tocopherol) to 800 IU *α*-tocopheryl acetate (536 mg *α*-tocopherol) per day and was compared to placebo in most studies. Five trials used synthetic (*all rac-*) *α*-tocopherol (ATBC, GISSI, PPP, PHS II, VEAPS) and 7 used natural (*RRR-*) *α*-tocopherol (HOPE, WHS, WACS, SPACE, CHAOS, (Milman et al., 2008; Takamatsu et al., 1995)).

Only one trial among patients with angiographically proven atherosclerosis observed a slightly higher number of fatal myocardial infarction cases in the *α*-tocopherol group (400–800 IU *RRR-α*-tocopherol/day; 268–536 mg *α*-tocopherol/day) compared to placebo (18 cases in 1035 randomised vs. 13 cases in 967 randomised, respectively) (Stephens et al., 1996). In the remaining studies, *α*-tocopherol supplementation did not increase the risk of myocardial infarction incidence (Boaz et al., 2000; Cook et al., 2007; de Gaetano, 2001; Hodis et al., 2002; Lee et al., 2005; Milman et al., 2008; Stephens et al., 1996; Takamatsu et al., 1995; Törnwall, Virtamo, Korhonen, Virtanen, Taylor, et al., 2004; Yusuf et al., 2000) or mortality (Boaz et al., 2000; Cook et al., 2007; Hodis et al., 2002; Lee et al., 2005; Sesso et al., 2008). No increased risk of angina was observed in the *α*-tocopherol group in any of the six trials which assessed this endpoint (Boaz et al., 2000; de Gaetano, 2001; Hodis et al., 2002; Sesso et al., 2008; Takamatsu et al., 1995; Yusuf et al., 2000).

Four trials also reported on CHD as a composite endpoint, namely on CHD incidence (Cook et al., 2007), CHD mortality (Törnwall, Virtamo, Korhonen, Virtanen, Taylor, et al., 2004; Yusuf et al., 2000) or CHD mortality plus non-fatal myocardial infarction combined (GISSI – Prevenzione Investigators, 1999). None of these trials report an increased risk of CHD in relation to *α*-tocopherol supplementation.

Additionally, four prospective observational studies meeting the inclusion criteria were identified, none of which reported a positive association between the intake of *α*-tocopherol and CHD incidence or mortality (Knekt et al., 2004; Kushi et al., 1996; Muntwyler et al., 2002; Rimm et al., 1993).

The Panel considers that the available BoE does not suggest a positive relationship between the intake of *α*-tocopherol and an increased risk of myocardial infarction, angina or CHD (composite endpoint). No comprehensive UA is performed.

3.4.2.3 | *Stroke*

Composite endpoint

A total of 12 publications reporting the results of 11 trials that examined the effect of *α*-tocopherol supplementation on the incidence of stroke as a composite outcome were identified.

Preliminary UA

The sample size ranged from 100 to 39,876 participants and duration follow-up from 1.4 to 10.1 years. The dose of α-tocopherol supplementation varied from 50 to 537 mg/day and was compared with placebo in most studies. Six trials used synthetic (*all rac*-) α-tocopherol (ATBC, PHS-II, GISSI, PPP, (Hodis et al., 2002; Steiner et al., 1995)) and five natural (*RRR*-) α-tocopherol (HOPE/HOPE-TOO, WHS, WACS, CHAOS and (Milman et al., 2008)).

None of the included trials reported an adverse effect of α-tocopherol supplementation on stroke incidence (Cook et al., 2007; de Gaetano, 2001; GISSI – Prevenzione Investigators, 1999; Hodis et al., 2002; Lee et al., 2005; Leppälä, Virtamo, Fogelholm, Huttunen, et al., 2000; Lonn et al., 2005; Milman et al., 2008; Sesso et al., 2008; Steiner et al., 1995) or mortality (Leppälä, Virtamo, Fogelholm, Huttunen, et al., 2000) [ATBC], (GISSI – Prevenzione Investigators, 1999) [GISSI], (Sesso et al., 2008) [PHS II], (Cook et al., 2007) [WACS] (Stephens et al., 1996) [CHAOS], and (Lee et al., 2005) [WHS]). The results from the ATBC post-trial follow-up study are also in line with this conclusion (Törnwall, Virtamo, Korhonen, Virtanen, Albanes, & Huttunen, 2004).

Two prospective observational studies assessing total 'vitamin E' intake (i.e. considering diet and supplements) in relation to the risk of stroke as a composite endpoint were also identified (Ascherio et al., 1999) (HPFS) and (Yochum et al., 2000) (WHS). Neither reported a positive association between 'vitamin E' intake and stroke incidence.

The Panel considers that the available BoE does not suggest a positive relationship between the intake of α-tocopherol and an increased risk of stroke (composite endpoint). No comprehensive UA is performed.

Ischaemic stroke

The systematic literature search identified nine articles, reporting findings from seven trials, on the effect of α-tocopherol supplementation on ischaemic stroke incidence (Boaz et al., 2000; Cook et al., 2007; Lee et al., 2005; Leppälä, Virtamo, Fogelholm, Huttunen, et al., 2000; Lippman et al., 2009; Sesso et al., 2008; Steiner et al., 1995; Törnwall, Virtamo, Korhonen, Virtanen, Albanes, & Huttunen, 2004; Virtamo et al., 2003). Only the ATBC reported on stroke mortality (Leppälä, Virtamo, Fogelholm, Huttunen, et al., 2000; Virtamo et al., 2003).

Preliminary UA

The sample size ranged from 100 to 39,876 participants and study follow-up duration from 1.4 to 10.1 years. The dose of α-tocopherol supplementation varied between 50 and 360 mg/day. Four of the trials used synthetic (*all rac*-) α-tocopherol (ATBC, PHS-II, SELECT and the study by Steiner et al., 1995) and the remaining used natural (*RRR*-) α-tocopherol (WHS, WACS and SPACE).

The risk estimates reported in the trials do not show an adverse effect of α-tocopherol supplementation on ischaemic stroke incidence or mortality. Results from the ATBC post-trial follow-up study are similar to those reported for the trial period (Törnwall, Virtamo, Korhonen, Virtanen, Albanes, & Huttunen, 2004).

The only observational study identified in the literature search (Ascherio et al., 1999) reported a null association between the intake total 'vitamin E' intake and incidence of ischaemic stroke.

The Panel considers that the available BoE does not suggest a positive relationship between the intake of α-tocopherol and an increased risk of ischaemic stroke. No comprehensive UA is performed.

Haemorrhagic stroke

The most common cause of haemorrhagic stroke, including intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH), is hypertension. Cigarette smoking, moderate or heavy alcohol consumption, antiplatelet and anticoagulant medications are other important risk factors for haemorrhagic stroke.

Ten publications, reporting the results of eight trials (Leppälä, Virtamo, Fogelholm, Albanes, et al., 2000; Leppälä, Virtamo, Fogelholm, Huttunen, et al., 2000) (ATBC); (Yusuf et al., 2000) (HOPE); (Leppälä, Virtamo, Fogelholm, Albanes, et al., 2000; Leppälä, Virtamo, Fogelholm, Huttunen, et al., 2000; Sesso et al., 2008) (ATBC); (Yusuf et al., 2000) (HOPE); (Sesso et al., 2008) (PHS II); (Lee et al., 2005) (WHS); (Cook et al., 2007) (WACS); (Lippman et al., 2009) (SELECT); and (Steiner et al., 1995), PPP), investigated the effect of α-tocopherol supplementation on the incidence of haemorrhagic stroke. Two RCTs also included fatal haemorrhagic stroke as an endpoint (SELECT (Lippman et al., 2009); ATBC (Leppälä, Virtamo, Fogelholm, Albanes, et al., 2000; Leppälä, Virtamo, Fogelholm, Huttunen, et al., 2000)).

Preliminary UA

The evidence table can be found in **Appendix B.2**. Key study characteristics, together with the effect estimates and related confidence intervals (CIs), are plotted in Figure 7.

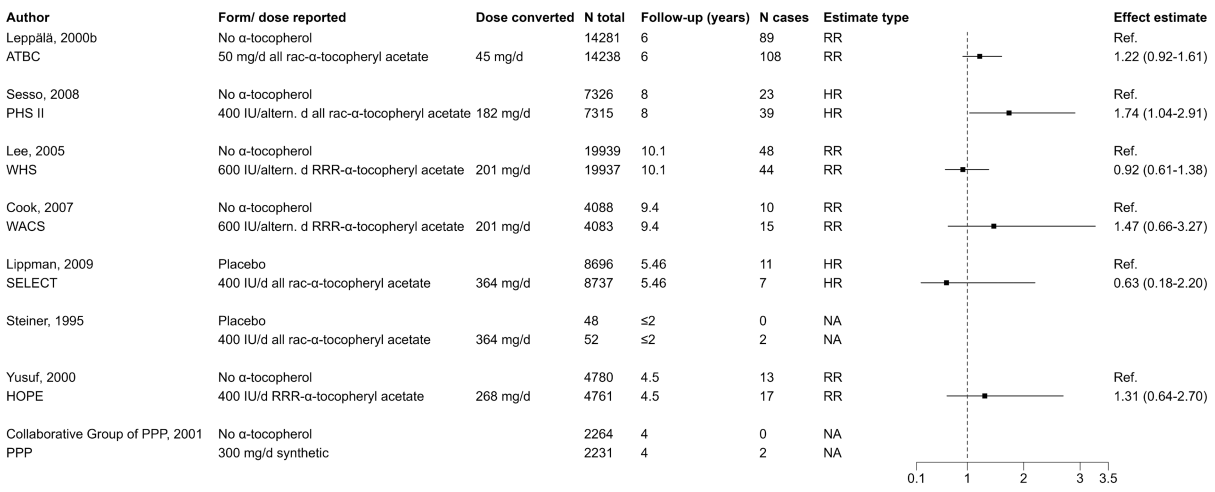

FIGURE 7 RCTs investigating the effect of a-tocopherol supplementation on the incidence of haemorrhagic stroke.
ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; HOPE, Heart Outcomes Prevention Evaluation; PHS II, Physicians' Health Study II; PPP, Primary Prevention Project; SELECT, Selenium and Vitamin E Cancer Prevention Trial; WACS, Women's Antioxidant Cardiovascular Study; WHS, Women's Health Study.
Note: Supplementation was converted to 'free' α-tocopherol in mg/day for all studies; doses given on alternate days were divided by 2 (column Dose converted). Based on the conversion reported in Steiner et al. (1995), the Panel assumes that the form of supplementation was *all rac*-α-tocopherol. The estimate for Leppälä, Virtamo, Fogelholm, Huttunen, et al. (2000) and Yusuf et al. (2000) were obtained from Schürks et al. (2010).

The sample size ranged from 100 to 39,876 participants and duration follow-up from less than 2–10.1 years. The dose of α-tocopherol supplementation varied from 50 to 300 mg/day and was compared with placebo in most studies. Five trials used synthetic (*all rac*-) α-tocopherol (ATBC, PHS-II, SELECT, PPP and the study by Steiner et al., 1995) and three natural (*RRR*-) α-tocopherol (HOPE, WHS, WACS).

TABLE 9 Characteristics of study participants*.

	ATBC (Leppälä, Virtamo, Fogelholm, Albanes, et al., 2000; Liede et al., 1998)	PHS II (Sesso et al., 2008)	WHS (Lee et al., 2005)	WACS (Bassuk et al., 2004; Cook et al., 2007)	SELECT (Christen et al., 2015; Lippman et al., 2009)	HOPE (Yusuf et al., 2000)	(Steiner et al., 1995)	PPP (de Gaetano, 2001)
Age, mean ± SD (years)	57.7	64.2 ± 9.1	54.6 ± 7.0	60.6 ± 8.9	62.3 (58.0–67.8)	66 ± 7	70.7 ± 11.6	64.4 ± 7.6
Smoking, current	100%	3.3%	13%	15.5%	8%	14.0%	–	15%
Hypertension (or history of)	38.7%	42.0%	25.6%	74.4%	37.2%	46.6%	59.6%	67%
Hypercholesterolaemia (or history of)/ Hyperlipidaemia	–	36.6%	29.3%	72.7%	–	65.3%	–	38%
Aspirin use	14%[a]	77.4%	50%[d]	52.5%[e]	42.0%[g]	77%	100%	50%[d]
Warfarin/anticoagulant use	Excluded	Excluded	Excluded	Excluded	Excluded	Nr	Excluded	Excluded
Statin use	NR	NR	NR	22.8%[f]	25.8%	28.4%[h]	NR	15%[h]
Diabetes mellitus	4.2%	6.3%	2.6%	18.7%	9.0%	38.6%	26.9%	16%
Heart disease	25.4%[b]	5.1%[c]	0%	64.7%	–	81.0%	30.8%	–

*Estimates are given for the α-tocopherol supplementation group in each study, unless otherwise specified.
[a]Reported for a random study subsample.
[b]Composite variable including coronary heart disease, myocardial infarction, valvular disease, arrhythmia, cardiac enlargement and congestive heart failure.
[c]Composite variable including nonfatal myocardial infarction or nonfatal stroke.
[d]By study design (2 × 2 factorial design with aspirin).
[e]Use ≥ 1 in the past month, reported for the total study sample.
[f]Use of cholesterol lowering drugs, reported for the total study sample.
[g]Doses ≤ 175 mg/day permitted by study design.
[h]Use of lipid-lowering drugs.

Virtually all trials excluded individuals on anticoagulants but included participants on aspirin, ranging from 14% (ATBC, based on the proportion of aspirin users reported in Liede et al. (1998))) to 77% (PHS II and HOPE) and up to 100% (Steiner

et al., 1995) of the study sample (Table 9). In three trials (WHS, PPP and Steiner et al. (1995))), aspirin was part of the intervention. From 25% (WHS) to 75% (WACS) of participants had diagnosed hypertension at baseline. The prevalence of heart disease ranged from 0% in the WHS, based on the study's inclusion criteria, to 81% in the HOPE, where participants had been selected for being at high risk for cardiovascular events on the basis of previous CVD, diabetes and other risk factors.

Supplementation with *α*-tocopherol increased the incidence of haemorrhagic stroke in six out of the eight included studies (Figure 7). Similar results to those in the trial period were reported for a 6-year post-trial follow-up of the ATBC (Törnwall, Virtamo, Korhonen, Virtanen, Albanes, & Huttunen, 2004). In the two trials which reported on fatal haemorrhagic stroke (SELECT and ATBC), the results were in the same direction as for the incidence of haemorrhagic stroke in both trials, with an increased risk reported in the ATBC (Leppälä, Virtamo, Fogelholm, Huttunen, et al., 2000), including the post-trial follow-up (Virtamo et al., 2003), and no increased risk reported in the SELECT (Lippman et al., 2009).

The Panel notes that the available evidence from RCTs suggests an increased risk of haemorrhagic stroke upon *α*-tocopherol supplementation as compared to no *α*-tocopherol supplementation or placebo. These studies included a high percentage of participants on secondary prevention for CVD and/or on treatment with antiplatelet medications. The Panel notes that these individuals are under medical care and that any *α*-tocopherol supplementation should be under medical supervision. The Panel considers that these individuals should be excluded from the target population of a UL for vitamin E (*α*-tocopherol). No comprehensive UA is performed.

One prospective observational study reporting on the association between total and supplemental 'vitamin E' intake and haemorrhagic stroke was identified (Ascherio et al., 1999). No association between either total or supplemental 'vitamin E' intake and incidence of haemorrhagic stroke was observed (**Appendix B.2**).

The Panel considers that the available evidence on the relationship between *α*-tocopherol supplementation and risk of haemorrhagic stroke cannot be used for establishing a UL for vitamin E (*α*-tocopherol).

3.4.2.4 | *Congestive heart failure*

CHF is a complex clinical syndrome of variable aetiology that results from any structural or functional impairment of ventricular filling or ejection of blood. Ischaemic heart disease is a leading cause of CHF.

Five trials examined the effect of *α*-tocopherol supplementation on the risk of CHF or mortality due to CHF (Chae et al., 2012; Lonn et al., 2005; Marchioli et al., 2006; Milman et al., 2008; Sesso et al., 2008).

Preliminary UA

The evidence table can be found in **Appendix B2**. Key study characteristics, together with the effect estimates and related CIs are plotted in Figure 8.

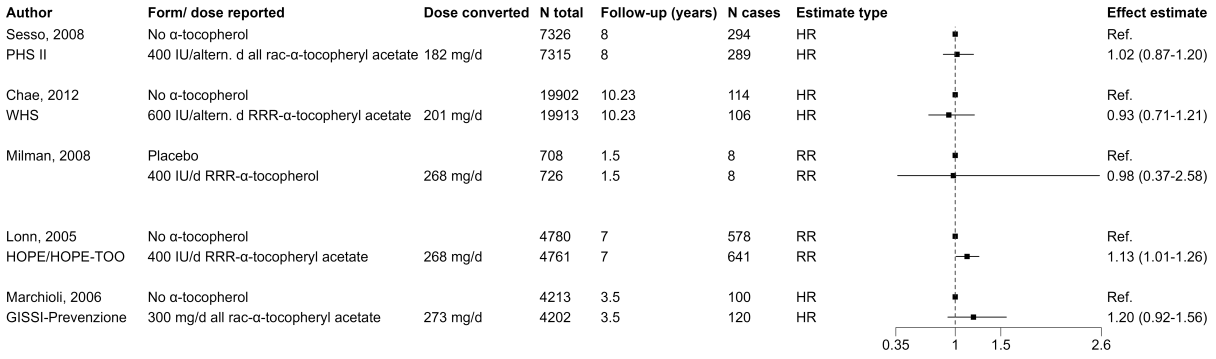

FIGURE 8 RCTs investigating the effect of *α*-tocopherol supplementation on the incidence of congestive heart failure.
GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; HOPE, Heart Outcomes Prevention Evaluation; HOPE-TOO, HOPE-The Ongoing Outcomes; PHS II, Physicians' Health Study II; WHS, Women's Health Study.
Note: Supplementation was converted to 'free' *α*-tocopherol in mg/day for all studies; doses given on alternate days were divided by 2 (column Dose converted).

The sample size ranged from 1434 to 39,815 participants and duration follow-up from 1.5 to 10.2 years. The dose of *α*-tocopherol supplementation varied from 400 IU *all rac-α*-tocopherol on alternate days (equivalent to 182 mg *α*-tocopherol/day) to 300 mg *all rac-α*-tocopheryl acetate per day (273 mg *α*-tocopherol/day) and was compared with placebo in most studies. Two trials used synthetic (*all rac-*) *α*-tocopherol (PHS-II, GISSI-Prevenzione) and three natural (*RRR-*) *α*-tocopherol (HOPE/HOPE-TOO, WHS and Milman et al. (2008)).

In two studies, *α*-tocopherol supplementation increased the risk of CHF in populations with a high proportion of participants (~53% and 100%) who had experienced a previous myocardial infarction (HOPE/HOPE-TOO, GISSI-Prevenzione). The other three trials, which recruited populations with no or a low proportion of participants (up to ~15%) with a previous myocardial infarction (i.e. WHS, PHS II, Milman et al. (2008)), provide no evidence for an adverse effect of *α*-tocopherol supplementation on this endpoint.

The Panel notes that available evidence from RCTs suggests an increased risk of CHF upon α-tocopherol supplementation following a myocardial infarction. The Panel notes that individuals at high risk of CHF (e.g. after a myocardial infarction) are under medical care and that any α-tocopherol supplementation should be under medical supervision. The Panel considers that these individuals should be excluded from the target population of a UL for vitamin E (α-tocopherol). No comprehensive UA is performed.

No eligible observational study was identified.

The Panel considers that the available evidence on the relationship between α-tocopherol supplementation and risk of congestive heart failure cannot be used for establishing a UL for vitamin E (α-tocopherol).

3.4.3 | Prostate cancer

Concerns about an adverse effect of α-tocopherol on the risk of prostate cancer have arisen from the Selenium and Vitamin E Cancer Prevention trial (SELECT) (Klein et al., 2011). A recent systematic review with broader inclusion criteria than those in the Protocol (Annex A), was identified (Loh et al., 2022) and served as the main source of data. An additional systematic literature search was conducted, covering the period since the literature search of the systematic review was conducted. The search strategy is provided in Annex B.

This literature search identified 17 articles, which report the results of four RCTs and nine observational studies. The flow chart is provided in **Appendix A.3**.

3.4.3.1 | *Intervention studies*

A total of eight publications reporting on four eligible RCTs examined the effect of α-tocopherol supplementation on the risk of prostate cancer (Gaziano et al., 2009; Heinonen et al., 1998; Klein et al., 2011; Lippman et al., 2009; Lonn et al., 2005; Virtamo et al., 2003; Virtamo et al., 2014; Wang et al., 2014). The paper by Virtamo et al. (2003) was retained as the primary source for the ATBC end-of-trial results, as it provided the most comprehensive report on prostate cancer risk. The paper by Heinonen et al. (1998) was retained as the primary source for the prostate cancer specific mortality in the ATBC end-of-trial results. For SELECT, PHS II and ATBC, results were reported both at the end of the trial and after an additional observational follow-up period.

Preliminary UA

The size of the trials ranged from around 7000 to almost 18,000 participants. One trial was conducted in the US (PHS II), one in Finland (ATBC), one in Canada, the US and Puerto Rico (SELECT), and one was an international collaboration (HOPE/HOPE-TOO). The trials included men with a mean age at baseline ranging from 57 years (ATBC) to 66 years (HOPE). Regarding other risk factors for prostate cancer, SELECT had a higher proportion of African American men, compared to the other trials. Information regarding family history of prostate cancer was not available.

The evidence table is provided in **Appendix B.3**. Key study characteristics, together with the effect estimates and related CIs are plotted in Figure 9. The figure presents the end-of-intervention results for each trial, as well as those of the follow-up observational phase, when available.

Author	Form/ dose reported	Dose converted	N total	Follow-up (years)	N cases	Estimate type	Effect estimate
Virtamo et al., 2003, ATBC	Placebo		7287	8 (max)	67	RR	Ref.
	50 mg/d all rac-α-tocopheryl acetate	45 mg/d	7286	8 (max)	43	RR	0.64 (0.44-0.94)
Virtamo et al., 2014, ATBC	Placebo		6388	18 (max)	605	RR	Ref.
Post-trial follow-up	50 mg/d all rac-α-tocopheryl acetate	45 mg/d	6388	18 (max)	553	RR	0.92 (0.82-1.03)
Gaziano et al., 2009, PHS II	No α-tocopherol		7000	8 (mean)	515	HR	Ref.
	400 IU/altern. d all rac-α-tocopheryl acetate	182 mg/d	6983	8 (mean)	493	HR	0.97 (0.85-1.09)
Wang et al., 2014, PHS II	No α-tocopherol			2.8 (mean)	173	HR	Ref.
Post-trial follow-up	400 IU/altern. d all rac-α-tocopheryl acetate	182 mg/d		2.8 (mean)	183	HR	1.06 (0.86-1.30)
Lippman et al., 2009, SELECT	Placebo		8696	4.56 (median)	416	HR	Ref.
	400 IU/d all rac-α-tocopheryl acetate	364 mg/d	8737	4.56 (median)	473	HR	1.13 (0.99-1.29)
Klein et al., 2011, SELECT	Placebo		7894	2.8 (max)	113	NR	
Post-trial follow-up	400 IU/d all rac-α-tocopheryl acetate	364 mg/d	7994	2.8 (max)	147	NR	
Lonn et al., 2005, HOPE	No α-tocopherol		4780	4.5 (mean)	119	RR	Ref.
	400 IU/d RRR-α-tocopheryl acetate	268 mg/d	4761	4.5 (mean)	116	RR	0.98 (0.76-1.26)
Lonn et al., 2005, HOPE-TOO	No α-tocopherol		3510	2.6 (mean)	101	RR	Ref.
	400 IU/d RRR-α-tocopheryl acetate	268 mg/d	3520	2.6 (mean)	91	RR	0.90 (0.68-1.19)

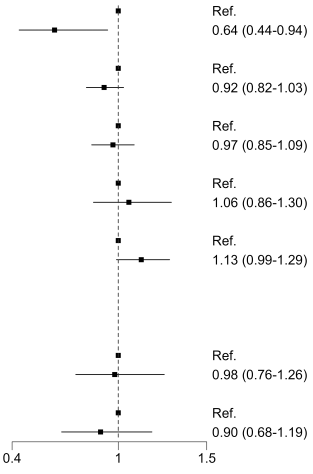

FIGURE 9 RCTs investigating the effect of α-tocopherol supplementation on prostate cancer risk.
ATBC, α-Tocopherol, β-Carotene Cancer Prevention Study; HOPE, Heart Outcomes Prevention Evaluation; HOPE-TOO, HOPE-The Ongoing Outcomes; PHS II, Physicians' Health Study II.
Notes: The effect estimates are expressed as estimate (95% CI). For the studies reporting results of the post-trial follow-up, the follow-up reflects the post-trial observation period. For Klein et al., 2011 the follow-up time was estimated based on information provided in the publication. Supplementation was converted to 'free' α-tocopherol in mg/day for all studies; doses given on alternate days were divided by 2 (column Dose converted).

The SELECT (Klein et al., 2011; Lippman et al., 2009) was a randomised placebo-controlled trial investigating the effect of vitamin E and selenium (alone or in combination) on prostate cancer prevention. Men were eligible if they were ≥ 50 years old if they were African American or ≥ 55 years of age for all other race and ethnicities, did not have a prior prostate cancer diagnosis, had a PSA in serum ≤ 4 ng/mL and a digital rectal examination (DRE) not suspicious for cancer. Participants were randomised to receive either vitamin E (400 IU/day of *all rac-α*-tocopheryl acetate; 364 mg *α*-tocopherol; *n* = 8737) or placebo (*n* = 8696) and/or selenium for a planned intervention time of 7–12 years. Participants were also offered a free multivitamin containing no selenium or vitamin E. Prostate cancer was self-reported by the participants and in most cases subsequently confirmed by central pathology review.

Following a pre-planned interim analysis, the independent data and safety monitoring committee recommended the early discontinuation of the trial because no evidence of benefit with either study agent was demonstrated. Lippman et al. (2009) evaluated the incidence of prostate cancer using data collected up to the time of study discontinuation. After a median intervention time of 5.5 years, the number of prostate cancer cases was higher in the *α*-tocopherol supplementation versus placebo group (473 vs. 416 prostate cancer cases, respectively; HR 1.13, 99% CI 0.95–1.35).

Unblinded follow-up continued for an additional 32 months from the date of study termination (post-trial follow-up). In analyses accounting for this additional follow-up (54,464 additional person-years), Klein et al. (2011) reported a higher number of prostate cancer cases in the *α*-tocopherol supplementation group, compared to the placebo diagnosed in the post-trial period (147 vs. 113, respectively). The overall number of prostate cancer cases, covering both the trial and post-trial follow-up period, was higher in the *α*-tocopherol supplementation group, compared to the placebo (620 vs. 529 prostate cancer cases; HR 1.17, 99% CI 1.004–1.36).

In the ATBC Study, 29,133 male smokers with a smoking history averaging one pack/day for 36 years were randomised to 50 mg/day *all rac-α*-tocopheryl acetate (45 mg/day *α*-tocopherol; *n* = 7286) or placebo (*n* = 7287) and/or *β*-carotene based on a 2 × 2 factorial design. The mean age of participants at baseline was 57.7 years. After randomisation volunteers were deemed ineligible (*n* = 113) due to history of cancer or serious illness limiting long-term participation, taking supplements of vitamin E, vitamin A or *β*-carotene in excess of predefined doses, and being treated with anticoagulants. The overall dropout rate was 30.0% (29.8% in the *α*-tocopherol group and 30.3% in the placebo group), including deaths. Overall average compliance was 93%, with no differences observed between intervention groups (study group-specific compliance was not reported). Cancer cases were identified through the Finnish cancer registry, and deaths from the national Register of Causes of Death.

In the analyses reported in Virtamo et al. (2003) reflecting the trial intervention period, 43 prostate cancer cases were reported in those receiving *α*-tocopherol only and 67 in those receiving placebo. The RR was 0.64 (95% CI 0.44–0.94). For the trial period, fewer prostate cancer deaths were reported for those receiving *α*-tocopherol compared to those who did not (23 vs. 39, respectively) (Heinonen et al., 1998).

Virtamo et al. (2014) reported on the 18-year period following the ATBC termination, including 25,563 participants who were alive at the beginning of the post-trial follow-up. During the post-trial follow-up, there were 2321 incident prostate cancers. No difference in incidence was observed between those who received *α*-tocopherol and those who received placebo (553 vs. 605 prostate cancer cases; RR 0.92, 95% CI 0.82–1.03). Body mass index (BMI) was reported to significantly modify the association between *α*-tocopherol and prostate cancer risk during the intervention and the post-trial follow-up. In men with BMI < 25 kg/m^2, the RR was 1.00 (95% CI 0.78–0.98), while in those with BMI greater than 25 kg/m^2 but lower than 30 kg/m^2, an RR of 0.87 (95% CI, 0.78–0.98) was reported when comparing *α*-tocopherol recipients versus non-recipients. In men with BMI ≥ 30 kg/m^2, comparing *α*-tocopherol recipients versus non-recipients, the RR was 1.25 (95% CI 1.01–1.55). A similar estimate was reported when the effect modification was assessed during the trial (RR 1.23, 95% CI 0.67–2.26). Fewer people died of prostate cancer during the post-trial follow-up among recipients of *α*-tocopherol compared to non-recipients (240 deaths vs. 289; RR 0.84, 95% CI 0.70–0.99).

The HOPE study was a 2 × 2 factorial trial of 400 IU/day *RRR-α*-tocopheryl acetate (268 mg/day *α*-tocopherol; *n* = 4761) versus placebo (*n* = 4780), in patients at high cardiovascular event risk. Compliance among the vitamin E intervention group was 89.2% at the final study visit (median follow-up of 5.2 years). Events were reported during the follow-up visits. Supporting documentation for each event was sent to the central project office (HOPE study investigators, 1996). Cancer events were adjudicated by a committee, based on medical reports, clinical summaries, imaging results, serum markers and other diagnostic procedures (Lonn et al., 2005). A total of 235 prostate cancer cases were observed in the HOPE study. Due to the benefit reported for ramipril, the extension trial (HOPE-TOO), continued testing the potential effect of *RRR-α*-tocopheryl acetate (400 IU/day) versus placebo in 174 of the 267 study centres which agreed to participate. Out of the 6114 participants in these centres, who were alive at the start of the study extension, 4732 agreed to continue their assigned intervention (*n* = 3994) or passive observation (*n* = 738). A similar number of prostate cancer cases was reported for *α*-tocopherol recipients versus non-recipients both in the main analysis (116 vs. 119 prostate cancer cases in *α*-tocopherol recipients vs. non-recipients; RR 0.98, 95% CI 0.76–1.26) and the sensitivity analysis including only the HOPE-TOO participants (91 vs. 101 prostate cancer cases in *α*-tocopherol recipients vs. non-recipients; RR 0.90, 95% CI 0.68–1.19).

The PHS II was a 2 × 2 × 2 × 2 factorial trial evaluating the effect of 400 IU *all rac-α*-tocopheryl acetate on alternate days (equivalent to 182 mg/day *α*-tocopherol; *n* = 7315) versus placebo (*n* = 7326), and/or vitamin C, beta-carotene or a multivitamin in the prevention of total and prostate cancer, cardiovascular disease and age-related eye diseases (i.e. cataracts and macular degeneration) in 14,641 male physicians (mean age 64.2 years). Participants who were taking anticoagulants were not eligible. Compliance at the end of follow-up was self-reported by the participants at 72% for the *all rac-α*-tocopheryl acetate group and 70% for the placebo group. Prostate cancer cases were self-reported, with the vast majority being subsequently confirmed by pathology or cytology reports. Rarely, a reported case of cancer was confirmed based on strong

clinical and radiological or laboratory marker evidence, when a pathology or cytology review was not conducted. During a mean follow-up of 8.0 years, 1008 prostate cancer cases were confirmed (Gaziano et al., 2009). Prostate cancer incidence rates were 9.1 per 1000 person years in *α*-tocopherol recipients, compared to 9.5 per 1000 person years in non-recipients. The reported HR for the association between *α*-tocopherol and prostate cancer risk was 0.97 (95% CI 0.85–1.09). There was no association with prostate cancer death (HR 1.01, 95% 0.64–1.58).

Wang et al. (2014) reported on the 2.8 years (mean) of post-trial follow-up of the PHS II. A total of 356 additional prostate cancer cases were reported for the post-trial follow-up (183 in the *α*-tocopherol treatment group and 173 in the placebo treatment group). In the post-trial follow-up period, the HR of the association between *α*-tocopherol and prostate cancer risk was 1.06 (95% CI 0.86, 1.30); the HR for prostate cancer death was 1.27 (95% CI 0.78, 2.04).

The Panel notes that important sources of heterogeneity exist across these trials. These sources include the chemical forms (synthetic vs. natural) and doses of *α*-tocopherol used, the duration of the intervention and the criteria used to recruit participants, which resulted in heterogeneous study populations (in terms of ethnicity, smoking habits, health status, co-exposures to other agents, i.e. other vitamins/minerals, drugs). No meta-analysis was conducted as the number of studies was too small to allow exploring the impact of these sources of heterogeneity (e.g. through stratified analysis).

Overall, the Panel notes that a 13% increased risk (HR 1.13, 99% CI 0.95–1.35 (Lippman et al., 2009)) of developing prostate cancer was found in the SELECT trial at a dose of 400 IU/day (364 mg *α*-tocopherol/day) for ca. 5.5 years. The three other trials found no effect of lower doses of *α*-tocopherol for similar or longer durations, i.e. 50 mg/day *all rac-α*-tocopherol acetate for 8 years in the ATBC (45 mg *α*-tocopherol/day), 400 IU on alternate days (182 mg *α*-tocopherol/day) for 8 years in the PHS II, and 400 IU/day (268 mg *α*-tocopherol/day) for ca. 4.5 years in the HOPE/HOPE-TOO trial. Given the heterogeneity of the studies, it is not known whether the effect observed in SELECT may be related to the form or dose of *α*-tocopherol used, the baseline characteristics of the participants or other unknown factors in this trial. No comprehensive UA is performed.

3.4.3.2 | *Observational studies*

Nine eligible prospective observational studies were retrieved. The evidence table is provided in **Appendix B.3**.

The studies were carried out in USA ($n = 6$), Canada ($n = 1$), Finland ($n = 1$) and Denmark ($n = 1$). FFQs were used to assess dietary 'vitamin E' intake in all studies; FFQs or questionnaires were used to assess supplemental 'vitamin E' intake.

When participants reported use of single supplements but information on the dose was missing, they were assigned 400 IU/day (Chan et al., 1999; Kirsh et al., 2006; Rodriguez et al., 2004; Wright et al., 2007). When participants reported use of multivitamins but information on the brand/dose was missing, they were assigned 30 IU/day (Agalliu et al., 2011; Kirsh et al., 2006; Wright et al., 2007). In all other studies, there is no indication on how missing information regarding the dose of supplemental *α*-tocopherol was handled (if applicable). Prostate cancer cases were identified either by self-reports and subsequently corroborated by medical and pathology reports, or by linkage to cancer registries.

Total 'vitamin E' intake

Five prospective observational studies (4 PC and one case-cohort study) reported on the association between total intake (i.e. from diet and supplements) and prostate cancer risk (Agalliu et al., 2011; Chan et al., 1999; Peters et al., 2008; Roswall et al., 2013; Weinstein et al., 2007). Weinstein et al. (2007) reported on total *α*-tocopherol intake, while the rest on total 'vitamin E' intake.

Key study characteristics, together with the effect estimates and related CIs are plotted in Figure 10. Due to limited information, the results of Chan et al. (1999) are not included in the plot.

Author	Form	Category	Intake	N total/ N cat	Follow-up (years)	N cases	Estimate type	Effect estimate
Weinstein et al., 2007, ATBC	a-tocopherol	Q1	≤ 7.06 mg/d	27111	19 (max)	322	RR	Ref.
PC	a-tocopherol	Q2	7.06-8.36 mg/d	27111	19 (max)	352	RR	1.08 (0.92 - 1.26)
	a-tocopherol	Q3	8.36-10.32 mg/d	27111	19 (max)	307	RR	0.95 (0.80 - 1.14)
	a-tocopherol	Q4	10.32-14.72 mg/d	27111	19 (max)	317	RR	0.96 (0.78 - 1.19)
	a-tocopherol	Q5	> 14.72 mg/d	27111	19 (max)	342	RR	1.00 (0.79 - 1.27)
Agalliu et al., 2011, CSDLH	"Vitamin E"	Q1	6.3 mg/d (median)	2525	7.7 (mean)	130	HR	Ref.
CC	"Vitamin E"	Q2	8.3 mg/d (median)	2525	7.7 (mean)	115	HR	0.86 (0.64 - 1.17)
	"Vitamin E"	Q3	14.6 mg/d (median)	2525	7.7 (mean)	155	HR	1.19 (0.89 - 1.59)
	"Vitamin E"	Q4	264.4 mg/d (median)	2525	7.7 (mean)	132	HR	1.01 (0.75 - 1.36)
	"Vitamin E"	Q5	462.0 mg/d (median)	2525	7.7 (mean)	129	HR	1.08 (0.80 - 1.45)
Peters et al., 2008, VITAL	"Vitamin E"	C1	<14.3 mg a-TE/d (10 y average)	8023	4 (max)	156	HR	Ref.
PC	"Vitamin E"	C2	14.3-<29.4 mg a-TE/d (10 y average)	8019	4 (max)	196	HR	1.20 (0.93 - 1.50)
	"Vitamin E"	C3	29.4-<98.1 mg a-TE/d (10 y average)	7989	4 (max)	195	HR	1.00 (0.78 - 1.30)
	"Vitamin E"	C4	≥ 98.1 mg a-TE/d (10 y average)	7974	4 (max)	217	HR	0.98 (0.77 - 1.30)
Rosswall et al., 2013,	"Vitamin E"	Q1	0 - ≤ 8.6 mg/d	26856	14.3 (median)	1571	HR	Ref.
Diet, Cancer and Health cohort	"Vitamin E"	Q2	> 8.6 - ≤ 12.0 mg/d	26856	14.3 (median)	1571	HR	1.00 (0.86 - 1.16)
PC	"Vitamin E"	Q3	> 12.0 - ≤ 17.7 mg/d	26856	14.3 (median)	1571	HR	0.92 (0.78 - 1.09)
	"Vitamin E"	Q4	> 17.7 mg/d	26856	14.3 (median)	1571	HR	0.90 (0.74 - 1.11)

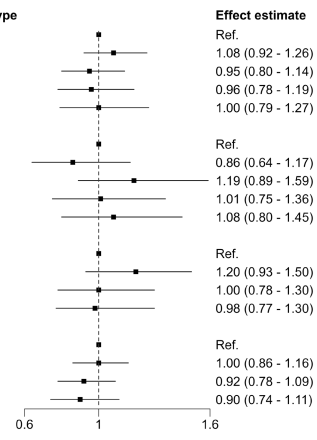

FIGURE 10 Results from observational studies on total 'vitamin E' intake and prostate cancer risk.
ATBC, *α*-Tocopherol, *β*-Carotene Cancer Prevention Study; CC, Case-cohort; CSDLH, Canadian Study of Diet, Lifestyle and Health; PC, Prospective cohort; VITAL, Vitamins and Lifestyle study.
Notes: Studies estimated total 'vitamin E' intake i.e. from diet and supplements. Peters et al., 2008 estimated the average daily intake over the previous 10 years of supplemental vitamin E intake by summing intake from individual supplements and intake from multivitamins in the 10-year period as: Years/10 × days per week/7 × dose. For Agalliu et al., 2011 and Peters et al., 2008 the follow-up time was estimated based on information provided in the publication. For Peters et al., 2008 number of participants per category is provided; in all other studies, the total number of participants is reported.

There was no evidence of an increased risk of prostate cancer associated with higher total 'vitamin E' or total *α*-tocopherol intake in any of the studies.

The Panel considers that the BoE from observational studies does not suggest a positive association between total 'vitamin E' or total *α*-tocopherol intake and risk of prostate cancer over the range of intakes examined in these studies.

Supplemental 'vitamin E' intake

Seven prospective observational studies reported on the association between supplemental 'vitamin E' intake and prostate cancer risk (Chan et al., 1999; Kirsh et al., 2006; Peters et al., 2008; Rodriguez et al., 2004; Roswall et al., 2013; Stram et al., 2006; Wright et al., 2007). Depending on the study, the supplemental 'vitamin E' intake was based on the use of single supplements, multivitamins or both single supplements and multivitamins.

Key study characteristics, together with the effect estimates and related CIs, are plotted in Figure 11.

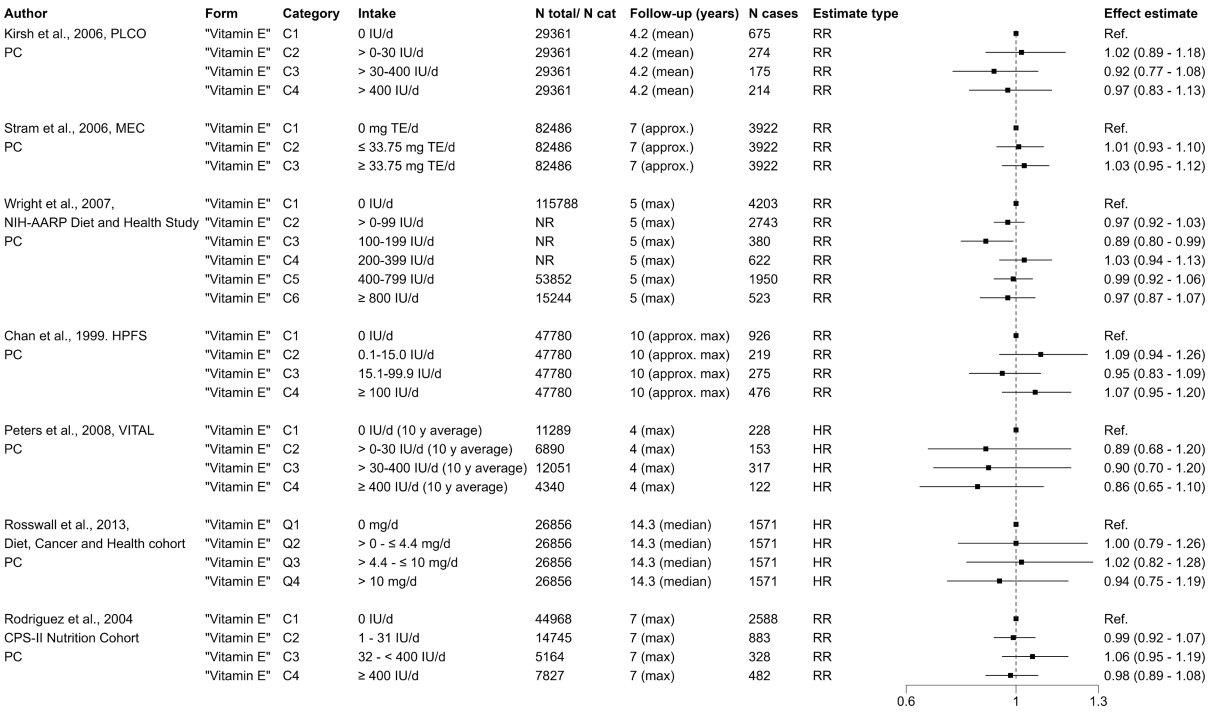

FIGURE 11 Results from observational studies on supplemental 'vitamin E' intake and prostate cancer.
CPS-II, Cancer Prevention Study II; HPFS, Health Professionals Follow-up Study; MEC, Hawaii-Los Angeles Multiethnic Cohort Study; NIH, National Institutes of Health; PC, Prospective cohort; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; VITAL, Vitamins and Lifestyle study.
Notes: Depending on the study, the supplemental 'vitamin E' intake was based on the use of single supplements, multivitamins or both single supplements and multivitamins. Peters et al. (2008) estimated the average daily intake over the previous 10 years of supplemental vitamin E intake by summing intake from individual supplements and intake from multivitamins in the 10-year period as: years/10 × days per week/7 × dose. For Chan et al. (1999), Peters et al. (2008) and Rodriguez et al. (2004), the follow-up time was estimated by the EFSA team based on information provided in the publication. For Wright et al. (2007), Peters et al. (2008) and Rodriguez et al. (2004)), number of participants per category is provided; in all other studies, the total number of participants is reported. For Stram et al. (2006) and Roswall et al. (2013), the total number of cases is reported.

There was no indication for an increased risk of prostate cancer associated with higher supplemental 'vitamin E' intake in any of the studies.

The Panel considers that the BoE from observational studies does not suggest a positive association between supplemental 'vitamin E' intake and risk of prostate cancer over the range of intakes (up to ≥ 800 IU/day) reported in these studies.

3.4.3.3 | *Animal data*

Because of the involvement of oxidative stress in carcinogenesis, a potential cancer prevention activity of *α*-tocopherol has been the subject of many studies in animal models. The text below focuses on experiments investigating prostate cancer.

McCormick et al. (2010) evaluated the effect of *all rac-α*-tocopherol acetate in a rat prostate cancer model in which animals received an intravenous injection of *N*-methyl-*N*-nitrosourea (MNU) followed by chronic androgen stimulation. They were randomised to receive either basal diet only (control), or basal diet supplemented with *α*-tocopherol at 2000 or 4000 mg/kg diet (i.e. 100 or 200 mg/kg bw per day) for 13 months. The number of adenocarcinoma in the dorsolateral plus anterior prostate in the control, low- and high-dose group were 14/40 (35%), 15/40 (38%) and 22/40 (55%) ($p < 0.10$ vs. dietary control). In contrast, the number of adenocarcinoma in seminal vesicle in the respective groups were 8 (20%), 4 (10%) and 2 (5%) ($p < 0.05$ vs. control).

Ozten et al. (2010) investigated whether *α*-tocopherol affected prostate carcinogenesis in a testosterone plus estradiol-treated NBL rat model. Rats were fed diets containing *all rac*-*α*-tocopherol acetate (2000 or 4000 mg/kg diet; i.e. 100 or 200 mg/kg bw/day) or a control diet for 1 year. *α*-tocopherol treatments did not affect prostate cancer incidence and multiplicity, while a reduction in the incidence of marked inflammation and marked epithelial dysplasia in the lateral prostate was found (dose-dependent). Total cancer incidence was similar across groups but an increased incidence of adenocarcinomas of the mammary glands of the groups treated with *α*-tocopherol compared to controls.

In a prostate carcinogenesis mice model (hCYP1A mice treated with 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP)), a lower percentage of glands with prostatic intraepithelial neoplasia was found among mice receiving a diet supplemented with *α*-tocopherol (0.2% diet) for 40 weeks compared to those receiving the control diet (Chen et al., 2016).

3.4.3.4 | *Overall conclusions on prostate cancer*

The panel notes the increased risk of prostate cancer reported in the SELECT, at a dose of 400 mg *all rac*-*α*-tocopherol acetate. However, this finding is not supported by three other RCTs, which used doses between 50 mg/day *all rac*-a-tocopheryl acetate and 400 IU/day *RRR*-*α*-tocopheryl acetate. Trials were heterogeneous regarding the form (natural vs. synthetic) or dose of *α*-tocopherol used, the baseline characteristics of the participants and other factors (i.e. ethnicity, smoking habits, health status, co-exposures to other agents). Observational prospective cohort studies do not provide supportive evidence for a positive relationship between *α*-tocopherol intake (including intake from food supplements) and risk of prostate cancer. Animal data do not provide supportive evidence for an increased risk of prostate cancer in response to *α*-tocopherol.

The panel considers that overall the available BoE is insufficient to conclude on a relationship between *α*-tocopherol intake and prostate cancer risk.

3.4.4 | Other adverse health effects

3.4.4.1 | *All-cause mortality*

Several systematic reviews and meta-analyses of RCTs have investigated the effect of 'vitamin E' supplementation on all-cause mortality (Abner et al., 2011; Bjelakovic et al., 2013; Miller III et al., 2005; O'Connor et al., 2022).[29] An increase of all-cause mortality was reported by Miller III et al. (2005) when pooling trials using 'vitamin E' supplemental doses ≥ 400 IU,[30] either alone or in combination with other vitamins/minerals. In a subsequent systematic review, Abner et al. (2011) found no evidence for an effect on mortality in subgroups analyses of trials using 'vitamin E' alone (11 trials) or vitamin E with other vitamins/minerals (46 trials). Including a larger number of studies using 'vitamin E' alone (20 trials), Bjelakovic et al. (2013) found no evidence for an effect of 'vitamin E' on mortality (RR 1.02, 95% CI 0.98–1.05, I2 = 0%). More recently, O'Connor et al. (2022) found no association between 'vitamin E' supplementation, alone (8 trials) or in combination with vitamin C (one trial) and all-cause mortality (OR, 1.02 [95% CI, 0.97–1.07]; 9 RCTs [*n* = 107,772]).

The panel notes that the nature of the outcome (composite of all causes of death) makes the interpretation of these data difficult.

The panel considers that the available evidence on the relationship between *α*-tocopherol supplementation and all-cause mortality cannot be used for establishing a UL for vitamin E (*α*-tocopherol).

3.4.4.2 | *Cataract risk*

A positive association between the use of 'vitamin E' as a single supplement (most common dose ~100 mg/day) and risk of developing age-related cataract has been reported in a prospective cohort study among Swedish Men (Zheng Selin et al., 2013). In contrast, no evidence for an increased risk with supplemental intake of 'vitamin E' was found in other prospective cohorts (PHS (Seddon et al., 1994); NHS (Christen et al., 2008; Hankinson et al., 1992); Longitudinal Study of Cataract (Leske et al., 1998); Beaver Dam Eye Study (Lyle et al., 1999)).

The literature search identified six publications reporting data from five trials reporting on the effect of *α*-tocopherol supplementation on the risk of developing cataracts. Cataracts risk was investigated as a secondary outcome in four studies [(Teikari et al., 1997; Teikari et al., 1998) (ATBC); (Christen et al., 2008) (WHS); (Christen et al., 2008) (PHS II); (Christen et al., 2010) (SELECT Eye Endpoints)], and as the primary outcome of the VECAT trial (McNeil et al., 2004), which aimed at studying the effect of *α*-tocopherol supplementation on the incidence or rate of progression of cataract. The endpoints were cases of cataract (total or by subtype), identified through an ophthalmological examination of the study participants and/or through Hospital Discharge Register (ATBC, VECAT) or self-reported and confirmed by medical records (PHS II, SELECT-SEE, WHS). The dose of *α*-tocopherol ranged between 45 mg/day (50 mg/day *all rac*-*α*-tocopheryl acetate) (ATBC) and 364 mg/day (400 IU/day *all rac*-*α*-tocopheryl acetate) (SELECT Eye Endpoints), and the duration of intervention was between 4 years (VECAT) and 9.7 years (WHS). The average age of participants at baseline ranged between 54 years (WHS)

[29]The literature search did not identify any additional study as compared to those included in these systematic reviews.

[30]The authors converted the dosage of vitamin E in each trial to international units (IU) per day, with reference to Bieri and McKenna (1981), https://doi.org/10.1093/ajcn/34.2.289.

and 66 years (VECAT). None of the studies indicated an increased risk of cataracts among the participants receiving the *α*-tocopherol supplementation compared to controls.

The Panel notes that the available body of evidence does not suggest a positive relationship between *α*-tocopherol supplementation and the risk of age-related cataracts.

The Panel considers that the available evidence on the relationship between *α*-tocopherol supplementation and risk of cataracts cannot be used for establishing a UL for vitamin E (*α*-tocopherol).

3.4.4.3 | *Pregnancy-related outcomes*

Rumbold et al. (2015) published a systematic review of RCTs to evaluate the safety of 'vitamin E' supplementation during pregnancy. A total of 21 trials were eligible for that review, of which only three trials administered supplemented 'vitamin E' alone versus placebo (Anthony et al., 1996; Sawhney et al., 2000; Shahraki, 2006). Two of those were available as conference abstracts and did not report the dose and form of 'vitamin E' used (Anthony et al., 1996; Sawhney et al., 2000). Shahraki (2006) aimed to assess the effect of 100 mg/day 'vitamin E' supplementation (form not specified) for 45 days on leg cramps. The study did not report adverse effects of *α*-tocopherol under the conditions of the intervention.

The present literature search identified two additional RCTs on *α*-tocopherol supplementation that were not included in the review by Rumbold et al. (2015). Bastani et al. (2011) randomised pregnant women to receive 296 mg/day *α*-tocopherol (400 IU/day *RRR*-*α*-tocopheryl acetate) or a placebo from week 14 of gestation to the end of pregnancy ($n = 104$ in the intervention group) and assessed the risk of preeclampsia, birth weight and Apgar score. Wangkheimayum et al. (2011) reported the effect of 2-week supplementation of 400 IU/day as *α*-tocopheryl acetate (source not specified) versus a placebo in women with pre-eclampsia ($n = 24$ in treatment group) on plasma concentrations of soluble P-selectin. These studies did not indicate adverse effects of *α*-tocopherol under the conditions of the interventions.

The Panel notes that available RCTs do not indicate adverse effects of *α*-tocopherol under the conditions of the interventions. However, data are scarce and provide limited relevant information for the safety assessment.

The Panel considers that the available evidence on the relationship between *α*-tocopherol intake and pregnancy-related outcomes cannot be used for establishing a UL for vitamin E (*α*-tocopherol).

3.4.4.4 | *Incidence and severity of respiratory infections*

The literature search identified 10 publications reporting data from three RCTs investigating the effect of *α*-tocopherol supplementation on the incidence of respiratory tract infections. Among these, four were selected for inclusion in this assessment (Graat et al., 2002; Hemilä et al., 2002; Hemilä et al., 2004; Meydani et al., 2004). The other papers are not described as they reported post hoc analyses of the same data (Hemilä, 2016a, 2016b; Hemilä et al., 2003; Hemilä et al., 2006; Hemilä & Kaprio, 2011; van Amsterdam et al., 2005).

Two trials were designed to assess the effect of *α*-tocopherol supplementation on incidence of acute respiratory tract infections (ARTI) in older adults (≥ 60 years). Based on a 2 × 2 factorial design, 652 community living older adults in the Netherlands were randomised to receive 400 mg/day *α*-tocopheryl acetate (source not specified), a multivitamin-mineral supplement, both or a placebo (Graat et al., 2002). Participants self-reported symptoms by telephone and a study nurse checked whether they met the definition of ARTI. When conducting microbiology and serology tests in a subsample of the symptomatic patients, infection was confirmed in 58% cases. During a median observation period of approximately 15 months, the incidence of ARTI was similar across groups. Comparisons of subjects receiving *α*-tocopherol versus no *α*-tocopherol indicated higher severity (illness duration, number of symptoms, fever episodes, restriction of activity) in those who had taken *α*-tocopherol.

In the other study, 617 older adults (≥ 65 years) residing in nursing homes in the USA were randomised to receive 182 mg/day *α*-tocopherol (200 IU/day *all rac*-*α*-tocopherol) or a placebo for 1 year (Meydani et al., 2004). Participants were examined by trained nurses throughout the study and diagnosis of ARTI was made by study physicians. No increased risk or increased duration of ARTI was found with *α*-tocopherol supplementation.

The two remaining papers reported on findings of the ATBC trial regarding the incidence of common colds, based on self-reporting at follow-up visits (not further verified) (Hemilä et al., 2002) and of hospital-treated pneumonia, ascertained through a national hospital discharge register (Hemilä et al., 2004). The follow-up period lasted 4 years for the first study and had a median duration of 5.8 years for the second study. The results of the two studies did not indicate an effect of supplementation with 45 mg/day *α*-tocopherol (50 mg/day *all rac*-*α*-tocopherol acetate) on the risk of common colds or hospital-treated pneumonia incidence.

The Panel notes that findings regarding an effect of *α*-tocopherol supplementation on respiratory tract infections are limited and inconsistent.

The Panel considers that the available evidence on the relationship between *α*-tocopherol supplementation and respiratory tract infections cannot be used for establishing a UL for vitamin E (*α*-tocopherol).

3.5 | Hazard characterisation

3.5.1 | Selection of the critical effect

The Panel systematically reviewed the available evidence on the relationship between high dietary (i.e. including fortified foods and food supplements) intake of *α*-tocopherol and impaired blood coagulation and risk of bleeding, cardiovascular-related endpoints and prostate cancer.

It is well established that high doses of *α*-tocopherol increase the risk of bleeding in animals, and that the mechanisms by which *α*-tocopherol could impair blood clotting could be similar in animals and humans. An interaction with vitamin K absorption and metabolism leading to prolonged PT and activated aPTT, and a decrease in platelet function, could be involved and explain why *α*-tocopherol may potentiate the effect of anticoagulant and antiplatelet medications (**Section 3.4.1**).

The Panel notes that the available evidence from RCTs including a high percentage of participants on secondary prevention for CVD and/or treatment with antiplatelet medications suggests an increased risk of haemorrhagic stroke upon *α*-tocopherol supplementation as compared to no *α*-tocopherol supplementation, placebo or no intervention. The Panel notes that available evidence from RCTs suggests an increased risk of CHF upon *α*-tocopherol supplementation following a myocardial infarction. The Panel notes that individuals on secondary prevention for CVD and/or treatment with antiplatelet medications are under medical care and that any *α*-tocopherol supplementation should be under medical supervision. The Panel considers that these individuals are outside of the target population of a UL for vitamin E (*α*-tocopherol).

The Panel considers that, overall, the available BoE is insufficient to conclude on a relationship between *α*-tocopherol intake and prostate cancer risk.

In line with the SCF conclusions, the Panel considers that the effect on blood clotting and the increased risk of bleeding is the critical effect to establish a UL for vitamin E (*α*-tocopherol) for the general population.

3.5.2 | Derivation of the UL

No relevant new evidence was retrieved regarding the risk of bleeding events with *α*-tocopherol supplementation in human intervention studies. The SCF previously established a NOAEL based on highest dose tested in the study by Meydani et al. (800 IU *all rac-α*-tocopherol), in which no effect was found on bleeding time. The Panel notes that two additional human intervention studies, which were not previously considered by the SCF, confirm this conclusion (**Section 3.4.1**). These findings are supported by a lack of effect on PT and/or aPTT in human intervention studies which tested similar or lower *α*-tocopherol doses (**Section 3.4.1**).

The Panel notes that 800 IU *all rac-α*-tocopheryl acetate is equivalent to 728 mg 'free' *α*-tocopherol (**Section 2.2.2**). In 2003, the SCF considered the dose of 800 IU *all rac-α*-tocopheryl acetate to correspond to 540 mg/day *α*-tocopherol equivalents.[31] The Panel notes that additional evidence has become available regarding the mechanisms by which *α*-tocopherol may affect blood coagulation, including an interaction with vitamin K at the level of intestinal absorption and hepatic metabolism, which is independent of the stereoisomeric forms of *α*-tocopherol (**Section 3.2.4.2**). The Panel therefore considers that all stereoisomers can be expected to have a similar activity in relation to the risk of bleeding. Despite this progress in mechanistic understanding, the Panel found no basis to change the UL previously established by the SCF. Considering the totality of the available evidence and related uncertainties (**Section 3.4**), the Panel thus retains the UL previously established by the SCF of 300 mg *α*-tocopherol/day for adults. The UL applies to all stereoisomeric forms of *α*-tocopherol.

The UL applies also to women during pregnancy and lactation, as no new evidence was found regarding specific adverse effects or different susceptibility in these groups.

In the absence of specific data on younger age groups, the SCF derived UL for children and adolescents, aged 1–17 years, by extrapolating the adult UL using allometric scaling (body weight$^{0.75}$). No new evidence was found investigating adverse effects of *α*-tocopherol supplementation in these age groups. The previously established ULs for *α*-tocopherol are also maintained by the NDA Panel for these population groups (Table 11).

There are no data to support a derivation of a UL for infants. On the other hand, there are no indications from the literature that infants may be more susceptible than adults to *α*-tocopherol toxicity. The Panel notes that vitamin K deficiency during early infancy could lead to vitamin K deficiency bleeding (VKDB). Vitamin K prophylaxis at birth is recommended (Mihatsch et al., 2016).

The following equations were applied (allometric scaling):

$$\mathrm{UL}_{\text{infant 4–6 months}} = \mathrm{UL}_{\text{adult}} \times \left(\text{body weight}_{\text{infant 4–6 months}} / \text{body weight}_{\text{adult}}\right)^{0.75} = 300 \times (7.2/70)^{0.75}$$

$$\mathrm{UL}_{\text{infant 7–11 months}} = \mathrm{UL}_{\text{adult}} \times \left(\text{body weight}_{\text{infant 7–11 months}} / \text{body weight}_{\text{adult}}\right)^{0.75} = 300 \times (8.6/70)^{0.75}$$

[31]The SCF converted all doses into *α*-tocopherol equivalents (*α*-TE). The conversion was based on factors established to account for the different biological activity of natural *(RRR-)* and synthetic *(all rac-)* forms regarding *α*-tocopherol physiological requirements.

Based on the reference body weight of the respective age groups and after rounding to the closest 10 mg,[32] a UL of 50 mg/day is established for infants 4–6 months and of 60 mg/day for infants 7–11 months (Table 10).

TABLE 10 UL for infants.

Age range	Reference bw males and females (kg)[a]	UL males and females (mg/day)
4–6 months	7.2	50
7–11 months	8.6	60

Abbreviations: bw, body weight, UL, tolerable upper intake level.

[a]The averages of the median weights-for-age for boys and girls at 5 and 9 months, respectively, were used as reference weights (WHO Multicentre Growth Reference Study Group, 2006).

3.6 | Risk characterisation

The ULs are established for the general European population and apply to vitamin E (*α*-tocopherol) intakes from all dietary sources. The UL applies to all stereoisomeric forms of *α*-tocopherol (**Section 3.5.2**).

ULs do not apply to individuals receiving anticoagulant or antiplatelet medications (e.g. aspirin) (**Section 2.1**), to patients on secondary prevention for CVD (**Section 3.4.2**) or to patients with vitamin K malabsorption syndromes (**Section 2.1**). ULs do not apply either to patients with specific conditions causing vitamin E deficiency (**Section 3.2.4.4**). The Panel notes that these population groups are under medical care, and hence, any *α*-tocopherol supplementation should be under medical supervision.

Harmonised data on *α*-tocopherol intake from all sources, including fortified foods and food supplements, for the European population are currently not available. Data on the intake of *α*-tocopherol from fortified foods and food supplements available from national surveys are scarce (**Section 3.3.3**).

The Panel considers that it is unlikely that the ULs for vitamin E (*α*-tocopherol) are exceeded in European populations, except for regular users of food supplements containing high doses of *α*-tocopherol (**Section 3.3**).

4 | CONCLUSIONS

The ULs presented in Table 11 are established for the intake of vitamin E (*α*-tocopherol) from all dietary sources. The UL applies to all stereoisomeric forms of *α*-tocopherol. ULs do not apply to individuals receiving anticoagulant or antiplatelet medications (e.g. aspirin), to patients on secondary prevention for CVD or to patients with vitamin K malabsorption syndromes. ULs do not apply either to patients with specific conditions causing vitamin E deficiency. These population groups are under medical care, and hence, any vitamin E (*α*-tocopherol) supplementation should be under medical supervision.

TABLE 11 ULs for vitamin E (*α*-tocopherol).[a]

Age group	UL for males and females (mg/day)
4–6 months	50
7–11 months	60
1–3 years	100
4–6 years	120
7–10 years	160
11–14 years	220
15–17 years	260
≥ 18 years	300
Pregnant women	300
Lactating women	300

[a]ULs apply to all stereoisomeric forms of *α*-tocopherol.

[32]It corresponds to < 10% variation compared to the unrounded figures (EFSA Scientific Committee, 2012).

5 | RECOMMENDATIONS FOR RESEARCH

- Further research is required regarding all groups of the population to characterise potential critical effects of excess α-tocopherol intake. Also, investigations of the potential vulnerability of specific subgroups of the population, such as infants and children, pregnant women and older adults, is needed, taking into account specific issues in terms of absorption, metabolism, distribution and excretion of α-tocopherol in these groups.
- Further research is needed on the mechanisms of interaction between vitamin E and vitamin K, including in populations not receiving warfarin.
- Further research is needed on the interaction of vitamin E with regular use of NSAIDs.
- Data on the consumption of fortified foods and food supplements containing α-tocopherol in EU populations are scarce. For the risk characterisation, there is a need to generate more and harmonised data on α-tocopherol intake in its different forms from food supplements and fortified foods.

ABBREVIATIONS

ADI	acceptable daily intake
ADME	Absorption, distribution, metabolism and excretion
ADP	adenosine diphosphate
AFC	Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with
AIs	Adequate Intakes
ANS	Panel on Food Additives and Nutrient Sources added to Food
aPTT	Activated partial thromboplastin time
AR	Average Requirements
ARTI	Acute respiratory tract infection
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
AVED	ataxia with isolated vitamin E deficiency
BMI	Body mass index
BoE	body of evidence
bw	body weight
CC	case-cohort study
CEHC	carboxyethyl hydroxychroman
CHAOS	Cambridge Heart Antioxidant Study
CHD	Coronary heart disease
CHF	Congestive heart failure
CHS	Cardiovascular Health Study
CI	Confidence Interval
CPS-II	Cancer Prevention Study II
CRALBP	cellular retinaldehyde binding protein
CSDLH	Canadian Study of Diet, Lifestyle and Health
CT	controlled trial
CVD	Cardiovascular disease
CYP4F2	cytochrome P450-4F2
DNFCS	Dutch National Food Consumption Survey
DRE	digital rectal exam
DRV	Dietary reference value
EVM	Expert Group on Vitamins and Minerals
FCBD	food composition database
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
FFQ	food-frequency questionnaire
FHS	Framingham Heart Study
FPQ	food propensity questionnaire
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico
GNPD	Global New Product Database
GWAS	Genome-wide association studies
HDL	high density lipoprotein
HELENA	Healthy Lifestyle in Europe by Nutrition in Adolescence
HOPE	Heart Outcomes Prevention Evaluation
HOPE-TOO	HOPE-The Ongoing Outcomes
HPFS	Health Professionals Follow-up Study
HR	Hazard Ratio
ICH	intracerebral haemorrhage
IOM	Institute of Medicine
IU	international unit

LDL	Low-density lipoprotein
LOAEL	lowest-observed-adverse-effect level
LoE	line of evidence
MEC	Hawaii-Los Angeles Multiethnic Cohort Study
min	minute(s)
MK-4	menaquinone-4
ML	Maximum Level
MNU	N-methyl-N-nitrosourea
NCC	nested case–control study
NDA	Nutrition, Novel Foods and Food Allergens
NHMRC	National Health and Medical Research Council
NHS	Nurses' Health Study
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
NR	Not reported
NRV	nutrient reference value
NSAID	Non-steroidal anti-inflammatory drug
NTP	National Toxicology Program
PC	prospective cohort study
PHS II	Physicians' Health Study II
PIVKA-II	inactive under-γ-carboxylated forms of prothrombin
PKC	protein kinase C
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PPP	Primary Prevention Project
PRIs	Population Reference Intakes
PSA	Prostate-specific antigen
PT	prothrombin time
RBC	red blood cells
RCT	randomised controlled trial
RP	reference point
SAH	subarachnoid haemorrhage
SCF	Scientific Committee on Food
SD	Standard deviation
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SELECT-SEE	SELECT Eye Endpoints
SPACE	Secondary Prevention with Antioxidants of Cardiovascular Disease
SPF	supernatant protein factor
sQ	subquestion
TAP	tocopherol associated protein
TAS	D-α-tocopheryl acid succinate
TIA	Transient ischaemic attack
UA	uncertainty analysis
UF	uncertainty factor
UL	tolerable upper intake levels
VEAPS	Vitamin E Atherosclerosis Progression Study
VECAT	Vitamin E, Cataract and Age-related Maculopathy Trial
VITAL	Vitamins and Lifestyle study
VKDB	vitamin K deficiency bleeding
VLDL	very low-density lipoprotein
WACS	Women's Antioxidant Cardiovascular Study
WHO	World Health Organization
WHS	Women's Health Study
α-CEHC	α-carboxyethyl hydroxychroman
α-TE	α-tocopherol equivalent
α-TTP	α-tocopherol transfer protein

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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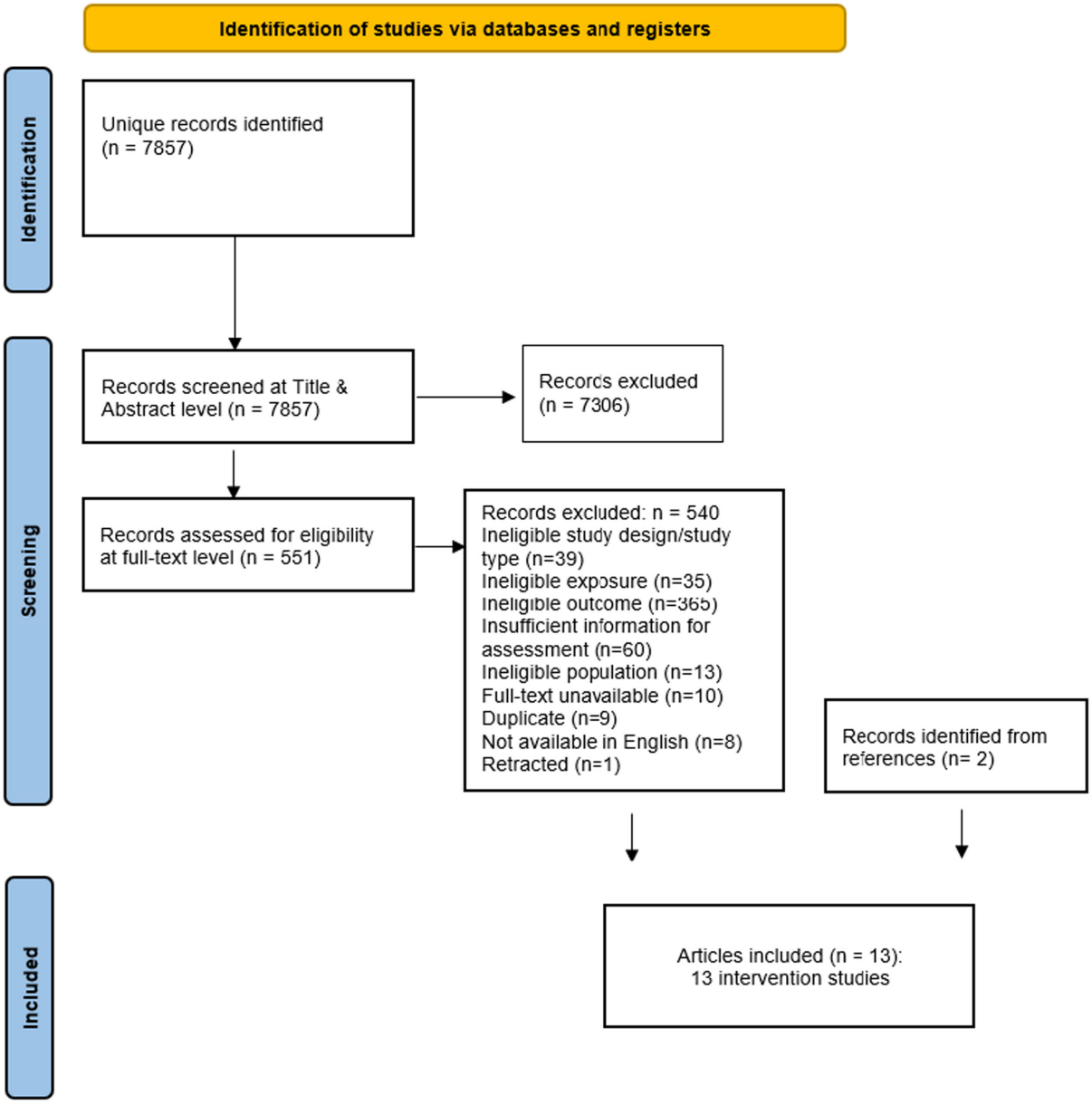
APPENDIX A

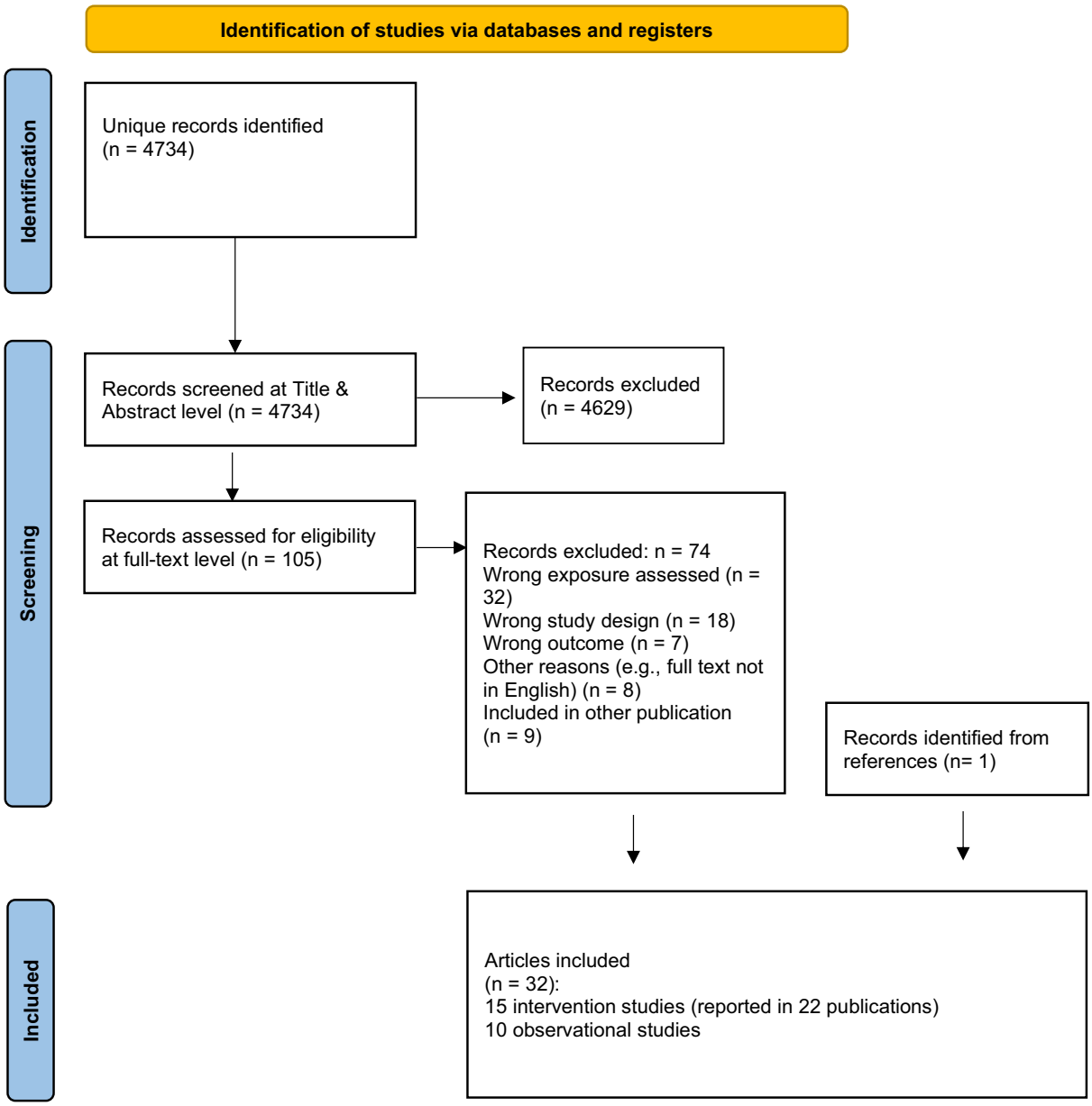
Literature screening and selection - Flow charts

A.1 | Flow chart for the selection of studies on impaired blood coagulation and risk of bleeding (sQ2)

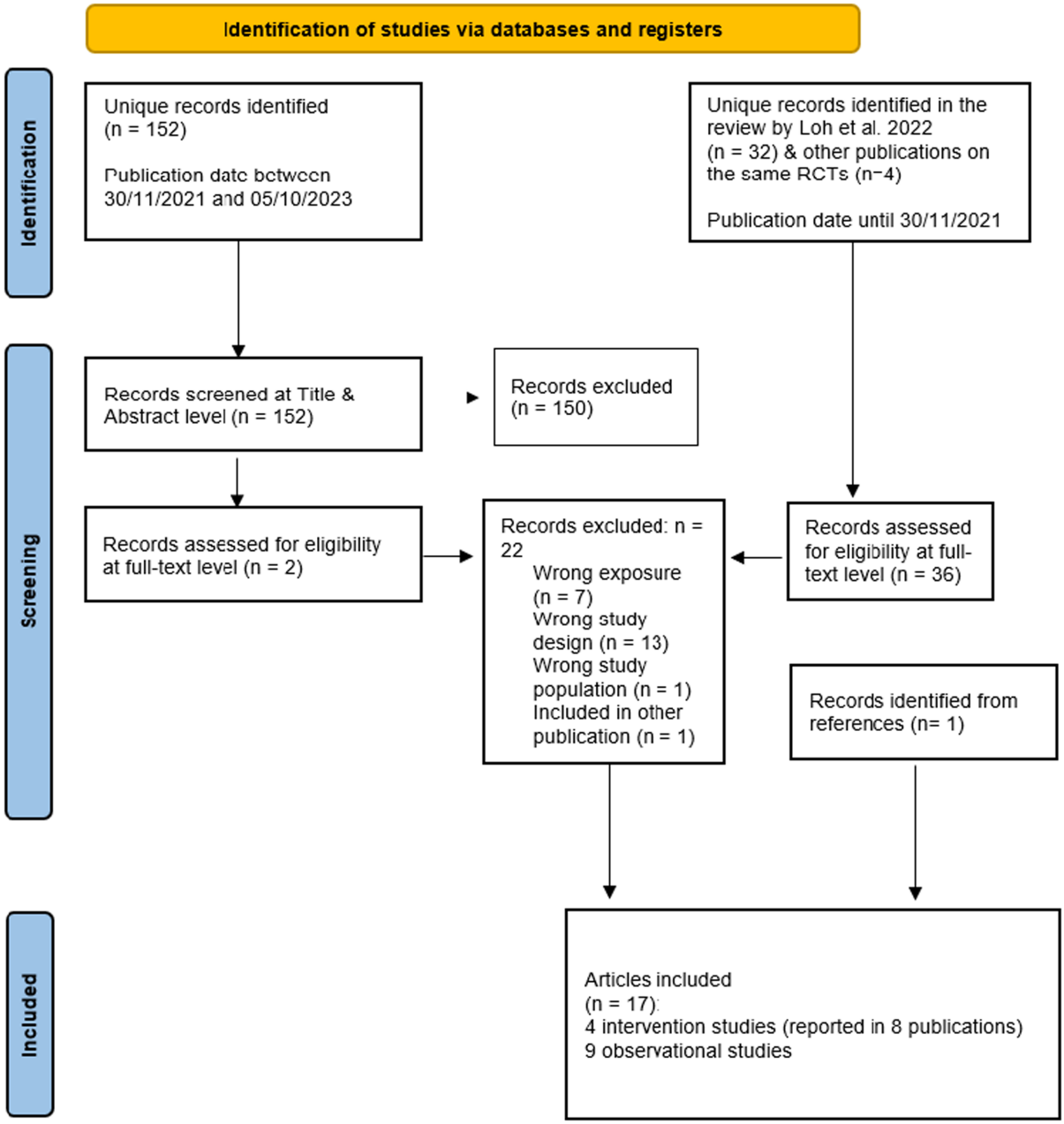


Note: In addition, 22 articles relevant to sQ5 were identified through this search.

A.2 | Flow chart for the selection of studies on cardiovascular disease (sQ3)



A.3 | Flow chart for the selection of studies on prostate cancer (sQ4)



APPENDIX B

Evidence tables

B.1 | Evidence tables on studies on impaired coagulation and bleeding risk

Reference country study duration funding	Design *N* = number randomised *n* = number analysed	Subjects' characteristics at baseline	Intervention	Outcome(s) assessed	Results
Stampfer et al. (1988) USA – 5 weeks Mixed	RCT, double-blind, placebo-controlled **Inclusion criteria**: No use of vitamin E within 1 months, no use of aspirin/other platelet-active agents for 2 weeks before the study and throughout **Exclusion criteria**: NR ***N*** = 20 ***n*** = NR	**Ethnicity:** NR **Age (years):** NR **Sex (female)**: 50% **BMI (kg/m^2):** NR **History of CVD:** NR **Current medication use (%):** NR **Vitamin K intake/status:** NR	**Supplement form:** NR **Doses** G1: 800 IU/day G2: placebo **Compliance:** 100% (self-reported)	**Bleeding time** **Method:** Simplate II device; once per forearm at each time **Platelet aggregation** **Method:** Addition of collagen (10 mg/L) or AA (1 mmol/L) **PT** **Method:** standard clinical haemostasis laboratory techniques **PTT** **Method:** standard clinical haemostasis laboratory techniques	Mean ± SD before/after intervention Bleeding time (min) G1: 6.73 ± 1.30/6.43 ± 1.86 G2: 6.28 ± 1.29/6.58 ± 1.49 *Mean changes in the vitamin E group* versus *the placebo group (data not shown) were not significant ($p > 0.05$; unpaired Student's t-test)* Extent of platelet aggregation (%): – after collagen stimulation G1: 88.8 ± 10.6/88.2 ± 10.6 G2: 83.9 ± 4.1/92.8 ± 11.9 – after AA stimulation: G1 79.4 ± 8.8/76.2 ± 6.3 G2: 80.8 ± 6.9/81.4 ± 7.6 *Mean changes in the vitamin E group* versus *the placebo group (data not shown) were not significant ($p > 0.05$)* PT, PTT *'No material differences between pretreatment and post-treatment values within either group or between the G1 and G2.' (data not shown)*
Meydani et al. (1998) USA – 4 months Mixed	RCT, double-blind, placebo-controlled **Inclusion criteria**: no acute or serious chronic disease, prescribed medication or NSAIDs on a regular basis, not taking vitamin or mineral supplements (prior 3 months), with serum vitamin E levels < 1.2 mg/dL, not vaccinated for hepatitis and pneumococcal vaccine, with a normal physical examination (chest radiograph, ECG, clinical chemistry profile, blood cell and differential counts and routine urine analysis) **Exclusion criteria**: dropouts and noncompliant subjects ***N*** = 88 ***n*** = 15–19/group	**Ethnicity:** NR **Age (years):** ≥ 65 **Sex (female)**: 50% **BMI (kg/m^2):** NR **History of CVD:** NR **Current medication use:** no regular use of anticoagulants, including NSAIDs, such as aspirin **Vitamin K intake/status:** '**n**ormal' – data not shown	**Supplement form:** *All rac-α*-tocopherol **Doses** G1: 60 IU/day G2: 200 IU/day G3: 800 IU/day G4: placebo **Compliance:** *'Six subjects were found to be noncompliant based on their serum vitamin E levels, pill count, and/or significant changes in their levels of other nutrients with known effects on the immune response'*	**Bleeding time** **Method:** Simplate II	Mean ± SD (seconds) before/after intervention, within group comparisons using paired Students' *t*-test Bleeding time (s) G1: 310 ± 78/345 ± 94 ($p > 0.05$) G2: 331 ± 68/293 ± 64 ($p > 0.05$) G3: 310 ± 89/288 ± 72 ($p > 0.05$) G4: 302 ± 97/263 ± 77 ($p > 0.05$)

(Continued)

Reference country study duration funding	Design *N* = number randomised *n* = number analysed	Subjects' characteristics at baseline	Intervention	Outcome(s) assessed	Results
Dereska et al. (2006) USA – 14 days NR	Uncontrolled, before-after intervention study **Inclusion criteria:** healthy volunteers, ≥ 18 years, no use of aspirin and NSAIDs for a minimum of 2 weeks **Exclusion criteria:** history of bleeding diathesis, hypertension, history of abnormal bleeding time, abnormally elevated or low platelet count, use of anticoagulants such as aspirin or other NSAIDs, coumadin, dipyridamole and sulfinpyrazone, anticoagulation drugs, antibiotics or injection of heparin or dextran 2 weeks before BL, history of recent liver disease, collagen vascular disease such as lupus, malignancy, current pregnancy, history of Vitamin E ingestion or known Vitamin K deficiency ***N*** = NR ***n*** = 40	**Ethnicity:** NR **Mean age (years):** 30.86 (range: 20–50) **Sex (female)**: 50% **BMI (kg/m^2):** NR **History of CVD:** NR **Current medication use:** subjects avoided medication that could affect coagulation and platelet aggregation for 28 days **Vitamin K intake/status:** individuals with known vitamin K deficiency were excluded at BL	**Supplement form:** DL-*α*-tocopherol acetate **Dose** 800 IU/day **Compliance:** 66%. 8 (20%) subjects missed 1 day of supplementation, 3 (8%) missed 2 days, and one (3%) subject missed 3–4 days	**Bleeding time** **Method:** measured using the PFA-100 instrument. The simulation of platelet adhesion, activation and aggregation after a vascular injury (bleeding time) was performed by one of two investigators on each sample before/after Vitamin E supplementation **Platelet aggregation** **Method:** measured by calculating the amplitude and slope for each aggregation curve using the AGGRO/LINK **PT** **Method:** HEMOCHRON Whole Blood Coagulation Systems Test Procedures **APPT** **Method:** HEMOCHRON Whole Blood Coagulation Systems Test Procedures	Mean ± SD before/after intervention, within group comparisons Bleeding time (s) 105.72 ± 31.78/96.25 ± 23.40 (p = 0.305) Platelet aggregation – Impedance aggregation (Ohms) 19.58 ± 7.16/18.2 ± 4.98 (p = 0.658) – Slope (Ohms/min) 11.88 ± 3.53/12.42 ± 3.41 (p = 0.522) PT (s) 61.38 ± 5.36/59.53 ± 5.95 (p = 0.217) APTT (s) 129.53 ± 9.19/129.85 ± 10.77 (p = 0.885)
Szczeklik et al. (1985) Poland – 28 days (14 days of placebo +14 days of active treatment) NR	RCT, single-blinded **Inclusion criteria:** healthy individuals, with standard laboratory tests including serum cholesterol and triglycerides were within normal ranges **Exclusion criteria:** NR ***N*** = 18 ***n*** = 18 G1 (n) = 9 G2 (n) = 9	**Ethnicity:** NR **Mean age (years):** 37 (range: 23–56) **Sex (female):** 33% **BMI (kg/m^2):** NR **History of CVD:** NR **Current medication use:** no use of any anti-inflammatory drug 2 weeks before BL, and no medication for 12 h before blood sampling **Vitamin K intake/status:** NR	**Supplement form:** *α*-tocopherol acetate **Dose** G1: placebo (14 days) + 300 mg/days (subsequent 14 days) G2: placebo (14 days) + 600 mg/days (subsequent 14 days) **Compliance:** NR	**Platelet aggregability** **Method:** measured in PRP using a Born aggregometer, with the lowest (threshold) concentrations of ADP and AA causing irreversible aggregation within 3 min (ADP) or 1 min (AA) being determined. Collagen was used in 4 concentrations: 0.2; 0.5; 1.0 and 3.0 μg/mL	*'Neither placebo nor any of the two doses of vitamin E produced changes in the parameters of platelet aggregability'*

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Reference country study duration funding	Design *N* = number randomised *n* = number analysed	Subjects' characteristics at baseline	Intervention	Outcome(s) assessed	Results
Calzada et al. (1997) UK – 8 weeks Mixed	RCT, double-blind, placebo-controlled **Inclusion criteria:** healthy volunteers **Exclusion criteria:** smoking, heavy drinking, consumption of antioxidant and mineral supplements, oral contraceptives, taking aspirin or specified drugs interfering with platelet functions for 2 weeks before the study and during its course ***N*** = NR ***n*** = 40 G1 (n): 10 G2 (n): 9 G3 (n): 9 G4 (n): 9	**Ethnicity:** NR **Mean age (years):** 31.2 ± 8.8 **Sex (female):** 40% **Mean BMI (kg/m^2):** 23.6 ± 3.7 **Vitamin K intake/status:** NR	**Supplement form:** DL-*α*-tocopherol acetate G1: 300 mg/days DL- *α*-tocopherol acetate G2: 250 mg/day L-ascorbic acid G3: 15 mg/days *β*-carotene G4: placebo **Compliance**: 98% (assessed by counting the number of pills returned)	**Platelet aggregation** **Method:** measured in PRP according to the turbidimetric Born method. Three agonists were used: ADP, AA and collagen (type I) and the extent of platelet aggregation was expressed in terms of % of change in light transmission 4 min after the addition of the agonist **Platelet responsiveness to PGE$_1$** **Method:** Inhibition of platelet aggregation by PGE1 was determined in PRP samples stimulated with ADP. The concentration of exogenous PGE$_1$ causing 50% inhibition of ADP-induced platelet aggregation (IC$_{50}$) was calculated from the dose-inhibition curve (percent inhibition of aggregation versus final concentration of PGE$_1$)	Mean ± SEM changes, compared with placebo group using unpaired Student's *t*-test Platelet aggregation (concentration of agonist causing 50% aggregation (EC$_{50}$)) ADP G1: 1.07 ± 0.24 ($p < 0.05$) G2: 1.12 ± 0.69 ($p > 0.05$) G3: 0.77 ± 0.32 ($p > 0.05$) G4: 0.04 ± 0.39 AA G1: 45.5 ± 23.2 ($p < 0.05$) G2: 42.6 ± 22.5 ($p < 0.05$) G3: 24.6 ± 33.8 ($p > 0.05$) G4: −58.3 ± 32.6 Collagen G1: 0.21 ± 0.08 ($p > 0.05$) G2: 0.23 ± 0.08 ($p > 0.05$) G3: 0.23 ± 0.10 ($p > 0.05$) G4: 0.00 ± 0.11 Platelet responsiveness to PGE$_1$ (IC$_{50}$) G1: −6.12 ± 1.74 ($p < 0.05$) G2: −4.56 ± 1.87 ($p > 0.05$) G3: −1.58 ± 1.62 ($p > 0.05$) G4: −1.60 ± 1.16 ($p > 0.05$)
Jandak et al. (1989)[a] USA - 4 weeks NR	Uncontrolled, before-after intervention study **Inclusion criteria:** healthy volunteer donors who had abstained from any medication, including aspirin and other NSAIDs, for at least 2 weeks **Exclusion criteria:** NR ***N*** = NR ***n*** = 6	**Ethnicity:** NR **Age range (years):** 28–52 **Sex (female)**: 50% **BMI (kg/m^2):** NR **History of CVD:** NR **Current medication use:** subjects abstained from medication (aspirin and NSAIDs) in the 2-week period prior to BL **History of tobacco use:** all were non-smokers **Vitamin K intake/status:** NR	**Supplement form:** D-*α*-tocopherol acetate **Doses:** 200 IU/days for 2 weeks and 400 IU/days for the subsequent 2 weeks **Compliance:** NR	**Platelet adhesion** **Method:** measured ex vivo in an area of parallel flow lines and low shear rate under standardised conditions before and after dietary supplementation in different surfaces (glass, collagen, fibronectin and fibrinogen)	Mean, within group comparisons using paired Student's *t*-test Platelet adhesion (cumulative platelet number × min^{-1}) Glass: BL: 11.46 200 IU/days: 1.59 400 IU/days: 2.34 $p < 0.01$ for 200 versus 400 IU/days $p < 0.05$ for 200 versus BL and 400 versus BL Collagen I: BL: 15.67 200 IU/days: 2.46 400 IU/days: 1.35 $p < 0.01$ for 400 IU/day versus BL $p < 0.05$ for 200 IU/day versus BL Fibronectin: BL: 22.40 200 IU/days: 6.61 400 IU/days: 4.50 $p < 0.05$ for 200 versus BL and 400 versus BL Fibrinogen: BL: 38.42 200 IU/days: 12.22 400 IU/days: 6.49 $p < 0.01$ for 200 versus 400 IU/days $p < 0.05$ for 200 versus BL and 400 versus BL

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Reference country study duration funding	Design *N* = number randomised *n* = number analysed	Subjects' characteristics at baseline	Intervention	Outcome(s) assessed	Results
Kitagawa & Mino (1989) Japan – 3 months Mixed	RCT, single-blinded, placebo-controlled **Inclusion criteria:** healthy male college student volunteers, with a completed health check ***N*** = 19 ***n*** = 19 G1 (n): 14 G2 (n): 5	**Age range (years):** 24–25 **Plasma *α*-tocopherol at BL:** 800 μg/100 mL **Vitamin K intake/status:** PIVKA-II < 0.5 μg/mL	**Supplement form:** RRR-*α*-tocopherol **Doses** G1: 600 mg/days RRR-*α*-tocopherol G2: placebo **Compliance:** NR	**PT** **Method:** NR **PTT** **Method:** NR	Mean ± SD before/after intervention PT (%) G1: 99 ± 4/97 ± 4 G2: 98 ± 4/98 ± 2 PPT (seconds) G1: 35.2 ± 2.1/35.0 ± 2.4 G2: 34.9 ± 2.6/35.1 ± 2.7
Liu et al. (2003) Sweden – 8 weeks Public	RCT **Inclusion**: Healthy subjects aged 33–74 years **Exclusion**: heavy drinking, smoking, taking other drugs or antioxidants (i.e. vitamin C) interfering with platelet function in the 2 weeks before the study and during experimental period ***N*** = 46 ***n*** = 46 G1: 18 G2: 18 G3: 10	**Ethnicity:** White **Mean age (years):** 52.2 ± 1.5 **Sex**: NR **BMI (kg/m^2):** NR **History of CVD (%):** NR **Family history of cardiovascular disease (%):** NR **Current medication use (%):** NR **Vitamin K status/intake:** NR	**Supplement form:** *All rac-α*-tocopherol acetate **Doses** G1: 100 mg/days *all rac-α*-tocopherol acetate G2: Mixed tocopherol (100 mg *γ*-, 40 mg *δ*-, 20 mg *α*-tocopherol) G3: untreated control **Compliance:** > 95%	**Platelet aggregation** **Method**: Platelets were stimulated by ADP and PMA. Aggregation studies were performed using a 4-channel chronolog aggregometer in duplicate. Following this, samples were centrifuged, and the supernatant from ADP-induced aggregation was used to measure NO release. Platelet pellets from ADP stimulation were analysed for ecNOS or SOD Western blot, while those from PMA stimulation were used for PKC Western blot analysis	*Significant within group ADP-induced platelet aggregation changes for the mixed tocopherol group only* *No significant changes were found in the α-tocopherol group or in the control group. No significant changes in PMA-induced platelet aggregation in any of the groups*
Mabile et al. (1999) UK – 10 weeks (6 weeks of supplementation) Mixed	Uncontrolled, before-after intervention study **Inclusion criteria:** healthy subjects **Exclusion criteria:** smoking, heavy drinking, consumption of antioxidant supplements, oral contraceptives, aspirin (or aspirin-containing drugs) and specific anti-inflammatory drugs, antibiotics, b-blockers, tricyclic anti-depressants, antihistamines, corticosteroids, garlic tablets, for 10 days before BL ***N*** = 22 ***n*** = 22	**Ethnicity:** NR **Mean age (years)**: 30 ± 5.7 **Sex (female)**: 54.5% **BMI (kg/m^2):** 24 ± 3.7 **History of CVD (%):** NR **Current medication use (%):** subjects taking oral contraceptives, aspirin (or aspirin-containing drugs) and specific anti-inflammatory drugs, antibiotics, b-blockers, tricyclic anti-depressants, antihistamines, corticosteroids, garlic tablets, for 10 days before BL were excluded **Plasma *α*-tocopherol at BL (μM):** 31.9 ± 10.7 **Vitamin K intake/status:** NR	**Supplement form:** Natural *α*-tocopherol **Doses** Week 1–4: 0 IU/days Week 5 & 6: 75 IU/days Week 7 & 8: 200 IU/days Week 9 & 10: 400 IU/days **Compliance:** 99% (assessed by pill count)	**Platelet aggregation** **Method:** measured in PRP turbidometrically in a Payton lumi-aggregometer. The extent of platelet aggregation was estimated quantitatively by measuring the height of the curve reached above baseline level 4 min after the addition of ADP and expressed as percent of change in light transmission **Platelet responsiveness to PGE_1** **Method:** determined in PRP samples stimulated by ADP. A dose-inhibition response (% inhibition of aggregation versus PGE_1 concentration) was determined and the concentration of PGE_1 causing 50% inhibition of ADP-induced aggregation (IC_{50}) was calculated	Platelet aggregation *α-tocopherol supplementation resulted in a decrease in the platelet sensitivity to ADP. The highest differences were observed after 2 weeks of supplementation with the lowest dose (75 IU/days), with no further changes in aggregation being identified with increasing α-tocopherol intake levels* Platelet responsiveness to PGE_1 *'The IC50 for PGE1 showed a 1.4-fold decrease ($p < 0.001$) following the first period of supplementation with the lowest dose (75 IU/days, reaching a 1.6-fold decrease ($p < 0.001$) at the end of the supplementation. The IC50 for PGE1 was significantly correlated to the platelet vitamin E levels for all supplementation periods ($p < 0.0001$)'*

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Reference country study duration funding	Design *N* = number randomised *n* = number analysed	Subjects' characteristics at baseline	Intervention	Outcome(s) assessed	Results
Morinobu et al. (2002) Japan – 28 days NR	Controlled trial **Inclusion criteria:** healthy adult male volunteers **Exclusion criteria:** NR ***N*** = 22 ***n*** = 22 G1 (n): 14 G2 (n): 8	**Ethnicity:** NR **Mean ± SD age (years):** G1: 29.3 ± 3.4 G2: 27.0 ± 1.2 **Sex (female):** 0% **Mean ± SD body weight (kg):** G1: 62.2 ± 5.7 G2: 61.0 ± 5.0 **History of CVD (%):** NR **Current medication use (%):** NR **Vitamin K intake/status:** mean ± SD at BL among G1 was 4.3 ± 0.4 mEq/L	**Supplement form:** D-*α*-tocopherol **Doses** G1: 800 mg/day G2: control **Compliance:** NR	**PT** **Method:** assessed by STA **APTT** **Method:** assessed by STA **Platelet aggregation** **Method:** assessed by HEMA TRACER 601. Aggregation was induced by ADP and collagen, and the results were expressed as the maximum aggregation rate	Mean ± SD PT (%) G1, day 0: 108 ± 9 G1, day 14: 107 ± 11 G1, day 28: 111 ± 6 G1, day 56: 113 ± 10 G2, day 0: 108 ± 9 G2, day 14: 106 ± 7 G2, day 28: 106 ± 9 APPT (seconds): G1, day 0: 35.8 ± 3.0 G1, day 14: 36.3 ± 3.0 G1, day 28: 33.6 ± 2.9 G1, day 56: 34.4 ± 1.7 G2, day 0: 36.5 ± 3.2 G2, day 14: 37.2 ± 1.7 G2, day 28: 35.2 ± 2.7 Platelet aggregation (ADP) (%): G1, day 0: 65.0 ± 18.1 G1, day 14: 50.1 ± 14.4 G1, day 28: 45.1 ± 16.5 G1, day 56: 43.6 ± 15.0 G2, day 0: 58.5 ± 18.0 G2, day 14: 61.8 ± 16.0 G2, day 28: 41.4 ± 22.4 Platelet aggregation (collagen) (%): G1, day 0: 84.1 ± 8.1 G1, day 14: 85.8 ± 2.5 G1, day 28: 84.5 ± 7.3 G1, day 56: 82.1 ± 5.4 G2, day 0: 84.1 ± 6.4 G2, day 14: 85.9 ± 2.9 G2, day 28: 81.4 ± 5.7 *No significant differences between both groups for any of the parameters*

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Reference country study duration funding	Design *N* = number randomised *n* = number analysed	Subjects' characteristics at baseline	Intervention	Outcome(s) assessed	Results
Silbert et al. (1990) Australia – 28 days (14 days of placebo +14 days of supplementation) NR	Uncontrolled, single-blinded, before-after intervention study **Inclusion criteria:** healthy male non-medical hospital workers **Exclusion criteria:** NR ***N*** = 9	**Ethnicity:** NR **Age range (years):** 41–63 **Sex (female):** 0% **BMI (kg/m^2):** NR **History of CVD (%):** NR **Current medication use:** No subject was on any medication on the 3 weeks prior to BL **Vitamin K intake/status:** NR	**Supplement form:** D-*α*-tocopherol **Doses** Placebo for 14 days and 1500 IU/day on the subsequent 14 days **Compliance:** NR	**Platelet aggregation method:** measured as the maximum change in electrical impedance induced in 5 min by ADP (2 and 8 μmol/L) and collagen (0.5 and 2 μg/mL) in whole blood and platelet rich plasma	Mean ± SD, within group comparisons using ANOVA Whole blood platelet aggregation (Ohms) with ADP 2 μmol/L BL: 10.0 ± 6.1 Placebo: 10.5 ± 4.7 Vitamin E: 10.4 ± 4.1 Whole blood platelet aggregation (Ohms) with ADP 8 μmol/L BL: 11.5 ± 4.1 Placebo: 12.3 ± 2.1 Vitamin E: 13.0 ± 2.8 Whole blood platelet aggregation (Ohms) with collagen 0.5 μg/mL BL: 7.5 ± 6.2 Placebo: 5.5 ± 7.6 Vitamin E: 8.7 ± 9.1 Whole blood platelet aggregation (Ohms) with collagen 2 μg/mL BL: 23.3 ± 5.3 Placebo: 22.5 ± 3.8 Vitamin E: 22.8 ± 4.6 Plasma platelet aggregation (Ohms) with ADP 2 μmol/L BL: 15.2 ± 3.1 Placebo: 14.2 ± 1.6 Vitamin E: 14.3 ± 2.6 Plasma platelet aggregation (Ohms) with ADP 8 μmol/L BL: 15.2 ± 3.1 Placebo: 14.2 ± 1.6 Vitamin E: 14.3 ± 2.6 Plasma platelet aggregation (Ohms) with collagen 0.5 μg/mL BL: 8.8 ± 4.1 Placebo: 8.5 ± 8.8 Vitamin E: 12.5 ± 6.5 Plasma platelet aggregation (Ohms) with collagen 2 μg/mL BL: 18.6 ± 1.8 Placebo: 17.8 ± 4.0 Vitamin E: 18.0 ± 2.7 No significant differences between the three study periods

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Reference country study duration funding	Design *N* = number randomised *n* = number analysed	Subjects' characteristics at baseline	Intervention	Outcome(s) assessed	Results
Steiner (1983) USA – 6 weeks Public	**Inclusion criteria:** healthy volunteers **Exclusion criteria:** ***N*** = 47	**Ethnicity:** NR **Age range (years):** 18–57 **Sex (female):** 57% **BMI (kg/m^2):** NR **History of CVD (%):** NR **Current medication use:** No subject was on any medication during the study period **Vitamin K intake/status:** NR	**Supplement form:** DL-*α*-tocopherol acetate **Doses** G1: 400 IU/day of DL-*α*-tocopherol acetate for 2 weeks, 800 IU/day for the subsequent 2 weeks and 1200 IU/day for the final 2 weeks +300 mg of aspirin on alternate days G2: 400 IU/day of DL-*α*-tocopherol acetate for 2 weeks, 800 IU/day for the subsequent 2 weeks and 1200 IU/day for the final 2 weeks G3: 300 mg of aspirin on alternate days G4: control (no treatment) **Compliance:** NR	**Platelet adhesion** **Method:** **Platelet aggregation** **Method:** measured in a Chrono-Log platelet aggregometer by continuous recording of the changes in light transmission on stirring the platelet suspensions at 1000 rpm at 37°C, induced by ADP, epinephrine and collagen.	Platelet adhesion *Vitamin E alone reduced platelet adhesion in a dose-dependent manner (changes were significant for the total 6-week period of the test ($p < 0.01$)). The combined use of vitamin E and aspirin had a similar effect on platelet adhesion to collagen. Aspirin alone showed no effect on platelet adhesiveness to collagen* Platelet aggregation *Vitamin E alone, administered in doses from 400 to 1200 IU/days decreased collagen-induced aggregation in women ($p < 0.05$). There were no statistically significant differences between the aspirin and aspirin + vitamin E groups*
Tsai et al. (1978) USA – 4 weeks Unclear funding	Randomised, double-blind, placebo controlled trial **Inclusion**: Healthy college student volunteers aged 18–35 **Exclusion**: taking more than 30 IU of supplementary vitamin E at baseline ***N*** = 202 ***n*** = 190 G1: 91 (49 F| 42 M) G2: 89 (46 F| 43 M)	**Ethnicity:** NR **Age range (years):** 18–35 **Sex (female)**: 53% **BMI (kg/m^2):** NR **History of CVD:** NR **Current medication use:** NR **Vitamin K intake/status:** NR	**Supplement form:** DL-*α*-tocopheryl acetate **Doses** G1: 600 IU/day G2: Placebo **Compliance:** NR	**PT** **Method:** A tube of EDTA-anticoagulated blood was taken during the 28-day sampling and used for prothrombin time determinations. Prothrombin time was assayed with a commercial kit	Mean ± SD at the end of the intervention PT (s) Males G1: 13.6 ± 0.9; G2: 13.4 ± 0.8 Females G1: 13.2 ± 1.0; G2: 13.1 ± 1.0 *No statistical difference was observed between the groups*

Abbreviations: AA, arachidonic acid; aPTT, activated partial thromboplastin time; ADP, adenosine diphosphate; BL, baseline; BMI, body mass index; CVD, cardiovascular disease; ECG, electrocardiogram; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; PIVKA-II, protein induced by vitamin K absence; PMA, phorbol 12-myristate 13-acetate; PRP, platelet-rich plasma; PT, prothrombin time; PTT, partial thromboplastin time; RCT, randomised controlled trial; SD, standard deviation; SEM, standard error of the mean.

[a]Results from Jandak et al. (1989) were extracted using WebPlotDigitizer 4.7. https://apps.automeris.io/wpd/.

B.2 | Evidence tables on trials on cardiovascular-related outcomes[a]

Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Steiner et al. (1995) USA – 2 years Private funding	**RCT, double-blind** **Inclusion:** ≥ 18 years with any of the following diagnosed conditions: (1) minor stroke, (2) reversible ischaemic neurologic deficit (RIND), (3) retinal ischaemic event or (4) transient ischaemic attack (TIA). Eligible if neurologic deficit occurred within 8 weeks of enrolment, performance status > 50% time out of bed **Exclusion:** vitamin E supplements, known allergy or contraindication to supplements, history of primary/secondary hypercoagulable state, using anticoagulants or platelet-active drugs other than aspirin, disorder other than atherosclerotic cerebrovascular disease that was thought to be responsible for the focal neurologic deficit, evidence of intracranial haemorrhage and concurrent medical or psychiatric disease ***N* = 100** ***n*** = 100 **G1** = 52 **G2** = 48	**Ethnicity:** primarily Caucasian **Age (years):** G1: 70.7 (11.6) G2: 71.4 (10.1) **Sex (male):** 42% (in both groups) **BMI (kg/m^2):** NR **Participants' history of CVD (%):** Myocardial infarction: G1: 8 G2: 19 Angina: G1: 4 G2: 8 Hypertension: G1: 60 G2: 58 **Family history of CVD (%):** NR **Diabetes (%):** G1: 27 G2: 27 **Current medication use (%):** NR. Anticoagulants and platelet-active drug use excluded a priori	**Supplement form:** *α*-tocopherol **Doses** G1: 400 IU/days vitamin E + 325 mg/days aspirin G2: 325 mg/days aspirin **Vitamin K status/intake:** NR **Compliance**: G1: 90% G2: 88%	**Total, haemorrhagic and ischaemic stroke (fatal and nonfatal)** All patients had a thorough neurologic evaluation by a neurologist, computerised axial tomography studies of the brain with and/or without contrast, carotid Doppler flow studies, and, in some cases, magnetic resonance imaging, routine laboratory examinations and electrocardiograms Patients followed until they reached a termination state (sustained complete stroke, major haemorrhage, recurrent TIA, switch to anti-coagulants or unable to follow protocol)	**Cases (*n*)** Total stroke (fatal or nonfatal) G1: 3; G2: 6 Haemorrhagic stroke G1: 2; G2: 0 Ischaemic stroke G1: 1; G2: 6 $p < 0.05$

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Boaz et al. (2000) Israel (6 centres) SPACE (Secondary Prevention with Antioxidants of Cardiovascular Disease) 1.4 year Public funding	**Double-blind, placebo controlled, secondary prevention RCT** **Inclusion:** stable haemodialysis patients, 40–75 years at BL with documented medical history of CVD **Exclusion:** anticoagulant therapy with warfarin sodium; known history of malignant disease (except non-melanoma skin cancer); active liver disease; treatment with hypolipaemic agents for less than 8 weeks before study start; pregnant or planning to become pregnant during study; any condition the treating physician deemed to preclude the patient on grounds of safety or study evaluation ***N*** = 196 ***n*** = 196 G1 = 99 G2 = 97	**Ethnicity:** NR **Age (years):** **G1**: 64.4 (8.8) **G2**: 64.9 (8.3) **Sex (male):** 69% (in both groups) **BMI (kg/m^2):** NR **Current smoking status (%):** G1: 14; G2: 25 **Participants' history of CVD (%):** **G1:** MI (52.5), Angina pectoris (21.2), stroke or TIA (18.2), peripheral vascular disease (8.1), hypertension (48.5) **G2**: MI (50.5), Angina pectoris (25.8), stroke or TIA (15.5), peripheral vascular disease (8.2), hypertension (42.3) **Family history of CVD (%):** NR **Diabetes (%):** G1: 42; G2: 43 **Current medication use (%):** **G1:** erythropoietin (78.7), calcium-channel blockers (58.6), aspirin (41.4), furosemide (17.2), β-blockers (19.1), lipid lowering agents (11.3), angiotensin-converting-enzyme (ACE) inhibitors (21.3) **G2:** erythropoietin (82.2), calcium-channel blockers (44.4), aspirin (41.1), furosemide (27.8), β-blockers (22.7), lipid lowering agents (14.4), ACE inhibitors (14.4)	**Supplement form:** natural α-tocopherol **Doses** **G1:** Placebo **G2:** 800 IU/day natural α-tocopherol *57% of patients in both groups were prescribed folate (5–10 mg/day), vitamin B6 (10–250 mg/day) and vitamin B12 (250 μg/day). Vitamin C (100–500 mg/day) was prescribed to 43% patients in both groups* **Vitamin K status/intake:** NR **Compliance:** NR	**CVD:** including acute MI (fatal and nonfatal), ischaemic stroke, peripheral vascular disease (excluding the arterio-venous fistula) in a limb not previously affected; and unstable angina **Non-fatal MI:** presence of at least two of: chest pain (typical duration & intensity), increased cardiac enzyme concentrations (at least 2x upper limit of normal) and diagnostic electrocardiographical changes **Fatal MI:** no necropsy data therefore defined as death within 24-h of entering hospital for MI **Death occurring outside hospital for which no other cause was assigned was regarded as sudden death and was included in the definition of CVD death together with fatal MI and fatal ischaemic stroke. Deaths were classified by the treating physician and reviewed by a member of the medical monitoring committee independently of the endpoint analysis* **Incident peripheral vascular disease**: onset of progressive & limiting intermittent claudication or rest pain in previously unaffected limbs (confirmed by duplex ultrasonography) Unstable angina was considered for analysis only in patients with no history of unstable angina or MI	Cox regression model adjusted for smoking **RR (95% CI) [*n* cases]** Total CVD (excl. sudden death) G1: 1 [33] G2: 0.46 (0.27–0.78) [15] MI (excl. sudden death) G1: 1 [17] G2: 0.30 (0.10–0.80) [5] Fatal MI (excl. sudden death) G1: 1 [8] G2: 0.26 (0.06–1.17) [2] Non-fatal MI G1: 1 [9] G2: 0.35 (0.10–1.24) [3] Death from CVD (includes sudden death) G1: 1 [15] G2: 0.61 (0.28–1.30) [9] Ischaemic Stroke G1: 1 [6] G2: 0.85 (0.30–2.70) [5] Unstable angina pectoris G1: 1 [4] G2: 0.51 (0.09–2.70) [2]

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Hodis et al. (2002) USA VEAPS (Vitamin E Atherosclerosis Progression Study) 3 year Mixed funding	**RCT, double-blind, placebo controlled** **Inclusion**: men and women ≥ 40 years old with LDL-C ≥ 3.37 mmol/L and no clinical signs or symptoms of CVD **Exclusion**: fasting triglycerides > 5.64 mmol/L, diabetes mellitus or fasting serum glucose ≥ 3.62 mmol/L, regular vitamin E supplement intake > 1 year, lipid standardised plasma vitamin E > 35 μmol/L, DBP ≥ 100 mm Hg, untreated thyroid disease, serum creatinine > 0.065 mmol/L, life-threatening disease with prognosis < 5 years or alcohol intake > 5 drinks daily ***N*** = 353 ***n*** = 332 G1 = 170 G2 = 162	**Ethnicity:** 75% non-Hispanic white **Age (year):** 56.2 ± 8.9 **Sex (male):** 48% **BMI (kg/m^2):** 27.8 ± 4.7 **Smoking status (%):** Current: 3 Former: 33 Never: 64 **History of CVD (%):** NR **Family history of CVD (%):** NR **Current medication use (%):** study methods describe that it was assessed but results not reported	**Supplement form:** DL-*α* -tocopherol **Doses** G1: Placebo G2: 400 IU/day DL-*α* -tocopherol **Vitamin K status/intake:** NR **Compliance (%):** G1: 92 G2: 91	**CV events, fatal and non-fatal MI** – ascertainment method NR	**Cardiovascular events (*n* of events)** G1: 14 [in 10 participants] G2: 11 [in 8 participants] *p* = 0.81 **Fatal MI (*n*)** G1: 1; G2: 1 **Non-fatal MI (*n*)** G1: 3; G2: 4 **Unstable angina (*n*)** G1: 1; G2: 2
Leppälä, Virtamo, Fogelholm, Huttunen, et al. (2000) Finland ATBC (Alpha-tocopherol Beta-carotene Cancer Prevention Study) 6.1 year (median) Public funding	**RCT, double-blind, placebo-controlled, 2 × 2 factorial** **Inclusion:** men aged 50–69 years old, who smoked 5 or more cigarettes daily, lived in the study area south-western Finland **Exclusion:** proven malignancy (except non-melanoma skin cancer or cancer in situ), severe angina pectoris (typical angina on walking on level ground), chronic renal insufficiency, cirrhosis of the liver, chronic alcoholism, anticoagulant therapy, other medical problems that might limit participation, known CHD at baseline, previous stroke at baseline and current use of supplements containing vitamin E, vitamin A or *β*-carotene ***N*** = 29,133 ***n*** = 28,519 G1: 14,281 G2: 14,238	**Ethnicity:** White **Age (y):** 57.7 **Sex (male):** 100% **BMI (kg/m^2):** 26.3 **History of CVD (%):** G1:24.0; G2: 25.4 (heart disease) **History of HT (%):** G1: 38.1; G2: 38.7 **History of DM (%):** G1: 4.1 G2: 4.2 **Family history of CVD (%):** NR **Current medication use (%):** with anticoagulant therapy excluded, other medications NR **Aspirin use:** ~ 14% (based on the estimate reported in Liede KE, Haukka JK, Saxén LM, Heinonen OP. Increased tendency towards gingival bleeding caused by joint effect of alpha-tocopherol supplementation and acetylsalicylic acid. Ann Med. 1998 Dec;30(6):542–6. doi: 10.3109/07853899709002602. PMID: 9920356)	**Supplement form:** DL-*α* -tocopherol acetate **Doses** G1: *α*-tocopherol non-recipients G2: 50 mg/day *α*-tocopherol **Vitamin K status/intake:** NR **Compliance:** 93% in all study groups (division of total unreturned capsules by the number of days active in the trial) – dropout rate including deaths 30%	Strokes were identified by record linkage to the National Hospital Discharge Register and the National register of Causes of Death, which used the International Classification of Diseases, ICD-8 used up to the end of 1986 ICD-9 used thereafter Deaths	**Stroke incidence** **All strokes** *Per 10,000 Person-Years (n)* G1: 66.6 (548); G2: 62.1 (509) *RR (95%CI)* G1: 1.00 G2: 0.93 (0.83–1.05) *p* = 0.25 **Subarachnoid haemorrhage** *Per 10,000 Person-Years (n)* G1: 4.1 (34); G2: 6.2 (51) *RR (95%CI)* G1: 1.00 G2: 1.50 (0.97–2.32) *p* = 0.07 **Intracerebral haemorrhage** *Per 10,000 Person-Years (n)* G1: 6.7 (55); G2: 7.0 (57) *RR (95%CI)* G1: 1.00 G2: 1.04 (0.72–1.51) *p* = 0.84 **Cerebral infarction** *Per 10,000 Person-Years (n)* G1: 52.8 (434); G2: 45.5 (373) *RR (95%CI)* G1: 1.00 G2: 0.86 (0.75–0.99) *p* = 0.03

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
					Mortality (fatal strokes) **All strokes** *Per 10,000 Person-Years (n)* G1: 8.5 (70); G2: 11.0 (90) *RR (95%CI)* G1: 1.00 G2: 1.29 (0.94–1.76) $p = 0.11$ **Subarachnoid haemorrhage** *Per 10,000 Person-Years (n)* G1: 1.2 (10); G2: 3.4 (28) *RR (95%CI)* G1: 1.00 G2: 2.81 (1.37–5.379) $p = 0.005$ **Intracerebral haemorrhage** *Per 10,000 Person-Years (n)* G1: 2.3 (19); G2: 3.8 (31) *RR (95%CI)* G1: 1.00 G2: 1.64 (0.93–2.90) $p = 0.09$ **Cerebral infarction** *Per 10,000 Person-Years (n)* G1: 4.4 (36); G2: 3.5 (29) *RR (95%CI)* G1: 1.00 G2: 0.81 (0.49–1.32) $p = 0.39$
Törnwall, Virtamo, Korhonen, Virtanen, Taylor, et al. (2004) Finland ATBC (Alpha-tocopherol Beta-carotene Cancer Prevention Study) 6.1 year (median) [+ 6 year post-trial follow-up] Public funding	**Randomised, double-blind, placebo-controlled, 2 × 2 factorial primary prevention trial** **Inclusion:** men aged 50–69 years old, who smoked 5 or more cigarettes daily, lived in the study area south-western Finland **Exclusion:** proven malignancy (except non-melanoma skin cancer or cancer in situ), severe angina pectoris (typical angina on walking on level ground), chronic renal insufficiency, cirrhosis of the liver, chronic alcoholism, anticoagulant therapy, other medical problems that might limit participation, known CHD at baseline and current use of supplements containing vitamin E, vitamin A or β-carotene	**Ethnicity:** White **Age (median (IQR), year):** G1: 56 (53–61) G2: 57 (53–61) **Sex (male):** 100% **BMI (median (IQR), kg/m^2):** G1: 25.9 (23.6–28.5) G2: 25.9 (23.7–28.4) **History of CVD (%):** 6.4% reported history of MI at baseline, diagnosed by a physician **Family history of CVD (%):** NR **Current medication use (%):** with anticoagulant therapy excluded, other medications NR	**Supplement form:** DL-α -tocopherol acetate **Doses** G1: Placebo G2: 50 mg/day α-tocopherol **Vitamin K status/intake:** NR **Compliance (median):** 99% in all study groups during active participation	**Major coronary events** (MCE) For individuals at risk of first-ever MCE, non-fatal MI and death from CHD were considered as endpoints For individuals who had reported history of MI at the beginning of the trial, post-trial endpoints included recurrent non-fatal MI and death from CHD Only the first post-trial event was registered as an endpoint Endpoints were identified through linkage with the national Hospital Discharge Register and the national Register of Causes of Death	**Incidence and RR of CHD** for subjects at risk of first-ever major coronary event Trial period **Major coronary event (MCE)** *Rate/1000 person-years (n), RR (95%CI)* G1: 13.59 (534), 1.00 G2: 13.33 (520), 0.98 (0.87–1.11) **Non-fatal MI** *Rate/1000 person-years (n), RR (95%CI)* G1: 7.54 (296), 1.00 G2: 7.92 (309), 1.05 (0.90–1.24) **Fatal CHD** *Rate/1000 person-years (n), RR (95%CI)* G1: 6.06 (238), 1.00 G2: 5.41 (211), 0.89 (0.74–1.08) Post-trial period

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
	N **=** 29,133 No history of MI: 27, 271 History of MI: 1862 At risk of first-ever MCE *Trial* ***n*** **=** 13,669 G1: 6849 G2: 6820 *Post-trial* *n* = 14,273 G1: 5841 G2: 5794 Subjects with pre-trial MI *Trial* *n* = 904 G1: 438 G2: 466 *Post-trial* *n* = 635 G1: 306 G2: 329				**Major coronary event** *Rate/1000 person-years (n), RR (95%CI)* G1: 16.08 (504), 1.00 G2: 15.16 (472), 0.94 (0.83–1.07) **Non-fatal MI** *Rate/1000 person-years (n), RR (95%CI)* G1: 7.66 (240), 1.00 G2: 7.23 (225), 0.94 (0.78–1.14) **Fatal CHD** *Rate/1000 person-years (n), RR (95%CI)* G1: 8.42 (264), 1.00 G2: 7.93 (247), 0.94 (0.79–1.12) Subjects with pre-trial MI Trial MCE *Rate/1000 person-years (n), RR (95%CI)* **G1:** 41.24 (93), 1.00 **G2:** 38.92 (94), 0.94 (0.70–1.26) Non-fatal MI *Rate/1000 person-years (n), RR (95%CI)* **G1:** 23.94 (54), 1.00 **G2: 16.56** (40), 0.69 (0.46–1.05) Fatal CHD *Rate/1000 person-years (n), RR (95%CI)* **G1: 17.29** (39), 1.00 **G2: 22.36** (54), 1.29 (0.85–1.97) Post-trial MCE *Rate/1000 person-years (n), RR (95%CI)* **G1: 45.25** (67), 1.00 **G2: 38.32** (60), 0.85 (0.59–1.21) Non-fatal MI *Rate/1000 person-years (n), RR (95%CI)* **G1: 19.59** (29), 1.00 **G2: 14.05** (22), 0.72 (0.41–1.26) Fatal CHD *Rate/1000 person-years (n), RR (95%CI)* **G1:** 25.66 (38), 1.00 **G2:** 24.27 (38), 0.95 (0.60–1.50)

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Törnwall, Virtamo, Korhonen, Virtanen, Albanes, & Huttunen, (2004) Finland ATBC (Alpha-tocopherol Beta-carotene Cancer Prevention Study) 6.1 year (median) [+ 6 year post-trial follow-up] Public funding	**Randomised, double-blind, placebo-controlled, 2 × 2 factorial primary prevention trial** **Inclusion:** same as above **Exclusion:** same as above ***N*** = 29,133 *N* = 24, 382 (at risk of first-ever stroke post-trial) At risk of first-ever stroke post-trial ***n*** = 12,268 G1: 6154 G2: 6114	**Ethnicity:** White **Age:** 50–69 year **Sex (male):** 100% **BMI (median (IQR), kg/m^2):** NR **Participants' history of CVD:** NR **Family history of CVD (%):** NR **Current medication use (%):** with anticoagulant therapy excluded, other medications NR	**Supplement form:** DL-*α* -tocopherol acetate **Doses** G1: Placebo G2: 50 mg/day *α*-tocopherol **Vitamin K status/intake:** NR **Compliance (median):** 99% in all study groups during active participation	**Stroke** Cases were identified from the National Hospital Discharge Register and from the Register of Causes of Death, which cover > 90% of acute stroke events in Finland. Both registers use the codes of the International Classification of Diseases (ICD). Specific codes used for each stroke type are described. Stroke was considered fatal if it led to death within 90 days from. Validation of diagnoses was conducted: 79%–90% valid by subtype	**Incidence and RR** of first-ever stroke **post-trial** **All stroke** *Rate/1000 person-years (n), RR (95%CI)* G1: 9.85 (325), 1.00 G2: 10.41 (340), 1.06 (0.91–1.23) **Cerebral Infarction** *Rate/1000 person-years (n), RR (95%CI)* G1: 8.09 (267), 1.00 G2: 8.91 (291), 1.10 (0.93–1.30) **Intracerebral haemorrhage** *Rate/1000 person-years (n), RR (95%CI)* G1: 1.09 (36), 1.00 G2: 0.83 (27), 0.76 (0.46–1.25) **Subarachnoid haemorrhage** *Rate/1000 person-years (n), RR (95%CI)* G1: 0.39 (13), 1.00 G2: 0.55 (18), 1.40 (0.69–2.85)
Virtamo et al. (2003) Finland ATBC (Alpha-tocopherol Beta-carotene Cancer Prevention Study) 6.1 year (median) [+ 6 year post-trial follow-up] Public funding	**Randomised, double-blind, placebo-controlled, 2 × 2 factorial primary prevention trial** **Inclusion:** same as above **Exclusion:** same as above ***N*** = 29,133 ***n*** = G1: 14,573 G2: 14,560	**Ethnicity:** White **Age (mean, year):** **Overall:** 63.5 **Sex (male):** 100% **BMI (mean, kg/m^2):** NR **Participants' history of CVD (%):** NR **Family history of CVD (%):** NR **Current medication use (%):** with anticoagulant therapy excluded, other medications NR	**Supplement form:** DL-*α* -tocopherol acetate **Doses** G1: *α*-tocopherol non-recipients G2: 50 mg/day *α*-tocopherol **Vitamin K status/intake:** NR **Compliance (median):** 99% in all study groups during active participation	Cause of death was identified through the Finnish Register of Causes of Death. In the analyses of mortality, follow-up continued until death or the end of follow-up (April 30 1999). Cause-specific data on deaths are presented in mutually exclusive cause-of-death categories based on specific codes in the International Classification of Diseases (8th, 9th and 10th edition)	**Cause-specific deaths** *Summary of* Figure 3 *(Whisker plots)* During the trial there was an increased RR of **mortality** from **haemorrhagic stroke** (low proportion of overall deaths), for *α*-tocopherol versus no *α*-tocopherol recipients. The RR of **mortality from non-haemorrhagic stroke** was borderline increased for *α*-tocopherol versus no *α*-tocopherol recipients, while mortality from other heart and vascular causes was borderline decreased. **Mortality from CHD** had the highest proportion of deaths overall but RR was similar for *α*-tocopherol versus no *α*-tocopherol recipients. Very similar RR were observed post-trial with the exception of mortality from non-haemorrhagic stroke which decreased for *α*-tocopherol versus no *α*-tocopherol recipients

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Stephens et al. (1996) United Kingdom Cambridge Heart Antioxidant Study (CHAOS) Duration (median, range): 510 day (3–981) Public funding	**Double-blind, placebo controlled, randomised trial** **Inclusion:** Patients with overt clinical and angiographically proven atherosclerosis **Exclusion:** Prior use of vitamin supplements containing vitamin E ***N*** = 2002 ***n*** = 2002 **G1:** 967 **G2:** 1037	**Ethnicity:** Majority white **Age (mean (SD), year):** G1: 61.8 (8.9) G2: 61.8 (9.3) **Sex (male, %):** G1: 87 G2: 82 **BMI (mean (SD), kg/m^2):** G1: 26.4 (3.4) G2: 26.5 (3.5) **Participants' history of CVD (%):** Study patients were at high risk of further CV events – 37.6% had triple vessel or left-main-stem coronary disease and 24.6% had moderate or severe left ventricular dysfunction **Family history of CVD (%):** first degree relative < 60 year old (G1: 40.2%, G2: 36.6%) **Current medication use (%):** calcium antagonist (G1: 68.9%, G2: 69.4%), *β*-blocker (G1: 33.7%, G2: 39.6%), nitrate (G1: 57.5%, G2: 53.8%). **Aspirin (mean (SD), mg/day)** G1: 82.6 (55.8) G2: 82.9 (53.3)	**Supplement form:** *α*-tocopherol (free 2R,4'R,8'R-*α*-tocopherol from natural sources in soya oil) **Doses** G1: Placebo G2: 800 or 400 IU *α*-tocopherol *The first 546 patients on active therapy took 800 IU (537 mg)/day vitamin E, then new recruitments took 400 IU (268 mg)/day vitamin E (dose constrained by the needs to exceed physiological concentration of α-tocopherol).* **Vitamin K status/intake:** NR **Compliance:** 73.2% of all prescribed intervention or placebo were requested as follow-up medications. 48% in placebo and 49% in intervention groups were 100% compliant with the trial medication.	**Major CV events** (CV death and non-fatal MI), and **non-fatal MI** alone Distinction was made between non-fatal MI and death because of greater diagnostic precision in non-fatal MI allowed by examination of electrocardiography, cardiac enzyme measurements and case notes over the hospital admission. For these cases, definite or probable MI was defined by a ratified modification of the MONICA criteria. The certified cause of death was judged to be cardiovascular if the cause was classified according to the ICD, 9th revision, as codes 410, 427, 428, 434 or 441. Necropsy data were available in 21 (34%) of 62 cases. All events were classified by a member of the study team independently of the main analysis Survival analysis by Kaplan–Meier curves. Risk analysis by Cox model.	***RR (95% CI)*** **Major CV event:** G1: 1 G2: 0.53 (0.34–0.83), $p = 0.005$ **Non-fatal MI:** G1: 1 G2: 0.23 (0.11–0.47), $p < 0.001$ **CV death:** G1: 1 G2: 1.18 (0.62–2.27), $p = 0.61$ **CV death (*n*)** *G1* versus *G2* Fatal MI: 13 versus 18 Stroke: 1 versus 1 Total CV deaths: 23 versus 27 **Non-fatal MI (*n*)** *G1* versus *G2:* 41 versus 14 *Kaplan–Meier survival analysis for treatment with α-tocopherol*: • reduced the rates of major CV events (log-rank $p = 0.015$) • reduced rates of non-fatal MI (log-rank $p = 0.0001$) • no effect on CV deaths (log-rank $p = 0.78$)
GISSI group (1999) **Italy** **GISSI** **Duration:** 3.5 year **Funding:** Public and Private	**Open-label RCT (multicentre)** **Inclusion:** Patients with recent (≤ 3 months) MI. No contradictions to dietary supplements (i.e. known allergy to *n*-3 PUFA or *α*-tocopherol, or known congenital defects of coagulation), able to provide informed consent, no unfavourable short-term outlook (e.g. overt congestive heart failure, cancers or other. No age limits **Exclusion:** Having any of the above not meeting eligibility criteria ***N*** = 11, 324 ***n*** = 5658 (four-way analysis) **G1:** 2828 **G2:** 2830	**Ethnicity:** NR **Age (mean (SD), year):** **G1:** 59.4 (10.5) **G2:** 59.5 (10.5) **Sex (male, %):** **G1:** 85.1 **G2:** 84.7 **BMI (mean (SD), kg/m^2):** **G1:** 26.4 (3.5) **G2:** 26.5 (3.6) **Participants' history of CVD (%):** 100% with recent MI **Family history of CVD (%):** NR **Current medication use (%):** Antiplatelet drugs G1: 91.5; G2: 91.2) ACE inhibitors G1: 48; G2: 45.7 *β*-blockers	**Supplement form:** synthetic *α*-tocopherol **G1: Placebo** **G2:** 300 mg/day Participants also randomised to *n*-3 PUFAs **Vitamin K status/intake:** NR **Compliance:** assessed refill drug supplies every 3 months but NR	**Combined efficacy endpoints**: cumulative rate of all-cause death, non-fatal MI and non-fatal stroke; and the cumulative rate of CV death, non-fatal myocardial infarction and non-fatal stroke. **Secondary analyses:** Each component of the primary endpoints, and for the main causes of death. **MI** was taken to be present if the investigator had identified it on a standard form or if a death certificate or hospital records showed a fatal MI **Non-fatal acute MI** = at least two of the following: chest pain of typical intensity and duration; ST segment elevation or depression of 1 mm	**Incidence of outcomes** *RR (95% CI) G1* versus *G2* **Combined endpoints:** • Death, non-fatal MI, non-fatal stroke: 0.89 (0.77–1.03) • CV death, non-fatal MI, non-fatal stroke: 0.88 (0.75–1.04) **Secondary analyses:** • CV deaths: 0.80 (0.65–0.99) • Non-fatal CV events: 1.02 (0.81–1.28) • CHD death and non-fatal MI: 0.87 (0.73–1.04) • Fatal and non-fatal stroke: 0.95 (0.61–1.47) **Patients receiving vitamin E and controls did not differ significantly when data analysed by factorial design.*

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
		G1: 44.2; G2: 44.8 Cholesterol-lowering drugs G1: 5.1; G2: 4.6)		or more in any limb lead of the electrocardiogram, of 2 mm or more in any precordial lead, or both; or at least a doubling in necrosis enzymes. Diagnosis of **non-fatal stroke** required unequivocal signs or symptoms of remaining neurological deficit, with sudden onset and a duration of > 24 h. Diagnosis of **fatal stroke** also used these criteria. Alternatively, the diagnosis documented in hospital records or on death certificates was used	
Marchioli et al. (2006) **Italy** **GISSI** **Duration:** 3.5 year **Funding:** Public and Private	**Open-label RCT (multicentre)** **Inclusion:** same as above + no diagnosis of heart failure and an echocardiographic measurement of EF (EF) at baseline **Exclusion:** same as above ***N*** = 11, 324 ***n*** = 8415 **Plac:** 4213 **Interv:** 4202	**Ethnicity:** NR **Age (mean (SD), year):** **Plac:** 58.4 (10.5) **Interv:** 58.4 (10.4) **Sex (male, %):** **Plac:** 85.8 **Interv:** 86.4 **BMI (mean (SD), kg/m^2):** NR **Participants' history of CVD (%):** 100% with recent MI **Family history of CVD (%):** NR **Current medication use (%):** Antiplatelet drugs G1: 92.8; G2: 93.0 ACE inhibitors G1: 42.9; G2: 42.4 *β*-blockers G1: 47.3; G2: 48.1	**Supplement form:** synthetic *α*-tocopherol **G1:** No *α*-tocopherol **G2:** 300 mg/day Participants also randomised to *n*-3 PUFAs **Vitamin K status/intake:** NR **Compliance:** assessed refill drug supplies every 3 months but NR	**Congestive heart failure (CHF)** was the primary endpoint. Heart failure at baseline = clinical diagnosis from CHF and/or prescription of ACE inhibitors, *β*-blockers, diuretics or nitrates for CHF management. Development of CHF during follow-up = the need of hospitalisation for CHF management or death from CHF as classified by an ad hoc Endpoint Validation Committee blinded to experimental treatments. EF (EF) was categorised according to statistical tertiles to avoid categories with low numbers of events	During trial 220 patients required hospitalisation or died of CHF. Patients receiving vitamin E had a statistically NS 20% (95% CI 0.92–1.56) increased risk for developing CHF *n (%)* EF > 58%: 2688 (31.9) EF 50–58%: 3201 (38) EF < 50%: 2526 (30) Patients with left ventricular dysfunction (EF < 50%) had a statistically significant 50% increase or risk of developing CHF

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Yusuf et al. (2000) 19 countries: Canada, USA, Mexico, Europe and South America (267 hospitals) HOPE (The Heart Outcomes Prevention Evaluation) 4.5 year Mixed funding	**Double-blind, 2 × 2 factorial design RCT** **Inclusion:** individuals > 55 years old at high risk of future vascular death or morbidity, with history of coronary artery disease, stroke, peripheral vascular disease or diabetes + at least one other CV risk factor (HT, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking or documented microalbuminuria) + written informed consent **Exclusion:** patients already on ACE inhibitors or vitamin E treatment, or for whom ACE inhibitors were indicated (hearth failure or LV dysfunction), heart failure, low EF (< 0.40), uncontrolled HT or overt nephropathy, or MI or stroke within 4 wks before the start of the study ***N*** **=** 10, 576 ***n*** **=** 9541 G1: 4780 G2: 4761	**Ethnicity:** NR **Age (mean (SD), year):** 66 (7) for both groups **Sex (male, %):** G1: 73.2 G2: 73.5 **BMI (kg/m^2):** 28 ± 4 for both groups **Participants' history of CVD (%):** MI G1: 53.0; G2: 52.5 Stable angina pectoris G1: 55.8; G2: 55.7 Unstable angina pectoris G1: 26.1; G2: 25.3 Coronary-artery bypass grafting: G1: 26.2; G2: 25.8 Percutaneous transluminal coronary angioplasty G1: 18.1; G2: 17.9) Stroke or TIA G1: 10.5; G2: 11.1 Peripheral vascular disease G1: 42.6; G2: 44.3 **Family history of CVD (%):** NR **Current medication use (%):** Aspirin or other antiplatelet drugs: G1: 75.6; G2: 77.0 Calcium channel blockers G1: 46.8; G2: 47.2 *β*-blockers G1: 39.1; G2: 39.9 Diuretics G1: 15.0; G2: 15.3 Lipid-lowering agents G1: 29.3; G2: 28.4	**Supplement form:** RRR-*α*-tocopheryl acetate **Doses** G1: *α*-tocopheryl non-recipients G2: 400 IU/day *α*-tocopheryl Participants also randomised to ramipril **Vitamin K status/intake:** NR **Compliance (%):** In G2: At 1 year: 94.2 At 2 year: 93.3 At 3 year: 91.3 At 4 year: 90.2 At final visit: 89.2	The primary outcome was a composite of MI, stroke and death from CV causes **Deaths due to CV causes**: unexpected deaths presumed to be due to ischaemic CVD occurring within 24 h after the onset of symptoms without clinical or post-mortem evidence of another cause; deaths from MI or stroke that occurred within 7 day after the MI or stroke; and deaths from CHF, dysrhythmia, pulmonary embolism or ruptured abdominal aortic aneurysm Deaths with **uncertain cause** presumed to be due to CVD. **MI** was diagnosed with at least 2/3 criteria: typical symptoms, increased cardiac enzyme levels (at least 2x the upper limit of normal) and diagnostic electrocardiographic changes **Stroke:** neurologic deficit lasting more than 24 h. A computed tomographic or magnetic resonance imaging examination was recommended to define the type of stroke **Unstable angina**: worsening angina/angina at rest requiring hospitalisation	**Incidence of primary outcomes** *RR (95% CI)* **Composite outcome**: G1: 1.00 G2: 1.05 (0.95–1.16), $p = 0.33$ **Death from CV causes**: G1: 1.00 G2: 1.05 (0.90–1.22), $p = 0.54$ **MI**: G1: 1.00 G2: 1.02 (0.90–1.15), $p = 0.74$ **Stroke**: G1: 1.00 G2: 1.17 (0.95–1.42), $p = 0.13$ **Vitamin E had no significant effect on the primary outcome either among patients who were receiving ramipril (338 events among those who were receiving vitamin E and 313 events among those who were receiving plac; RR:1.08) or among patients who were not receiving ramipril (421 and 405 events, respectively; RR:1.05).* **Incidence of secondary outcomes:** *RR, (95% CI)* **New-onset angina**: G1: 1.00 G2: 1.15 (0.97–1.37), $p = 0.11$ **Worsening angina**: G1: 1.00 G2: 1.02 (0.94–1.11), $p = 0.63$ **Heart failure**: G1: 1.00 G2: 1.17 (1.03–1.32), $p = 0.02$ **Adverse effects (*n*):** 17 patients assigned to vitamin E had haemorrhagic stroke versus 13 not assigned to vitamin E

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Lonn et al. (2005) 19 countries: Canada, USA, Mexico, Europe and South America (267 hospitals) HOPE & HOPE-TOO 7.2 year Mixed funding	**Double-blind, 2 × 2 factorial design RCT** **Inclusion:** same as above **Exclusion:** same as above (Yusuf et al., 2000) ***N*** **=** 10,576 ***n*** **=** 9, 541 (primary analysis) G1: 4780 G2: 4761 ***n*** **=** 7030 (sensitivity analysis) G1: 3510 G2: 3520	**Ethnicity:** NR **Age (mean (SD), year):** 66 (7) for both groups **Sex (male, %):** G1: 74 G2: 74.1 **BMI (mean (SD), kg/m^2):** 28 (4) for both groups **Participants' history of CVD, for participants at centres continuing in the HOPE-TOO trial extension (%):** MI G1: 53.6; G2: 52.6 Coronary artery disease G1: 80.3; G2: 80.9 Stroke or TIA G1: 10.9; G2: 11.1 Stable angina pectoris G1: 57.9; G2: 58.2 Unstable angina pectoris G1: 27.9; G2: 27.5 Peripheral arterial disease G1: 41.1; G2: 42.3 Hypertension G1: 45.8; G2: 45.5 **Family history of CVD (%):** NR **Current medication use (%):** Antiplatelet drugs G1: 75.7; G2: 76.7 Calcium channel blockers G1: 46.4; G2: 46.7 *β*-blockers G1: 39.8; G2: 40.2 Diuretics G1: 15.3; G2: 15.2 Hypolipidaemic agents G1: 30.1; G2: 28.3	**Supplement form:** RRR-*α*-tocopheryl acetate **Doses** G1: *α*-tocopheryl non-recipients G2: 400 IU/day *α*-tocopheryl Participants also randomised to ramipril *1–7% of population also took vitamin C, β-carotene and multivitamins* **Vitamin K status/intake:** NR **Compliance (%):** In G2 group: At 1 year: 94.2 At 2 year: 93.3 At 3 year: 91.3 At 4 year: 90.2 At final visit: 89.2	Outcomes assessed as above. Sensitivity analysis of post follow-up assessments Primary outcomes in this analysis included cancer incidence, cancer deaths, and major CV events (MI, stroke, and CV death). Secondary outcomes included heart failure, hospitalisation for unstable angina and revascularisations	**Incidence of primary outcomes – primary analysis (all patients)** *RR (95% CI)* **Composite outcome**: G1: 1.00 G2: 1.04 (0.96–1.14), $p = 0.34$ **MI**: G1: 1.00 G2: 1.06 (0.96–1.18), $p = 0.27$ **Stroke**: G1: 1.00 G2: 1.10 (0.93–1.31), $p = 0.27$ **Death from CV causes**: G1: 1.00 G2: 1.02 (0.91–1.10), $p = 0.79$ **All heart failure:** G1: 1.00 G2: 1.13 (1.01–1.26), $p = 0.85$ **Incidence of primary outcomes – Results for patients at centres continuing in the HOPE-TOO trial extension** *RR (95% CI)* **Composite outcome**: G1: 1.00 G2: 1.05 (0.95–1.16), $p = 0.31$ **MI**: G1: 1.00 G2: 1.09 (0.97–1.22), $p > 0.99$ **Stroke**: G1: 1.00 G2: 1.09 (0.90–1.33), $p = 0.39$ **Death from CV causes**: G1: 1.00 G2: 1.01 (0.87–1.16), $p = 0.93$ **All heart failure**: G1: 1.00 G2: 1.19 (1.05–1.35), $p = 0.007$

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
PPP Collaborative Group, 2001 Italy PPP (Primary Prevention Project) 4 year (median) 16,390 (person-year) Private funding	**Open-label 2 × 2 factorial design RCT** **Inclusion:** old age (≥ 65 years); HT (SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg on at least three separate occasions); hypercholesterolaemia (total blood cholesterol ≥ 6.4 mmol/L on at least two separate occasions); diabetes mellitus (fasting venous plasma glucose concentration ≥ 7.8 mmol/L on at least two separate occasions, chronic drug treatment for any of the three latter conditions, obesity (BMI ≥ 30 kg/m^2); and family history of MI before 55-year old in at least one parent or sibling **Exclusion:** treatment with antiplatelet drugs (history of vascular events or diseases); chronic use of anti-inflammatory agents or anticoagulants; contraindications to aspirin; diseases with predictable poor short-term prognosis; and predictable psychological or logistical difficulties affecting compliance with the trial requirements ***N*** = 4784 ***n*** = 4495 G1: 2264 G2: 2231	**Ethnicity:** NR **Age (mean (SD), year):** G1: 64.4 (7.7) G2: 64.4 (7.6) **Sex (male, %):** G1: 43 G2: 42 **BMI (mean (SD), kg/m^2):** G1: 27.8 (4.7) G2: 27.5 (4.6) **Participants' history of CVD (%):** Hypertension G1: 69; G2: 67 Hypercholesterolaemia G1: 39; G2: 38 **Family history of CVD (%):** Premature MI G1: 11; G2: 10 **Current medication use (%):** Antihypertensive drugs G1: 68; G2: 65 Lipid lowering drugs G1: 16; G2: 15 Antidiabetic G1: 12; G2:12	**Supplement form:** synthetic *α*-tocopherol **Doses** G1: *α*-tocopherol non-recipients G2: 300 mg/day *α*-tocopherol **Vitamin K status/intake:** NR **Compliance:** In G2 group % that stopped taking treatment: At 1 year: 13.1 At end: 13.6 + 0.2% not randomised to G2 were taking vitamin E	Main combined endpoint: CV death, non-fatal myocardial infarction, non-fatal stroke CV events or diseases: with one of CV death, non-fatal MI, non-fatal stroke, angina pectoris, TIA, peripheral-artery disease, revascularisation procedure **CV death**: deaths occurring within 28 days after the onset of the documented diagnosis of MI or stroke in the absence of any other evident cause; sudden deaths; deaths from heart failure; and all other deaths classified as CV (ICD 9th edition, clinical modification codes 390–459). Acute MI: at least two of the following: chest pain of typical intensity and duration, transient increase of serum enzyme concentration indicating myocardial damage, and typical electrocardiographical changes. Stroke: unequivocal signs or symptoms of neurological deficit, with sudden onset, leading to death or lasting longer than 24 h. **Strokes were classified** as ischaemic or haemorrhagic when imaging or necropsy findings were available. **Stroke was defined** as disabling on the basis of a Rankin score ≥3, centrally assessed by telephone interview, and done by a single rater who was unaware of treatment allocation, 6 months after acute event	**Incidence of outcomes** *RR (95% CI)* **Composite outcome**: G1: 1.00 G2: 1.07 (0.74–1.56) **Total CV events**: G1: 1.00 G2: 0.94 (0.77–1.16) **CV deaths**: G1: 1.00 G2: 0.86 (0.49–1.52) **All MI**: G1: 1.00 G2: 0.89 (0.52–1.58) **Non-fatal MI**: G1: 1.00 G2: 1.01 (0.56–2.03) **All Stroke**: G1: 1.00 G2: 1.24 (0.66–2.31) **Non-fatal Stroke**: G1: 1.00 G2: 1.56 (0.77–3.13) **Angina pectoris**: G1: 1.00 G2: 1.22 (0.86–1.73) Intracranial (not parenchymal) bleeding G1: 0; G2: 2

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Devaraj et al. (2007) **USA** **Duration:** 2 year **Funding**: Public (NIH)	**Double blind RCT** **Inclusion:** Patients with coronary artery disease (CAD) age of 40–70 year; receiving hypolipidaemic drug therapy for ≥ 1 year, and evidence of a prior myocardial infarction (> 1 year after the event) or stable exertional angina **Exclusion:** LDL cholesterol > 130 mg/dL, serum triacylglycerols > 350 mg/dL, liver enzymes > 2 times upper limit of the reference range, homocysteine > 15 μmol/L despite folate supplementation, untreated hypo- or hyperthyroidism, recent MI (< 6 months), history of stroke or TIA, uncontrolled HT (BP 150/95 mmHg on 2 visits) or congestive heart failure, malabsorption, treatment with corticosteroids/androgens, alcohol consumption [≥ 1 oz/day (30 mL/day to ≈24 g alcohol/day)], previous use of high-dose antioxidant supplements in the past 1 year, or likelihood of moving from the area in 3 year, non-stable dose of thiazide diuretics, non-stable dose and < 1 year use of contraceptive agents or hormone replacement therapy ***N*** = 90 ***n*** = 90 **G1**: 46 **G2**: 44	**Ethnicity:** NR **Age (mean (SD), year):** **G1:** 62 (6) **G2:** 59 (7) **Sex (male, %):** **G1:** 70; **G2:** 73 **BMI (mean ± SD, kg/m^2):** **G1: 30 ± 5; G2: 31 ± 7** **Diabetes (%):** **G1:** 41; G2: 41 **Participants' history of CVD (%):** Hypertension G1: 57; G2: 66 **Family history of CVD (%):** NR **Current medication use (%):** **S**tatins G1:89; G2: 91	**Supplement form:** RRR-*α*-tocopherol **G1: Placebo** **G2:** 1200 IU/day **Vitamin K status/intake:** NR **Compliance (%):** 91 (pill count)	NR	CV events (MI, stroke, bypass surgery, percutaneous coronary angioplasty, TIA, angina and death) were not significantly different in the interv group than in the plac group (16% versus 28%; $p = 0.21$)

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Cook et al. (2007) **USA** **WACS** **Duration (mean):** 9.4 year **Funding:** Public and Private	RCT, double-blind, placebo-controlled, 2 × 2 × 2 factorial design **Inclusion criteria:** female health professionals at high risk of CVD, ≥ 40 year, with prior history of CVD or ≥ 3 risk factors for CVD (self-reported diagnosis of HT, high cholesterol, or DM, parental history of premature MI (before age 60), BMI ≥ 30 kg/m^2, current cigarette smoking and inconsistent report of prior CVD), postmenopausal or no intention of becoming pregnant **Exclusion criteria:** self-reported history of cancer (excluding nonmelanoma skin cancer) within the past 10 years, any serious non-CVD illness, currently using warfarin or other anticoagulants ***N*** = 8171 ***n*** = 8171 **G1:** 4088 **G2:** 4083	**Ethnicity:** NR **Mean age ± SD (y):** G1: 60.6 ± 8.8 G2: 60.6 ± 8.9 **Sex (male, %):** 0 **BMI (mean (SD), kg/m^2):** **G1:** 30.3 ± 6.7 **G2:** 30.3 ± 6.6 **History of CVD (%):** G1: 63.5; G2: 64.7 **History of HT (%):** G1: 75.8; G2: 74.4 **History of high cholesterol (%):** G1: 73; G2: 72.7 **History of DM (%):** G1:19.6; G2: 18.7 **Family history of CVD (%):** G1: 37.9; G2: 36.7 **Current medication use (%):** Aspirin: 52.5% Cholesterol lowering drugs: 22.8% (total sample; based on the estimate reported in Bassuk, S. S., Albert, C. M., Cook, N. R., Zaharris, E., MacFadyen, J. G., Danielson, E., Van Denburgh, M., Buring, J. E., & Manson, J. E. (2004). The Women's Antioxidant Cardiovascular Study: Design and baseline characteristics of participants. Journal of Womens Health (Larchmt), *13*(1), 99–117. https://doi.org/10.1089/154099904322836519	**Supplement form:** D-*α*-tocopherol acetate **G1:** No *α*-tocopherol **G2:** 600 IU/every other day *Participants in both groups were also randomised to vitamin* C *and/or β-*carotene *and/or placebo* **Vitamin K status/intake:** NR **Compliance (%):** 76% at 4 year and 68% at 8 year (defined as taking at least 2/3 of study pills)	Women reported endpoints through questionnaire, letter or phone call. Deaths were reported by family members, postal authorities or through the National Death Index Endpoints reviewed by a committee of physicians blinded to treatment assignment. Only *confirmed endpoints were included in the analyses*, except for total mortality which included 66 reported deaths with no death certificate **Combined endpoint of CVD**: incident MI, stroke, coronary revascularisation procedures (coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)), and CV mortality **Confirmation**: **MI**: symptoms met WHO criteria and cardiac enzymes or diagnostic electrocardiograms were abnormal **Stroke:** a new neurologic deficit of sudden onset that persisted for more than 24 h or until death within 24 h. Clinical information, computed tomographic scans and magnetic resonance images used to distinguish haemorrhagic from ischaemic events **Death due to CV cause:** by examination of autopsy reports, death certificates, medical records and information obtained from the next of kin or other family members	**Incidence of CV outcomes** *RR (95% CI)* **Combined outcome**: 0.94 (0.85–1.04) **MI, stroke, CVD death**: 0.90 (0.78–1.03) **Total MI**: 0.91 (0.72–1.15) **Fatal MI**: 1.11 (0.57–2.18) **Non-fatal MI:** 0.88 (0.69–1.14) **Total CHD**: 0.96 (0.85–1.09) **Stroke**: 0.84 (0.67–1.05), $p = 0.12$ **Ischaemic stroke**: 0.79 (0.62–1.01) **Haemorrhagic stroke**: 1.47 (0.66–3.27) **Fatal stroke**: 1.15 (0.58–2.28 **Non-fatal stroke**: 0.80 (0.63–1.02) **CVD death**: 0.94 (0.77–1.15)

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Sesso et al. (2008) **USA** **PHS II** **Duration (mean):** 8 year **Funding**: Mixed	**2 × 2 × 2 × 2 factorial design, double blind RCT** *12 wk run-in period* **Inclusion criteria:** men ≥ 50 year, with history of MI, stroke or cancer **Exclusion criteria:** history of cirrhosis, active liver disease, on anticoagulants, reported serious illness impeding participation to the trial ***N*** **=** 14,641 ***n*** **=** 14,641 G1: 7326 G2: 7315	**Ethnicity:** NR **Mean age ± SD (y):** G1: 64.3 ± 9.2; G2: 64.2 ± 9.1 **Sex (male, %):** 100 **Mean BMI ± SD (kg/m^2):** G1: 26.0 ± 3.7; G2: 26.0 ± 3.6 **History of CVD (%):** G1: 5.2; G2: 5.1 **History of HT (%):** G1: 42.5; G2: 42.0 **Family history of CVD (%):** G1: 10.1; G2: 10.5 **Current medication use (%):** aspirin (77.4 in both groups)	**Supplement form:** synthetic *α*-tocopherol G1: No *α*-tocopherol G2: 400 IU/every other day *Participants were also randomised to vitamin C, multivitamin & β-carotene* **Vitamin K status/intake:** NR **Compliance (%):** at 4 years 78% for intervention group and 77% for placebo group (taking at least 2/3 of study pills)	**Composite endpoint of major CV events**: non-fatal MI, non-fatal stroke and CVD death. For each endpoint reported by participants by follow-up questionnaire, letter, telephone call and other correspondence, permission was requested to examine relevant medical records **MI** was confirmed by evidence of symptoms in presence of either diagnostic elevations of cardiac enzymes or diagnostic changes on electrocardiograms. For fatal MI the diagnosis was accepted based on autopsy findings **Stroke** confirmed as a typical neurologic deficit of sudden or rapid onset and vascular origin, and lasted > 24 h. **Stroke subtypes were** classified according to National Survey of Stroke criteria **Deaths** were reported by family members or postal authorities	**Incidence of outcomes** *HR (95% CI)* **Major CV events**: 1.01 (0.90–1.13) **Total MI**: 0.90 (0.75–1.07) **Fatal MI**: 0.75 (0.43–1.31) **Total stroke** (fatal and non): 1.07 (0.89–1.29) **Fatal stroke**: 0.86 (0.58–1.27) **Ischaemic stroke**: 1.00 (0.82–1.22) **Haemorrhagic stroke**: 1.74 (1.04–2.91) **CV death**: 1.07 (0.90–1.28) **CHF**: 1.02 (0.87–1.20) **Angina**: 0.94 (0.85–1.05) Covariates: age, PHS cohort, randomisation assignment and CVD at BL
Milman et al. (2008) **Israel** **Duration:** 18 months but there was an early termination of the study **Funding:**	**Double blind RCT** **Inclusion:** individuals ≥ 55 year old with Type 2 Diabetes Mellitus, with haptoglobin (major antioxidant) genotype Hp 2–2. **Exclusion:** uncontrolled HT, MI or stroke within 1 month before enrolment, unwillingness to stop antioxidant supplements, known allergy to vitamin E, individuals with the Hp 1–1 and Hp 2–1 genotypes ***N*** **=** 3054 ***n*** **=** 1434 **Plac:** 708 **Interv:** 726	**Ethnicity:** NR **Age (mean (SD), year): Plac:** 69.5 (8.1) **Interv:** 68.7 (8.1) **Sex (male, %):** **Plac:** 47.9 **Interv:** 47.4 **BMI (mean (SD), kg/m^2):** NR **Prevalence of CVD**: 25% **Participants' history of CVD (%):** MI (Plac: 14.4, Interv: 14.7), Stroke (Plac: 5.4, Interv: 6.5), HT (Plac: 74.8, Interv: 70.8) **Family history of CVD (%):** NR **Current medication use (%):** aspirin (Plac: 37.1, Interv: 37.6), statins (Plac: 58.6, Interv: 53.2), *β*-blockers (Plac: 39.3, Interv: 38.1), ACE inhibitors (Plac: 51.1, Interv: 44.2), Metformin (Plac: 57.9, Interv: 58.7) *Statins and ACE inhibitors between groups significantly different*	**Supplement form:** natural source D-*α*-tocopherol **Dose:** 400 IU/day **Vitamin K status/intake:** NR **Compliance (%):** by telephone interviews (prevalence NR)	Composite outcome: MI, stroke and CV death Kaplan–Meier plot and log-rank test for survival analysis Secondary end points: total mortality, hospitalisation for congestive heart failure and coronary revascularisation Prevalence tested using chi-squared test or Fisher exact test Analysis for differences between included versus excluded participants according to genotype was also conducted	**Composite endpoint**: significant decrease in the interv group versus the plac group (HR 0.47 [95% CI 0.27 to 0.82], $p = 0.01$ by log-rank) **Prevalence of outcome** *n (%) plac* versus *interv* **Composite outcome**: 33 (4.7) versus 16 (2.2) **MI**: 17 (2.4) versus 7 (1.0) **Stroke**: 11 (1.6) versus 6 (00.8) **CV death**: 5 (0.7) versus 3 (0.4) **CHF**: 8 (1.1) versus 8 (1.1)

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Lee et al. (2005) **USA** **WHS** **Duration (mean (range)):** 10.1 year (8.2–10.9) **Funding**: Public and Private	**2 × 2 factorial design, double blind RCT** *3-month run-in* **Inclusion:** healthy female healthcare professionals, ≥ 45 year old **Exclusion:** previous CHD, CVD, cancer (except Non-melanoma skin cancer), or other major chronic illnesses, adverse effects from aspirin, use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) > 1/week, use of anticoagulants or corticosteroids, use of individual supplements of vitamin A, E or *β*-carotene > 1/week ***N*** = 39,876 ***n*** = 39,876 **Plac:** 19,939 **Interv:** 19,937	**Ethnicity:** NR **Age (mean (SD), year):** 54.6 (7.0) in both groups **Sex (male, %):** 0 **BMI (mean (SD), kg/m^2):** Plac: 26.03 (5.06) Interv: 26.04 (5.07) **Participants' history of CVD (%):** HT (Plac: 26.2, Interv: 25.6) **Family history of CVD (%):** MI (Plac: 12.9, Interv: 13.0) **Current medication use (%):** Postmenopausal hormone therapy (Plac: 30.0, Interv: 30.1)	**Supplement form:** natural source *α*-tocopherol **Dose:** 600 IU every other day **Co-supplementation:** aspirin 100 mg every other day **Multivitamin use**: **Plac**: 38.4 **Interv**: 39.2 **Vitamin K status/intake:** NR **Compliance (%):** 78.9% at 5 year and 71.6% at 10 year (defined as taking at least 2/3 of study pills)	Women reported endpoints through questionnaire, letter or phone call. Deaths were reported by family members, postal authorities or through the National Death Index Endpoints reviewed by a committee of physicians blinded to treatment assignment. Only *confirmed endpoints were included in the analyses*, except for total mortality which included 66 reported deaths with no death certificate Composite outcome: first major CV event (MI, non-fatal stroke or CV death). Secondary outcomes were the individual CV events Confirmation of endpoints as in Cook et al. (2007) above	**Incidence of outcomes** *RR (95% CI)* **Composite outcome**: 0.93 (0.82–1.05) **Total MI**: 1.01 (0.82–1.23) **Non-fatal MI**: 1.02 (0.83–1.25) **Fatal MI**: 0.0.86 (0.40–1.85) **Total stroke**: 0.98 (0.82–1.17) **Non-fatal stroke**: 0.99 (0.82–1.19) **Fatal stroke**: 0.88 (0.49–1.57) **Ischaemic stroke**: 0.99 (0.81–1.20) **Haemorrhagic stroke**: 0.92 (0.61–1.38) **CV death**: 0.76 (0.59–0.98)
Chae et al. (2012) **USA** **WHS** **Duration (mean):** 10.1 year **Funding**: Public and Private	**2 × 2 factorial design, double blind RCT** **Inclusion:** same as above **Exclusion:** same as above ***N*** = 39,876 ***n*** = 39,815 **Plac:** 19,902 **Interv:** 19,913	**Ethnicity (%):** Non-Hispanic white (Plac: 94.9, Interv: 94.7) **Age (mean (SD), year):** 60.3 in both groups **Sex (male, %):** 0 **BMI (% plac versus interv):** < 25.0 kg/m^2: 50.8 versus 50.5 25–29.9 kg/m^2: 30.9 versus 31.2 ≥ 30 kg/m^2: 18.3 versus 18.3 **Participants' history of CVD (%):** HT (Plac: 26.1, Interv: 25.6) **Family history of CVD (%):** NR **Current medication use (%):** Postmenopausal hormone therapy (Plac: 30.0, Interv: 30.1)	**Supplement form:** natural source *α*-tocopherol **Dose:** 600 IU every other day **Co-supplementation:** aspirin 100 mg every other day **Multivitamin use**: **Plac**: 38.4 **Interv**: 39.2 **Vitamin K status/intake:** NR **Compliance (%):** 78.9% at 5 year and 71.6% at 10 year (defined as taking at least 2/3 of study pills)	For this analysis, the primary endpoint was all incident HF, which included both definite and probable cases of non-fatal and fatal HF Women who reported the diagnosis of HF, were sent a supplemental questionnaire to collect additional information regarding symptoms, diagnostic evaluation, current medical therapy and functional status and to request permission to obtain and review their relevant medical records. These were reviewed by cardiologists blinded to treatment assignment Information on left ventricular EF (LVEF) within 3 months of the diagnosis of incident HF was collected - The majority of the EF data were derived from echocardiography (68.8%) or left ventriculography (25.0%). Cases of incident nonfatal HF were confirmed if either the Framingham Heart Study or Cardiovascular Health Study criteria were met	**Incidence of outcomes** *HR (95% CI)* **All HF**: 0.91 (0.70–1.19), $p = 0.48$ **Systolic HF (EF < 50%):** 1.25 (0.83–1.89) **HF with normal EF (EF ≥ 50%)**: 0.59 (0.37–0.92)

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
				Fully adjusted for: age at randomisation, aspirin assignment and β-carotene assignment, ethnicity, HT, hypercholesterolaemia, diabetes, BMI, smoking status, alcohol use, physical activity, menopausal status and current hormone use, multivitamin use and interim myocardial infarction as a time varying covariate	
Lippman et al. (2009) **USA, Canada, Puerto Rico** **SELECT** **Duration:** 7–12 year **Funding:** Public and Private	**Double blind RCT** **Inclusion:** age ≥ 50 year (African American men) or ≥ 55 year (all other men), a serum prostate-specific antigen level of ≤ 4 ng/mL, digital rectal examination not suspicious for prostate cancer **Exclusion:** prior prostate cancer diagnosis, use of anticoagulant therapy other than 175 mg/day or less of acetylsalicylic acid or 81 mg/day or less of acetylsalicylic acid with clopidogrel bisulfate, history of haemorrhagic stroke and normal BP ***N*** = 35,533 ***n*** = 34,887 **G1:** 8696 **G2:** 8737	**Ethnicity (%):** Non-Hispanic white (79 both groups), African American (Plac: 12, Interv: 13), Hispanic non-African American (Plac: 6, Interv: 5), Hispanic African American (1 both groups), Other (2 both groups) **Age (median (IQR), year):** **G1**: 62.6 (58.1–67.8) **G2**: 62.3 (58.0–67.8) **Sex (male, %): 100** **Family history of CVD (%):** NR The following information was obtained from Christen, W. G., Glynn, R. J., Gaziano, J. M., Darke, A. K., Crowley, J. J., Goodman, P. J., Lippman, S. M., Lad, T. E., Bearden, J. D., Goodman, G. E., Minasian, L. M., Thompson, I. M., Jr, Blanke, C. D., & Klein, E. A. (2015). Age-related cataract in men in the selenium and vitamin E cancer prevention trial eye endpoints study: A randomised clinical trial. JAMA Ophthalmology, *133*(1), 17–24. https://doi.org/10.1001/jamaophthalmol.2014.3478 **Participants' history of CVD (%):** History of hypertension: 18.7 History of diabetes: 4.6 **Current medication use (%):** Aspirin: 21.0 Statin: 12.7	**Supplement form:** all rac-α-tocopheryl acetate G1: Placebo **G2:** 400 IU/day **G3:** Selenium **G4:** 400 IU/day + selenium **Vitamin K status/intake:** NR **Compliance (%):** pill count At 1 year: 85 both groups At 2 year: 80 both groups At 3 year: 75 both groups At 4 year: 70 both groups At 5 year: 67 plac. & 69 interv	**CV event** data collected in detail from the trial beginning via questionnaire A Social Security Death Index search was conducted in July 2008 for participants who had a last contact date of > 18 months before the search.	**Incidence of outcomes** *RR (99% CI), comparisons G1* versus *G2* Any CV events/death: 0.98 (0.88–1.09) Haemorrhagic stroke: 0.63 (0.18–2.20) Ischaemic stroke: 0.87 (0.53–1.44) Not specified stroke: 0.56 (0.24–1.32) **Deaths** *HR (99% CI)* CV: 0.84 (0.61–1.15) Haemorrhagic stroke: 1.12 (0.32–3.92) Other CV: 0.82 (0.59–1.14)

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Reference country study duration funding	Design (*N*: Number randomised, *n*: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome (s)	Results
Takamatsu et al. (1995) Japan 6 year Private funding	**Double blind RCT** **Inclusion:** Healthy volunteers free of acute and chronic illness, including HTN **Exclusion:** oral contraceptive use, pregnant or lactating women ***N*** = 161 ***n*** = 147 G1: 73 G2: 74	**Ethnicity:** Asian **Age (year):** G1: 47.3 ± 6.3 G2: 46.5 ± 5.2 **Sex (male):** 37% **BMI (kg/m^2):** G1: 22.8 ± 2.6 G2: 22.7 ± 2.3 Smoking status - Current smokers (%): G1: 30 G2: 36 **Participants' history of CVD (%):** NR but free of chronic disease and HTN at baseline **Family history of CVD (%):** NR **Current medication use (%):** NR	**Supplement form:** D-*α*-tocopheryl acetate **Doses** G1: 3 mg/day *α*-tocopheryl G2: 100 mg/day *α*-tocopheryl **Vitamin K status/intake:** NR **Compliance (%):** G1: 91.3 ± 10.2 G2: 89.6 ± 9.2 During study period, in G1, 4 withdrew because of myocardial damage, 2 because of angina pectoris and 1 because of myocardial infarction	**Myocardial infarction** and **angina pectoris** – ascertainment method NR.	*'The morbidity rate of myocardial infarction and/or angina pectoris revealed no differences.'* (Data not shown)

Abbreviations: ACE, angiotensin-converting-enzyme; ATBC, Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group; BMI, body-mass index; CHAOS, Cambridge Heart Antioxidant Study; CHD, Coronary Heart Disease; CHF, Congestive Heart Failure; CI, Confidence Interval; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; EF, ejection fraction, HOPE, Heart Outcomes Prevention Evaluation; HF, heart failure; HOPE-TOO, HOPE–The Ongoing Outcomes; HR, hazard ratio, HT, Hypertension, interv, intervention; MICRO-HOPE, Microalbuminuria, Cardiovascular and Renal Outcomes in the HOPE; MI, Myocardial Infarction; NR, not reported; NS, non-significant, PHS II, The Physicians' Health Study II; plac, placebo; PPP, Primary Prevention Project; SBP, systolic blood pressure; SELECT, The Selenium and Vitamin E Cancer Prevention Trial; SPACE, Secondary Prevention with Antioxidants of Cardiovascular Disease; TIA, Transient Ischaemic Attack; VEAPS, The Vitamin E Atherosclerosis Prevention Study; WHS, Women's Health Survey; WACS, Women's Antioxidant Cardiovascular Study.

[a]Values reported as mean ± standard deviation or median (inter quartile range) unless otherwise indicated.

B.3 | Observational studies

B.3.1 | Total and/or supplemental intake and risk of cardiovascular related outcomes

Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
Ascherio et al. (1999) **Design:** Prospective observational study **Follow-up:** 8 year **Funding:** Public	*n* = 43,738 **Population sampled:** men **Exclusion criteria:** We excluded from analysis 1595 men who did not have 1) a daily caloric intake between 800 and 4200 kcal and 2) fewer than 70 blanks (among 131 listed food items) on the food-frequency questionnaire. We also excluded men with previous myocardial infarction, angina, coronary artery surgery, stroke, transient ischaemic attack, peripheral arterial disease or diabetes **Loss to follow-up** = circa 6% **Age (years):** 40–75 **Participants' history of cardiovascular disease (%):** NR **Family history of cardiovascular disease (%):** NR **Current medication use (aspirin %) for total vitamin E intake quintiles:** Q1: 22 Q2: 32 **BMI (kg/m^2) for total vitamin E intake quintiles):** Q1: 25.7 Q5: 25.2 **Race/ethnicity:** NR	**Method:** If a participant reported an incident stroke on a follow-up questionnaire, we asked for permission to review that participant's medical records. Strokes were confirmed if they were characterised by a typical neurologic defect of sudden or rapid onset that lasted at least 24 h and was attributable to a cerebrovascular event. Strokes caused by infection or neoplasia were excluded. Reviews were conducted by physicians who had no knowledge of participants' risk factor status. Strokes were subclassified, according to the criteria of the National Survey of Stroke, as due to ischaemia (embolism or thrombosis), subarachnoid haemorrhage, intracerebral haemorrhage or an unknown cause (29). If no records could be obtained, a stroke was considered probable if it necessitated hospitalisation and was corroborated by additional information provided in a letter or interview. Deaths were initially reported by next-of-kin, co-workers, postal authorities or the National Death Index. Fatal strokes were confirmed by medical records (84%) or autopsy reports (2%) or were considered probable if medical records or autopsy reports could not be obtained and stroke was listed as the underlying cause of death on the death certificate (14%).	**Method:** Repeated and validated dietary assessments were done by using a self-administered 131-item food-frequency questionnaire, which included questions on dose and duration of vitamin supplement use **Info on vitamin K status/ intake:** NR **Quintiles of Supplemental Vitamin E (*α*-tocopherol) use:** Q1: 0 IU/day Q2: < 25 IU/day Q3: 25–99 IU/day Q4: 100–249 IU/day Q5: ≥ 250 IU/day **Quintiles per person-years of Supplemental Vitamin E (*α*-tocopherol) use:** Q1: 183598 Q2: 54799 Q3: 28414 Q4: 12901 Q5: 43321 **Quintiles for duration of Vitamin E supplement use (y):** Q1: None Q2: 0–1 Q3: 2–4 Q4: 5–9 Q5: ≥ 10	**Total cases for quintiles of Vitamin E use:** Total stroke: 328 Ischaemic stroke: 210 Haemorrhagic stroke: 70 Unclassified: 48 Total cases for quintiles of Vitamin E duration of use: Total stroke: 303 Ischaemic stroke: 196 Haemorrhagic stroke: 66 **Cases/person years:** 328 strokes/323394 person-years	Multivariate Relative Risk (95% CI): **Multivariate Relative Risks for Stroke According to Use of Vitamin Supplements (Updated after 4 years of follow-up): Covariates** were calendar time (2-year intervals), total energy intake (continuous variable), smoking (current; past; and 1–14, 15–24 or $25 cigarettes/day), alcohol consumption (5, 5–9, 10–14, 15–29 or ≥ 30 g/day), history of hypertension, parental history of myocardial infarction before 65 years of age, profession and quintiles of body mass index and physical activity, in addition to age **Multivariate Relative Risk for Stroke According to Duration of Supplement Use: Covariates** were calendar time (2-year intervals), total energy intake (continuous variable), smoking (current; past; and 1–14, 15–24 or $25 cigarettes/day), alcohol consumption (5, 5–9, 10–14, 15–29 or $30 g/day), history of hypertension, parental history of myocardial infarction before 65 years of age, profession and quintiles of body mass index and physical activity, in addition to age.	**RR (95% CI)** **Total stroke (Supplement Vitamin E use):** *p* value for trend: > 0.2 Q1: Reference Q2: 1.00 (0.74–1.36) Q3: 1.01 (0.68–1.49) Q4: 1.00 (0.58–1.73) Q5: 1.13 (0.84–1.52) **Ischaemic stroke (Supplement Vitamin E use):** *p* value for trend: > 0.2 Q1: Reference Q2: 0.88 (0.60–1.31) Q3: 0.89 (0.54–1.47) Q4: 0.89 (0.54–1.47) Q5: 1.16 (0.81–1.67) **Haemorrhagic stroke (Supplement Vitamin E use):** *p* value for trend: > 0.2 Q1: Reference Q2: 0.74 (0.36–1.53) Q3: 0.93 (0.39–2.22) Q4: 2.00 (0.84–4.75) Q5: 1.03 (0.52–2.03) **Total stroke (Duration of supplement Vitamin E use):** *p* value for trend: > 0.2 Q1: Reference Q2: 1.79 (0.92–3.51) Q3: 0.93 (0.54–1.59) Q4: 1.12 (0.71–1.75) Q5: 0.96 (0.63–1.46) **Ischaemic stroke (Duration of supplement Vitamin E use):** *p* value for trend: > 0.2 Q1: Reference Q2: 1.88 (0.83–4.28) Q3: 0.84 (0.41–1.72) Q4: 1.09 (0.62–1.93) Q5: 1.06 (0.64–1.75) **Haemorrhagic stroke (Duration of supplement Vitamin E use):** *p* value for trend: 0.15 Q1: Reference Q2: 1.75 (0.43–7.21) Q3: 1.52 (0.61–3.83) Q4: 1.51 (0.65–3.53 Q5: 0.61 (0.19–1.95)

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
Pocobelli et al. (2009) **Design: Prospective** **Follow-up:** 10 year **Funding:** Public	*n* = 77,719 **Population sampled:** men and women residents of Washington State **Exclusion criteria:** we excluded 1 participant with no follow-up time and 45 participants who reported having a malabsorption condition (e.g. a prior gastroplasty) at baseline (these conditions are associated with decreased nutrient absorption); **Loss to follow-up** **Age (years): 50–76** **Participants' history of cardiovascular disease (%):** NR **Family history of cardiovascular disease (%):** NR **Current medication use:** **BMI (kg/m2):** **Race/ethnicity (%):** **White:** 92 **Hispanic:** 1 **Black:** 1 **American Indian/Alaska native:** 1 **Asian or Pacific Islander:** 2 **Other/missing data**: 2 **Morbidity score (% of participants)**: Level 1 (0): 46 Level 2 (> 0–< 0.5): 36 Level 3 (0.5–< 1.0): 10 Level 4 (1.0–< 1.5): 5 Level 5 (1.5–< 2.0): 2 Level 5 (2.0–< 2.5): 1 Level 6 (2.5–< 3.0): 0 Level 7 (≥ 3.0): 0 Missing data: 0	**Method:** We linked the cohort to the Washington State Death Certificate System to identify deaths occurring through December 31, 2006 (*n* ¼ 3535). Additional deaths were identified from the Social Security Death Index (*n* ¼ 37), linkage with the western Washington Surveillance, Epidemiology and End Results cancer registry (*n* ¼ 2), and notification by relatives (*n* ¼ 3), for a total of 3577 deaths. The date of death was available for all deaths. Information on cause of death was available only for deaths identified through the Washington State Death Certificate System. It was determined from the underlying cause of death coded using the International Classification of Diseases, Tenth Revision (ICD-10) (30). We classified deaths as being due to CVD (ICD-10 codes I00–I15, I20–I52 and I60–I99), cancer (ICD-10 codes C00–D48) or other causes.	**Method:** mailed self-administered questionnaire **Info on vitamin K status/ intake:** NR **Quintiles of Vitamin E duration of use (years) and subjects' % for each:** Q1: None (52%) Q2: 1–3 (12%) Q3: 4–6 (11%) Q4: 7–9 (6%) Q5: ≥ 10 (15%) Qx: Missing data (4%) **Quartiles of Vit. E dose on days taken (mg/ day) and subjects' % for each:** Q1: None (52%) Q2: 30–200 (5%) Q3: 400 (30%) Q4: 600–800 (9%) Qx: Missing data (4%) *Of single supplements (and mixtures other than multivitamins) **Quartiles of Vit E. dose on Ten-year average (mg/day) and subjects' % for each:** Q1: None (26%) Q2: 1.3–42.0 (25%) Q3: 42.1–215.0 (24%) Q4: 215.1–1.000 (24%) Qx: Missing data (1%) *From single supplements (and mixtures than multivitamins) plus multivitamins	**Total cases/ person-years:** **3577/387,801** **Mortality rates: number of deaths/1000 person-years** **Mortality rate per Sextiles of Vitamin E use (years):** Q1: 10.07 Q2: 7.24 Q3: 7.58 Q4: 8.73 Q5: 9.28 Qx: 9.52 **Mortality rate per quintiles of Vit. E dose on days taken (mg/day) and subjects' % for each:** Q1: 10.07 Q2: 8.16 Q3: 7.94 Q4: 8.44 Qx: 10.84 **Mortality rate per quintiles of Vit E. dose on 10-year average (mg/day) and subjects' % for each:** Q1: 10.38 Q2: 9.42 Q3: 7.97 Q4: 8.86 Qx: 15.03	**M3:** HR was adjusted for a history of cardiovascular disease at baseline (defined as a previous heart attack, coronary bypass surgery, angioplasty, a diagnosis of angina or a previous stroke); use of blood pressure medication in the past 2 weeks; history of heart attack in a first degree relative; and diabetes at baseline, in addition to all of the variables listed in footnote 'c' of Table 2, except morbidity score, mother's age at death and father's age at death.	**HR 95% CI for total mortality associated with Supplement use** **Quintiles of Vitamin E duration of use:** **M1:** *p*-trend: N/A Q1: 1.00 (Referent) Q2: 0.77 (0.69–0.87) Q3: 0.74 (0.65–0.83) Q4: 0.80 (0.69–0.92) Q5: 0.74 (0.67–0.82) Qx: - **M2:** *p*-trend: N/A Q1: 1.00 (Referent) Q2: 0.89 (0.79–1.00) Q3: 0.83 (0.73–0.94) Q4: 1.00 (0.86–1.16) Q5: 0.89 (0.80–0.99) Qx: - **Quartiles of Vitamin E dose on days taken:** **M1:** *p*-trend: N/A Q1: 1.00 (Referent) Q2: 0.81 (0.68–0.95) Q3: 0.70 (0.65–0.76) Q4: 0.84 (0.74–0.95) Qx: - **M2:** *p*–trend: 0.010 Q1: 1.00 (Referent) Q2: 0.85 (0.71–1.01) Q3: 0.88 (0.81–0.96) Q4: 0.91 (0.80, 1.04) Qx: - **Quartiles of Vitamin E dose on Ten-year average:** **M1:** *p*-trend: < 0.001 Q1: 1.00 (Referent) Q2: 0.92 (0.84–1.01) Q3: 0.74 (0.68–0.82) Q4: 0.72 (0.66–0.79) Q5: - **M2**: *p*-trend: 0.008 Q1: 1.00 (Referent) Q2: 0.97 (0.88–1.06) Q3: 0.89 (0.81–0.98) Q4: 0.89 (0.81–0.98) Q5: -

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
	The following conditions, categorised as yes or no, were modelled simultaneously in sex-specific and age-adjusted models **to obtain the morbidity score**: current use of medication for depression or anxiety; current use of blood pressure medication; a history of lung cancer, colon cancer, bladder cancer, leukaemia, pancreatic cancer, non-Hodgkin's lymphoma, melanoma, prostate cancer, breast cancer, cervical cancer, uterine cancer, ovarian cancer or all other cancers combined; coronary heart disease (defined as a previous heart attack, coronary bypass surgery, angioplasty or diagnosis of angina); stroke; congestive heart disease; rheumatoid arthritis; diabetes; viral hepatitis; cirrhosis of the liver; other chronic liver disease; emphysema; chronic bronchitis or chronic obstructive pulmonary disease; kidney disease; ulcerative colitis or Crohn's disease; Parkinson's disease; and osteoporosis in women				**M3:** HR was adjusted for a history of cardiovascular disease at baseline (defined as a previous heart attack, coronary bypass surgery, angioplasty, a diagnosis of angina or a previous stroke); use of blood pressure medication in the past 2 weeks; history of heart attack in a first degree relative; and diabetes at baseline, in addition to all of the variables listed in footnote 'c' of Table 2, except morbidity score, mother's age at death and father's age at death.	**Mortality based on Tertiles of Vitamin E dose taken on 10-year average for subjects with a history of cardiovascular disease** M3: *p*-trend: 0.027 Q2: 0.80 (0.59–1.09) Q3: 0.70 (0.51–0.96) Q4: 0.73 (0.54–0.99) **Mortality based on Tertiles of Vitamin E dose taken on Ten-Year average for subjects with no history of cardiovascular disease** M3 *p*-trend: 0.012 Q2: 0.77 (0.66–0.99) Q3: 0.79 (0.61–1.03) Q4: 0.70 (0.53–0.91) **Other HR reported in the paper for the tertiles (Q2-Q3-Q4) of Vit. E dose on 3-year average:** HR 95% CI for total mortality associated with Supplement use based on sex, smoking status, BMI, Morbidity score

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
Rimm et al. (1993) **Design:** Prospective investigation **Follow-up:** 4 year **Funding:** NR	*n* = 17,916 (using Vitamin E supplement) out of 39,910 **Population sampled:** male health professionals **Exclusion criteria:** If the participants reported daily energy intake outside of the range 800–4200 kcal or who left blank 70 or more questions about food on the dietary questionnaire. Men who reported myocardial infarction, angina, stroke, coronary-artery bypass grafting or angioplasty, diabetes or hypercholesterolaemia **Loss to follow-up** **Age (years):** 40–75 **Participants' history of cardiovascular disease (%):** NR **Family history of cardiovascular disease (%):** NR **Current medication use:** Reported only for dietary Vit. E intake (not supplemental) **BMI (kg/m2):** Reported only for dietary Vit. E intake (not supplemental) **Race/ethnicity:** NR	**Method:** Fatal coronary disease, nonfatal myocardial infarction, coronary artery bypass grafting and percutaneous transluminal coronary angioplasty were considered as endpoints. Illness was self-reported, and permission was requested to review medical records. Deaths were reported by next of kin, co-workers, postal authorities or the National Death Index. Fatal infarctions were confirmed from medical records or autopsy reports. Fatal infarctions were considered from medical records or autopsy reports. Fatal coronary disease was also considered confirmed if it was listed as the underlying cause of the death certificate, and a diagnosis of incident coronary disease	**Method: dietary questionnaire** **Info on vitamin K status/ intake:** NR **Quintile groups of Vit. E supplemental intake (IU/day):** *p*-trend: Q1: 0 Q2: < 25 Q3: 25–99 Q4: 100–249 Q5: ≥ 250 **Quintile groups for years of supplement use of Vit. E (y):** Q1: No use Q2: 0–1 Q3: 2–4 Q4: 5–9 Q5: ≥ 10	**Total cases of coronary heart disease per supplemental Vit. E intake quintiles:** Q1: 406 Q2: 120 Q3: 40 Q4: 17 Q5: 84 **Total cases of coronary heart disease per quintile groups for years of supplement use of Vit. E:** Q1: 556 Q2: 11 Q3: 19 Q4: 32 Q5: 35	**Statistical methods:** RR adjusted by the Mantel–Haenszel method and to test for linear trends Mantel extension test was used **M1:** Multivariate logistic regression analysis with control for age (in five-year categories), smoking status (never, smoked, formerly smoked or currently smoking less than 15, 15–24 or 25 or more cigarettes per day), body mass index (the weight in kilograms divided by the square of the height in meters) (in quintile groups), total calories (in quintile groups), dietary fibre (in quintile groups), alcohol consumption (0, 0.1 to 15, 15.1 to 30 or 30.1 or more g per day), reported hypertension, regular aspirin use, physical activity (more than 90 min per week), parental history of myocardial infarction before the age of 60, and profession. Multivariate with antioxidants indicates that quintile groups for vitamin E, carotene and vitamin C were added to the multivariate model. The lowest quintile group served as the reference category in each analysis. CI denotes confidence interval.	**RR 95% CI** **RR for coronary heart disease per quintiles of Vit. E supplemental intake:** **M1:** *p*-trend: 0.22 Q1: 1.00 Q2: 0.85 (0.69–1.05) Q3: 0.78 (0.59–1.08) Q4: 0.54 (0.33–0.88) Q5: 0.70 (0.55–0.89) **RR for coronary disease for quintiles of years of supplement use:** **M1:** *p*-trend: 0.10 Q1: 1.0 Q2: 0.95 (0.52–1.75) Q3: 0.59 (0.37–0.93) Q4: 0.78 (0.54–1.12) Q5: 0.65 (0.46–0.92)

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
Stampfer et al. (1993) **Design:** Prospective study **Follow-up:** 8 year **Funding:** NR	*n* = 87,245 **Population sampled:** female registered nurses living in 11 states **Exclusion criteria:** women who left 10 or more items blank, whose reported food scores were implausible, and who had a history of cancer (except non-melanoma skin cancer), angina, myocardial infarction, stroke or other cardiovascular disease **Loss to follow-up**: NR **Age (years):** 34–59 **Participants' history of cardiovascular disease (%):** NR **Family history of cardiovascular disease (%):** NR **Current medication use:** NR **BMI (kg/m2):** NR **Race/ethnicity:** NR	**Method:** Follow-up questionnaires. Women who reported diagnoses of cardiovascular disease were asked for permission to examine their medical records. A myocardial infarction was considered confirmed if it met the World Health Organization criteria of symptoms and either typical electrocardiographic changes or elevated cardiac enzymes. Infarctions of indeterminate age were excluded. We designated as probable infarctions those that were reported by the nurse, required hospitalisation and were corroborated by additional information (in a letter or telephone interview), but for which records were unobtainable. Most deaths were reported by relatives or postal authorities. We searched the National Death Index for the names of non-respondents and estimate that over 98% of deaths were identified.	**Method:** dietary questionnaire **Info on vitamin K status/ intake:** NR **Quintile groups of Total Vit. E intake (including supplemental intake) expressed as median and range (IU/day):** Q1: 2.8 Q2: 4.2 Q3: 5.9 Q4: 17 Q5: 208	**Cases of coronary heart disease per 1000 person-years for Vitamin E users and nonusers:** Users: 0.52/1000 Nonusers: 0.86/1000	**Statistical methods:** **M1**-adjusted for age **M2**-adjusted for age and smoking **M3**-adjusted for age (in 5 years categories), time period. Quetelet index (in 5 categories), smoking (never smoked, formerly smoked, or currently smoking 1–14, 15–24, 25–34 or 35 or more cigarettes per day), alcohol intake (none, or 0.1–4.9, 5.0–14.9, or 15 or more grams per day), menopausal status (premenopausal, postmenopausal or status uncertain), postmenopausal hormone use (never, formerly or currently), exercise (works up a sweat less than once per week or once or more per week), regular use of aspirin, hypertension, high cholesterol level, diabetes, total energy intake (in quintiles), use of vitamin E supplements and use of multivitamin supplements **M4:** Adjusted for age + All the women were free of diagnosed cardiovascular disease and cancer (except non-melanoma skin cancer) at the start of the observation period in 1980. In this and each subsequent model, women who had these diagnoses at the start of each 2-year questionnaire cycle were excluded from further follow-up **M5**: M3+ adjusted further for intake of carotene and vitamin C.	**RR CI 95% of Major Coronary Heart Disease** **RR for quintiles of Vit. E total intake:** **M1:** *p*-trend: < 0.001 Q1: 1.0 Q2: 0.90 (0.70–1.16) Q3: 1.00 (0.78–1.27) Q4: 0.68 (0.52–0.89) Q5: 0.59 (0.45–0.78) **RR for quintiles of total Vit. E intake:** **M2** *p*-trend: < 0.001 Q1: 1.0 Q2: 1.00 (0.78–1.28) Q3: 1.15 (0.90–1.48) Q4: 0.74 (0.57–0.98) Q5: 0.66 (0.50–0.87) **RR associated with vitamin use:** **M4:** **Vitamin E. users:** 0.57 (0.41–0.78) **Multivitamins users:** 0.78 (0.64–0.96) **M5:** Vitamin E. users: 0.69 (0.49–0.97) Multivitamins users: 0.92 (0.74–1.15) **RR associated with Cardiovascular outcomes according to the use of multivitamins and vitamin E supplements:** **M4:** **Major coronary disease:** Vit. E supplements: 0.54 (0.36–0.82) Multivitamins: 0.88 (0.70–1.09) **Cardiovascular mortality:** Vit. E supplements: 0.58 (0.30–1.12) Multivitamins: 0.77 (0.58–1.16) **Ischaemic stroke:** Vit. E supplements: 0.71 (0.39–1.31) Multivitamins: 0.86 (0.59–1.24) **Coronary-artery surgery (includes coronary-artery bypass grafting and percutaneous transluminal coronary angioplasty):** Vit. E supplements: 0.73 (0.48–1.09) Multivitamins: 0.76 (0.59–0.97) **Overall mortality:** Vit. E supplements: 0.87 (0.69–1.10) Multivitamins: 1.10 (0.94–1.27)

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
Muntwyler et al. (2002) **Design:** Prospective cohort study **Follow-up:** 5.5 year **Funding:** Public	*n* = 83,639 **Population sampled:** male physicians residing in the US with no history of CVD or cancer **Exclusion criteria: history of CVD** (myocardial infarction or angina pectoris, stroke or transient ischaemic attack, or use of digitalis, nitrates or warfarin sodium) and/or cancer except non-melanoma skin cancer. Patients with no information on vitamin supplementation were also excluded **Loss to follow-up**: NR **Age (years):** 40–84 **Participants' history of cardiovascular disease (%):** NR **Family history of cardiovascular disease (%):** NR **Current medication use:** NR **BMI (kg/m2):** NR **Race/ethnicity: NR**	**Method:** Using the National Death Index, death certificates were obtained for the respondents who died through January 31, 1988. The deaths were classified by trained nosologists using the first revision of the Ninth International Classification of Diseases in conjunction with the Automated Classification of Medical Entities Decision Tables to manually select underlying cause of death. Endpoints for this analysis were coronary heart disease (CHD) mortality (codes 410–414) and total CVD mortality (codes 390–459).	**Method:** self-administered dietary questionnaire **Info on vitamin K status/ intake:** NR **Quintile groups of Total Vit. E intake (including supplemental intake) expressed as median and range (IU/day):** Q1: 2.8 Q2: 4.2 Q3: 5.9 Q4: 17 Q5: 208	NR	**Statistical methods:** Proportional hazard models were used to examine the association of intake of vitamin E with total CVD mortality and CHD mortality **M1:** Age adjusted **M2:** Adjusted for history of hypertension, history of hypercholesterolaemia, current and past smoking, alcohol intake, physical activity, body mass index, complementary vitamins and randomisation status; *n* = 67,644	**RR 95% CI** **Total cardiovascular disease (CVD) and coronary heart disease (CHD) mortality according to vitamin E supplementation:** **M1:** CVD: 0.91 (0.74–1.12) CHD: 0.84 (0.63–1.12) **M2:** CVD: 0.92 (0.70–1.21) CHD: 0.88 (0.61–1.27) **Relative risks among participants taking vitamin E supplements and total CVD and CHD mortality:** **M2:** **Total CVD mortality:** High dose supplementation (≥ 400) IU/day): 1.09 (0.74–1.59) Supplement intake for ≥ 4 years at baseline:0.82 (0.54–1.24) Without major CVD risk factors: 0.72 (0.44–1.18) **Total CHD mortality:** High dose supplementation (≥ 400) IU/day): 0.80 (0.45–1.42) Supplement intake for ≥ 4 years at baseline: 0.41 (0.19–0.85) Without major CVD risk factors: 0.71 (0.36–1.38)
Knekt et al. (2004) **Design:** cohort study pooling 9 prospective studies **Follow-up:** 10 year **Funding:** Public	*n* = 156,949 (all studies) **Population sampled:** 9 studies: AHS: 5043 females and 4321 males; ARIC: 7277 females and 5859 males; ATBC: 4739 males; FMC: 2113 females and 2584 males; GPS: 823 females and 1001 males; HPFS: 19687 males; IWHS: 16896 females; NHS (a): 48639 females; NHS (b) 21,450 females; VIP: 8187 females and 8330 males **Exclusion criteria:** Criteria for exclusion of persons from the population at risk were age < 35 y, history of cardiovascular disease or cancer (except non-malignant skin cancer) and extreme energy intake (i.e., > or <3 SDs from the study-specific log-transformed energy intake) at baseline. Subjects receiving vitamin E or beta-carotene supplements in the ATBC trial were also excluded from the analyses **Loss to follow-up**: NR **Age (years):** Table 1 of the paper **Participants' history of cardiovascular disease (%):** NR	**Method:** Validated methods to define nonfatal and fatal CHD cases (codes 410–414 in the International Classification of Diseases, 8th revision) were used in 8 studies (21). Because the Iowa Women's Health Study had only self-reported data on nonfatal CHD, we used only fatal coronary cases from that cohort.	**Method:** Diet was measured by using a food-frequency questionnaire in 7 cohorts and by using a dietary history interview or food records in 2 cohorts **Info on vitamin K status/ intake:** NR **Quintiles of Vitamin E supplement use:** Q1: 0 Q2: < 25 Q3: 25–99 Q4: 100–249 Q5: ≥ 250	**Cohort studies with information on supplement intake:** **Incidence (cases/ baseline cohort size):** ATBC (Males): 336/5520 HPFS (Males): 1401/42806 IWHS: (Females): - NHS (a) (Females): 464/83218 NHS (b) (Females): 835/63794 All studies: 3036/227243 **Mortality (cases/ baseline cohort size):** ATBC (Males): 132/5520 HPFS (Males): 483/42806 IWHS: (Females): 362/31905	**Statistical methods:** For all nutrients, the energy-adjusted intake was estimated by using the residual method **M1:** RRs were adjusted for age, energy intake (kcal/day), smoking status [never, past, current smoker (1–4, 5–14, 15–24, ≥ 25 cigarettes/ day)], BMI (in kg/m2; < 23, 23–24.9, 25–27.4, 27.5–29.9, ≥ 30), physical activity (levels 1–5), education (less than high school, high school graduate, more than high school), alcohol intake (0, < 5, 5–9.9, 10–14.9, 15–29.9, 30–49.9, ≥ 50 mL/ day), history of diabetes, hypercholesterolaemia or serum cholesterol (quintiles), hypertension or blood pressure and postmenopausal hormone use among the women	**RR 95% CI** **RR of the incidence of major coronary heart disease (CHD) events according to the use of vitamin supplements:** **M3:** *p*-trend: 0.52 *p*-heterogeneity: 0.83 Q1: 1.00 Q2: 0.92 (0.81–1.06) Q3: 1.00 (0.83–1.20) Q4: 0.88 (0.70–1.12) Q5: 0.94 (0.81–1.09) **RR of the incidence of major coronary heart disease (CHD) mortality according to the use of vitamin supplements:** **M3:** *p*-trend: 1.00 *p*-heterogeneity: 0.04 Q1: 1.00 Q2: 1.03 (0.85–1.25) Q3: 0.82 (0.59–1.14) Q4: 1.18 (0.86–1.69) Q5: 0.98 (0.64–1.48)

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
	Family history of cardiovascular disease (%): NR **Current medication use:** NR **BMI (kg/m2):** NR **Race/ethnicity:** NR			NHS (a) (Females): 120/83218 NHS (b) (Females): 267/63794 All studies: 1364/227243	**M2:** RRs were adjusted for all of the factors in multivariate model 1 plus intakes of energy-adjusted saturated fatty acids, cholesterol, flavonoids, folate with supplements, vitamin B-6 with supplements and cereal fibre. **M3**: For multivariate model 3, RRs were adjusted for all of the factors in multivariate model 2 plus dietary intakes of total carotene, vitamin C and vitamin E	**Pooled relative risks of the incidence of major coronary heart disease (CHD) events and CHD mortality for quintiles of energy-adjusted overall (dietary and supplemental combined) vitamin E intake in the pooled analysis of the cohort studies reporting supplemental intakes:** **M3**: *p*-trend: 0.89 *p*-heterogeneity: 0.03 Q1: 1.00 Q2: 0.97 (0.81–1.16) Q3: 0.84 (0.70–1.02) Q4: 0.98 (0.78–1.23) Q5: 1.01 (0.70–1.45)
Buijsse et al. (2008) **Design:** prospective population-based cohort study **Follow-up:** 15 year **Funding:** NR	*n* = 559 **Population sampled:** men **Exclusion criteria:** prevalent disease cases (CVD, cancer and diabetes) **Loss to follow-up**: NR **Age (years):** 65–84 **Participants' history of cardiovascular disease (%):** NR **Family history of cardiovascular disease (%):** NR **Current medication use:** NR **BMI (kg/m^2):** NR **Race/ethnicity:** NR	**Method:** The history of previous myocardial infarction, stroke and cancer was ascertained using a questionnaire and was verified with information from general practitioners or hospital discharge information. Information on the history of diabetes mellitus was obtained from a standardised questionnaire Information on the cause of death during 15 y of follow-up was obtained from hospital discharge data, cancer registries, and/or general practitioners. One clinical epidemiologist ascertained the final causes of death. The underlying causes of death were coded according to the Ninth Revision of the International Classification of Diseases (ICD-9). CVD cover ICD-9 codes 390–459. This included ischaemic heart disease (ICD-9 codes 410–414) and stroke (codes 430–438) as main causes and also other diseases of the circulatory system. The first, second and third cause of death was used to identify mortality from CVD.	**Method:** Information on habitual food consumption was collected in 1985, 1990 and 1995 by using a cross-check dietary history method adapted to Dutch conditions. The intake of nutrients and energy was calculated using the Netherlands food composition table from 1987 to 1988, 1989 to 1990 and 1996, respectively **Info on vitamin K status/ intake:** NR	**CVD deaths/Person-years:**197/5744	**Statistical methods:** Cox regression models **M1:** Adjusted for age and energy **M2:** Adjusted for age energy and smoking **M3:** Adjusted for age (cont.), energy (cont.), BMI (cont.), physical activity (cont.), alcohol consumption (yes or no), socioeconomic status (high vs. medium and low), use of aspirin (yes or no), use of antihypertensive drugs (yes or no) and use of anticoagulants (yes or no). **M4:** As for Model A, with additional adjustment for diet prescription, intake of fibre, b-carotene, folate, SFA, trans fatty acids and PUFA. The intake of vitamin C was adjusted for the intake of vitamin E and vice versa.	**RR CI 95%** **RR of 15-y cardiovascular mortality by intake of antioxidant vitamin E from diet and supplements** **M1:** *p*-trend: 0.03 Lowest: 1.00 Middle: 0.75 (0.52–1.08) Highest: 0.65 (0.44–0.94) **M2:** *p*-trend: 0.03 Lowest: 1.00 Middle: 0.75 (0.52–1.08) Highest: 0.65 (0.45–0.95) **M3:** *p*-trend: 0.05 Lowest: 1.00 Middle: 0.76 (0.52–1.10) Highest: 0.67 (0.46–0.98) **M4:** *p*-trend: 0.12 Lowest: 1.00 Middle: 0.82 (0.56–1.21) Highest: 0.73 (0.49–1.08)

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
Kushi et al. (1996) **Country:** USA **Study design:** prospective cohort study **Follow-up:** approximately 7 year (early 1986 -not specified- until 31 December 1992) **Funding:** Public	**Population sampled:** postmenopausal women with no cardiovascular disease **Age (years):** 55–69 **Exclusion criteria:** Premenopausal women were excluded, 30+ items left blank in FFQ, energy intake implausibly high or low, prevalent angina/heart disease/heart attack ***N*:**41,836 ***n*:** 34,486 **Loss to follow-up:** 0% **Participants history of cardiovascular disease:** NR **Family history of cardiovascular disease:** NR **Any oestrogen-replacement therapy (%) for total vitamin E intake quintiles:** Q1: 34.0 Q2: 35.6 Q3: 35.7 Q4: 40.2 Q5: 45.0 **BMI (kg/m2) for total vitamin E intake quintiles:** Q1: 27.2 Q2: 27.1 Q3: 27.2 Q4: 26.6 Q5: 26.6 **Hypertension (%) for total vitamin E intake quintiles:** Q1: 38.8 Q2: 37.0 Q3: 35.9 Q4: 35.4 Q5: 34.0 **Diabetes mellitus (%) for total vitamin E intake quintiles:** Q1: 6.7 Q2: 5.6 Q3: 5.8 Q4: 5.6 Q5: 5.0 **Race/ethnicity:** NR	**Ascertainment of outcome:** by consulting the State Health Registry of Iowa + deaths reported in response to follow-up questionnaires mailed in 1988, 1990 and 1992, and were identified by linking women who did not respond with the National Death Indexà Women were considered to have died of coronary heart disease if the cause of death was assigned to codes 410 to 429 of the International Classification of diseases, 9th revision (code not validated in the study)	**Exposure groups:** **Exposure assessment method** **Method:** baseline questionnaire to investigate risk of coronary heart disease +127 item FFQ+ questions asking to specify the type of fat used, the brand of cooking oil, the names of other regularly consumed foods, brand names of multivitamin preparations and breakfast cereals, current use and dosage of supplements of specific vitamins. To evaluate the reliability of the questionnaire, the study compared the vitamin intake in a subgroup of 44 women with their mean intake estimated from five 24-h dietary-recall interviews. The validity of estimates of vitamin intake from FFQ has been examined in comparison with plasma levels of beta-carotene and alpha-tocopherol in the Nurses' Health Study **Info on vitamin K status/ intake:** NR **Quintile of vitamin E intake from food and supplements:** Q1: 5.68 IU/day Q2: 5.69–7.82 IU/day Q3: 7.83–12.18 IU/day Q4: 12.19–35.58 IU/day Q5: ≥ 35.59 IU/day	**Incident cases *n*/participants** ***n* of deaths/ participants from CHD according to quintile of Vitamin E intake from Food and Supplements:** Q1: 52 Q2: 58 Q3: 38 Q4: 43 Q5: 51 ***n* of deaths/ participants from CHD according to quintile of Vitamin E intake from Food only:** Q1: 36 Q2: 30 Q3: 36 Q4: 25 Q5: 35 ***n* of deaths/ participants from CHD according to quintile of Vitamin E intake from supplements:** Q1: 162 Q2: 30 Q3: 21 Q4: 8 Q5: 21	**Test/Model covariates** Association vitamin E-death from coronary heart disease examined primarily by proportional-hazards regression analysis. Covariates: age, total energy intake, history of hypertension, history of diabetes mellitus, BMI, WHR, history of cigarette smoking, level of physical activity, oestrogen replacement therapy and alcohol intake.	**Results** **RR (95% CI) of Death from CHD, According to Quintile of Vitamin E intake from food and supplements:** **Age and energy adjusted:** Q1: 1.0 Q2: 0.95 (0.65–1.40) Q3: 0.53 (0.34–0.84) Q4: 0.61 (0.39–0.95) Q5: 0.78 (0.52–1.18) *p*: 0.88 **Multivariate adjusted:** Q1: 1.0 Q2: 1.05 (0.69–1.69) Q3: 0.52 (0.31–0.87) Q4: 0.68 (0.41–1.10) Q5: 0.96 (0.62–1.51) *p*: 0.27 **RR (95% CI) of Death from CHD, According to Quintile of Vitamin E intake from food only:** **Age and energy adjusted:** Q1: 1.0 Q2: 0.68 (0.42–1.12) Q3: 0.71 (0.43–1.17) Q4: 0.42 (0.24–0.75) Q5: 0.42 (0.22–0.82) *p*: 0.008 **Multivariate adjusted:** Q1: 1.0 Q2: 0.70 (0.41–1.18) Q3: 0.76 (0.44–1.29) Q4: 0.32 (0.7–0.63) Q5: 0.38 (0.18–0.80) *p*: 0.004 **RR (95% CI) of Death from CHD, According to Quintile of Vitamin E intake from supplements:** **Age and energy adjusted:** Q1: 1.0 Q2: 0.76 (0.51–1.12) Q3: 0.95 (0.60–1.50) Q4: 0.97 (0.48–1.97) Q5:0.82 (0.52–1.29) *p*: 0.78 **Multivariate adjusted:** Q1: 1.0 Q2: 0.83 (0.54–1.28) Q3: 0.95 (0.56–1.59) Q4: 1.25 (0.58–2.68) Q5:1.09 (0.67–1.77) *p*: 0.39

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
			Quintile of vitamin E intake from Food (IU/day): Q1: ≤ 4.91 IU/day Q2: 4.92–6.24 IU/day Q3: 6.25–7.62 IU/day Q4: 7.63–9.63 IU/day Q5: ≥ 9.64 IU/day **Quintiles of Supplemental Vitamin E use (IU/day):** Q1: 0 IU/day Q2: 1–25 IU/day Q3: 26–100 IU/day Q4: 101–250 IU/day Q5: ≥ 250 IU/day			
Sheng et al. (2022) **Study name:** Singapore Chinese Health Study **Country:** China **Study design:** prospective cohort study **Follow-up:** 25 year **Funding:** Public	**Population sampled:** general population from southern China, same sample used in the Singapore Chinese Health Study cohort. **Age at baseline (years; mean ± SD):** 57.0 ± 8.0 **Exclusion criteria**: extreme energy intake (men: < 700 kcal/day or > 3700 kcal/day; women:3000 kcal/day); missing value of dietary antioxidant nutrients at baseline. ***N*:** 63,257 ***n*:** 62,063 **Race/ethnicity:** Asian **Loss to follow-up:** 0.08% (56 subjects) **Characteristics of the study population by quartiles of the CDAI in the Singapore Chinese Health Study:** ***N*:** Q1: 15,515 Q2: 15,516 Q3: 15,516 Q4: 15,516 **Women (*n*, %):** Q1: 6857 (44.20) Q2: 9296 (59.91) Q3: 9365 (60.36) Q4: 9110 (58.71) **Family history of cardiovascular disease:** NR **Current medication use:** NR **BMI (kg/m^2; median, IR):** Q1: 23.0 (20.9–24.2) Q2: 23.1 (21.1–24.4)	**Ascertainment of outcome** Deaths from all-cause, CVD, respiratory diseases and cancer were identified through linkage with the nationwide registry of births and deaths in Singapore. International Classification of Diseases ninth/tenth revision codes to classify causes of deaths from CVD (390–459 or I00–I99), Deaths from CVD were further specified as ischaemic heart disease (410–414 or I20–I25), and stroke (430–438 or I60–I69). The latter codes for stroke included haemorrhagic stroke (430–432 or I60–I62) and ischaemic/non-specified stroke (433–438 or I63–I69).	**Exposure groups** **Exposure assessment method** Validated FFQ during baseline visits by trained interviewers + Singapore Food Composition Database to calculate the consumption of daily nutrients as well as energy intake for this cohort. Information on supplement use of selected vitamins, including vitamin E was collected. Indices of dietary total antioxidant capacity (DTAC) were then derived using two well-adopted methods: the Comprehensive Dietary Antioxidant Index (CDAI) and the Vitamin C Equivalent Antioxidant Capacity (VCEAC).	**Incident cases *n*/participants** **Related to vitamin E consumption from food/ supplements**: NR **Cardiovascular mortality according to quartiles of the energy-adjusted CDAI (*n*/participants):** Q1:2258 Q2:1987 Q3:1740 Q4:1538	**Test/Model covariates** Cox proportional hazards regression models to examine associations of quartiles of independent variables with all-cause and cause-specific mortality. Covariates: demographics (age, sex, education and dialect group), weight, height, lifestyle factors (cigarette smoking status, alcohol consumption, physical activity level, sleep durations, dietary habits and supplement uses), and medical history (hypertension, diabetes, coronary artery disease, stroke and cancer)	**Results** **Multivariable-adjusted HR for cardiovascular diseases mortality according to quartiles of the energy-adjusted CDAI in the Singapore Chinese Health Study:** Model 1*: Q1: 1 Q2:0.89 (0.84, 0.95) Q3:0.86 (0.80, 0.91) Q4:0.79 (0.74, 0.85) $p < 0.001$ Model 2**: Q1: 1 Q2: 0.89 (0.84, 0.95) Q3: 0.87 (0.81, 0.92) Q4: 0.82 (0.76, 0.88 $p < 0.001$ * adjusted for age at baseline, sex, dialect group, total energy intake, level of education, BMI, smoking status, alcohol consumption, physical activity level, sleep durations, baseline history of hypertension, diabetes, coronary artery disease, stroke and cancer; **additionally adjusted for dietary intakes of red meat, poultry, dairy products, fish/shellfish and weekly supplement use **Multivariable adjusted HR and 95% CI of Death from Cardiovascular diseases, according to quartiles of energy-adjusted daily intakes of vitamin E in the DTAC** (see forest plot): 0.88 (0.81, 0.93) $p < 0.001$

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
	Q3: 23.1 (21.1–24.8) Q4: 23.1 (21.2–25.1) **Medical History at baseline:** **Hypertension (*n*, %)**: Q1: 3318 (21.39) Q2: 3660 (23.59) Q3: 3764 (24.26) Q4: 4013 (25.86) **Coronary artery disease (*n*, %):** Q1: 619 (3.99) Q2: 620 (4.00) Q3: 626 (4.03) Q4: 680 (4.38) **Stroke (*n*, %):** Q1: 279 (1.80) Q2: 223 (1.44) Q3: 192 (1.24) Q4: 229 (1.48) **Diabetes mellitus (*n*, %)**: Q1: 1251 (8.06) Q2: 1438 (9.27) Q3: 1432 (9.23) Q4: 1437 (9.26) **Weekly supplement use (*n*, %):** Q1: 172 (1.11) Q2: 282 (1.82) Q3: 545 (3.51) Q4: 2910 (18.75)					
Yochum et al. (2000) **Country:** USA **Study design:** prospective cohort study **Follow-up**: 11 year **Funding:** Public	**Population sampled:** Post-menopausal women **Age at baseline (years):** 55–69 **Exclusion criteria:** pre-menopausal status at the time the questionnaire was completed prevalent angina, heart disease, or had a heart attack; implausible energy intakes (< 2.5 or > 20.9 MJ/day); skipped >30 items on the FFQ. ***N*:** 41,836 ***n*:** 34,492 **Race/ethnicity:** NR **Loss to follow-up:** NR **Association of various cardiovascular disease risk factors at baseline, according to total intakes of vitamins E from foods and supplements:** SD: 148.04 **Age (y, median):** Q1: 61.4 Q2: 61.4	**Ascertainment of outcome:** Deaths were identified annually through the State Health Registry of Iowa, and through the National Death Index. Underlying cause of death was assigned by state vital registries with use of the Manual of International Classification of Diseases, 9th revision à if codes 430 through 438 death due to stroke. Ischaemic and haemorrhagic strokes were not analysed separately.	**Exposure groups** **Exposure assessment method** Dietary intake assessed using a 127-item FFQ, + assessment of mineral/ vitamin supplement intake. The brand of multivitamin used and the frequency and dose of specific vitamins were recorded. No data on duration of use. The questionnaire also contained questions about the specific brand of oil used in cooking, the type of breakfast cereal typically eaten and the brand of multivitamin used	**Incident cases *n*/participants** à**According to quintile of antioxidant intake from food and supplements (*n*):** Q1: 47 Q2: 53 Q3: 34 Q4: 31 Q5: 50 à**According to quintile of antioxidant intake from diet only (*n*):** Q1: 47 Q2: 45 Q3: 48 Q4: 38 Q5: 37	**Test/Model covariates** The risk of death from stroke in the higher quintiles of intake compared with the lowest was then examined by using proportional hazards regression analysis. Intake of antioxidant vitamins derived exclusively from supplements considered in relation to death from stroke. Covariates: Age, energy intake, BMI, WHR, smoking status, diabetes mellitus, hypertension, physical activity, oestrogen replacement therapy, alcohol intake, marital status, education level.	**Results** **RR (95% CI) of death from stroke according to quintile of vitamin E intake from food and supplements:** Age and energy adjusted: Q1: 1.0 Q2: 1.00 (0.67, 1.51) Q3: 0.57 (0.35, 0.93) Q4: 0.52 (0.32, 0.86) Q5: 0.88 (0.57, 1.34) *p*: 0.41 Adjusted for non-dietary variables: Q1:1.0 Q2:1.20 (0.78, 1.84) Q3:0.75 (0.45, 1.24) Q4:0.60 (0.35, 1.02) Q5:1.08 (0.68, 1.71) *p*: 0.25 Multivariate adjusted: Q1:1.0 Q2:1.21 (0.78, 1.86) Q3:0.76 (0.45, 1.27) Q4:0.58 (0.34, 0.99)

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Reference Study name Country Study design Follow-up Funding	Original cohort (*N* total) Population sampled Exclusion criteria Study population (*n*)	Ascertainment of outcome	Exposure groups Exposure assessment method	Incident cases *n*/ person-years *n*/participants	Test/Model covariates	Results
	Q3: 61.5 Q4: 61.6 Q5: 61.6 SD: 4.18 **BMI (kg/m^2, median):** Q1: 27.2 Q2: 27.1 Q3: 27.1 Q4: 26.6 Q5: 26.6 SD: 5.07 **WHR (median):** Q1: 0.843 Q2: 0.837 Q3: 0.836 Q4: 0.835 Q5: 0.831 SD: 0.086 **Diabetes mellitus (%, median)** Q1: 7.0 Q2: 5.5 Q3: 5.6 Q4: 5.5 Q5: 5.2 **Hypertension (%, median):** Q1: 39.1 Q2: 37.0 Q3: 35.9 Q4: 35.3 Q5: 33.8 **Current oestrogen replacement therapy (%, median):** Q1: 33.6 Q2: 36.1 Q3: 35.8 Q4: 39.8 Q5: 45.2		**Quintiles of median vitamin E intake (mg/day) from food and supplements:** Q1: 4.9 Q2: 7.0 Q3: 9.7 Q4: 22.1 Q5: 238.4 **Quintiles of median vitamin E intake (mg/day) from diet only:** Q1: 4.4 Q2: 6.0 Q3: 7.4 Q4: 9.0 Q5: 12.3 **Quintiles of median vitamin E intake (mg/day) from supplements:** Q1: 0 Q2: 1–25 Q3: 26–100 Q4: 101–250 Q5: > 250	à**According to quintile of antioxidant intake from supplements (*n*):** Q1: 135 Q2: 29 Q3: 18 Q4: 12 Q5: 21	**Test/Model covariates** The risk of death from stroke in the higher quintiles of intake compared with the lowest was then examined by using proportional hazards regression analysis. Intake of antioxidant vitamins derived exclusively from supplements considered in relation to death from stroke. Covariates: Age, energy intake, BMI, WHR, smoking status, diabetes mellitus, hypertension, physical activity, oestrogen replacement therapy, alcohol intake, marital status, education level. Further adjustment for intakes of cholesterol, saturated fat, fish, dietary fibre, whole grains and other antioxidants. Examination of risk of death from stroke on the basis of foods that were concentrated sources of vitamin E. ***Adjusted for non-dietary values:** age, total energy intake, BMI, WHR, high blood pressure, diabetes, use of oestrogen replacement therapy, alcohol intake, education, marital status, pack-years of smoking and physical activity level, intakes of cholesterol, saturated fat, fish, vitamin C, carotenoids, dietary fibre, whole grains.	Q5:0.91 (0.55, 1.52) *p*: 0.86 **RR (95% CI) of death from stroke according to quintile of vitamin E intake from supplements:** Age and energy adjusted: Q1: 1.0 Q2: 0.66 (0.35, 1.24) Q3: 1.56 (0.93, 2.61) Q4: 1.17 (0.43, 3.19) Q5:0.83 (0.45, 1.56) *p*: 0.25 Adjusted for non-dietary variables: Q1:1.0 Q2:0.75 (0.47, 1.22) Q3:1.29 (0.82, 2.02) Q4:1.20 (0.53, 2.72) Q5: 0.67 (0.38, 1.18) Multivariate adjusted: Q1:1.0 Q2:0.76 (0.47, 1.22) Q3:1.28 (0.82, 2.01) Q4:1.21 (0.53, 2.75) Q5:1.21 (0.38, 1.19)

Abbreviations: BMI, body mass index; CDAI, Comprehensive Dietary Antioxidant Index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular diseases; DTAC, dietary total antioxidant capacity; FFQ, food frequency questionnaire; HR, hazard ratio; M1,2,3,4,5, models of multivariate logistic regression analysis; NR, not reported; RR, relative risk; VCEAC, Vitamin C Equivalent Antioxidant Capacity; WHR, waist-to-height ratio.

B.4 | Evidence tables on prostate cancer

B.4.1 | Intervention studies

Reference country study duration funding	Design (N: Number randomised, n: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome(s)	Results
Gaziano et al. (2009) **USA, PHS II** **Duration:** mean 8.0 year **Funding:** Mixed (private and public)	RCT, double blind, placebo-controlled factorial trial **Inclusion criteria**: male physicians, aged ≥ 50 years ***N*** **=** 14,641 (7641 from PHS I and 7000 new) G1: 3656 G2: 3659 G3: 3673 G4: 3653 **Exclusion criteria**: history of cirrhosis, active liver disease, anticoagulants use, illness precluding participation (except for history of MI, stroke or cancer) and history of prostate cancer. ***n*** **=** 13,983 G1: 3497 G2: 3486 G3: 3509 G4: 3491	**Ethnicity:** **Age:** ~64.3 year **BMI:** 26.0 ± 3.6 kg/m^2 **Parental history of prostate cancer:** ~ 10% **Aspirin use:** 77.4%	**Supplement form:** synthetic *α*-tocopherol and/or synthetic ascorbic acid **Doses** G1: 400 IU *α*-tocopherol altern. days +500 mg/day vitamin C G2: 400 IU *α*-tocopherol altern. days + placebo vitamin C G3: placebo *α*-tocopherol +500 mg/day vitamin C G4: placebo *α*-tocopherol + placebo vitamin C Participants were randomised to *β*-carotene and multivitamin or their placebos **Vitamin K status/intake:** NR **Compliance** at 4 years: 78% in G1 and 77% in G4 at the end of follow-up: 72% in G1 and 70% in G4	Self-reported (follow-up questionnaire, letter, telephone call and other correspondence); Ascertained based on medical records (pathology and cytology reports in most cases and rarely by clinical, radiologic or laboratory evidence), death certificates.	**Prostate cancer incidence** Incidence rates (per 1000 person-years) G1 + G2: 9.1 G3 + G4: 9.5 **Cox proportional hazards model, HR (95% CI) [*n* cases]** G3 + G4: 1.00 [515] G1 + G2: 0.97 (0.85–1.09) [493] Covariates: age, PHS cohort (original PHS I participant, new PHS participant) and randomisation group (*β*-carotene, multivitamin and either *α*-tocopherol or vitamin C). *p-value for interaction between randomised vitamin E and vitamin C assignments: 0.55.* *No change when censoring at the time of vitamin E non-compliance. No effect modification by BL history of cancer, risk factors and other randomised interventions from PHS II. No change when restricting to person-time and events after 4 years or after 6 years of treatment.*
Wang et al. (2014) **USA, PHS II -***Observational follow-up* **Duration**: 2.8 year (observational follow-up) **Funding:** Mixed (public and private)	*As above*	*As above for trial BL* **Subjects' characteristics for post-trial observational phase:** NR	*As above*	*As above*	**Prostate cancer incidence** **Cox proportional hazards models, HR (95% CI) [*n* cases]** **- Trial phase:** G3 + G4: 1.00 [520] G1 + G2: 0.96 (0.85–1.09) [497] - **Post-trial observational phase:** G3 + G4: 1.00 [173] G1 + G2: 1.06 (0.86–1.30) [183] **- Intervention plus post-trial observation:** G3 + G4: 1.00 [693] G1 + G2: 0.99 (0.89–1.10) [680] Covariates: age, PHS cohort (PHS I participants, new participants) and other randomised assignments *No effect modification by cancer risk factors, other PHS II randomised treatment or periods of follow-up.*

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Reference country study duration funding	Design (N: Number randomised, n: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome(s)	Results
Lonn et al. (2005) **19 countries, HOPE/HOPE-TOO** **Duration:** median 7.0 year (HOPE + HOPE-TOO) **Funding:** Mixed (public and private)	Multicentre, double-blind, randomised trial **Inclusion criteria:** age ≥ 55 year, history of coronary or peripheral arterial disease, prior stroke or DM plus at least 1 other cardiovascular risk factor. **Exclusion criteria:** heart failure, low ejection fraction (< 40%), uncontrolled hypertension, overt nephropathy, sustained MI or stroke ≤ 4 weeks before BL, planned revascularisation, taking angiotensin-converting enzyme inhibitors or vitamin E ***N*:** 9541 (HOPE) + 7030 (HOPE-TOO) G1: 4761 + 3520 G2: 4780 + 3510	**Ethnicity:** White: 89.9% Hispanic: 5.6% Asian: 1.6% Black: 1.5% Native American: 0.5% Other: 0.9% **Female sex**: ~ 26% **Mean age**: 66 ± 7 year **Mean BMI**: 28 ± 4 kg/m^2 **Current aspirin or other anti-platelet agent use:** ~ 76% ***β*-blockers use:** ~ 40% **Lipid-lowering agents:** ~ 29% **Diuretics:** ~ 15% **Calcium channel blockers**: ~ 47%	**Supplement form:** RRR-a-tocopheryl acetate **Doses** G1: 400 IU/day G2: placebo In addition, men in each group were randomised to ramipril or placebo in HOPE; all received ramipril in HOPE-TOO. **Background nutrient intake:** NR **Vitamin K status/intake:** NR **Compliance:** 'high'	Cases were ascertained by an adjudication committee, with specific expertise in cancer using pathology (or cytology) reports, discharge and other clinical summaries, and results of imaging, serum markers and other diagnostic procedures. Clinical summaries were available for all reported cancers. In addition, microscopic confirmation was available for 70.1%, direct tumour visualisation for 0.8% and imaging reports, tumour markers or other laboratory investigations for 10.7%.	**Prostate cancer incidence** **Cox proportional hazards models, HR (95% CI) [*n* cases]** All HOPE participants: G1: 1.00 [116] G2: 0.98 (0.76–1.26) [119] HOPE-TOO only G2: 1.00 [101] G1: 0.90 (0.68–1.19) [91] *Stratified for assignment to ramipril or placebo, to account for the factorial study design. No interaction between ramipril and vitamin E*
Heinonen et al. (1998) **Finland, ATBC** **Duration:** 5–8 year (median 6.1) **Funding:** Public	*As above*	*As above* **Median background vitamin E intake:** ~ 10.3 mg/day **History of prostatic hyperplasia:** ~ 4.0% **Medication:** NR	*As above*	Finnish Cancer Registry and Finnish register of death, with medical records reviewed by clinicians at the central study office for diagnostic confirmation and staging (AJCC 1992 criteria).	**Prostate cancer incident cases (%)** G1: 43 (0.6) G2: 80 (1.1) G3: 56 (0.8) G4: 67 (0.9) **Difference between cumulative incidence among active *α*-tocopherol (G1) and placebo (G4)**: – 36% (95% CI −56% to −6%) **Difference between cumulative incidence among active *α*-tocopherol (G1 + G3) and placebo *α*-tocopherol (G2 + G4):** −32% (95% CI −47% to −12%) **Difference between incidence rates of stage II–IV tumours among active *α*-tocopherol (G1 + G3) and placebo *α*-tocopherol (G2 + G4):** – 40% (95% CI −55% to −20%) *No effect of supplementation on stage 0–I cancers. No interaction between a-tocopherol and b-carotene supplementation effects (likelihood ratio test: p = 0.75).*

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Reference country study duration funding	Design (N: Number randomised, n: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome(s)	Results
Virtamo et al. (2003) **Finland, ATBC –** *Observational follow-up* **Duration:** 6 years of observational follow-up **Funding:** Public	*As above for trial period* **Participants included in post-trial follow-up phase 1 (1993–1996):** 25,390 G1: 6388 G2: 6306 G3: 6308 G4: 6388 **Participants included in post-trial follow-up phase 2 (1996–1999):** 22,770 G1: 5788 G2: 5615 G3: 5622 G4: 5745	*As above for trial period* **Subjects' characteristics at the beginning of post-trial period** **Mean age:** 63.5 year **Mean nr of cigarettes:** 20.4/day **Mean y of smoking:** 35.5 year **Taking nontrial vitamin E supplements:** 4.8% **Mean dose from vitamin E supplements:** 20 mg/day	*As above*	For the post-trial period, cases were identified via the Finnish Cancer Registry, death certificates and the National Hospital Discharge Register. Medical records from all potential cases were reviewed by two oncologists.	**Prostate cancer incidence, by regimen** **Poisson regression models, RR (95% CI) [*n* cases]** **- Trial phase:** G4: 1.00 [67] G1: 0.64 (0.44–0.94) [43] Incidence rate (per 10,000 person-years): G1: 10.2 G4: 15.8 - **Post-trial observation phase 1:** G4: 1.00 [74] G1: 0.73 (0.51–1.04) [54] Incidence rate (per 10,000 person-years): G1: 29.6 G4: 40.5 - **Posttrial observation phase 2:** G4: 1.00 [104] G1: 0.94 (0.72–1.24) [96] Incidence rate (per 10,000 person-years): G1: 60.6 G4: 64.2 **Prostate cancer incidence, by *α*-tocopherol supplementation** **Poisson regression models, RR (95% CI)** **- Trial phase:** G2 + G4: 1.00 G1 + G3: 0.66 (0.52–0.86) - **Posttrial observation phase I:** G2 + G4: 1.00 G1 + G3: 0.89 (0.70–1.12) - **Posttrial observation phase II:** G2 + G4: 1.00 G1 + G3: 0.88 (0.72–1.07)
Virtamo et al. (2014) **Finland, ATBC –** *Observational follow-up* **Duration:** 18 year of observational follow-up **Funding:** Public	*As above* **Participants included in posttrial follow-up:** 25,563 G1: 6388 G2: 6305 G3: 6308 G4: 6388 Number of men included in the analysis (no prostate cancer at start of post-trial follow up): 25,389	*As above*	*As above*	*As above*	**Prostate cancer incidence, posttrial observational phase** Incidence rate (per 10.000 person-years) G1: 73.3 G4: 79.6 **Poisson regression models, RR (95% CI) [*n* cases]** By regimen: G4: 1.00 [605] G1: 0.92 (0.82–1.03) [553] By *α*-tocopherol supplementation: G2 + G4: 1.00 [1181] G1 + G3: 0.97 (0.89–1.05) [1140]

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Reference country study duration funding	Design (N: Number randomised, n: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome(s)	Results
Lippman et al. (2009) **USA, Canada, Puerto Rico, SELECT** **Duration:** 5.5 year **Funding:** Public	RCT, double-blinded, placebo-controlled **Selection criteria:** ≥ 50 years for African American men and ≥ 55 years for all other men; no prior prostate cancer diagnosis, serum PSA ≤ 4 ng/mL, unsuspicious digital rectal examination, no current use of anticoagulant therapy other than ≤ 175 mg/day acetylsalicylic acid or ≤ 81 mg/day acetylsalicylic acid with clopidogrel bisulfate, no history of haemorrhagic stroke and with normal blood pressure ***N***: G1: 8904 G2: 8856 **Exclusions:** participants from of 2 sites due to poor data and participant management and regulatory issues), clinical ineligibility or with insufficient data to assess eligibility. **Loss to follow-up**: 5.1% ***n*:** G1: 8737 G2: 8696	**Ethnicity:** White: 79% African American: 13% Hispanic (non-African American): 5% Hispanic (African American): 1% Other: 2% **Median age:** ~ 62.5 year **Median (IQR) PSA:** 1.1 (0.6–1.9) ng/mL **Median cholesterol-adjusted *α*-tocopherol:** ~ 12.65 μg/mL	**Supplement form:** all rac-*α*-tocopheryl acetate G1: 400 IU/day all rac-*α*-tocopheryl acetate G2: placebo In addition, men in each group were randomised to selenium or its placebos (2 × 2 factorial design) *(data not extracted)* **Background nutrient intake:** NR **Vitamin K status/intake:** NR **Compliance (pill counts):** averaged 83% at year 1 and 65% at year 5. **Median (IQR) cholesterol-adjusted *α*-tocopherol (μg/mL)**: After 2 years G1: 18.4 (15.1–22.9) G2: 12.1 (10.8–13.7) After 4 years G1: 16.6 (13.9–22.6) G2: 12.1 (10.0–14.4)	Self-reported, confirmed by medical records with diagnostic method (prostate biopsy/other) and clinical stage (T stage, N stage, M stage, Glascan score). Tissue and the corresponding pathology report were sent to the central pathology laboratory for confirmation.	**Prostate cancer incidence** 5-year cumulative incidence rate (%): G1: 4.93 G2: 4.43 **Cox proportional hazards models, HR (95% CI) [*n* cases]** G2: 1.00 [416] G1: 1.13 (0.99–1.29) (99% CI, 0.95–1.35) [416] *Cancer stage and grade similar across groups*

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Reference country study duration funding	Design (N: Number randomised, n: Number analysed)	Subject characteristics at baseline	Intervention	Ascertainment of outcome(s)	Results
Klein et al. (2011) **USA, Canada, Puerto Rico, SELECT –** *Observational follow up* **Duration:** 2.8 year of observational follow-up **Funding:** Public	*As above* ***n* (end of observational follow up)**: G1: 7650 G2: 7594	*As above* **Subjects' characteristics at the beginning of posttrial period:** NR	*as above*	*As above*	**Prostate cancer incidence** **Cox proportional hazards models, HR (99% CI) [*n* cases]** **-Trial phase** G2: 1.00 [416] G1: 1.13 (0.95–1.35) [473] **-Trial + posttrial observational period:** G2: 1.00 [529] G1: 1.17 (1.00–1.36) [620] **Aggressive prostate cancer incidence (Gleason ≥7)** **Cox proportional hazards models, HR (99% CI) [*n* cases]** G2: 1.00 [133] G1: 1.16 (0.86–1.58) [155]

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BL, baseline; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HOPE, Heart Outcomes Prevention Evaluation trial; HOPE-TOO, HOPE–The Ongoing Outcomes trial; HR, hazard ratio; IQR, interquartile range; IU, international units; MI, myocardial infarction; NR, not reported; PHS, Physicians' Health Study; PSA, prostate specific antigen; RCT, randomised controlled trial; RR, relative risk; SELECT, Selenium and Vitamin E Cancer Prevention Trial.

[a]Values reported as mean ± standard deviation or median (inter quartile range) unless otherwise indicated.

B.5 | Observational studies for total and/or supplemental intake and risk of prostate cancer

Reference study name country study design follow-up funding	Original cohort (N total) population sampled exclusion criteria study population (*n*)	Ascertainment of outcome	Exposure groups exposure assessment method	Incident cases *n*/person-years *n*/participants	Test/model covariates	Results
Kirsh et al. (2006) **PLCO** **USA** **Design:** PC **Follow-up:** mean 4.2 years **Funding:** Public	**Inclusion criteria:** Men aged 55–74, in the screening arm of the PLCO trial, without prior prostate, colon or lung cancer; not under cancer treatment (excluding nonmelanoma skin cancer); without surgical removal of the prostate, lung or colon; without recent finasteride use or more than one PSA test; without involvement in another screening or cancer prevention trial. ***N*:** 38,352 **Exclusion criteria:** history of cancer other than nonmelanoma skin cancer; absence of initial PSA test or DRE; having an initial screening examination but no subsequent contact; incomplete BL risk factor questionnaire; failure to provide a dietary questionnaire or with missing data (more than seven items); energy intake in the top or bottom 1% of the reported energy intake distribution; initial screening examination occurring upon randomisation **Loss to follow-up:** 9% ***n*:** 29,361 **Ethnicity (%):** White: 90.7 Asian/Pacific Islanders: 4.0 Black: 3.3 Hispanic: 1.8 American Indians/Alaskan Natives: 0.2 **Vitamin supplement users** **Mean age at BL (SD)**: 63.4 years (5.3) **Mean BMI (SD)**: 27.8 kg/m^2 (4.1) **Family history of prostate:** 7.2% **Average no. of screens/year:** 0.85 **Smoking status (%)**: never: 29.4; current: 12.0; former: 50.9 **Mean physical activity (SD):** 2.1 h/week (1.9) **Daily aspirin use:** 24.8% **Vitamin supplement nonusers** **Mean age at BL (SD)**: 63.2 years (5.3) **Mean BMI (SD):** 27.3 kg/m^2(4.1) **Family history of prostate cancer:** 7.3% **Average no. of screens/years:** 0.86 **Smoking status (%):** never: 29.7; current: 9.8; former: 52.3 **Mean physical activity (SD):** 2.4 h/wk (1.9) **Daily aspirin use:** 35.0%	Serum PSA testing at study entry and annually for 5 years; DRE at study entry and annually for 3 years. PSA level > 4 ng/mL or suspicious DRE referred to prostate cancer diagnostic evaluation. Medical records, including pathology reports, were obtained for suspected cases, and death certificates, medical and pathology records obtained for deceased participants	**Assessment:** Self-administered FFQ for background diet intake and detailed information on vitamin E supplement use. **Exposure groups:** **1) Supplemental vitamin E intake range (IU/day)** Q1: 0 Q2: > 0–30 Q3: > 30–400 Q4: > 400 **2) Duration of Vitamin E supplementation (years)** T1: 0 T2: > 0–2 T3: 3–4 T4: 5–9 T5: ≥ 10 Vitamin E supplement users: 15,155 (52%) Mean dietary vitamin E intake among users: 12 mg *α*-Teq/day Mean vitamin E intake from supplements among users: 279 IU/day Vitamin K status/intake: NR	**Cases/persons:** 1338/29,361 **Cases per Vitamin E supplemental quintiles:** Q1: 675 Q2: 274 Q3: 175 Q4: 214 Cases per Vitamin E dietary intake quintiles: Q1: 263 Q2: 256 Q3: 271 Q4: 258 Q5: 290- Cases per *α*-tocopherol dietary intake quintiles: Q1: 260 Q2: 248 Q3: 266 Q4: 275 Q5: 289	**Cox proportional hazards models** **Covariates:** age, total energy, race, study center, family history of prostate cancer, BMI, physical activity, fat intake, red meat intake, history of DM, aspirin use and number of screening examinations during follow-up	**RR (95% CI):** **Supplemental vitamin E intake:** Q1: 1.00 Q2: 1.02 (0.89–1.18) Q3: 0.92 (0.77–1.08) Q4: 0.97 (0.83–1.13) **Duration of vitamin E supplementation:** T1: 1.00 T2: 0.92 (0.76–1.12) T3: 0.97 (0.75–1.26) T4: 0.87 (0.67–1.13) T5: 0.84 (0.69–1.02)

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Reference study name country study design follow-up funding	Original cohort (N total) population sampled exclusion criteria study population (*n*)	Ascertainment of outcome	Exposure groups exposure assessment method	Incident cases *n*/person-years *n*/participants	Test/model covariates	Results
Rodriguez et al. (2004) **CPS-II Nutrition Cohort** **USA** **Design:** PC **Follow-up:** 8 year **Funding:** NR	**Original study (*N*):** 86,404 **Inclusion criteria:** Male participants in the CPS-II nutrition cohort **Exclusion criteria:** prevalent cancer cases at BL (except non-melanoma skin cancer) or whose self-report of prostate cancer could not be confirmed; incomplete information on vitamin E use ***n*:** 72,704 **Medication:** NR	Self-reported and verified by medical records, from linkage with state cancer registries or death certificates, if recorded as the underlying cause of death Advanced prostate cancer was defined as cases at stage C and D according to the Whitmore-Jewett staging system, those classified as regional or distant by a state cancer registry, and prostate cancer deaths identified by linkage with the National Death Index	**Assessment:** Self-administered FFQ **Exposure groups: Vitamin E supplement intake (IU/day)** G1: None G2: 1–31 G3: 32- < 400 G4: ≥ 400 Age-adjusted mean dietary vitamin E intake among exposure groups (g/day): G1: 8.9 G2: 8.8 G3: 9.0 G4: 9.0 Vitamin K status/intake: NR	**All prostate cancer incidence** **Cases (*n*):** G1: 2588 G2: 883 G3: 328 G4: 482 **Person-years (*n*):** G1: 271,727 G2: 88,946 G3: 30,659 G4: 46,185 **Advanced prostate cancers incidence** **Cases (*n*):** G1: 413 G2: 125 G3: 61 G4: 69 **Person-years (*n*):** G1: 264,199 G2: 86,275 G3: 29,811 G4: 44,752	**Cox proportional hazards models** **Covariates:** age, race, education, family history of prostate cancer, smoking, BMI, energy, fat, lycopene and calcium intake, PSA history	**RR (95% CI):** **All prostate cancer incidence** G1: 1.00 G2: 1.03 (0.96–1.11) G3: 1.11 (0.99–1.25) G4: 1.04 (0.94–1.15) **Advanced prostate cancer incidence** G1: 1.00 G2: 0.94 (0.76–1.15) G3: 1.29 (0.98–1.70) G4: 0.97 (0.74–1.26)
Wright et al. (2007) **NIH-AARP** **USA** **Design:** PC **Follow-up:** 5 year **Funding**: public	**Inclusion criteria:** members of the AARP ***N*:** 617,119 **Exclusion criteria:** women, incomplete or duplicated BL questionnaire, deaths or relocation out of the study area before BL, withdrawals, questionnaires completed by proxy respondents, prior cancer diagnosis except non-melanoma skin cancer, extreme energy or tocopherol intake values ***n*:** 295,344 **Medication:** NR	Probabilistic linkage of the NIH-AARP cohort database to those of the state cancer registries (method validated against self-report confirmed by medical records with an estimated 90% accuracy) Localised (organ confined) prostate cancer defined as cases with a clinical or pathologic stage of T1a-T2b and N0M0 according to the American Joint Committee on Cancer 1997 Tumour-Node-Metastasis classification system. Advanced cases were those with clinical or pathologic stage T3, T4 or N1 or M1, and those who died from prostate cancer	**Assessment:** Supplemental vitamin E use assessed by a self-administered questionnaire on single nutrient and multivitamin supplement use **Exposure groups: Vitamin E supplemental intake (IU/day):** G1: 0 G2: > 0–99 G3: 100–199 G4: 200–399 G5: 400–799 G6: ≥ 800 Vitamin K status/intake: NR	**All prostate cancer incidence** **Cases (*n*):** G1: 4023 G2: 2743 G3: 380 G4: 622 G5: 1950 G6: 523 **Localised prostate cancer incidence** **Cases (*n*):** G1: 3459 G2: 2330 G3: 319 G4: 527 G5: 1680 G6: 450 **Advanced prostate cancer incidence** **Cases (*n*):** G1: 564 G2: 413 G3: 61 G4: 95 G5: 270 G6: 73	**Cox proportional hazards models** **Covariates:** age, race, smoking, education, history of DM, family history of prostate cancer, BMI and dietary intakes of red meat, a-linolenic acid, vitamin C (including supplements) and β-carotene (including supplements)	**RR (95% CI):** **All cases** G1: 1.00 G2: 0.97 (0.92–1.03) G3: 0.89 (0.80–0.99) G4: 1.03 (0.94–1.13) G5: 0.99 (0.92–1.06) G6: 0.97 (0.87–1.07) **Localised cases** G1: 1.00 G2: 0.97 (0.91–1.03) G3: 0.88 (0.78–0.99) G4: 1.03 (0.93–1.14) G5: 1.00 (0.93–1.08) G6: 0.99 (0.88–1.10) **Advanced cases** G1: 1.00 G2: 1.00 (0.87–1.16) G3: 0.94 (0.71–1.25) G4: 1.02 (0.80–1.29) G5: 0.89 (0.74–1.07) G6: 0.86 (0.65–1.13)

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Reference study name country study design follow-up funding	Original cohort (N total) population sampled exclusion criteria study population (*n*)	Ascertainment of outcome	Exposure groups exposure assessment method	Incident cases *n*/person-years *n*/participants	Test/model covariates	Results
Weinstein et al. (2017) **ATBC** **Finland** **Design:** PC **Follow-up**: 19 year **Funding:** public	**Inclusion criteria:** 50–69 year-old men, smoking at least five cigarettes/day, without prior cancer (other than non-melanoma skin cancer or carcinoma in situ), history of serious illness or current use of vitamins E (> 20 mg/day) and A (> 20,000 IU/day) ***N*:** 29,133 **Exclusion criteria:** incomplete dietary information ***n*:** 27,111 **Medication**: NR	Incident prostate cancer identified by medical records and reviewed centrally by study oncologists/pathologists for diagnostic confirmation on staging (up to April 1999). Between April 1999 and April 2004, cases were identified through the Finnish cancer registry	**Assessment:** Self-administered FFQ to assess total *α*-tocopherol intake (sum of dietary intake plus contribution of Vitamin E from multivitamin supplements) **Exposure Groups: Total *α*-tocopherol intake (mg/day):** Q1: ≤ 7.06 Q2: > 7.06 to ≤ 8.36 Q3: > 8.36 to ≤ 10.32 Q4: > 10.32 to ≤ 14.72 Q5: > 14.72	**Prostate cancer incidence** **Cases (*n*):** Q1: 322 Q2: 352 Q3: 307 Q4: 317 Q5: 342	**Cox proportional hazard models** **Covariates:** age at randomisation, trial intervention arm, weight, urban residence, education and intakes of total energy, fat, polyunsaturated fatty acids, vitamin C and lycopene	**RR (95% CI)** Q1: 1.00 Q2: 1.08 (0.92–1.26) Q3: 0.95 (0.80–1.14) Q4: 0.96 (0.78–1.19) Q5: 1.00 (0.79–1.17)
Stram et al. (2006) **MEC** **USA** **Design:** PC **Duration**: ~ 7 year **Funding:** public	**Inclusion criteria:** Men and women aged 45–75 years in Hawaii (mostly Japanese Americans, Native Hawaiians and Whites in Hawaii) and California (mostly African Americans and Latinos) ***N*:** 215,000 **Exclusion Criteria:** members of other ethnic groups, women, men with previous occurrence of prostate cancer, missing or incomplete data on personal characteristics (height, weight, educational status, smoking), unrealistic values of consumption of total energy or its components ***n*:** 82,486 **Medication:** NR	Linkage to the SEER registries and National Death Index (for vital status)	**Assessment: S**elf-administered questionnaire and dietary intake through an FFQ **Exposure groups – Vitamin E supplemental intake (mg *α*-Teq./day):** G1: 0 G2: > 0–≤ 33.75 G3: > 33.75 Vitamin E supplement users: 41.1% Vitamin E dietary intake (mg *α*-Teq./1000 kcal): Q1: ≤ 3.9 Q2: > 3.9–≤ 4.5 Q3: > 4.5–≤ 5.1 Q4: > 5.1–≤ 6.0 Q5: > 6.0 Vitamin K status/intake: NR	**Prostate cancer incidence among the whole sample** **Cases (*n*):** 3922	**Cox proportional hazard models** **Covariates:** age, ethnicity, education, BMI, smoking and family history of prostate cancer	**RR (95% CI):** G1: 1.00 G2: 1.01 (0.93–1.10) G3: 1.03 (0.95–1.12)

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Reference study name country study design follow-up funding	Original cohort (N total) population sampled exclusion criteria study population (*n*)	Ascertainment of outcome	Exposure groups exposure assessment method	Incident cases *n*/person-years *n*/participants	Test/model covariates	Results
Chan et al. (1999) **HPFS** **USA** **Design:** PC **Duration:** 10 year **Funding:** mixed	**Inclusion criteria:** male health professionals with 40–75 years of age at BL ***N*:** 51,529 **Exclusion criteria:** history of cancer (other than nonmelanoma skin cancer) at BL, and incomplete BL dietary questionnaire ***n***: 47,780 **Medication:** NR	Self-reported or reported by next of kin for deceased participants, confirmed by hospital records and pathology reports. Medical reports reviewed by a study physician who also classified stage of disease based on initial work-up, prostatectomy reports and bone scan results	**Assessment:** self-administered questionnaire to assess supplemental vitamin E intake from specific supplements and multivitamins, every 2 years **Exposure groups: Supplemental vitamin E intake (IU/day)** G1: 0 G2: 0.1–15.0 G3: 15.1–99.9 G4: ≥ 100.0 Age-standardised BL characteristics by use of supplemental vitamin E among users (*n* = 20,828): Mean age: 53.8 years Mean BMI: 24.7 kg/m^2 Mean dietary vit. E: 11.5 IU/day Mean supplemental vit. E: 191 IU/day Mean physical activity level: 24.4 MET-h/weeks Family history of prostate cancer in 1990: 5.7% Never-smokers: 48.4% Distant past smokers: 30.0% Current smokers/recent quitters: 21.6% Nonusers (*n* = 26,952): Mean age: 55.3 years Mean BMI: 25.1 kg/m^2 Mean dietary vitamin E: 11.1 IU/day Mean supplemental vit. E: 0 IU/day Family history of prostate cancer in 1990: 5.4% Never-smokers: 48.6% Distant past smokers: 29.0% Current smokers/recent quitters: 22.4% Vitamin K status/intake: NR	**Total non-A1 prostate cancer incidence** **Cases (*n*):** G1: 926 G2: 219 G3: 275 G4: 476 **Person-years (*n*):** G1: 238,779 G2: 49,284 G3: 64,374 G4: 88,645 **Extraprostatic cancer incidence** **Cases (*n*):** G1: 242 G2: 61 G3: 85 G4: 134 **Metastatic or fatal prostate cancer incidence** **Cases (*n*):** G1: 110 G2: 33 G3: 34 G4: 55	Comparison between incidence rates among users and non-users of vitamin E and the Mantel–Haenszel summary estimator to adjust for age and pooled logistic regression models to adjust for potential confounders **Covariates:** age, study period, family history of prostate cancer, smoking, current BMI, BMI at 21 years, physical activity, vasectomy status, and total energy, calcium, lycopene, fructose and fat intake in 1986	**RR (95% CI):** **Total non-A1 prostate cancer** G1: 1.00 G2: 1.09 (0.94–1.26) G3: 0.95 (0.94–1.26) G4: 1.07 (0.95–1.20) **Extraprostatic cancer** G1: 1.00 G2: 1.12 (0.84–1.49) G3: 1.16 (0.90–1.49) G4: 1.22 (0.98–1.52) **Metastatic or fatal prostate cancer** G1: 1.00 G2: 1.26 (0.85–1.87) G3: 1.03 (0.70–1.52) G4: 1.14 (0.82–1.59) *Total vitamin E (foods and supplements) and total non-A1, extraprostatic or fatal/metastatic prostate cancer:* *RRs (95% CIs) for comparison of extreme quintiles: 1.00 (0.86–1.17), 0.96 (0.72–1.27) and 0.89 (0.58–1.36), respectively* *2-year lag between intake of supplemental vitamin E and total non-A1, extraprostatic or fatal/metastatic prostate cancer:* *RRs (95% CIs) for comparison of ≥ 100 IU/day for at least 2 years* versus *none: 1.05 (0.93–1.18), 1.22 (0.98–1.53) and 1.15 (0.82–1.62), respectively*

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Reference study name country study design follow-up funding	Original cohort (N total) population sampled exclusion criteria study population (*n*)	Ascertainment of outcome	Exposure groups exposure assessment method	Incident cases *n*/person-years *n*/participants	Test/model covariates	Results
Peters et al. (2008) **VITAL** **USA** **Design:** PC **Duration:** ~2 year **Funding:** public	**Inclusion criteria:** men aged 50–76 that lived in the 13-county area in western Washington State covered by the SEER cancer registry ***N*:** 37,382 **Exclusion criteria:** men who reported a history of prostate cancer at BL, did not answer the question on history of prostate cancer or had a diagnosis of non-invasive prostate carcinoma during follow-up, who had missing information on variables included in the analysis, an incomplete FFQ or with an energy intake < 800 or > 5000 kcal. **Loss to follow-up:** NR ***n*:** 35,242 **Medication:** NR	Linkage to the western Washington State SEER cancer registry. The SEER registry ascertains cancer cases through all hospitals in the area, offices of pathologists, oncologists and radiotherapists, and from Washington State death certificates. Local stage cancer was defined as organ-confined disease, and regional and distant stage cancer as advanced disease	**Assessment:** vitamin E supplement use assessed through a self-administered questionnaire (for the period of 10 years prior to BL); dietary intake assessed using a self-administered FFQ (previous 12 months from BL) **Exposure groups:** **1) Supplemental vitamin E intake (IU/day)** G1: 0 G2: > 0–≤ 30 G3: > 30–< 400 G4: ≥ 400 **2) Total vitamin E intake (mg *α*-TE/day)** G1: < 14.3 G2: 14.3–< 29.4 G3: 29.4–< 98.1 G4: ≥ 98.1 Vitamin K status/intake: NR	**Total prostate cancer incidence** **1) Cases by supplemental vitamin E intake (*n* (%)):** G1: 228 (27.8) G2: 153 (18.7) G3: 317 (38.7) G4: 122 (14.9) **2) Cases by total vitamin E intake (*n* (%)):** G1: 156 (20.4) G2: 196 (25.7) G3: 195 (25.5) G4: 217 (28.4)	**Cox proportional hazards models** **Covariates:** age, family history of prostate cancer, benign prostatic hyperplasia, income, multivitamin use, energy intake, PSA screening in the 2 years before BL	**HR (95% CI):** **Total prostate cancer incidence** **1) Supplemental vitamin E intake** G1: 1.00 G2: 0.89 (0.68–1.20) G3: 0.90 (0.70–1.20) G4: 0.86 (0.65–1.10) **2) Total vitamin E intake** G1: 1.00 G2: 1.20 (0.93–1.50) G3: 1.00 (0.78–1.30) G4: 0.98 (0.77–1.30) **Local prostate cancer incidence** **1) Supplemental vitamin E intake** G1: 1.00 G2: 0.90 (0.67–1.20) G3: 0.95 (0.73–1.20) G4: 0.93 (0.68–1.30) **Advanced prostate cancer incidence** **1) Supplemental vitamin E intake** G1: 1.00 G2: 0.78 (0.39–1.60) G3: 0.60 (0.30–1.20) G4: 0.43 (0.19–1.00)
Roswall et al. (2013) **DCHCS** **Denmark** **Design:** PC **Duration:** 14.3 year **Funding:** private	**Inclusion criteria:** Danish men aged 50–64, residency in the Copenhagen or Aarhus area and no previous cancer diagnosis in the Danish Cancer Registry ***N*:** 27,178 **Exclusion criteria:** having cancer before BL and if information on confounders/exposure was missing participants for the analyses. **Loss to follow-up:** NR ***n*:** 26,856 **Medication:** NR	Prostate cancer incident cases identified through the Danish Cancer Registry. Aggressive cases were identified by reviewing medical records and defined as those with a Gleason score ≥ 7, PSA > 15, T-stage ≥ 3, *N*-stage ≥ 1 or M-stage ≥ 1	**Assessment:** BL diet and supplement intake assessed by a self-administered FFQ **Exposure groups:** **1) Supplemental vitamin E intake (mg/day)** G1: 0 G2: > 0–≤ 4.4 G3: > 4.4–≤ 10.0 G4: > 10.0 **2) Total Vitamin E intake (mg/day)** G1: 0–≤ 8.6 G2: > 8.6–≤ 12.0 G3: > 12.0–≤ 17.7 G4: > 17.7 Vitamin K status/intake: NR	**Prostate cancer incidence** **Cases (*n*):** 1571 **Prostate cancer aggressivity (*n* (%)):** Aggressive: 842 (53.6) Non-aggressive: 329 (20.9) Unknown: 400 (25.5)	**Cox proportional hazards models** **Covariates**: age, vitamin C, folate, beta-carotene, selenium and red meat intake, height, weight, education, alcohol consumption	**HR (95% CI):** **Total prostate cancer incidence** **1) Supplemental vitamin E intake** G1: 1.0 G2: 1.00 (0.79–1.26) G3: 1.02 (0.82–1.28) G4: 0.94 (0.75–1.19) **2) Total vitamin E intake** G1: 1.0 G2: 1.00 (0.86–1.16) G3: 0.92 (0.78–1.09) G4: 0.90 (0.74–1.11)

(Continued)

Reference study name country study design follow-up funding	Original cohort (N total) population sampled exclusion criteria study population (*n*)	Ascertainment of outcome	Exposure groups exposure assessment method	Incident cases *n*/person-years *n*/participants	Test/model covariates	Results
Agalliu et al. (2011) **CSDLH** **Canada** **Design:** case-cohort **Duration:** 4.3 years for cases and 7.7 years for the subcohort **Funding:** public	**Inclusion criteria:** male alumni from the Ontario component of the CSDLH study, recruited between 1995 and 1998. All incident cases identified were included, along with a subcohort comprising an age-stratified random sample of the Ontario cohort at BL ***N*:** 2681 **Exclusion criteria:** prevalent cases of prostate cancer at BL **Loss to follow-up:** NR ***n*:** 2525 **Medication:** NR	Incident cases identified by record linkage with the Ontario Cancer Registry Non-advanced prostate cancer: localised (AJCC stage I or II) and a Gleason score of 2–7 Advanced prostate cancer: regional or metastatic spread (AJCC stage III or IV) or with a Gleason score of 8–10	**Assessment:** self-administered FFQ to assess diet and supplement intake (total vitamin E) **Exposure groups:** **Total vitamin E (median, mg/day)** Q1: 6.3 Q2: 8.3 Q3: 14.6 Q4: 264.4 Q5: 462.0 Total vitamin E intake (mean (SD)): Cases: 175.5 (251.2) mg/day Subcohort: 177.7 (289.0) mg/day Vitamin K status/intake: NR	**All prostate cancer cases:** Q1: 130 Q2: 115 Q3: 155 Q4: 132 Q5: 129 **Non-advanced prostate cancer** Q1: 82 Q2: 75 Q3: 107 Q4: 81 Q5: 78 **Advanced prostate cancer** Q1: 33 Q2: 28 Q3: 34 Q4: 36 Q5: 42	**Cox proportional hazard models:** method described by Langholz and Jiao 2007[a] to calculate the asymptotic variance estimates for a stratified subcohort, which were used to calculate the 95% CIs **Covariates:** Age at BL, race, BMI, physical activity and education	**HR (95% CI):** **All prostate cancers** Q1: 1.00 Q2: 0.86 (0.64–1.17) Q3: 1.19 (0.89–1.59) Q4: 1.01 (0.75–1.36) Q5: 1.08 (0.80–1.45) **Non-advanced prostate cancer** Q1: 1.00 Q2: 0.90 (0.62–1.29) Q3: 1.32 (0.94–1.86) Q4: 0.99 (0.69–1.41) Q5: 1.04 (0.72–1.48) **Advanced prostate cancer** Q1: 1.00 Q2: 0.82 (0.48–1.41) Q3: 1.02 (0.60–1.71) Q4: 1.05 (0.63–1.75) Q5: 1.39 (0.85–2.27)

Abbreviations: AJCC, American Joint Commission on Cancer Staging; ATBC, The a-Tocopherol, h-Carotene Cancer Prevention Study; BL, baseline; BMI, body mass index; CI, confidence interval; CPS-II, Cancer Prevention Study II; CSDLH, Canadian Study of Diet, Lifestyle and Health; DM, diabetes mellitus; DRE, digital rectal examination; FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-up Study; IU, international units; MEC, Hawaii–Los Angeles Multiethnic Cohort Study; MET, metabolic equivalent of task; HR, hazard ratio; NIH-AARP, National Institutes of Health - American Association of Retired Persons Diet and Health Study; NR, not reported; PC, prospective cohort; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results; VITAL, Vitamins and Lifestyle study.

[a]Langholz, B., & Jiao, J. (2007). Computational methods for case-cohort studies. Computational Statistis and Data Analysis, 51, 3737–3748.

ANNEXES

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Annex B – Literature screening strategy.
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